ISSN 2219-2808 (online)

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2022 January 9; 11(1): 1-92

Published by Baishideng Publishing Group Inc

WJCP

World Journal of Clinical Pediatrics

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INDEXING/ABSTRACTING

The *WJCP* is now abstracted and indexed in PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Pediatrics

ISSN
ISSN 2219-2808 (online)

LAUNCH DATE
June 8, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
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https://www.wjgnet.com/2219-2808/editorialboard.htm

PUBLICATION DATE
January 9, 2022

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World J Clin Pediatr 2022 January 9; 11(1): 1-13

DOI: 10.5409/wjcp.v11.i1.1

ISSN 2219-2808 (online)

MINIREVIEWS

Psychotropic drug abuse in pregnancy and its impact on child neurodevelopment: A review

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Author contributions: Etemadi-Aleagha A contributed to the conception of the research idea, design, paper drafting and revision for important intellectual content; Akhgari M was involved in providing acquisition and interpretation of data, drafting and revision for important intellectual content; all authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Country/Territory of origin: Iran

Specialty type: Neurosciences

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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Abstract

Substance abuse by women of child-bearing age and fetal in utero drug exposure has increased in the number of infants born with health issues. Prenatal exposure to psychoactive substances can lead to neurological and neurodevelopmental deficits later in life. Useful data concerning the effects of psychoactive drugs on fetal neurodevelopmental status are sparse. Understanding the neurodevelopmental consequences of prenatally drug-exposed children has become a pressing global concern. The aim of this review is to gather current evidence and information on neurodevelopmental outcomes of in utero drug exposure. A literature search was performed on the PubMed, Scopus, and Google Scholar databases using the terms "psychotropic drugs", "neurodevelopmental consequences", "prenatal drug exposure", and "pregnancy". Available studies on in utero drug exposure were reviewed and found to support the idea that some degree of health issues are present in fetuses and children. Different psychoactive substances have profound neurodevelopmental consequences, such as structural brain changes, poor attention span, Down syndrome, attention deficit hyperactivity disorder, autism spectrum disorder, imbalances in neurotransmitter levels, and many structural deficits. The pervasive use of psychoactive drugs in women of child-bearing age is an important health concern. Further scientific efforts are needed to investigate the effect of prenatal exposure to psychoactive drugs on children.

Key Words: Psychotropic drugs; Pregnancy; Prenatal substance exposure; Brain; Neurodevelopmental outcomes; Fetus

Received: February 26, 2021
Peer-review started: February 26, 2021
First decision: April 20, 2021
Revised: April 21, 2021
Accepted: November 29, 2021
Article in press: November 29, 2021
Published online: January 9, 2022

P-Reviewer: Matowicka-Karna J
S-Editor: Gong ZM
L-Editor: Filipodia
P-Editor: Gong ZM

Core Tip: Use of psychotropic drugs during pregnancy is thought to contribute to the pathophysiology of neurodevelopmental disorders in children. In utero, drug exposure is related to different factors such as drug dose, its chemical structure that influences the entrance of the drug to the fetus body, drug distribution and elimination. However, neurodevelopmental consequences like autism, Down syndrome and structural deficits are the results of in utero drug exposure. Evidence from previous studies confirmed that in utero drug exposure played a key role in the etiology of neurological problems later in life, providing information and insights for preventing substance abuse in women.

Citation: Etemadi-Aleagha A, Akhgari M. Psychotropic drug abuse in pregnancy and its impact on child neurodevelopment: A review. *World J Clin Pediatr* 2022; 11(1): 1-13
URL: https://www.wjgnet.com/2219-2808/full/v11/i1/1.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i1.1

INTRODUCTION

Addiction to drugs is defined as the repeated use of addictive substances that cause a set of physiological and behavioral effects. The repeated use of drugs, cravings, and withdrawal symptoms after stopping drug use are among the most important typical symptoms of addiction[1]. The prevalence of the non-medical and recreational use of drugs and substances among women remains at a level comparable to that of men[2]. Alongside the increasing trend of drug abuse, there has been a corresponding rise in the use (and abuse) of licit or illicit drugs in women of child-bearing age[3]. Drug use among pregnant women may result in several medical complications, both for the mother and her child. There are many critical variables involved in the effects of drugs of abuse on fetal brain development. These variables include the duration, timing, and magnitude of exposure, as well as how much of the drug enters the fetus blood and central nervous system (CNS). As the amount of absorbed drug is not equal along different routes of drug administration (oral, inhalation, smoking, and injection), their effects on a fetus's vital organs and fetal toxicity also differ[1]. Human research on pregnant mothers using illicit drugs has demonstrated associations between substance use and pregnancy loss[1].

There are several issues regarding drug abuse during pregnancy and its impact on child neurodevelopment. There are some practical difficulties in studying human embryos during in utero drug exposure. Drug-dependent mothers often use multiple drugs from different categories with various pharmacologic properties. This situation renders it challenging to study the effect of a single drug on the fetus's neurodevelopment in isolation. Other factors, such as the mother's hormones and blood glucose level, also influence the child's neurodevelopment[4]. However, studies based on self-reports of illicit drug use during pregnancy are subject to an underrepresentation bias [5].

Prenatal drug exposure is a rising global phenomenon with significant variability across countries[6]. Fetal brain development takes place during pregnancy. The first trimester of pregnancy is a particularly important period of development[7]. Exposure to drugs and substances early in life has long-lasting adverse effects on brain structure and function[5]. Embryonic exposure to drugs and addictive substances can change the cellular morphology of cortical neurons. Previous reports have confirmed that the cerebral cortex is greatly affected by drugs. The architecture of neurons, receptor function, and the synaptic plasticity of many inhibitory and excitatory neurons in the marginal system of the midbrain cortex are altered by drug use[8]. Prenatal exposure to drugs is one of the important issues that impact the CNS development of a fetus and, subsequently, his/her future behavior. Experimental and animal studies offer evidence that prenatal neurodevelopmental insults continue to involve fetal, neonatal, infant, and childhood CNS development[9]. Understanding the relationship between prenatal drug exposure and its effects on children's neurodevelopmental outcomes is a problematic task for researchers[10]. Associations between prenatal drug exposure and neurodevelopmental consequences in children are complicated because of confounding factors such as the type of drug used and its dose, environmental circumstances, and individual genetic profiles. Such circumstances limit researchers' ability to

understand the connection between in utero drug exposure and late childhood consequences[9].

Previous studies focused on the fetal health consequences of individual drug classes. The aim of this review is to summarize the effects of different categories of substances abused by pregnant women and their effects on children, including a detailed description of neurodevelopment difficulties.

DRUG PHARMACOKINETICS DURING PREGNANCY

Numerous factors play important roles in fetal exposure to drugs including drug dose, maternal drug pharmacokinetic parameters, drug distribution and elimination in the fetus body. However, three main factors determine a drug's transfer rate from placenta to fetus body; drug lipophilicity, the pH gradient across the placenta, and drug's protein-binding properties[11]. Non-ionized, low molecular weight and lipid-soluble drugs are freely absorbed from the placenta to the fetus body. Two important factors are responsible for drug equilibration between maternal and fetal blood compartments; concentration gradient (fetal/maternal drug ratio) and the placental blood flow[11]. The metabolic power of the fetus for the metabolism of drugs and substances administered to the mother is not completed during the first 3 mo of fetus life, resulting in the exposure of the fetus to high quantities of drugs[11]. Physiologic changes during pregnancy affect several pharmacokinetic parameters such as absorption, distribution, metabolism, and excretion of drugs[11]. The first pharmacokinetic parameter, absorption, decreases during pregnancy as a result of gastric emptying time reduction as well as the small bowel drug transit time[11]. There is an escalation of maternal plasma volume during pregnancy, which can be increased by 50% during the last trimesters of pregnancy, thus leading to lower plasma concentration of drugs[11,12]. Most psychotropic substances have a lipophilic chemical structure and show a greater volume of distribution during pregnancy[12]. It is important to mention that hormonal induction or inhibition of metabolic processes plays an important role in pharmacokinetic changes of psychoactive substances during pregnancy[12].

PSYCHOACTIVE DRUGS AND SUBSTANCE CLASSIFICATIONS

Cannabis and synthetic cannabinoid receptors agonists

Cannabis consists of the flowering or fruiting tops of the cannabis plants — its *sativa*, *ruderalis,* and *indica* subspecies contain a number of chemical substances. The most predominant substance with psychoactive properties is *delta*-9-tetrahydrocannabinol, commonly known as THC. Other cannabinoids are cannabidiol (CBD) and cannabinol (CBN). The term "cannabis" is defined as different products obtained from the cannabis plant.

Marijuana, also known as cannabis, is obtained from plants of the *cannabis* genus that are members of the Cannabaceae family. The pharmacologically active ingredients of marijuana are the phytocannabinoids that interact with cannabinoid receptors. Tetrahydrocannabinol (THC) and cannabidiolic acid are two products of cannabinoids. There are many slang and street names for marijuana, including herb, weed, hashish, ganja, and grass. THC is the active ingredient of resin produced from the leaves and buds of female plants. The cannabis plant contains about 500 chemical compounds, 100 of which are structurally and chemically related to THC. These compounds, together with THC, are called cannabinoids[13]. CB1 and CB2 are two known cannabinoid G protein-coupled receptors. CB1 is found on axons and nerve terminals in the CNS[14]. Meanwhile, CB2 receptors are mostly expressed on immune cells[14]. Two active components of the cannabis plant (THC and CBD) are CB1 and CB2 receptor agonists. CB1 receptor agonists mediate decreased neuronal signaling across synapses[13]. Dried leaves of cannabis plant is shown in Figure 1.

Common routes of administration of cannabis products: Marijuana inhalation is the fastest route by which THC enters systemic blood circulation. Marijuana inhalation can be performed through smoking, dabbing, or vaporization. Different oral preparations, including drops, cakes, tinctures, candies, snacks, and drinks, are produced as oral marijuana. Rectal and vaginal suppositories are also made from oils and waxes that contain marijuana[15].

Figure 1 Dried leaves of cannabis plant.

Marijuana pharmacokinetics in pregnancy: Maternal use of marijuana has a high frequency due to the perception that marijuana is safe and can be used during pregnancy[16]. Human and animal studies have demonstrated that THC rapidly crosses the placenta and that its concentration in fetal blood correlates with that in maternal blood. A placenta's normal physiology and transport mechanisms are affected by marijuana. The permeability of the placental barrier to licit and illicit drugs increases due to CBD exposure, thus enhancing fetal exposure to other drugs and poisons. Other human studies have confirmed that prenatal exposure to cannabis reduces blood flow that is essential to supply the placenta. After oral administration, the amount of THC absorbed exceeds 90%. However, due to first-pass hepatic metabolism, its bioavailability is limited to less than 20%. In contrast, after marijuana smoking, THC bypasses the first-pass hepatic metabolism, resulting in highly irregular bioavailability. However, its concentration reduces due to losses through sidestream smoke, absorption by cigarette butts, and pyrolysis[17,18].

Effect of cannabis use in pregnancy and childhood outcomes: Studies on the effects of marijuana in pregnancy are confounded by nutritional inadequacy and multi-substance abuse that can show synergistic effects[19]. Animal and human studies on the effect of THC in fetal brains have demonstrated structural brain changes, especially in the nucleus accumbens[20,21]. One previous study showed that marijuana use was significantly associated with stillbirth, spontaneous preterm birth, and decreased birth weight[22]. Cannabis use was evidenced by tetrahydrocannabinolic acid positive screens in umbilical cord homogenate. This result was confounded by concurrent maternal tobacco use[23].

Prenatal marijuana use has a high prevalence as a recreational drug or to alleviate nausea and morning sickness. Babies exposed to prenatal cannabis suffer from problems associated with neurological development. These problems are manifested as changing responses to visual stimuli, shivering, and high-pitched cry[24]. Memory and skill gap problems are other important difficulties among school-aged children exposed to cannabis in the prenatal phase[25]. Neurologic tests and intelligence quotient (IQ) estimation manifested variable degrees of impairment in visual memory, perception, and language comprehension in different periods of children's lives. Children also suffered from poor sustained attention and high hyperactivity and impulsivity[26].

A study conducted in Hawaii showed that many birth defects, including Down syndrome, cardiovascular issues, arm and hand defects, and orofacial clefts, are more prevalent among children exposed to cannabis during gestation[27]. Another study in Canada confirmed that congenital defects were more common in territories where cannabis is smoked more often than in other territories[28]. Concerningly, the elevated rates of acute lymphoid leukemia (ALL), acute myeloid leukemia (AML), rhabdomyosarcoma, and neuroblastoma in the pediatric population suggest further implications of cannabinoid-induced genotoxicity[27].

Synthetic cannabinoid receptor agonists: Synthetic cannabinoid receptor agonists are designed substances with structural features that allow binding to cannabinoid receptors. These substances mimic the effects of cannabis but are not licensed for medical use. In an experimental study conducted to evaluate the effect of synthetic cannabinoid receptor agonists on cortical and sub-cortical brain areas across postnatal

development, it was concluded that the administration of synthetic cannabinoid receptors has a disparate effect on neural morphology in adult and adolescent rats. Their results suggest that neural circuits in the adolescent brain may be more vulnerable to drugs[29].

Opium, opiates, and opioids

Opium is defined as the coagulated juice obtained from the plant *Papaver somniferum*.

There are a number of alkaloids with psychoactive properties which can be extracted from opium. Morphine, codeine, thebaine, papaverine, and noscapine are the major alkaloids in opium. Heroin (diacetylmorphine, diamorphine) is a semi-synthetic opiate obtained from the acetylation of morphine.

Opioids' mechanism of action: The pharmacologic properties of morphine, heroin, and other opiates are mediated through the activation of opioid receptors. There are different types of opioid receptors. Among them, μ (mu) receptors mediate analgesic and behavioral effects[30].

Opioids refer to opiates and their synthetic congeners, which can be synthetic or semi-synthetic. Their pharmacologic properties are similar to those of morphine. Synthetic derivatives of opioids have different chemical structures and can be extremely potent. Fentanyl derivatives, methadone, and buprenorphine are classified as synthetic opioids[30].

Opioid use during pregnancy and its outcomes: The prevalence of opioid use among women of child-bearing age has increased dramatically. In utero exposure to opioids can have a direct effect on neuronal development[10]. Before environmental confounding factors influence child neurodevelopment, neurological changes can be observed shortly after birth in opioid-exposed infants[31]. Along with adverse neonatal outcomes associated with prenatal opioid exposure (stillbirth, premature delivery, and reduced gestational age), brain growth and poor neurodevelopmental outcomes are important health issues[32].

However, maternal confounding factors, such as the concomitant use of alcohol and cigarettes, and multi-drug use during pregnancy (and their effects on neurodevelopmental outcomes), should not be neglected[33]. Damage to the central and peripheral nervous systems of fetuses is the leading adverse effect of opioids use in pregnancy [8]. The most significant consequences of opioid exposure on fetal neural development are neural tube defects and neonatal abstinence syndrome[8]. Incomplete closure of neural tube during 4 or 5 wk of embryonic neural tube development is a congenital malformation caused by opioids. It is demonstrating as anencephaly, encephalocele, and spina bifida[8,34]. Opioids can change connections and sizes between different parts of the brain, including the basal ganglia, thalamus, and cerebellar white matter. Also, the myelination process in developing oligodendrocytes is altered as a result of the effect of opioids on the fetus brain[35]. Opioid-exposed children suffer from lower cognitive and psychomotor scores and poor social-emotional consequences during infancy and preschool age. Preschool- and school-age children exposed to opioids during the prenatal period tend to have below-average IQ scores and language development and skills, as well as high attention problem scores. Results of previous findings strengthen the idea that opioid-exposed children suffer from a wide variety of long-term neurodevelopmental disorders. These problems were seen among infants born to opioid-dependent mothers taking methadone[3]. According to previous studies, methadone-exposed infants exhibit a more dysregulated pattern of neurobehavioral disorders at the time of birth in comparison to unexposed infants[3,36].

Prescription opioids are used as pain relievers and as substitutes for opioids in drug rehabilitation programs. However, these groups of substances are commonly abused by women of child-bearing age[8]. Methadone is a highly lipophilic substance with a low molecular weight. It readily crosses the placenta and reaches the embryo. Experimental and animal model studies have demonstrated that methadone has a profound impact on a child's neuronal development and brain function. It has been confirmed that methadone has deleterious effects at the critical stages of neuronal myelin formation[4,37]. Stoetzer *et al*[38] indicated that methadone disrupts locomotor activity. Methadone and other opioids have a negative influence on ion channels, thereby altering neuronal network activities. Methadone disrupts the integrity of human cortical organoids in a dose- and stage-dependent manner. Methadone also antagonizes NMDA receptors in human cortical organoids[4].

It has been confirmed that poor attention, regulation, and quality of movement result from in utero methadone exposure. Methadone-exposed infants suffer from excitability, regulation, signs of stress, abstinence, neurological deficits, and intel-

lectual disabilities later in life. Results of follow-up studies in children at 24 mo of age revealed that distinct neurobehavioral profiles, such as poor cognitive and motor development, persist over the first 4.5 years of a child's life[3,4]. However, there was no difference between infants prenatally exposed to methadone in comparison with unexposed infants at the gestational age.

Stimulants

Amphetamine-type stimulants: The term amphetamine-type stimulants (ATSs) refers to a group of substances that are mostly synthetic. The principal members are amphetamine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA, ecstasy). ATSs have stimulatory effects on the CNS, as they interfere with the dopamine, norepinephrine, and serotonin systems[30].

Amphetamines mechanism of action: Amphetamine and methamphetamine affect neurotransmitter levels through various mechanisms. The mechanism of ATSs is mainly based on direct interactions with neurons and the information transmitted between them. Each specific substance has its own mechanism of action, but the basic principles remain the same. ATSs increase neurotransmitter concentrations in neuron synapses. On the other hand, ATSs are also classified as non-catecholamine sympathetic drugs that do not have catecholamine chemical structures and do not influence receptors[1]. Once methamphetamine enters the CNS, it releases noradrenaline, dopamine, and serotonin, and it mediates an increase in monoamine concentrations in neuronal cytosols and synapses. Neurotransmitter reabsorption inhibition is another mechanism by which ATSs increase neurotransmitter concentrations in neuronal synapses. Monoamine oxidase (MAO) is an enzyme involved in the degeneration and inactivation of monoamines. The methyl group on the alpha carbon in methamphetamine structure inhibits MAO activity, resulting in an increased monoamine concentration[1]. The combination of these processes stimulates the CNS. Methamphetamine acts mainly *via* interference with dopaminergic and serotonergic neuronal response pathways. In other words, methamphetamine can be classified as a non-catecholamine sympathetic substance[1].

Methamphetamine pharmacokinetics: Methamphetamine is absorbed freely through the gastrointestinal tract. It passes through the blood-brain barrier (BBB) with greater ease than its less lipophilic analogues, such as amphetamine. Methamphetamine is widely distributed throughout the body. It is metabolized differently in various animal species. In the human body, a substantial amount of methamphetamine is excreted unchanged *via* urine as a parent drug. Hydroxymethamphetamine is one of the methamphetamine metabolites that is formed *via* hydroxylation in the liver and excreted in the urine. The other metabolite is amphetamine, which is produced as a result of the N-demethylation of methamphetamine[1].

Neurotoxic effects of methamphetamine: The neurotoxic effects of methamphetamine occur as a result of highly reactive free radical production due to dopamine auto-oxidation. Also, vesicular pool storage depletion to the cytoplasmic compartment in dopaminergic neurons induces intraneuronal oxidation, which is one of the primary causes of dopamine terminal injury[39]. In conclusion, the imbalance among the vesicular, cytoplasmic, and extracellular dopamine pools is important in the neurotoxic action of methamphetamine. After long-term exposure to methamphetamine, dopaminergic receptors are degraded, dopamine production decreases, and withdrawal symptoms arise[40].

Different parts of the brain responsible for pleasure, motor control, and addiction are connected to each other by dopaminergic and serotonergic pathways. Monoamine transporters, such as dopamine, serotonin, and norepinephrine transporters, aid methamphetamine's entrance to the neuron body. Methamphetamine displaces monoamine pools in vesicular and intracellular compartments, and it facilitates the release of monoamines into the synaptic space[41].

Methamphetamine is a neurotoxic substance that can cause striatal nerve terminal degeneration. Dopamine extracellular concentrations are elevated *via* the migration of dopamine from intracellular pools to the extracellular space induced by methamphetamine. Methamphetamine exerts its neurotoxic effect *via* the auto-oxidation of dopamine into highly reactive free radicals[1,39,41]. The primary cause of dopamine terminal injury is the redistribution of dopamine from vesicular stores to the cytoplasmic compartment, which causes intraneuronal oxidation[1,39]. In methamphetamine-addicted subjects and long-term users, reduced dopamine production and a loss of dopaminergic receptors trigger the need to increase the dosage of the abused substance[40]. Methamphetamine-induced hyperthermia is mediated by dopamine

receptor overactivation. However, as dopamine stores deplete over time, serotonin starts to play the main role. Methamphetamine reduces forebrain serotonin concentrations causing depression and sleep disorders.

Methamphetamine use during pregnancy and its outcomes: Women are more sensitive to methamphetamine than men. Unfortunately, methamphetamine use among pregnant women has increased. Pregnancy has an important effect on a woman's sensitivity to drugs. In addition to malnutrition in addicted pregnant women, sensitivity to some drugs, such as cocaine, increases, sometimes causing sudden fetal death[42,43]. Methamphetamine's concentration peak, distribution volume, and biological half-life are affected by physiological changes and altered body water volume during pregnancy. Many factors change in the placenta throughout pregnancy. The placenta's cellular membrane, protein binding, nutrient and oxygen transfer capacity, blood flow rate, and drug permeability to the fetus are strongly affected by drug use[1]. Previous studies have confirmed that methamphetamine passes the placental barrier easily. It was also shown that half of the methamphetamine concentration can be detected in the fetal blood circulatory system when compared to maternal blood[44,45]. Methamphetamine is mainly metabolized in the liver, but the enzymatic system in the fetal liver is not yet able to handle large amounts of drugs. After repeated exposure to methamphetamine, high drug concentrations can be found in fetal plasma[44]. Due to the oxidant activity of methamphetamine and reactive oxygen species production, antioxidant levels are decreased in the embryo during maternal methamphetamine use, resulting in oxidative damage to lipids, proteins, and DNA[46].

Previous studies demonstrated that methamphetamine decreases dopamine and noradrenaline levels, followed by an increase in synaptic activity that produces neurotoxic effects on the CNS. Cui *et al*[47] showed that methamphetamine combined with monoamine neurotransmitters can disturb fetal brain development.

Issues regarding methamphetamine exposure during the prenatal period are associated with impaired neurological development[48]. Infants suffering from prenatal exposure to methamphetamine show neurobehavioral development manifestations, such as poor movement, electroencephalogram (EEG) changes, elevated stress levels, and physical tension[48,49]. Other studies confirmed low birth weight, stillbirth, and intrauterine growth retardation in methamphetamine-exposed children[50]. Fetus brain structure can also be affected by methamphetamine. Previous studies offer evidence of decreased volumes of subcortical structures such as the putamen, globus pallidus, caudate nucleus, and hippocampus; smaller striatum; and fewer dopamine (D2) receptors due to prenatal methamphetamine exposure[51]. However, these children do not suffer from language problems or low IQ[52]. Young school-aged children exposed to methamphetamine during their prenatal life exhibit problems related to adapting with their peers and cognition. They show anxiety, emotional instability, aggression, and personality disorders such as attention deficit hyperactivity disorder (ADHD)[53].

Coca and cocaine

Cocaine is obtained from the plant *Erythroxylon coca*. It consists of different kinds of alkaloids, including cocaine (the main psychoactive substance of coca leaves), benzoylecgonine, and ecgonine[30]. Cocaine exerts its stimulant activity by affecting the brain's dopamine, norepinephrine, and serotonin neurotransmitter systems. However, cocaine's effect on the level of dopamine is more pronounced than that of methamphetamine and amphetamine[30].

Cocaine's mechanism of action: Cocaine binds to monoamine transporters in the fetal brain. Animal model studies have described decreased dopaminergic, beta-adrenergic, and serotonergic receptor expressions in the embryonic brain following prenatal cocaine exposure[5].

Long-term repercussions of cocaine exposure have been found in GABA and glutamate neurotransmitters systems, resulting in an increase in the numerical density and anatomical alterations of glutamatergic neurons. These changes suggest alterations in neocortical connectivity that can cause behavioral and cognitive deficits [5,54].

Cocaine use during pregnancy and its outcomes: Recent studies report that cocaine use among pregnant women continues to be a public health concern. Fetal cocaine exposure during pregnancy disrupts brain monoamines, especially dopamine, during a critical stage of brain development. Animal-based and experimental studies permit rigorous and hypothesis-driven explorations of the effect of prenatal cocaine exposure

on brain development. There are some confounding factors in the human-based studies, such as multi-drug use. Multi-drug use is common among cocaine users. They often use alcohol, nicotine, and marijuana with cocaine[5].

Prenatal cocaine exposure can affect early brain development. It causes fetal growth retardation, seizure, respiratory distress, cerebral malformation, and, in some instances, sudden infant death syndrome. An infant's behavioral profile correlates with the timing of cocaine exposure. Cocaine exposure during the first and second trimesters causes abnormal reflexes, but its exposure during the second and third trimesters induces reductions in motor maturity and muscle tone[5]. Other consequences of prenatal cocaine exposure are disrupted arousal regulation, attention, emotional reactivity, and reward systems[5]. Children exposed prenatally to cocaine have shown specific language and cognitive deficits, behavioral problems, and impaired social development[5,55]. Abnormal brain development can be exhibited as decreased head circumference and microcephaly as a result of high levels of prenatal cocaine exposure. In fact, head circumference is a good predictor of neurobehavioral deficits in prenatal cocaine-exposed children. Magnetic resonance imaging (MRI) of brains revealed size reductions in cortical and subcortical structures, including a smaller caudate, corpus callosum, and pallidum. In contrast, the amygdala's size increases[56]. Significant reductions in the volume of cortical gray matter, thalamus, and putamen resulted from in utero cocaine exposure[57]. Brain wave activity changes and seizures are other outcomes of prenatal cocaine exposure. Prenatal cocaine-induced seizures continue throughout the child's initial months of life and, in some cases, even after 6 mo, suggesting long-term neurodevelopmental consequences of early life cocaine exposure[58].

Previous studies have confirmed that cocaine- or heroin-exposed infants are impacted by a combination of drugs (known as cocktails) with a variety of pharmacologic properties[7,59]. Cocaine users often use other substances, such as alcohol and tobacco, simultaneously[7].

Hallucinogens

Hallucinogens are naturally occurring or synthetic substances that induce hallucinations and distortions in consciousness and perception, thinking and feeling, often accompanied by some degree of auditory or visual hallucinations. They are also known as "psychedelics," and they produce synaesthesia and alter the user's perception of reality. Hallucinogenic agents fall into different chemical groups, including tryptamine (lysergic acid diethylamide or LSD and psilocin) and phenethylamines (mescaline, the main psychoactive component of peyote cactus). Hallucinogens mediate their hallucinogenic activity through interactions with serotonin receptors. LSD is one of the most potent hallucinogenic substances. It is derived from lysergic acid, an alkaloid found in a fungus named *Claviceps purpurea.* LSD's mechanism of action is similar to those of other hallucinogens. LSD exerts its hallucinogenic effect *via* its agonistic activity at the serotonin receptor 5-HT_{2A}. Serotonin is a neurotransmitter with biogenic properties. It acts as a neurotrophic agent in neuronal development processes such as neurogenesis and neuronal differentiation[60]. It has been shown that each agent that alters serotonergic signaling is linked to neurodevelopmental disorders such as autism spectrum disorder (ASD), ADHD, depression, and schizophrenia. Previous studies have demonstrated that normal placental structure and function are associated with equilibrium in serotonin signaling[61]. In fact, deficient placental serotonin levels are correlated with fetal growth restriction, anxiogenic behavior, and ASD[61].

Alcohol

Alcohol pharmacokinetics during pregnancy: Alcohol is absorbed readily from the placenta into the fetal bloodstream. Prenatal alcohol exposure begins with the dispersion of alcohol through the placenta to the fetal compartment. The chemical structure of ethanol enables rapid diffusion across the placental barrier and dispersion throughout the body water. The time needed to obtain an equilibrium between fetal and maternal alcohol concentration is one to two hours. Alcohol dehydrogenase is the enzyme responsible for ethanol metabolism in the mother, placenta, fetus, and neonates, though this occurs with different concentrations and activities. Available studies showed that the metabolic capacity of a fetus for ethanol oxidation is limited and that the majority of ethanol metabolism takes place in the maternal body to clear ethanol from the fetal-maternal unit. Small amounts of ethanol can be excreted unchanged through pulmonary excretion and in fetal urine, which can accumulate in amniotic fluid. It has been shown that the reuptake of amniotic fluid by the fetus has a

dramatic effect on the duration of fetal exposure to alcohol[62].

Alcohol (ethanol) use in pregnancy predisposes developing fetuses to health risks and is linked to adverse prenatal outcomes and fetal alcohol spectrum disorder (FASD)[63]. Many pregnancies are unintended. Therefore, a fetus may unintentionally be predisposed to alcohol in utero during critical embryonic development stages. Some health issues of alcohol use during pregnancy are miscarriage, preterm labor, stillbirth, and intrauterine growth restriction[64,65]. Women are more sensitive to alcohol than men due to their greater alcohol absorption and slower metabolism rate. Therefore, women exhibit higher blood alcohol levels than men upon drinking equal amounts of alcohol[63]. There are some varieties in response to alcohol in the fetal and neonatal stages. Several factors, such as the clearance rate of alcohol in the body, genetic variability, fetal developmental sensitivity, time (critical stages of organ formation), duration of alcohol and multi-drug use, influence the dose-response relationship between the amount of alcohol consumed during pregnancy and child health outcomes.

Alcohol use during pregnancy and its outcomes: Intrauterine alcohol exposure is associated with various fetal structural anomalies, including renal, cardiac, and craniofacial malformations. Children sometimes have complications with vision, hearing, short palpebral fissures, smooth philtrum, and a thin vermilion border of the upper lip as the most important craniofacial structural impairments[66]. Children with FASD may show abnormal facial features; low height and/or weight; and CNS complications such as small head circumference, poor attention and coordination, and hyperactive behaviors.

New psychoactive substances: New psychoactive substances (NPSs) are designer analogues of licit or illicit drugs designed for recreational use. The rapid growth in the global production of NPSs poses a considerable public health risk. These substances have spread in the market under names such as “legal highs”, “research chemicals”, and “bath salts”[67]. However, little is known about the adverse effects, health issues, and psychological properties of these new emerging substances. Safety data on the effect of prenatal exposure to NPSs, their toxicity, and their carcinogenic potential are either not available or limited[68]. Previous studies have pointed out that prenatal exposure to some classes of NPSs represents a risk to fetal health since several newborn outcomes such as neonatal abstinence syndrome have been correlated with these substances[69].

Synthetic cathinones have beta-keto-phenethylamine chemical structures. Their structure and mechanism of action are similar to those of ATS. Mephedrone, 3,4-methylenedioxypyrovalerone (MDPV), and methylone are classified as synthetic cathinones. It has been reported that mephedrone exposure during the gestational phase boosts the risk of low birth weight and stillbirth. Salimi *et al*[70]’s study on animal models showed that repeated use of mephedrone induces hippocampal damage, resulting in learning and memory process impairment. Table 1 shows different psychotropic drugs that are commonly used during pregnancy.

CONCLUSION

Pregnancy evolves a myriad of physiological variations in body organs that result in unavoidably significant changes in drug delivery to the fetus. Notably, many licit and illicit psychoactive drugs are designed to reach the brain and penetrate human barriers such as the BBB and the placenta (thus reaching the fetus body).

Substance use during pregnancy is associated with an increased risk of neurodevelopmental disorders. Drugs may have subtle outcomes in the late fetal development period when the main organs are formed. Some of these harmful consequences are altered brain formation, imbalanced neurotransmitter volume, changes in receptor expression, and unusual fetal growth patterns. Taken together, findings from previous studies suggest that being born to a drug abuser is a reliable indicator for later neurodevelopmental issues.

Further research is needed on the amount and timing of substance use during pregnancy and childhood health consequences. As NPSs are not categorized as controlled substances in many countries, the effects of prenatal exposure to these psychoactive chemicals and their neurodevelopmental outcomes are obscure and should be considered further.

Table 1 Commonly used psychotropic drugs during pregnancy

Drug classification	Drugs	Common forms	Routes of administration
Cannabis	Marijuana Hashish Synthetic cannabinoid receptor agonists	Greenish-gray mixture of dried different parts of cannabis plant; resin (hashish) or sticky, black liquid (hash oil)	Smoking, dabbing, or vaporization; Eaten (drops, cakes, tinctures, candies, snacks, and drinks); Suppositories
Narcotics	Opium Heroin Synthetic opioids (methadone, tramadol, buprenorphine)	Sticky brown gum; White or brownish powder, or black substance known as "black tar"; Colorful methadone and tramadol tablets with imprinted logos, capsules, powder, liquid	Injected, smoked, snorted; Swallowed
Stimulants	Amphetamine-type stimulants (Amphetamine, Methamphetamine, Ecstasy) Cocaine	White powder, crystal or shiny blue-white "rocks"; Colorful ecstasy tablets with imprinted logos, capsules; White powder and rock crystal cocaine	Snorted, smoked, injected, swallowed
Hallucinogens	LSD, psilocin mescaline (peyote)	Decorated squares of absorbent paper that LSD has been added to, Tablet, capsule, clear liquid; small pills (dots); Peyote cacti	Swallowed, absorbed through mouth tissues (paper squares); Mixed in food or brewed as tea
Alcohol	Ethyl alcohol	Alcoholic beverages with different alcohol content	Ingested

LSD: Lysergic acid diethylamide.

Limitations

The majority of the previous studies focused on early neurodevelopment, thereby limiting assessment of long-term impacts of prenatal drug exposure.

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World J Clin Pediatr 2022 January 9; 11(1): 14-26

DOI: 10.5409/wjcp.v11.i1.14

ISSN 2219-2808 (online)

MINIREVIEWS

Sickle cell nephropathy: A review of novel biomarkers and their potential roles in early detection of renal involvement

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Author contributions: Baghdadi RM formulated the idea; Baghdadi RM, Alahmadi SA, Algaydi AM, and Fakieh BE investigated and extracted data; Baghdadi RM, Alahmadi SA, Algaydi AM, and Fakieh BE wrote and prepared the original draft; Baghdadi RM, Alahmadi SA, and Fakieh BE reviewed and edited; Safdar OY supervised; all authors have read and agreed to the published version of the manuscript; all authors have contributed substantially to this paper.

Conflict-of-interest statement: The authors declare no conflict of interests for this article.

Country/Territory of origin: Saudi Arabia

Specialty type: Pediatrics

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review report's scientific quality classification

Grade A (Excellent): 0

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Abstract

Whether the underlying mutations are homozygous, heterozygous, or co-inherited with other hemoglobinopathies, sickle cell disease is known to afflict the kidneys, leading to the clinical entity known as sickle cell nephropathy (SCN). Although common, SCN remains diagnostically elusive. Conventional studies performed in the context of renal disorders often fail to detect early stage SCN. This makes the quest for early diagnosis and treatment more challenging, and it increases the burden of chronic kidney disease-related morbidity among patients. Novel diagnostic tools have been employed to overcome this limitation. In this study, we discuss various biomarkers of SCN, including those employed in clinical practice and others recently identified in experimental settings, such as markers of vascular injury, endothelial dysfunction, tubulo-glomerular damage, and oxidative stress. These include kidney injury molecule-1, monocyte chemoattractant protein-1, N-acetyl-B-D-glucosaminidase, ceruloplasmin, orosomucoid, nephrin, and cation channels, among others. Furthermore, we explore the potential of novel biomarkers for refining diagnostic and therapeutic approaches and describe some obstacles that still need to be overcome. We highlight the importance of a collaborative approach to standardize the use of promising new biomarkers. Finally, we outline the limitations of conventional markers of renal damage as extensions of the pathogenic process occurring at the level of the organ and its functional subunits, with a discussion of the expected pattern of clinical and biochemical progression among patients with SCN.

Key Words: Sickle cell disease; Sickle cell nephropathy; Chronic kidney disease; Kidney injury molecule-1; Monocyte chemoattractant protein-1; N-acetyl-B-D-glucosaminidase

Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 28, 2021
Peer-review started: February 28, 2021
First decision: July 30, 2021
Revised: August 12, 2021
Accepted: November 15, 2021
Article in press: November 15, 2021
Published online: January 9, 2022

P-Reviewer: Ata F
S-Editor: Chang KL
L-Editor: Filipodia
P-Editor: Chang KL

Core Tip: This study discusses the expected clinical and biochemical progression among patients with sickle cell nephropathy, the utility of various biomarkers, and the limitations of conventional biomarkers. Novel biomarkers used in combination have been demonstrated to have a higher diagnostic yield as compared to that of individual markers, necessitating a collaborative approach in the standardization and utilization of promising biomarkers such as kidney injury molecule-1, monocyte chemoattractant protein-1, N-acetyl-B-D-glucosaminidase, ceruloplasmin, orosomucoid, nephrin, cation channels, and endothelial dysfunction.

Citation: Safdar OY, Baghdadi RM, Alahmadi SA, Fakieh BE, Algaydi AM. Sickle cell nephropathy: A review of novel biomarkers and their potential roles in early detection of renal involvement. *World J Clin Pediatr* 2022; 11(1): 14-26
URL: https://www.wjgnet.com/2219-2808/full/v11/i1/14.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i1.14

INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy with a global burden of more than 30000 newborns per year. SCD is a broad term used to describe a variety of recognized mutations, including homozygous mutations, heterozygous mutations, and mutations co-inherited with other hemoglobinopathies. The resultant erythrocyte abnormalities instigate a host of sequelae with multi-organ repercussions. The pathogenesis involves vaso-occlusive events, ischemic end-organ damage, reperfusion injury, endothelial dysfunction, vasculopathies, and oxidative stress, among other contributing factors[1]. The disease process is further complicated by an increased predisposition to infections. This is linked to impaired splenic function, micronutrient deficiencies, and sluggish circulation combined with regions of infarction, which act as favorable foci for infections. In addition, therapeutic interventions such as blood transfusions and lines for vascular access predispose patients to blood-borne infections, siderophilic organisms, and catheter-related infections[2]. Notably, chronic transfusion programs are linked to iron overload and endocrine dysfunction with a profound effect on growth and sexual maturation, which is particularly relevant to the pediatric population.

SCD can affect the kidneys through multiple pathways outlined below. The resultant entity, known as sickle cell nephropathy (SCN), typically presents during early childhood. Unfortunately, prompt diagnosis of early SCN is difficult. Therefore, it is necessary to discover new diagnostic biomarkers to facilitate the diagnosis of early stage SCN, enabling timely treatment and reducing related morbidity and mortality.

In this review, we discuss biomarkers of SCD, explore the applications of novel biomarkers for diagnostic and therapeutic approaches, and outline the limitations of conventional markers of renal damage.

PATHOPHYSIOLOGY

The pathogenesis of SCN is multifaceted and involves the effects of different components on different regions of the kidney. The extent of these effects depends on the disease chronicity and severity.

Altered hemodynamics at the level of the glomerulus and the resulting hyperfiltration have been attributed to various biochemical properties of sickling, including local factors such as the release of vasorelaxants and global factors such as increased cardiac output in chronic anemia, leading to increased renal blood flow. Consistent with Brenner's hyperfiltration theory, these changes have been described as precursors to structural changes ranging from endothelial hyperplasia and mesangial proliferation to glomerular sclerosis[3]. These glomerular changes lead to the onset of proteinuria[4].

At the level of the medullary nephron, the same conditions that contribute to normal physiology pertaining to the exchange of solutes and the control of urinary concentrations have deleterious effects on red blood cells that are prone to sickling.

The concentration gradient created by the "countercurrent" system is paramount to the unique ability of mammalian kidneys to concentrate urine. The countercurrent system is jeopardized by fast transit states; therefore, low renal blood flow in the medulla contributes to the osmolarity gradient. Combined, these factors create a climate of relative hypoxia and hyperosmolarity within the medulla[5]. Among susceptible individuals, these conditions promote red blood cell (RBC) sickling.

Wang *et al*[6] examined this phenomenon on a molecular level using SCD-mice and non-SCD mice to further study the medullary changes and their link to concentration defects. The SCD-mice exhibited elevated urinary vasopressin levels and increased abundance of aquaporin 2, urea transporter A1, and epithelial Na channels-beta subunit. The mice were shown to concentrate urine under water-replete conditions in a vasopressin-dependent compensatory mechanism. However, under water-restricted conditions, the medullary concentration ability among SCD-mice was significantly compromised as compared to the non-SCD population, with changes in urinary osmolarity equal to 28% and 104%, respectively.

Dehydrated RBCs lose solutes through a K-Cl cotransporter, a Ca^{2+}-activated K^+ channel (Gardos channel), and uniquely through the nonselective "P_{sickle}" channel that is activated by conditions of low oxygen tension[7]. Widespread RBC adhesion and inflammation within the vasa recta ensure that hemolysis causes the release of free hemoglobin, which sequesters nitric oxide and causes an overall increase in vascular tone[5]. Consequently, juxtamedullary nephrons are impaired, and defective countercurrent exchange mechanisms fail to reabsorb free water. This produces the early findings of SCN, including nocturia, polyuria, and an increased susceptibility to volume depletion. Additionally, these features are particularly problematic among this patient population because volume loss can precipitate vaso-occlusive crises as well as prerenal acute kidney infection (AKI), complicating the original renal insult.

Long-term tubular compromise is accompanied by concentration defects, impaired distal tubular function with renal tubular acidosis, and compensatory increases in proximal convoluted tubule function. The cascade of damage and the factors leading to its acceleration are shown in Figure 1.

In addition to the events described above and their consequences, pathogenesis may be aggravated by the presence of renal cysts, which have been reported to occur more frequently in patients with SCD and in younger patient groups than in the general population[8]. Other pathological changes, such as renal amyloidosis, have been described in case reports and have been shown to be resistant to interventions such as hydroxyurea and angiotensin converting enzyme inhibitors[9].

A summary of pathogenic changes and modifying factors were shown in Figure 1.

CLINICAL FEATURES AND PROGRESSION

As previously described, hyposthenuria is an early constituent of the temporal continuum of the SCN. Its presence is reflective of chronic complications and the cause of acute decline from baseline function. Previously, a negative correlation between the degree of hyposthenuria and fetal hemoglobin has been reported, and a positive correlation with age has been observed. Similar to the general population, patients with SCD in the pediatric age group may experience nocturnal enuresis, which may be partly due to delayed maturation. Unlike in patients without SCD, this otherwise nonalarming presentation is compounded by nocturnal polyuria owing to hyposthenuria as well as the potential effects of cerebral vasculopathy on bladder control. Although most patients outgrow this phenomenon, up to 10% of individuals may continue to experience this phenomenon as high school students, resulting in severe effects on psychosocial well-being[10].

Glomerular hyperfiltration is another relatively early finding. Hyperfiltration occurs with glomerular filtration rates (GFRs) of 1.50-2.34 mL/s/1.73 m^2 or more and is commonly observed early in infancy or in children with SCD[11]. Moreover, hyperfiltration can be followed by progressive declines in the estimated GFR (eGFR), as demonstrated in approximately one-third of adult patients with SCD[12]. Two widely cited clinical trials, BABYHUG and HUTSLE, confirmed this pattern with high GFR values among entrants from ages 9 to 12 mo and showed a progressive increase in short-term follow-up. The latter study further demonstrated that high GFR values persisted into early adulthood. By the fourth decade of life, however, renal clearance deteriorates and GFR exhibits a declining pattern[11].

Hyperfiltration with eGFR values greater than 2.17-2.34 mL/s/1.73 m^2 is linked to microalbuminuria (3.39-33.90 mg/mmol)[11]. Microalbuminuria is estimated to affect

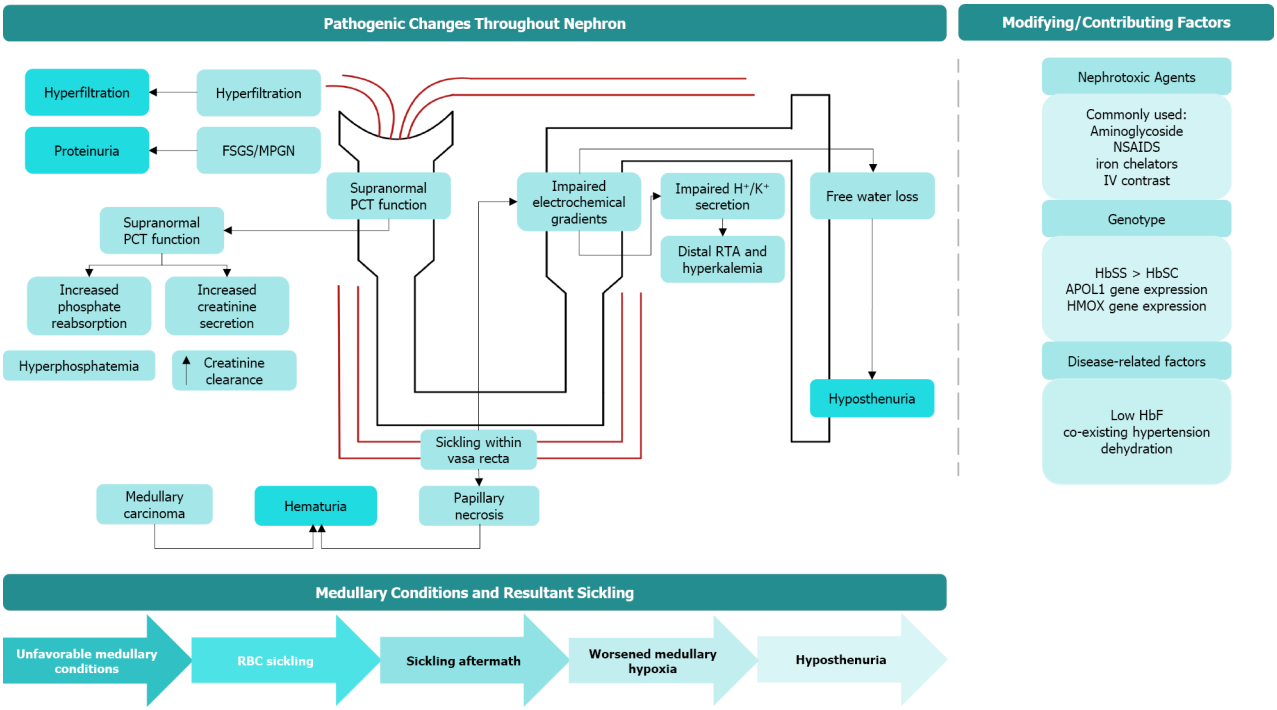

Figure 1 Summary of pathogenic changes and modifying factors. FSGS: Focal segmental glomerulosclerosis; MPGN: Membranoproliferative glomerulonephritis; PCT: Proximal convoluted tubule; RTA: Renal tubular acidosis; NSAIDs: Nonsteroidal anti-inflammatory drugs; IV: Intravenous; HbSS: Classic sickle cell; HbSC: Hemoglobin C sickle cell; APOL1: Apolipoprotein L1 gene; HMOX: Heme oxygenase 1 gene; HbF: Fetal hemoglobin; RBC: Red blood cell.

20%-35% of patients during adolescence, and progressive glomerular changes in response to a hemodynamic environment persist with age, eventually leading to macroalbuminuria (> 33.90 mg/mmol) in 60% of adult patients[13]. Glomerular changes that result in increased permeability to proteins have been described as products of chronic glomerular capillary hypertension. Furthermore, Roy *et al*[14] demonstrated that angiotensin II signaling contributes to glomerulopathy, independent of hemodynamic changes and hyperfiltration, thereby acting as a biomarker of glomerular damage in SCD, with or without hyperfiltration[12]. Another study proposed that inflammatory processes are responsible for the development of proteinuria, demonstrating a correlation between the levels of inflammatory mediators and albumin/creatinine ratios (ACR) in urine[15].

Niss *et al*[12] recognized that although the association between SCN and albuminuria is well established, there is a gap in our understanding of the progression of albuminuria with age. Their longitudinal study of 303 patients with SCD estimated that the progression of albuminuria occurs at a rate of 0.4 mg/mmol per year and suggested an ACR of 11.3 mg/mmol as a surrogate of persistent proteinuria among affected patients.

Hematuria

Hematuria, either microscopic or macroscopic, is reported in 13%-30% of patients with SCD, correlating positively with increased age and male sex[11,16]. Additionally, hematuria can be attributed to vaso-occlusive events and micro-infarctions, resulting in ischemic parenchymal injury and papillary necrosis. Capillary congestion in the medulla also contributes to the process by causing RBC leakage into the renal tubules [13]. Although normally asymptomatic, this process can produce abdominal colic and back pain when extensive. A less common yet more worrisome etiology to consider in the setting of hematuria among patients with SCD is medullary cell carcinoma, which may present during early childhood or adulthood[17].

Hypertension

Generally, blood pressure values among patients with SCD appear to be lower than those in the medically free population. This is attributed to unbalanced fluid losses and possibly to a reduction in systemic vascular resistance[13]. Paradoxically, when present, hypertension has been shown to be predictive of poorer outcomes with increased incidences of both AKI and chronic kidney disease (CKD)[18]. The term

"relative systemic hypertension" has been employed to describe relative elevations in blood pressure among patients with SCD. Relative systemic hypertension is observed in 45% of patients and is defined as a systolic blood pressure of 16.0-18.5 kPa and diastolic blood pressure of 9.3-11.9 kPa.

Novelli *et al*[19] demonstrated through a large cohort of 661 patients that pulse pressure has a higher yield than systolic and diastolic blood pressures in predicting long-term outcomes related to SCD vasculopathy. Thus, pulse pressure is also independently associated with proteinuria and elevated serum creatinine levels.

CKD and end-stage renal disease

The aforementioned pathogenic components accumulate over time and culminate in end-stage renal disease (ESRD). Some modifying factors, also described in Figure 1, increase the likelihood of patients succumbing to CKD. ESRD has been linked to risk factors such as older age, hypertension, proteinuria, hematuria, and deteriorating anemic state[16]. Notably, Yeruva *et al*[18] reported a 2-3-fold increase in the incidence of CKD in patients with SCD when compared with patients without SCD, based on a study performed over a 6-year period. Statistical variations between different studies have been noted and have been linked to discrepancies in the definition of renal failure as well as the different equations used to estimate GFR. These differences may lead to underestimation of the reported incidence and prevalence of renal impairment.

Compared with patients with non-SCD CKDs, patients in this category may experience rapid deterioration of kidney function, posing unique challenges in the area of renal replacement therapy. One issue is vascular access for hemodialysis in patients with frequent hospital admissions and compromised peripheral access[16]. More major issues revolve around the higher rates of mortality due to dialysis-related complications. Finally, although renal transplantation is the optimal therapeutic approach for patients with ESRD, patients with SCD perform poorly on transplant waiting lists[20]. If successful in obtaining a kidney, however, prognostic outcomes post-transplant are similar to those with ESRD due to other etiologies[21].

Furthermore, patients with SCD and renal failure display higher propensities for developing chronic restrictive pulmonary disease, leg ulcers, and stroke than those with intact kidney function.

Conventional renal studies and their limitations in SCN

Routine follow-up protocols currently implemented in SCD follow-up utilize conventional renal studies to diagnose SCN. These include blood pressure assessments, urinalyses, metabolic panels featuring creatinine, and selective imaging based on these findings. The eGFR values are often extrapolated from creatinine-based equations. Creatinine levels, under the influence of muscle mass and hydration status, have limitations in the general population. Among patients with SCD, such limitations are compounded by the effects of hyperfiltration and hypersecretion into the renal tubules. Thus, the rate of creatinine clearance may be misleading in the early stages of the disease. This is exemplified in numerous studies. For example, Asnani *et al*[22] reported that serum creatinine only started rising after the GFR level decreased below 0.84 mL/s. A similar conclusion was made by Guasch *et al*[23], who showed that serum creatinine levels started to rise once the GFR fell below 0.5 mL/s.

The discrepancy between estimated and measured GFRs among patients with SCD is one of the factors hindering our understanding and management of SCN[24]. Current estimating equations vary in the SCN setting[25]. The CKD epidemiology equation produced estimates that were comparable to the measured GFR values, according to Arlet *et al*[26] and Asnani *et al*[27]. Additionally, a study by Asnani *et al*[25] compared eGFR values among 98 patients against values measured using 99m-Tecnetium diethylenetriamine pentaacetic acid nuclear renal scans and showed that the creatinine-based modification of diet in renal disease formula overestimated GFR values by a mean of 1.18 mL/s. The creatinine-based EPI formula yielded improved concordance rates between measured and estimated values, with a mean overestimation of 0.69 mL/s.

Another formula used to estimate GFR, specifically among the pediatric population, is the Schwartz formula, which considers the height and enzymatically measured serum creatinine levels of the patients. In a study of the effects of hydroxyurea on infant renal capacity, a double-blinded randomized controlled trial, BABYHUG, compared the estimated GFR as per the Schwartz formula with quantitative GFR measurements in 176 infants. The age of the infants ranged from 9 to 19 mo. The results showed that this formula markedly overestimated GFR and was found to be useful only in children with low GFRs. Considering the natural history of the disease and the late decrease in GFR, CKD may need to be redefined in SCN using criteria for

a decline in estimated GFR from baseline. This would require a consistent method of routine GFR measurements, starting from a predetermined baseline age[24].

Another limitation pertaining to GFR measurements among patients with SCD is its influence on poor nutritional status, which could lead to eGFR underestimation and hence, premature CKD determination[28].

Cystatin C-based GFR

Cystatin C is a non-glycosylated low-molecular-weight protein produced by all nucleated cells. Its production rate increases during inflammatory events, and the protein undergoes renal metabolism, which is characterized by free filtration at the glomerulus followed by reabsorption by tubular epithelial cells[29]. Relative to creatinine clearance, cystatin C is described as a superior marker for GFR because it is not affected by height, sex, diet, and muscle bulk[30]. Its renal handling is also advantageous in that unlike creatinine, it is not secreted by tubules.

Asnani *et al*[31] corroborated this finding in a study examining 98 subjects with SCD, which presented a significant correlation between serum cystatin C and measured GFR, serum creatinine, urine ACR (r = 0.79), and systolic blood pressure.

Tantawy *et al*[32] reported the sensitivity and specificity of serum cystatin C at 91% and 90%, respectively. These values were superior to those of serum creatinine, with a sensitivity of 79% and a specificity of 85%. Another study conducted by Economou *et al*[33] concluded that 36% of patients with chronic hemolytic anemia showed high serum cystatin C levels.

The implications of these findings have been explored in the domain of management and monitoring of patient responses to hydroxyurea because patients managed with hydroxyurea have been shown to have relatively low cystatin C levels [32]. Additionally, the utility of cystatin C in SCD has been shown to extend to extrarenal complications as well as SCN, with a positive correlation between cystatin C levels and carotid intima-media thickness[32].

Alternatives to both creatinine and cystatin have also been explored. For example, beta-trace protein (BTP) is a low-molecular-weight glycoprotein that is easily filtered by the glomerulus with very little or no tubular reabsorption. In 1997, Hoffmann *et al* [34] discovered increased levels of serum BTP among hemodialysis patients and suggested that BTP is a potential diagnostic marker for renal disease.

Beta-2-microglobulin, a constituent of class I major histocompatibility molecules, has also been explored as a surrogate for GFR estimation. This protein was found to be strongly correlated with measured GFR values. However, its values may fluctuate in response to inflammatory processes and lymphoproliferative diseases. Moreover, to date, only Inker *et al*[35] reported a GFR equation based on a combination of BTP and Beta-2-microglobulin. Unfortunately, this equation did not show any advantages over equations combining creatinine and cystatin C in a variety of populations.

Estimated GFR formulas employed in sickle cell nephropathy were shown in Table 1.

NOVEL BIOMARKERS

As previously discussed, findings from conventional renal studies, otherwise referred to as first-generation biomarkers, have numerous shortcomings. Owing to the kidney's functional reserve, elevations in blood urea nitrogen and creatinine are not appropriately reflective of early renal damage or impending AKI. The limitations of this well-recognized hindrance expand beyond the scope of SCN. The collaborative InnoMedPredTox project, for example, explores biochemical alternatives to conventional renal studies in the interest of detecting nephrotoxicity to determine pharmaceutical safety[36]. Fortunately, the demand for novel biomarkers is coupled with great strides in biomedical capabilities and high-throughput omics.

Validating new diagnostic biomarkers requires the fulfillment of certain criteria and the consideration of a variety of logistics, including diagnostic yield *vs* cost effectiveness. The following criteria were established by the Predictive Safety Testing Consortium Nephrology Working Group in their quest to identify novel biomarkers that could be employed in the early detection of nephrotoxicity. The principles of their criteria, listed in Table 1, may be extrapolated to satisfy the context of SCN[37]. An exception to this may be the point labeled "2," which is less applicable to nonpharmacological settings. Applying these principles to the context of SCD, the ideal biomarker for SCN should predate clinically apparent findings, creatinine elevation, microalbuminuria, and compromised GFR. This is key in the process of early intervention to halt

Table 1 Estimated glomerular filtration rate formulas employed in sickle cell nephropathy

Formula	Equation
CKD-EPI (Cr)	F with Cr ≤ 62 μmol/L (≤ 0.7 mg/dL): 144 × (creatinine/0.7) - 0.329 × 0.993 age (× 1.159 if Black); F with Cr > 62 μmol/L (> 0.7 mg/dL): 144 × (creatinine/0.7) - 1.209 × 0.993 age (× 1.159 if Black) M with Cr ≤ 80 μmol/L (≤ 0.9 mg/dL): 141 × (creatinine/0.9) - 0.411 × 0.993 age (× 1.159 if Black); M with Cr > 80 μmol/L (> 0.9 mg/dL): 141 × (creatinine/0.9) - 1.209 × 0.993 age (× 1.159 if Black)
MDRD	175 × creatinine - 1.154 × age - 0.203 × 0.742 (if female)
Schwartz	0.413 × [height (cm)/creatinine]
CKD-EPI (Cystatin C)	Cystatin C ≤ 0.8 mg/L: 133 × (cystatin C/0.8) - 0.499 × 0.996 age (× 0.932 if female); Cystatin C > 0.8 mg/L: 133 × (cystatin C/0.8) - 1.328 × 0.996 age (× 0.932 if female)

CKD-EPI: Chronic kidney disease epidemiology; Cr: Creatinine; F: Female, M: Male; MDRD: Modification of diet in renal disease.

the progression of CKD. Furthermore, oscillations in values in response to injury and recovery may be ideal for monitoring disease progression and response to therapy. Noninvasive accessibility to biomarkers in urine or plasma samples is another point that must be fulfilled for increased convenience in clinical settings. Localization of kidney injury may shed light on the pathogenic process and aid in a targeted treatment approach. However, some markers discussed below are indicative of global changes, as opposed to localized insults.

Ideal features of biomarkers used to detect drug-induced kidney toxicity were listed in Table 2.

Jerebtsova *et al*[38] recognized that despite considerable efforts being dedicated to the discovery and validation of novel biomarkers of renal damage there have yet to be groundbreaking discoveries that are clinically applicable. The authors also cited shortcomings in proteomic technology over the past decade as a reason for this and discussed logistic issues in the domain of sample collection, result reproducibility, and validation tools, leading to a proposal of the roles of new proteomic technology in bypassing previous limitations. The authors also suggested that, although urine samples are readily available, one must consider the impact of concentration defects on the urinary concentrations of the studied biomarkers.

A summary of studies of novel biomarkers were listed in Table 3.

Kidney injury molecule-1

Kidney injury molecule-1 (KIM-1) is a transmembrane protein expressed by renal cells after exposure to injurious stimuli[13]. Its relationship with diabetes, nephrogenic medications, and ischemia has been well established in animal models and cohort studies. Elevated values have been shown to acutely herald inflammation and chronic fibrosis. Moreover, its urinary excretion parallels tissue levels[39]. In one experimental study conducted by InnoMedPredTox, rats were exposed to nephrotoxic agents, and among other biomarkers, urinary KIM-1 was subsequently quantified by polymerase chain reaction, enzyme-linked immunosorbent assay, and immunohistochemistry. KIM-1 expression was found to correlate with histopathological alterations occurring at the level of the outer cortex, even in the setting of normal kidney function. This revealed the potential applications of KIM-1 as an early and sensitive noninvasive marker of renal injury[36]. Currently, KIM-1 is used as a biomarker for predicting chemo-induced nephrotoxicity. In a cross-sectional study examining AKI in adult patients undergoing cardiac surgery, elevated values were predictive of postoperative AKI[40].

The hypoxic, proinflammatory conditions of the kidney in SCD imply the applicability of this utility to the context of SCN. Sundaram *et al*[41] and Niss *et al*[12] demonstrated a positive correlation within their samples with albuminuria and ACR as endpoints, respectively. Although both of these studies confirmed the sensitivity of the biomarker, questions regarding the diagnostic yield of KIM-1 have been raised. For example, KIM-1 is expressed in the liver, spleen, and kidneys and plays roles in immune tolerance and viral uncoating; genetic polymorphisms may affect its expression and therefore the efficacy of intracellular tracking.

Monocyte chemoattractant protein-1

Monocyte chemoattractant protein-1 (MCP-1) is a powerful chemotactic agent induced by proinflammatory cytokines. This protein is involved in recruiting monocytes/

Table 2 Ideal features of biomarkers used to detect drug-induced kidney toxicity

	Features
(1)	Identifies kidney injury early (before renal reserve is dissipated and levels of serum creatinine increase)
(2)	Reflects the degree of toxicity, in order to characterize dose dependence
(3)	Displays similar reliability across species, including humans
(4)	Localizes to the site of kidney injury
(5)	Tracks the progression of injury and recovery from damage
(6)	Is well characterized with respect to the limitations of its capacities
(7)	Is accessible in readily available body fluids or tissues

macrophages to areas of renal damage. Macrophages are well-established fibrogenic agents in the setting of chronic inflammation. Similarly, renal fibrosis and ESRD-related histopathological changes are expected to be expedited by this chemokine[42]. These findings have been corroborated by animal models and clinical studies examining this agent in the setting of lupus nephritis and diabetic nephropathy[43, 44]. Additionally, MCP-1 is produced by tubules and glomeruli, and its urinary excretion is proportional to its tissue concentration.

The application of MCP-1 to SCN was first reported by Laurentino *et al*[13], and the findings were further confirmed by Belisário *et al*[15] in 2020. Other contributions by Belisario and colleagues showed a positive correlation between MCP-1 levels and ACR as well as between inflammatory mediators and RAS molecules.

N-acetyl-B-D-glucosaminidase

N-acetyl-B-D-glucosaminidase is a lysosomal enzyme that is synthesized by proximal tubular epithelial cells and liberated into the urine in the context of proximal tubular injury[45]. Other authors have verified its potential in predicting the onset of diabetes among patients with diabetes. Sundaram *et al*[41] obtained similar results when exploring the potential of N-acetyl-B-D-glucosaminidase as an early marker of SCN. Their results demonstrated elevations in N-acetyl-B-D-glucosaminidase activity, even among patients without microalbuminuria, highlighting its possible role in early detection.

Ceruloplasmin and orosomucoid

To identify potential biomarkers with elevations predating the onset of albuminuria, Jerebtsova *et al*[46-48] employed mass spectrometry in the analysis of 20 non-albuminuric urine samples. The samples were further subdivided according to the presence or absence of urinary hemoglobin. Of the 270 proteins identified, 18 extracellular proteins were shown to be significantly upregulated or downregulated in hemoglobinuric samples. Further analysis of ceruloplasmin showed that this protein was positively correlated with hemoglobinuria. Further associations with proteins linked to iron metabolism were explored because the samples showed increased ceruloplasmin, transferrin, and ferritin to creatinine ratios in urinary samples when compared with healthy controls. As an extension of this study, orosomucoid, a major acute-phase protein, was also studied as a potential biomarker. Its relationship with other kidney disorders, including diabetic nephropathy and lupus nephritis, has already been demonstrated. Moreover, orosomucoid was found to be correlated with urinary ceruloplasmin values and CKD progression.

Nephrin

Nephrin is a transmembrane protein that exhibits podocyte cytoskeletal structural integrity. Its presence in the urine is indicative of damage localized to the glomerulus. At the molecular level, various factors are associated with functional disruption of nephrin and have been linked to various glomerulopathies, systemic lupus erythematosus, preeclampsia, and hyperglycemia. Its use as a biomarker of early pathological changes has been studied in these disorders with variable results[49]. A study conducted at a tertiary center in Malawi was the first to explore this biomarker among patients with SCD. The results showed that nephrin-to-creatinine urinary ratios were significantly associated with albuminuria. A cutoff value of 622 ng/mg was identified as predictive of albuminuria with a sensitivity of 96% and a specificity of 64%[50]. The

Table 3 Summary of studies of novel biomarkers

Ref.	Study design	Sample size	Endpoints	Finding(s)	Criteria fulfillment
KIM-1					
Sundaram *et al* [41]	Cross-sectional (United States)	116 (ages 5-65 yr, mean age: 18 yr)	MiA: UACR 3.39-33.90 mg/mmol MaA: UACR > 33.90 mg/mmol	KIM-1 detectable in all SCD samples, increased with MiA (P = 0.005), further increased with MaA (P = 0.0015)	Early detection (MiA); reflects severity; localized damage to PCT; detected in urine
Niss *et al*[12]	Prospective longitudinal, mean FU 23 mo (United States)	303 (2-64 yr, mean age: 21 yr)	Albuminuria: Urine albumin ≥ 11.3 mg/mmol)	KIM-1 linked to baseline and persistent albuminuria with P < 0.001	Applicable to larger samples
MCP-1					
Laurentino *et al* [13]	Prospective cohort (Brazil)	50(33.2 ± 10.2 yr)	ELISA, urine sample	Increased urinary MCP-1 in SCD (SSHU: 168.2 ± 90.1 and SS: 231.4 ± 123.7) P < 0.0001 relative to the control group (42.1 ± 27.6)	Reflects oxidative stress; localized damage to PCT + glomerulus; detected in urine
Belisário *et al* [15]	Prospective longitudinal, mean FU 1.1 yr	213 (1.6-19yr)	ELISA	Increased urinary MCP-1 positively related to ACR with P < 0.0001	Positively correlated with other biomarkers; detected in urine
Ceruloplasmin					
Jerebtsova *et al* [46]	Cross-sectional cohort	54	Hemoglobinuria: Hgb/CRE > 0.8 ng/mL CKD stage: Stage 0: eGFR > 1 mL/s/1.73 m^2; Stage 1: eGFR > 1.5 mL/s/1.73 m^2; Stage 2: eGFR 1-1.49 mL/s/1.73 m^2; Stage 3: eGFR 0.5-0.99 mL/s/1.73 m^2; Stage 5: eGFR < 0.25 mL/s/1.73 m^2	CP significantly (31 ×) higher among samples with hemoglobinuria with $P = 1.8 \times 10^5$; Urinary CP/CRE, TF/CRE, and Ftn/CRE were all significantly higher than in non-SCD controls; CP/CRE (only) positively correlated with CKD stage (n = 34, P = 0.0008); ROC analysis: Sensitivity, 68.75%; specificity, 95.65%	Reflects iron handling defects in SCN; high sensitivity/specificity; detected in urine
Orosomucoid					
Jerebtsova *et al* [47]	Cross-sectional cohort	54	Hemoglobinuria: Hgb/CRE > 0.8 ng/ mL and CKD stage	ORM significantly higher among samples with hemoglobinuria with $P = 8.4 \times 10^3$; ORM positively correlated with CKD stage (n = 34, r = 0.51, P = 0.0014); ROC analysis: Sensitivity, 87.1%; specificity, 86.6%	Acute-phase protein; high sensitivity/specificity; detected in urine
Jerebtsova *et al* [48]	Cross-sectional cohort	51 HbSSand 15 HbSC	Hemoglobinuria: Hgb/CRE > 0.8 ng/ mL and CKD stage	PORM significantly higher among HbSS population with UORM/CRE; positively correlated with CKD progression (P = 0.0013); ROC analysis: Sensitivity, 60%; specificity, 78.26%	Acute-phase protein; high sensitivity/specificity; detected in urine
Nephrin					
Heimlich *et al* [50]	Prospective cohort	101 [median age: 9 yr (IQR: 4-11 yr)]	Urine albumin: Creatinine ≥ 3.39 mg/mmol	Urinary NCR higher in HbSS than in HbAA; NCR significantly associated with albuminuria (odds ratio = 1.002, 95% confidence interval: 1.001-1.003, P = 0.0003); at an NCR cut-off value of 622 ng/mg: R (albuminuria × 45.9); at NCR ≥ 622 ng/mg: Sensitivity, 96%; specificity, 64%	Reflects glomerular injury; localized damage to glomerulus; detected in urine; modest specificity, PPV; high sensitivity and negative predictive value
Cation Channels					
Brewin *et al*[51]	Prospective cohort (Brazil)	112 (10.7 ± 4.1 yr; 4-19 yr)	Hyperfiltration: GFR > 2.34 mL/s/1.73 m^2; microalbuminuria: > 3 mg/mmol	eGFR, modestly positively correlated with Gardos channel and Psickle (r = 0.234, P = 0.002) and (r = 0.326, P = 0.005), respectively; ACR, positively correlated with Gardos channel (r = 0.246, P = 0.013) and Psickle (r = 0.207, P = 0.033) activity; KCC activity, negatively associated with ACR (r = 0.334, P = 0.007),	Reflects RBC permeability; detected in RBC samples; strong predictor of microalbuminuria

				suggesting renoprotection	
Endothelial Injury					
Youssry *et al* [53]	Prospective cross-sectional (Egypt)	47	PCR, blood samples	Urinary NCR higher in HbSS than in HbAA NCR significantly associated with albuminuria (odds ratio = 1.002, 95% confidence interval: 1.001-1.003, P = 0.0003); at NCR cut-off value of 622 ng/mg: R (albuminuria × 45.9); at NCR ≥ 622 ng/mg: Sensitivity, 96%; specificity, 64%	Reflects glomerular injury; localized damage to glomerulus; detected in urine; modest specificity, PPV; high sensitivity and negative predictive value

ACR: Albumin/creatinine ratio; CP: Ceruloplasmin; CP/CRE: Ceruloplasmin/creatinine ratio; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; ELISA: Enzyme-linked immunosorbent assay; Ftn/CRE: Ferritin/creatinine ratio; FU: Follow-up; Hgb/CRE: Hemoglobin/creatinine ratio; Hgb/CRE: Hemoglobin/creatinine ratio; IQR: Inter-quartile range; KIM-1: Kidney injury molecule-1; KCC: KCl co-transporter; MaA: Macroalbuminuria; MiA: Microalbuminuria; MCP-1: Monocyte chemoattractant protein-1; NCR: Nephrin/creatinine ratio; ORM: Orosomucoid; PCR: Polymerase chain reaction; PCT: Proximal convoluted tubules; PORM: Plasma ORM; PPV: Positive predictive value; ROC: Receiver operating characteristic; RBC: Red blood cell; SCD: Sickle cell disease; SS: Sickle cell disease patients not taking hydroxyurea; SSHU: Sickle cell disease patients taking hydroxyurea; TF/CRE : Transferrin/creatinine ratio; UACR: Urine albumin/creatinine ratio; UORM: Urinary orosomucoid.

authors concluded that nephrin may have applications in predicting glomerulopathy and its progression.

Cation channels

The pathophysiology of SCN has been widely described with reference to the microenvironment of the kidney and its promotion of sickling. However, the molecular pathogenesis of cellular damage has not been thoroughly evaluated. One of the more novel approaches for understanding SCD pathology involves examination of the cation transport system and its role in promoting solute loss, subsequent dehydration, and sickling[7]. Brewin *et al*[51] investigated the potential application of this principle to the early detection of SCN. Radioactive rubidium (86Rb+) was used to measure the activity of the K-Cl cotransporter, Ca^{2+}-activated K^+ channel (Gardos channel), and P_{sickle} channel among patients with SCD. According to their findings, the Gardos channel and P_{sickle} channel were both positively correlated with eGFR and ACR. Although these findings have not yet been confirmed in larger cohorts, detecting changes at the level of altered cellular permeability may prove valuable in determining the prognosis prior to the onset of renal damage. Furthermore, pharmacological interventions targeting these channels offer a potential focus for targeted treatment in the future.

Endothelial dysfunction

Endothelial dysfunction is thought to be related to SCN. Mediators such as endothelin-1 (ET-1) and soluble fms-like tyrosine kinase-1 have been studied as contributors to pathogenesis, possible diagnostic markers, and even targets for therapeutics. In an experimental animal study, Heimlich *et al*[50] studied ET-1, an established strong vasoconstrictor, proliferative, and proinflammatory molecule that elicits the production of reactive oxygen species in the pathway, leading up to SCN and oxidative damage. These results confirmed the role of ET-1 in humanized sickle cell mice, demonstrating elevated mRNA expression of *ET-1* and its receptor *ETA*.

Furthermore, Saleh *et al*[52] confirmed the increased binding to the aforementioned receptor within the renal vasculature and showed that antagonism of this receptor is linked to decreased urinary protein and nephrin excretion. This has already been established in animal models dedicated to the study of diabetic nephropathy. Closely related to this principle, an Egyptian study explored the effects of SCD on the production of soluble fms-like tyrosine kinase-1, an anti-angiogenic vascular endothelial growth factor receptor and found that its overexpression was linked to vascular dysfunction[53].

Further studies

Future studies extrapolated from animal-based findings can pave the way for future biomarkers to be explored. For example, a study by Ofori-Acquah *et al*[54] that was targeting SCD mice exhibited that SCD mice had marked deficiency of the protein hemopexin. This biological event in turn leads to a compensatory response, which is an increase in the protein a-1-microglobulin, as discussed above.

The results found a strong correlation between hemopexin deficiency and the induction of AKI in SCD mice under hemolytic stress. Human studies that explore this protein as a biomarker, among others should also be contemplated in the future[54].

CONCLUSION

Because of its devastating effects on patient mortality, morbidity, and quality of life, SCN has become a major research target. Approaches to both management and diagnosis have not yet been optimized, despite rigorous efforts from investigators in the field. Multiple authors have cited a lack of longitudinal studies as the primary limitation in the standardization and validation of their findings. Most of our current understanding of SCN stems from cross-sectional studies as opposed to large-sample cohorts with prospective follow-up of long-term renal performance. However, according to electronic databases of clinical trials, studies assessing novel parameters and their responses to interventions are underway.

Furthermore, several authors have demonstrated that the diagnostic yield of combinations of novel biomarkers may exceed that of individual markers, necessitating a collaborative approach in the standardization and utilization of promising biomarkers. As highlighted earlier, the lack of efficient renal studies is not a problem exclusive to SCN. Rather, first-generation renal studies should be supplemented with newer investigations detecting impeding, rather than irreversible, losses of renal reserve. This highlights the importance of follow-up studies documenting the performance of the abovementioned biomarkers in larger populations, for extended durations, and their fluctuations in response to interventions and crises.

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 January 9; 11(1): 27-37

DOI: 10.5409/wjcp.v11.i1.27

ISSN 2219-2808 (online)

MINIREVIEWS

Hereditary pancreatitis: An updated review in pediatrics

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Author contributions: Panchoo AV performed data acquisition, drafting the manuscript and preparation of the figures and tables; VanNess GH, Rivera-Rivera E and Laborda TJ provided input in writing the paper; Panchoo AV, VanNess GH, Rivera-Rivera E and Laborda TJ performed critical revision and final approval of the submitted manuscript.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Country/Territory of origin: United States

Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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Abstract

Hereditary Pancreatitis (HP) has emerged as a significant cause of acute, acute recurrent and chronic pancreatitis in the pediatric population. Given that it presents similarly to other causes of pancreatitis, a positive family history and/or isolation of a gene mutation are vital in its designation. Inheritance patterns remain complex, but mutations involving the PRSS1, SPINK1, CFTR and CTRC genes are commonly implicated. Since being first described in 1952, dozens of genetic alterations that modify the action of pancreatic enzymes have been identified. Among children, these variants have been isolated in more than 50% of patients with chronic pancreatitis. Recent research has noted that such mutations in PRSS1, SPINK1 and CFTR genes are also associated with a faster progression from acute pancreatitis to chronic pancreatitis. Patients with HP are at increased risk of developing diabetes mellitus, exocrine pancreatic insufficiency, and pancreatic adenocarcinoma. Management follows a multi-disciplinary approach with avoidance of triggers, surveillance of associated conditions, treatment of pancreatic insufficiency and use of endoscopic and surgical interventions for complications. With significant sequela, morbidity and a progressive nature, a thorough understanding of the etiology, pathophysiologic mechanisms, diagnostic evaluation, current management strategies and future research considerations for this evolving disease entity in pediatrics is warranted.

Key Words: Hereditary pancreatitis; Acute pancreatitis; Acute recurrent pancreatitis; Chronic pancreatitis; Pancreatitis; Pediatrics

Received: March 31, 2021
Peer-review started: March 31, 2021
First decision: July 27, 2021
Revised: August 8, 2021
Accepted: November 22, 2021
Article in press: November 22, 2021
Published online: January 9, 2022

P-Reviewer: Kitamura K
S-Editor: Wang LL
L-Editor: A
P-Editor: Wang LL

Core Tip: Herediatry Pancreatitis is associated with the inheritance of pathologic genetic mutations. Recent work in pediatrics has isolated genetic variants responsible for early onset and rapidly progressive disease. Early identification of at risk patients and timely referral to appropriate tertiary centers has the ability to limit health care cost and substantial sequelae of this aggressive disease continuum. Further research is warranted to better define preventative management strategies.

Citation: Panchoo AV, VanNess GH, Rivera-Rivera E, Laborda TJ. Hereditary pancreatitis: An updated review in pediatrics. *World J Clin Pediatr* 2022; 11(1): 27-37
URL: https://www.wjgnet.com/2219-2808/full/v11/i1/27.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i1.27

INTRODUCTION

Acute pancreatitis (AP) in pediatrics is on the rise, with incidence rates now similar to that of the adult population[1]. In many children AP is self-limiting with a largely uncomplicated course[2]. However, single center reports have noted that as much as 35% of patients experience recurrent attacks with development of chronic pancreatitis (CP)[3]. Pediatric CP is associated with a high disease burden and complications, necessitating multiple hospitalizations, procedures, psychiatric comorbidities and days away from school, all impacting negatively on the quality of life (QOL) of affected patients[4].

In pediatrics, the rapid progression from the initial episode of AP to CP is striking, with a median time of 3.79 years[5]. Such an aggressive disease continuum calls for a closer analysis of the etiologies involved in childhood pancreatitis. Alcohol and cigarette smoking are well established risk factors for acute recurrent pancreatitis (ARP) and CP in adults, but these are uncommon among children. Risk factors in the pediatric setting are more varied and include; infections, systemic illness, trauma, pancreatic ductal anomalies, metabolic disease, biliary/obstructive causes and hereditary factors such as gene mutations[4,6]. With the implementation of more widespread genetic testing, mutations in pancreatitis related genes have now been demonstrated to be commonly implicated in both pediatric ARP and CP[4].

Historically, herediatry pancreatitis (HP) was grouped and defined as pancreatitis in association with highly penetrant germline mutations, with particular reference to *cationic trypsinogen (PRSS1)* gene defects. Pancreatitis associated with the inheritance of other genetic variants in a non-autosomal dominant manner were termed as familial pancreatitis[7]. However, these designations have changed as more pancreatitis related gene mutations have been discovered and complex inheritance patterns have been characterized. Some have adopted the definition that HP describes patients with pathologic genetic variants predisposing them to the development of pancreatitis. Such a definition would therefore, also encompass genetic mutations inherited in both an autosomal recessive or complex pattern, namely those of the serine *protease inhibitor Kazal type 1 (SPINK1)* and *cystic fibrosis transmembrane conductance regulator (CFTR)* genes[8].

Recent work in pediatrics has implicated particular gene mutations in early onset and rapidly advancing disease[5,9]. This together, with several unique features, and a significantly increased risk of pancreatic carcinoma, places HP as a disease process under intense debate and study. In this regard, we aim to review the historical perspectives, clinical features, genetics, diagnostic evaluation, current management strategies and future research considerations for this evolving disease entity in pediatrics.

HISTORICAL PERSPECTIVES

The emergence of HP as a unique entity was first noted in 1952, wherein, the authors reported the pedigree of six family members (four definite and two probable),

spanning three generations with repeated episodes of pancreatitis. Age of onset ranged from 5 to 23 years of age, with clinical features and complications seeming to occur in an autosomal dominant inheritance pattern[10]. Since, more than 100 families with HP have been reported. In 1996, an exceptional family genealogy was studied between 1800 and 1993, involving 249 members across eight generations. Such a series yielded 63 definite and 17 probable cases of HP. Importantly, this report confirmed an autosomal dominant pattern of inheritance with variable penetrance[11]. Later that year, Whitcomb and colleagues, discovered the first genetic mutation associated with the HP phenotype; an arginine to histidine substitution at codon 122 of the *PRSS1* gene, further designated as the *R122H* variant[12]. Since, dozens of mutations of the *PRSS1* and other genes associated with HP have been identified.

EPIDEMIOLOGY

True prevalence rates of HP may be difficult to determine given infrequent genetic testing outside of specialized centers[13]. The prevalence has been estimated to be 0.3 per 100,000 persons in France[14], but, this, along with worldwide estimates are likely under representations of actual figures.

Germline mutations are common in both pediatric ARP and CP. In a recent cross-sectional study of a multinational, pediatric cohort, 48% of patients with ARP and 73% of CP patients were noted to have at least one gene mutation implicated in HP. Having said that, not all patients in this study underwent testing for pancreatitis-associated gene mutations, and in those who did, the genetic panel was rarely comprehensive, making the true impact of childhood HP likely more significant than reported[4].

CLINICAL FEATURES

HP generally presents as an acute episode of pancreatitis, manifested by significant abdominal pain, nausea and vomiting, with amylase and/or lipase levels more than 3 times the upper limit of normal. If abdominal imaging is warranted features consistent with AP can be noted; typically acute interstitial pancreatic edema, peripancreatic inflammation, fluid collections or pancreatic/peripancreatic necrosis[15]. Given inherent genetic mutations, patients are predisposed to recurrent episodes of AP. In particular, pediatric patients experience a rapid progression from the initial episode of AP to CP, with a median time of 3.79 years being described. Children with pathogenic *PRSS1* mutations progress at a faster rate to CP, as compared to patients without *PRSS1* variants (median time to CP: 2.52 *vs* 4.48 years; $P < 0.05$)[5]. Such an aggressive disease process leads to chronic parenchymal and ductal changes (Figures 1 and 2). These include hyperechoic foci with and without shadowing, main pancreatic duct calculi, lobularity with honeycombing, cystic changes, duct dilation, hyperechoic duct margins, dilated side branches and hyperechoic stranding. The Rosemont Criteria can be used to categorize such imaging findings, however its use in pediatrics has not been validated[15,16].

All in all, the clinical spectrum of pancreatic disease noted with pediatric HP closely resembles other etiologies of ARP and CP, albeit, at a faster rate of progression with particular phenotypes. There are however, a few notable distinguishing features. HP tends to have an earlier presentation. Variants of the *PRSS1, chymotrypsin C (CTRC) and carboxypeptidase A1 (CPA1)* genes are associated with early disease onset, particularly before 10 years of age[9,14]. Additionally, there is some evidence to suggest that a maternal pattern of inheritance confers earlier disease onset as compared to a paternal pattern of inheritance[17]. At this time there is no compelling evidence to indicate that patients with HP develop exocrine or endocrine insufficiency at a faster rate[13]. However, given an earlier progression to CP in certain HP phenotypes, such a protracted disease course with ongoing pancreatic parenchymal damage and atrophy, may represent a contributory factor to the rapid development of exocrine pancreatic insufficiency and diabetes noted in children with ARP[5].

HP in the adult setting confers an increased risk of pancreatic cancer, with a lifetime risk of at least 40% for developing carcinoma of the pancreas among HP adults[17]. Of note environmental factors, namely tobacco smoking and alcohol consumption may act as confounders in this population. Further analysis controlling for smoking did reveal a relative risk of approximately 7% for the development of pancreatic cancer among adults with a *PRSS1* gene mutation[18]. To the best of our knowledge, the risk of pancreatic cancer in childhood CP, let alone pediatric HP, remains unknown[19].

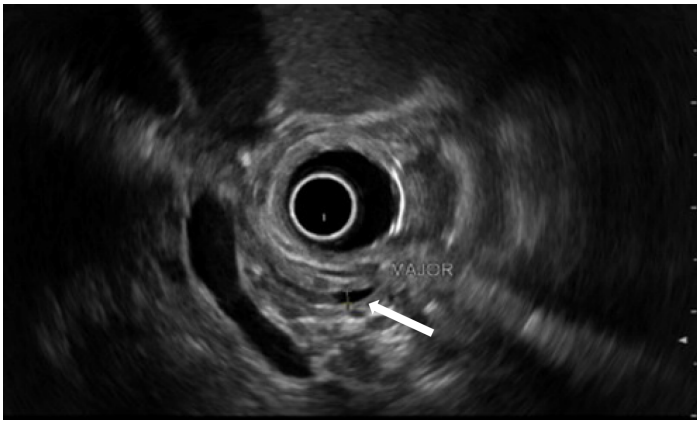

Figure 1 Radial endoscopic ultrasound in a 13 year old male with SPINK1 and CTRC gene mutations demonstrating pancreatic duct dilatation (arrow) in addition to chronic parenchymal changes: Honeycombing with lobularity, non-shadowing hyperechoic foci, cystic changes and hyperechoic duct margins.

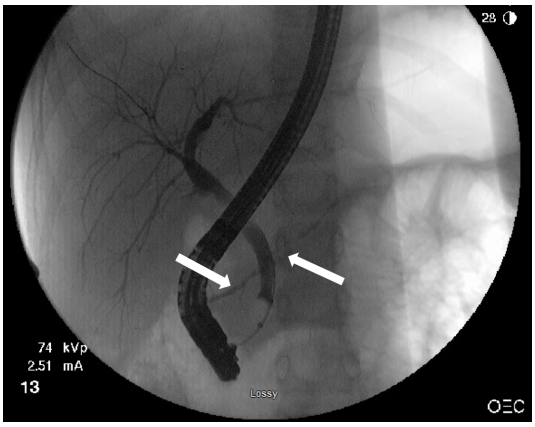

Figure 2 Endoscopic retrograde cholangiopancreatography in a 10 year old male with a CFTR gene mutation and pancreas divisum demonstrating contrast entering the dorsal pancreatic duct (arrows) from the common bile duct during a balloon occlusion cholangiogram. This occurred due to a fistula between the common bile duct and pancreatic duct secondary to repeated episodes of acute pancreatitis.

PANCREATITIS RELATED GENE MUTATIONS

It was not until 1996 that the first pancreatitis related gene variant, the *R122H* mutation of the *PRSS1* gene was discovered. Since then, numerous pathogenic mutations of the *PRSS1* and additional genes have been identified[12]. Other notable genes associated with HP include, *SPINK1, CFTR, CTRC, CPA1, calcium-sensing receptor (CASR)* and *claudin*-2. In many instances, HP seems to involve a complex interplay of genetic and environment factors that causes an imbalance in protease regulation leading to pancreatic parenchymal injury. From recent analyses, these genetic mutations have been grouped and classified into disease causing or modifiers of disease[7,20-22]. The following section describes the inheritance pattern and proposed mechanism of action of the major pancreatitis related variants implicated in HP. A summary of this information has also been provided (Table 1).

PRSS1

Pathogenic variants of *PRSS1* have been isolated in >60% of large families afflicted with HP, spanning numerous generations[7]. Although dozens of *PRSS1* mutations have been identified, *R112H, N29I and A16V* are the most common disease causing variants. These are all inherited in an autosomal dominant manner. *R122H* (80% penetrance, 78% of mutations) and *N29I* (93% penetrance, 12% of mutations) together are estimated to account for approximately 90% of *PRSS1* HP cases[14,23].

The *R122H* mutation has been classified as a gain of function mutation that prevents autolysis of trypsin, which increases trypsin stability, thereby allowing for enhanced enzyme activation and pancreatic digestion[24]. Similarly, *N29I* mutation results in

Table 1 Prominent pathogenic pancreatitis related gene variants

Pathogenic gene (Variant)	Inheritance pattern	Mechanism of action
PRSS1 (R122H)	Autosomal dominant	Impaired autolysis of trypsin
PRSS1 (N29I)	Autosomal dominant	Increased autoactivation of trypsin
PRSS1 (A16V)	Autosomal dominant	Possible increase in trypsin activation
CFTR (R75Q)	Autosomal recessive	Impaired zymogen secretion
Disease modifiers		
SPINK1 (N34S)	Autosomal recessive	Decreased trypsin inhibition
CTRC (A73T, V235I, R253W, K247_R254del)	Autosomal dominant or multigeneic	Impaired lysis of trypsin

increased autoactivation of trypsin, also allowing for unchecked pancreatic autodigestion[25]. As a result, *R122H and N29I* mutations generally follow a similar clinic presentation. On the other hand, the mechanism by which the *A16V PRSS1* gene variant cause disease remains incompletely understood. Some evidence suggest that the *A16V* mutation increases the secretion of the *CTRC* protein, ultimately leading to a fourfold increase in activation of trypsin[26].

SPINK1

The *SPINK1* gene encodes an acute phase reactant that functions as a trypsin inhibitor. Pathogenic *SPINK1* mutations are loss of function mutations leading to decreased trypsin inhibition, predisposing to pancreatitis[27]. The *N34S* variant is the most common haplotype reported globally. In the majority of cases *SPINK1* mutations are inherited in a heterozygous form and require other genetic and/or environmental factors to effect pancreatitis. As such, they are better considered as disease modifiers [28].

CFTR

Mutations in the *CFTR* gene are also associated with HP. One would readily associate the F508-delta variant with the typical multisystem cystic fibrosis syndrome. Such a variant is rarely associated with HP, but rather inheritance of a milder variant in an autosomal recessive manner, such as the *R75Q* mutation has been implicated with recurrent attacks of AP[29]. The presence of the *R75Q* mutation is associated with at least a 40 fold increased probability of developing pancreatitis when compared to the general population[30]. Bicarbonate secretion is essential for the release of pancreatic zymogens. A dysfunctional variant such as the *R75Q* mutation, leads to failure of acinar cell alkalization. As such, zymogens are not released, and once protease activation ensues, autodigestion of surrounding pancreatic tissue occurs leading to episodes of AP[22].

CTRC

The *CTRC* gene encodes for chymotrypsin C, a protease involved in trypsin regulation. Loss of function mutations in this gene, impair tyrpsin lysis and reduce the protective function against developing CP. Numerous CTRC gene variants, including *A73T, V235I, R253W*, and *K247_R254del* act by this mechanism. Such variants do not seem to be causative of HP when found in isolation, but are rather seen in concert with other genetic mutations (*SPINK1* or *CFTR*) or environmental factors[31,32].

Other genetic mutations

There are several less studied genetic variants that appear to contribute to HP. One example is the *CASR* gene, which encodes for a plasma membrane calcium sensing receptor involved in regulation of intracellular calcium levels and thereby, trypsin stability[33]. Another notable genetic variant involves the *CPA1* gene. This gene encodes for carboxypeptidase A1, which also functions as a pancreatic protease. Pathogenic defects of CPA1 are believed to confer a propensity towards developing HP through trypsin misfolding and aggregation, cumulating in increased endoplasmic reticulum stress[34]. The *CLND2* gene is located on the X chromosome and encodes claudin-2, which mediates sodium and water transport in the proximal pancreatic duct. From the results of a genome wide susceptibility study, mutations of the *CLND2* gene appear to mediate an atypical distribution of claudin-2, and consequently

increase the risk of alcohol induced pancreatitis, particularly in males[35,36].

DIAGNOSTIC EVALUATION

The investigation of HP typically begins with an extensive history to delineate previous episodes of acute pancreatitis, as well as an extended family history of clinical symptoms, aimed at identifying possible inheritance patterns. Diagnostic criteria for AP, ARP and CP in the pediatric population follow those outlined by the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) consortium. Once 2 of the following 3 are met AP is diagnosed; suggestive abdominal pain, serum amylase or lipase at least 3 times the upper limit of normal and/or characteristic imaging findings. If a patient has normalization of amylase and lipase levels and symptoms, or complete resolution of pain for at least 1 mo in between episodes of AP, this is termed ARP. CP is diagnosed when imaging findings of chronic pancreatic injury is noted along with at least one of; typical abdominal pain, endocrine or exocrine insufficiency[13,15].

Abdominal imaging studies may be required to assess for radiographic features of acute or chronic pancreatitis. In the pediatric setting such a radiologic workup generally begins with non-invasive cross-sectional imaging, mainly computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP). Endoscopic ultrasonography (EUS) can be considered if the aforementioned studies fail to establish a diagnosis, etiology or adequately outline the extent of disease. Use of endoscopic retrograde cholangiopancreatography (ERCP) solely for diagnostic purposes in pediatrics is discouraged, mainly due to procedure related risks and similar diagnostic capabilities of MRCP in children[37].

When HP is suspected genetic testing to identify pathogenic pancreatitis related gene variants may be warranted. Criteria have been proposed to assist in determining which patients should undergo genetic evaluation (Table 2). Once the patient satisfies at least one of these, testing is recommended[38,39]. The decision to test children, whether symptomatic or asymptomatic can have considerable psychosocial impact not only for patients, but also their families. Consequently, it is recommended, that such testing and interpretation of results is best done with the assistance of an experienced genetics provider[21,40].

MANAGEMENT

HP can present at any juncture of the pancreatitis continuum. Generally children are brought to specialist medical attention and subsequently diagnosed after experiencing repeated episodes of AP. As with AP resulting from other etiologies, management generally involves early aggressive fluid hydration with appropriate monitoring, adequate pain control and early enteral nutrition. Invariably patients experience repeated pancreatic insults and complications necessitating further medical care, endoscopic and surgical procedures[13]. Given the early and aggressive nature of disease associated with pancreatitis related gene variants[5,9,14] we aim to examine the role that preventative measures and other therapeutic modalities can have in the management of HP among children.

Preventative measures

Substantial alcohol consumption is a well described predisposing factor for AP and subsequent progression to eventual CP among adult studies[41,42]. Similarly, data from the adult population has demonstrated that tobacco use is associated with pancreatic disease progression and development of pancreatic calcifications in a dose-dependent manner[42,43]. Expert consensus strongly recommend that pediatric providers caution their patients against the use of tobacco and ethanol due to the negative short and long-term effects on pancreatic health [19].

Inflammatory processes that underlie the pathophysiology of CP involves antioxidant depletion and oxidative stress. Supplementation of antioxidants has been proposed as a mechanism to prevent CP progression and the development of exocrine pancreatic insufficiency (EPI). To date, insufficient data exists to recommend antioxidant supplementation in children with CP for such indications[19,44].

Studies from the adult population have also implicated truncal obesity as a risk factor for severe AP, mainly due to the pathogenic role that peripancreatic or intrapan-

Table 2 Criteria Necessary for Genetic Testing of Pancreatitis related Gene Variants

Criteria necessary
Documented pancreatitis in a child without a definite cause
Acute recurrent pancreatitis without an identifiable etiology
Idiopathic chronic pancreatitis in patients younger than 25 years old
Family history of idiopathic chronic pancreatitis or acute recurrent pancreatitis
Relatives with known pancreatitis related gene mutations
Patients eligible for participation in approved study protocols

creatic fat plays in the development of pancreatic necrosis [45]. Interestingly, overweight or obese children have been found to be less likely to develop CP compared to children with a normal BMI. Obese children generally also experience their first episode of AP later than their non-obese counterparts. However, research examining the effects of BMI on CP outcomes in pediatrics remains limited and the current expert consensus recommendation is for pediatricians to recommend a balanced, healthy diet and lifestyle for their patients afflicted with CP [19].

Unfortunately, aside from these lifestyle modifications, there remain no novel therapeutic agents available for preventing repeated episodes of AP and the eventual progression to CP in patients with HP. In this regard, present treatment strategies are focused on managing the natural history of HP as opposed to preventing or delaying disease progression. Further research is warranted to better define 'optimal' preventative management in this population.

Medical management

Pediatric patients with progressive pancreatic disease are at risk for a number of sequelae which are best managed with a multidisciplinary approach. Given the significant postprandial abdominal pain and discomfort associated with ARP and CP, many patients are at risk of macro- and micronutrient deficiencies. With the help of a clinical dietician, growth and nutritional status should be carefully evaluated at every clinic visit (at least every 6-12 mo). Dietary education should also be provided to prevent obesity and malnutrition[19,44].

In a recent report of data analyzed among pediatric patients with ARP, it was noted that 18% and 7.7% developed EPI and diabetes mellitus respectively within 6 years of the initial AP attack[5]. EPI can be subclinical or present with steatorrhea, poor growth and nutritional deficiencies, particularly of fat-soluble vitamins. These patients should be provided with pancreatic enzyme replacement therapy, along with monitoring of fat-soluble vitamin levels at least every 12-18 mo. Screening for endocrine pancreatic insufficiency should be done at least yearly with a HbA1c and fasting glucose level. Should these values be outside the reference range, referral to a pediatric endocrinologist is indicated[19].

Pediatric CP is associated with a considerable disease burden, impairing quality of life and significantly disrupting childhood educational activities. These children can require frequent emergency room visits, hospitalizations and absences from school, mainly for management and control of chronic, severe pain[46]. In this regard, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition pancreas committee has set forth a number of recommendations to address pain management in pediatric patients with CP. These recommendations stress the importance of working alongside physical therapists, psychologists and pain specialists to institute a multi-modal approach to pain management. Before immediately using a non-opioid to opioid analgesic 'step-up' approach, neuromodulators, cognitive behavioral therapy and physical therapy should be considered as adjunctive measures for pain management[19].

Endoscopic therapy

As the sequalae of HP progress, endoscopic interventions may become necessary. As previously noted, EUS can play a diagnostic role if conventional cross-sectional imaging modalities fail to establish an etiology or disease extent. Among adults, therapeutic EUS is increasingly being considered as a first therapy for pancreatic walled off necrosis, and psuedocysts[47]. Though conservative measures should always be considered for pediatric pancreatic fluid collections, expert consensus from

the pancreas committee of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) recommend EUS intervention when endoscopic drainage is indicated.

Given associated procedural risks, ERCP use solely for diagnostic purposes is discouraged. However, therapeutic benefits have been derived among children with pancreatic duct stenting and removal of pancreatic calculi. Such patients have experienced improvement in symptoms and reduction in pancreatitis episodes[48,49].

Special considerations apply when undertaking these advanced endoscopic procedures in pediatrics. Theapeutic EUS, and in particular ERCP should only be undertaken after all the potential risks and possible need for multiple procedures are thoroughly discussed with caregivers. In addition, patients under 10-15 kg, may require specialized equipment not available in most centers. Primary physicians should consider referral to an appropriate tertiary center if therapeutic endoscopic procedures are required, as these procedures should ideally be done by endoscopists with ample experience in the pediatric setting.

Surgical therapy

Pancreatic necrotic collections and psuedocysts not amendable to endoscopic intervention may require surgical drainage[13]. Incapacitating CP that has failed medical and endoscopic therapy may benefit from conventional surgical approaches. A longitudinal pancreaticojejunostomy (Puestow procedure) can be utilized as a drainage procedure for an obstructed main pancreatic duct, whereas with involvement of the pancreatic head, a pancreaticoduodenectomy has proven some (Whipple procedure) benefit among adult patients[50,51]. Such procedures compromise islet cell yield and if undertaken, the remaining pancreatic tissue would still be subject to repeated insults. In this regard, its applicability to pediatric HP remains questionable [50,52,53]. Ultimately, pediatric patients with unremitting constant pain and grossly impaired quality of life proceed to total pancreatectomy with islet autotransplantation (TPIAT). Unfortunately this procedure commits the patient to lifelong pancreatic enzyme replacement therapy and a high likelihood of becoming insulin dependent, however, it has demonstrated improved quality of life and substantial pain relief. No formal criteria exist for which pediatric patients should proceed to TPIAT, so this decision should ideally involve a multidisciplinary team of pediatric pain specialists, surgeons, endocrinologists, gastroenterologists and dietitians[50,53,54].

CONCLUSION

HP has emerged as a significant cause of AP, ARP and CP in the pediatric setting. Given that it presents similarly to other causes of pancreatitis, a positive family history and/or isolation of a pathogenic pancreatitis related gene mutation are vital in its designation. Since the discovery of the first genetic mutation associated with the HP phenotype in 1996, dozens of other genetic defects have been identified, with varying inheritance patterns. More recent work among pediatric patients has associated particular variants with early onset and rapid progression, potentially making pediatric HP an aggressive disease with significant sequelae and substantial burden. Primary care physicians can play a vital role in identifying at risk patients with careful screening, and providing timely referral to tertiary centers adept at genetic testing and managing the continuum of pediatric pancreatitis. This model has the ability to limit health care cost and reduce the negative psychosocial effects on patients and families. Further work should focus on analyzing the impact that genetic and other risk factors have on the natural history and progression of pediatric pancreatitis, so that preventative interventions can be implemented to limit debilitating disease.

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 January 9; 11(1): 38-47

DOI: 10.5409/wjcp.v11.i1.38

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Basic Study

Levels of vocational satisfaction, burnout and compassion fatigue of health professionals working in pediatric clinics

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Author contributions: Koyuncu O and Arslan S performed the measurements, processed the experimental data, performed the analysis, drafted the manuscript and aided in interpreting the results and worked on the manuscript; all authors discussed the results and commented on the manuscript.

Institutional review board statement: The approval of the Sakarya University Faculty of Medicine Ethics Committee was obtained to evaluate the ethical suitability of the research at the same time (dated 142.07.2018 and numbered 142).

Conflict-of-interest statement: No any conflict of interest.

Data sharing statement: No additional data are available.

Country/Territory of origin: Turkey

Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review report's scientific quality classification

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Abstract

BACKGROUND

Burnout and compassion fatigue are affecting the quality of professional life.

AIM

To investigate the levels of vocational satisfaction, burnout, and compassion fatigue and factors that may be related to health professionals working in children's clinics.

METHODS

The study sample was in the west of Turkey. Data were collected using the questionnaire form and the quality of life scale for employees.

RESULTS

The findings obtained in this study showed that the level of vocational satisfaction of female health professionals and the burnout level of male health professionals were higher. The professional satisfaction of the doctors was lower than that of the nurses and midwives, and the mean score of burnout and fatigue was high.

CONCLUSION

Further studies are needed on this topic to help improve the factors that may affect the professional quality of life of health professionals.

Key Words: Health professionals; Professional life quality; Professional satisfaction; Burnout; Compassion fatigue

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 15, 2021
Peer-review started: March 15, 2021
First decision: March 31, 2021
Revised: April 15, 2021
Accepted: August 24, 2021
Article in press: August 24, 2021
Published online: January 9, 2022

P-Reviewer: Sun C
S-Editor: Gao CC
L-Editor: Kerr C
P-Editor: Li JH

Core tip: The right of health professionals to choose the clinic where they work; the fact that they do not constantly change the places where they work; a low number of night shifts; and adequate numbers of personnel have positive effects on the quality of professional life. It has be suggested to improve the working conditions and make them more favorable, and to satisfy the working individuals economically and emotionally. Health professionals and managers should work together to create a healthy work environment, increase professional satisfaction, and prevent burnout and fatigue.

Citation: Koyuncu O, Arslan S. Levels of vocational satisfaction, burnout and compassion fatigue of health professionals working in pediatric clinics. *World J Clin Pediatr* 2022; 11(1): 38-47
URL: https://www.wjgnet.com/2219-2808/full/v11/i1/38.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i1.38

INTRODUCTION

Vocational satisfaction may occur when employees evaluate their jobs[1-6]. It is crucial for hospitals and employees to know the level of satisfaction of working individuals in their professional lives and what parameters may influence them. Vocational satisfaction is one of the most significant factors that increase the productivity of working individuals by corporate metrics[5-7].

Some vocational groups require close contact with people. Intense emotional responses are observed in these individuals, as employees in these professions are in close contact with people for long periods. Health professionals are especially at risk concerning burnout, as they are exposed to high levels of stress due to their institutional structure and working conditions. It should not be forgotten that a high risk of burnout will have negative effects on the professional quality of life[1,8,9].

Compassion has been one of the virtues of all religions and societies since the start of recorded history and has been defined as the feeling of being related to pain and suffering in other individuals[4,10-12]. It is an indispensable and essential quality for health professionals. Negative feedback sent to health insurance companies related to patient satisfaction has recently increased. Thus, the concepts of compassion and compassionate care have started to attract more significance[10-15]. The concept of compassion is considered to be an excellent component in health professionals worldwide[4-12]. Recently, studies on compassionate care scales have been conducted and compassionate healthcare models have been created worldwide. We define compassionate care as a care model that can be shown as the quality level of hospitals; can create satisfaction for patients and their relatives; has no financial costs; accelerates recovery; and has positive physiological effects on patients[10-15].

It may be emotionally exhausting and traumatizing for health professionals to care for sick or dying children. In addition, the fact that parents experience this process one-on-one and under intense stress may be redirected to healthcare professionals as a separate trauma. Exposure to these traumas for a long time may cause many physical, psychological and emotional problems in healthcare professionals working in pediatric clinics[4,10,12,14]. This study aimed to investigate the level of vocational satisfaction, burnout, compassion fatigue and other potentially related factors in pediatric clinics.

MATERIALS AND METHODS

This research was a descriptive study to investigate the levels of vocational satisfaction, burnout, and compassion fatigue and other factors that may be related to health professionals working in children's clinics.

Population and sample

The study population worked in the Child Health and Disease Clinics of the Hospitals of Sakarya Province between 1 November and 15 December 2018 and who had direct contact with patients. The study was conducted on 128 healthcare professionals

working in children's clinics on the same date and who agreed to participate in this research.

Data collection tools and questionnaire

The data in this study were collected using the questionnaire form created by the researchers and the quality of life scale for employees (QoLSE).

There were questions regarding the sociodemographic (*e.g.*, gender, age, marital status, and educational status) and study characteristics that were thought to be related to professional quality of life, vocational satisfaction, burnout and compassion fatigue in the personal information form created by the researchers. QoLSE was developed by Stamm[16] to detect the symptoms of vocational satisfaction, burnout, and compassion fatigue, and a Turkish validity and reliability study was performed by Yeşil *et al*[17]. The scale is a self-report assessment tool consisting of three subscales and 30 items. Items 1, 4, 15, 17 and 29 needed to be reversed and calculated during the evaluation of the scores obtained from the scale. The items in the scale were evaluated on a six-digit chart ranging from never (0) to very often (5).

Data assessment

While the relationships between the scores obtained from the scale were evaluated using correlation analysis, the relationships between the sociodemographic and professional characteristics of the healthcare professionals and the scores obtained from the scale were evaluated by Mann–Whitney U test in binary groups and Kruskal–Wallis tests in more than two groups.

Ethical aspects of this research

Ethical principles and rules were followed during this research. To conduct this study, ethical approval from the Sakarya University Faculty of Medicine Ethics Committee was obtained (dated 142.07.2018 and numbered 142). The purpose of this study was explained to the health professionals included in the sample, and their written and verbal consent was obtained.

RESULTS

The average age of health professionals participating in this study was 31.54 years. The majority of them were women (84.4%), married (61.7%), nurses (64.8%), undergraduate graduates (47.7%) and had no children (53.1%) (Table 1). The rate of the health professionals who worked 3–5 years in child health and disease was 35.2%. It was seen that 57% of health professionals were assigned by the administrative supervisor, 78.1% of them were on duty, and 88.3% of them worked at the public hospital. A total of 85.2% of the health professionals participating in this study worked overtime in the last 6 mo. A total of 89% of the participants were partially or completely dissatisfied with their working conditions and the reasons for dissatisfaction included insufficiency of the main social facilities (31.3%), communication problems in the work environment (24.2%), and inappropriateness of physical conditions (21.1%). A total of 51.6% of the participants encountered child death in the clinic where they worked in the last 6 mo. Within the scope of this research, the average weekly working hours of health professionals was 51.80 (Table 2). A total of 19.04% of the researchers stated that their encounters with child deaths had positive effects in terms of gaining experience in intervention, and 66.6% of them stated that they had negative effects emotionally (sadness, pain, grief) within the scope of this research. It was seen that 42.85% of them were affected between 1 and 3 d when the duration of exposure was examined (Table 3). The mean scores of female healthcare professionals in QoLSE Vocational Satisfaction Sub-dimension, and the mean scores of the male healthcare professionals in QoLSE Burnout Sub-dimension were significantly higher than those of the females healthcare professionals ($P < 0.05$).

When examined according to occupations, doctors' Vocational Satisfaction Sub-dimension mean score was significantly lower than that of nurses and midwives ($P < 0.05$), while the Burnout Sub-dimension and Compassion Fatigue Sub-dimension mean scores were significantly higher ($P < 0.05$). In the comparison made by looking at the educational status of the health professionals participating in this study, the Vocational Satisfaction Sub-dimension average score of postgraduate graduates was significantly lower, while the Burnout Sub-dimension average score was significantly higher ($P < 0.05$). The mean score of the Vocational Satisfaction Sub-dimension of the employees with night shift work compared to other groups was significantly lower (P

Table 1 Distribution of health professionals by sociodemographic characteristics (*n* = 128)

Features	*n*	%
Age, mean ± SD (min–max)	31.54 ± 9.123 (19.0–64.0)	
Gender		
Male	20	15.6
Female	108	84.4
Profession		
Doctor	26	20.3
Nurse	83	64.8
Midwife	19	14.8
Marital status		
The married	79	61.7
Single	49	38.3
Having children		
No	68	53.1
1	29	22.7
2	25	19.5
≥ 3	6	4.7

< 0.05). In the comparison made according to the satisfaction of the health professionals with their working conditions, the Vocational Satisfaction Sub-dimension mean score of the dissatisfied people was significantly lower and the Burnout Sub-dimension mean score was significantly higher ($P < 0.05$) (Table 4).

DISCUSSION

It is stated that the low level of professional satisfaction of health professionals leads to a weakened relationship with their patients, negative attitudes towards their profession, or failure to fulfill their job-related responsibilities. However, to our knowledge, it has been reported that patients are more satisfied with the care and treatment of health professionals with high professional satisfaction[18-21]. Health professionals suffer from burnout syndrome and fatigue, which is the most important determinant of work quality of life[1,2,3,9,22,23]. Burnout and compassion fatigue in healthcare professionals may result in decreased patient satisfaction and unhealthy results[1,2,3,9,22,23].

Female healthcare professionals constitute 84.4% of the group that participated in our study. The reason for this is that there are more female healthcare professionals in the nurse and midwife vocational groups in Turkey[6,7,24]. In this study, the rate of participants whose educational status was undergraduate and graduate was 72.7%. The postgraduate education level was 25%. This ratio is between 3% and 21% in studies conducted in Turkey[5,6,7,18,24]. The reason why it is higher compared to other studies may be the increase in the number of nurses and midwives with undergraduate degrees and the participation of doctors in the study group.

A total of 57% of the health professionals participating in our study had been appointed by the administrative supervisor to the clinic where they worked and 78.1% of them worked night shifts. This may reduce the quality of professional life and cause burnout and compassion fatigue in health professionals. A total of 70.3% of the health professionals participating in this study worked in departments where the number of staff was not sufficient, and they had been on duty for 3 wk per month for the last 6 mo. They had to come to work several times and 85.2% worked although they were ill.

It has been determined that health professionals are not partially or completely satisfied with their working conditions. They expressed the reasons for dissatisfaction as insufficient social facilities (31.3%), lack of communication in the environment (24.2%) and inappropriateness of physical conditions (21.1%). It was also found that

Table 2 Distribution of healthcare professionals by work features (*n* = 128)

Features	*n*	%
Working time in child health and disease		
< 1 yr	32	25.0
1–2 yr	10	7.8
3–5 yr	45	35.2
≥ 6 yr	41	32.0
How did she/he settle in the clinic where she worked?		
By myself	37	28.9
My profession	18	14.1
By administration	73	57.0
How it works		
Continuous day	22	17.2
Seizure	100	78.1
Other[a]	6	4.7
Hospital worked		
Public hospital	113	88.3
Private hospital	15	11.7
Overtime work in the last 6 mo		
Yes	109	85.2
No	19	14.8
Satisfaction with working conditions		
Yes	14	10.9
No	52	40.6
Partially	62	48.4
Reasons for dissatisfaction		
Communication problems in the working environment	31	24.2
Inadequate social facilities	40	31.3
Incompatibility of physical conditions in the environment	27	21.1
Economic shortcomings	15	11.7
Failure to rise on duty	1	0.8
Other	14	10.9
Confrontation with child death in the clinic working in the last 6 mo		
Yes	66	51.6
No	62	48.4
Weekly average hours of operation mean ± SD (min–max)	51.80 ± 11.918 (32.0–120.0)	

[a]In some clinics, they work with an 8-h shift system or 08:00-00:00 and 16:00-00:00 h.

their professions did not satisfy or only partially satisfied them economically. In another study, inconveniences in the working system (42.8%), economic inadequacy (32.2%) and lack of social opportunities (25.4%) were the main reasons for dissatisfaction with occupational life[24]. The average weekly working hours of the health professionals participating in the study were 51.8. According to Eurostat data, the average weekly working hours of full-time employees in the EU-28 is 37.1[25]. This period is specified as 45 h in labor law, but is 51.8 h, which is above international

Table 3 Effects of health professionals participating in this research when they come against child deaths in the last six months (*n* = 42)

Features	*n*	%
Positive effects		
Gaining experience in intervention	8	19.04
Getting used to death	2	4.76
Negative effects		
Emotional (sadness, pain, grief)	28	66.6
Decreasing from professional motivation	4	9.52
Affected times		
< 1 d	10	23.80
1–3 d	18	42.85
3–10 d	5	11.90
> 10 d	9	21.42

standards, in many developing countries. It was found that 22% of working individuals had an average weekly working time of > 48 h in all countries in a study conducted by the International Labor Organization[25].

A total of 19.04% of the health professionals participating in this study stated that their encounters with child deaths had positive effects on gaining experience in intervention, and 66.6% stated that they had negative emotional effects (sadness, pain, grief). Given the duration of the effects, it was seen that 42.85% were affected between 1 and 3 d. This indicates that because doctors, nurses and midwives are working long hours, the negative effects of child mortality during working hours should be considered. We note that the negative effects of the event occurring in one shift may continue into the next shift. These negative effects affect the professional quality of life, burnout and compassion fatigue.

In this study, the average QoLSE Vocational Satisfaction Sub-dimension and QoLSE Burnout Sub-dimension scores of female healthcare professionals were significantly higher ($P < 0.05$). Similarly, Cañadas-De la Fuente *et al*[26] found that burnout syndrome was higher in male nurses. In Kılıç's[7] study, the mean scores of the female nurses' Traumatic Stress Symptoms Scale and QoLSE Burnout and Coordination Fatigue Sub-dimensions were significantly higher ($P < 0.05$) than those of male nurses.

When examined according to occupations, doctors' Vocational Satisfaction Sub-dimension mean score was significantly lower than that of nurses and midwives ($P < 0.05$), while the Burnout Sub-dimension and Compassion Fatigue Sub-dimension mean scores were significantly higher ($P < 0.05$). To our knowledge, there is not any research into this subject.

In the comparison made by looking at the educational status of the health professionals participating in this study, the Vocational Satisfaction Sub-dimension average score of postgraduate graduates was significantly lower, while the Burnout Sub-dimension average score was significantly higher ($P < 0.05$). In the study of Kılıç[7], the mean score of QoLSE Vocational Satisfaction sub-dimension of nurses trained at high school level was statistically higher than that of nurses at other education levels. Nurses who received their education at a master's level mean score of QoLSE Compassion Fatigue Sub-dimension was significantly higher than that of nurses at other education levels.

The mean score of the Vocational Satisfaction Sub-dimension of the employees who worked night shifts was significantly lower than in the other groups ($P < 0.05$). These conditions may decrease the quality of the professional life of the health professionals working night shifts and cause burnout and fatigue to be more frequent [7,18,27].

In this study, a significant negative correlation was found between the weekly average working hours of the health professionals and QoLSE Vocational Satisfaction Sub-dimension. A significant positive correlation was found between the weekly average working hours and the Burnout Sub-dimension. A weak positive correlation was found between the weekly average working hours and Compassion Fatigue Sub-dimension ($P < 0.05$). In this study, the professional satisfaction of nurses working > 40 h/wk was lower than that of nurses working ≤ 40 h/wk[5,17]. In a study by Marcum

Table 4 Distribution of the scores of health professionals scored from quality of life scale for employees sub-dimensions (*n* = 128)

Features of health professionals	QoLSE vocational satisfaction sub-dimension		QoLSE burnout sub-dimension		QoLSE mercy fatigue sub-dimension	
	mean ± SD	Med (min–max)	mean ± SD	Med (min–max)	mean ± SD	Med (min-max)
Gender						
Female	34.86 ± 9.0	35.0 (9.0-50.0)	17.58 ± 6.23	17.50 (2.0-36.0)	15.50 ± 6.86	14.0 (0.0-40.0)
Male	26.45 ± 10.91	25.50 (8.0-49.0)	23.10 ± 6.70	24.50 (9.0-36.0)	15.45 ± 6.93	15.0 (3.0-31.0)
P value[a]	**0.001**		**0.001**		0.911	
Profession						
Doctor	28.76 ± 9.30	29.0 (9.0-49.0)	23.50 ± 5.65	24.50 (9.0-36.0)	18.65 ± 7.23	17.0 (8.0-40.0)
Nurse	34.53 ± 9.53	36.0 (8.0-50.0)	17.20 ± 6.25	17.0 (2.0-36.0)	14.39 ± 6.63	13.0 (0.0-37.0)
Midwife	35.78 ± 9.86	36.0 (8.0-50.0)	16.94 ± 6.02	17.0 (7.0-26.0)	15.94 ± 6.15	16.0 (5.0-27.0)
P value[b]	**0.014**		**0.000**		**0.020**	
Education status						
Medical career high school	38.33 ± 9.55	40.0 (17.0-50.0)	17.47 ± 6.33	17.0 (6.0-26.0)	13.80 ± 7.59	15.0 (0.0-25.0)
Two-year degree	33.65 ± 9.69	35.50 (9.0-48.0)	18.90 ± 7.14	17.50 (10.0-36.0)	16.30 ± 8.12	13.50 (7.0-37.0)
Bachelor degree	34.15 ± 9.84	35.0 (8.0-50.0)	16.75 ± 6.07	17.0 (2.0-33.0)	14.44 ± 5.92	13.0 (3.0-27.0)
Master degree	30.09 ± 9.01	30.50 (9.0-49.0)	21.84 ± 6.27	22.0 (9.0-36.0)	17.78 ± 6.97	17.0 (8.0-40.0)
P value[b]	**0.039**		**0.007**		0.167	
Hospital worked						
Public hospital	32.38 ± 9.61	33.0 (8.0-50.0)	18.97 ± 6.33	19.0 (6.0-36.0)	15.46 ± 6.84	14.0 (0.0-40.0)
Private hospital	42.33 ± 5.80	44.0 (33.0-50.0)	14.46 ± 7.40	13.0 (2.0-27.0)	15.73 ± 7.11	17.0 (5.0-25.0)
P value[a]	**0.000**		**0.029**		0.716	
How it works						
Continuous day	41.59 ± 8.06	44.0 (18.0-50.0)	15.81 ± 5.79	15.0 (6.0-27.0)	14.04 ± 6.5	12.50 (5.0-27.0)
Night shift	31.75 ± 9.29	32.50 (8.0-50.0)	18.94 ± 6.30	19.0 (6.0-36.0)	15.67 ± 6.31	15.0 (0.0-37.0)
Other[a]	34.0 ± 9.71	36.0 (18.0-44.0)	19.83 ± 11.78	22.0 (2.0-33.0)	17.83 ± 14.37	12.0 (3.0-40.0)
P value[b]	**0.000**		0.109		0.514	
Satisfaction with working conditions						
Yes	38.14 ± 10.91	44.0 (19.0-50.0)	15.57 ± 6.0	17.50 (7.0-26.0)	15.0 ± 5.98	13.0 (7.0-25.0)
No	29.80 ± 11.01	29.50 (8.0-50.0)	21.03 ± 7.06	21.0 (6.0-36.0)	14.92 ± 7.99	15.0 (0.0-40.0)
Partially	35.64 ± 7.13	36.0 (14.0-49.0)	16.91 ± 5.58	17.0 (2.0-28.0)	16.08 ± 5.99	15.0 (6.0-28.0)
P value[b]	**0.020**		**0.009**		0.789	

[a]Mann–Whitney *U* test.
[b]Kruskal–Wallis test. QoLSE: Quality of Life Scale for Employees.

et al[28] of factors related to compassion fatigue and burnout in American nurses included age, years worked as a nurse, working environment, coping mechanisms and specialties.

In the comparison made according to the satisfaction of the health professionals with their working conditions, the Occupational Satisfaction Sub-dimension mean score of the dissatisfied professionals was significantly lower, and the Burnout Sub-dimension mean score was significantly higher ($P < 0.05$). It is crucial not to ignore employee satisfaction to ensure patient satisfaction. To achieve this satisfaction, managers need to take the necessary steps to improve working conditions.

CONCLUSION

The right of health professionals to choose the clinic where they work; the fact that they do not constantly change the places where they work; a low number of night shifts; and adequate numbers of personnel have positive effects on the quality of professional life. It may be appropriate to reduce overtime hours, and if not, overtime wages should be sufficient and regular to satisfy employees. It can be suggested to improve the working conditions and make them more favorable, and to satisfy employees economically and emotionally. The average weekly working hours can be 45, as stated in labor law. Health professionals who are met with child deaths should be given the necessary time to overcome the negative effects that they experience. Factors that help reduce compassion fatigue and burnout, as well as factors that allow staff and managers to be appreciated, will increase the quality of professional life. Health professionals and managers should work together to create a healthy work environment, increase professional satisfaction and prevent burnout and fatigue.

ARTICLE HIGHLIGHTS

Research background

Burnout and compassion fatigue are affecting the quality of professional life.

Research motivation

Doctors and nurses working in pediatric clinics caring for sick or dying children for a long time can develop compassion fatigue. This may affect their professional quality of life.

Research objectives

This study has been done to determine the levels of professional satisfaction, burnout and compassion fatigue of nurses and doctors working in pediatric clinics and related factors.

Research methods

This was a descriptive study.

Research results

The mean scores of female healthcare professionals in Quality of Life Scale for Employees (QoLSE) Vocational Satisfaction Sub-Dimension and the mean scores of the male healthcare professionals in QoLSE Burnout Sub-Dimension were significantly higher than those of the females ($P < 0.05$). When examined according to professions, the QoLSE Occupational Satisfaction Sub-Dimension mean scores of doctors were significantly lower than those of the nurses and midwives ($P < 0.05$), while the QoLSE Burnout Sub-Dimension and Empathy Fatigue Sub-Dimension mean scores of the doctors were higher ($P < 0.05$). In the comparison made according to the satisfaction of health professionals with their working conditions, the QoLSE Occupational Satisfaction Sub-Dimension mean score of the dissatisfied professionals was significantly lower and the QoLSE Burnout Sub-Dimension mean score was significantly higher.

Research conclusions

The working conditions of health professionals should be improved physically and socially, and time should be given to allow them to get rid of the negative emotions they have experienced after child deaths.

Research perspectives

In this context, it is essential to collect information that will improve the risk profile associated with burnout syndrome among health professionals working in the field of child health and diseases. Future research should focus on identifying the protection factors or positive aspects that enable healthcare professionals to successfully cope with burnout.

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 January 9; 11(1): 48-60

DOI: 10.5409/wjcp.v11.i1.48

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Basic Study

Impact of stimulant medication on behaviour and executive functions in children with attention-deficit/hyperactivity disorder

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Author contributions: Hai T assisted with data collection, analyzed and interpreted the data and wrote the manuscript; Duffy HA assisted with data collection and reviewing of the manuscript; Lemay JA assisted with data collection; Lemay JF is the principal investigator of the study, designed the study and edited the manuscript; all authors approved the final version of the article.

Institutional review board statement: Ethics approval for the following research has been renewed by the Conjoint Health Research Ethics Board (CHREB) at the University of Calgary. The CHREB is constituted and operates in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); Health Canada Food and Drug Regulations Division 5; Part C; ICH Guidance E6: Good Clinical Practice and the provisions and regulations of the Health Information Act, RSA 2000 c H-5. Ethics ID: REB15-3068_REN4.

Conflict-of-interest statement: The

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Abstract

BACKGROUND

Children with attention-deficit/hyperactivity disorder (ADHD) often exhibit behaviour challenges and deficits in executive functions (EF). Psychostimulant medications [*e.g.*, methylphenidate (MPH)] are commonly prescribed for children with ADHD and are considered effective in 70% of the cases. Furthermore, only a handful of studies have investigated the long-term impact of MPH medication on EF and behaviour.

AIM

To evaluate behaviour and EF challenges in children with ADHD who were involved in an MPH treatment trial across three-time points.

METHODS

Thirty-seven children with ADHD completed a stimulant medication trial to study the short- and long-term impact of medication. Children with ADHD completed three neuropsychological assessments [Continuous Performance Test (CPT)-II, Digit Span Backwards and Spatial Span Backwards]. Parents of children with ADHD completed behaviour rating scales [Behaviour Rating Inventory of Executive Functioning (BRIEF) and Behaviour Assessment System for Children-Second Edition (BASC-2)]. Participants were evaluated at: (1) Baseline (no medication); and (2) Best-dose (BD; following four-week MPH treatment). Additionally, 18 participants returned for a long-term naturalistic follow up (FU; up to two years following BD).

RESULTS

Repeated measure analyses of variance found significant effects of time on two subscales of BRIEF and four subscales of BASC-2. Neuropsychological assess-

authors declare no competing financial interests. No conflict of interest to report.

Data sharing statement: Dataset available from the corresponding author at jf.lemay@ahs.ca.

Supported by the Alberta Children's Hospital Foundation, Werklund School of Education, University of Calgary.

Country/Territory of origin: Canada

Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 24, 2021
Peer-review started: March 24, 2021
First decision: June 17, 2021
Revised: July 8, 2021
Accepted: December 2, 2021
Article in press: December 2, 2021
Published online: January 9, 2022

P-Reviewer: Nassar G, Pillar G
S-Editor: Zhang H
L-Editor: A
P-Editor: Zhang H

ments showed some improvement, but not on all tasks following the medication trial. These improvements did not sustain at FU, with increases in EF and behaviour challenges, and a decline in performance on the CPT-II task being observed.

CONCLUSION
Parents of children with ADHD reported improvements in EF and behaviours during the MPH trial but were not sustained at FU. Combining screening tools and neuropsychological assessments may be useful for monitoring medication responses.

Key Words: Attention-deficit/hyperactive disorder; Behaviour; Executive functions; Stimulant medications

Core Tip: Parents of children with attention-deficit/hyperactivity disorder reported improvements in executive function and behaviours during the methylphenidate trial, but these improvements did not sustain at the long-term follow up condition. Combining screening tools and neuropsychological assessments may be useful for monitoring psychostimulant medication responses as children enter their adolescent years.

Citation: Hai T, Duffy HA, Lemay JA, Lemay JF. Impact of stimulant medication on behaviour and executive functions in children with attention-deficit/hyperactivity disorder. *World J Clin Pediatr* 2022; 11(1): 48-60
URL: https://www.wjgnet.com/2219-2808/full/v11/i1/48.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i1.48

INTRODUCTION

Deficits in executive function (EF) skills and behaviour challenges are commonly reported in children with attention-deficit/hyperactivity disorder (ADHD)[1,2]. ADHD, a neurodevelopmental disorder, is highly prevalent (5%-7%) in school-aged children[3,4]. Symptoms of ADHD typically include developmentally inappropriate levels of inattention, or impulsivity, and hyperactivity[5].

Children with ADHD often exhibit challenges associated with behaviour as well as EF[2]. In the literature, EF is an umbrella term that refers to a complex range of cognitive abilities, including working memory, goal-directed planning, impulse control, cognitive flexibility, and self-monitoring[6]. There is presently no consensus in the literature regarding the exact definition of EF, with upwards of 18 different available definitions included across studies[7]. Nevertheless, it is accepted that EF represents a family of top-down cognitive processes that are needed to make judgments and decisions and initiate purposeful behaviour[8]. As well, EF challenges are known to impact children with ADHD academically and behaviourally, as well as with their interpersonal relationships[2,9,10]. For instance, EF challenges can impact or affect performance at school, including task initiation, organizing thoughts to complete written assignments, using problem-solving skills to complete math calculations, switching from one task to another, and keeping track of task completion[11]. At home, EF challenges can manifest as trouble initiating or completing house chores, inflexibility to changing routines, or difficulty regulating and modulating emotions [12]. Socially, EF challenges may result in continual interruption of others or difficulty engaging in appropriate reciprocal conversation[9].

The measurement of EF in children with ADHD is generally done through either performance-based neuropsychological measures or behaviour rating scales. Both the performance-based measures and rating scales are considered to be reliable measures of EF[1]. However, the relationship between performance-based and behaviour ratings of EF is less clear, especially when evaluating whether they measure the same underlying construct. Furthermore, children with ADHD exhibit variable EF performance on neuropsychological tests when measured in a lab setting[13]. The current

study included a combination of parent behaviour rating scales and neuropsychological measures to gain a more thorough understanding of EF challenges in children with ADHD.

Currently, psychostimulant medications [*e.g.*, methylphenidate (MPH)], along with behavioural interventions, are the most common treatment options for children with ADHD[14-17]. Stimulant medications are considered effective in about 70% of the cases[1,15], and the efficacy and safety of psychostimulants for the treatment of ADHD have been well documented[18]. Specifically, numerous research studies have consistently demonstrated that stimulants such as MPH improve executive and nonexecutive memory, reaction time, reaction time variability, and response inhibition in individuals with ADHD[18-20]. Short-term efficacy for pharmacological treatments is supported by all major evidence-based guidelines, including the Canadian ADHD Resource Alliance guidelines[15,16]. Conversely, findings related to the long-term impact of MPH, including the multimodal treatment of ADHD study (MTA), have been inconsistent with some studies finding sustained behavioural improvement following medication trials[21], while other studies failed to demonstrate long-term behavioural improvements[22,23].

Given that psychostimulant medications are commonly prescribed for children with ADHD[18], it is important to understand the developmental impact of these medications as children enter their adolescent years. Few studies to date have conducted a naturalistic follow up (FU) of children with ADHD who were part of a treatment trial [24,25]. Naturalistic FU studies are different from randomized controlled FU studies, as the participants are no longer part of the active treatment trial and follow what would be considered typical outpatient treatment through their healthcare professionals. As of spring 2021, no study to our knowledge has included parental behaviour rating scales and performance on neuropsychological assessments to evaluate the long-term naturalistic impact of stimulant medications use on behaviour, learning, and EF in children with ADHD.

The purpose of the present study was to investigate the short- and long-term (naturalistic FU) impact of stimulant medications in children with ADHD using both behaviour rating scales completed by parents and neuropsychological performance-based measures. The study aims to answer the following research questions:

(1) What are the changes in behaviour and EF as observed by parents of children with ADHD at baseline (BL; no medication) compared to best-dose (BD; MPH dose that was recommended by their primary care physician) condition (following a four-week trial of MPH treatment)?

(2) What are the changes in EF performance in children with ADHD at BL (no medication) compared to BD condition (following a four-week trial of MPH treatment)?

(3) What are the changes in EF and behaviour at the long-term FU (6 mo to 2 years following long-acting MPH treatment trial) as observed by parents?

(4) What are the changes in EF performance at the long-term FU (6 mo to 2 years following long-acting MPH treatment trial)?

MATERIALS AND METHODS

Participants

Children with ADHD: A total of 37 eligible participants with ADHD were included for analyses in the current study. Participants were excluded from the analyses if they did not return for the best-dose condition, were on medications at BL or did not meet the inclusion criteria. For the long-term naturalistic FU portion of the study, a total of 21 families elected to take part in the study.

All participants had to have: (1) A confirmed diagnosis of ADHD through a standard-of-care health professional prior to study participation; (2) The healthcare professional overseeing their progress and a diagnosis of ADHD; (3) Parent ratings of child's current ADHD behaviour ratings using the Behaviour Assessment System for Children-Second Edition (BASC-2)[26], to indicate the child currently meets DSM-5 ADHD criteria[5]; and (4) A cognitive screener reporting no intellectual disability (scaled score > 4) on both the vocabulary multiple choice and the matrix reasoning subtests from the Wechsler Intelligence Scale for Children-Fourth Edition Integrated (WISC-IV Integrated)[27]. The children were not involved in any behavioural intervention during the medication trial. However, they were allowed to take part in behavioural intervention during the naturalistic FU condition.

Measures

Neuropsychological measures: Children with ADHD completed neuropsychological measures related to working memory and inhibition. Parents of children with ADHD completed two additional standardized behaviour rating scales (questionnaires).

Conners Continuous Performance Test: The Conners Continuous Performance Test (CPT-II) is a computerized task that requires sustained attention to visually presented stimuli[28]. The CPT-II is a 15-min task, with a total of 360 trials where respondents are presented with letters appearing on a computer screen at varying rates (*i.e.*, 1-, 2-, or 4-second inter-stimulus intervals). Participants are required to press the spacebar whenever a "target" letter appears on the screen and refrain from responding (*i.e.*, pressing the spacebar) whenever the non-target stimulus (*i.e.*, letter "X") appears. The CPT-II provides an array of scores following task completion. For the purposes of this study, only the Omission and the Commission errors score was evaluated. Omission errors indicate the number of times the child missed the target item when it was presented. Commission errors represent errors where the child incorrectly pressed the spacebar in response to the non-target stimulus. The reliability coefficient for omission and commission errors were 0.85 and 0.83 respectively. Test-retest reliability for omission and commission errors were 0.48 and 0.65, suggestive of adequate consistency across administrations[29].

WISC-IV Integrated Digit Span Backwards: Digit span tasks are used to evaluate verbal working memory. The Digit Span Backwards task requires children to listen to orally presented numbers with spans increasing in length and repeating in reverse order[27]. The number of digits recalled correctly in the reverse order is used for scoring purposes. Participants were awarded one point if they correctly repeated the sequence in backward order and zero points for an incorrect or incomplete answer or no response. The overall Digit Span Backward reliability coefficient is 0.81 for the normative sample, suggestive of good internal consistency. Test-retest reliability for the Digit Span Backward subtest was 0.74, indicating adequate stability across time [30].

WISC-IV Integrated Spatial Span Backwards: Spatial Span tasks are used to assess visuospatial working memory and require participants to encode and immediately recall a series of presented stimuli mentally. The WISC-IV Integrated Spatial Span board consists of ten cubes attached in a random order to a whiteboard. During the Spatial Span task, examinees observed the examiner tapping a prearranged sequence of blocks on the board at a rate of one block per second. Participants were required to tap the blocks in the reverse order of that demonstrated by the examiner. Participants were awarded one point if they tapped the blocks in the correct backward order or zero points if they provided an incorrect order or no response. The overall Spatial Span Backward task reliability coefficient for the normative sample was found to be 0.81, suggestive of good internal consistency[31].

Parent questionnaires: Parents in the current study completed two behaviour rating scales.

The Behaviour Assessment System for Children (BASC-2) is a widely utilized, norm-referenced rating scale designed to assess emotional, behavioural, and adaptive functioning among children and adolescents[27]. The parent rating scale (PRS) provides T-scores (M = 50; SD = 10) for four broad composite scales [externalizing problems (EP), internalizing problems (IP), behavioural symptoms index (BSI), and adaptive skills (AS)]. For the EP, IP, and BSI composites and associated clinical scales, T-scores of 70 and above are considered clinically significant and suggest a high level of maladjustment. In contrast, lower scores within the adaptive domain denote more problematic behaviours; T-scores of 30 and below are considered clinically significant. Reliability coefficients of the BASC-2 rating scale range between 0.90 and 0.95 for the composite scores, suggestive of strong internal consistency. The BASC-2 PRS composite scales also have high test-retest reliability (0.78 to 0.92)[25].

The Behaviour Rating Inventory of Executive Functioning (BRIEF) was used to assess parental perceptions of EF skills[28,32]. The BRIEF is a questionnaire for parents of school-aged children (ages 5 to 18) that is used to determine a range of EF skills at home and in the community. The BRIEF parent form consists of 86 items within eight theoretically and empirically derived clinical scales and three composite scores that measure different aspects of EF. The BRIEF parent rating scale has high internal consistency (0.80 to 0.98) and test-retest reliability (0.82)[26].

Procedure

The current study was part of a larger-scale project investigating the effect of medications on EF, academic, behavioural, and neuroimaging outcomes in children with ADHD. The larger study used a quasi-experimental, cross-sectional design with simple random sampling. ADHD participants were recruited through referrals from healthcare professionals in a Western Canadian city. The study research assistant conducted the ADHD screening measures to evaluate eligibility for the study before seeking informed consent for participating in the study. Parents completed the rating scales to ensure that their child met the eligibility criteria. If data from the parent behaviour rating scales did not indicate clinical range for attention and hyperactivity problems of at least 1.5 SDs above the norm for the child's age, the child and parent were thanked for their participation, and no further testing took place. Following receiving consent, the study research assistants completed additional screener assessment that included the two subtests from the WISC-IV Integrated intellectual screener. If the child was found to be intellectually deficient on the two WISC-Integrated screener measures (*e.g.*, a scaled score of four or less, M = 10, SD = 3), the physician was notified, and the trial was terminated.

Participants completed assessments at three-time points, BL, post medication trial (BD) and at long-term naturalistic FU. All eligible participants were then scheduled for additional assessments.

BL: On the second testing session, eligible participants were scheduled to complete additional neuropsychological measures, and parents completed further questionnaires. The appointment lasted approximately 90 min. Participants and parents were thanked and compensated for their participation.

Post-treatment trial: Following taking medications for four weeks, participants returned to complete the same neuropsychological assessments completed at BL. Parents also completed rating scales.

FU: Parents of participants with ADHD, who were part of the initial medication trial, were invited to participate in an additional study component that included the completion of parent behaviour rating scales and neuropsychological testing. Families that participated in all components of the current study were evaluated at three separate time points: (1) BL: no medication; (2) BD: following a four-week trial of MPH treatment; and (3) Long-term naturalistic FU: 6 mo to 2 years following BD, see Figure 1.

Data analyses

The Statistical Package for the Social Sciences version 26 was used to conduct all analyses. A preliminary inspection of the data was performed for accuracy and examination of missing values and outliers before running any analyses. Additionally, the assumptions of normality and Mauchly's Test of Sphericity were evaluated in order to conduct parametric data analyses[33].

Descriptive statistics such as mean and standard deviations were calculated. Repeated measures analyses of variance (RmANOVA) were conducted to evaluate changes in EF and behavioural challenges. Specifically, changes were measured between the BL and BD time points. Additionally, changes were measured between the BD and FU time points for participants participating in the long-term FU. Biological sex differences between boys and girls were also conducted across the different EF, behaviour, and adaptive skills ratings.

RESULTS

Participant demographic information

Table 1 presents the sample characteristics regarding their cognitive and behavioural screening measures.

Difference in parent behaviour and EF ratings between BL and BD condition

Table 2 summarizes the BASC-2 behavioural rating results. Analyses revealed a significant difference between BL and BD conditions, EP, F (1, 29) = 44.18, $P \leq 0.001$, partial eta square = 0.60, IP, F (1, 29) = 19.98, $P \leq 0.001$, partial eta square = 0.41, BSI, F (1, 29) = 83.04, $P \leq 0.001$, partial eta square = 0.74, and AS scores, F (1, 29) range = 44.98 , $P \leq 0.001$, partial eta square = 0.61. Specifically, significant improvements across all

Table 1 Participant demographic information at baseline (T1)

Variable	mean ± SD (*n* = 37)
Age	10.11 ± 1.27
Cognitive Tasks	
WISC-IV-I VC SS	98.11 ± 11.69
WISC-IV-I MR SS	97.70 ± 12.89
BASC-2 Attention Problem T-Score	69.59 ± 6.31
BASC-2 Hyperactivity T-Score	71.73 ± 12.77
WJ-III Reading	90.49 ± 13.19
WJ-III Math	80.95 ± 13.86
WJ-III Written Language	87.03 ± 14.75
Biological Sex	*n* (%)
Female	16 (43.2)
Male	21 (56.8)

WISC-IV: Wechsler Intelligence Scale for Children, Fourth Edition; VC SS: Vocabulary Subtest Standard Score; MR SS: Matrix Reasoning Standard Score; BASC-2: Behaviour Assessment System for Children-Second Edition; WJ-III: Woodcock Johnson Test of Achievement, Third Edition.

Table 2 Behaviour Assessment System for Children-Second Edition parent symptom reports measured over the three-time points

Variable	BL T-score mean ± SD (*n* = 37)	BD T-score mean ± SD (*n* = 30)	BD-BL (*P* value)	FU T-score mean ± SD (*n* = 18)	FU-BD (*P* value)
Externalizing problems	68.95 ± 13.20	54.83 ± 8.42	$P < 0.001$	63.72 ± 10.26	$P = 0.003$
Internalizing problems	62.86 ± 15.34	52.53 ± 13.0	$P < 0.001$	60.89 ± 13.07	$P = 0.063$
Behaviour symptoms index	72.32 ± 10.20	57.13 ± 7.73	$P < 0.001$	68.06 ± 9.47	$P < 0.001$
Adaptive behaviours	33.95 ± 8.92	40.57 ± 9.22	$P < 0.001$	38.72 ± 8.79	$P = 0.124$

Mean scores on the Behaviour Assessment System for Children-Second Edition subscales; externalizing problems, internalizing problems, behavioural symptom index and adaptive skills, as rated by parents at three-time points: (1) Baseline; (2) Best-dose; and (3) Follow-up. BL: Baseline; BD: Best-dose; FU: Follow-up.

behavioural indices (EP, IP, BSI) were observed in addition to a significant increase in adaptive skills between the BL and BD time points.

Table 3 summarizes the BRIEF rating scale results. Similar to the BASC-2 scores, results from the BRIEF parent rating scale showed significant improvement from BL to BD condition, BRIEF behavioural regulation index [BRI; F (1, 30) = 90.48, $P \leq 0.001$, partial eta square = 0.75) and metacognition index [MI; F (1, 30) = 94.38, $P \leq 0.001$, partial eta square = 0.76).

Difference in EF performance between BL and BD condition

Results indicated significant differences in performance between BL and BD conditions on the CPT omission errors, F (1, 32) = 14.38, $P \leq 0.001$, partial eta square = 0.31. No significant difference was observed in performance on the CPT commission errors, F (1, 32) = 2.93, $P \geq 0.05$, partial eta square = 0.08, Digit Span Backwards, F (1, 30) = 1.89, $P \geq 0.05$, partial eta square = 0.06 and Spatial Span Backwards, F (1, 30) = 0.97, $P \geq 0.05$, partial eta square = 0.03 tasks, see Table 4.

Difference in parent behaviour and EF ratings between BD condition and long-term FU

Analyses revealed a significant effect of time on the EP, F (1, 16) = 12.73, $P \leq 0.01$, partial eta square = 0.44, and BSI, F (1, 16) = 19.38, $P \leq 0.001$, partial eta square = 0.55. Specifically, significant decrease in behaviour was observed by parents at FU time

Table 3 Behaviour Rating Inventory of Executive Functioning-Second Edition parent symptom reports measured over the three-time points

Variable	BL T-score mean ± SD (*n* = 37)	BD T-score mean ± SD (*n* = 31)	BD-BL (*P* value)	FU T-score mean ± SD (*n* = 18)	FU-BD (*P* value)
Behavioural regulation index	72.43 ± 11.94	53.42 ± 8.78	$P < 0.001$	68.28 ± 13.23	$P = 0.001$
Metacognition index	74.76 ± 7.72	57.94 ± 8.48	$P < 0.001$	72.06 ± 9.51	$P < 0.001$

Mean scores on the BRIEF subscales; Behavioural Regulation Index and Metacognition Index as rated by parents at three-time points: (1) Baseline; (2) Best-dose; and (3) Follow-up. BL: Baseline; BD: Best-dose; FU: Follow-up.

Table 4 Neuropsychological Test Performance Scores measured over the three-time points

Variable	BL T-score mean ± SD (*n* = 37)	BD T-score mean ± SD (*n* = 33)	BD-BL (*P* value)	FU T-score mean ± SD (*n* = 18)	FU-BD (*P* value)
CPT omission errors (T-Score)	61.11 ± 15.76	52.88 ± 8.09	$P = 0.001$	49.34 ± 5.90	$P = 0.10$
CPT commission errors (T-Score)	53.59 ± 6.74	49.70 ± 11.75	$P = 0.097$	49.69 ± 10.17	$P = 0.04$
Digit Span Backwards	95.54 ± 11.04	99.19 ± 11.48	$P = 0.059$	96.94 ± 15.54	$P = 0.055$
Spatial Span Backwards	105.68 ± 12.42	108.23 ± 13.0	$P = 0.332$	108.06 ± 12.96	$P = 0.782$

Mean scores on the Continuous performance test commission errors (T-scores) and Wechsler Intelligence Scale for Children, Fourth Edition (standard score) at three-time points: (1) Baseline; (2) Best-dose; and (3) Follow-up. CPT: Continuous performance test; BL: Baseline; BD: Best-dose; FU: Follow-up.

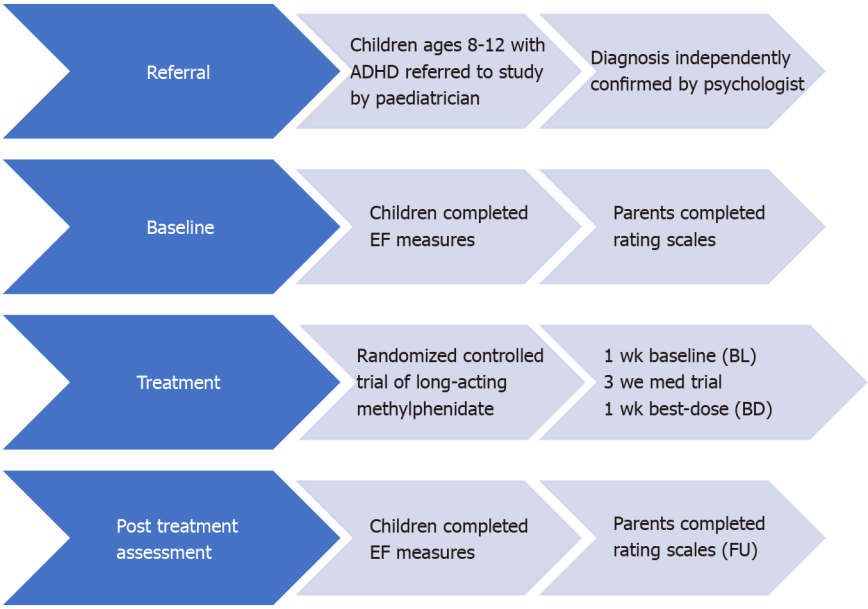

Figure 1 Study flowchart demonstrating the different assessments completed by parents and children with attention-deficit/hyperactivity disorder at the three-time points: Baseline, best-dose and follow-up as part of the study. ADHD: Attention-deficit/hyperactivity disorder; EF: Executive function; BL: Baseline; BD: Best-dose; FU: Follow-up.

point (6 mo to 2 years after the MPH trial).

No significant difference was observed between BL and FU for the IP, F (1, 16) = 4.00, $P \geq 0.05$, partial eta square = 0.20, and AS, F (1, 16) = 2.63, $P \geq 0.05$, partial eta square = 0.14, suggesting no change in internalizing problems and adaptive skills were observed at the FU time.

No significant group differences were observed for any of the BASC-2 scales (EP, IP, BSI, AS) during the FU condition for individuals who were still taking medications compared to those who discontinued taking medications, F (4, 13) = 0.30, $P \geq 0.05$.

Lastly, no significant overall group differences emerged for any of the BASC-2 scales (EP, IP, BSI, AS) at the FU condition for biological sex, F (4, 13) = 2.35, $P \geq 0.05$. However, when analyzing univariately, parents reported higher scores on the Internalizing Problems scale for females compared to males, F (1, 16) = 9.83, $P \leq 0.05$).

The BRIEF parent ratings are presented in Table 3. The EF ratings completed by parents on the BRIEF revealed a significant effect over time: BRIEF BRI [F (1, 16) = 16.16, $P \leq 0.001$, partial eta square = 0.50] and MI [F (1, 16) = 31/64, $P \leq 0.001$, partial eta square = 0.66]. Specifically, results show an increase in symptom ratings between time points BD (BRI M = 54.47; MI M = 59.12) and FU time points (BRI M = 67.12; MI M = 71.71).

MANOVA was used to investigate the impact of medications on EF at the FU time point. Results indicated no significant differences between BRIEF ratings (BRI and MI) at FU condition between participants still taking medications compared to participants who had discontinued, F (2, 15) = 0.40, $P \geq 0.05$. No significant overall biological sex differences between BRIEF ratings (BRI and MI) at FU condition were observed, F (2, 15) = 3.10, $P \geq 0.05$. However, the univariate analyses indicated parents reporting higher BRIEF-MI ratings for males than for females, F (1, 16) = 6.10, $P \leq 0.05$.

Difference in neuropsychological performance between BD condition and long-term FU

RmANOVA analyses were conducted to investigate the difference in neuropsychological test performance across the BD and FU. Results indicated significant differences over time on the CPT omission errors, F (1, 19) = 5.58, $P \leq 0.05$, partial eta square = 0.28). No significant difference over time on the CPT commission errors, F (1, 19) = 3.80 , $P \geq 0.05$, partial eta square = 0.17, Digit Span Backwards, F (1, 15) = 4.31, $P \geq 0.05$, partial eta square = 0.22 and spatial span backwards, F (1, 17) = 0.12, $P \geq 0.05$, partial eta square = 0.007) tasks. Furthermore, MANOVA was used to investigate the impact of medications on EF performance measures at the FU time point. Results indicated no significant difference at FU condition between participants still taking medications compared to participants who had discontinued, F (4, 13) = 1.24, $P \geq 0.05$. No biological sex differences on neuropsychological test performances were observed at the FU condition, F (4, 13) = 1.08, $P \geq 0.05$.

DISCUSSION

The purpose of this study was to evaluate the short- and long-term impact of psychostimulant medications on EF and behaviour across three-time points in children with ADHD who were involved in a medication treatment trial.

In terms of parent behaviour ratings, parents observed improved behaviour in children with ADHD following the medication trial across various internalizing, externalizing, and adaptive domains. This is consistent with previous studies investigating the efficacy of stimulants for children with ADHD[14]. However, this improvement in parent behaviour ratings did not sustain at the naturalistic long-term FU condition, thus indicating that children with ADHD continue to struggle with behaviour challenges in the adolescent years. These results are in contrast to two of the previous naturalistic long-term FU studies where the authors did not find any significant difference between post-test and FU time points, except for inattention[24, 25]. The observed differences in results could be due to different FU timelines between the studies, with the current study's FU condition ranging from 6 mo to 2 years after initial MPH treatment compared to a range of 4.5-8.0 years after treatment in the other studies. Previous studies also included combined treatment modalities, whereas the current study only implemented pharmacotherapy intervention. It is also important to mention that the current findings are consistent with Molina *et al*[22] findings from the MTA study, the largest medication study to date with children with ADHD. This shows that the long-term impact of stimulant medication is variable across individuals and is dependent on other mediating and moderating factors[34].

A number of additional factors could have contributed to the lack of sustained behavioural improvement as measured by parent behaviour ratings. It is conceivable that children become tolerant to medication over time, and thus the effectiveness of the medication declines. Moreover, it is also plausible that adherence to medication was better in the BD medication condition compared to the FU condition when the children were no longer part of the treatment trial. Additionally, other external variables could have impacted the perceived effect of medications as reported by parents; for example, parents could have noticed heightened sleep and/or appetite issues as well as

increased emotional lability, which may lead to increased perceived behavioural challenges. As well, it is possible that as children develop and reach the early adolescent years, they require more support to manage increasing educational and social demands. Thus, effective curricula and targeted interventions would be beneficial to complement medication treatment. Consequently, it is important for clinicians and other healthcare professionals to be aware of continued challenges in behaviour in children with ADHD during adolescent years.

Similar to the behaviour ratings described above, parents also reported significant improvements in EF skills as measured by the BRIEF parent rating scale. These results are consistent with previous studies where increases in EF skills were witnessed by parents following medication treatment[35]. However, the reported improvements in EF skills did not sustain at the long-term FU condition.

While some of the study participants did not continue with their medication treatment, there were no significant differences in EF ratings between the medicated and non-medicated groups, suggesting that other potential variables may have impacted the perceived efficacy of the medication during the FU condition. It is possible that as children with ADHD develop during their adolescent years, their EF challenges increase. Therefore, adolescents with ADHD would likely benefit from additional interventions to supplement medications to support this increasing need.

Given the discrepancies reported in the literature between parent rating scale and performance-based measures[1], the impact of stimulant medication on neuropsychological test performance was also evaluated. Results showed improved performance following the medication trial on the CPT omission errors score. However, CPT commission errors did not change following the four-week medication trial. Similarly, performance on the two working memory tasks (Digit Span Backwards and Spatial Span Backwards) did not change following the medication trial.

At the long-term FU condition, performance on the CPT omission decreased, and the improvement shown after the medication trial did not sustain. There were no significant changes in performance on the CPT commission error and the two working memory tasks. It is possible that these differences in performance could be task specific as the CPT-II task requires sustained attention and concentration. By way of comparison, the digit span backwards and the spatial span backwards is a much shorter task. It is also possible that children with ADHD need additional interventions on top of medications as they enter their early adolescent years.

While this study adds valuable information to the existing literature on ADHD, the observed results should still be evaluated in the context of some limitations. We included a naturalistic FU where it is possible for participants to follow other psychosocial treatments or stop treatment after the post-test, possibly causing differences between initial treatment conditions at FU. Another notable limitation of the current study was the sample size as not all participants enrolled in the medication trial returned for the naturalistic FU portion of the study. While this research included an appropriate sample size to obtain statistically significant findings, the sample size is still considered small. As such, future studies need to be conducted to replicate the results. The small sample size also did not allow investigation of differences between the different presentations of ADHD; as such, the varying presentation subtypes (*i.e.*, inattentive and combined) were collapsed into one heterogeneous group. Another limitation that was not considered in this study is the changes in lifestyle habits of the children with ADHD. It is possible that changes in sleep, diet and appetite could have impacted the effect of the stimulant medication. Lastly, this study only included data from parents. It would have been beneficial to obtain teacher ratings as well, in order to understand the impact of medications at school.

CONCLUSION

The current study provided valuable information about the impact of stimulant medication on behaviour and EF in children with ADHD. Results showed improvement in EF skills and behaviour in children with ADHD following medication treatment. These improvements were reported by parents through standardized behaviour rating scales. Neuropsychological tests of response inhibition also showed improved performance following medication treatment. However, these improvements did not sustain when reassessed at the FU time point based on parent behaviour rating scales. Additionally, neuropsychological assessment results were inconclusive, with no significant differences emerging on the CPT-II commission errors, the Digit Span Backwards and the Spatial Span Backwards tasks. In spite of this, performance

on the CPT-II omission errors declined at the FU condition. Based on these observed findings, these results suggest that healthcare professionals working with individuals with ADHD should consider some form of medication FU to understand the efficacy of continued medication usage. Furthermore, it is possible that as children enter the adolescent years, they may require supplementary psychosocial support combined with pharmacotherapy to ensure more sustained treatment out-comes. Future research investigating the long-term impact of stimulant medication will be helpful to better understand the efficacy of stimulant medications and replicate findings obtained from the current study.

ARTICLE HIGHLIGHTS

Research background

Children with attention-deficit/hyperactivity disorder (ADHD) often exhibit behaviour challenges and deficits in executive function (EF) skills. Typically, psychostimulant medications [*e.g.*, methylphenidate (MPH)] are commonly prescribed for children with ADHD. However, psychostimulants are considered effective in 70% of the cases and often have undesirable side effects, including changes in appetite, weight, and sleep. Furthermore, only a handful of studies have investigated the naturalistic long-term impact of MPH medication on EF and behaviour.

Research motivation

The main topics investigated in the current study were to measure EF and behaviour challenges in children with ADHD using both parent rating scale and neuropsychological assessment measures.

Research objectives

The main objectives of the current study were to evaluate behaviour and EF challenges in children with ADHD who were involved in a MPH treatment trial. The participants were assessed across three-time points using both parent rating scale and neuropsychological assessment measures to understand the short-term and long-term naturalistic impact of stimulant medications.

Research methods

Thirty-seven children with ADHD completed a stimulant medication trial (MPH). Children with ADHD completed neuropsychological assessments assessing working memory (Digit Span Backwards and Spatial Span Backwards) and response inhibition (Continuous Performance Test-2). Parents of children with ADHD completed behaviour rating scales related to executive function [Behaviour Rating Inventory of Executive Function (BRIEF)] and behaviour [Behaviour Assessment System for Children, second edition (BASC-2)]. Participants were evaluated at: (1) Baseline (no medication); and (2) Best-dose (BD; following four-week MPH treatment). Additionally, 18 participants returned for a long-term naturalistic follow up (FU; up to two years following BD).

Research results

The results of the current study found significant effects over time on two subscales of BRIEF and four subscales of BASC-2 measures indicating impact on behaviour and EF according to parents. Neuropsychological assessments showed some improvement, but not on all tasks following the medication trial. These improvements did not sustain at FU, with increases in EF and behaviour challenges and a decline in performance on the CPT-II task being observed.

Research conclusions

Parents of children with ADHD reported improvements in EF and behaviours during the MPH trial but were not sustained at FU. Neuropsychological assessment findings were not consistent with participants showing improvement on some response inhibition tasks but not on the working memory tasks. As a result, it is important to combine screening tools and neuropsychological assessments for monitoring medication responses.

Research perspectives

The current study provided information about the impact of stimulant medication on behaviour and EF in children with ADHD. Results showed improvement in EF skills and behaviour in children with ADHD following medication treatment. These improvements were reported by parents through standardized behaviour rating scales. Neuropsychological tests of response inhibition also showed improved performance following medication treatment. However, these improvements did not sustain when reassessed at the FU time point based on parent behaviour rating scales. It is important for healthcare professionals working with individuals with ADHD to consider medication FU to understand the efficacy of continued medication usage. Furthermore, it is possible that as children enter the adolescent years, they may require supplementary psychosocial support combined with pharmacotherapy to ensure more sustained treatment outcomes. Future research investigating the long-term impact of stimulant medication will be helpful to better understand the efficacy of stimulant medications and replicate findings obtained from the current study.

ACKNOWLEDGEMENTS

The authors would like to thank the children and adolescents and their families for their participation. Thank you to Linda Beatty for her assistance in manuscript formatting.

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World J Clin Pediatr 2022 January 9; 11(1): 61-70

DOI: 10.5409/wjcp.v11.i1.61

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Case Control Study

Vestibular function for children with insulin dependent diabetes using cervical vestibular evoked myogenic potentials testing

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Institutional review board statement: The study protocol was approved by the local research ethics committee of Faculty of medicine, Assiut University, Assiut, Egypt, No. AUFM_PED_232/2019.

Informed consent statement: Parents/guardians provided their written informed consent for participation of their children in the study.

Conflict-of-interest statement: The authors declared no conflict of interest.

STROBE statement: The authors

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Abstract

BACKGROUND

Healthy vestibular system adjusts balance during static and dynamic conditions. This is important for normal development (standing up and walking). Vestipulopathies (central and peripheral) are common complications of diabetes in adult population. Related studies are scare in children with type 1 diabetes (T1D).

AIM

To assess saccular function of otolith organ in children with T1D and predictors for its dysfunction.

METHODS

Cervical vestibular evoked myogenic potential (cVEMP) was used for objective evaluation.

RESULTS

The study included 40 patients (boys = 15; girls = 25). Patients had mean age of 13.63 ± 1.50 years, duration of diabetes of 5.62 ± 2.80 years, frequent attacks of diabetic ketoacidosis (55%) and hypoglycemia (30%), hyperlipidemia (20%), hypertension (12.5%) and peripheral neuropathy (40%). Dizziness was found in 10%. Compared to healthy children (n = 25), patients had prolonged cVEMP P1 and N1 latencies and reduced P1-N1 amplitude. Bilateral cVEMP abnormalities were found in 60% (*vs* 25% for unilateral abnormalities). Higher frequencies and severe vestibulopathies were found with chronic diabetes of > 5 years, hemoglobin A1c values > 7%, frequent diabetic ketoacidosis and hypoglycemic

have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: Egypt

Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 6, 2021
Peer-review started: January 6, 2021
First decision: June 5, 2021
Revised: July 17, 2021
Accepted: November 15, 2021
Article in press: November 15, 2021
Published online: January 9, 2022

P-Reviewer: Cucuzza ME
S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Fan JR

attacks and presence of dizziness. Regression analyses showed that predictors for prolonged P1 latencies and reduced P1-N1 amplitudes were only chronic diabetes (> 5 years) {odds ratio (OR) = 2.80 [95% confidence interval (CI): 1.80–5.33], P = 0.01; OR = 3.42 (95%CI: 2.82–6.81)} and its severity (hemoglobin A1c > 7%) [OR = 3.05 (95%CI: 2.55–6.82), P = 0.01; OR = 4.20 (95%CI: 3.55–8.50), P = 0.001].

CONCLUSION
Dysfunction or injury of the saccular macula and its pathways is prevalent in children with T1D. Optimum glycemic control is important to prevent diabetes related vestipulopathies.

Key Words: Children; Type 1 diabetes; Otolith organ; Cervical vestibular evoked myogenic potential

Core Tip: Vestipulopathies are common complications of diabetes. The vestibular system is crucial for early normal motor and mental developments. Vestibular evoked myogenic potential testing is objective, noninvasive, inexpensive, rapid and reliable. It is used to assess the function of otolith organs (saccule and utricle) of the inner ear. The otolith organs register forces related to linear acceleration and static tilt to the gravitational axis. Cervical vestibular evoked myogenic potential is vestibulo-collic reflex record from neck muscles in response to acoustic stimulation. It provides information about type 1 hair cells in saccular macula, inferior vestibular nerve, vestibular nuclei, lateral and medial vestibulospinal tracts and accessory nerve nuclei. This study aimed to evaluate saccular function in children with type 1 diabetes and predictors of its abnormalities.

Citation: Hamed SA, Metwalley KA, Farghaly HS, Oseily AM. Vestibular function for children with insulin dependent diabetes using cervical vestibular evoked myogenic potentials testing. *World J Clin Pediatr* 2022; 11(1): 61-70
URL: https://www.wjgnet.com/2219-2808/full/v11/i1/61.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i1.61

INTRODUCTION

Large epidemiological studies in the United States have shown an increase in the prevalence of type 1 diabetes (T1D) from 1.48/1000 to 1.93/1000 between years of 2001 and 2009. They also have shown an increase in the annual incidence of T1D in children and adolescents by 1.4% during the years 2002 to 2012[1]. In Egypt, the annual incidence of T1D in younger children (age: Below 15 years) has been estimated to be 8/100000[2]. Previous studies reported that diabetes mellitus (DM) is the cause of peripheral and central auditory and vestibular systems' dysfunctions (*i.e.* vestibulopathies)[3-9]. Vestibular system is important for healthy motor (standing up and walking) development. It adjusts balance during static condition and motion. The vestibular end organs and their connections maintain gaze and postural stabilities through the vestibulo-ocular and vestibulo-spinal reflexes[10,11]. Studies found significant associations between diabetes and manifestations of vestibular dysfunction (*e.g.*, imbalance, unsteadiness, vertigo, *etc.*) independent to other diabetic complications that cause balance disturbance, including proprioception impairment with diabetic neuropathy and defective vision with diabetic retinopathy[10,12]. Functional testing of vestibular system are (1) Caloric irrigation, rotatory chair testing, head-impulse test (HIT) and electronystagmography (ENG) or videonystagmography (VNG), tests for semicircular canals or horizontal angular head acceleration (vestibulo-ocular) and superior vestibular nerve functions; and (2) Vestibular evoked myogenic potentials (VEMPs), tests for otolith organs' (saccule and utricle) functions[13]. The otolith organs register forces related to linear acceleration and static tilt with gravity [11,13]. VEMP testing is objective, noninvasive, inexpensive, rapid and reliable. It causes no discomfort to subjects compared to ENG or VNG. There are two common

types of VEMP recording: (1) Ocular or oVEMP: It is used to assess the integrity of the utricle or a superior vestibular nerve function; and (2) Cervical or cervical VEMP (cVEMP): It is used to assess the integrity of saccular macula or an inferior vestibular nerve function. cVEMP is a short-latency vestibulo-collic reflex (VCR) recorded from neck muscles in response to acoustic stimulation. The otolith organs sense intense acoustic stimulation due to its anatomical proximity to the cochlea[13]. The VCR arc is composed of: (1) Receptors, which are type 1 vestibular hair cells of saccular macula; (2) Afferent pathway, which is the inferior vestibular nerve that relays in the vestibular nuclei; and (3) Efferent fibers of vestibular nuclei, which run along the lateral and medial vestibulo-spinal tracts to the accessory nerve nucleus to supply the sternocleidomastoid muscle (SCM)[14].

Objectives

Studies of vestibular function in children with T1D are lacking. We aimed to assess saccule and its connections' functions using cVEMP testing. The predictors (demographic, clinical and laboratory variables) of vestibular dysfunctions were also determined.

MATERIALS AND METHODS

Study design, period, region

This is a cross sectional case-control study. It included 40 children with T1D (boys = 10, 25%; girls = 30, 75%) and 25 healthy children (boys = 9, 36%; girls = 16, 64%; age range: 9-18 years; mean: 15.44 ± 1.22 years). Children with diabetes were recruited over a year (December 2019–November 2020) from the Endocrinology Clinic of Children's Hospital, Assiut University, Assiut, Egypt. Healthy children were patients' friends and schoolmates. Excluded were children with: (1) External or middle ear diseases; (2) History of head or neck injuries or limitation of neck movements; (3) History of otologic surgery; (4) Regular or recent intake of ototoxic drugs; and (5) History of primary neurologic, psychiatric or other medical disease.

The protocol of work was approved by the research ethics committee of Faculty of Medicine, Assiut University, Assiut, Egypt, No. AUFM_PED_232/2019. Informed written consent to participate in the study was obtained from children's parents or guardians.

Methods

Clinical evaluation: Detailed ear, nose and throat, physical and neurological data were gathered. Data included age at onset and duration of diabetes, family history of diabetes and insulin dose. They also included history of diabetic complications [whether due to the disease or its medications: *e.g.*, diabetic ketoacidosis (DKA), retinopathy, nephropathy, peripheral neuropathy, hypoglycemia, *etc.*], comorbid medical conditions (*e.g.*, other endocrinal disease, hypertension, hyperlipidemia, *etc.*) and hearing or vestibular symptoms. All underwent medical, neurological and ear, nose and throat examinations. The presence of peripheral neuropathy was diagnosed by clinical manifestations and abnormal nerve conduction velocity study in at least two nerves; one must have been the sural nerve.

Audiologic assessment: It included otoscopic ear examination; screening audiograms (250–4000 Hz), tympanometry (200 top–400 dapa) and acoustic (stapedius) reflex (Middle Ear Analyzer Interacoustics, Az26, Assens, Denmark). Speech discrimination thresholds were assessed by identifying the hearing level for understanding and repeating a set of 10 monosyllables. Typically, normal Speech Discrimination Score ranges from 90% to 100%.

Vestibular assessment: It was done by recording cVEMP response from each ear (GN Otometrics, Schaumburg, IL, United States). The stimulus was air-conducted tone burst at frequency of 500 Hz, intensity of 100 dBnHL and rate of 5.1/s. Responses to 200 stimuli were averaged and band-pass filtered between 30-300 Hz for each repetition. The child lay supine and was instructed to turn the head to contralateral side and look at a fixed target on the examination room's wall and right after towards a fixed point located above this target, to induce a vertical viewing angle of approximately 30° above the horizontal plane. The impedance values for the device were checked before each recording to be < 5 KOhms. Four surface electrodes were applied: (1) An active electrode, placed on the middle of ipsilateral SCM; (2) A reference

electrode, placed on ipsilateral mastoid; (3) A ground electrode, placed on the forehead; and (4) A forth electrode, placed on the contralateral mastoid. Data acquisition was accepted by the device if SCM electromyography (EMG) activity was 50-100 μV. Rectified EMGs from 20 milliseconds (ms) before to 80 ms afterwards were collected. To control for the individual differences of SCM contractions during recording, the raw amplitude of each recording was divided over the mean rectified EMG activities, which were recorded for 10 ms before the stimulus onset. VEMP parameters were: (1) Latencies of P1 (P13) and N1 (N23) waves; (2) P1-N1 peak-to-peak amplitude; and (3) Amplitude asymmetry ratio (AR), an inter-aural amplitude difference. AR suggests the side of pathology in unilateral lesions or the severely injured side in bilateral lesions. AR is calculated as follows: AR% = (AL - AR)/(AL + AR) × 100, where AL and AR are the amplitudes due to stimulation of the left and right ears. A clinically significant AR% is > 35%[15]. The absence of defined P1 and N1 waves indicate absent cVEMP response.

Statistical analysis

SPSS, version 22.0 (SPSS Inc., Armonk, NY, United States) was used for statistical analyses. Normality of data was checked by Kolmogorov–Smirnov test. Descriptive statistics were expressed as means ± SD or medians (25^{th}, 50^{th}, 75^{th} percentiles). Differences between groups were calculated by inference statistics (Chi-square with Fisher's exact tests or Mann-Whitney *U* test). Abnormal P1 or N1 latencies were considered if exceeded at least two standard deviations of the mean value for controls. Abnormal P1-N1 amplitude was considered if was less than the 5^{th} percentile of the mean value for controls. Correlations between cVEMP and subjects' variables were done using Spearman's correlation coefficient. The independent associations between vestibular and subjects' variables were determined using multiple logistic regression analysis by calculating the odds ratio (OR) and 95% confidence interval (95%CI). For 2-sided statistics, significant values were considered with probability value less than 0.05.

RESULTS

In this study, 130 ears were examined (patients = 80; controls = 50). Children with T1D had mean age of 13.63 ± 1.50 years and duration of illness of 5.62 ± 2.80 years. Frequent DKA and hypoglycemic attacks were found in 55% and 30%, respectively. The reported comorbid medical conditions and diabetic complications were hyperlipidemia (20%), hypertension (12.5%) and sensory peripheral neuropathy (40%). Manifestations of peripheral neuropathy were lower limbs' numbness, stoking hypoesthesia and reduced sensory unit potential's amplitudes of sural nerves without (axonal neuropathy) or with prolonged distal latencies or reduced nerve conduction velocities (demyelinating neuropathy) (Table 1). Both children with diabetes and healthy children had normal otoscopic ear examination, acoustic reflexes, pure tone audiogram and Speech Discrimination Scores (right ear: 96.32 ± 2.50; left ear = 93.44 ± 2.28) and type A tympanometry. Dizziness, not related to hypoglycemia, was reported in 10% (*n* = 6).

Compared to healthy children, patients had significant prolongation in cVEMP P1 and N1 latencies and reduction in P1-N1 amplitudes (Table 2). Bilateral cVEMP abnormalities were found in 25% (for latencies) and 60% (for amplitude), respectively. AR was found in 25%. No sex difference was found in cVEMP changes. Children with chronic diabetes with duration > 5 years had prolonged P1 and N1 ($P = 0.006$; $P = 0.01$) latencies and reduced P1-N1 amplitudes ($P = 0.001$) compared to those with short diabetes duration (≤ 5 years). Children with dizziness had prolonged P1 and N1 ($P = 0.02$; $P = 0.02$) latencies and reduced P1-N1 amplitudes ($P = 0.01$) compared to those without dizziness. Children with high hemoglobin A1c (HbA1c)% values (> 7%) had prolonged P1 and N1 ($P = 0.01$; $P = 0.01$) latencies and reduced P1-N1 amplitudes ($P = 0.001$) compared to those with HbA1c% values ≤ 7%. Children with history of DKA attacks had prolonged P1 and N1 ($P = 0.003$; $P = 0.001$) latencies and reduced P1-N1 amplitudes ($P = 0.01$) compared to those without. Children with hypoglycemic attacks had prolonged P1 and N1 ($P = 0.02$; $P = 0.03$) latencies and reduced P1-N1 amplitudes ($P = 0.03$) compared to those without. Children with peripheral neuropathy had prolonged P1 and N1 ($P = 0.001$; $P = 0.03$) latencies and reduced P1-N1 amplitudes ($P = 0.02$) compared to those without (Table 3). Significant correlations were identified between P1 with N1 latencies ($r = 0.335$, $P = 0.01$) but not between P1 with P1-N1

Table 1 The demographic, clinical and laboratory characteristics of the studied children

Demographic, clinical and laboratory characteristics	Patients (*n* = 40)	Controls (*n* = 25)	*P* value
Age, yr	10-18 (13.63 ± 1.50)	9-18 (15.44 ± 1.22)	0.438
Sex, *n* (%)			
Male	10 (25)	9 (36)	0.185
Female	30 (75)	16 (64)	0.223
BMI	15.70-25.30 (20.53 ± 2.52)	15.20-27.50 (18.86 ± 2.63)	0.278
Systolic blood pressure, mmHg	100-130 (110.80 ± 10.50)	100-120 (105.00 ± 8.50)	0.365
Diastolic blood pressure, mmHg	60-80 (70.55 ± 2.34)	60-70 (68.33 ± 5.20)	0.544
Age at onset of diabetes, yr	4–15 (8.54 ± 2.33)	-	-
Duration of diabetes, yr	3–10 (5.62 ± 2.80)	-	-
≤ 5	9 (22.5)		
> 5	31 (77.5)		
DKA, *n* (%)	22 (55)	-	-
Number of attacks	0–6 (3.44 ± 0.43)		
Hypoglycemia, *n* (%)	12 (30)	-	-
Number of attacks	0–6 (2.50 ± 0.32)		
Family history of diabetes, *n* (%)	18 (45)	3 (12)	0.01
Hb1Ac, *n* (%)	5.00–15.65 (8.68 ± 1.50)	3.00–6.00 (3.90 ± 0.25)	0.001
≤ 7%	4 (10)		
> 7%	36 (90)		
Insulin dose, IU/kg/d	0.80–2.10 (1.70 ± 0.32)	-	-
Lipid profile, mg/dL			
Total cholesterol	100-250 (180.20 ± 20.50)	90–200 (140.21 ± 15.65)	0.06
Triglycerides	60-280 (168.52 ± 22.50)	50–120 (80.50 ± 20.58)	0.001
LDL	50-160 (100.65 ± 10.62)	65–110 (85.43 ± 6.46)	0.08
HDL	45-65 (55.52 ± 5.33)	35–70 (48.33± 5.62)	0.364
Comorbid medical conditions, *n* (%)			
Hypertension	5 (12.5)	-	-
Hypercholesterolemia/dyslipidemia	8 (20)	-	-
Serum creatinine, mg/dL	0.54–1.20 (0.80 ± 0.15)	0.40–0.90 (0.62 ± 0.05)	0.450
Diabetic complications, *n* (%)			
Nephropathy	6 (15)	-	-
Peripheral neuropathy	16 (40)	-	-
Dizziness, *n* (%)	6 (10)	-	-

BMI: Body mass index; LDL: Low density lipoprotein; HDL: High density lipoprotein; Hb1Ac: Hemoglobin A1c; DKA: Diabetic ketoacidosis.

amplitudes (r = 0.230, P = 0.185). Multiple regression analysis showed that presence of prolonged P1 latencies and reduced P1-N1 amplitudes were significantly correlated with longer diabetes duration (> 5 years) [OR = 2.80 (95%CI: 1.80–5.33), P = 0.01; OR = 3.42 (95%CI: 2.82–6.81)] and higher HbA1c levels (> 7%) [OR = 3.05 (95%CI: 2.55–6.82), P = 0.01; OR = 4.20 (95%CI: 3.55–8.50), P = 0.001] but not with the presence of complications or comorbid medical conditions or dizziness.

Table 2 Cervical vestibular evoked myogenic potential results of the studied groups (mean ± SD)

Variables	Children with T1D (*n* = 40)	Controls (*n* = 25)	*P* value (P1)	*P* value (P2)
P1 latency, *n*[1] (%)				
Unilateral	6 (15)	-	-	-
Bilateral	10 (25)	-	-	-
Range, ms				
Right ear	18.00–22.00 (20.16 ± 1.34)	10.40–16.40 (12.03 ± 1.01)	0.03	0.542
Left ear	13.00–29.00 (20.40 ± 1.10)	10.40–17.60 (14.25 ± 1.68)	0.02	
N1 latency, *n*[1] (%)				
Unilateral	6 (15)	-	-	-
Bilateral	10 (25)	-	-	-
Range, ms				
Right ear	22.00–33.00 (28.30 ± 2.66)	18.65–26.70 (22.43 ± 1.82)	0.04	0.364
Left ear	24.00–36.80 (32.35 ± 2.84)	16.82–30.82 (26.45 ± 1.02)	0.03	
P1-N1 amplitude, *n*[1] (%)				
Unilateral	10 (25)	-	-	-
Bilateral	24 (60)	-	-	-
Range, μV				
Right ear				
Range	20.00–90.00	48.60–92.80	0.001	0.458
Median	44.20	72.43		
25th	36.00	60.35		
50th	40.45	76.44		
75th	48.55	86.62		
Left ear				
Range	26.68–86.00	46.03–98.00	0.001	
Median	46.20	74.68		
25th	33.25	54.36		
50th	45.00	80.00		
75th	56.25	88.56		
AR				
Range	1.12–66.20	0.0-15.8	0.001	
Median	18.30	4.88		
25th	6.58	1.88		
50th	13.36	2.90		
75th	32.44	6.30		
n[1] (%)	10 (25)	0		

[1]Number of subjects with vestibular evoked myogenic potential abnormalities results.

P1: Significance for patients *vs* controls; P2: Significance for patients' right *vs* left ear; AR: Asymmetry ratio; T1D: Type 1 diabetes.

DISCUSSION

Developments in research have shown that vestipulopathies are common complications of DM[7-9]. The results of this study showed that: (1) The majority (75%) of children with T1D had asymptomatic vestibular dysfunctions. Few had dizziness

Table 3 Cervical vestibular evoked myogenic potential's results for children with type 1 diabetes in relation to their demographic, clinical and laboratory variables

Variables	P1	N1	P1-N1 amplitude	AR
Sex				
Male (*n* = 10)	22.35 ± 1.12	26.32 ± 2.30	44.82	10.33
P1	0.02	0.320	0.01	0.01
Female (*n* = 30)	18.22 ± 1.63	32.55 ± 1.22	38.36	16.85
P1	0.04	0.01	0.001	0.001
P2	0.125	0.01	0.06	0.126
Duration of diabetes, yr				
≤ 5 yr (*n* = 9)	16.68 ± 1.23	22.65 ± 2.22	38.30	6.50
P1	0.02	0.244	0.03	0.05
> 5 yr (*n* = 31)	28.33 ± 1.11	35.07 ± 2.31	56.26	18.68
P1	0.01	0.01	0.001	0.0001
P2	0.006	0.01	0.001	0.452
Dizziness				
Yes (*n* = 6)	26.03 ± 1.33	34.68 ± 2.57	38.64	10.64
P1	0.002	0.01	0.001	0.01
No (*n* = 32)	16.23 ± 1.28	28.05 ± 2.28	56.00	16.28
P1	0.138	0.302	0.001	0.001
P2	0.02	0.03	0.01	0.06
Hb1Ac, %				
≤ 7 (*n* = 4)	16.83 ± 1.30	22.01 ± 1.20	60.00	8.64
P1	0.306	0.358	0.08	0.023
> 7 (*n* = 36)	25.633 ± 1.28	34.55 ± 1.33	32.50	18.28
P1	0.04	0.01	0.001	0.804
P2	0.01	0.01	0.001	0.246
DKA				
Yes (*n* = 22)	27.23 ± 1.20	34.25 ± 1.88	38.50	16.35
P1	0.01	0.01	0.001	0.001
No (*n* = 18)	14.84 ± 1.11	21.15 ± 1.23	55.84	8.00
P1	0.358	0.682	0.01	0.04
P2	0.003	0.001	0.01	0.323
Hypoglycemia	26.86 ± 1.80	34.22 ± 2.02	30.40	12.86
Yes (*n* = 12)				
P1	0.01	0.01	0.001	0.01
No (*n* = 28)	16.50 ± 1.44	25.24 ± 2.562	54.68	10.35
P1	0.05	0.05	0.01	0.01
P2	0.02	0.03	0.03	0.286
Peripheral neuropathy				
Yes (*n* = 16)	23.28 ± 1.30	32.26 ± 1.45	35.06	16.60
P1	0.001	0.01	0.001	0.01
No (*n* = 24)	16.44 ± 1.03	24.24 ± 1.40	52.66	13.44

P1	0.458	0.542	0.01	0.01
P2	0.02	0.03	0.02	0.322
Control subjects	13.22 ± 1.30	23.82 ± 1.37	74.68	4.88

DKA: Diabetic ketoacidosis; P1: Significance *vs* controls; P2: Significance for a *vs* b for each variable.

(10%); (2) Bilateral vestibular dysfunction was more frequent than unilateral (25%-60% *vs* 10%-25%); and (3) Chronicity and severity of diabetes are the predictors for its related vestipulopathies.

The authors in this study found reduced P1-N1 amplitudes in 85% of children with T1D, and 40% had prolonged P1 and N1 latencies. Previous studies reported similar findings. Kamali *et al*[7] found prolonged P13 and N23 latencies ($P < 0.05$) but normal absolute and relative P1-N1 amplitudes of cVEMP in patients with T1D ($n = 10$) with an age range from 15 to 40 years compared to matched healthy subjects ($n = 24$). Their patients did not have diabetic neuropathy. Konukseven *et al*[8] found prolonged oVEMP and cVEMP latencies in patients with diabetes ($n = 30$) compared to prediabetes ($n = 30$) and healthy controls ($n = 31$). They did not find differences in VEMP amplitudes among the three groups. Kalkan *et al*[9] found reduced cVEMP and oVEMP amplitudes in patients with diabetes whether they had ($n = 33$) or did not ($n = 33$) have polyneuropathy compared to healthy controls ($n = 35$). The authors found no differences in vHIT values among the three groups.

Research studies have suggested the localization of injury within the vestibular organs and their pathways based on cVEMP abnormal findings. They suggested that reduced P1-N1 amplitude is due to labyrinthine pathology, while prolonged P1 and N1 latencies are due to retrolabyrinthine pathology[16]. Murofushi *et al*[16] observed prolonged P13 of cVEMP (*i.e.* slow conduction) with multiple sclerosis and large acoustic neuroma, suggesting brainstem pathology secondary to demyelination in the vestibulo-spinal tract.

We reported dizziness in few patients (10%, $n = 6$). They had unilateral prolonged P1 and N1 latencies and reduced P1-N1 amplitudes. In accordance, Biurrun *et al*[3] did not report dizziness or imbalance with diabetes. Gawron *et al*[4] reported dizziness and imbalance in only 6.3%. It has been observed that vestibular manifestations occur with unilateral lesion or asymmetrical bilateral lesions[3-9]. Diabetes is a metabolic systemic disease. The symmetrical bilateral inner ear dysfunction is the most acceptable explanation for the lack of vestibular symptoms with bilateral compared to unilateral lesions[3,4].

We observed differences in VEMP changes in relation to diabetes duration (*i.e.* > 5 years *vs* ≤ 5 years), severity of diabetes (*i.e.* HbA1c > 7% *vs* ≤ 7%), presence of absence of complications (*i.e.* DKA, hypoglycemia, peripheral neuropathy, *etc.*) and clinical symptoms (*i.e.* dizziness). However, the results of regression analysis showed that the only predictors for vestibular dysfunctions were chronic and severe diabetes. In accordance, Bektas *et al*[6] found no significant difference in cVEMP results between patients with T2D [with ($n = 25$) or without ($n = 25$) peripheral neuropathy] and healthy controls ($n = 21$). Kamali *et al*[7] found prolonged cVEMP latency with T1D and had polyneuropathy, an indication of disease severity.

DM is chronic metabolic disease and a common vascular risk factor. Chronic hyperglycemia causes (1) Tissue injury by advanced glycation end products and oxidative stress factors. Also, the toxic injury to connective tissue results in thickening of the vascular walls and macro- and micro-angiopathies[17,18] and demyelination of the nerves[17]. Kocdor *et al*[18] found selective reduction in type I vestibular hair cells (sensory epithelia) with diabetes. Myers *et al*[17] found large disrupted portions of myelin sheath lamellae of the vestibular and auditory nerves in induced diabetic rats. They also found thinning of the myelin sheath and smaller axonal fibers' diameters, indicating oxidative stress injury; and (2) Alterations of inner ear fluid metabolism. Some suggested that the homeostasis of vestibular structures is very sensitive and rapidly injured by diabetic metabolic disturbance[19].

The strength of the study is the direct evaluation of the function of the saccule and its connections in children with T1D. However, this study has limitations: (1) Small sample size, however, this is an exploratory study done on nationally understudied population; and (2) The cross-sectional study design. Further longitudinal large sample size studies from children with T1D are required to determine the temporal relationship between the development of clinical and objective vestibular and/or auditory manifestations.

CONCLUSION

The results of the study provide evidence for the frequent injury of the saccula of the inner ear and its central pathway with T1D. Predictors for vestibular dysfunction are chronic and severe diabetes. As vestibulopathy is a common comorbid cause of impaired gaze and postural stabilities with diabetes, glycemic control is important to prevent vestibular diabetic complications.

ARTICLE HIGHLIGHTS

Research background

Integrity of vestibular organs and their reflexes is critical for maintaining balance in static condition and during motion and gaze stabilization. In healthy individuals, the brain organizes and integrates information from vision, proprioception and vestibular system. Diabetes is a common chronic metabolic/systemic disease. It causes complications in every organ of the body, especially the eyes, kidney, nerves, heart and blood vessels. Experimental and clinical studies provide evidence that peripheral and/or central auditory and/or vestibular systems' dysfunctions are common complications of diabetes. The mechanism of diabetic vestipulopathy is complex and still has to be explored. It may be related to diabetic complications or its comorbid conditions. It may also be due to alteration of inner ears homeostasis due to diabetic metabolic alterations associated with poor glycemic control.

Research motivation

Vestibulopathy is a known complication in adults with diabetes. The research hotspots include (1) Identification of the spectrum of vestibular and auditory manifestations due to diabetes mellitus and their predictors; (2) Understanding the temporal relation between the onset of diabetes and the development of auditory or vestibular manifestations; and (3) Determining whether diabetes itself and/or its comorbid medical conditions are causes of auditory and vestibular complications.

Research objectives

In children, this is the first study that systematically estimated the prevalence and predictors of vestibular injury or dysfunction with type 1 diabetes.

Research methods

Cervical vestibular evoked myogenic potential (cVEMP) type of VEMP testing was used for assessment of the saccular function of the otolith organ and its pathways.

Research results

Bilateral changes in cVEMP abnormalities are more frequent than unilateral. They are associated with chronic and severe diabetes.

Research conclusions

Injury of the saccule of the inner ear and its central connection occurs with type 1 diabetes.

Research perspectives

Multidisciplinary team is required to follow up regularly children with diabetes for prevention and early identification and treatment of associated complications. The treating endocrinologists have to optimize management of diabetes and its associated comorbidities and complications.

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 January 9; 11(1): 71-84

DOI: 10.5409/wjcp.v11.i1.71

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Case Control Study

Tissue Doppler, speckling tracking and four-dimensional echocardiographic assessment of right ventricular function in children with dilated cardiomyopathy

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Author contributions: Elrazaky O, Srour E, and Shabana AH did the echocardiographic studies and collected the data; Mawlana W and Al-Biltagi M analyzed the data and wrote the manuscript; all the authors revised and agreed to the final version of the manuscript.

Institutional review board statement: We performed the study according to the latest version of Helsinki's Declaration. The Institutional Ethical and Research Review Board of Faculty of Medicine, Tanta University, approved the study.

Informed consent statement: All parents, guardians, or next of kin signed informed consent for the minors to participate in this study.

Conflict-of-interest statement: The authors declare no conflict of interest for this article.

Data sharing statement: Data are available upon reasonable request.

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Abstract

BACKGROUND

Right ventricular (RV) function is frequently overlooked during dilated cardiomyopathy (DCM) evaluation.

AIM

To evaluate RV function in children with idiopathic DCM using relatively recent echocardiographic modalities.

METHODS

We prospectively studied the cardiac function in 50 children with idiopathic DCM and 50 healthy children as a control group, using four-dimensional echocardiography (4-DE), Tissue Doppler Imaging (TDI), and two-dimensional-speckles tracking echocardiography (2-D-STE). RV EF was measured by 4-DE.

RESULTS

The auto left (LV) ejection fractions (EF) measured by 2-D-STE were significantly lower in the patients' group than in the control. The sphericity index was also significantly lower in children with DCM than in the control. RV EF measured by 4-DE was significantly lower in the patient's group than the control. RV S wave, e´/a' ratio, myocardial performance index (MPI), and tricuspid annular plane systolic excursion (TAPSE) were significantly impaired in children with DCM than in control. Both LV and RV global longitudinal strains (GLS) were significantly reduced in children with DCM than in control. RVGLS was significantly associated with the duration since diagnosis, tricuspid annulus S wave, RV MPI,

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: Egypt

Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: June 4, 2021
Peer-review started: June 4, 2021
First decision: October 17, 2021
Revised: October 21, 2021
Accepted: December 22, 2021
Article in press: December 22, 2021
Published online: January 9, 2022

P-Reviewer: Zhang DM
S-Editor: Wu YXJ
L-Editor: A
P-Editor: Wu YXJ

and TAPSE, but not with the age of the patients, RV EF, or e´/a' ratio.

CONCLUSION
There was impairment of the RV LGS and other systolic and diastolic parameters in children with DCM. STE and TDI can help to detect the early decline of RV function.

Key Words: Tissue Doppler; Speckling tracking Echocardiography; Dilated cardiomyopathy; Children; Right ventricle

Core Tip: Cardiomyopathies are a group of cardiac muscle disorders characterized by mechanical and/or electrical impairment that give rise to dilated, hypertrophic or restrictive pathophysiology. In the current study, we prospectively studied the cardiac function in 50 children with idiopathic dilated cardiomyopathy (DCM) and 50 healthy children as a control group using Tissue Doppler Imaging (TDI) and two-dimensional-speckles tracking echocardiography. Right ventricular (RV) ejection fractions was measured by four-dimensional echocardiography. We found impairment of the RV LGS and other systolic and diastolic parameters in children with DCM. Speckles tracking echocardiography and TDI can help to detect the early decline of RV function.

Citation: Al-Biltagi M, Elrazaky O, Mawlana W, Srour E, Shabana AH. Tissue Doppler, speckling tracking and four-dimensional echocardiographic assessment of right ventricular function in children with dilated cardiomyopathy. *World J Clin Pediatr* 2022; 11(1): 71-84
URL: https://www.wjgnet.com/2219-2808/full/v11/i1/71.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i1.71

INTRODUCTION

Cardiomyopathies are a group of cardiac muscle disorders characterized by mechanical and/or electrical impairment that give rise to dilated, hypertrophic or restrictive pathophysiology. Dilated cardiomyopathy (DCM) is a clinical condition associated with left ventricular (LV) or biventricular dilation with an impaired contraction that is not related/caused by abnormal loading conditions (such as hypertension or valvular heart disease) or ischemic changes due to coronary artery disease[1]. It is the most common form of cardiomyopathy and accounts for approximately 55%-60% of all childhood cardiomyopathies, with an average prevalence rate of 1/200000 children. It could be idiopathic or secondary to other causes such as infections (primarily viral), exposure to drugs, toxins, or allergens, metabolic, endocrine, autoimmune, or other systemic diseases. It is commonly diagnosed in younger children with an average age at diagnosis of 2 years[2].

Clinical presentation of DCM mainly relates to the degree of LV or biventricular systolic dysfunction leading to pump failure. Heart failure signs and symptoms may be fulminant, acute, subacute, or chronic[1]. DCM diagnosis is primarily based on echocardiography that can readily identify the dilated chambers and the impaired function of left or both ventricles using M-mode, 2-dimensional echocardiography[3]. Tissue Doppler imaging (TDI) is a relatively new echocardiographic technique, useful to study the myocardial function of children with different pathologies[4]. Two-dimensional speckle tracking imaging is another relatively new echocardiographic modality that can provide non-Doppler, less angle-dependent, and objective quantification of myocardial deformation and left/right ventricular (LV/RV) systolic and diastolic dynamics by analyzing the motion of speckles identified on routine 2-dimensional sonograms. In addition, by tracking the displacement of the speckles during the cardiac cycle, strain and the strain rate can be rapidly measured offline after good image acquisition[5].

Most of the studies concerned with the diagnosis of dilated cardiomyopathies in children focus on LV function. As the disease usually starts in LV then RV, early detection of RV dysfunction could have a prognostic benefit. Unfortunately, few

studies examined RV function[6-9]. So, this work aimed to evaluate the RV function and structure using tissue Doppler and speckling tracking echocardiography in children with primary dilated cardiomyopathy and correlate with other echocardiographic findings.

MATERIALS AND METHODS

The research was a prospective cross-section study between April 2018 to June 2019. It involved 50 children with primary idiopathic dilated cardiomyopathy; aged between six months and eight years, selected in the order in which they were identified, with regular attendance to Pediatric Cardiology Unit in a Tertiary Care University Hospital. It also included o 50 healthy children of matching age and sex, coming for routine health check-up without any systemic disease that could affect the heart (control group). All parents, guardians, or next of kin signed informed consent for the minors to participate in this study. The Institutional Ethical and Research Review Board of Faculty of Medicine, Tanta University, approved the study.

The diagnosis of DCM based on the detection of dilatation of ventricles (LV) dilatation > 112% corrected to body surface area (BSA), age, and sex, or two standard deviations (SD) from the normal upper limit corrected to age, sex, and BSA plus (5%) and presence of systolic dysfunction [fractional shortening (FS) < 25% and/or left ventricle ejection fraction (LV EF) < 45%] detected in m-mode and 2-D echocardiography following the recommendation of the 2006 American Heart Association and 2017 British Society of Echocardiography[10]. Exclusion criteria included children with congenital or acquired heart diseases and children with dilated cardiomyopathy secondary to systemic diseases such as infections (ruled out by the history and laboratory tests for the previous infection with the common viral and bacterial causes), arrhythmias, endocrine diseases, neuromuscular diseases, rheumatologic and immunological diseases, nutritional deficiencies, conditions leading to ischemia, drug or toxins-induced, and systemic diseases.

All children had complete history taking (including personal, birth, developmental, feeding, and family history) and comprehensive clinical examination (including general, regional, and systemic examination). Cardiac examination aimed to detect cardiomegaly and evidence of the presence of a cardiac murmur. In addition, all children had echocardiographic examinations, including 2-D, M-mode, TDI, and 2D-speckles tracking echocardiography (STE).

Echocardiography

Echocardiography was done using (Vingmed Vivid-7, General Electric Vingmed, and Milwaukee, Wisconsin, United States). The examination was performed using an S7 probe and V3 matrix real-time 3-dimensional probes at a depth of 16 cm in all the standard echocardiographic views following the American Society of Echocardiography recommendation[11]. All children were examined in the right anterior oblique position, when possible, while breathing room air or on oxygen supplement when required. Cardiovascular anomalies were carefully searched for and excluded by all standard views. LV EF, LV FS, end-diastolic and end-systolic volumes, systolic pulmonary artery pressure by using tricuspid regurgitation jet, and LV and RV diastolic function were measured according to the guidelines of the American Society of Echocardiography[12]. Tricuspid annular plane systolic excursion (TAPSE) was measured by 2-D echocardiography-guided M-mode from the apical 4-chamber view, with the cursor was placed at the free wall side of the tricuspid annulus. Care was taken to align the sample volume as vertically as possible concerning the cardiac apex. Maximal TAPSE was determined by the total excursion of the tricuspid annulus from its highest position after atrial ascent to the lowest point of descent during ventricular systole. The sphericity index (SI) was measured by calculating the ratio between the length (mitral annulus to apex in the apical view) and diameter (mid-cavity level in the short-axis view) of the LV. The smaller the SI is, the more globular the ventricle will be. It also predicts the functional capacity of patients with LV dysfunction[13]. Simultaneous ECG tracings obtained during M-mode recording were used to measure R-R intervals. Measurements were repeated on three occasions, and the average was obtained[14].

All children had three-dimensional (3-D)-echocardiography immediately after the 2-D-echocardiographic examination, using the same ultrasound machine equipped with a 4V probe. RV 3-D images were obtained in a full-volume dataset from the apical 4-chamber view, optimized for analysis of RV function. All the measurements of RV

volumes and EF were made offline, using dedicated software. The semi-automatic analysis was performed using a manual tracing of the endocardial borders in end-systolic and end-diastolic frames in the sagittal, four-chamber, and coronal views. Besides, end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume, and EF were calculated using the software (Figure 1).

TDI

We used the same machine and probe to perform TDI at a depth of 16 cm in the parasternal and apical views (standard long axis and two- and four-chamber images). The baseline was adjusted to a low-velocity range (-20-20 cm/s) while using the pulsed-wave angle-corrected colour-coded TDI filters. The Doppler frame rates were varied between 80 and 115 frames/s depending on the sector width of the range of interest. We settled the setting to the minimal gain to reduce the background noise and get the highest quality images. The 2-millimeters sample volume was placed within the myocardium equidistant from the endocardial and epicardial borders.

The pulsed-wave TDI recorded the myocardial velocity curves of the septal mitral valve annulus, lateral mitral valve annulus, and lateral tricuspid valve annulus from the apical four-chamber planes. The timing of cardiac cycle events and their relations to respiratory events were defined by simultaneously tracing the electrocardiogram and respiration curve monitoring. The beginning of the QRS complex was the reference point. At least ten cardiac cycles were recorded at a speed of 100 mm/s. The images were stored electronically.

The systolic and diastolic mitral and tricuspid annulus velocities were determined by placing the PW-TDI sample volume at the level of the septal tricuspid annulus. In the spectral TDI display, the antegrade systolic wave S reflected the systolic function of either RV or LV, e´ retrograde wave reflected the early passive ventricular filling, while the retrograde a´ wave represented the atrial contraction. The early/atrial (e´/a´) ratio of tricuspid or mitral valve annulus reflected the diastolic function of the RV or LV (Figure 2). The isometric contraction time (ICT) (was defined as the time duration between the end of a´ wave to the beginning of S wave by TDI), the isometric relaxation time (IRT) (was defined as the interval between the end of S wave and the beginning of the early wave), and myocardial contraction time (CT) were measured by TDI[15]. Myocardial Performance or Tei index is a Doppler-derived time interval index that combines systolic and diastolic cardiac performance. It was calculated as previously described by Tei and colleagues, using the following formula: ICT + IRT/CT. Both ICT and IRT were corrected for heart rate[16-17]. We used the mean values for three heartbeats during expiration for the analysis, and all the measurements obtained by TDI were indexed for children's body surface area.

Speckle tracking technique (RV longitudinal systolic strain and function analysis)

We used a 3.5-MHz transducer at a depth of 16 cm in the standard apical 4-chamber view (4-chamber image) to acquire an adequate image with novel speckle-tracking software (Figure 3). To prevent foreshortening, we visualized the apex of the left ventricle adequately. Then, 2-D speckle tracking strain imaging was used to study LV and RV deformation on standard grayscale images (frame rate, 55 ± 11 frames/s). It tracked the characteristic pattern of natural acoustic markers in the myocardial wall ("speckles") from frame to frame throughout the cardiac cycle. Two-D longitudinal strain for all RV myocardial segments includes three segments from the lateral (anterior) wall (basal, mid, and apical) and three corresponding segments of the interventricular septum (because of the significant contribution of the interventricular septum to RV ejection). The myocardial strain was then calculated by the change in position of the speckle pattern to the initial position. Peak systolic longitudinal strain was calculated by averaging the peak systolic values of the six segments. Regional lengthening of myocardial strain was expressed as a positive value and thinning or shortening as a negative value[18].

4D RV EF

We obtained RV 4D images in a full-volume dataset from the apical four-chamber view, optimized for analysis of RV function. In addition, we obtained multi-beat (3-6 beats) data on the multislice (short axis) visualization mode to ensure the full inclusion of the right ventricle in the dataset. We obtained all RV volumes and EF measurements offline, using dedicated software (Echo PAC PC, 113; GE, Horten, Norway). We conducted a semi-automated analysis, with a manual tracing of endocardial borders in end-systolic and end-diastolic frames in the sagittal, four-chamber, and coronal views, from the full-volume dataset. In addition, we calculated EDV, ESV, stroke volume, and

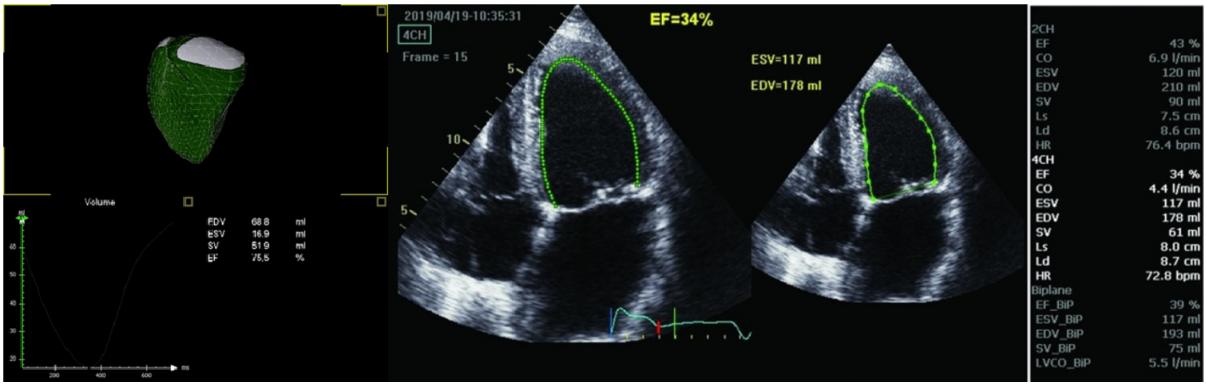

Figure 1 Three-dimensional echocardiographic reconstruction of the delineation of right ventricular ejection fraction. The endocardial border is traced throughout the cardiac cycle using speckle tracking, and the software automatically locates end-systolic and end-diastolic frames. Example of a four-dimensional echocardiographic reconstruction of the delineation of the right ventricle seen from the septal side (end-diastolic volume 68.8 mL, end-systolic volume 16.9 mL, and ejection fraction 75.5%). The mesh is the right ventricle at end-diastole, in green at end-systole. The pulmonary valve is shown in white on the upper left side, the tricuspid valve is shown on the upper right side, and the right ventricular apex toward the bottom.

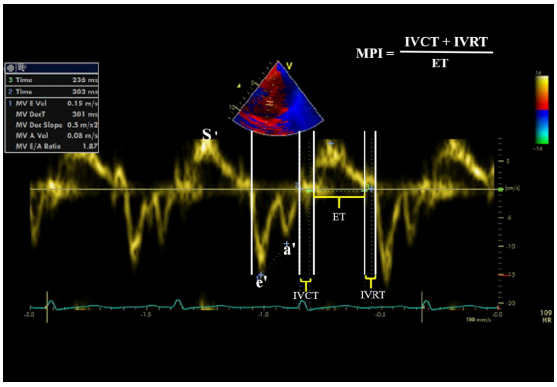

Figure 2 Tissue Doppler echocardiography of septal annulus showed the main tissue waves (S, e´ and a´ waves) and how to calculate Myocardial Performance Index. e´ and a´ Early and late filling waves by tissue Doppler; S wave: Myocardial systolic excursion velocity. IVCT: Isovolumic contraction time; IVRT: Isovolumic relaxation time; MPI: Myocardial Performance Index; ET: Ejection time.

EF using the software (Figure 1)[19].

Reproducibility

Intra-observer variability for echocardiographic data was done for patients and controls, where the same sonographer repeated examinations twice on the same day of diagnosis. Intra-observer agreement in interpreting echocardiographic data was determined using Cohen kappa (κ) statistics.

Statistical analysis

We used Power and Precision V3 program to estimate the power level of the primary endpoint (e´/a´ ratio with a level of 1.2 ± 0.25) (http://www.Power-Analysis.com). It was more than 90% when using 50 patients for each group. We did the statistical analysis using SPSS version 22. We presented the data as mean ± SD and percentages as indicated. We checked the data for normal distribution (about 72% of the results were within one SD from the mean values, and about 96% were within two SD from the mean values). Categorical variables were evaluated using student *t*-test, Chi-square, and *F*-test (ANOVA). The Pearson correlation coefficient examined the correlation of different parameters. P value < 0.05 was considered statistically significant.

RESULTS

Figure 4 shows the flow chart of the study, which enrolled 50 children with idiopathic

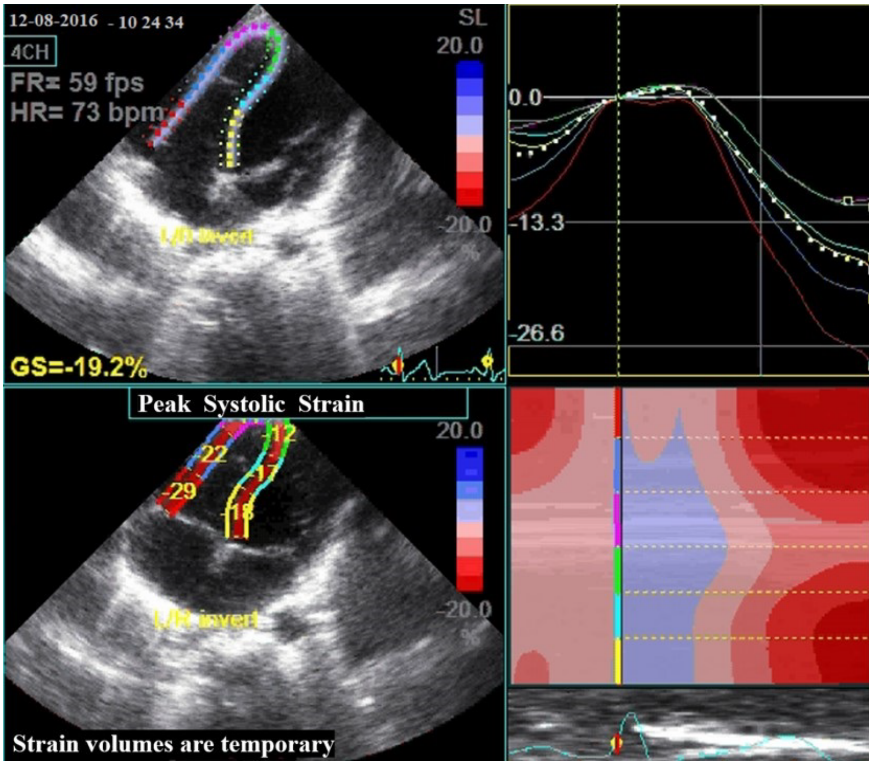

Figure 3 Right ventricular global longitudinal strain measures of a healthy child from the standard four-apical views using two-Dimension speckle tracking method. The upper left quadrant shows tracking. The right half shows color-coded segmental strain curves and average strain curve (dashed line). The lower left quadrant depicts an anatomic M-mode. The dashed yellow line = Time to peak (from R-wave to maximum systolic strain.

Figure 4 The flow chart of the study. DCM: During dilated cardiomyopathy.

DCM and 50 clinically healthy children as a control group in the current study. Table 1 shows the demographics and the clinical data of the studied groups with no significant differences between the two groups regarding age and gender. However, DCM was more prevalent in males than in females (1.8:1). There was also more history of consanguinity and a more positive family history of DCM among children with DCM than in the control group. The table also showed that the patients' group had significantly lower body weight, height, BMI, systolic and diastolic BP, and higher heart rate than the control group. About 58% of the DCM group showed systolic dysfunction when using RV EF measured by 4D echocardiography. The percentage of RV systolic dysfunction increased to 70% when using TAPSE. RV diastolic dysfunction by low RV e´/a´ ratio using tissue Doppler.

Table 2, Figures 5 and 6, show the echocardiographic parameters in both groups. The auto left ventricle ejection fraction measured by STE was significantly lower in the patients' group than in the control. At the same time, the LV SI, which measures the ratio of the LV long axis to the short axis, was significantly lower in the children with

Table 1 Demographic and clinical data of children with during dilated cardiomyopathies and control group

Variables (mean ± SD)	Children with DCM (*n* = 50)	Controls (*n* = 50)	*t*	*P* value
Age	4.9 ± 2.3	5.56 ± 2.4	0.18	> 0.05
Sex				
Male	32 (64.0%)	31 (62%)	ZS: 0.2	> 0.05
Female	18 (36.0%)	19 (38%)	ZS: 0.2	> 0.05
Consanguinity	23 (46%)	5 (10%)	-4	0.0001[1]
Family history of DCM, *n* (%)	4 (8)	0		
Weight	16.92 ± 5.95	20.60 ± 5.97	3	0.002[1]
Length (cm)	98 ± 4.8	105 ± 4.4	7.6	0.0001[1]
BMI	17.6 ± 2.1	18.7 ± 2.5	2.4	0.02[1]
Heart rate	105 ± 12	91 ± 7	7.1	0.0001[1]
Systolic BP	86 ± 8	98 ± 7	8	0/0001[1]
Diastolic BP	63 ± 4	68 ± 5	5.5	0.0001[1]

[1]Significant ($P < 0.05$).

BMI: Body mass index; BP: Blood pressure; ZS: Z-score; DCM: During dilated cardiomyopathy; SD: Standard deviation.

DCM than in control ($P < 0.0001$). The tissue-Doppler derived mitral annulus S wave (which indicates LV systolic function), and e´/a´ ratio (which indicates LV diastolic function) were significantly lower in the patients' group than in control ($P < 0.0001$). It also showed that LV myocardial performance index (MPI) (which reflects the global systolic and diastolic ventricular function) was more prolonged in the patients' group than in the control ($P < 0.0001$). The speckle tracking echocardiography showed that the LV global longitudinal strains (GLS) was more significantly impaired in the patients' group than in the control group ($P < 0.0001$). The table also showed RV echocardiographic parameters in both groups. TAPSE was significantly reduced in children with DCM than in the control. The auto RV EF measured by 4DE and the tissue Doppler-derived S wave and e´/a´ ratio were significantly lower, while RV MPI was more prolonged, and the systolic pulmonary pressure was significantly higher in the children with DCM than in control group. At the same time, the values of RV GLS, RV apical, mid, and basal strains were significantly lower in children with DMC than in the control group.

Table 3 shows the linear regression analysis of RV GLS with some clinical and echocardiographic parameters among the studied children with dilated cardiomyopathy. It was significantly associated with the duration since diagnosis, tricuspid annulus S wave, RV MPI, and TAPSE; while it did not show significant association with age or weight of the patients; RV e´/a´ ratio; or RV EF.

DISCUSSION

Primary DCM is the presence of left or biventricular dilatation with severely impaired systolic function despite the absence of abnormal loading conditions. It is present in approximately 30%-40% of the cases. The pathological involvement is predominantly limited to the myocardium and is associated with a strong genetic inheritance in idiopathic cases[20]. It usually involves LV with some dysfunction of RV with a common clinical presentation of congestive cardiac failure. Recent studies showed the importance of RV dysfunction as a significant prognostic predictor of cardiac mortality [21]. Unfortunately, few studies are concerned with RV function in children with idiopathic DCM.

Assessment of cardiac size and function using various echocardiographic modes is an integral part of evaluating the child's status. Using 4-D echocardiography allows us to have an external view of the heart with multiple internal perspectives[22]. As cardiac dilation precedes dysfunction in many cases of dilated cardiomyopathy, precise assessment of chamber dimensions, indexed according to body surface area, is essential for early diagnosis and the long-term follow-up of DCM[23]. Therefore, a

Table 2 Echocardiographic data of children with dilated cardiomyopathies and control group

Variables (mean ± SD)	Children with DCM (*n* = 50)	Controls (*n* = 50)	*t*	*P* value
LV echocardiographic parameters				
Auto LV EF (speckle tracking)	43.4 ± 11.7	65.2 ± 7.6	11	0.0001[1]
Sphericity index	1.2 ± 0.35	1.6 ± 0.3	6.2	0.0001[1]
Presence of mitral regurgitation, *n* (%)	43 (86)	1 (2)	ZS: 6.6	0.0001[1]
Mitral annulus systolic velocity (cm/sec)	3.7 ± 1.1	6.933 ± 0.785	16.9	0.0001[1]
Mitral annulus e´/a´ ratio	1.15 ± 0.4	1.540 ± 0.246	5.8	0.0001[1]
LV IVRT	75.0 ± 18.3	64.0 ± 7.2	4	0.0001[1]
LV MPI	1.9± 0.3	0.4 ± 0.08	423	0.0001[1]
LV GLS	-12.7 ± 4.9	-24.4 ± 1.6	16	0.0001[1]
RV echocardiographic parameters				
4D RV EF	32.2 ± 10.5	46.2 ± 10.7	8.7	0.0001[1]
Tricuspid annulus S wave (cm/sec)	4.42 ± 0.82	6.9 ± 0.8	15	0.0001[1]
Tricuspid annulus e´/a´ ratio	1.17 ± 0.25	1.52 ± 0.3	6.34	0.0001[1]
RV MPI	0.86 ± 0.16	0.40 ± 0.08	18.2	0.0001[1]
Mean pulmonary pressure (mmHg)	28.5 ± 6	21 ± 4	7.4	0.0001[1]
TAPSE (mm)	12.00 ± 3.56	19.30 ± 2.5	12.5	0.0001[1]
RV GLS	-10.34 ± 4.6	-24.30 ± 2.9	18.5	0.0001[1]
RV apical strain	-13.3 ± 4.3	-26.70 ± 1.3	21	0.0001[1]
RV mid strain	-12.4 ± 3.9	-23.20 ± 1.7	17.9	0.0001[1]
RV basal strain	-13.7 ± 4.8	-25.30 ± 1.5	16.3	0.0001[1]

[1]Significant ($P < 0.05$).

EF: Ejection fraction; LVGLS: Left ventricular global longitudinal systolic strain; IVRT: Isovolumic relaxation time; LV: Left ventricle; MPI: Myocardial Performance Index; RV GLS: Right ventricular global longitudinal systolic strain; TAPSE: Tricuspid annular plane systolic excursion, RV: Right ventricle; ZS: Z-score.

comprehensive echocardiographic examination is indicated in cases with DCM, not only to assess LV size and function, but also to establish the diagnosis, identify the phenotype of DCM and the associated cardiac abnormalities such as valve disease, highlight the features requiring specific therapeutic management, and identify high-risk features associated with an adverse prognosis, including RV dysfunction[11].

Due to the complex three-dimensional geometry of RV wall motion (which affects the evaluation accuracy of the local dynamics derived indices), there is a need to quantify these factors accurately, which becomes possible by using 4-D echocardiography. The relatively newly developed real time 4-D echocardiography has the potential to circumvent the limitations induced by the RV complex anatomy as it does not rely on 2-D views[24]. In the current study, we assessed LV and RV functions using recent echocardiographic modalities (tissue Doppler, speckle tracking, and real-time 4-D echocardiography) in children with dilated cardiomyopathy. We found a marked reduction of LV systolic ejection fraction (EF) measured by real-time 3-Dimensional echocardiography compared to the control. Similar findings were reported by Gentile *et al*[25] which support that EF is an easy and sensitive tool for evaluating LV systolic function.

Tissue Doppler-derived mitral annulus systolic velocity (S wave) was significantly lower in our patients' group than the control, matched with previous studies confirming usefulness for measuring the S as a tool for assessing systolic function. There was also a significant reduction of the mean value of LV (e´/a´ ratio) in our cases with DCM compared to control, clarifying the effect of LV systolic impairment on LV diastolic function[26,27]. These data confirm the presence of diastolic dysfunction in patients with dilated cardiomyopathy and impaired LV filling, which may even precede the presence of systolic dysfunction. These findings agreed with

Table 3 Multiple linear regression showing clinical and echocardiographic parameters that were independently associated with the longitudinal strain of the right ventricle among the studied children with dilated cardiomyopathy (*n* = 50)

Variables	RV LGS (%) among children with dilated cardiomyopathy (*n* = 50)	
	β standardized coefficients	*P* value
Age (yr)	-0.274	0.057
Duration since diagnosis	0.578	0.001[1]
Weight (kg)	0.273	0.058
Tricuspid annulus (S) (cm/sec)	0.384	0.008[1]
RV e´/a´ ratio	0.277	0.059
RV MPI	-0.357	0.01[1]
RV EF (%)	0.119	0.435
TAPSE (mm)	0.670	0.0001[1]

[1]Significant ($P < 0.05$).

RV EF: Right ventricular ejection fraction; LS: Longitudinal strain; MPI: Myocardial performance index; S: systolic velocity by tissue Doppler; TAPSE: Tricuspid annular plane systolic excursion.

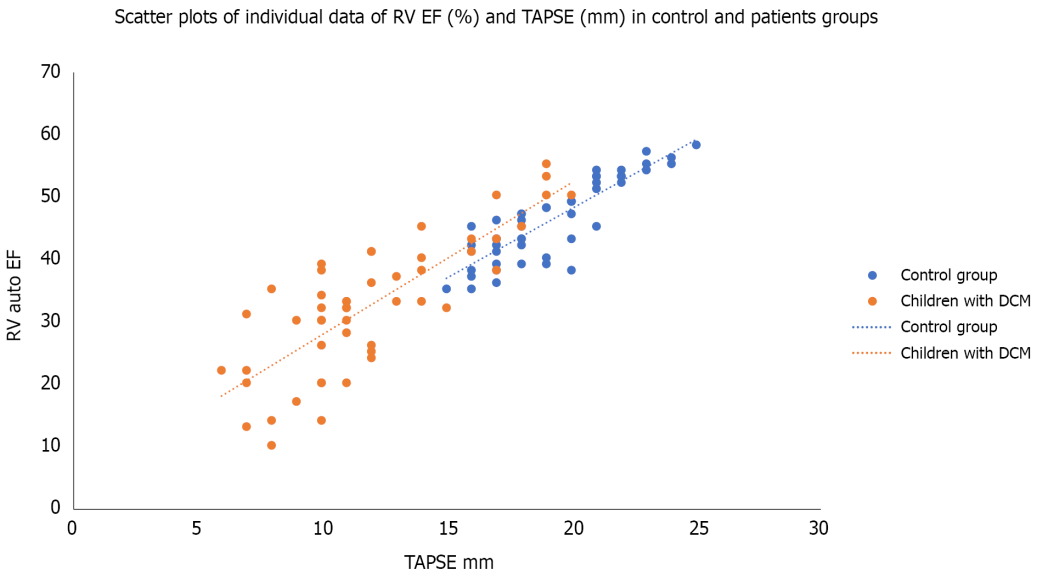

Figure 5 Scatter plots of individual data of Right Ventricular Ejection Fraction (%) and tricuspid annular plane systolic excursion (mm) in control and patients' groups. DCM: During dilated cardiomyopathy; RV EF: Right ventricular ejection fraction; TAPSE: Tricuspid annular plane systolic excursion.

Friedberg *et al*[28] who found that diastolic dysfunction and mechanical desynchrony were more common in children with DCM than in the control. Like other previous reports[26,29], the tissue Doppler-derived MPI of LV in DCM cases was significantly prolonged compared to control, in the current study. This finding could be related to LV systolic and diastolic dysfunction reported in our patients, as the MPI reflects both the systolic and diastolic function of the ventricles.

There is a strong need to assess the SI in patients with DCM due to the presence of a broad spectrum of LV trabeculations, the dynamic interaction between subendocardial and subepicardial fiber helices in LV, and the increase in LV end-diastolic and end-systolic volumes. In addition, the presence of a broad spectrum of LV trabeculations among heart diseases, especially in DCM, could make differentiation of LV non-compaction cardiomyopathy from DCM difficult[30]. Meanwhile, the dynamic interaction between subendocardial and subepicardial fiber helices in LV causing twisting deformation plays a vital role in LV function[31].

The increase in LV end-diastolic and end-systolic volumes causes an increase in the myocardial mass and a change in the chamber geometry to a more spherical shape

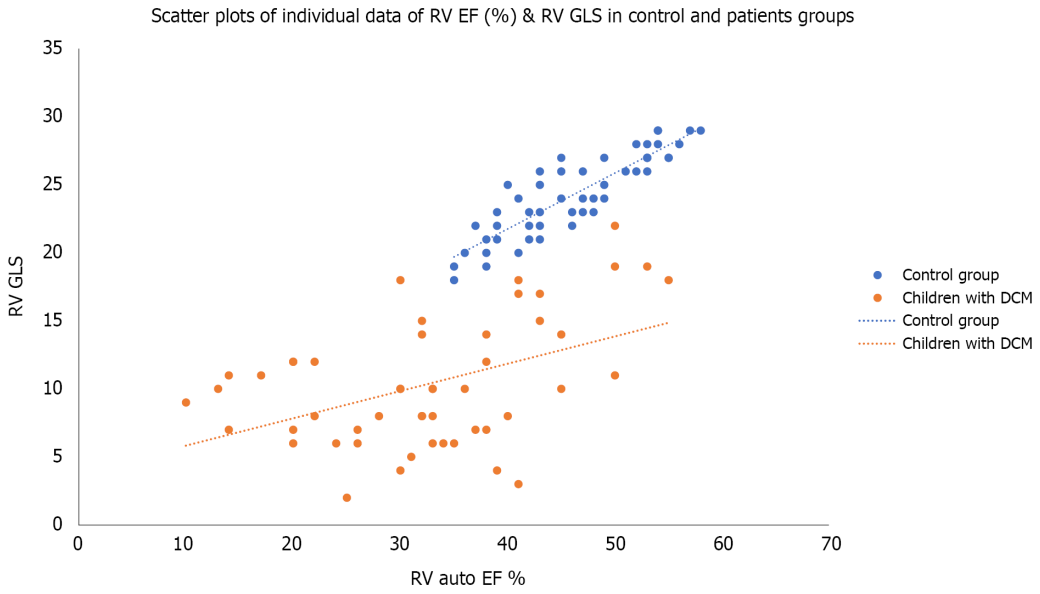

Figure 6 Scatter plots of individual data of right ventricular ejection fraction (%) and right ventricular global longitudinal strain (mm) in control and patients' groups. DCM: During dilated cardiomyopathy; RV EF: Right ventricular ejection fraction; GLS: Global longitudinal strains.

because of heart failure[30]. In the current study, there was a significant reduction in the SI of patients when compared with the controls. Previous studies supported that the LV SI was the strongest independent predictor of basal and apical LV peak systolic rotation and instantaneous LV peak systolic twist. So, LV apical rotation and twist are significantly influenced by LV configuration[13,32].

Ventricular strain can be determined by TDI, 2-D STE (which determines LV GLS %). Unlike the TDI-derived strain, which is angle-dependent, 2-D STE is less angle-dependent and can measure the strain by tracking the speckles, which are acoustic backscatter generated by ultrasound interactions with the myocardium[33]. Due to the complex orientation of the fibers in the intact LV wall, the myocardial deformation occurs in three dimensions and can be characterized not only in the longitudinal direction but also in the circumferential and radial directions. Sub-epicardial fibers play a significant role in radial and longitudinal strains, and sub-endocardial fibers play an essential role in circumferential strain. In the current study, LV GLS was significantly impaired in children with DCM compared to control. This finding agreed with several publications reporting different types of systolic strain impairment in patients with DCM[34].

Assessment of the RV function is paramount, especially in predicting the outcome, as it plays an important role in determining cardiac symptoms and exercise capacity in chronic heart failure. However, it is not easy to study the RV due to its complex anatomy and physiology. The current study showed a significant systolic dysfunction of the RV (as indicated by the reduced RV EF, TAPSE, and S', and increased RV MPI) in children with DCM compared to the controls. RV dysfunction may be due to the close interaction between LV and RV function. The RV has mainly transverse muscle fibers in its free wall and shares oblique fibers in the IVS with the LV. Subsequently, its contraction augments RV contraction; a condition defined as systolic ventricular interaction[21].

The presence of MR further impairs the already compromised LV systolic and diastolic functions observed in children with DCM. The resulting dysfunction consequently led to pulmonary venous congestion, pulmonary hypertension, and increasing the RV afterload. Furthermore, these changes make the RV contraction more dependent on the oblique septal fibers, which are mechanically more efficient than the transverse fibers in the free wall. Besides, the marked impairment of the global LV deformation (including the IVS containing these oblique fibers) further reduces the systolic ventricular interaction and reduces the RV deformation. Moreover, as the LV acquires a more spherical shape, the septal fibers become less oblique, decreasing their mechanical efficiency with more and more deterioration of the RV deformation. This deterioration will further impair the RV GLS, as observed in our study. This finding also agreed with several publications reporting the decrease of the longitudinal systolic strain in cases of dilated cardiomyopathy[26,35].

The current study reported a significant RV GLS with tricuspid annulus S wave, RV MPI, and TABSE. However, the RV GLS was not associated with either the RV EF or RV e´/a´ ratio. Although RV MPI, RV S, and RV TABSE are tissue-dependent factors, reflecting the RV systolic function, they are more reliable than RV EF, which is load-dependent. This finding agreed with the work done by Agha *et al*[6] 2015, who found that TAPSE, S wave, and RV MPI were significantly correlated with the LV GLS. However, they also found a positive correlation of e´ wave and e´/a´ ratio with the LV GLS[6]. The differences between the current study and their study arise because they correlated the RV MPI, RV S wave, RV e´/a´ ratio, and RV TABSE with LV GLS and not RV GLS as observed in our study. Another difference was using the linear regression analysis in the current study to avoid any confounding factor. Seo *et al*[7] also found a significant association of the RV-Free wall LS with the prognosis in patients with DCM. Similarly, Zairi *et al*[8] found that TAPSE, S, Tei index, and strain of the lateral wall of the RV were independent predictors of major cardiovascular events in non-ischemic dilated cardiomyopathy. Tigen *et al*[9] also observed that the RV free wall basal segment longitudinal strain was sensitive to predict RV systolic dysfunction.

Early recognition of the RV dysfunction could help early detection of complications; and give us enough window to interfere with aggressive intervention, including cardiac transplantation, to avoid the increase in mortality rate. However, there are some limitations to the current study. The study was conducted as a cross-sectional study without doing serial echocardiographic examination and relating worsening cardiac function with the possibility of complications. The study also had relatively few numbers of patients.

CONCLUSION

There was impairment of the RV LGS and other systolic and diastolic parameters in children with DCM. Speckle tracking echocardiography and tissue Doppler can help detect the RV function's early decline, which serves as a good prognostic factor.

ARTICLE HIGHLIGHTS

Research background

Dilated cardiomyopathy (DCM) is a clinical condition associated with left ventricular (LV) or biventricular dilation with an impaired contraction. Clinical presentation of DCM mainly relates to the degree of LV or biventricular systolic dysfunction leading to pump failure.

Research motivation

To diagnose early cardiac dysfunction in dilated cardiomyopathy, we need to perform a cardiac examination using a tool with high sensitivity. M-mode, 2-dimensional echocardiography, tissue Doppler imaging (TDI), and Two-dimensional speckle tracking imaging are commonly used echocardiographic modalities to provide accurate and early detection of cardiac dysfunction.

Research objectives

The study aimed to evaluate right ventricular (RV) function in children with idiopathic DCM using relatively recent echocardiographic modalities.

Research methods

The study was a prospective case-control study, including 50 children with idiopathic DCM and 50 healthy children as a control group, to study RV function using four-dimensional echocardiography (4-DE), TDI, and two-dimensional-speckles tracking echocardiography (2-D-STE). RV ejection fractions (EF) was measured by 4-DE.

Research results

The auto left (LV) EF measured by 2-D-STE were significantly lower in the patients' group than in the control. The sphericity index was also significantly lower in children with DCM than in the control. RV EF measured by 4-DE was significantly lower in the patient's group than the control. RV S wave, e´/a´ ratio, myocardial performance index

(MPI), and tricuspid annular plane systolic excursion (TAPSE) were significantly impaired in children with DCM than in control. Both LV and RV global longitudinal strains (GLS) were significantly reduced in children with DCM than in control. RVGLS was significantly associated with the duration since diagnosis, tricuspid annulus S wave, RV MPI, and TAPSE, but not with the age of the patients, RV EF, or e´/a´ ratio.

Research conclusions

Impairment of the RV LGS and other systolic and diastolic parameters in children with DCM using STE and TDI can help detect RV function's early decline.

Research perspectives

We need to do a serial long-term echocardiographic study and relate worsening cardiac function to the possibility of complications.

ACKNOWLEDGEMENTS

We thank the anonymous referees for their useful suggestions.

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World J Clin Pediatr 2022 January 9; 11(1): 85-92

DOI: 10.5409/wjcp.v11.i1.85

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Observational Study

Correlation of cardiac troponin T levels with inotrope requirement, hypoxic-ischemic encephalopathy, and survival in asphyxiated neonates

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Author contributions: Yellanthoor RB and Rajamanickam D conceptualized the study, analyzed and interpreted the data; Rajamanickam D collected the data; Yellanthoor RB wrote the manuscript and critically revised it; both Yellanthoor RB and Rajamanickam D approved the final manuscript.

Institutional review board statement: Ethical approval was obtained from the Institutional Ethical Committee.

Conflict-of-interest statement: Authors declare that there is no conflict of interest.

Data sharing statement: Authors agree to share the data at the reasonable request.

STROBE statement: The authors have read the STROBE Statement—a checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—a checklist of items.

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Abstract

BACKGROUND

Cardiac involvement in neonates with perinatal asphyxia not only complicates perinatal management but also contributes to increased mortality.

AIM

To assess cardiac troponin T (cTnT) levels in asphyxiated neonates and their correlation with echocardiography findings, inotrope requirement, hypoxic-ischemic encephalopathy (HIE) stages, and mortality.

METHODS

cTnT levels, echocardiographic findings, the requirement of inotropes, HIE stages, and outcome were studied in neonates of gestational age ≥ 34 wk with perinatal asphyxia.

RESULTS

Among 57 neonates with perinatal asphyxia, male gender, cesarean section, forceps/vacuum-assisted vaginal delivery and late preterm included 33 (57.9%), 23 (40.4%), 3 (5.3%), and 12 (21.1%) respectively. The mean gestational age was 38.4 wk (1.6 wk). HIE stages I, II, and III were observed in 7 (12.3%), 37 (64.9%), and 9 (15.8%) neonates respectively. 26 (45.6%) neonates had echocardiographic changes and 19 (33.3%) required inotropes. cTnT levels were elevated in 41 (71.9%) neonates [median (IQR); 0.285 (0.211-0.422) ng/mL]. The Median cTnT level showed an increasing trend with increasing changes in echocardiography (P = 0.002). Two neonates with mitral regurgitation and global hypokinesia had the

Country/Territory of origin: India

Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 9, 2021
Peer-review started: January 9, 2021
First decision: May 6, 2021
Revised: June 20, 2021
Accepted: December 7, 2021
Article in press: December 7, 2021
Published online: January 9, 2022

P-Reviewer: Spasojevic SD
S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

highest cTnT levels (1.99 and 0.651 ng/mL). Of 31 neonates with normal echocardiography, 18 (58.06%) showed elevated cTnT. cTnT levels were significantly higher in those who required inotropic support than those who did not (P = 0.007). Neonates with HIE stage III had significantly higher cTnT levels compared to those with HIE stage I/II (P = 0.013). Survivors had lower median cTnT levels [0.210 (0.122-0.316) ng/mL] than who succumbed [0.597 (0.356-1.146) ng/mL].

CONCLUSION
cTnT levels suggestive of cardiac involvement were observed in 71.9% of asphyxiated neonates. cTnT levels correlated with echocardiography findings, inotrope requirement, HIE stages, and mortality.

Key Words: Asphyxia; Cardiac dysfunction; Inotropes; Neonates; troponin T; Survival

Core Tip: Cardiac involvement in perinatal asphyxia complicates the management and increases mortality. We assessed cardiac troponin T (cTnT) levels in asphyxiated neonates and their correlation with echocardiography findings, hypoxic-ischemic encephalopathy (HIE) stages, and mortality. Elevated cTnT levels suggestive of cardiac involvement were found in 71.9% of neonates and correlated with increasing grades of ischemic changes in echocardiography. cTnT levels were elevated in 58% of neonates in the absence of echocardiographic findings. Significantly higher cTnT levels in neonates with HIE stage III than those with HIE stage I and II as well as higher cTnT levels in non-survivors than survivors show its predictive role.

Citation: Yellanthoor RB, Rajamanickam D. Correlation of cardiac troponin T levels with inotrope requirement, hypoxic-ischemic encephalopathy, and survival in asphyxiated neonates. *World J Clin Pediatr* 2022; 11(1): 85-92
URL: https://www.wjgnet.com/2219-2808/full/v11/i1/85.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i1.85

INTRODUCTION

The myocardium is vulnerable to ischemic injury in asphyxiated neonates[1-5]. Perinatal asphyxia causes significant morbidity and mortality, especially in developing countries[6-9]. The cardiac involvement in perinatal asphyxia varies. The reported asphyxial cardiomyopathy in neonates ranges from 24%-78%[3-6].

Ischemic cardiac dysfunction results in decreased cardiovascular reserve. The affected neonates may present with myocardial failure, bradycardia, and hypotension along with morbidities related to other systems. The assessment of the extent of myocardial injury and appropriate management influence treatment and outcome. Clinical assessment alone is considered inadequate to guide management or predict the outcome. Serum creatinine kinase muscle-brain isoenzyme (CK-MB) lacks cardiac specificity in the neonate and the levels are affected by gestational age, mode of delivery, and birth weight. CK-MB levels were reported to be 2 to 5 times higher in neonates born by normal vaginal delivery as compared to those born by cesarean section[2]. Echocardiography helps in identifying the extent of cardiac dysfunction but needs expertise.

Cardiac troponin T (cTnT) has been explored as a more specific biomarker for the diagnosis of myocardial injury in asphyxiated neonates[10,11]. Troponin T can be detected at earlier stages than CK-MB and it also remains high for a longer period[10]. Further, cTnT levels are found to be elevated in 30%-50% of cases having normal CK-MB levels[2]. The levels also may correlate with mortality. In this context, we aimed to evaluate the role of cTnT in perinatally asphyxiated neonates as a marker of myocardial injury and assess its correlation with inotrope use, hypoxic-ischemic encephalopathy (HIE), and mortality.

MATERIALS AND METHODS

Neonates of gestational age ≥ 34 wk with perinatal asphyxia were prospectively studied over two years in a neonatal intensive care unit of a University teaching hospital. The demographic and birth details, clinical examination data were collected. cTnT levels, echocardiographic findings, the requirement of inotropes, evidence of other system involvement, HIE in particular, and outcome were collected.

About 0.5 mL of blood collected using standard sampling tubes (BD red vacutainers) was processed for estimation of cTnT levels. Biochemical analysis of cTnT levels in this study was done with an Elecsys 2010 and Cobase 411 analyzer using the Elecsys Troponin Ths (high sensitive) STAT (short turnaround time) Immunoassay (Roche Diagnostics, Germany). This is an electrochemiluminescent sandwich enzyme-linked immunosorbent assay. The total duration of the assay is 9 min. The lower limit of detection is 3 ng/L or 3 pg/mL, if the values are below this level it was reported as < 3 ng/L. The upper limit of detection is 10000 ng/L or 10000 pg/mL, if the values are above this level it was reported as > 10000 ng/L or up to 100000 ng/L for the 10-fold diluted sample. The kit specifications include the sensitivity of 99% and specificity of 98% at 100 ng/L and, the sensitivity of 100% and specificity of 75% at 14 ng/L. Normal values for cTnT: Interquartile Range: 0.01–0.062/mL, 95th centile: 0.153 ng/mL, 99th centile: 0.244 ng/mL. For the study purpose, cTnT levels of more than 0.15 ng/mL were considered elevated.

Neonate was considered to have perinatal asphyxia if he/she met any of the following criteria: Need of bag and mask or bag and tube ventilation at birth with Apgar score of ≤ 6 at 5 min; hypoxic encephalopathy features (lethargy, seizures, hypotonia, coma or irritability); cord blood pH ≤ 7.0, or arterial pH in neonates ≤ 7.2. Neonates with congenital heart defects, major anomalies, and those who expired within the first hour of birth were excluded.

HIE was considered in asphyxiated neonates if they had neurologic manifestations (seizures, coma, hypotonia). HIE was divided into Sarnat stages 1, 2, and 3 based on standard clinical features[3,4,12]. Heart rate < 100/min was considered bradycardia. Systolic and or diastolic blood pressure (BP) equal to or lower than the 5th percentile for age and sex was considered hypotension. Capillary filling time (CFT) > 3 s was considered as increased CFT.

Echocardiograph was obtained with the "Philips CX-50" machine. Following echocardiographic findings were considered as suggestive of myocardial ischemia: Mitral regurgitation (MR) or right ventricular (RV)/left ventricular (LV)/global hypokinesia, tricuspid regurgitation (TR), and pulmonary artery hypertension (PAH) with TR[2]. Renal dysfunction was considered if creatinine level was more than the upper limit of the normal reference range for gestational age with or without urine output < 1 mL/kg/h[2]. Transaminase levels more than twice the normal levels (normal aspartate transaminase (AST) up to 40 U/L and alanine transaminase (ALT) up to 45 U/L) were considered as hepatic dysfunction.

The results are expressed as frequencies and percentages. Data were analyzed using SPSS v16.0 software. Differences in the median of quantitative data among different stages of HIE and echocardiographic changes were compared by Kruskal- Wallis test and proportions by Chi-Square tests. A $P < 0.05$ was considered statistically significant. Ethical approval was obtained from the Institutional Ethical Committee. Informed consent was obtained from the parents.

RESULTS

This study included 57 neonates with perinatal asphyxia (Figure 1). Male gender, lower segment cesarean section (LSCS), forceps or vacuum-assisted vaginal delivery, and late preterm included 33 (57.9%), 23 (40.4%), 3 (5.3%), and 12 (21.1%) respectively. The mean gestational age was 38.4 ± 1.6 wk.

Mode of resuscitation at birth included intubation in 26 (45.6%) and bag and mask ventilation in 15 (26.3%). Organ involvement in perinatal asphyxia included brain in 53 (93%), hepatic in 35 (61.4%), renal in 26 (45.6%), and cardiac in 30 (52.6%). Mechanical ventilation was needed in 20 (35.1%) neonates. HIE stage 1, 2 and 3 were observed in 7 (12.3%), 37 (64.9%) and 9 (15.8%) neonates respectively. Four neonates did not have HIE. Six neonates died.

Of 57 asphyxiated neonates, 26 (45.6%) neonates had echocardiographic changes. MR with global hypokinesia was observed in two (3.5%) neonates. Inotropic support was required in 19 (33.3%) neonates.

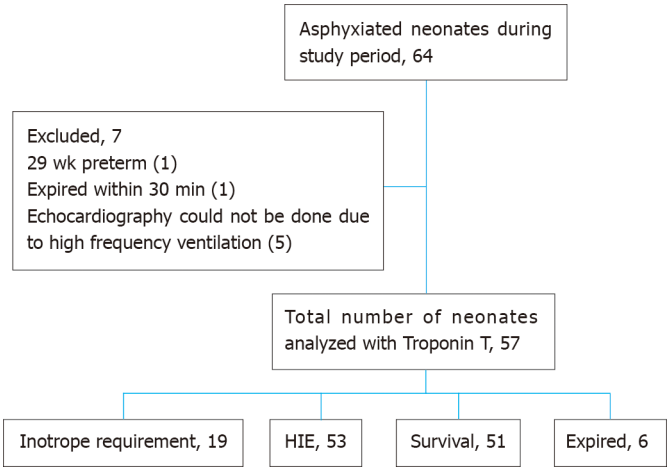

Figure 1 Study flow chart. HIE: Hypoxic-ischemic encephalopathy.

Elevated cTnT levels were observed in 41 (71.9%) neonates studied, with median (IQR) of 0.285 (0.211-0.422) ng/mL. The maximum value observed was 1.99 ng/mL (Table 1).

The median cTnT level showed an increasing trend with the increase in changes in echocardiography (P = 0.002 Kruskal-Wallis Test) (Table 2). MR with global hypokinesia was observed in two neonates with high cTnT levels (1.99, 0.651 ng/mL) who eventually succumbed. Of 31 neonates with normal echocardiography findings, 18 (58.06%) cases had elevated cTnT levels.

cTnT levels in those who required inotropic support were significantly higher when compared to those who did not require inotropic support (P = 0.007, Chi-Square test) (Table 3).

Neonates who had HIE stage III had significantly higher levels of cTnT levels when compared to neonates with HIE stage I and II (P = 0.013 Kruskal-Wallis test) (Table 4). Six out of these 9 neonates with HIE stage III, having much higher cTnT levels succumbed.

Six neonates among 57 enrolled with perinatal asphyxia died. Median cTnT levels in those who survived were 0.210 (0.122-0.316) ng/mL which is comparatively lower than the median cTnT level in those who succumbed [0.597 (0.356-1.146) ng/mL] (Table 5).

DISCUSSION

Cardiac involvement secondary to tissue ischemia in neonates with perinatal asphyxia can occur as a part of a multi-organ involvement or isolated cardiac event[12-16]. Myocardium involvement not only complicates perinatal management but also increases mortality. The present study has identified the significant role of cTnT levels in identifying cardiac involvement, its correlation with echocardiography findings, inotrope requirement, HIE stages, and mortality.

In severely asphyxiated infants, cardiac dysfunction more commonly affects the right ventricle. The various manifestations related to cardiac dysfunction are respiratory distress, congestive cardiac failure, hypotension, delayed capillary refilling time, bradycardia, cardiogenic shock, and systolic murmur due to MR and TR[8,17]. Sinus bradycardia and lowered systemic BP are commonly seen in neonatal hypoxic ischemia. These features are observed in the present study. Costa *et al*[18] looked at BP in asphyxiated newborns. They observed significantly lower systolic and diastolic BPs in asphyxiated neonates compared to control newborns[18]. Hypotension is a late sign of under-perfusion. Hypotension is often due to peripheral vasodilatation or poor cardiac output. González de Dios *et al*[19] studied cardiac involvement (n = 31) in 156 asphyxiated term neonates. They categorized dysrhythmias and mild hypotension as minor cardiac involvement and TR, myocardial ischemia, cardiogenic shock, or hypovolemic shock as major cardiac involvement[19].

Echocardiography certainly could guide the management of these infants about fluid resuscitation and choice of inotropic support. Echocardiography is helpful in the early identification of tricuspid insufficiency, compromised LV output, and stroke volume in infants who suffer from perinatal asphyxia. Echocardiographic findings

Table 1 Cardiac troponin T levels in perinatally asphyxiated neonates

cTnT levels (ng/mL)	*n* (%)	Median	IQR
Normal	16 (28.1)	0.084	0.052-0.114
Elevated	41 (71.9)	0.285	0.211-0.422

cTnT: Cardiac troponin T.

Table 2 Correlation of cardiac troponin T levels with echocardiograph findings (*n* = 57)

Echocardiograph findings	*n* (%)	cTnT levels (ng/mL); median (IQR)
Normal	31 (54.4)	0.193 (0.085-0.282)
TR	8 (14.03)	0.223 (0.199-0.266)
PAH with TR	16 (28.07)	0.405 (0.228-0.557)
MR + Global hypokinesia	2 (3.5)	1.99, 0.651[1]

[1]Exact values mentioned.
TR: Tricuspid regurgitation; PAH: Pulmonary artery hypertension; MR: Mitral regurgitation; cTnT: Cardiac troponin T.

Table 3 Correlation of cardiac troponin T levels with inotrope requirement (*n* = 57)

Inotrope use	*n* (%)	cTnT levels (ng/mL); median (IQR)
Inotrope not required	38 (66.6)	0.192 (0.087-0.272)
Inotrope required	19 (33.4)	0.394 (0.269-0.543)

cTnT: Cardiac troponin T.

Table 4 Correlation of cardiac troponin T levels with stages of hypoxic ischemic encephalopathy (*n* = 53)

HIE stages	*n* (%)	cTnT levels (ng/mL); median (IQR)
Stage 1	7 (13.2)	0.086 (0.047-0.271)
Stage 2	37 (69.8)	0.255 (0.133-0.349)
Stage 3	9 (17.0)	0.394 (0.239-0.758)

cTnT: Cardiac troponin T; HIE: Hypoxic-ischemic encephalopathy.

Table 5 Correlation of cardiac troponin T levels with survival (*n* = 57)

	n (%)	cTnT levels (ng/mL); median (IQR)
Survived	51 (89.5)	0.210 (0.122-0.316)
Succumbed	6 (10.5)	0.597 (0.356-1.146)

cTnT: Cardiac troponin T.

such as regional wall abnormalities, increased echogenicity of papillary muscle, compromised LV function, and tricuspid or mitral valve insufficiency resulting in reduced contractility, low cardiac output, decreased stroke volume, and elevated pressure of pulmonary artery suggest myocardial ischemia[17,19]. The mitral valve insufficiency and patent ductus arteriosus correlate with severe degrees of asphyxia injury. Tricuspid insufficiency was observed significantly at a higher rate in as-

phyxiated neonates than healthy neonates and it was more frequent with increasing severity of asphyxia[18]. Most of these features were observed as the main findings in echocardiography in the present study.

In asphyxiated neonates, despite preferential myocardial perfusion, hypoxia leads to myocardial damage. If ischemia progresses, especially beyond 20 min, over 60% of the cellular adenosine triphosphate will be used up, lactate in myocardial tissue increases about 12 times, glycogen and creatine phosphate reserves decrease resulting in dramatic structural changes[10,20,21]. This also causes damage to the cell membrane and releases CK-MB and cTnT into the bloodstream. CK-MB levels although significantly elevated in asphyxiated infants they do not appear to discriminate well those infants with cardiovascular compromise[10,21]. The highest levels occur at 12 h following birth and the levels decrease by 48 h of life[20].

The structure of troponin T is unique to the myocardium. Troponin concentration in the myocardium is much higher compared to CK-MB. In healthy humans, troponin levels in plasma are negligible. The troponin levels raise within a few hours after the acute ischemic episode and remain high for 10–14 d. This increases the diagnostic time range[2].

The present study has identified elevated cTnT levels in 71.9% of asphyxiated neonates and established a correlation of these levels with echocardiographic findings. Costa *et al*[18] reported significantly higher cTnT in neonates having echocardiograph signs of myocardial damage[18]. They also found that cTnT levels in neonates suffering from asphyxia with echocardiography changes were higher compared with those of normal newborns. TR was observed in all asphyxiated neonates. The cTnT levels ≥ 0.21 ng/mL had a significant association with abnormal echocardiographic findings. This cTnT level had 100% specificity and 39% sensitivity. The authors suggested the cTnT 0.19 ng/mL as the differentiating cut-off level. In the present study, all neonates with echocardiographic findings of asphyxia had cTnT levels beyond this cut of value. The two neonates with global hypokinesia on echocardiograph had the highest cTnT levels and both of them died.

Myocardial dysfunction also impacts cerebral hemodynamics and decreases cerebral perfusion[22-25]. Cerebral hemodynamic disturbances such as a decreased rate of flow of blood including the velocity of highest systolic blood flow and velocity of blood flow at the end of diastole, raised index of pulsatility and resistance observed among neonates suffering from perinatal asphyxia are more frequent in infants who have cardiac dysfunction affecting the left ventricle. In the present study, neonates with HIE stage 3 had the highest cTnT levels. Higher cTnT levels in neonates with HIE and its correlation with mortality was also reported by Bhasin and Kohli[25] The limitation of the present study includes not analyzing the values of cTnT during therapeutic hypothermia and its changes as a prognostic marker of the final outcome.

CONCLUSION

Elevated cTnT levels suggestive of cardiac involvement in 71.9% of asphyxiated neonates establish its importance. The cTnT levels correlate with an increasing grade in echocardiography findings. Elevated cTnT levels in 58% of neonates with normal echocardiography findings suggest its biomarker role even in the absence of echocardiographic findings. Elevated cTnT levels in neonates with HIE stage III being significantly higher than those with HIE stage I and II show its predictive role. cTnT levels in non-survivors are likely to be much higher than those among survivors.

ARTICLE HIGHLIGHTS

Research background

The myocardial ischemic injury in asphyxiated neonates complicates management and may lead to higher mortality. Cardiac troponin T (cTnT) levels are expected to rise early in myocardial ischemia and remain high for about two weeks.

Research motivation

cTnT levels are better markers than Serum creatinine kinase muscle-brain isoenzyme levels and could be predictive of mortality.

Research objectives
The present study determined cTnT levels in asphyxiated neonates and found out its relationship with echocardiography findings, inotrope requirement, hypoxic-ischemic encephalopathy (HIE) stages, and mortality.

Research methods
cTnT levels are estimated in all asphyxiated neonates along with echocardiography evaluation.

Research results
Among asphyxiated neonates, cTnT levels were elevated in 71.9%. Further, the cTnT levels correlated with increasing grades of ischemic changes in echocardiography. Elevated cTnT levels in 58% of neonates with normal echocardiography findings suggested its role as a biomarker. cTnT levels in neonates with HIE stage III were significantly higher than those with HIE stage I and II. cTnT levels were higher in non-survivors than survivors.

Research conclusions
cTnT could be a potential and clinically useful biomarker for asphyxia related myocardial injury in neonates.

Research perspectives
Further studies to determine the exact cut of levels of cTnT predicting mortality are needed.

ACKNOWLEDGEMENTS

Authors thank the Head and staff members of the Department of Paediatrics for their kind help, suggestions, and cooperation for the study.

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ISSN 2219-2808 (online)

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2022 March 9; 11(2): 93-214

Published by Baishideng Publishing Group Inc

WJCP

World Journal of Clinical Pediatrics

Contents

Bimonthly Volume 11 Number 2 March 9, 2022

World Journal of Clinical Pediatrics

Bimonthly Volume 11 Number 2 March 9, 2022

Contents

NAME OF JOURNAL
World Journal of Clinical Pediatrics

ISSN
ISSN 2219-2808 (online)

LAUNCH DATE
June 8, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Toru Watanabe, Consolato M Sergi, Elena Daniela Serban, Surjit Singh

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2219-2808/editorialboard.htm

PUBLICATION DATE
March 9, 2022

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World J Clin Pediatr 2022 March 9; 11(2): 93-104

DOI: 10.5409/wjcp.v11.i2.93

ISSN 2219-2808 (online)

OPINION REVIEW

Current status of nitrous oxide use in pediatric patients

Nishkarsh Gupta, Anju Gupta, R M Vishnu Narayanan

Specialty type: Anesthesiology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D, D
Grade E (Poor): 0

P-Reviewer: Mapesa WA, Kenya; Mondardini MC, Italy

Received: April 25, 2021
Peer-review started: April 25, 2021
First decision: June 17, 2021
Revised: July 4, 2021
Accepted: February 25, 2022
Article in press: February 25, 2022
Published online: March 9, 2022

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Abstract

Nitrous oxide is one of the most commonly used inhalational anesthetic agents used in practice. It is a cost-effective, pleasant, safe, and versatile anesthetic agent with many desirable properties like good quality analgesia, decreased awareness, accelerated induction and recovery from anesthesia, and reduced utilization of other expensive inhalational agents with potential cost savings. The use of nitrous oxide has been questioned by a lot of studies and case reports perceiving its adverse systemic, hematological, immune, and neurologic adverse effects. However, the literature in the recent past has tried to resolve the controversies related to its use. The concerns over an increase in cardiovascular complications and mortality following nitrous oxide use have been negated by recent data. However, its use in certain vulnerable populations like children with cobalamin and folate deficiency or defects in their metabolic pathways remains a cause of concern for its toxic effects. In this narrative review, we aim to discuss the pharmacological properties of nitrous oxide, the potential advantages and drawbacks of the use of nitrous oxide in children, address the neurodevelopmental and other systemic effects, and throw light on the evidence regarding the safety of nitrous oxide use and its current role in pediatric procedural sedation and anesthesia practice. The literature related to its use in the pediatric population for painful procedures and surgeries has been summarized.

Key Words: Child; Nitrous oxide; Vitamin B12; Vulnerable populations; Anesthesiology; Anesthetics; Folic acid; Metabolic networks and pathways

Core Tip: The literature is insufficient presently to advise either the routine use or complete elimination of nitrous oxide, and further research is needed to fully establish its role in pediatric anesthesia practice. No major adverse effects have been reported in large trials on the use of nitrous oxide in children despite the prevailing concerns over its safety in this population. A reasonable and balanced approach should be adopted to individualize its use considering its risks and benefits as related to a particular case.

Citation: Gupta N, Gupta A, Narayanan RMV. Current status of nitrous oxide use in pediatric patients. *World J Clin Pediatr* 2022; 11(2): 93-104
URL: https://www.wjgnet.com/2219-2808/full/v11/i2/93.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i2.93

INTRODUCTION

Nitrous oxide has been a part of the routine anesthetic practice for over 15 decades. From being the fad of recreational use at parties, nitrous oxide has evolved to hold an important place in contemporary practice of anesthesia[1]. It was first synthesized by Joseph Priestly in 1772, and 7 years later Humphrey Davy established its analgesic and psychotropic potential. However, Davy's suggestion on using it as an anesthetic did not gain popularity until 1844 when Gardner Colton demonstrated its analgesic properties and Horace Wells demonstrated the first use of nitrous oxide for analgesia for painless tooth extraction. From the year 1868, the commercial availability of compressed nitrous oxide cylinders led to its universal adoption as an ether adjunct. Consequently, it was widely used for general procedural sedation in dentistry, obstetric analgesia, and during general anesthesia with other anesthetic agents. Its additive use with ether provided smoother induction, reduced ether requirements, cardiorespiratory stability, and faster emergence.

While its advantages were being appreciated, various concerns about its metabolic and other adverse effects begin to be recognized in the middle of the nineteenth century, including reports of fatalities from the faulty delivery systems, which led to an ongoing debate on whether it should be abandoned. Results of a few large-scale trials further fueled the debate and challenged its continued use in anesthesia practice. Nitrous oxide can also have a direct environmental impact as it is a major contributor of greenhouse gases. This has questioned its role in sustainable and eco-friendly anesthetic practice. However, the anesthetic use of nitrous oxide contributes to only 2% of the nitrous oxide source in the atmosphere.

The use of nitrous oxide continues to be a vacillation for many anesthesiologists due to the inconclusiveness of the currently available data. In this review, we discuss the present status of nitrous oxide in pediatric anesthesia practice. We will go through the pharmacological properties of nitrous oxide followed by the pros and cons of using nitrous oxide, addressing the neurodevelopmental and other systemic effects. The conclusions of the landmark trials regarding nitrous oxide will be summarized followed by the literature related to its use in pediatric procedural sedation and surgeries.

METHODS

Studies published prior to August 2019 were retrieved from the electronic databases (Google Scholar, Cochrane Central Register of Controlled Trials on The Cochrane Library, PubMed and EMBASE), and their references were additionally scrutinized for any further relevant articles that investigated nitrous oxide. The literature search was done by independent authors, and the following search terms were used in various combinations using Boolean operators (such as AND, OR, NOT): Pediatric patients, pediatric, children, neonates, infants, adolescents, nitrous oxide, laughing gas, N2O, sedation, conscious sedation, procedural sedation, pain, analgesia, anesthesia, homocysteine, methionine synthase, teratogenic, teratogen, teratogens, teratogenesis, postoperative nausea and vomiting, postoperative nausea and/or vomiting (PONV), postoperative vomiting, postoperative nausea, postoperative emesis, environmental effects, ozone depletion, occupational, occupation, exposure, hazard, anesthesia dental, emergency service, post-traumatic stress disorder, chronic postsurgical pain, and CPSP. We got 779 results, and after eliminating duplication, adult trials, and articles in languages other than English, 137 articles were found suitable and were studied.

PHARMACOLOGICAL PROPERTIES OF NITROUS OXIDE

Nitrous oxide occurs as a colorless, odorless gas at room temperature and pressure. Though the exact

mechanism of action is not known, it is postulated to act on dopaminergic, Gamma aminobutyric acid, alpha 2, and N-methyl-d-aspartate (NMDA) receptors to produce sedation and analgesia. However, nitrous oxide does not produce skeletal muscle relaxation. After inhalation, nitrous oxide is primarily excreted *via* the lungs unchanged. Nitrous oxide is the least potent volatile agent with a minimum alveolar concentration of 105%. Nitrous oxide has a blood gas partition coefficient of 0.47, which confers it low solubility.

Interaction with anesthetic agents

Use of nitrous oxide in combination with other inhalational agents provides an additive anesthetic action since the minimum alveolar concentration of nitrous oxide is directly additive to theirs. Nitrous oxide in 60%-70% concentration equals a minimum alveolar concentration value of around 0.55-0.65[1,2]. It accelerates the time of anesthetic induction when used in conjunction with poorly soluble inhalational agents. Nitrous oxide as a component of anesthesia has shown to reduce the utilization of inhalational agents, propofol, and opioids[2,3]. During inhalational induction with mask in children, high concentration of nitrous oxide facilitates a faster loss of consciousness by concentration effect and second gas effect. The use of nitrous oxide during induction has proven to increase the mask acceptance in children and lower incidence of airway related complications. However, nitrous oxide favors the incidence of excitatory phenomena with sevoflurane during inhalational induction. It has been seen that adding up nitrous oxide to other inhalational anesthetic agents decreases the occurrence of hemodynamic suppression as compared to use of equipotent doses of volatile agents alone[2].

Advantages and disadvantages of nitrous oxide

Nitrous oxide is a cheap anesthetic agent and reduces the utilization of other potent volatile agents and opioids. Therefore, the overall expenses and associated adverse effects are lowered. Along with the additive action with other inhalational agents, the major advantage of nitrous oxide is that it provides good amnesia and hence prevents awareness. Nitrous oxide has been a popular agent for use in pediatric anesthesia during surgical procedures as a constituent of anesthetic gas mixture in addition to other volatile agents and opioids. In addition, it has been used for providing procedural sedation in the emergency room and for various urological procedures and ontological procedures. Nitrous oxide also has been used for mild sedation and analgesia in children undergoing dental procedures, upper gastrointestinal endoscopy, fiberoptic bronchoscopy, and venipuncture procedures. Nitrous oxide has been shown to significantly reduce chronic postsurgical pain (CPSP) in recent studies due to its antagonist action on NMDA receptors, which have been purported to have a role in central sensitization and establishment of CPSP[4].

Nevertheless, nitrous oxide has numerous detrimental effects that may limit its overall clinical application. These consist of an increased risk of PONV, neurologic and hematologic complications, diffusion hypoxia, its property of expanding closed spaces, ozone depletion potential, and recent concerns of adverse consequences on the developing brain[5,6]. There were also concerns of immunosuppression and impairment of wound healing due to inhibition of mononuclear cell proliferation and neutrophil chemotaxis[5-7]. The advantages and disadvantages of nitrous oxide have been summed up in the Table 1. Some of the disadvantages quoted are controversial as discussed later in the chapter.

Systemic effects

The systemic effects of nitrous oxide are summarized in the table below (Table 2). Nitrous oxide oxidizes the cobalt atom of the enzyme methionine synthetase and thereby permanently inactivates it, which in turn interferes with the metabolism of vitamin B12 and folate (Figure 1). Hence, the transformation of homocysteine to S-adenosylmethionine is impaired, which is a substrate for the chemical reaction involving tetrahydrofolate and thymidine during DNA synthesis. A short nitrous oxide exposure of only 30 min was found to decrease the methionine synthetase enzyme activity by 50% in rats, while it became almost untraceable after 6 h[8].

Acute neurologic signs and pancytopenia were seen in an infant after nitrous oxide anesthesia, and vitamin B12 supplementation treated the symptoms[9]. The problem would be magnified in patients having preexisting methionine synthase deficiency where nitrous oxide exposure can precipitate pernicious anemia (manifesting as spinal cord subacute combined degeneration and megaloblastic anemia), psychomotor delay, growth retardation, and neurological symptoms[10,11].

Nitrous oxide has also been noticed to increase blood homocysteine levels. Similarly, nitrous oxide facilitated reduction in methionine synthase enzyme activity in patients with Type-III Homocystinuria (due to a defect in methylene tetrahydrofolate reductase), can complicate into myelopathy, macrocytic anemia, and death. A report described a cataclysmic event in a child who was anesthetized with nitrous oxide and developed convulsions and apneic episodes postoperatively and later succumbed[11].

A preliminary study on metabolic effects of repeated exposure to nitrous oxide concluded that homocysteine levels did not consistently correlate with cumulative nitrous oxide exposure and children predisposed to metabolic and nutritional disturbance[12]. Though this finding is reassuring, considering the gravity of consequences, nitrous oxide should be used with caution in children with congenital

Table 1 Advantages and disadvantages of nitrous oxide use for anesthesia

Advantages	Disadvantages
Analgesia	Low potency
Reduced awareness	Risk of diffusion hypoxia
Colorless and odorless	PONV [risk ratio 1.21 (CI: 1.04-1.40); $P = 0.014$][2]
Inexpensive (Rs 50/patient)[1]	Ability to expand air filled cavities
Faster onset and emergence (elimination half-life 5 min)	Increases cuff pressure of ETT and LMA
Minimal metabolism (< 0.004%)	Hematological/neurological toxicity
Cardiorespiratory stability	Immune deficiency?
Prevents CPSP	Reproductive effects
Treatment-resistant refractory depression	Myocardial ischemia?
	Greenhouse gas
	Apoptosis in developing brains

[1]Cost of nitrous oxide used in dentistry in Indian rupees per patient.
[2]Risk ratio for the overall effect of nitrous oxide on postoperative nausea/vomiting.
PONV: Postoperative nausea/vomiting; CPSP: Chronic postsurgical pain; ETT: Endotracheal tube; LMA: Laryngeal mask airway; CI: Confidence interval.

Table 2 Systemic effects of nitrous oxide

Respiratory system	Decreases tidal volume and respiratory rate
	Reduced ventilatory response to carbon dioxide and hypoxia
Central nervous system	Loss of awareness
	Analgesia
	Increased cerebral blood flow and intracranial pressure
	(Concentration > 70%)
Cardiovascular system	Sympathomimetic
	Direct myocardial depression
Hemodynamic effects	Combination with other inhalational agents reduce the incidence of hypotension when compared to administration of the agents alone

deficiency or defective enzymes that are involved in the pathway to DNA synthesis or in patients at risk of vitamin B12 deficiency (*e.g.*, pernicious anemia, post-illeal resection surgery, vegetarians, malnourished children, and infants on complete breast feeds).

Postoperative nausea and vomiting: Nitrous oxide administration is considered an independent risk factor for PONV. Nitrous oxide heightens the risk of PONV by up to 20% in adults[13]. Notwithstanding, nitrous oxide did not increase the incidence of PONV in children when used as an adjuvant to other volatile agents[14]. The incidence and severity of PONV did not vary between those receiving 70% nitrous oxide during anesthesia as compared to those who did not[15]. Nonetheless, in combination with propofol it did increase the occurrence of PONV[15].

Environmental and occupational exposure safety: The National Institute of Occupational Safety and Health has set an upper limit for safe workplace exposure to nitrous oxide of 25 ppm. However, the environmental levels may reach up to 2000 ppm in the absence of scavenging, and many grave problems like neurological, hematologic, genotoxic, and reproductive may develop in exposed team[16, 17]. Pediatric anesthesiologists may be at the highest risk because of exposure to nitrous oxide and other inhalation agents at high concentrations and flows during the inhalation induction process and during anesthesia. In addition, nitrous oxide has been implicated in ozone destruction in the atmospheric stratosphere[18]. However, all clinical applications of nitrous oxide combined amount to < 2% of pollution related to its use and is probably of little significance, if any.

Neurodevelopmental effects: Similar to other inhalational agents, there has been a concern of nitrous

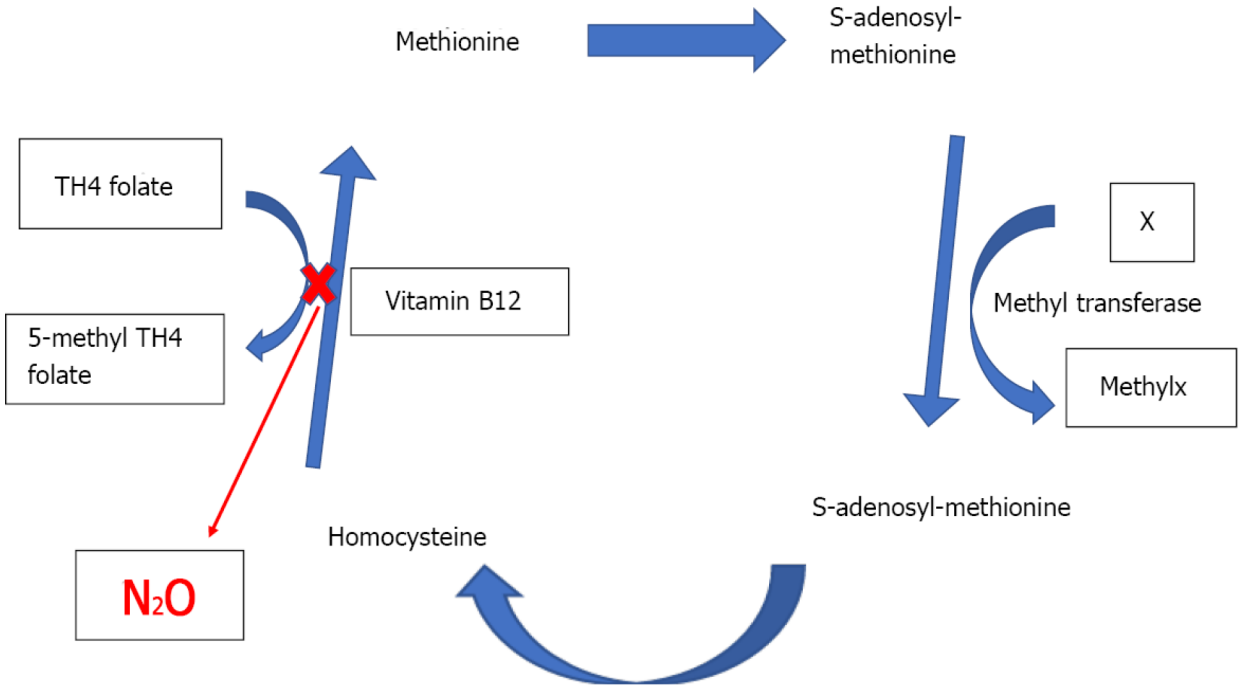

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Figure 1 Metabolic effects of nitrous oxide. Modified from: Nunn JF. Clinical aspects of the interaction between nitrous oxide and vitamin B12. Br J Anaesth 1987; 59: 3-13. N_2O: Nitrous oxide.

oxide in accelerating apoptosis in the developing brain leading to neurotoxicity[6,7,19]. The human brain continues to develop after birth for several years undergoing synaptogenesis where new synaptic connections are formed by neuronal rearrangement. At the same time, unwanted neurons undergo apoptosis. It has been proposed that nitrous oxide along with many other anesthetics may hasten neuronal apoptosis and lead to cerebral toxicity and behavioral and learning impairments later in life.

Animal studies have observed that high dose or repeated exposure to NMDA antagonists such as nitrous oxide can lead to irreversible brain damage[19,20]. Intriguingly, one rat study revealed that use of nitrous oxide alone did not increase apoptosis, but its use in combination with isoflurane considerably enhanced neuronal cell death[19]. Another rat study demonstrated that nitrous oxide with isoflurane and midazolam given for 6 h led to widespread apoptosis as well as memory and learning disability[20]. In contrast, xenon, which is an inert gas with anaesthetic properties, has been found to mitigate isoflurane related apoptosis in rat brain[21]. However, at present no human data has proven its role for harmful neurodevelopmental effects. Therefore, at present, the literature does not advocate its complete exclusion from practice of pediatric anesthesia due to this concern. However, recently the United States Food and Drug Administration released a safety alert on the risk of potential neurotoxicity of general anesthetic drugs (including nitrous oxide) in children < 3 years, and the use of general anesthesia will remain under scrutiny until the risk is categorically ruled out in the future by robust evidence.

Nitrous oxide and closed air spaces

Nitrous oxide is 30 times more blood soluble than nitrogen (air) despite being a relatively insoluble agent otherwise. The blood gas partition coefficient of nitrous oxide is 0.47 as opposed to 0.015 of nitrogen. So, nitrous oxide diffuses quickly into a closed gas space resulting in significant clinical consequences. Expansion of the airspace can cause distension of expansible spaces and increased pressure in non-expansible spaces.

It has been shown that due to the high blood flow in lungs, 75% nitrous oxide can double the volume of a pneumothorax in 10 min and triple in 30 min. Nitrous oxide can cause increased middle ear pressure, intraocular pressure, and intracranial pressure. However, it is not necessary to stop nitrous oxide prior to dura closure in craniotomy[22]. Use of nitrous oxide in bowel surgeries can increase the bowel gas causing over distension, increasing abdominal pressure, and compromising respiration[23]. The risk of venous air embolism is increased with administration of nitrous oxide by decreasing the lethal dose of volume of air embolism. Whenever venous air embolism is diagnosed, nitrous oxide administration should be halted[24]. The air-filled cuffs of endotracheal tubes and laryngeal mask airways are also susceptible to expansion with the use of nitrous oxide. The increased cuff pressure can

lead to surrounding mucosal ischemia due to impaired perfusion[25].

Hence, it is advisable to avoid the use of nitrous oxide in laparoscopic, bowel, middle ear, and vitreoretinal surgeries and to use with caution in neurosurgeries.

DISCUSSION

The present review identified the literature explaining why the usage of nitrous oxide has been under constant scrutiny, the current role of nitrous oxide in contemporary pediatric anesthesia, procedural sedation, and exploring its potential novel benefits like prevention of CPSP in the pediatric population.

Landmark trials and systematic reviews on undesirable effects of nitrous oxide as a component of general anesthetic gas mixture

Many large-scale studies and meta-analyses have been conducted to study the unfavorable effects of nitrous oxide[26-30]. The results of these trials and meta-analyses highlight why the usage of nitrous oxide have been contentious despite its remarkably safe journey of over one and a half centuries in anesthesia and its multiple advantages as a component of balanced anesthesia. A summary of the most landmark articles exploring the effects of use of nitrous oxide as a component of anesthesia have been complied in Table 3. These trials have been labelled as 'landmark' trials for nitrous oxide because of the vast magnitude of data studied and since they turned out to be trailblazers in the history of nitrous oxide use and had a direct influence on the worldwide practice of nitrous oxide anesthesia.

The ENIGMA trial by Myles *et al*[26] was the first major trial that recruited 2050 patients and compared no nitrous oxide (80% oxygen with 20% nitrogen) and nitrous oxide-based anesthesia (70% N_2O and 30% oxygen). The primary endpoint of this trial was the length of hospital stay. The secondary outcomes comprised of the length of intensive care unit stay and the incidence of postsurgical complications including death within 30 d of surgery. This trial set up a major controversary as use of nitrous oxide as a part of anesthetic gas mixture led to an increased incidence of cardiopulmonary complications, stroke, wound infection, and even mortality in the nitrous oxide cohort. This trial questioned the use of nitrous oxide and was followed by a period of nitrous oxide free anesthesia almost globally.

However, the authors countered their own findings in their next multicentric randomized study with a larger sample size of 7112 patients who had a history of coronary artery disease and were undergoing any major non-cardiac surgery[27]. They assessed the effect of the use of nitrous oxide on the incidence of mortality and any cardiovascular complication (*e.g.*, stroke, myocardial infarction, pulmonary embolism, or cardiac arrest) that occurred within 30 d of undergoing surgery. They found that the risk of cardiovascular complications, surgical-site infection, or death at 1 year were not found to be increased in the nitrous oxide group, and the risk of PONV was found to be only mildly increased[27].

To the great relief of proponents of nitrous oxide, a large trial by Turan *et al*[28], which evaluated 49016 patients who underwent noncardiac surgery, evaluated the relationship between intraoperative nitrous oxide use and 30d mortality and major postoperative complications. They documented a reduction in pulmonary complications and mortality rates with the use of nitrous oxide, while cardiac risk was not found to be increased.

A Cochrane review further substantiated the fact that use of nitrous oxide was not associated with an increased risk of pneumonia, acute myocardial infarction, stroke, wound infection, venous thromboembolic phenomenon, or increased length of hospital stay or in-hospital mortality[29]. The effect of nitrous oxide on intraoperative awareness is also contentious with some studies reporting increased incidence while others finding a protective effect of nitrous oxide. A recent Cochrane review by Hounsome *et al*[30] assessed the effect of nitrous oxide on the risk of accidental awareness under anesthesia in 5-year-old and older patients. However, despite the inclusion of 3520 patients, they found only three awareness events and could not come to a definitive conclusion regarding this.

Role of nitrous oxide in procedural sedation and analgesia

Nitrous oxide is frequently used for procedural pain relief (*e.g.*, bone marrow aspiration, intercostal drain insertion, venipuncture, lumber puncture, wound sutures, dental extraction, *etc.*)[31-35]. If used with proper precautions, no major adverse effects have been reported with nitrous oxide use for sedation[36-39].

The use of nitrous oxide in concentrations up to 50% with oxygen during pediatric procedures is an effective substitute for parenteral sedation in minor surgical procedures as it provides pain and anxiety alleviation, maintains protective airway reflexes, and is safe[31-33]. Entonox, which is a mixture of 50% nitrous oxide with 50% oxygen in equal proportions, is a good analgesic agent described in pediatric minor procedures like wound and burn dressing, suturing and suture removal, urinary catheterization, change of gastrostomy tube, synovial fluid and bone marrow aspiration, acute trauma, fracture reduction, lumbar puncture, and minor dental procedures. However, there is evidence on safe administration of nitrous oxide in delivered concentrations of 20%-70% in children without any major reported adverse events, and hence the cut-off value for procedural sedation should not be arbitrarily limited to 50% for fear of complications[33].

Table 3 Summary of results of the key clinical trials and systematic reviews in relation to use of nitrous oxide as a component of anesthesia

Trial	Ref.	Main findings
ENIGMA Trial	Myles *et al* [26], 2007	Increased rates of major complications (OR: 0.71; 95%CI: 0.56-0.89; $P = 0.003$) myocardial infarction, stroke, pneumonia, pulmonary embolism, wound infection, severe PONV (OR: 0.40; 95%CI: 0.31-0.51; $P < 0.001$), and death.
ENIGMA II Trial	Myles *et al* [27], 2014	Risk of death at 1 year, cardiovascular complications (combined RR for death and cardiovascular complications was 0.96, 95%CI: 0.83-1.12; $P = 0.64$) or surgical-site infection in the nitrous oxide group not increased ($P = 0.61$). Risk of PONV was reduced by one third in the patients not exposed to nitrous oxide ($P < 0.0001$), but the absolute risk reduction was only 4%.
A large retrospective analysis of registries	Turan *et al* [28], 2013	Patients receiving nitrous oxide had 40% lower risk of pulmonary complication (OR: 95% Bonferroni-adjusted CI: 0.59, 0.44-0.78) and death (OR: 97.5%CI: 0.67, 0.46-0.97; $P = 0.02$), while cardiovascular complications were comparable.
Cochrane review on complications with use of nitrous oxide	Sun *et al*[29], 2015	Nitrous oxide increased the incidence of pulmonary atelectasis (OR: 1.57, 95%CI: 1.18-2.10, $P = 0.002$) but had no effects on the rates of in-hospital mortality, pneumonia, myocardial infarction, stroke, venous thromboembolism, wound infection, or length of hospital stay.
Cochrane review on accidental awareness with use of nitrous oxide	Hounsome *et al*[30], 2016	Despite the inclusion of 3520 participants, only three awareness events were reported by two studies. In one study the event was due to technical failure. Due to the low quality of evidence, the authors could not determine whether the use of nitrous oxide in general anesthesia increases, decreases, or has no effect on the risk of accidental awareness.

ENIGMA: Evaluation of Nitrous oxide In a Gas Mixture for Anesthesia; PONV: Postoperative nausea and vomiting; OR: Odds ratio; CI: Confidence interval; RR: Risk ratio.

At present there is limited evidence regarding the efficacy of nitrous oxide in infants and neonates. In one prospective cohort trial, nitrous oxide was successfully utilized for sedation during tracheal intubation in preterm infants undergoing surfactant therapy[34]. In another randomized trial, the use of nitrous oxide in combination with lignocaine/prilocaine 5% ointment was found to have significantly lower pain scores when compared to topical cream or nitrous alone for injection in infants[35].

A French multicentric prospective survey assessed the side-effects among 35942 data sheets (mainly pediatric) where Entonox was used as a sole agent for procedural pain[36]. Overall, 4.4% adverse effects were reported, with the commonest being neuropsychiatric and gastrointestinal complaints (86%). Others were PONV and agitation or euphoria.

The rapid psychomotor recovery with nitrous oxide enables quicker patient discharge and removes the need for a patient to be escorted. In a French survey by Annequin *et al*[37] that assessed 1025 pediatric procedures describing the use of Entonox, Entonox alone provided unsatisfactory pain relief. Crying and physical restraint was required in many children < 3 years of age. Notwithstanding, the use of nitrous oxide was observed to have better effectiveness compared to oral midazolam for sedation during skin suturing in children[38].

Nitrous oxide is frequently used in pediatric dental procedures, and > 90% children undergoing a dental extraction procedure effectively completed the procedure under nitrous oxide sedation[32]. Nitrous oxide and midazolam were compared with the combination technique for moderate (conscious) sedation to decrease fear and anxiety associated with dental procedures in a systematic review and meta-analysis that included 534 participants[39]. Their main findings were that the combination of the two agents provides the best features and lead to fewer adverse effects due to midazolam by reducing the total dose while also facilitating better acceptance of the nitrous oxide inhalation technique and improving the recovery time.

The American Academy of Pediatric Dentistry released Guidelines in 2009 stating that the use of oxygen saturation monitoring with pulse oximetry was not mandatory for children getting only nitrous oxide for sedation in dental procedures. Similarly, guidelines from the British Dental Society did not recommend preoperative fasting before its administration. In general, the risk of aspiration during use of nitrous oxide for sedation is low, even among the non-fasted children[40-42]. However, most anesthesia-related guidelines would still recommend the standard 2 h of fasting with clear fluids before nitrous oxide sedation as there is a lack of literature directly assessing airway patency during nitrous oxide sedation and the fasting requirements.

In the majority of trials for procedural sedation and analgesia in children, nitrous oxide has been found to be favored as a combination technique in addition to use of topical creams, other sedatives, or both agents, while data is insufficient for its use as a sole agent[43-49]. The summary of various trials on procedural sedation and analgesia have been summed up in Table 4.

Use of nitrous oxide for burns victims and other chronic conditions

There is not much data on the chronic use of nitrous oxide for procedural sedation in burn victims for procedures such as burn dressings and other chronic conditions demanding repeated exposures. Few

Table 4 Summary of various trials on use of nitrous oxide for alleviation of procedural pain and sedation in children

Ref.	Main study objective	Setting/procedures	Number of children; Age	Findings
Babl *et al* [43], 2008	Depth of sedation and incidence of adverse effects with various N_2O concentrations	Pediatric ER procedures	762; 1-17 yr	N_2O in high concentration (70%) and continuous flow was found to be a safe agent for procedural sedation and analgesia in toddlers and older children
Babl *et al* [44], 2010	Sedation practices and the associated adverse events profile	Procedural sedation and analgesia from registry database at the largest Australian pediatric ER of a children's hospital	2002; 1-17 yr	N_2O was used in majority cases (81%), and incidence of serious adverse events was low. (desaturation, n = 2; seizures, n = 2, and chest pain, n = 1)
Brown *et al* [45], 2009	Evaluate the PediSedate (a N_2O delivery system combined with an interactive video component) for reducing children's behavioral distress	Children who received the PediSedate before invasive procedures	40; 3-9 yr	PediSedate is an effective system for procedural sedation in children
Ekbom *et al* [46], 2011	To find out whether oral midazolam or 50% N_2O, or 10% N_2O; along with lidocaine/prilocaine ointment is most effective in gaining IV access in obese or growth retarded children	Children and adolescents undergoing IV access at a Children's Hospital in Stockholm, Sweden	90; 5-18yr	50% N_2O resulted in an improved rate of IV access, a shorter procedure time, and a better experience for these children
Jimenez *et al*[47], 2012	Comparison of N_2O and hematoma block with and without trans-mucosal fentanyl for sedation and analgesia in the reduction of radioulnar fractures.	Retrospective, observational study, in children with radioulnar fractures in a pediatric ER	81; 4-15 yr	The combination of all 3 agents in pediatric ER improved analgesia compared with only N_2O and hematoma block combination
Lee *et al* [48], 2012	Comparison of the sedaoanalgesia profile of N_2O *vs* IV ketamine	Prospective, randomized study at ER of a single academic center in children undergoing primary repair of a laceration wound	32; 3-10 yr	N_2O was found preferable to ketamine because it provides a faster recovery, is safe, and maintains a suitable safe plane of sedation
Srinivasan *et al*[49], 2013	Determine the effectiveness and safety of procedural sedation performed using ketamine (0.5-1 mg/kg) or N_2O (50%-70%).	Retrospective review and analysis of a quality improvement database for procedural sedations performed at St Louis Children's Hospital undergoing sedation by pediatric hospitalists	8870; 7 mo to 4 yr	Combination of ketamine and N_2O provides lowest rates of complications. Respiratory and cardiovascular events occurred more frequently with ketamine, whereas NV, sedation level not achieved, and procedure not completed were more frequent with N_2O

N_2O: Nitrous oxide; ER: Emergency room; IV: Intravenous; NV: Nausea vomiting.

studies have reported its use in burns but have not specifically reported that data for better analysis. Recently, nitrous oxide has gained attention for its role in treatment-resistant refractory depression[50]. A recent study has elucidated its mechanism to be mediated through neuronal nitric oxide synthase activation in the medial prefrontal cortex[51]. However, there is no pediatric literature in this regard. Considering the recent evidence, the Food and Drug Administration alert on anesthesia related neurotoxicity in young children, and the risk of its metabolic toxicity on repeated exposures, caution should be employed while considering its use for pain and sedation for chronic conditions[52].

Role of nitrous oxide in prevention of chronic postsurgical pain

The proposed mechanism of action of nitrous oxide is by acting as a NMDA receptor antagonist, and nitrous oxide anesthesia has a potential preventive action on the development of CPSP, though it is still not proven and there is limited evidence in the pediatric subpopulation. A follow-up study of the ENIGMA-II trial at 3 mo found that use of nitrous oxide decreased the incidence of CPSP and documented that a history of severe postoperative pain in the first week of surgery, any wound related complication, and having an abdominal incision were the factors associated with increased risk of CPSP [53].

The same group of investigators later evaluated the ENIGMA-II trial participants at 12 mo of exposure to nitrous oxide and concluded that its administration had no overall benefit on CPSP, but potential benefits were found in Asian patients and patients with specific polymorphisms of the tetrahydrofolate reductase gene[54]. It was proposed that these phenotypes were more susceptible to the inhibitory effects of nitrous oxide, thereby resulting in reduced DNA synthesis. This culminated in an impaired gene expression thereby leading to impaired neuronal plasticity and neuro-inflammation.

DO WE HAVE A BETTER ALTERNATIVE?

There are several drugs being used presently as supplements to general anesthesia that have the potential to reduce the incidence of intraoperative awareness like benzodiazepines, opioids, and alpha2 adrenoceptor agonists. Nevertheless, none of these would offer comparable amnesia, analgesia and cardiovascular stability of the same degree provided by nitrous oxide[20,27,33,36,54]. Recently, xenon, which is an inert gas, has been proposed as a suitable alternative to nitrous oxide. Xenon has profound analgesic properties and superior cardiovascular stability than nitrous oxide. Furthermore, its use has not been associated with harmful neurodevelopmental consequences on developing brain. Hence, it can be considered an attractive option to nitrous oxide in pediatric anesthesia in the future[21]. Presently, its clinical value has been limited mainly by its expense.

CONCLUSION

The present narrative review summarized the data related to usage of nitrous oxide in pediatric patients. At present there is insufficient evidence to support or refute its continued usage in pediatric practice. Though several new anesthetic agents have been developed, an alternative as flexible and cost-effective as nitrous oxide is yet to be discovered. Certain adverse effects of nitrous oxide like diffusion hypoxia, its ability to expand closed airspaces, increased risk of PONV, ozone depletion, hematologic and neurologic complications, adverse effects on developing brain, and immunosuppression remain a concern to pediatric anesthesiologists. At clinically used concentrations and duration, its use does not appear to be related to hematologic complications and neurobehavioral effects on the developing brain. Its use in children seems justified as a constituent of anesthetic gas mixture and for procedural sedation in the pediatric population for light to moderate pain procedures barring its well-recognized contraindications. Combination techniques utilizing nitrous oxide in addition to topical local anesthetics and/or other sedatives have been found to be most effective for procedural sedation, and no major adverse effects reported from even large-scale trials. An individualized approach weighing the risks and benefits of nitrous oxide would be optimal in a particular case. Future perspectives include large-scale research into its specific long-term adverse effects on the developing brain in children in different conditions of administrations, research to fill the gaps in knowledge related to procedural sedation and exploring its potential novel benefits like prevention of CPSP in the pediatric subpopulation.

FOOTNOTES

Author contributions: Gupta N and Gupta A contributed equally to this work; Gupta N contributed to the concept and data retrieval; Gupta N and Gupta A designed the narrative review, analyzed the data and wrote the manuscript; Gupta A and Narayanan M R V retrieved the data and performed the data analysis and research; all authors have read and approved the final manuscript.

Conflict-of-interest statement: There are no conflicts of interest for any of the authors. None of the authors has received any fees for serving as a speaker, a position, such as consultant and/or an advisory board member or research funding from any organization. Also, the authors do not hold stocks and/or shares in any such firm and do not have a patent.

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S-Editor: Wu YXJ
L-Editor: Filipodia
P-Editor: Wu YXJ

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World Journal of Clinical Pediatrics

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World J Clin Pediatr 2022 March 9; 11(2): 105-119

DOI: 10.5409/wjcp.v11.i2.105

ISSN 2219-2808 (online)

REVIEW

Non-pharmacological management of pediatric functional abdominal pain disorders: Current evidence and future perspectives

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Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Kesavelu D, Pavlovic M

Received: March 20, 2021
Peer-review started: March 20, 2021
First decision: July 18, 2021
Revised: July 19, 2021
Accepted: February 11, 2022
Article in press: February 11, 2022
Published online: March 9, 2022

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Abstract

Functional abdominal pain disorders (FAPDs) are an important and prevalent cause of functional gastrointestinal disorders among children, encompassing the diagnoses of functional dyspepsia, irritable bowel syndrome, abdominal migraine, and the one not previously present in Rome III, functional abdominal pain not otherwise specified. In the absence of sufficiently effective and safe pharmacological treatments for this public problem, non-pharmacological therapies emerge as a viable means of treating these patients, avoiding not only possible side effects, but also unnecessary prescription, since many of the pharmacological treatments prescribed do not have good efficacy when compared to placebo. Thus, the present study provides a review of current and relevant evidence on non-pharmacological management of FAPDs, covering the most commonly indicated treatments, from cognitive behavioral therapy to meditation, acupuncture, yoga, massage, spinal manipulation, moxibustion, and physical activities. In addition, this article also analyzes the quality of publications in the area, assessing whether it is possible to state if non-pharmacological therapies are viable, safe, and sufficiently well-based for an appropriate and effective prescription of these treatments. Finally, it is possible to observe an increase not only in the number of publications on the non-pharmacological treatments for FAPDs in recent years, but also an increase in the quality of these publications. Finally, the sample selection of satisfactory age groups in these studies enables the formulation of specific guidelines for this age group, thus avoiding the need for adaptation of prescriptions initially made for adults, but for children use.

Key Words: Functional abdominal pain disorder; Pediatrics; Rome IV; Behavioral intervention; Non-pharmacological treatment; Complementary medicine

Core Tip: Functional abdominal pain disorders are an important and prevalent cause of functional gastrointestinal disorders among children. In the absence of sufficiently effective and safe pharmacological treatments for this public problem, non-pharmacological therapies emerge as a viable means of treating these patients. Thus, the present study provides a review of current and relevant evidence on non-pharmacological management of these disorders, as cognitive behavioral therapy, meditation, acupuncture, and others. This article also analyzes the quality of publications in the area, assessing whether it is possible to state if non-pharmacological therapies are viable, safe, and sufficiently well-based for an appropriate and effective prescription.

Citation: Cordeiro Santos ML, da Silva Júnior RT, de Brito BB, França da Silva FA, Santos Marques H, Lima de SouzaGonçalves V, Costa dos Santos T, Ladeia Cirne C, Silva NOE, Oliveira MV, de Melo FF. Non-pharmacological management of pediatric functional abdominal pain disorders: Current evidence and future perspectives. *World J Clin Pediatr* 2022; 11(2): 105-119
URL: https://www.wjgnet.com/2219-2808/full/v11/i2/105.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i2.105

INTRODUCTION

Functional gastrointestinal disorders (FGIDs) are a group of diseases defined by morphological and physiological changes that affect from the gastrointestinal tract (GIT) to the central nervous system (CNS). Among the main changes listed in this group, there are disorders of intestinal motility, visceral hypersensitivity, and changes in the mucosa and in the host's immune responses, in addition to possible changes in the normal microbiome of the intestinal environment[1].

FGIDs are stratified in alphabetical letters from A to H, with the present article focused on non-pharmacological treatment specifically for group H (FGIDs in children or adolescents), subtype H2, defined as functional abdominal pain disorders (FAPDs) by the Rome IV criteria. This group consists of functional dyspepsia (H2a), irritable bowel syndrome (IBS) (H2b), abdominal migraine (H2c), and functional abdominal pain not otherwise specified (H2d), with the latter not previously present in Rome III[2].

With regard to the diagnosis of FGIDs, the 2016 Rome IV criteria removed the obligation to rule out organic causes using complementary tests, making the clinical evaluation criteria sufficient for diagnosis, thus avoiding the exposure of these patients to unnecessary testing[1]. In this sense, complementary/laboratory examinations are not required for diagnosis after careful clinical examination and in the absence of alarm criteria that suggest organic causes or complications of FAPDs. The following is considered alarm criteria: Family history of inflammatory bowel disease, celiac disease, or peptic ulcer disease; persistent right upper or right lower quadrant pain; dysphagia; odynophagia; persistent vomiting; gastrointestinal blood loss; nocturnal diarrhea; arthritis; perirectal disease; involuntary weight loss; deceleration of linear growth; delayed puberty and unexplained fever[1]. The stratified diagnostic criteria for FAPDs are shown in Table 1.

Regarding the prevalence of FAPDs, it is estimated that about 13.5% (95% confidence interval [CI]: 11.8-15.3) of the children worldwide present one of the diseases in this group, with emphasis on IBS, representing 8.8% (95%CI: 6.2-11.9) of that number. In addition, risk factors for the development of FADPs were identified as being female (15.9% prevalence *vs* 11.5% male) and the presence of anxiety, depression, stress symptoms, or traumatic life events[3].

In view of the important prevalence of FAPDs, it is necessary to establish effective and adequate treatments, ensuring not only the control of symptoms but also the safety of patients. In addition, because studies of pharmacological safety in an age group are insufficient, the use of efficient non-pharmacological therapies in the treatment of the pediatric public is ideal. Thus, the aim of this article is to understand, through a review of the literature available in the main databases, the use of different non-pharmacological therapies in the treatment of FAPDs in children, analyzing from how they have been indicated to the levels of evidence that sustains their prescription.

Table 1 Diagnostic criteria for functional abdominal pain disorders in children and adolescents

H	FGIDs in children or adolescents
H2	Functional abdominal pain disorders
H2a	Diagnostic criteria for functional dyspepsia
	One or more of the following symptoms at least 4 d per month: (1) Postprandial fullness; (2) Early satiation; (3) Epigastric pain or burning not associated with defecation; and (4) After appropriate evaluation, the symptoms cannot be fully explained by another medical condition
	Within FD, the following subtypes are now adopted: (1) Postprandial distress syndrome; and (2) Epigastric pain syndrome
H2b	Diagnostic criteria for irritable bowel syndrome
	All of the following: (1) Abdominal pain at least 4 d per month (associated with one or more of the following: (a) Related to defecation; (b) Change in frequency of stool; and (c) Change in appearance of stool); (2) In children with constipation, the pain does not resolve with resolution of the constipation; and (3) After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.
H2c	Diagnostic criteria for abdominal migraine
	All of the following occurring at least twice: (1) Paroxysmal episodes of intense, acute periumbilical, midline or diffuse abdominal pain lasting 1 h or more; (2) Episodes are separated by weeks to months; (3) The pain is incapacitating and interferes with normal activities; Stereotypical pattern and symptoms in the individual patient; (4) The pain is associated with 2 or more of the following: (a) Anorexia; (b) Nausea; (c) Vomiting; (d) Headache; (e) Photophobia; and (f) Pallor; and (5) After appropriate evaluation, the symptoms cannot be fully explained by another medical condition
H2d	Diagnostic criteria for functional abdominal pain not otherwise specified
	All of the following at least 4 times per month: Episodic or continuous abdominal pain that does not occur solely during physiologic events; Insufficient criteria for irritable bowel syndrome, functional dyspepsia, or abdominal migraine; After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition

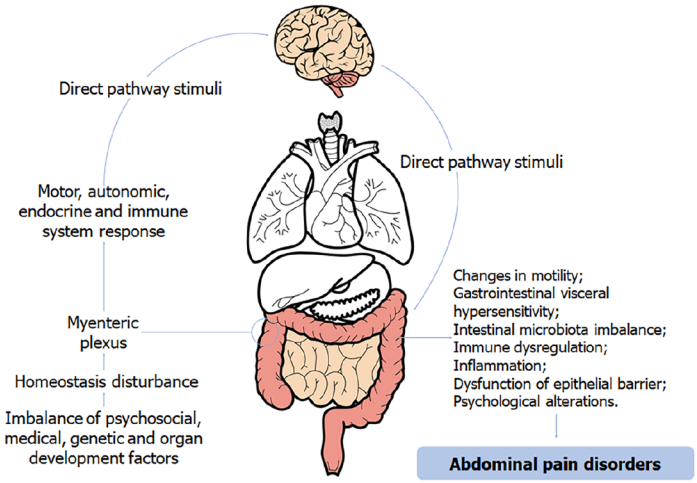
All criteria must be fulfilled for at least 2 mo before diagnosis[1,2]. FGIDs: Functional gastrointestinal disorders; FD: Functional dyspepsia.

PATHOGENESIS

The pathogenesis of FAPDs in children is not well understood; however, it has currently been observed that the microbiota-intestine-brain axis plays an important role in these diseases, as pathophysiological development seems to be linked to changes in its integrity and/or functionality[4]. This neuroanatomical axis has an integrated and complex circuit that processes information about the emotional, sensory, and cognitive situation. In this sense, there are direct connections from the CNS and the GIT with myenteric plexus act on the individual's motor, autonomic, endocrine and immune system[5]. The influence of this neuronal circuit has a direct reflex on the CNS and can trigger responses that result in changes in motility, gastrointestinal visceral hypersensitivity, intestinal microbiota, immune dysregulation, inflammation, and dysfunction of barriers[6]. This is the most accepted hypothesis in the biopsychosocial model of FAPDs in children, and is linked to psychosocial, medical, genetic, and developmental factors of the organs and circuits involved in this axis. Disturbances on these systems and their homeostasis may result in some disorders. This axis is represented graphically in Figure 1.

A study with patients with IBS demonstrated that gastrointestinal motility problems are linked to delayed gastric emptying and increased intestinal transit[7]. In another study conducted in Texas, USA, impaired myoelectric activity in the gastric environment was observed in patients with functional dyspepsia. The result of measuring myoelectric activity suggested a decrease in normal slow waves and an excessive amount of arrhythmic waves, resulting in impaired coordination of gastric slow waves[8]. Riezzo *et al*[9] evaluated 52 children with non-ulcer dyspepsia and 114 healthy children, and changes in the electrical activity of the gastric environment and delayed gastric emptying were also observed. In addition, serotonin receptors and transporters may play an important role in this integrated response relationship of the gut-brain axis[10]. Further studies on this topic are needed, since there are still few publications on the contribution of altered gastric motility in children with these functional disorders, and most of these are with adult patients.

Gastrointestinal visceral hypersensitivity is the most widespread and accepted mechanism of abdominal pain in the literature[11]. The perceptual response of hyperalgesia is characterized by changes in the signal processing of the primary neurons afferent from the enteric nervous system to the CNS, which interprets this stimulus as abdominal pain and triggers a series of reflexes that are recognized as pain[11,12]. Therefore, visceral sensitivity is also regulated at various levels of the microbiota-intestine-brain axis, such as the enteric mucosa and submucosa, medulla, thalamus, and cerebral cortex[12], which demonstrates an integrated sensory response throughout this axis. In a study of 51 children, a decrease in sensory threshold was observed in patients with FGIDs when compared to children with organic diseases[13], which indicates that this decreased sensory threshold associated with changes in neuronal stimuli is possibly the explanation of visceral hypersensitivity in FGIDs.



DOI: 10.5409/wjcp.v11.i2.105

Figure 1 Graphical representation of the gut-brain axis in the pathogenesis of functional abdominal pain in pediatric populations.

Evidence shows that the microbiota of patients with FGIDs differs from healthy people[14]. In a recent systematic review with patients with IBS, with three studies included with children, a significant increase in the bacterial population of the family *Enterobacteriaceae* and *Lactobacillaceae* and genus *Bacteroides* in patients with IBS when compared with the control group was observed. In addition, there was a decrease in bacterial colonization of *Bifidobacterium spp*., *Faecalibacterium spp*., and *Faecalibacterium prausnitzii*[15], which plays an important role in the balance of the immune system in the intestine[16]. However, the role of the microbiota in relation to functional diseases in children is not well established. Most studies evaluated fecal samples from adult patients with IBS and have limitations in relation to sample collection, and diet and medication used by the patient. In this sense, more studies would be important in order to understand the influence that the way of delivery, metabolome and other microorganisms have on the intestinal microbiota of these children.

Homeostasis of the microbiota-intestine-brain axis is essential to maintain the integrity of the immune system, and disturbances in this balance can generate uncontrolled inflammation in the gastrointestinal mucosa. Interestingly, infiltration of mast cells, eosinophils, and lymphocytes has been observed in intestinal environment of patients with functional disorders. In particular, mast cell recruitment is involved in epithelial and neuromuscular dysfunction[17]. These inflammatory cells are close to neurosensorial fibers of the GIT mucosa and have a relevant role in altering neurogenic inflammatory pathways and in perception of pain in response to harmful stimuli[18]. In addition, the degree of inflammation in the GIT mucosa can cause injuries and, consequently, a rupture of barriers that restrict bacterial colonization under normal conditions. As a result, bacterial overgrowth can be observed, which can culminate in FGIDs[12,19].

High self-perceived prevalence of food intolerances has been reported in children with IBS[20]. These symptoms are associated with nutritional behavioral changes and children's diet[21]; however, the knowledge about how nutritional factors influence functional gastrointestinal diseases is still unclear. Therefore, greater knowledge about a possible adequate nutritional pattern for maintaining the balance of the microbiota-intestine-brain axis may be ideal for a better understanding of the relationship between food and the intestinal microbiota in that axis.

The psychological factors and their relationship to intestinal motility are well understood. Some studies have already demonstrated the physiological effects on the GIT, triggered by anger, fear, and anxiety[12]. In a recent review, the authors concluded that although it is still unclear whether FGIDs may have psychological factors as their etiology, there is strong evidence that these factors exacerbate and contribute to maintenance of pain[22]. An interesting correlational study found a decrease in the symptoms of functional disorders in children in summer, when compared to spring (P = 0.017). The authors correlated this improvement to the vacation period when they are exposed to fewer stressors, but were unable to distinguish what is the cause and what is the effect of decreasing symptoms[23]. Also, the hypothalamus-pituitary-adrenal axis may have an interaction with the microbiota-intestine-brain axis, releasing cortisol and corticotropin, which stimulate metabolic stress and cause a release of mast cells and pro-inflammatory cytokines[4]. Stress factors can also deregulate the balance of the intestinal microbiota, increasing the permeability of epithelial tissue, and facilitating the entry of pathogens that can create an inflammatory environment. In addition, the release of cytokines such as IFNγ, IL-1, and IL-6 can stimulate an immune response in the CNS and reflect an exacerbation of psychological symptoms[24]. With this, it becomes increasingly important that children with symptoms related to FGIDs receive the integration of the psychological examination in their global care[25].

In view of all these factors discussed, it is clear that the pathogenesis of these functional disorders does not affect only one organic system. Although not well understood, the etiologies of these disorders are found in all areas of the individual's biopsychosocial being, and are present in organic, nutritional, and psychological neuronal axes. More robust studies with better levels of evidence on the pathogenesis of these functional disorders in children are needed.

PHARMACOLOGICAL TREATMENTS

The published literature on treatments for FAPDs is still scarce, and the effectiveness of pharmacological therapy lacks studies that provide quality scientific evidence[26]. Although there are a large number of studies indicating pharmacological efficacy in relation to placebo, most studies that analyze pharmacological intervention have a small sample size, are uncontrolled or non-randomized, and even present controversial or incomplete results. In addition, most studies have methodological flaws that prevent authors from drawing significant conclusions about effectiveness[27-31]. Therefore, the current guidelines and studies recommend that the initial approach to pediatric patients with these disorders be non-pharmacological and then choose the pharmacological one, observing for possible side effects[32]. Potential pharmacological treatments for FADPs have been identified based on the gut-brain axis, mainly including antispasmodics, antidepressants, secretagogues, antihistamines, anti-reflux agents, calcium channel blockers, serotonin antagonists, laxatives, antibiotics, and hormone therapy[33].

Antispasmodics

This category includes drugs that reduce intestinal contraction through different mechanisms of action. Kline *et al*[34] in his double-blind study of 50 children with IBS, found reduced pain severity in 76% of patients at 2 wk after using peppermint, against 19% by placebo. The use of peppermint is based on its menthol component that reduces colon spasms by blocking Ca^{2+} channels and no side effects have been reported. Pourmoghaddas *et al*[35] and Karabulut *et al*[36] evaluated, respectively, the use of mebeverine and trimebutine, medications that have specific action on smooth muscle cells. In the first study, the authors found no statistically significant differences in relation to the use of placebo[35]. In the second, the results indicated a relief in abdominal pain, but they were obtained based on questions asked to parents, and not to children, just as the study was not blinded or controlled[36]. The only other study that reported the use of trimebutine in children was that of Giannetti *et al*[37], but the number of patients treated was very low, and the study was not intended to assess the effectiveness of this particular medication, but rather a variety of other approaches. Narang *et al*[38] tested drotaverine compared to placebo in 132 children for 4 wk, and although the authors reported a decrease in episodes of abdominal pain, they did not describe the intensity of the pain.

Antidepressants

Amitriptyline has been studied in FAPDs, mainly in adults, due to a probable change in pain perception. Bahar *et al*[28] found improved quality of life (measured through a questionnaire) and diarrhea, and inconsistent pain improvement in some, but not in all, areas of the abdomen and only at certain times *vs* placebo. The study conducted by Saps *et al*[29] also using amitriptyline *vs* placebo for 4 wk treatment did not indicate a significant difference between groups. The group using amitriptyline stood out only in improving anxiety. Another antidepressant, citalopram, was tested by Roohafza *et al* [39] in their study with 115 children with abdominal functional disorders. There was also no significant difference in symptom improvement between the treated group and the placebo group. Cooper *et al*[40] reported, in a review, very low quality evidence to support the use of amitriptyline, citalopram, and gabapentin, in addition to which none of the studies analyzed achieved the desired primary result of abdominal pain relief of 30% or more.

Antihistamines

The change in the concentration of serotonin in the intestine may be responsible for causing visceral dysmotility and hypersensitivity. Therefore, this class may have potential in the treatment of abdominal pain in children. Cyproheptadine was evaluated by Sadeghian *et al*[27] in a double-blind, placebo-controlled study with 29 children over 2 wk. At the end of the study, cyproheptadine demonstrated a better decrease in the intensity and frequency of pain, as well as an improvement in the assessment of general condition. However, this study showed limited follow-up, low methodological quality, and use of non-validated questionnaires. Madani *et al*[41], in a follow-up of pediatric patients for 7 years, indicated that cyproheptadine was effective in 73% of patients and safe in 68%. In a recent review, the same authors confirmed the effectiveness of this medication[42].

Antibiotics

Used in an attempt to alter the harmful intestinal microbiota in two different trials with a small sample of pediatric patients, rifaximin (approved in 2015 by the FDA for the treatment of adults with IBS-D) and cotrimoxazole did not indicate statistical differences compared to the placebo group[30,43]. In the

first study, the authors assessed abdominal pain, episodes of diarrhea and constipation, feeling of incomplete or effective evacuation, urgency to evacuate, effort to evacuate, and the presence of some fecal secretion. Erythromycin, another antibiotic that appears to have agonist properties of the motilin receptor in the stomach, has been reported to be useful in relieving symptoms of abdominal pain and dyspepsia in adults, but there is still insufficient pediatric data for clinical indication[44].

Serotonin antagonists

One of the only medications in this class reported in studies was pizotifen. Symon *et al*[45] comparing it to placebo, reported that the children in the study showed a reduction in the "Severity Index" related to abdominal pain. However, this study presented a small sample of 16 patients with abdominal migraine, was interrupted before more patients were included in the study, and used a scale with no validation [45].

H2 receptor antagonists

In the study of See *et al*[46], 25 children with dyspepsia and functional abdominal pain were treated with famotidine or placebo. At the end of the study, there was no significant difference in treatment regarding the frequency of abdominal pain, pain intensity, and dyspeptic symptoms. In addition, the group that received famotidine had an improvement in the overall assessment of 66.7%, while the group that received placebo had a 15.4% improvement in this same parameter. However, the authors provided insufficient data to establish a confidence interval between these percentages[46].

Prokinetics

Domperidone was used in a placebo controlled trial to assess the response in children with functional dyspepsia[47]. According to the results, patients did not show a different cure rate between domperidone and placebo after 8 wk, and no data was reported to indicate improvement in nausea - an important symptom in this pathology. However, after being followed for 6 mo, the children who received the medication showed an increase in the cure rate and in the overall assessment. Prokinetics have been used mainly in situations where functional abdominal pain is accompanied by constipation or delayed gastric emptying, as in IBS. Nevertheless, in several regions of the world, they have their commercialization restricted due to its side effects, including cardiovascular events[48].

Proton pump inhibitors

Proton pump inhibitors are usually indicated for the treatment of dyspeptic symptoms, since they end up acting in the acidic environment of the digestive tract. Karjoo and Kane[49], in their study with 153 patients aged 6 to 18 years with abdominal pain and dyspepsia, reported a significant improvement in symptoms, especially those who were resistant to the use of H2 antagonists. The patients in this study were treated with high-dose ranitidine hydrochloride and omeprazole as the main proton-pump inhibitor[49].

Hormonal treatments

Melatonin, a hormone produced by the pineal gland, has also been studied in the treatment of these pathologies, and its use is justified by a possible improvement in sleep. Zybach *et al*[50] analyzed the efficacy of melatonin in children with functional dyspepsia for 2 wk in a double-blind, randomized, placebo-controlled crossover study with a small sample of 12 patients. They found a positive clinical response in 42% of individuals with melatonin *vs* 50% of individuals who received placebo. In this sense, no efficacy was observed in the use of melatonin for the relief of abdominal pain in functional conditions[50].

Secretagogues

Some secretagogues have been evaluated in functional conditions that generate abdominal pain, such as IBS with a predominance of constipation. In an uncontrolled trial in children and adolescents, the use of lubiprostone was shown to be beneficial in increasing the frequency of spontaneous evacuation and pain[31]. In another double-blind, randomized, controlled study[51], the frequency of bowel movements, pain, effort, and consistency of stools did not show a statistically significant difference when comparing lubiprostone and placebo. Thus, further controlled studies are needed to confirm the effectiveness of this medication for the treatment of abdominal pain specifically, as they are already confirmed to be beneficial in the treatment for constipation. On the other hand, linaclotide is currently approved by the FDA and the European Medicines Agency for the therapy of chronic constipation in adults. At the moment, there are no published studies reporting efficacy and safety of the use of linaclotide in children, but there is a double-blind multicenter study under development, with children and adolescents, to assess this (NCT02559817)[52].

In view of the high prevalence of FAPDs in children, their high impact on quality of life, and lack of significant studies, there is still a gap in the search for safe and effective pharmacological therapies, with well-developed, randomized, controlled and multicenter studies. It is also important to highlight that this process is important to prevent maleficent effects of these drugs in a system that is still ongoing

neuroplasticity changes and growth development. In addition, it is necessary to pay attention to the cost-benefit ratio that the medication will offer, especially in relation to placebo and non-pharmacological therapies[51,52].

NON-PHARMACOLOGICAL TREATMENTS

The incorporation of integrative and complementary non-pharmacological interventions in management of the pediatric chronic pain has demonstrated to be viable and effective for this population[53,54]. Such methods can lead to long-term results due to changes in the neural circuits that regulate habits, affection, and cognitive responses to pain[55]. Thereby, treatments such as cognitive behavioral therapy (CBT), acupuncture, spinal manipulation, exercise, among others come to assist the health professionals in pediatric chronic pain therapy. As an aim of this study, we based the classification of integrative and complementary practices on the structure proposed by the database Biblioteca Virtual de Saúde – Medicinas Tradicional Complementares e Integrativas das Américas (BVS-MTCI), developed by the Traditional Complementary and Integrative Medicine Web of America[56].

Mind-body therapies

Cognitive behavioral therapy: CBT is based on the premise that thoughts, emotions, and behaviors are linked, as well as how someone perceives a situation can significantly influence emotional, behavioral and physiological responses[54]. CBT involves the teaching of coping and distraction strategies and relaxation techniques; identification and change of pain-related thoughts; and modification of family responses to pain. This method can involve the family itself or may focus only on the child, as well as be performed face-to-face or remotely[57,58]. Family approach seeks to alter environmental factors that might reinforce the child's pain behavior within the family and to identify and treat factors that may precipitate in it[58].

There is growing support for CBT for children with FAPDs[59]. Multiple components are typically used in CBT, such as education about the pain, increasing self-confidence[60], cognitive restructuring of maladaptive thoughts, exposure exercises, relaxation, and parent management techniques[61]. In exposure-based CBT for FAPDs, the patients gradually expose themselves to symptom-provoking stimuli (such as eating pizza) and approach situations in which symptoms are perceived as intolerable (such as being in school). This approach is hypothesized to decrease fear and avoidance related to symptoms and thereby enables symptom reduction[61].

A randomized clinical trial with 104 children aged 7-18 years investigated the effectiveness of a 6 weekly session CBT protocol compared with 6 visits to a pediatric gastroenterologist and the impact of these interventions on pain. This CBT session resulted in a significant reduction of abdominal pain in 60% of children with FAP up to 1 year after treatment, and the CBT is more effective than intensive medical care directly after treatment[62]. Another study showed that children who received CBT improved significantly more than the control group on abdominal pain-related symptoms and coping strategies, as well as parental solicitousness in response to pain behaviors. Moreover, many of these differences were maintained 6 mo after intervention[63].

Furthermore, Internet-delivered CBT (Internet-CBT) may help to bridge this treatment gap. Internet-CBT holds several advantages over traditional face-to-face therapy: It can be delivered to people in remote areas, patients can access the treatment without taking time off from school or work, and it requires fewer therapist hours per patient[64].

One study reported outcomes in adolescents aged 13–17 years with IBS who received a 10-wk session of Internet-delivered exposure CBT, compared with wait-list controls. There was a large change before and after treatment in gastrointestinal symptoms, with a medium effect size, and improved anxiety, school absenteeism, and adolescent-rated and parent-rated quality of life. After 6 mo, the results were stable or significantly improved[65].

Furthermore, a randomized clinical trial with 90 children diagnosed with FAPDs, based on the Rome IV criteria, found that Internet-CBT has the potential to increase the availability of treatment for a number of patients and reduce health care costs[66]. Moreover, more than half of the children in the Internet-CBT group reported a 30% or greater improvement of their gastrointestinal symptom severity at the 10-wk follow-up evaluation *vs* 32% of the children in the treatment-as-usual group[66].

Meditation: Meditation can be defined as a form of mental training that aims to improve an individual's core psychological capacities, such as attentional and emotional self-regulation[67]. Meditative techniques include transcendental meditation, mindfulness-based stress reduction, and mindfulness-based cognitive therapy[68]. Of these practices, mindfulness meditation has received most attention in neuroscience[69]. In current clinical and research contexts, mindfulness meditation is typically described as non-judgemental attention to experiences in the present moment and requires both the regulation of attention and the ability to approach one's experiences with openness and acceptance[69,70]. This nonjudgmental focus on present-moment experience appears to be a potentially avenue in helping adolescents attend to pain adaptively[71].

An increasing body of literature has demonstrated that mindfulness interventions are feasible and efficacious in adult pain populations[72,73]. On the other hand, pediatric populations that experienced chronic pain conditions, as neuropathic and abdominal pain, have demonstrated initial feasibility and acceptability of mindfulness-based interventions (MBIs)[74,75]. While preliminary research among pediatric pain populations demonstrates feasibility and acceptability of MBIs, additional studies are necessary to investigate mindfulness in children and adolescents with chronic pain. Thus, this intervention may be low cost or free adjunctive treatments that have fewer side effects as compared to pharmacological interventions[54].

Traditional health system

Acupuncture: Acupuncture is an ancient medical procedure that has been practiced in China and other East Asian countries. The technique involves the placement of small needles at various locations in the body and related therapies include electroacupuncture, acupressure, moxibustion (*i.e.*, burning of an herb near an acupoint to create local warming), laser stimulation of acupoints, and non-invasive stimulation of acupoints utilizing a transcutaneous electrical nerve stimulator[54].

The mechanisms of the relationship between acupuncture and improvement of the pain remain uncertain. Studies have shown that the acupuncture may involve normalization of activity in areas of the limbic system often referred to as the "pain matrix" (*i.e.*, the insula, anterior cingulate gyrus, and prefrontal cortex)[76], or can stimulate endorphin release[77]. This method is also postulated to have effects on acid secretion, gastrointestinal motility, and sensation of visceral pain, possibly mediated through the release of opioid peptides in the central and enteric nervous system[38].

However, while substantial research has shown acupuncture to be an effective therapy for pain among the adult population, there is limited research on acupuncture with regard to the treatment of pain among pediatric patients[78]. Despite this scarce literature, a systematic review published identified common minor adverse effects and rare serious harms in pediatric acupuncture[79]. Puncture redness is the most commonly reported side effect, followed by needle pain and light-headedness[80].

A systematic review of randomized controlled trials on the use of acupuncture in infantile colic shows that acupuncture appears to be effective in alleviating the symptoms of colic, including crying and feeding and stooling problems. However, due to the small sample sizes of the included studies, more randomized clinical trials are necessary[81]. Another case series study found that minimal acupuncture in infantile colic is an effective and easy treatment procedure[82].

A difficulty in treating the pediatric population is children's fear of needles. The treatment periods are reduced compared with the treatment of adults and closely monitored. Non-invasive modalities, such as electrical stimulation or laser, on acupoints and acupressure seem to be well accepted by younger children[80].

Although acupuncture is safe when administered by appropriately trained and credentialed practitioners, there are some children who have a fear of needles or for medical reasons such as low platelet count or immunodeficiency that may not be recommended to receive acupuncture. For those patients, other techniques such as acupressure[78], laser acupuncture, topical magnets, and acupressure beads may be used. They may also be used as adjunctive treatments following needle placement[83].

Moxibustion: A meta-analysis compared the effectiveness of the use of moxibustion with conventional drugs for inflammatory bowel disease and concluded that this method may be useful in the treatment of the disease. There was a significant improvement of general symptoms related to the disease (P = 0.0001); however, regarding specific symptoms, only abdominal distension (P = 0.03) and frequency of defecation (P = 0.02) were significant. Moreover, the authors highlighted that there is a low number of clinical trials evaluating this treatment[84]. In a recent study, Liu and Zeng[85] evaluated the effectiveness of the umbilical therapy combined with moxibustion for diarrhea in pediatric patients. The results showed that the treatment significantly improved the symptoms of diarrhea (P = 0.05) and was associated with a shorter recovery time for the children (P = 0.05)[85]. Another Chinese study used moxibustion to treat 120 children with abdominal pain. The effectiveness rate of the treatment after 3 mo was 94.78%, compared to 80.77% in the control group[86].

Yoga: Yoga has been shown to be an exercise that provides several benefits for children, including improvements in the emotional control, anxiety, and depression[87,88]. Moreover, it seems to be effective in assuaging pain associated with some abdominal disturbances in that population[26]. A study carried out by Brands *et al*[89] evaluated the repercussions of Yoga practice in 20 children (age range: 8-18 years) with inflammatory bowel syndrome or abdominal pain. The children participated in 10 Yoga sessions, lasting 1.5 h each, being observed that the exercises reduced the severity and frequency of abdominal pain immediately after the classes. Moreover, after 3 mo of continued exercises at home, the children continued to report improvements; however, the status of the preexisting conditions was not modified[89]. A recent study enrolling adolescents aged from 14 to 17 years with inflammatory bowel disease demonstrated that the use of Yoga for 6 wk resulted in an improvement of abdominal pain, sleep, and visceral hypersensitivity among responding participants. Nonetheless, the findings for the abdominal symptoms were not statistically significant (P = 0.8) and the study sample was small (n = 18)[90]. As for Evans *et al*[91], the study showed that an intervention with Yoga as a

complementary treatment benefits young adults with IBD with a reduction of symptoms. In contrast, a systematic review has stated that the existing studies on Yoga and inflammatory bowel disease do not present satisfactory scientific quality. Therefore, it concluded that, although Yoga is a safe practice for pediatric patients, there are no official recommendations for its use[92].

Manual therapy

Massage: Therapeutic massage has been associated with a significant improvement among pediatric patients with chronic pain due to several diseases, including abdominal disturbances. A study evaluated various techniques such as compression, triggering points, petrissage, tapotement, and effleurage, and concluded that the use of massages is a reasonable option as an adjuvant treatment since they reduce pain, agony, discomfort, and humor alterations[93]. Nam *et al*[94] observed the effects of flavoring massages of the abdominal meridians in children with cerebral lesions and concluded that the use of the therapy 3 to 5 times a week was associated with an improvement in constipation. Another study including patients aged from 4 to 18 years demonstrated that the combined use of isometric training of abdominal muscles, respiratory exercises, and abdominal massages resulted in the reduction of the frequency of evacuation among patients with chronic functional constipation (P = 0.01). The treatment was based on sessions of 40 min each, two times a week, for 12 wk[95]. A systematic review evaluated the occurrence of adverse events related to massotherapy in premature babies and reported that it may lead to mild and severe side effects including hematoma, status epilepticus, and volvulus. However, the study identified publication bias and, therefore, it was not possible to identify the causal relationship between the adverse events and massotherapy, though authors recommend caution to perform this method in premature newborns[96]. Moreover, a study including 40 babies showed that abdominal massage with lavender oil has the potential to reduce colic in children aged from 2 to 6 mo. The results were obtained based on the frequency of weekly cries of the patients, and those who underwent massage with lavender oil used to cry less often than the individuals from the control group (P < 0.05)[97]. In a recently published study, Al Qahtani and Ahmed recommended the development of educational programs aiming to teach abdominal massage and feet reflexology techniques for parents, since it is an effective way to improve abdominal colic in babies[98].

Spinal manipulation: The relationship between spinal manipulation and improvement of symptoms related to abdominal disorders is controversial. Some studies have indicated that the therapy may be associated with an improvement of abdominal pain among children[26,99]. On the other hand, a systematic review of clinical trials was not able to conclude that the spinal manipulation is an effective therapeutic practice against infant colic, and the author stated that the low quality of the studies contributes to the lack of consistent recommendations on that issue[100]. Another recent systematic review showed that the spinal manipulation has some advantages in the control of some types of pain such as lumbar and cervical pain; however, the knowledge on the benefit of that technique against infant colic is still limited since there are many contradictory and low-quality studies evaluating that therapy[101]. In that context, a review evaluated the safety of the performance of spinal manipulation in children and concluded that most side effects reported were mild and that moderate-to-severe adverse events linked to this technique remain unknown[102]. In contrast, Vohra *et al*[103] suggested that the manipulation of the spine may be related to severe side effects in the pediatric population. However, important limitations were highlighted in both studies.

Physical activities: Boradyn *et al*[104] carried out a study including 25 children aged from 5 to 11 years to evaluate the impact of the lifestyle in pediatric patients diagnosed with functional abdominal pain. The results showed that the practice of physical activities might increase the frequency of evacuation among children (P = 0.031); however, the data regarding the relationship between exercises and abdominal pain were not statistically significant[104]. A recent study observed an association between the practice of physical activities and the development of constipation among children and identified that infants who often practice exercises had a lower odds of acquiring the disorder than sedentary individuals (P = 0.016)[105]. Complementally, a study that evaluated the effectiveness of alternative complementary medicine for functional abdominal pain observed that 49% of the patients enrolled used to practice exercises to improve their symptoms. Moreover, individuals who rated their condition as severe tend to practice exercises more often than those who rate their disorders as mild or moderate (P = 0.043)[106]. Kichline *et al*[107] recently observed that young individuals with chronic abdominal pain did not use to practice physical activities 60 min per day. In addition, another study evaluated socioeconomic factors involved in the probability of occurrence of gastrointestinal disorders related to abdominal pain and concluded that the low practice of exercises is positively associated with the disorder (P = 0.028)[108,109].

In view of the individual discussion of each of these non-pharmacological therapies, the level of evidence for each of them is stratified in Table 2, in addition to the analysis of the public of each study (adults/children) and the timeline of the publications in each of those areas.

Table 2 Levels of evidence for different non-pharmacological therapies in the treatment of pediatric functional abdominal pain disorders

Therapy	Year of study	Type of sample	Level of evidence	Ref.
CBT	2010	C	II	[62]
	2013	C	II	[61]
	2017	C	II	[64]
	2019	C	II	[65][1]
Meditation	2016	C	I	[74]
	2016	A	I	[72]
	2017	C	II	[73][1]
	2017	A	III	[71]
Acupuncture	2008	A/C	I	[79]
	2011	C	II	[78]
	2011	C	IV	[81]
	2018	C	II	[80][1]
Yoga	2011	C	IV	[92]
	2014	A/C	III	[94]
	2016	A/C	II	[95]
	2018	C	IV	[93][1]
Massage	2008	C	III	[96]
	2012	C	III	[100]
	2013	C	III	[97]
	2013	C	III	[98]
	2020	C	III	[99][1]
	2020	C	IV	[101]
Spinal manipulation	2007	C	II	[99]
	2009	C	II	[96]
	2012	C	II	[95]
	2019	C	II	[97]
	2020	C	II	[98][1]
	2020	C	III	[26]
Moxibustion	2016	A	II	[100]
	2016	A/C	V	[102]
	2019	C	IV	[101][1]
Physical activities	2018	C	II	[104]
	2019	C	II	[106]
	2019	C	III	[107]
	2020	C	II	[103][1]
	2020	C	II	[105]

Adapted from the American Society of Plastic Surgeons rating scale for risk studies, 2011[108].
[1]The references with best-level of evidence and most recent for each non-pharmacological therapy are highlighted.
A: Adults; C: Children; CBT: Cognitive behavioral therapy.

CONCLUSION

It is possible to conclude that there is a need for safe and effective treatments for the management of FAPDs in the pediatric public. In this sense, and in view of the low quality and insufficient satisfactory results of pharmacological therapies, non-pharmacological treatments emerge as a viable and important solution to this problem of increasing numbers worldwide. In the meantime, it is possible to see a stimulus and an increasing amount of better evidence to support the prescription of these therapies in clinical practice, achieving better results and greater safety for patients. Finally, with these studies being made with sample selections of satisfactory age groups, the formulation of specific guidelines for this age group is made possible, as there is no need for adaptation of prescriptions initially made for adults for children.

FOOTNOTES

Author contributions: All authors equally contributed to this paper with conception and design, literature review and analysis, manuscript drafting, critical revision, and editing, and approval of the final version.

Conflict-of-interest statement: No potential conflicts of interest exist.

Country/Territory of origin: Brazil

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S-Editor: Ma YJ
L-Editor: Wang TQ
P-Editor: Ma YJ

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 March 9; 11(2): 120-135

DOI: 10.5409/wjcp.v11.i2.120

ISSN 2219-2808 (online)

REVIEW

Classification, prevalence and integrated care for neurodevelopmental and child mental health disorders: A brief overview for paediatricians

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Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Rodrigues AT, Verrotti A

Received: March 23, 2021
Peer-review started: March 23, 2021
First decision: October 17, 2021
Revised: October 29, 2021
Accepted: January 13, 2022
Article in press: January 13, 2022
Published online: March 9, 2022

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Abstract

'Neurodevelopmental disorders' comprise a group of congenital or acquired long-term conditions that are attributed to disturbance of the brain and or neuromuscular system and create functional limitations, including autism spectrum disorder, attention deficit/ hyperactivity disorder, tic disorder/ Tourette's syndrome, developmental language disorders and intellectual disability. Cerebral palsy and epilepsy are often associated with these conditions within the broader framework of paediatric neurodisability. Co-occurrence with each other and with other mental health disorders including anxiety and mood disorders and behavioural disturbance is often the norm. Together these are referred to as neurodevelopmental, emotional, behavioural, and intellectual disorders (NDEBIDs) in this paper. Varying prevalence rates for NDEBID have been reported in developed countries, up to 15%, based on varying methodologies and definitions. NDEBIDs are commonly managed by either child health paediatricians or child/ adolescent mental health (CAMH) professionals, working within multidisciplinary teams alongside social care, education, allied healthcare practitioners and voluntary sector. Fragmented services are common problems for children and young people with multi-morbidity, and often complicated by sub-threshold diagnoses. Despite repeated reviews, limited consensus among clinicians about classification of the various NDEBIDs may hamper service improvement based upon research. The recently developed "Mental, Behavioural and Neurodevelopmental disorder" chapter of the International Classification of Diseases-11 offers a way forward. In this narrative review we search the extant literature and discussed a brief overview of the aetiology and prevalence of NDEBID, enumerate common problems associated with current classification systems and provide recommendations for a more integrated approach to the

nosology and clinical care of these related conditions.

Key Words: Neurodevelopmental disorders; Mental health disorders; Adolescents; Child health; Mental health services; Emotional problems; Behavioural problem; Sub-threshold diagnosis; Sleep disorders; Integrated care

Core Tip: Neurodevelopmental, emotional, behavioural, and intellectual disorders (NDEBID) in this paper refers to many congenital or acquired long-term neurodevelopmental, neurological or muscular disorders, with the often co-occurring mental health disorders presenting in Community Child Health or child/adolescent mental health settings. This paper provides a brief overview of the aetiology and prevalence of NDEBIDs, highlights common problems associated with the current classification systems and aims to stimulate discussion among professionals towards consensus agreement on how best to classify the NDEBIDs. It makes a strong case for integrated care between paediatric and mental health services for optimal assessment and management of children and young people with NDEBIDs.

Citation: Ogundele MO, Morton M. Classification, prevalence and integrated care for neurodevelopmental and child mental health disorders: A brief overview for paediatricians. *World J Clin Pediatr* 2022; 11(2): 120-135
URL: https://www.wjgnet.com/2219-2808/full/v11/i2/120.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i2.120

INTRODUCTION

Childhood mental health and neurodevelopmental disorders are very common and represent a significant public health challenge. These disorders encompass a wide range of clinical entities of diverse aetiologies and pathogenesis. There are arguments for and against the clinical utility of a paediatric approach of grouping the emotional and mood disorders arising in childhood and adolescence (including anxiety and depression), neurobehavioural disorders [including attention deficit hyperactivity disorder (ADHD)], neurodisabilities [including cerebral palsy, epilepsy, autism spectrum disorder (ASD) and sensory processing disorders] with the typical neurodevelopmental disorders (such as intellectual and language disorders), considering their complex aetiologies and pathogenesis[1-5]. Some researchers have argued for the use of the term Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations, to encourage the early identification of neurodevelopmental, emotional, behavioural, and intellectual disorders (NDEBIDs) in vulnerable children (*e.g.*, those exposed to abuse or neglect) leading to multidisciplinary evaluations and potentially long-term follow-up by paediatricians, psychologists, speech therapists and other allied health care professionals[6-9]. Children and young people (CYP) with mental health and neurodevelopmental disorders are usually seen by teams in Community Child Health (CCH) services (with paediatricians and allied health professionals - physiotherapists, occupational therapists, speech and language therapists, dieticians and specialist nurses) or child and adolescent mental health service (CAMHS) with psychiatrists, psychologists, therapists, nurses and social workers. They also need to work closely with other multi-agency teams with professionals from social care, education, the voluntary sector and allied healthcare practitioners.

Mental health disorders (MHD) including behavioural and emotional problems, anxiety, depression, substance misuse disorder, eating disorders, self-harm, post-traumatic disorders, bipolar disorder, schizophrenia and some developmental disorders (often including autism and ADHD) among other difficulties are usually managed by the CAMHS teams[10]. MHDs are common and increasing in the United Kingdom child and adolescent population[11], leading to pressure on CAMHS. CAMHS in the United Kingdom may set boundaries to manage their work stream and if services decline referrals these may remain with CCH[12].

CCH paediatricians are specialists managing CYP with neuro-behavioural and neurodevelopmental disorders, disabilities, those with complex health needs (including end of life care), special educational needs, safeguarding, child sexual abuse, child public health[13]. They form part of integrated teams involving the education, social care and voluntary sectors[2,9,14]. The range of services offered within the CCH is variable across the United Kingdom with each team providing a unique range of statutory and non-statutory functions[13]. CCH paediatricians invariably have to deal with CYP with MHD and behavioural problems as they work with child safeguarding services or CYP under the care of the public system[9,15]. However, they are less likely to regard themselves as having expertise to manage "mental health" disorders and may avoid making some mental health diagnoses. Nevertheless, some common

MHDs including presentations that may fall below the threshold of clinical diagnoses are commonly managed under the care of CCH including self-harm, substance misuse and attachment difficulties.

In this paper, we have taken the pragmatic approach of referring to the CYP who are likely to come under the radar of joint care between CCH and CAMHS as having NDEBID. Different terminologies of "disorders", "difficulties" and "problems" may be used when referring to childhood NDEBID conditions. We will restrict ourselves to the "disorder" terminology in this paper.

Classification systems for childhood MHD continue to receive considerable attention from three main global professional bodies, including the World Health Organization (WHO), the American Psychiatric Association (APA) and the United States National Institute of Mental Health, using both varying and overlapping frameworks[16]. Their latest publications respectively, the eleventh revision of the international classification of diseases and related health problems (ICD-11), the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and Research Domain Criteria (RDoC), constitute the most widely used standardised classification systems used by researchers and clinicians worldwide. Revision of these classification systems has been accompanied by vigorous debates in the scientific literature, among clinicians and health advocates, and in the lay media[17]. Though the RDoC system is not intended for immediate clinical use, it provides a basis for research framework which accommodates the study of all causal factors together including the neurological, biological, psychological, social, and cultural structures and processes that underlie mental illness broadly[16].

This narrative review documents findings from a search of the extant literature and discusses a brief overview of the aetiology and prevalence of NDEBIDs, enumerate common problems faced by clinicians in reference to the current classification systems and management of common NDEBIDs and proffers some recommendations for addressing these problems. The content derives from a review of relevant published literature indexed by Ovid, pubmed, pubmed medical central, CINAHL, Embase, Database of Abstracts and Reviews, and the Cochrane Database of Systematic reviews and other online sources, with relevant themes identified.

We note an argument for bringing sleep disorders under the same wider umbrella with NDEBID. We make a case for a more integrated approach to the nosology and clinical care of these related conditions. We also argue for the necessity of simultaneous interventions for the total profile of difficulties and impairments that accompany the primary diagnosis, even if these do not reach the required threshold for a so-called comorbid diagnosis.

Genetic and environmental causes of NDEBIDs

Though the exact causes of various NDEBID are unknown, studies have identified a complex interplay between genetic vulnerability and adverse environmental factors that increase the risk of developing any of these disorders. These include perinatal, maternal, family, parenting, socio-economic, biologic and personal risk factors. Genetics can play an important role in many neurodevelopmental disorders, and some cases of certain conditions such as intellectual disability are associated with specific genes. There are many genetic causes of intellectual disabilities such as Down's, Prader-Willi, Williams and Fragile X syndromes. The co-existence of disorders and the development of one problem into another raise important research questions, such as the possibility of shared aetiologies and risk factors associated with heterogeneous phenotypes[18,19].

The evidence is clear that the early years are critical for brain development, with a profound impact on children's cognitive, social and emotional development, which affects them into later life[20]. Maternal use of alcohol, tobacco, or illicit drugs during pregnancy and more subtle effects such as maternal stress or anxiety; exposure to socioeconomic adversity; parental maladaptive behaviour; childhood exposure to abuse and inter-parental violence; cognitive ability, and affiliation with deviant peers in early adolescence have been shown to predispose to childhood behavioural disorders[21,22]. Other risk factors include preterm birth; low birthweight and the effects of nutrition[23] and chronic disease[24] on child development. Lead, methyl-mercury, and polychlorinated biphenyls are widespread environmental contaminants associated with adverse effects on a child's developing brain and nervous system in multiple studies[19]. Effects of adverse prenatal adverse factors are mediated in the foetus by stress hormones such as cortisol. However, it is often difficult to say definitively what constitutes a risky level of prenatal exposure for any given child[25].

Global prevalence of NDEBID conditions

The global rate of mental disorders among CYP aged 5-17 years has been estimated to be 6.7% (including conduct disorders: 5.0%, ADHD: 5.5%, ASD: 16.1%, depression: 6.2%, anxiety: 3.2%)[26]. In England, rates are increasing; one in eight (12.8%) 5-19 years old had at least one MHD assessed in a 2017 study, with 17-19 years old girls having the highest prevalence rate of one in four (25%). Rates of emotional disorders (anxiety and depression) showed the biggest increase, from 3.9% in 2004 to 5.8% in 2017[11]. Rates have increased further during the coronavirus disease pandemic to rates of 1 in 6 of 5-16 years old with a probable mental disorder (2020-wave-1-follow-up). Limited consensus among clinicians and researchers about the classification of the various NDEBID conditions has hampered universal comparison of service-based research findings and population-based studies[27]. A wide range of prevalence rates for NDEBIDs have been reported in developed countries, up to 15% of children's population), including up to 10% prevalence for developmental delay[28-30]. The commonest childhood

neurodevelopmental disorders are ADHD, ASD, tic disorders (TD)/Tourette's syndrome (TS), intellectual (learning) disability (ID), developmental delay and developmental coordination disorder (DCD)[2]. ADHD is the commonest childhood neuro-behavioural disorder, affecting up to 5% of school-age children. Reported prevalence of these conditions varies (for example, prevalence of DCD from 1.5% to 20% depending on how it is defined)[31]. Conflicting prevalence rates have been reported in both developed and developing countries worldwide, due to differences in study methodology and definitions used[27]. Table 1 shows the wide range of reported prevalence rates for a selected group of NDEBIDs, including some extreme cases such as attachment difficulties and disorders, where there are diffe-rences in terminology that lead to apparent variations in prevalence up to 100 times or more.

Evidence-based assessment

Diagnosis of most NDEBIDs remains primarily clinical, based on detailed history-taking as well as observation of a child's appearance and performance. This should include general medical, develop-mental, family, social, educational and emotional history. Physical and neurological examination should include assessment of vision, hearing, dysmorphic features, neurocutaneous stigmata, motor skills, mental state and cognitive assessment. Condition-specific and generic observer feedback on rating scales and questionnaires can be used to complement direct clinical observations to arrive at a diagnosis.

There is no single diagnostic tool available for the confirmation of childhood behavioural disorders. Diagnosis is usually based on various combinations of more or less subjective reports of parental, teacher, professional or other observer feedback on a variety of psychometric questionnaires or screening tools[32] and all such assess-ments may be prone to biases. There is often a marked discrepancy between various respondents giving feedback on screening questionnaires. The published literature suggests that parents often report more symptoms and diagnoses of oppositional defiant disorder (ODD) and conduct disorder than teachers, and parent-teacher agreement is often low except when behaviour report feedback is obtained within the same context[33].

There are several well validated screening tools that are designed to identify children and adolescents who are at-risk of having MHD and/or those who would most benefit from more in-depth assessment [34]. These have potential usefulness in early identification of NDEBIDs among vulnerable groups of CYP, leading to effective interventions[9]. There are also many established rating scales and clinical instruments to assess NDEBIDs (*e.g.*, the Autism-Tics, ADHD, and other Co-morbidities inventory is reported to have a good to excellent sensitivity and specificity[18]).

Recent advances in computerized Continuous Performance Task (CPT) tests have greatly improved their clinical utility in the assessment of some NDEBIDs[35]. Such objective representation of the symptoms of NDEBIDs visually presented with the aid of diagrams and graphs, could enable parents, and often patients, to gain a better understanding of their condition and to better appreciate and comply with the medical management proposed by the clinician[36].

PROBLEMS ASSOCIATED WITH THE CURRENT CLASSIFICATION OF NDEBID CONDITIONS

Confusing terminologies: "Disorders", "difficulties" and "problems"

Some authors have questioned the differences in the use of terminologies of "disorders", "difficulties" and "problems" when referring to childhood NDEBID conditions. Detailed discussion about the merits and demerits of each term is outside the scope of this paper. "Difficulties" or "problems" tend to be used in research or clinical settings where approved or validated diagnostic tools based on one or more classification systems for disorder diagnoses have not been formally used, but clinical impressions have been based on the experienced clinicians' appraisal of the CYP's profile of difficulties and multi-modal impairments[37,38]. Clinical expertise determines clinicians' use of diagnoses; paediatricians and psychiatrists each have areas of competence and these areas overlap incompletely (Figure 1). Another situation where the term "difficulties" may be preferred is in preschool children where the outcome of problems identified at an early stage is less certain. Challenging behaviours and emotional difficulties are common but these are therefore more likely to be recognized as "problems" rather than "disorders", as it is thought that psychiatric diagnoses need to be used cautiously in the pre-school age group[39].

Sub-clinical presentations and sub-threshold diagnosis

NDEBID are often diagnosed by using various methods relying on observation and questioning such as compilation of sufficient numbers of symptoms and reaching thresholds on psychometric tests, with recognition of a specific impairment. Sub-threshold diagnoses (insufficient symptoms to make a diagnosis but some evidence of impairment) are common in CYP, and are clinically important in terms of predicting poorer adult mental health and functional outcomes[40]. A group of child develop-ment multidisciplinary professions have emphasized that "a specific diagnosis may not be identified" in many neurodisabilities[41]. It has been observed that children suffer some significant neurodevelop-mental disabilities that may not reach the threshold for a specific diagnosis but still require compre-

Table 1 The reported prevalence rates and some definition of neurodevelopmental, emotional, behavioural, and intellectual disorders conditions commonly seen in Community Child Health settings

Categories/diagnosis	Characteristics	Reported prevalence	Ref.
All NDEBIDs	Four broad categories: emotional (8.1%), behavioural (4.6%), hyperactivity and other less common disorders	12.8% to 18%	[11, 30,85]
Behaviour difficulties/disorders	Externalising disorders; Disruptive behavioural disorders (including ADHD, CD and ODD)	7.5 to 10%	[11, 32]
Attention deficit/hyperactive disorder	Pervasive symptoms, onset before age of 12, causing significant impairment and categorised into: (1) Predominantly inattentive; (2) Predominantly hyperactive-impulsive; or (3) Combined type	1% to 9%	[51, 86-88]
Autism spectrum disorder	Early onset, pervasive and persistent deficits in: (1) Social communication and social interaction across multiple contexts; and (2) Restricted, repetitive patterns of behaviour, interests or activities	0.76% to 3.5 %	[51, 89-91]
Emotional disorders	Internalising disorders; Including anxiety, depression and mood disorders	8.1%	[11]
Attachment difficulties/disorders	Attachment difficulties include insecure attachment patterns and disorganised attachments, which can often evolve into coercive or compulsive caregiving patterns; Attachment disorders in DSM5: Reactive attachment disorder and disinhibited social engagement disorder; ICD-10 classification: Reactive attachment disorder and disinhibited attachment disorder	0.005% to 1.4%[1]	[7,85, 92]
Substance abuse	Someone who has ever taken drugs; Someone who has taken drugs in the last year; Someone who has taken drugs in the last month	7% to 37%: 11-15 yr; 20%: 16-24 yr	[93]
Self harm	A range of behaviours when someone hurts themselves on purpose	6.4% to 22%	[94-96]
All neurodisabilities	A group of congenital or acquired long-term conditions that are attributed to impairment of the brain and/or neuromuscular system and create functional limitations	3% to 15%	[41, 51,97, 98]
Visual impairments	Any cause of visual acuity to a level of 0·5 logMAR (6/18 Snellen) in each eye; Any specific visual processing, or eye movement problems *e.g.*, nystagmus	5.19 per 10000 (0.05%) to 5.7%[1]	[99-101]
Developmental coordination disorder	Early onset of coordinated motor skills is far below expected level for age; Motor skill difficulties significantly interfere with daily activities, academic/school productivity, prevocational and vocational activities, leisure and play; Not better explained by intellectual delay, visual impairment, or other neurological conditions that affect movement	0.8% to 6%	[31, 91, 102, 103]
Hearing impairments	Any hearing loss greater than 30 (or 35) dB in the better ear, including to glue ear (otitis media); Hearing loss: Reduced ability to hear sounds in the same way as other people at 20 dB or better; Hearing loss that adversely affects a child's educational performance	0.05 to 0.3%	[10, 51,71, 104]
Sensory processing disorder	A condition in which the brain and nervous system have trouble processing or integrating stimulus with 3 possible components: Sensory modulation disorder is a problem with turning sensory messages into controlled behaviours that match the nature and intensity of the sensory information; Sensory-based motor disorder is a problem with stabilising, moving or planning a series of movements in response to sensory demands; Sensory discrimination disorder is a problem with sensing similarities and differences between sensations; Not currently recognised as a distinct medical diagnosis	3.2% to 16%	[105-108]
Epilepsy	A disease characterized by an enduring predisposition to generate epileptic seizures and typical neurobiological, cognitive, psychological, and social consequences, fulfilling any of the following: (1) At least two unprovoked (or reflex) seizures occurring greater than 24 h apart; (2) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 yr; (3) Diagnosis of an epilepsy syndrome	0.05% to 0.7%	[51, 109, 110]
Cerebral palsy	A neurological disorder of body movement and muscle coordination caused by a non-progressive brain injury or malformation that occurs while the child's brain is under development. Cerebral palsy primarily affects, with related intellectual disability, seizures; problems with vision, hearing, or speech; changes in the spine (such as scoliosis); or joint problems	0.1% to 0.4%	[51, 111]
Sleep difficulties/disorders	Parent report of difficulty falling and/or staying asleep; Repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite age-appropriate time and opportunity for sleep and results in daytime functional impairment for the child and/or family	3% to 36%[2]	[112, 113]
Foetal alcohol spectrum disorders	Group of disorders due to permanent brain damage in individuals exposed to alcohol during pregnancy resulting in a spectrum of physical, emotional, memory, language, behavioural and neurological impairments	0.77% to 6%	[114-117]
All developmental delays	Also called developmental disabilities or disorders; Group of conditions due to impairment in physical, learning, language, or behaviour areas beginning during the developmental period and may impact day-to-day functioning, and usually last throughout a person's lifetime; Any delay in	10% to 17% (5.7% to 7% in infancy)	[28, 29, 118,

	developmental milestones		119]
Speech and language disorder/delay	Also called Specific language impairment; A communication disorder that interferes with the development of language skills in children who have no hearing loss or intellectual disabilities. It can affect a child's speaking, listening, reading, and writing	1.7% to 7%	[51, 120]
Intellectual (learning) disability	3 core criteria of reduced ability to understand new or complex information, impaired social independence, starting in childhood; Intelligence quotient of less than 70	2.1% to 3.6%	[121, 122]
Specific intellectual (learning) disability/disorder	Experience of any problems in a traditional classroom setting, including dyslexia, dyscalculia and generalized intellectual disability	1%	[51]
Global developmental delays	Delay in two or more developmental domains of gross/fine motor, speech/language, cognition, social/personal and activities of daily living; Used in early childhood suggesting need for specific diagnosis in later in life	1 to 3% (< 5 yr) to 12% by 9 mo	[28, 29, 118, 123]

[1]More than 100 times differences.

[2]More than 10 times differences.

NDEBIDs: Neurodevelopmental, emotional, behavioural, and intellectual disorders; ADHD: Attention deficit hyperactivity disorder; ICD: International classification of diseases; CD: Conduct disorder; ODD: Oppositional defiant disorder.

hensive assessments[42]. For example, the National Institute for Health and Care Excellence encourages professionals to recognize, assess and offer treatment for attachment difficulties in CYP who are in public care, many of which would not reach the threshold for formal diagnosis of reactive attachment disorder and disinhibited social engagement disorder, as defined in DSM-5 or ICD-11[38] which would typically only be diagnosed by a CAMHS teams[43].

One value of a diagnosis is that it enables confidence in using evidence-based interventions. Very little research is available to support psychiatric interventions when there is no diagnosis, even though most interventions are evaluated by the use of scales that measure change in dimensions of difficulty rather than a diagnosis changing. However excessive reliance on diagnostic labels can lead clinicians to focus on narrow checklists of symptoms, with little consideration of what is actually causing the patient's problems, thereby impeding holistic care and complete recovery of the patient[44]. Many authors have raised concerns about "unpredictable over-diagnosis" and "systematic medicalization of normality" due to overreliance on diagnostic labels[45].

Symptoms of co-morbidities not achieving the threshold for a diagnosis are an important source of heterogeneity that may be captured in RDoC for the purpose of research but are missed in classifications used in clinical practice. This highlights the need to extend clinical assessments beyond core diagnostic criteria; considering dimensions of symptoms, functioning, and social factors will lead to a more comprehensive management plan. If CYP have symptoms which fall just below the diagnostic threshold and are interfering with function, then interventions typically used for those diagnosed might be helpful.

There is still a need for better clinical classification of 'sub-threshold' presentations, which raises the question of how to gather and collate evidence for intervention in such cases. In ICD-11, this difficulty is partly addressed for some conditions (for example, the development of classification for personality traits, that do not reach criteria for a "disorder" diagnosis). However, the use of these categories has not yet been established in CAMHS. It might be argued that similar categories could be of value in other areas of classification, such as the specific neurodevelopmental disorders. The necessity of comprehensive assessment and simultaneous interventions for the total profile of difficulties that accompany the primary diagnosis, even if the comorbidities do not reach the required threshold for a specific diagnosis, has been emphasised[40].

Conflicts within current classification systems

Classification of diseases involves the categorization of relevant concepts for the purposes of systematic recording or analysis based on one or more logical rules. Definitions of various childhood MHDs have not been consistent in the published literature and there is a wide overlap among various classification systems. The much wider terminology of neurodevelopmental, emotional, behavioural and intellectual problems has been suggested by some authors, emphasizing the overlap and common co-morbidity between Neurodevelopmental and MHD[9,30,46,47].

DSM-5 recognizes the place of neurodevelopmental disorders including ASD, ADHD, communication, motor and learning disorders within its classification of mental disorders and has a chapter for them[48]. However, other conditions that have their onset during childhood and adolescence, including conduct disorder and reactive attachment disorder, are located elsewhere in the manual.

The ICD-11 has a new chapter title "Mental, Behavioural or Neurodevelopmental Disorders" (06) grouping together many of the NDEBID including behavioural issues like ADHD, (conduct disorder and ODD), anxiety and mood disorders, developmental disorders including ASD, ID and specific conditions such as DCD with a link to the chapter on diseases of the nervous system (08) for TD/TS.

New diagnoses of gaming and hoarding disorders, as well as substance misuse disorders have also been brought under this chapter[49].

Sleep disorders have been brought together under a separate chapter in ICD-11 titled "Sleep-wake Disorders" (07), while epilepsy and cerebral palsy (often included in the definition of neurodevelopmental disabilities) are classified under a different chapter in ICD-11 (08) and are not coded in DSM-5.

Peculiar case of sleep disorders

It is well recognized that sleep problems are disproportionately more common among CYP with NDEBID and require particular attention in the clinic. Sleep disorders have been traditionally classified under different systems but now have their own chapter in ICD-11. Both the DSM-5 (APA 2013) and the International Classification of Sleep Disorders-third edition (ICSD-3)[50] are key reference standards for the diagnosis of sleep disorders. DSM-5 has 3 different categorical classifications for sleep disorders including "sleep-wake disorders", "breathing-related sleep disorders" and "parasomnias"[48]. Other sleep difficulties including excessive daytime sleepiness, circadian rhythm sleep disorders and sleep-related movement disorders are also included. Similar terminologies are found in ICD-11. It is a welcome development that the DSM-5 and ICD-11 criteria for sleep disorders now mirror more closely the ICSD-3 classification system. This should enable a more consistent approach to the labelling of sleep disorders in the future. From a child health perspective, the common occurrence of sleep disorders with NDEBIDs makes an argument for bringing these together under the same wider umbrella.

Conflicting definitions of NDEBIDs and varying prevalence rates

The ICD, like other classification systems, is designed to allow the systematic recording, analysis, interpretation and comparison of mortality and morbidity data collected in different countries and at different times[49]. Classification systems have invaluable roles in epidemiological studies, including monitoring of incidence and prevalence of diseases, and other health problems in relation to other variables. Criteria and labels for many of the NDEBIDs have changed with each revision of classification systems. This together with the lack of consensus among clinicians about the classification of the various childhood NDEBIDs, has led to widely varying estimates of disease prevalence rates, and has made universal comparison of research findings almost impossible[5]. It is therefore not surprising that a wide range of prevalence rates have been reported for different conditions (Table 1).

Recorded prevalence of childhood disabilities is an example of where diverse rates have been reported within the same country. In the United Kingdom, one study reported 7.3% of CYP aged 0-18 years (8.8% of boys and 5.8% of girls) as disabled[41] while on the other hand, Blackburn *et al*[51] reported that 6% of all children were disabled with 3%-4% having neurodevelopmental impairments in England. Furthermore, worldwide comparison is difficult to find as different countries have varying definitions for "disabilities"[41].

Multiple terms have been used to describe the "Neurodevelopmental disorders (NDD)"; these include neurodevelopmental "disorders", "impairments" and "disabilities". Other authors have used the term "Neurodisabilities". It is difficult to be sure that these terminologies are used to describe the same group of disorders. For example, the following three definitions appear to be referring to the same conditions. The term 'neurodevelopmental disorders' applies to a group of disorders of early onset that affect both cognitive and social communicative development, are multi-factorial in origin, display important sex differences where males are more commonly affected than females, and have a chronic course with impairment generally lasting into adulthood[5]. The European Union defined "neurodevelopmental disorders" as disabilities in the functioning of the brain that affect a child's behaviour, memory or ability to learn *e.g.*, mental retardation, dyslexia, ADHD, learning deficits and autism. In the United Kingdom, "neurodisability" has been described as a group of congenital or acquired long-term conditions that are attributed to impairment of the brain and/or neuromuscular system and create functional limitations. Conditions may vary over time, occur alone or in combination, and include a broad range of severity and complexity. Their impact may include difficulties with movement, cognition, hearing and vision, communication, emotion, and behaviour[41]. Similarly, there has been little consensus among international researchers about the definition of individual "neurodevelopmental disorders". Many authors have argued that the NDDs lack precise boundaries in their clinical definitions, epidemiology and genetics. Many symptoms are not unique to any single NDD, and several NDDs have clusters of symptoms in common[52]. Some have argued that the term NDD is unhelpful and should be abandoned[5].

Traditional segregation of CCH and CAMH services despite overlapping clinical roles

Despite the high prevalence of long-term co-occurring mental disorders in CYP with NDD and intellectual disorders[29,53,54], the involvement of psychiatric and psychological professionals, who are mostly part of CAMHS rather than paediatric services, in the provision of support for the health disorders problems comorbid with NDDs is not consistent throughout the United Kingdom and other advanced countries. Services that are designed to support these CYP often tend to be fragmented and disjointed such that the CYP have to attend multiple clinic appointments with different health-care providers and professional groups each looking at only one aspect of their complex need often without

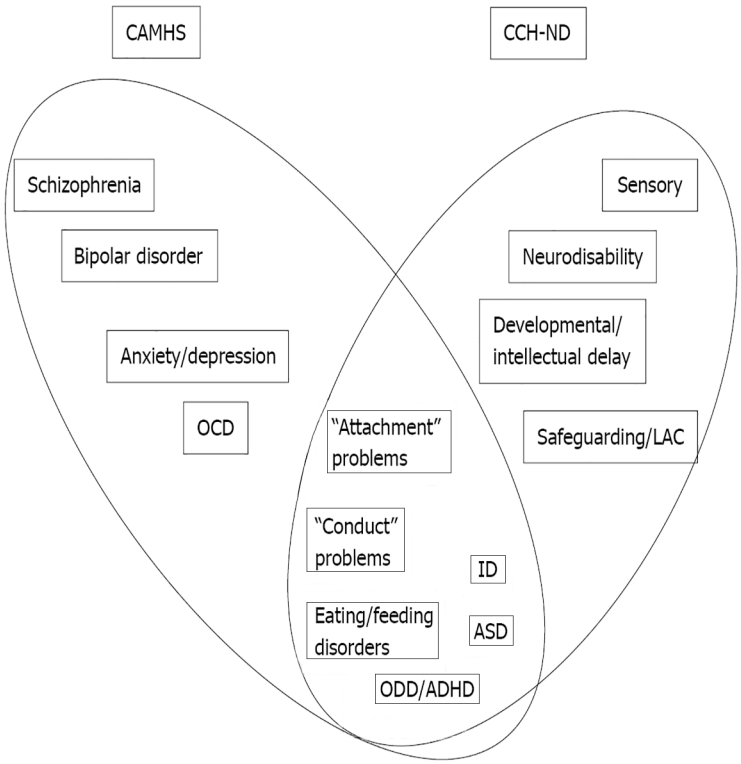

Figure 1 Showing a schematic representation of the overlap between some neurodevelopmental, behavioural, emotional and psychiatric disorders with an overlap between current child and adolescent mental health service and Community Child Health services. CCH-ND: Community Child Health/Neurodevelopmental Paediatrics; OCD: Obsessive compulsive disorder; CAMHS: Child and adolescent mental health service; ID: Intellectual disorder; ASD: Autism spectrum disorder; ODD: Oppositional defiant disorder; ADHD: Attention deficit hyperactivity disorder.

any coordination[9,42].

In the United Kingdom and other developed countries, NDEBID conditions are commonly managed by either CCH paediatricians or CAMH psychiatrists within multidisciplinary teams of other allied professionals[2]. The split between these services can be even more complex such that for the same diagnosis such as ASD, some younger children may be seen by CCH while older young people are seen by CAMHS[55]. Despite the natural overlap between the roles of CCH paediatricians and mental health practitioners (Figure 1), there is often very little interaction or joint-working between CCH and CAMH services in the United Kingdom, even though this collaboration is regarded as highly desirable and necessary[12].

The likelihood of CAMHS professionals working jointly with CCH paediatricians is highly variable and seems to be reducing over the years, in the face of service pressures. For example, while ADHD was originally the remit of CAMHS, CCH services have played an increasingly important role in managing this condition. Thus 63% of CCH services managed ADHD in 2016 compared to only 15% in 2006[13]. The Royal College of Paediatrics and Child Health Workforce Census 2013 revealed a decline in regular joint educational meetings between CCH and CAMHS professionals from 15.4% in 2011 to 12.8% in 2013, a reduction in ad hoc meetings with CAMHS from 42% to 26.8% and an increase from 11.7% to 15% of services that have no direct contact with their local CAMHS[56]. A recent report from the United Kingdom highlighted two CAMHS that do not provide access to children with ADHD or autism[57].

Stigma among professionals is another potential barrier to integration of services for CYPs with NDDs and co-morbid MHD. There is evidence to suggest that some health professionals have negative attitudes towards CYP affected by mental illness[58,59]. The stigmatising attitude towards CYP with mental health could also extend to stigmatisation of professionals who work in CAMHS[60] through a process known as "courtesy stigma"[61]. The implication is that if professionals working in CCH and other paediatric services have negative stigmatising attitudes towards CYP with mental health difficulties and or towards professionals working in CAMHS, they may be less likely to think favourably about integrating services for CYPs with NDDs and additional mental health needs[62].

RECOMMENDATIONS FOR ADDRESSING CLASSIFICATION-RELATED PROBLEMS FOR NDEBID CONDITIONS

Value of a unified classification of mental health and NDD

There are grounds for agreement on aspects of the scientific basis for the grouping together of neurodevelopmental and some MHD. First, clinical overlap between these disorders is high and they also behave as highly correlated traits. Thus, research that focuses on a single diagnosis (*e.g.*, autism) should allow for testing the contribution of accompanying neurodevelopmental difficulties. Secondly, NDD share common features with some related MHD including onset early in development, tendency to show a steady course and affecting males more commonly than females. Thirdly, there is a strong genetic overlap across different neurodevelopmental problems[37]. Finally, comorbidity between neurodevelopmental and MHD is well recognized as a factor in the care of children with certain neurological diagnoses, with epilepsy the most prominent example[63], thus grouping them together could help to better enhance the study of the scientific basis and epidemiology of their co-occurrence, as well as improving clinical management.

Studies have shown that CYP with NDEBIDs are at increased risk of developing sleep disorders as well as secondary MHDs such as anxiety, depression, obsessive compulsive disorder (OCD), self-harming, suicidal behaviours, and conduct disorder in up to 50% of those affected[29,53,64,65]. The clinical and research advantages from considering NDDs together with the MHD[40] form the basis for our use of the NDEBID terminology in this paper.

Many clinicians and researchers have questioned the fundamental reason for having more than one classification system used worldwide[5]. Unifying classification systems based on empirical and scientific foundations agreed by consensus among global specialists would probably aid rapid advancement of research across all countries and regions worldwide. There is also evidence that patients and families of CYP with NDEBIDs would also prefer a more unified and integrated approach to their care. When a wide range of stakeholders including families, referrers and CAMHS professionals were requested to state their priority values, "a need for a common language for all agencies when discussing mental health" and "a holistic approach where problems are not inappropriately medicalised" were some of the regular themes found[66]. The global status of the WHO means that ICD is the system most likely to meet this aim and the most recent revision of ICD-11 has made a clear departure from the preceding versions with the new chapter heading of "Mental, Behavioural and NDD" and a sub-heading that brings together a range of conditions previously classified under various headings such as "behavioural and emotional disorders" and "pervasive developmental disorder". This approach is based on assumption of improved clinical utility and global applicability. While this should be regarded as a welcome development, there are still arguments from some clinicians and researchers against this. For example, various conditions (from severe ASD to mild coordination disorder) contained under this grouping differ from each other such that they have little in common[5].

Focusing on impairments and complexities over diagnosis

Complexity and comorbidities are common features of many NDEBIDs and pose a great challenge to clinicians. It is often the complexity of a case that leads to a need for intervention in sub-threshold disorders. Unfortunately, this problem has not been properly addressed in research. Many families, referrers and CAMHS professionals have been reported placing high values on "a holistic approach where problems are not inappropriately medicalised" and "services that take into account what is important in CYP's lives"[66].

Research methodologies using small N studies may help to explore the value of interventions in complex cases and agreement on a shared language for sub-threshold disorders would facilitate this kind of research[67]. In this regard, DSM-5 has introduced the concepts of "clinical case formulation" and "clinical significance". It defines clinical significance of a disorder in terms of consideration of thresholds of a person's distress or impairment in his or her social, occupational and/or other important areas of functioning in daily life. The clinical formulation can co-exist with diagnostic classification and provides an alternative to a multiaxial system requirement, with a clinical summary of the social, psychological and biological factors that contribute to the development of a mental disorder. It allows more homogeneous subgroupings of a disorder to indicate shared features[68].

Need for greater care integration for CYP with NDEBIDs

There is strong evidence that children with neurodevelopmental and intellectual disorders have three to four-fold increase in the prevalence of co-occurring mental disorders into adulthood[2,9,69]. For example, pooled prevalence for co-occurring MHD in autism is estimated at 28% [95% cumulative incidence (CI): 25-32] for ADHD; 20% (17-23) for anxiety disorders; 13% (9-17) for sleep-wake disorders; 12% (10-15) for disruptive, impulse-control, and conduct disorders; 11% (9-13) for depressive disorders; 9% (7-10) for OCD; 5% (3-6) for bipolar disorders; and 4% (3-5) for schizophrenia spectrum disorders [64]. In a Swedish community sample, 87% of children with ADHD had at least one co-morbid condition, with rates of ODD of 60%, DCD (47%), 'reading/writing disorders' (40%) and TD (33%), even "sub-threshold" ADHD was associated with a similar rate of co-morbid DCD[70].

Effective management of CYP with MHD and behavioural difficulties requires access to psychological therapies and sometimes, psychotropic medications, which most CCH paediatricians are not trained to use. Similarly, CAMHS teams may lack the expertise required to deal with children with sensory or motor impairments. These conditions are best seen and treated within a comprehensive integrated CCH/CAMH service with teams of specialist professionals working together to provide holistic care[9].

The need for integrated care for CYP with NDEBIDs and mental health difficulties has been recognized for many years and is a priority goal for the WHO[71]. Integrated care involves overcoming the breakdown in communication and collaboration that can arise between different parts of the system and different groups of professionals, whilst respecting necessary professional boundaries. An important feature of integrated care is moving beyond pathways for specific diseases[72,73]. System integration across borders/barriers between different sectors of the health services and other systems such as social care and education is the ideal way of preventing adverse outcomes and poor patient experience due to systemic barriers[74]. Close integration of preventive and therapeutic mental health into traditional CCH services accessible to vulnerable CYP and their families within the public care system been identified as the best way to provide them with optimal holistic care they need[75].

Since co-occurrence of NDD is the rule rather than the exception in clinical practice, grouping professional expertise, services and resources for CYP with NDEBIDs organized as part of a neurodevelopmental hub of expertise has been advocated as the optimal option for achieving holistic and comprehensive care[40]. The bio-psycho-social and ecological origins of NDEBIDs and associated mental health difficulties make it imperative that assessment and treatment of affected CYP should be multimodal, comprehensive and holistic, to capture the full range of CYP's needs in order to produce a full formulation and profile to inform their care plans.

Integrated CCH/CAMH care would provide a framework for a more joined-up assessment and treatment in a manner that is more compatible with the complex needs of CYP with NDEBIDs conditions[9,15,76]. Of course, this should not impede the independent professional activities of CAMHS and CCH where joint working is not required.

Evidence from many countries and cultures show that fear of mental health stigma can prevent CYP from seeking help[77]. The negative impact of stigma on help-seeking may be more noticeable among minority ethnic groups living in Western Europe and North America[78-80]. Provision of holistic care within integrated CCH/CAMH services could help to mitigate negative impact of mental health stigma on help-seeking behaviour among CYP with NDEBID[81,82]. Primary care settings such as routine paediatric clinic or family medicine/general practitioner have been reported to possess several desirable characteristics that make them ideal settings for providing effective mental health services to CYP. They are not associated with the stigma typical for bespoke CAMHS, they are often in a local familiar setting, with access to friendly healthcare providers[32,83,84].

It is pleasing to note that a few services across the United Kingdom are beginning to pilot or implement holistic multi-disciplinary clinical pathways for all NDEBID, rather than restricted pathways for individual conditions[42].

CONCLUSION

Recent progress made in the current classification of NDEBIDs has been described. Previous attempts at classifying NDEBID conditions have been fraught with difficulties as there are many possible constructs that need to be taken into consideration. Classification based on causality is particularly problematic because the aetiology of these disorders is not only multi-causal but also incompletely understood[5]. The ICD-11 (and less so with DSM-5) have taken the lead in following a pragmatic approach where the NDEBID conditions are grouped together based on their similar neurobiological phenotypes, until further advances in neurosciences permit more categorical classifications based on aetiologies.

In many countries worldwide, one or more of the NDEBIDs would be assessed and treated by CCH/paediatric services while others and any associated mental health difficulties may be addressed by CAMHS separately and often in a disjointed fashion[9]. Diagnosis of NDEBIDs based on subjective assessment of behaviour by clinicians and carers is prone to biases but reliable standardized instruments can support diagnosis. Recent advances such as computerized CPT tests have potential in the assessment of some NDEBIDs.

Despite the concerns of some authors, it might be reasonable to suggest that the latest WHO classification (ICD-11) could form the basis for a shared understanding acceptable to both the CCH and CAMHS. A more unified approach to classification offers a basis for an integrated care approach, with more consistent collaboration between CCH and CAMH services to address stigma and ensure more holistic care for CYP with NDEBIDs. We note the case for bringing sleep disorders in CYP under the same wider umbrella as the NDEBIDs. We also argue for simultaneous interventions for the total profile of difficulties that accompany the primary diagnosis, even if these do not reach the required threshold for a so-called comorbid diagnosis.

FOOTNOTES

Author contributions: Ogundele MO conceived the idea, Ogundele MO and Morton M reviewed the literature and prepared the manuscript.

Conflict-of-interest statement: The authors declare no conflict of interest for this article.

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 March 9; 11(2): 136-150

DOI: 10.5409/wjcp.v11.i2.136

ISSN 2219-2808 (online)

REVIEW

Druggable monogenic immune defects hidden in diverse medical specialties: Focus on overlap syndromes

Valentina Boz, Chiara Zanchi, Laura Levantino, Guglielmo Riccio, Alberto Tommasini

Specialty type: Immunology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Pongcharoen S

Received: May 26, 2021
Peer-review started: May 26, 2021
First decision: July 30, 2021
Revised: August 3, 2021
Accepted: January 8, 2022
Article in press: January 8, 2022
Published online: March 9, 2022

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Abstract

In the last two decades two new paradigms changed our way of perceiving primary immunodeficiencies: An increasing number of immune defects are more associated with inflammatory or autoimmune features rather than with infections. Some primary immune defects are due to hyperactive pathways that can be targeted by specific inhibitors, providing innovative precision treatments that can change the natural history of diseases. In this article we review some of these "druggable" inborn errors of immunity and describe how they can be suspected and diagnosed in diverse pediatric and adult medicine specialties. Since the availability of precision treatments can dramatically impact the course of these diseases, preventing the development of organ damage, it is crucial to widen the awareness of these conditions and to provide practical hints for a prompt detection and cure.

Key Words: Inborn errors of immunity; Primary immunodeficiency diseases; Precision treatments; Immunodysregulation; Autoimmunity; Overlap syndromes

Core Tip: High-throughput genetic testing have allowed to describe monogenic immune disorders, characterized by combinations of infective, inflammatory, autoimmune, lymphoproliferative, neoplastic features. The term "inborn errors of immunity" (IEIs) is increasingly proposed instead of "primary immunodeficiency" to include defects with a prevalently dysregulatory pathogenesis, resulting in autoimmunity, inflammation, lymphoproliferation, risk of malignancies. It is crucial to widen the awareness of these disorders, as they may mimic multifactorial disorders (rheumatology, gastroenterology, hematology, dermatology, allergology) and some of these are druggable. The awareness of druggable IEIs is the focus of this review, with the aim of favoring a prompter diagnosis and a better cure.

Citation: Boz V, Zanchi C, Levantino L, Riccio G, Tommasini A. Druggable monogenic immune defects hidden in diverse medical specialties: Focus on overlap syndromes. *World J Clin Pediatr* 2022; 11(2): 136-150
URL: https://www.wjgnet.com/2219-2808/full/v11/i2/136.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i2.136

INTRODUCTION

Primary immunodeficiencies are a growing group of monogenic disorders related to dysregulated immune processes, which can result in autoinflammation, autoimmunity, lymphoproliferation and/or risk of malignancy in addition to the paradigmatic recurrent infections: In this sense, the term "inborn errors of immunity" (IEIs) has recently been proposed to underline the heterogeneous phenotype of immune deficiencies[1,2].

Improved diagnostics of monogenic immune disorders, together with the availability of medications acting on disease-related mechanisms recently led to the development of precision therapies which can improve or correct the phenotype of some IEIs[3-6]. The mutations involved in these disorders are usually associated with gain-of-function (GOF) of proteins (often kinases) or hyperactivity of pathways, which can be targeted by specific medications and thus sometimes referred to as "druggable". For concision, we indicate IEIs with druggable pathogenic mechanisms as druggable IEI (D-IEIs).

Of note, since immunodeficiency may develop significant organ damage due to infection or autoimmunity, early detection of D-IEIs is crucial to benefit from appropriate treatments[7]. Although a deep clinical-laboratory evaluation can help an experienced immunologist to concentrate suspicion on one of these disorders, the use of next generation sequencing (NGS) offers a powerful tool to diagnose D-IEIs, allowing to examine all the candidate genes at once[8-10]. However, due to the wide heterogeneity of IEIs, it may be difficult to select patients for genetic analysis.

In fact, from a phenotypic point of view, due to their origin from general disturbances in immune regulation, D-IEIs tend to affect multiple organs and systems, composing complex clinical pictures that overlap disorders of distinct medical specialties, and tend to fully manifest over the time, with the definition of typical clinical pictures only in adults. Thus, patients with D-IEI can initially be diagnosed – especially in pediatric age - with common multifactorial disorders, pertaining to various medical specialties and displaying atypical clinical presentations such as unusual age of development, multiorgan involvement and response to therapies. These factors are congruent with the immune dysregulation theory.

In light of this, the aim of this review is to widen the awareness of "druggable" IEIs which may be hidden in various medical specialties, in order to promote an earlier diagnosis and a better therapy in this field.

IEI may present druggable autoimmune, inflammatory and/or lymphoproliferative manifestations

We present a list of druggable IEIs, with prevalent autoimmune, inflammatory and/or lymphoproliferative aspects, which may mimic common multifactorial disorders, and therefore are at risk of being missed, until significant organ damage manifests. Since effective treatments are now available for immune disorders, it is of crucial importance to consider the possibility of a primary immune defect in subjects presenting with clinical pictures suggestive of immune dysregulation, particularly those that overlap distinct rheumatological, gastroenterological, endocrinological and dermatological/allergic disorders (Table 1). As described elsewhere, there is now a trend of anticipating the time of genetic analysis, reserving more in-depth immunological investigations for a later time, with the aim of determining the role of any variants of uncertain significance found in candidate genes[7].

IPEX is a monogenic immune disorder (due to mutations in *FOXP3*) characterized by an impaired development of Treg cells, resulting in failure of peripheral immune tolerance, with autoimmunity and allergic manifestations[11-13]. The disease typically presents in infancy with enteropathy, cutaneous disorders with eczema and nail changes, and endocrinopathies [*e.g.*, type 1 diabetes mellitus (T1DM), thyroiditis]. Several other autoimmune manifestations may also be found. The treatment may benefit from sirolimus or tacrolimus, in addition to nutrition and glucocorticoids, but only hematopoietic stem

Table 1 Characteristics of pathologies

	Gene	Meccanism	Immune assessment	Clinicsautoimmunity	Lymphoproliferation	Infections	Therapy
APDS	*PIK3CDPIK3R1*	PI3K delta hyperactivation	Hypogammaglobulinemia IgA and IgG lowSenescent CD8 T cellsDNT	IBD; diabetes; arthritis	Lymphadenopathy, splenomegaly	Recurrent respiratory infections; herpes virus infections	HSCT; antibioticsrituximab and rapamycin;PI3Kδ inhibitors
STAT3 GOF	*STAT3*	STAT3 hyperactivation	Hypogammaglobulinemia; decrease NK cells; decrease memory B cells; decrease regulatory T cells	Autoimmune cytopenia; diabetes; thyroiditis; arthritis	Adenopathy, hepatosplenomegaly	Herpes virus infections; fungal infections; bacterial infections; respiratory infections	JACK inhibitors
APECED	*AIRE*	Decrease of negative selection of autoreactive T cells in thymus	Autoantibodies;CD8+ effector T cells;FOXP3+ regulatory T cells	Autoimmune hypoparathyroidism;Addison's disease		Chronic Candida infection	Hormone replacement therapy according to affected organs; immunosuppressive therapies; rituximab
CTLA4 deficiency	*CTLA4*	Defective switch off of lymphocyte activation	Hypogammaglobulinemia; DNT;increase of regulatory T cells with reduced expression of FOXP3;CD19+ B cells and switched memory B	Autoimmunecytopenia; hemolytic anemia and thrombocytopenia	Splenomegaly;chronic lymphadenopathy;hepatomegaly	Respiratory tract infections	Sirolimus; abatacept; HSCT
LRBA deficiency	*LRBA*	Defective switch off of lymphocyte activation	Hypogammaglobulinemia; DNT; FOXP3+regulatory T cells;CD19+ B cells;Natural Killer cells; increase of CD4+ and CD8+ memory T cells	Autoimmune gastritis;autoimmunecytopenia; hemolytic anemia; IBD;Autoimmune enteropathy	Splenomegaly;hepatomegaly	Respiratory infections	sirolimus; abatacept; HSCT
IPEX	*FOXP3*	Failure of immune tolerance	Loss of FOXP3+ T cells;increased of Th2 and Th17 cells;autoantibodiesHypergammaglobulinemia IgA, IgE	Autoimmune enteropathy; autoimmune hemolytic anemia; autoimmune thrombocytopenia; autoimmune neutropenia; autoimmune thyroiditis; nephropathy; hepatitis		Skin infections	Glucocorticoids;Msirolimus;Mtacrolimus; abatacept; HSCT
STAT1 GOF	*STAT1*	STAT1 hyperactivation due to increase STAT1 phosphorylation	Low Th17 cells; low switched memory B cells;Hypergammaglobulinemia IgG	Chronic mucocutaneous candidiasis; hypothyroidism; autoimmune cytopenia, hepatopathy; psoriasis	Hepatomegaly; splenomegaly	Fungal, viral and mycobacterial infections; skin infections; Respiratory infections	Antifungal treatment; antibiotic prophylaxis; JACK inhibitors
DADA2	*ADA2*	Reduced activity level of the adenosine deaminase 2	Hypogammaglobulinemia; increases macrophage release of TNF-α; upregulation of neutrophil activity; upregulation of pro-inflammatory cytokines; upregulation of type 1 interferon	Vasculitis, immunodeficiency; autoimmune neutropenia; autoimmune cytopenia	Splenomegaly; lymphadenopathy; hepatomegaly	Verrucosis; herpes virus infections; increased	Anti-TNF treatment (etanercept, infliximab,adalimumab); high-dose of glucocorticoids; HSCT; immunosuppressive drugs in isolated cases (mycophenolate,

			stimulated genes; aberrant B cell development and differentiation; decrease in NK		susceptibility to infection with dsDNA viruses	azathioprine, cyclosporine, rituximab, sirolimus, tacrolimus)
TNFAIP3 deficiency	*TNFAIP3*	Excessive activation of NF-kB signalling	Antinuclear and anti-DNA antibodies; increased production of interferons and proinflammatory cytokines	Autoimmune cytopenias		Anti-TNF treatment; anti-IL1 treatment; glucocorticoid; colchicine

Characteristics of pathologies[10,20,28,31,37,44,49,52,53]. HSCT: Hematopoietic stem cell transplantation; IBD: Inflammatory bowel disease.

cell transplantation allows a cure, the success of which is related to an early diagnosis[14-16]. Proof of concept for immunoregulation with abatacept was obtained in scurfy mice, which are considered a good animal model for the IPEX[17,18].

APECED is a monogenic immune disorder (due to mutations in *AIRE*) characterized by an abnormal presentation of self-antigens in the thymus, resulting in the failure of central immune tolerance, with autoimmunity[19-21]. The disease usually presents in infancy with recurrent and severe candidiasis (with susceptibility associated to IL17-neutralizing antibodies) and parathyroid and adrenal autoimmunity, but over time other autoimmune disorders (*e.g.*, hepatitis, thyroiditis, vitiligo, alopecia, gastritis) are also observed[22,23]. Even if there is still no precision therapy for APECED, it is important to make an early diagnosis to establish a proper follow-up with prompt detection of new autoimmune phenomena, infections and malignancies[24,25].

CTLA4 and LRBA deficiencies are monogenic immune disorders associated with an impaired regulation of lymphocyte activation and development, resulting in autoimmunity and lymphoproliferation, but also infections[26-30]. Clinical features include hepatosplenomegaly, enteropathy, eczema, autoimmune cytopenia, arthritis, lupus-like features, hypogammaglobulinemia recurrence of infections and risk of malignancies (particularly due to chronic EBV infection). hematopoietic stem cell transplantation (HSCT) can cure the disease, however the treatment of milder cases may benefit from the use of CTLA4-Ig (abatacept)[28,30,31].

APDS (type I and II) are monogenic immune disorders associated with an impaired regulation of T and B cells maturation and survival, resulting in lymphoproliferation, autoimmunity and infections[32-35]. Clinical features include recurrent infections (especially respiratory, often complicated by the development of bronchiectasis and cutaneous) lymphoproliferative manifestations with risk of lymphoma[36-38], enteropathy and systemic lupus erythematosus (SLE)-like features. The immune defect is complex, with hypogammaglobulinemia with normal or increased IgM, reduced number of recent thymic emigrants and accumulation of senescent CD8 T cells. The pathogenic mechanisms can be partially reversed with drugs inhibiting the PIK3delta kinase, with a great potential in reducing the disease severity[39].

Monoallelic GOF mutations in *STAT1* are associated with susceptibility to infections from bacteria and fungi, autoimmune disorders and rheumatologic manifestations, due to increased activation of interferon stimulated genes[40,41]. Since hyperactive STAT1 still depends on the trigger from Janus kinases, the use of JAK inhibitors can partially restore a physiological balance with great clinical benefit both on inflammatory and on infectious symptoms[42,43]. In a recent report, treatment with JAK

inhibitors led to the reversal of autoimmune diabetes in a boy with STAT1 GOG[40].

Monoallelic GOF mutations in *STAT3* are associated with autoimmune and lymphoproliferative disorders[44]. Patients may present autoimmune enteropathy, celiac disease-like changes in the jejunum, eczema, autoimmune polyendocrinopathy, lymphoproliferation with increased CD4- CD8- double negative T cells and risk of hematologic malignancies and hypogammaglobulinemia with recurrent infection. The use of JAK inhibitors can lead to significant clinical improvement in this case too[45].

DADA2 deficiency is a combined immunodeficiency due to the defective function of the adenosine deaminase-2enzyme. The disease is associated with lymphoproliferation, variable hypogammaglobulinemia and susceptibility to infection, arthritis, livedo reticularis, erythema nodosum, purpura and vasculitis with a picture of polyarteritis nodosa and ischemic strokes[46,47]. The main complaints of the disease are driven by TNF-alpha: Thus, there is a formal recommendation to start anti-TNF treatment as early as possible[48].

A20 haploinsufficiency is a monogenic immune disorder (due to mutations in *TNFAIP3*) characterized by an abnormal activation of NF-kB signalling, resulting in a phenotype similar to Behcet's disease (BD)[49]. Indeed, clinical features include uveitis, recurrent oral and genital ulcerations, rash, abscesses and periodic fever. However, some patients may present with ulcerative colitis or with signs of SLE-like autoantibodies, increased production of interferons, autoimmune cytopenias and sometimes nephritis[50-52]. Anti-TNF treatment has been proven of great efficacy in several patients, even if it could be ineffective on lupus-related complaints[53].

There are many other rare IEIs that may present with complex features of immune dysregulation, such as lymphoproliferation, autoimmunity, inflammation, and risk of malignancies. However, the therapeutic implications of diagnosing these IEIs are not as straightforward as those for druggable diseases.

IEI MAY MIMIC COMMON MULTIFACTORIAL DISORDERS IN DIVERSE MEDICAL SPECIALTIES

IEIs may present in diverse medical specialties mimicking more common multifactorial disorders. However, there are typical clinical pictures or peculiar sets of features that can raise suspicion of an IEI. After discussing the relevance of such conditions to specific medical specialties, we will propose red flags to help address the suspicion of an IEI in a multidisciplinary setting (Figure 1).

Rheumatology

SLE: SLE is quite rare in children before pubertal age[54-56]. Cases with very early onset should always raise suspicion of an underpinning genetic disorder, with particular reference to complement deficiencies and interferonopathies[57,58]. Some cases may be anticipated by blood cells cytopenia or liver involvement. Arthritis may present a devious clinical course with slow development of contractures. A significant history of infections can sometimes be recorded. In many cases, the clinical picture is not the one that is the most typical of SLE, and classification criteria for SLE are not always completely met. NGS gene panels or whole exome sequencing have been proposed to allow an early detection of monogenic mimics of SLE[59,60]. A recent large study demonstrated that a monogenic cause could be found in 23% of patients meeting at least one of the following inclusion criteria: *i.e.*, (1) Age of disease onset under 5 years; (2) Family history of autoimmune disease; (3) Syndromic SLE; and (4) Complicated conditions, such as life-threatening and refractory SLE[61]. Of particular importance is a prompt detection of druggable disorders like interferonopathies or STAT1 GOF immunodeficiency, which can benefit from the use of JAK inhibitors[42,60,62,63], or immune dysregulation deficiencies such as activated PIK3d syndrome that can benefit from PIK3δ inhibitors[61,64,65].

BD: BD is a complex inflammatory and autoimmune disorder with great clinical heterogeneity. BD is rare in pediatrics and often presents for many years in an incomplete form, mainly with recurrent oral and/or genital ulcerations and sometimes periodic fevers. Vasculitis, central nervous system or eye involvement are more typical of older children and adults. BD occurring in early childhood can also be underpinned by monogenic immune defects. Mounting evidence supports the opportunity of searching for monogenic mimics of BD in pediatrics, in particular in subjects with very early disease onset, positive familial history and severe phenotypes[52,66-68]. Some of these monogenic cases may present clinical pictures overlapping with SLE or Inflammatory bowel disease (IBD), as is in the case of STAT1 GOF and A20 haploinsufficiency. The molecular diagnosis in these cases can allow a targeted therapeutic choice and a proper follow-up.

Juvenile idiopathic arthritis is not so rare and is rarely associated with an underlying monogenic disorder. However, there are rare atypical cases, usually with polyarticular involvement refractory to conventional therapies, which may be associated with inflammatory involvement of liver or lungs, uncovering a more complex inflammatory pathogenesis, as in the cases of interferon-related disorders like COPA syndrome (also known as Autoimmune Interstitial Lung, Joint, and Kidney disease, OMIM #

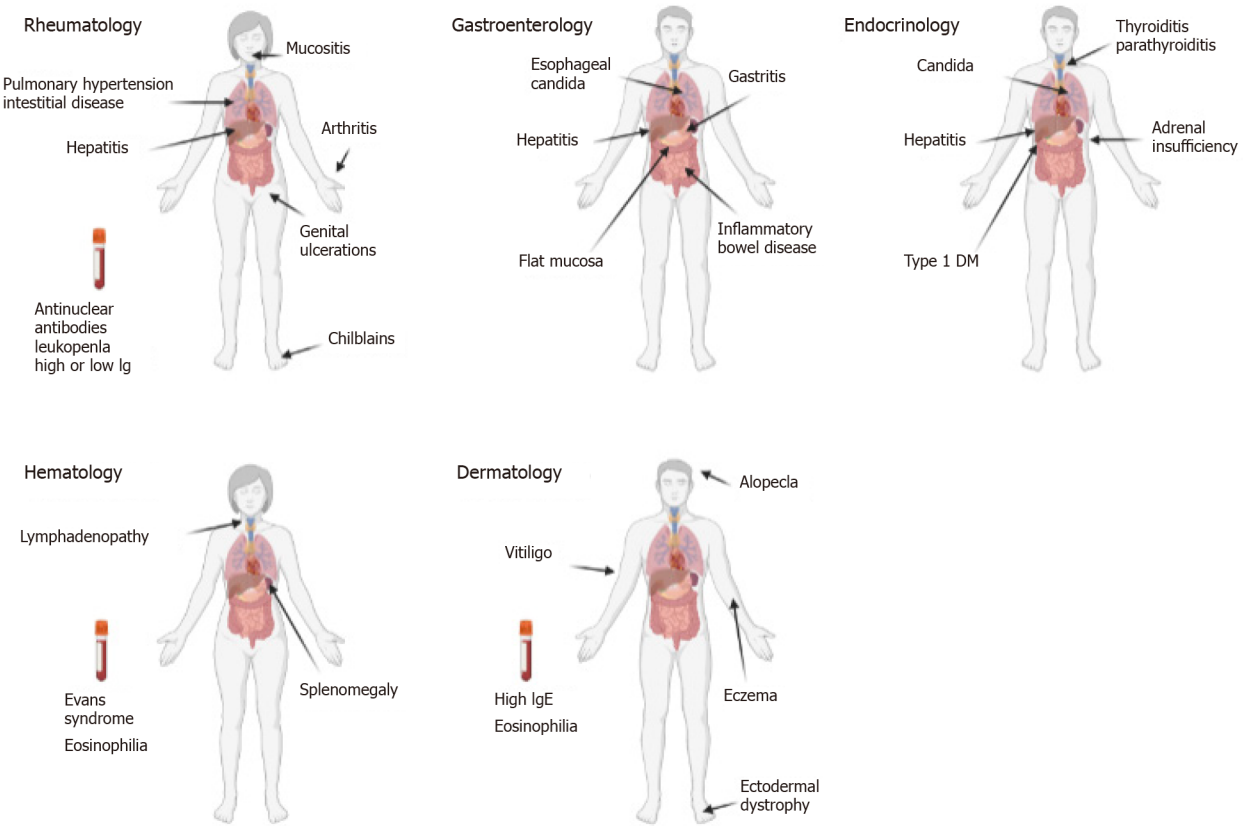

Figure 1 Symptoms and laboratory findings supportive of druggable inborn errors of immunity in various medical specialties.

616414), which can benefit from JAK inhibitors[42,69]. Other rare monogenic causes of arthritis in children include immune dysregulation disorders like CTLA4 or LRBA deficiency[30,70], which can be effectively treated by abatacept[30,70], Blau disease and LACC1 deficiency, which present some overlap with sarcoidosis-like granulomatous disorders[71,72].

Gastroenterology

IBD: IBD can occur at any age, however cases with very early onset are more likely due to monogenic defects[73,74]. Although the majority of monogenic IBD cases occur in children diagnosed before 6 years of age (prevalence of 7%-10%), recent reports suggest the presence of rare variants causing monogenic IBD also in children diagnosed older than 6-years of age. Several genes involved in monogenic IBD were identified, classified in six categories based on action mechanisms, namely defects in the epithelial barrier, T- and B-cell defect, hyperinflammatory and autoinflammatory disorders, phagocytic defects and immunoregulation defects, included IL-10 signaling defects[75].

The clinical picture can be indistinguishable from IBD, however the presence of consanguinity, family history of autoimmune diseases and some histological and clinical features associated with extraintestinal manifestations, should raise the suspicion of an IEI. For example, autoimmune enteropathy and eosinophilic infiltrates may support the diagnosis of an underlying inborn immune defect. On a clinical ground, the presence of lymphoproliferative signs, the association with autoimmune phenomena in other organs, the increased burden of infections and the refractoriness to conventional therapies should prompt considering an IEI. The finding of lymphopenia, neutropenia or hypogammaglobulinemia can help address the suspicion of specific conditions. Eosinophilia can also be of great clinical significance. Some typical immunodeficiencies should be considered in cases with very early onset in infancy: Wiskott Aldrich Syndrome may present in the first days of life with inflammatory colitis, thrombocytopenia and infectious or inflammatory complaints; chronic granulomatous disease can mimic an IBD even before the occurrence of serious infections; combined immunodeficiency can present with intestinal inflammation and failure to thrive. Severe perianal disease, folliculitis and arthritis in early infancy suggest the presence of IL-10 signaling defects[76]. It is crucial to consider all these possibilities, as the diagnostic workout can be quite straightforward, if we pay attention to blood cell count, platelet count and volume, lymphocyte subsets and basic functional assays like the study of the oxidative burst in neutrophils or the dihydrorhodamine assay[7]. Various recent experiences proved the utility of performing high throughput genetic testing in children with very early onset IBD or in those with complex clinical pictures supportive of widespread immunodysregulation, with the aim of planning appropriate and targeted treatment[77].

Autoimmune enteropathy: Autoimmune enteropathy is a rare disorder characterized by intractable diarrhea, growth failure, presence of anti-enterocyte autoantibodies and typical mucosal changes with lymphocyte infiltrates and increased apoptotic cells[78,79]. Most cases occur during the first year of life with severe primarily secretory diarrhea[78]. The association with extra-intestinal diseases like insulin-dependent diabetes, thyroiditis, membranous glomerulopathy, interstitial nephritis and the presence of numerous autoantibodies (*e.g*., antinuclear, anti-smooth-muscle, anti-parietal cells, pancreatic islets...), should raise suspicion of IPEX syndrome. Furthermore, early diarrhea and malabsorption can occur in up to 25% of patients with APECED, due to the destruction of intestinal endocrine cells; in these cases, small bowel biopsies show mild damage, in contrast with the inflammation present in autoimmune enteropathy. An early enteropathy with a relative paucity of inflammatory cells in a patient with a history of recurrent infections should be suspicious for CVID[80,81]. Recent literature reports a series of patients with both LRBA deficiency and CTLA-4 haploinsufficiency with gastrointestinal manifestations, including autoimmune enteropathy, lymphocytic duodenitis resembling celiac disease and autoimmune gastritis[82,83].

Parenteral nutrition, steroids and immunosuppressants like cyclosporin A and tacrolimus are the cornerstones of the therapy. If an IEI can be found in a significant proportion of children with early onset IBD, this is even more true for autoimmune enteropathy[78]. In most cases underpinned by IEIs, HSCT can be the treatment of choice. However, when HSCT is not possible or has to be delayed, a treatment with abatacept or sirolimus may be a valuable option for CTLA4 and LRBA deficiency or for IPEX respectively[30].

Atrophic autoimmune gastritis: Atrophic autoimmune gastritis is an autoimmune disorder associated with chronic gastric autoimmunity, vitamin B12-dependent anemia and increased risk of developing gastric cancer[84]. This condition is often found associated with other immune disorders like common variable immunodeficiency, autoimmune thyroid disease and T1DM[85]. However, some patients may initially present only gastrointestinal complaints with gastritis[83]. Considering that this is a rare disorder in children, the likelihood of finding a monogenic cause is high, and an immunologic and genetic workup should be carried out before the patient develops further autoimmune phenomena. APECED, IPEX and immune dysregulatory disorders are examples of monogenic diseases that can present with autoimmune atrophic gastritis, even if it is rare for autoimmune gastritis to be the sole complaint[83,86,87].

Non celiac flat mucosa: The main cause of flat mucosa in jejunum is active celiac disease (CD), due to gluten-dependent immune activation in the lamina propria of the intestinal mucosa[88,89]. Similar findings can be found in subjects in whom CD has been ruled out, based on negative testing for anti-transglutaminase antibodies and/or absence of the predisposing HLA haplotypes and/or refractoriness to gluten free diet[83,90]. In these cases, intestinal inflammation may be related to an immune defect like common variable immunodeficiency. A flat jejunal mucosa has been described in subjects with immune dysregulatory diseases including IPEX, CTLA4 and LRB immunodeficiency, often in association with other gastrointestinal immune-mediated diseases, like autoimmune gastritis, autoimmune enteropathy or inflammatory bowel disease[83,91].

Esophageal candidiasis: Muco-cutaneous candidiasis is rarely observed in healthy children above the age of 1 year. Seldomly, therapies with oral glucocorticoids may facilitate the development of candidiasis in older children too, however the recurrence of the problem and the extension of the infection to the esophagus should always prompt the suspicion of an underlying immune defect. The underlying causes of chronic muco-cutaneous candidiasis may be monogenic, such as single gene mutations in the autoimmune regulator, signal transducer and activator of transcription-1 (*STAT1*) and -3 (*STAT3*), and many others genes (*CARD9*, *TYK2*, *DOCK8*, *CD25*, *IL-1RA*, *RORC*..), or the result of polymorphisms in genes encoding Dectin-1, NACHT LRR and PYD-containing protein 3, protein tyrosine phosphatase non receptor type-22, and Toll-like receptors which contribute to candida infection susceptibility[92-94]. It is worth noting that candida infections can sometimes be misinterpreted as the results of glucocorticoid treatments administered for other immune complaints, as some patients may present SLE-like phenomena (IL12RB1, STAT1 GOF) or autoimmune manifestations (APECED). Indeed, it is uncertain whether severe diffuse mucosal candidiasis reported in a subset of subjects with SLE are the result of immunosuppressive therapy or the marker of a possible underlying immunodeficiency[95].

Endocrinology

Autoimmune polyglandular syndromes: Endocrine glands are the most typical targets of organ-specific autoimmunity, probably related to the cell-specific expression of proteins involved in the highly specialized machinery of hormone production. Based on distinct patterns of involvement of diverse endocrine systems, autoimmune polyglandular syndromes (APS) have been classified in three groups (APS1-3). Overall, APS have been associated with a general failure of maintaining immune tolerance to specialized tissue. This can be due to a defective presentation of tissue antigens in the thymus during lymphocyte development (as in APECED), improper control of autoreactive lymphocytes in target organs (as in IPEX and IPEX-like disorders) or to breakdown of tolerance by medications (as with

checkpoint inhibitors used to induce anti-cancer immunity).

The combination of hypoparathyroidism and adrenal insufficiency (APS1) with muco-cutaneous candidiasis and ectodermal dystrophy is typical of APECED, however patients may initially present only with a single autoimmune disease. In these cases, the search for autoantibodies can help anticipate further autoimmune disorders, avoiding the risks of a hyperacute onset of disease. APS2 is characterized by T1DM, autoimmune thyroiditis and Addison Disease and is considered a multifactorial disorder associated with the HLA class II locus. APS3 is characterized by T1DM and autoimmune thyroiditis and can be either due to monogenic druggable immune defects (IPEX-like disorders) or to multifactorial causes including HLA class II variants. The presence of dermatitis, autoimmune cytopenia or lymphoproliferation in addition to autoimmune endocrine diseases should always raise suspicion of a monogenic immune dysregulation disorder.

The therapy is mainly based on the replacement of defective hormones. However, in cases associated with significant immune dysregulation, a prompt immune modulation can prevent the development of further autoimmune or infectious diseases, in particular in the cases of druggable IEIs responsive to abatacept and/or sirolimus.

Hematology

Evans syndrome: Evans syndrome is characterized by the association of autoimmune hemolytic anemia with immune thrombocytopenic purpura. The two autoimmune conditions can occur simultaneously or in sequence. In some cases, autoimmune neutropenia can also be present. The term "Evans syndrome" refers to cases in which another definite diagnosis has not been made. However, a search for underlying immune defects may reveal the presence of a monogenic disease in a significant proportion of cases, in particular among those associated with signs of lymphoproliferation, that may be due to immune dysregulation immunodeficiencies[96]. The diagnosis of autoimmune lymphoproliferative syndromes (ALPS), activated PI3Kδ syndromes, IPEX syndrome, and CTLA4 or LRBA deficiencies can pave the way to the administration of targeted therapies like sirolimus, PI3Kδ inhibitors, and abatacept. Of note, sirolimus has been proven effective also in subjects with idiopathic Evans syndrome, suggesting that the disease may share relevant pathogenic features with ALPS. Since autoimmune cytopenias may be the presenting clinical condition in subjects with a common variable immunodeficiency or in SLE, a study of immunoglobulins, antinuclear antibodies and lymphocyte subpopulations is warranted in all subjects with Evans syndrome. Specific cytometric analyses may also give significant hints for rare IEIs[7].

Dermatology and allergology

Refractory eczema: Eczema is a common complaint in young children. If not treated properly, an active eczema can favor the development of allergies and other immune disturbances, fueling a vicious circle of inflammation, scratch injuries and infection. In most cases the disease can be easily treated until it wanes and disappears with age. However, in some rare cases the eczematous dermatitis shows a severe course and a refractoriness to treatments from the first weeks of life. These cases are often associated with poor growth or failure to thrive and sometimes with a history of infections. Blood examinations are usually performed to rule out a severe combined immunodeficiency or a Wiskott Aldrich Syndrome. However, other immune dysregulations are not as easy to diagnose. Peripheral eosinophilia is a clue to diagnosis, but a genetic panel for primary immune defects may be worthwhile in all severe cases. A diagnostic algorithm for IEIs associated with atopic phenotypes has been recently proposed by the Immunology Task Force of the Italian Society of Pediatric Allergy and Immunology[97].

Alopecia, vitiligo: Autoimmune alopecia and vitiligo may present in children at any age. The presence of autoimmune disorders in relatives, like thyroiditis is also common. However, if these complaints present together with other autoimmune or inflammatory disorders or with laboratory abnormalities like eosinophilia or a positive inflammatory index, it may be reasonable to perform an immunological and genetic investigation. For example, when associated with panniculitis, alopecia can rise suspicion of an interferon related disease like CANDLE syndrome, which can benefit from JAK inhibitors; if associated with severe dermatitis it may make you think of an immune dysregulation, like IPEX or CTLA4 or LRBA deficiency. It is worth noting that tofacitinib and other JAK inhibitors, and to a lesser extent abatacept, have been successfully used in subjects with alopecia areata even in the absence of a known underlying immune defect[98-100].

OVERLAP SYNDROMES MAY HIDE MONOGENIC DISORDERS

As described in the paragraphs above, IEIs may present with simultaneous or sequential involvements of various organs and systems. Many cases actually present substantial clinical overlap between disorders pertaining to different medical specialties. Whilst overlap syndromes are not rare in adult rheumatology or gastroenterology, this kind of conditions are not frequently encountered in children. Thus, we propose that IEIs should be considered in every child with immunological complaints overlapping diagnoses that are not usually seen in combination at this age. Since not all cases appear

Table 2 Clinical and laboratory red flags

Clinical red flags
Early onset in childhood: The development of complex inflammatory disorders before puberty and particularly before early childhood rises suspicion of a congenital immune dysregulation
Overlap of symptoms in distinct specialties: A clinical history of distinct rheumatologic and non-rheumatologic conditions is not common in pediatrics, addressing a monogenic disorder
Lymphoproliferative manifestations: The presence of splenomegaly and/or lymphadenopathy in association with inflammatory or autoimmune diseases suggests an underlying inborn error of immunity.
Recurrent infections: The recurrence of severe or atypical infections (especially candidiasis) in association with inflammatory or autoimmune diseases is rarely a consequence of immunomodulatory therapies in children, but it does suggest an immunological defect
Familiarity with autoimmunity: The clustering of autoimmune disorders in families acknowledges a likely monogenic cause
Laboratory red flags
Hypogammaglobulinemia
Hypergammaglobulinemia
Leukopenia
Hypereosinophilia
Wide positivity of autoantibodies
Positive interferon signature

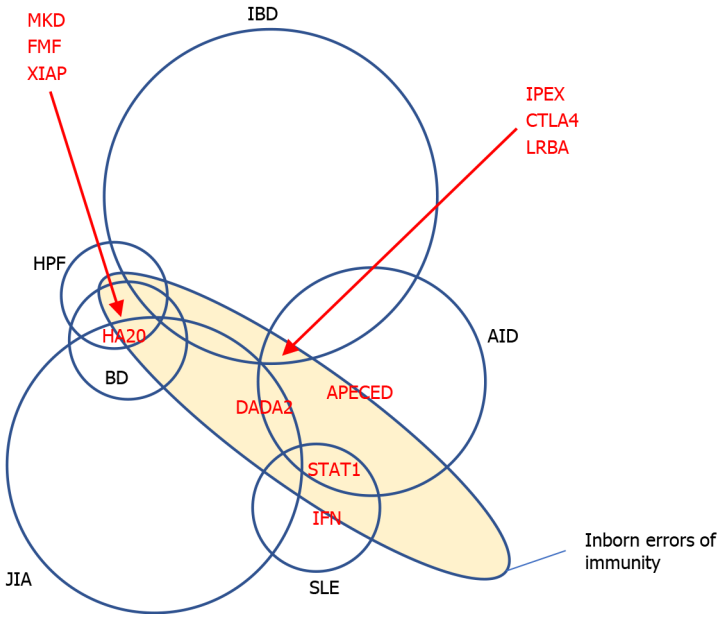

Figure 2 Some druggable inborn errors of immunities in areas of intersection between more common gnoseological entities: In red druggable inborn errors of immunities and in black common gnoseological entities. JIA: Juvenile idiopathic arthritis; BD: Bowel disease; A20: A20 haploinsufficiency; HPF: hereditary periodic fever; IBD: Inflammatory bowel disease; CTLA4: Cytotoxic T-Lymphocyte antigen 4; IPEX: Immunodysregulation polyendocrinopathy enteropathy X-linked; LRBA: Lipopolysaccharide-responsive and beige-like anchor protein; STAT1: Signal transducer and activator of transcription 1; SLE: Systemic lupus erythematosus.

severe at beginning, the correct diagnosis may be often delayed to adult age or even missed. However, to recognize the underpinning monogenic disorder, in particular for druggable ones, it is crucial to choose molecularly targeted therapies able to prevent the development of further damages.

In Figure 2, we propose a schematic view of some druggable IEIs in areas of intersection between more common gnoseological entities. In Table 2, we highlight some "red flags" that could help consider a druggable IEI when dealing with complex immune disorders in any medical specialty.

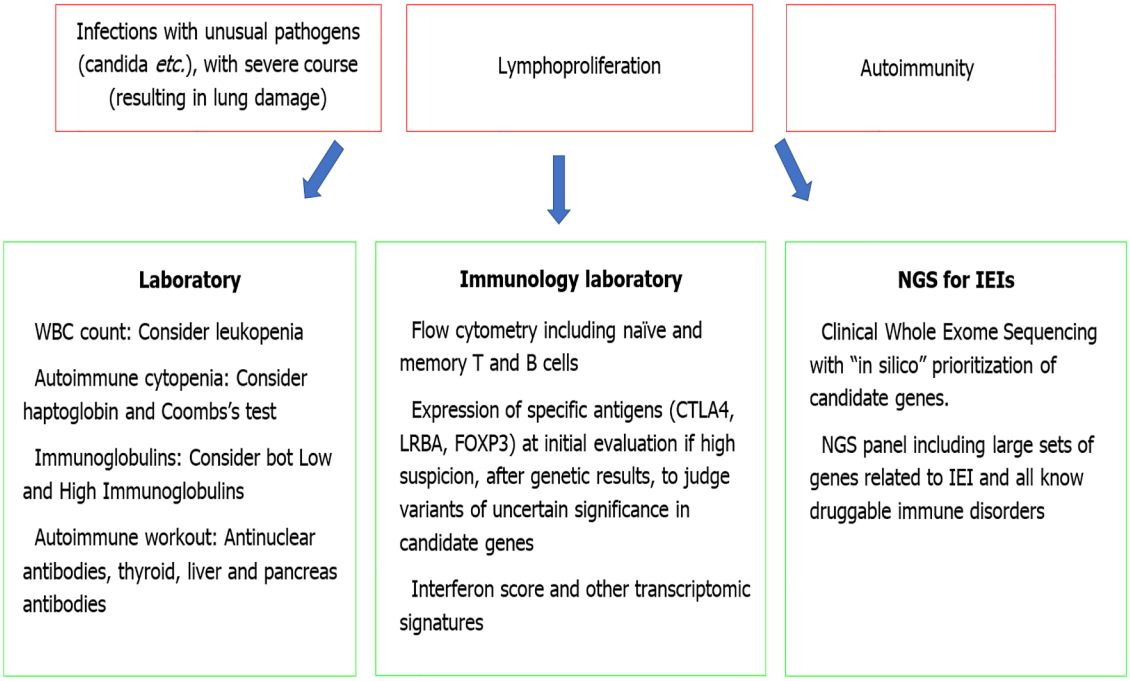

Figure 3 A simplified diagram for suspicion and diagnosis of druggable inborn errors of immunity in clinical practice.

CONCLUSION

Monogenic immune disorders are very rare, especially in subjects with adolescent/adult-onset diseases. Monogenic causes are more likely in subjects with a very early onset than in older ages. We thus provide some hints on when to suspect a group of monogenic disorders, the natural history of which can be favorably influenced by the availability of effective treatments (Figure 3).

FOOTNOTES

Author contributions: Boz V and Levantino L wrote the manuscript; Zanchi C discussed the results and revised the manuscript; Riccio G corrected the manuscript draft; Tommasini A coordinated and approved the work.

Supported by the Italian Ministry of Health RF-2016-02362384; and the IRCCS Burlo Garofolo, No. RC 24/17.

Conflict-of-interest statement: The authors have no conflict of interest

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S-Editor: Liu M
L-Editor: A
P-Editor: Liu M

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World Journal of Clinical Pediatrics

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World J Clin Pediatr 2022 March 9; 11(2): 151-159

DOI: 10.5409/wjcp.v11.i2.151

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Retrospective Study

Barriers and challenges affecting parents' use of adrenaline auto-injector in children with anaphylaxis

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Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Nag DS

Received: April 13, 2021
Peer-review started: April 13, 2021
First decision: July 27, 2021
Revised: August 2, 2021
Accepted: January 19, 2022
Article in press: January 19, 2022
Published online: March 9, 2022

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Abstract

BACKGROUND

Anaphylaxis is a life-threatening condition that develops as a reaction to exposure to an allergen which can be found in common foods such as cow's milk, egg, fish, and nuts in children. The use of an intramuscular adrenaline auto-injector (AAI) is considered the most essential treatment in these situations and parents and caregivers are always encouraged to carry this device for use in an emergency which commonly takes place in public places such as restaurants, schools, and parks, where medical staff are not guaranteed to be available. However, previous studies, in different settings, have reported underuse of the AAI by parents.

AIM

To explore the reasons for underutilisation of the AAI in our community.

METHODS

A cohort of parents attending the paediatric allergy clinic at Al Ain Hospital in the United Arab Emirates completed a questionnaire survey aimed at assessing their understanding and knowledge of their child's allergy management, including their aptitude with the use of the AAI, as well as their competence and comfort in providing this treatment in an emergency.

RESULTS

Of 47 parents participating in the study, 39 were Emirati parents (83% and most

parents who completed the survey were mothers (66%). As expected, food was the main cause of allergic reactions requiring prescription of the auto-injector device. Tree nuts and peanuts were noted to be the most common offending food in these children (62% and 38%, respectively). A doctor provided demonstrations and training on using the auto-injector device to 94% of the parents. More than two-thirds of the parents and caregivers (79%) were deemed knowledgeable on the indication for use of the device. Reluctance to administer the device was expressed by many of the parents, despite their satisfaction with the coaching they received on using the device in the study.

CONCLUSION

Ongoing coaching and teaching of parents on use of the AAI is paramount. However, this should be carried out together with psychological support to aid the parents to eliminate their hesitancy and acquire sufficient confidence in using the device when needed. Group teaching and sharing experiences is an excellent educational technique in a non-formal setting. Paediatric clinic play therapists can also have a role in needle phobia desensitisation for parents and children. More research is needed to explore the lack of empowerment and other reasons behind their fear and anxiety in using the device to plan effective interventions.

Key Words: Anaphylaxis; Adrenaline; Food allergy; Barriers; Education; Management

Core Tip: This is a retrospective study evaluating parents' knowledge of the indications and use of adrenaline auto-injectors in children with anaphylaxis. The state of mind of parents towards the use of the device during anaphylactic episodes in terms of stress, anxiety, comfort, and confidence with the use of the adrenaline auto-injector (AAI) were also evaluated. The study concluded that training and education on how to use the AAI are important, but the psychological status of these parents should not be overlooked, and that sufficient psychological support should be provided in order to assist them to overcome stress and anxiety.

Citation: Narchi H, Elghoudi A, Al Dhaheri K. Barriers and challenges affecting parents' use of adrenaline auto-injector in children with anaphylaxis. *World J Clin Pediatr* 2022; 11(2): 151-159
URL: https://www.wjgnet.com/2219-2808/full/v11/i2/151.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i2.151

INTRODUCTION

Anaphylaxis is a potentially severe and deadly condition that affects multiple body systems with a rapid onset allergic reaction[1]. Adrenaline is the only and immediate choice of drug in the community and the healthcare system, considered for all ages. Moreover, in children, the leading cause of anaphylaxis is food allergy that commonly occurs in public settings such as shopping centres, public parks, restaurants, and schools by triggering food allergens such as peanuts, tree nuts, shrimp, fish, sesame, cow's milk, and egg. In addition, the main food allergens may vary according to ethnicity. For patients with other underlying allergic conditions such as asthma, the risk of anaphylaxis can be higher. Age is also considered a risk factor, with teenagers being the highest risk group. Within our local community in Al Ain city, the prevalence of food allergy has been reported to be up to 8% in children, mainly caused by fish, fruit, and egg[2]. Additionally, information from a systematic review shows that in children, the incidence of food-induced anaphylaxis globally ranges between 1-77 per 100000 people and about 1-761 per 100000 people may face anaphylaxis from any cause[3].

MATERIALS AND METHODS

Following the effective and efficient diagnosis and treatment of the initial food allergic reaction, children with anaphylaxis are mostly referred to their local child allergy service, where age-appropriate advice is delivered to these children and their parents. The allergy action plan focuses on avoiding the offending food and promptly administering the adrenaline auto-injector (AAI) when and as needed. Food remains the main trigger of anaphylaxis in public places[4]. To overcome this condition, it is mandatory for parents of children with food allergies, caregivers, and school nurses to remain vigilant and detect and

treat food-induced anaphylaxis in children using the AAI. Potential or manifested anaphylaxis with hives along with respiratory, cardiovascular symptoms or neurological symptoms such as a reduced level of consciousness, is ideally treated by lying the patient flat and raising the legs to help restore the circulation along with immediate administration of the AAI into the mid outer thigh with the preferred route being an intramuscular injection[4]. According to the European Academy of Allergy and Clinical Immunology (EAACI), the prescribing indications for AAI are either relative or absolute indications. The relative signs include previous mild or moderate reactions to traces of food, mild or moderate reaction to a food with asthma, medical help remoteness, and teenagers as a risk-taker group. The absolute indications exclusively include allergy to venom in adults, food allergy with moderate to severe asthma, a disorder of mast cells with high baseline serum tryptase, previous idiopathic anaphylaxis, previous exercise-induced anaphylaxis, and previous anaphylaxis to food allergens[4]. Our practice is that we usually prescribe two AAI devices, one for school and one for the home. In some exceptional circumstances, the number may change; for example, as per family conditions such as divorce or separation where the child may stay and spend a long time in two different places; or obesity as in these situations the child sometimes needs more than two AAI devices. At each clinic visit, the parents are provided with repeated technical and medical information and a demonstration on use of the AAI device.

We always prescribe AAI to all the children who need it; it was observed that the parents sometimes do not pay attention to the expiry date and renewal of their children's AAI[5]. Moreover, in an actual anaphylaxis situation, some do not appreciate the urgent need for AAI administration. Instead, they prefer to rush to the nearest emergency department. The delay in providing lifesaving treatment may potentially result in life-threatening events. Some do not carry the device all the time, and they do not even know how to use it properly[6]. According to recent studies, mortality has been linked with anaphylaxis cases; it was primarily related to AAI delay, underuse, and faulty administration techniques[7], and more than 50% of anaphylaxis patients did not receive the required amount of AAI.

However, the findings of previous reports from other populations with different traditions, nationalities, and cultures are different to our current population. As a result, we decided to explore our local population's current practice and compliance in Al Ain city using the AAI to treat children with anaphylaxis.

Statistical analysis

A previous clinic audit revealed that, despite prior training, approximately 3% of parents remained unsure how and when to use the AAI. Therefore, we calculated that a representative sample size of 45 families in our clinic population would be required to give the study an adequate power of 80% with 5% error and 95% confidence. In addition, groups were reported as percentages and numbers, and to quantify the qualitative information, a Likert scale was used. The statistical analysis also compared the univariate association between the outcomes of interest and the explanatory variables using ANOVA (analysis of variance) for more than three groups and an unpaired Students t-test for two variables. Moreover, an ordered logistic model tested the association between explanatory variables and outcomes while correcting for potential cofounders. Therefore, the statistical analysis was performed with the two-tailed P value < 0.05 as significant and STATA 15.0 software (StataCorp, Texas, United States).

RESULTS

The results were obtained after conducting 47 questionnaires that were mainly (83%, n=39) completed by Emirati families, with mothers accounting for 66% of the respondents. Furthermore, after performing the analysis, it was found that (45%, n = 21) of the children experienced anaphylaxis. 89% of the children prescribed with the AAI were under five (Table 1). On answering the question of their willingness to use the AAI in unintentional allergic response causing anaphylaxis, 79% (n = 37) declared that they would use the AAI. In the questions intended to assess knowledge of the AAI indication, approximately 19% of the respondents stated that they would use the AAI device in a situation of rashes that affected the lips and caused swelling. About 2% of the respondents admitted a complete lack of knowledge of AAI usage. The allergy doctors trained 94% of the parents, and 36% of the parents felt confident and competent to use the AAI after experiencing AAI usage at least once in an actual situation. Most of the children were prescribed two AAI devices, one for school and one for the home.

As shown in Table 2, the most common food allergens reported were tree nuts (62%) followed by peanuts (38.5%). The data showed that sesame was a typical offending food which was not the case in the region previously.

Figure 1 and Table 3 detail parental perceptions and insights of their satisfaction, capability, and comfort with the training sessions on use of the AAI device. About 72% of the respondents strongly admitted being comfortable in using the AAI device, and 59.6% moderately agreed. In comparison, 12.8% felt neutral, 19% were unsure about usage, and 8.5% did not show interest in using the device. However, approximately 80.8% of the respondents demonstrated their overall competency in using the AAI device, 14.9% showed competency, while 66% were moderately competent, and 19% were unsure

Table 1 Characteristics of the 47 participating families

Informant		
	Father	16 (34)
	Mother	31 (66)
Child's nationality		
	Emirati	39 (83)
	Foreign	8 (17)
Child's age group		
	< 5 yr	21 (45)
	5-10 yr	20 (42)
	> 10 yr	6 (13)
Child's sex		
	Male	25 (53)
	Female	22 (47)
Indication for AAI		
	Food allergy	42 (89)
	Idiopathic anaphylaxis	2 (4)
	Insect/venom-induced allergy	3 (7)
Number of AAI prescribed		
	1	10 (21)
	2	33 (70)
	3	3 (7)
	4	1 (2)
Parents' awareness of when to use the AAI		
	Rash with breathing difficulty	37 (79)
	Rash with swollen lips	9 (19)
	Unsure	1 (2)
Training provided by		
	Doctor	44 (94)
	Nurse	1 (2)
	Pharmacist	1 (2)
	Do not remember	1 (2)
Has used an AAI before		17 (36)

Results expressed as number (percentage). AAI: Adrenaline auto-injector.

about their competence. Other results showed that 89% of the respondents were satisfied with the AAI device training, about 55% were moderately satisfied, and 31.9% were delighted. However, 10.6% were not satisfied with the training received and usage, and only 2% were unsatisfied.

Therefore, no significant difference was found after performing the univariate analysis, with minor differences in using the AAI device by parents and their level of satisfaction while training, their level of competency in its use, and the comparison between the past and the current usage of the device. The relationship between the training by non-physicians and physician trainers is shown in Table 3.

However, in the ordered logistic regression model, adjusting for potential cofounders, the baseline characteristics associated with the parental comfort level for use of the AAI were evaluated and only their previous use of AAI was significantly associated with their competency in using the device (Table 4).

Table 2 Frequency of food allergens causing anaphylaxis as reported by parents

Allergen	*n*	%
Tree nuts	29	62
Peanuts	18	38.5
Egg	9	19
Cow's milk	8	17
Sesame	7	15
Shrimp	4	8.5
Strawberry	4	8.5
Wheat	3	6.5
Lentil	3	6.5
Others	11	23

Table 3 Univariate analysis of parents and children's characteristics in association with their reported outcome of training on a Likert scale

		Satisfaction with the training received	Competency in using the AAI	Comfortable and not scared to use the AAI
Child's gender	Male	3.3 ± 1.0	3.5 ± 0.6	3.5 ± 0.7
	Female	3.2 ± 1.1	3.7 ± 0.8	3.3 ± 0.9
	P value[1]	0.7	0.2	0.5
Age group (yr)	< 5	3.3 ± 1.1	3.6 ± 0.7	3.5 ± 0.8
	5-10	3.3 ± 1.0	3.7 ± 0.8	3.4 ± 0.8
	> 10	2.8 ± 1.1	3.6 ± 0.8	3.1 ± 0.9
	P value[2]	0.6	0.8	0.7
Diagnosis	Food allergy	3.2 ± 1.1	3.6 ± 0.7	3.4 ± 0.8
	Idiopathic anaphylaxis	2.5 ± 0.7	3.0 ± 0	2.5 ± 0.7
	Insect/venom induced allergy	3.6 ± 0.6	3.6 ± 0.6	3.3 ± 0.6
	P value[2]	0.5	0.4	0.2

[1]Student unpaired *t*-test.
[2]Analysis of variance (ANOVA). AAI: Adrenaline auto-injector.

DISCUSSION

The present study highlights the risk of anaphylaxis and its factors, which significantly influence the parental usage of AAI devices in the local population in Al Ain city, UAE.

Cases of anaphylaxis are commonly triggered in children by food allergens such as nuts. Furthermore, in local studies, about 15% of anaphylaxis cases (unreported previously) were induced by sesame[2], an uncommon food allergen in the Middle East and North Africa region as it is widely used and almost all children would have been exposed to it or its oil very early in life.

Our results show that the parents' comfort level and self-perceived practical capability in using the AAI were less than expected; even with parents' education and training sessions, we observed persistent doubts in administration of the AAI. Moreover, regardless of training from the allergy specialist, and as the majority expressed insufficient awareness on when to administer, which probably reflected the level of anxiety in thinking any allergic reaction is anaphylaxis, or it could have been due to inadequate information provided when the AAI was prescribed.

The number of parents who admitted being uncomfortable or unsure about using the AAI is concerning and may harm their use of the device when needed. According to the findings of a previous study, a similar number of parents of children aged from 0 to 18 years experiencing anaphylaxis and

Table 4 Association between parents' reported outcome of training and baseline characteristics in an ordered logistic regression model

	Satisfaction with the training received	Competence in using the AAI	Comfortable and not scared to use the AAI
Informant	0.7 (-5.6,2.1); 0.2	-0.9 (-2.2, 0.4); 0.2	-0.4 (-1.7, 0.8); 0.4
Nationality	-0.5 (-2.1, 1.0); 0.5	0.5 (-1.1, 2.1); 0.5	-0.1 (-1.6, 1.3); 0.8
Age group	-0.5 (-1.4, 0.4), 0.3	0.1 (-0.8, 1.1); 0.7	-0.3 (-1.2, 0.6); 0.5
Gender	-0.2 ((-1.4, 1.0); 0.7	-0.2 (-1.4, 1.0); 0.7	0.7 (-0.4, 1.9); 0.2
Diagnosis	0.2 (-0.9, 1.4); 0.6	-0.4 (-1.5, 0.8); 0.5	-0.4 (-1.6, 0.7); 0.5
Training provider	0.4 (-2.2, 3.0); 0.7	-16.4 (-4320, 4287); 0.9	-1.2 (-4.0, 1.5); 0.3
Has used AAI before	0.3 (-0.9, 1.6); 0.6	1.6 (0.2, 2.9); 0.02	0.1 (-1.1, 1.4); 0.8

AAI: Adrenaline auto-injector.

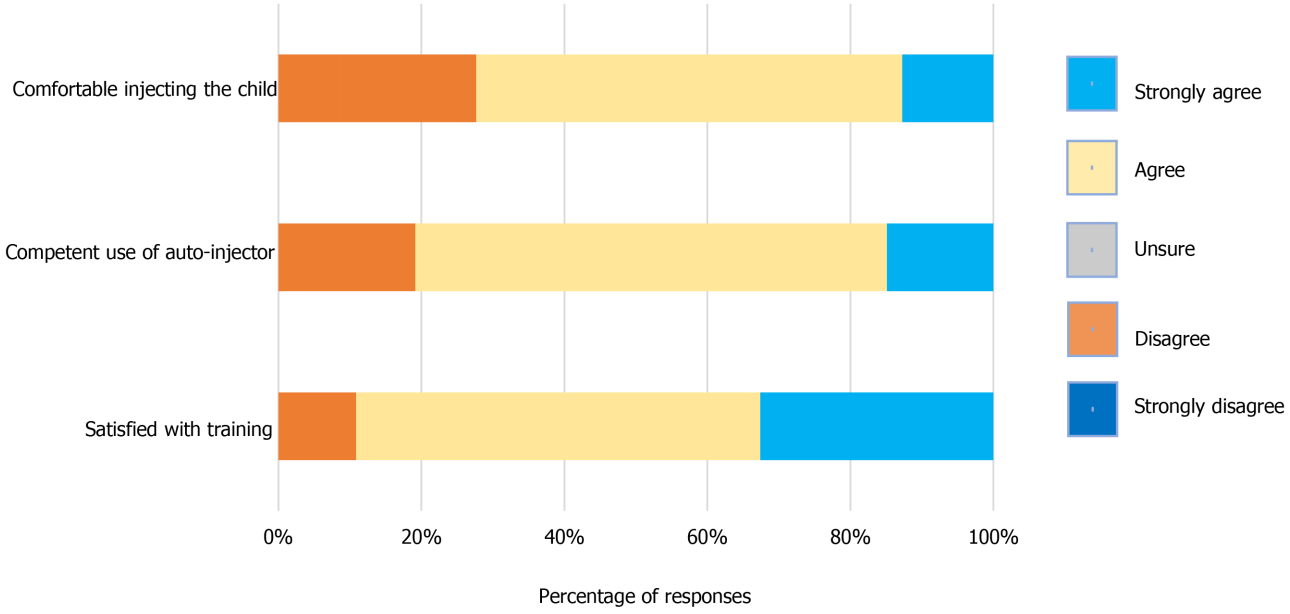

Figure 1 Parental responses regarding the outcome of training they received on how to use an adrenaline auto-injector.

food allergies used an AAI device. Furthermore, 75% of participants displayed proper technique and abilities for using the auto-injector device[9].

Considering the anxiety and psychological effect of having a child with a food allergy, and as many of the respondents were mothers, it is possible that the psychological effect of anxiety and stress encountered by these mothers affected mental function reflected in the lack of confidence in using the AAI despite satisfaction with the training received. The effect of having a child with a food allergy and potential anaphylaxis in limiting the mental capacity in making sound decisions regarding the child's care has been well documented in the literature[10], and it may even outweigh the stress associated with having a child experiencing diabetes mellitus type I and other chronic diseases[9].

The highlighted difficulties associated with training demonstrate that more effort is needed to sufficiently train parents in anaphylaxis management of their children by providing them with a quality-training session in a calm and friendly atmosphere aided by audio-visual and tactile experiences using the trainer AAI device in the training sessions. Although parents did not admit to suffering undefined psychosomatic factors undermining their use of the device, it has been shown that it is not information or earlier anaphylaxis experience that increases the ease of parents in using the AAI. We deduce that authorisation together with continuous education on the use of the device and preventing anxiety correlate with parents' level of comfort[10]. Therefore, to address these issues, caregivers and parents of these children should be encouraged to practice with an outdated AAI on objects such as an orange, apple, and cardboard instead of discarding them as this type of practice may help improve their level of confidence.

The variety and number of psychological stresses that parents face appear to have been underestimated as they influence the success of any parental empowerment and training, and must be addressed by providing psychological support[11,12]. Group meetings of these parents would provide an opportunity to share experiences of fear, worries, and anxieties using the AAI, which might be beneficial in overcoming the psychological barrier[11].

Our study included a self-administered questionnaire, which could have been skewed by parental recall bias or a desire to satisfy the treating physician. A face-to-face interview with the help of a simulation manikin might have overcome these restrictions and would provide a more objective assessment of the parents' confidence and technical ability than just recalling or interpreting occurrences. Our standard practice is to use an AAI trainer to educate and review previous knowledge and skills in using the device at every clinic visit. We delayed the training until parents completed the surveys to reduce bias.

The single-centre and small sample size are other limitations, which majorly prevented the generalizability of the findings to our local community in our city or the UAE. More extensive multicentre research involving other local paediatric clinics would have been beneficial to address such constraints.

Qualitative research, including face-to-face interviews, will be required to better understand the parents' attitudes and beliefs in controlling allergic reactions in their children. The goal would be to elicit, document, and analyse their reactions, opinions, and sentiments concerning the psychological impact of their child's allergy on them and their mental process. Clinicians and psychologists might use this knowledge to design suitable treatments to aid the family.

CONCLUSION

There is a requirement to advance and recover the psychological barrier and consolidate educational provision for parents whose children have an anaphylaxis risk. Furthermore, AAI trainer devices must be present in schools and the home for periodical practice, which helps to generate and maintain their confidence. The AAI trainer devices are helpful as a visual and tactual tool to overcome the fear of the lack of skills in treating anaphylaxis and ideally should be made available to all parents. In addition, it is practical to use outdated AAI devices on objects such as oranges, apples, and so on. Group teaching and sharing experiences are an excellent way to enhance learning and reduce stress. Psychology input unfortunately remains a luxury and is unavailable in most health providers. Play therapists could also have a role as they are capable of explaining needle phobia desensitisation to children and their parents.

ARTICLE HIGHLIGHTS

Research background

Food allergy is common in the paediatric age group and food allergic reactions commonly occur in the community. The adrenaline auto-injector (AAI), issued to groups of children at risk of anaphylaxis, remains the first and only drug of choice for treating anaphylaxis. However, data from different parts of the world demonstrate that AAI is underused by parents and caregivers. The rationale behind this attitude is multilateral and could be attributed to issues such as poor training on the use of the auto-injector device, not understanding when it should be used, and both fear and anxiety of using it.

Research motivation

From our daily observations in the local paediatric allergy clinic, we found many cases of anaphylaxis that occurred at home due to the ingestion of offending food, and parents opted to call 999 or bring the child to the emergency department rather than using the AAI prescribed at the scene. Obviously, underuse of the AAI can put the affected child at risk of severe morbidity or mortality. In every clinic, we reviewed the indication for use of the AAI by parents and provided a visual demonstration on how to use it.

Research objectives

To study the attitude of parents of children at risk of anaphylaxis with regard to the use of AAI in an attempt to identify what prevents these parents from using the AAI when needed. The results of this research would help professionals to be more focused on certain issues when providing counselling and training on the use of the AAI to this cohort of parents.

Research methods

Parents of children with previous or potential anaphylaxis who have been issued with an AAI were requested to complete a paper questionnaire on their understanding of the indications for use of the AAI, competence in using the device, confidence and empowerment in using it in stressful emergency

situations.

Research results

The vast majority of parents admitted receiving good and informative training on using the device and demonstrated good knowledge on its indications. However, that was not enough to provide them with the confidence and courage to use the device due to other factors such as anxiety, fear, or not wanting to hurt the child with the AAI needle. Psychological uneasiness in using the device can limit parents' ability to use it.

Research conclusions

In addition to routine training in these groups of parents on the indication of using the AAI and the technique on how to use it, health professionals need to pay attention to the psychological factor which could prevent these parents from underusing the device when needed. Psychological, behavioural therapy and needle phobia desensitisation would help to overcome the barriers of phobia and anxiety which could interfere with sound decision-making in the treatment of their children in emergency situations.

Research perspectives

Parent training on the use of AAI should be structured and focused. Audio-visual tools should be available in the clinic to help with training. However, the fear factor and the psychological status of these parents should not be overlooked. A routine referral or referral of selected cases to the local psychological service should be accessible to these parents. Play therapists can also have an important role in both children and parents by reducing needle phobia when present.

ACKNOWLEDGEMENTS

We are indebted to the parents who participated in the study by sharing their experiences and feelings.

FOOTNOTES

Author contributions: Elghoudi A designed the research protocol, sought ethical approval, collected the data, and was involved in writing the manuscript; Narchi H conducted the statistical analyses, constructed the tables and the graph, and participated in writing the manuscript; Dhaheri KA participated in data collection and writing the manuscript; all authors read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by Al Ain Hospital Ethical Research Committee Review board (reference number AAHHEC-01-20-001).

Institutional animal care and use committee statement: No animals were involved in the study.

Informed consent statement: Signed informed consent was obtained from all parents who participated in the study.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest to disclose.

Data sharing statement: The anonymised data can be obtained from the principal investigator (ahmed.elghoudi1@gmail.com) upon reasonable request.

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S-Editor: Wang LL
L-Editor: Webster JR
P-Editor: Wang LL

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 March 9; 11(2): 160-172

DOI: 10.5409/wjcp.v11.i2.160

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Observational Study

Functional constipation in Bangladeshi school aged children: A hidden misty at community

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Wang FC

Received: April 22, 2021
Peer-review started: April 22, 2021
First decision: May 24, 2021
Revised: June 2, 2021
Accepted: January 5, 2022
Article in press: January 5, 2022
Published online: March 9, 2022

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Abstract

BACKGROUND

Constipation is a common problem in children and a frequent cause of hospital visit in both primary & specialized care, which needs proper evaluation & management. Presentation of constipation is variable among children. In Bangladesh there has been no published data regarding constipation in community among school aged children.

AIM

To determine the magnitude of functional constipation and its risk factors in community among Bangladeshi school children.

METHODS

This descriptive cross sectional study was conducted in different schools of Dhaka division, Bangladesh. All school aged children between 5-16 years of age who attended school were included in this study. Samples were collected randomly. Proper clinical history & physical examinations (without digital rectal examination) & available investigations (if done previously) were recorded. Diagnosis of functional constipation was done by Rome IV criteria and was compared with children without constipation. Children with any red flag sign, known chronic

disease or any findings suggestive of organic disease and on treatment of constipation were excluded. Statistical analysis of the results was done by using Windows based software device with Statistical Packages for Social Science 20. For all statistical tests, *P* value of less than 0.05 was considered as statistically significant.

RESULTS

Total study populations were 707 and male was 443 and female 264. Among them, 134 (19%) children had constipation. In constipated children, 78 children fulfilled the Rome IV criteria for functional constipation and it was 11% of total population. Mean age of children having functional constipation was 11.24 ± 3.54 years and Male female ratio was 1:1.78. Anorexia, nausea, abdominal pain, hard stool, blood with hard stool, alternate hard and loose stool and fecal mass in left iliac fossa were analyzed between two group and all were significantly higher in children with functional constipation group. Children of school, where toilet numbers were inadequate had 2.5 times more constipation risk in comparison to children of school with adequate toilet number (OR = 2.493, 95%CI: 1.214-5.120). Children who feel embarrassed to use toilet at school, had 3.6 times higher risk of constipation (OR = 3.552, 95%CI: 1.435-8.794). Here children with H/O affected sibs and parents/grandparents had 4 and 2.6 times more chance of constipation respectively in comparison to children without H/O affected sibs (OR = 3.977, 95%CI: 1.884–8.397) and parents/grandparents (OR = 2.569, 95%CI: 1.172-5.629). Children with inadequate fluid intake had 2 times more risk of constipation in comparison to children with adequate fluid intake (OR = 1.972, 95%CI: 1.135-3.426). Children who passed electronic screen time of > 2 h/d had 2 times more chance of constipation in comparison to children who passed electronic screen time < 2 h (OR = 2.138, 95%CI: 1.063-4.301).

CONCLUSION

Constipation is not uncommon in Bangladeshi school aged children. Inadequate toilet number, family history of constipation, inadequate fluid intake, feeling embarrassed to use toilet at school, and electronic screen time for > 2 h/d were found as risk factors in the present study for functional constipation.

Key Words: Bangladesh; Children; Functional constipation

Core Tip: The current study is the first population-based study of childhood constipation in Bangladesh. Frequency of constipation and functional constipation was 19% and 11% respectively. Inadequate toilet number, family history of constipation, inadequate fluid intake, feeling embarrassed to use toilet at school, and electronic screen time for > 2 h/d were found as risk factors in the present study for functional constipation. Alternate hard and loose stool as one of the presentation of functional constipation.

Citation: Benzamin M, Karim AB, Rukunuzzaman M, Mazumder MW, Rana M, Alam R, Islam MM, Alam MS, Hossen K, Yasmin A, Fathema K, Khadga M, Aishy AS. Functional constipation in Bangladeshi school aged children: A hidden misty at community. *World J Clin Pediatr* 2022; 11(2): 160-172

URL: https://www.wjgnet.com/2219-2808/full/v11/i2/160.htm

DOI: https://dx.doi.org/10.5409/wjcp.v11.i2.160

INTRODUCTION

Constipation is a common problem in children and it is frequently overlooked. Constipation is not a disease; rather, it's only a symptom. Patients have variable perception regarding constipation, some regard constipation as straining or hard pellet like stool or infrequent defecation or inability to defecate when desire. Constipation is generally defined as infrequent stool, passage of hard stool or both[1]. But North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) defined constipation as delay or difficulty in defecation, present for 2 or more weeks and sufficient to cause significant distress to the patient[2].

Children with constipation quite often visit a general practitioner or pediatrician. These children are also regularly seen on the emergency ward or even admitted to the hospital for treatment. Although functional constipation is not related to mortality but significantly hamper the quality of life. In children constipation may be functional or due to organic causes. In contrast to organic causes, functional

constipation (FC) is not a result of a structural or biochemical abnormality. Constipation due to organic causes may contribute to mortality of patient. In functional constipation, onset of symptoms is within the first year in half of the cases, and the prevalence is highest in 2nd and 4–5 years of age[3]. FC is often not a self-limiting condition: despite treatment, one-third to half of the patients has significant problems after 5 years and symptoms persist into adulthood in approximately 25% of cases[4].

The prevalence of childhood constipation has been documented, with highly variable results from study to study and from country to country, ranging from 1% to 30%[3]. Despite the variations of prevalence in different countries, there is a global trend of increasing rate of childhood constipation, and this increase remains unexplained. The marked socioeconomic, cultural, political and demographic variations that exist between and within the different continents could influence the risk factors and prevalence of childhood FC[5]. The common belief is that constipation is not common in South-Asian countries like India, Bangladesh as diet is rich in fibre here. There are very few studies related to constipation in developing countries specially in South-Asian countries[6].

Most recently Rajindrajith[7] and Khanna *et al*[8] showed that it is not uncommon in sub-continental countries. On departmental survey in out-patient department of paediatric gastroenterology and nutrition, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, almost 40% patients presented with constipation. But there is no published data in Bangladesh about childhood constipation. The current study is the first population-based study of childhood constipation in Bangladesh. The present study has been undertaken to observe the clinical profile and risk factors of functional constipation in community among the Bangladeshi school aged children.

MATERIALS AND METHODS

This cross sectional study was conducted at different primary school and high school of Dhaka division of Bangladesh, from August 2018 to July 2019. The inclusion criteria were children of age 5-16 years who attended the school. The exclusion criteria were children already on treatment for constipation and any red flag sign or known chronic disease or symptoms suggestive of disease.

Sampling technique

A multistage sampling technique was used to select participants. Study place was selected by simple random sampling. Four schools and one madrasa were randomly selected. The schools were then stratified based on location as urban or rural and based on ownership as private or public schools. The participants were selected randomly from different class. Only those students, whose parents gave written consent willingly, were recruited in the study. The detailed clinical history, physical examination findings and investigation reports (if available) were recorded in a predesigned standard data sheet.

History was obtained directly from the students and parents, which included basic demography, age at onset of constipation/symptoms, duration of symptoms, consistency, frequency, volume/size of stool, straining, pain during defecation, bleeding per rectum/blood mixed stool, fecal soiling, abdominal pain, withholding behavior, urinary incontinence/burning urine, history of other sibs/family members affected, detailed family history.

Also history was taken regarding diet pattern (on 3 d recall method), outdoor activity/exercise, any school related condition, social history, past medical and surgical history, history regarding the red flag signs.

Physical examination of all samples was done by researcher himself. The following data were obtained during physical examination: fever, mouth ulcer, abnormal thyroid gland, growth parameters, skin survey, per abdominal examination, tone/reflex of lower limb, spine of vertebra, abdominal distension. Other significant physical findings were also recorded.

Diagnosis of constipation by NASPGHAN and functional constipation was done by Rome IV criteria and if there was red flag sign, organic cause was considered.

Among them who fulfilled the criteria of functional constipation were included in group 1 (children with functional constipation) and others were included in group 2 (children without constipation).

Operational definition

Constipation: NASPGHAN defines constipation as a delay or difficulty in defecation, present for 2 or more weeks and sufficient to cause significant distress to the patient[2]. Functional Constipation: As per Rome IV criteria, functional constipation is defined as presence of at least two of the followings at least once per week for a minimum period of one month: Two or fewer defecations in the toilet per week in a child of a developmental age of at least 4 years; At least one episode of fecal incontinence per week; History of retentive posturing or excessive volitional stool retention; History of painful or hard bowel movements; Presence of a large fecal mass in the rectum; History of large-diameter stools that may obstruct the toilet. The symptoms cannot be fully explained by another medical condition.

Table 1 Demographic data of children with functional constipation and without constipation

Characteristics	Functional constipation (*n* = 78), *n* (%)	Without constipation (*n* = 573), *n* (%)	*P* value
Sex			0.003[1]
Male	38 (48.7)	378 (66)	
Female	40 (51.3)	195 (34)	
Age (mean ± SD, yr)	11.24 ± 3.51	12.67 ± 2.40	0.001[2]
Place of residence			0.190[1]
Rural	17 (21.8)	156 (27.2)	
Urban	61 (78.2)	417 (72.8)	
Religion			0.214[1]
Muslim	77 (98.7)	551 (96.2)	
Hinduism	1 (1.3)	22 (3.8)	

[1]Chi-square test.
[2]*t*–test.
P value < 0.05 considered as statistically significant.

In addition, the symptoms are insufficient to fulfill the diagnostic criteria of irritable bowel syndrome [9].

Red flag sings: H/O delayed passage of meconium, difficulty in passing stool from birth, ribbon like stool, failure to thrive, bilious vomiting, no response to treatment, coarse facial profile, abnormal thyroid gland, abnormal lumbo-sacral spine, abnormal neurological findings of lower limb, perianal disease, severe abdominal distention, blood in stool in absence of anal fissure[10].

Normal dietary fiber intake: age in years plus 5 g/d[11].

Normal water intake**:** children with body weight 1-10 kg = 100 mL/kg, for children with body weight 11-20 kg = 1000 mL + 50 mL/kg for every kg over 10 kg of body weight, for children with body weight above 20 kg = 1500 mL + 20 mL for every kilogram above 20 kg of body weight[12].

Weight for age and height for age less than 3rd percentile was considered as underweight and stunted respectively[13].

Overweight: Body mass index for age more than 85th percentile was considered as overweight[13].

Statistical method

After collection, data were checked manually and analyzed by computer based program Statistical package of social science 22.0 (Chicago, Illinois, 2016). Results were expressed as mean ± SD, or number or percentage. Chi-square test was used for categorical data while student t-test was used for comparison of continuous variable data. Binary logistic regression analysis was used to find risk factors. *P* value < 0.05 was considered as statistically significant.

Ethical issues

Prior to the commencement of this study, the thesis protocol was approved by the Institutional Review Board of BSMMU, Dhaka.

RESULTS

Total study populations were 707 and males-443, females-264. Among them, 134 (19%) children had constipation. Among the male children, 65 (14.67%) and among the female children, 69 (26.14%) had constipation. Male-female ratio of constipated child was 1:1.78. In constipated children, 78 children fulfilled the Rome IV criteria for functional constipation and it was 11% of total population. Among other 56 constipated children, 21 patients had one or more red flag sign, 6 were known case of hypothyroidism and rest 29 children had no red flag sign but they did not fulfill the Rome IV criteria.

Table 1 showing demographic data analysis of studied population and here Rome IV criteria were fulfilled by 78 children. Among the male (420) children, 38 (9.1%) had functional constipation and among the female (242) children, 40 (17%) had functional constipation and *P* value is significant. Male female ratio was 1:1.9.

Mean age of children having functional constipation was 11.24 ± 3.51 years and children without constipation were 12.67 ± 2.40 years and p value is significant.

Table 2 Symptoms analysis of children with functional constipation and without constipation

Characteristics	Functional constipation (*n* = 78), *n* (%)	Without constipation (*n* = 573), *n* (%)	*P* value
Anorexia			0.001[1]
Yes	35 (44.9)	124 (21.6)	
No	43 (55.1)	449 (78.4)	
Nausea			0.001[1]
Yes	17 (21.8)	46 (8)	
No	61 (78.2)	527 (92)	
Abdominal pain			0.001[1]
Yes	37 (47.4)	122 (21.3)	
No	41 (52.6)	451 (78.7)	
Hard stool			0.001[1]
Yes	63 (80.8)	32 (5.6%)	
No	15 (19.2)	541 (94.4)	
Blood with hard stool			0.001[1]
Yes	6 (7.7)	3 (0.5)	
No	72 (92.3)	570 (99.5)	
Alternative hard and loose stool			0.001[1]
Yes	22 (28.2)	10 (1.7)	
No	56 (71.8)	563 (98.3)	
Abdominal distension			0.537[1]
Yes	0 (0)	78 (100)	
No	78 (100)	566 (98.8)	
Fecal mass in LIF			0.001[1]
Yes	12 (15.4)	0 (0%)	
No	66 (84.6)	573 (100)	

[1]Chi-square test, *P* value < 0.05 considered as statistically significant.

Residential area and religion of the studied group had no significant influence on constipation.

Table 2 showing symptoms analysis of studied population and here anorexia, nausea, abdominal pain, hard stool, blood with hard stool, alternative hard and loose stool, abdominal distension and fecal mass in left iliac fossa were analyzed between two groups and all were significantly higher in children with functional constipation group except abdominal distension.

Table 3 showing descriptive data of bowel habits of studied group and here defecation frequency at 2 d interval, 3 d interval, incontinence, painful bowel movements, H/O retentive posturing and large diameter stool all were significantly higher in children with functional constipation group.

Table 4 showing the school related factors analysis of studied population and here children with long periods of school, less number toilets at school/dormitory and feel embarrassed to use toilet at school had higher percentage of constipation and p value is significant.

Table 5 showing family related factors analysis of studied population. Here history of constipation in other siblings, history of constipation in parents/grandparents, family size, birth order, parent's education, household income, single or joint family was considered. But only children having history of constipation in other siblings and history of constipation in parents/grandparents were significant.

Table 6 showing diet related factors analysis of studied population. Here children with less fiber intake and less fluid intake had higher percentage of constipation and p value is significant.

Table 7 showing physical activity related factors analysis of studied group and children who preferred television; mobile watching for more than 2 h per day had higher percentage of constipation and *P* value is significant.

Table 8 showing Binary logistic regression analysis done for age, sex, residential school, long duration school, toilet number, feeling embarrassed to use toilet, H/O affected sibs and grandparents, fluid and

Table 3 Descriptive data of bowel habits of children with functional constipation and without constipation

Characteristics	Functional constipation (*n* = 78), *n* (%)	Without constipation (*n* = 573), *n* (%)	*P* value
Defecation frequency			0.001[1]
Daily	43 (55.1)	501 (87.4)	
1 d interval	3 (3.8)	48 (8.4)	
2 d interval	12 (15.4)	24 (4.2)	
3 d interval	20 (25.6)	0 (0)	
Incontinence			0.014[1]
Yes	2 (2.6)	0 (0)	
No	76 (97.4)	573 (100)	
Painful bowel movements			0.001[1]
Yes	60 (76.9)	2 (0.3)	
No	18 (23.1)	571 (99.7)	
H/O retentive posturing			0.001[1]
Yes	7 (9)	0 (0)	
No	71 (91)	573	
Large diameter stool			0.001[1]
Yes	72 (92.3)	2 (0.3)	
No	6 (7.7)	571 (99.7)	

[1]Chi-square test, *P* value < 0.05 considered as statistically significant.

fiber intake, physical activity and electronic screen time/day. Here inadequate toilet number, family history of affected sibs, parents/grandparents, inadequate fluid intake, feeling embarrassed to use toilet at school, and electronic screen time of > 2 h/d were found significant. Children of school, where toilet numbers were inadequate had 2.5 times more constipation risk in comparison to children of school with adequate toilet number (OR = 2.493, 95%CI: 1.214-5.120). Children who feel embarrassed to use toilet at school, had 3.6 times higher risk of constipation (OR = 3.552, 95%CI: 1.435-8.794). Here children with H/O affected sibs and parents/grandparents had 4 and 2.6 times more chance of constipation respectively in comparison to children without H/O affected sibs (OR = 3.977, 95%CI: 1.884-8.397) and parents/grandparents (OR = 2.569, 95%CI: 1.172-5.629). Children with inadequate fluid intake had 2 times more risk of constipation in comparison to children with adequate fluid intake (OR = 1.972, 95%CI: 1.135-3.426). Children who passed electronic screen time of > 2 h/d had 2 times more chance of constipation in comparison to children who passed electronic screen time < 2 h (OR = 2.138, 95%CI: 1.063-4.301).

DISCUSSION

The common belief is that constipation is not common in South-Asian countries like Bangladesh as here diet is rich in fiber. There are very few studies and very little information about constipation in developing countries especially in South-Asian countries. In the present study, 19% children were found to have constipation. In Saudi school aged children, prevalence of chronic constipation was 32.2%[14]. In china, the prevalence rate in pediatric population was 18.8%[15]. In Taiwan, the prevalence of constipation in pediatric population was 32.2%[16]. In Nigeria, Udoh *et al*[17] found 27% FC among adolescent Nigerians. Prevalence of childhood constipation varies from 0.7% to 29% around the world and median was 12%[18].

In the present study, prevalence of functional constipation was 11%. In Sri Lanka, prevalence of functional constipation in school aged children was 15.4%[7]. In Columbia, prevalence of functional constipation in school aged children was 13.2%[19]. In India, prevalence of functional constipation in children 2-12 years of age was 30.8%[20]. In Indonesia among school aged children, prevalence was 18.3%[21]. These findings are almost similar to findings of present study.

In the present study, 9.1% males and 17% females had functional constipation and male to female ratio was 1:1.9. In Saudi children too, females were affected more than males and male to female ratio

Table 4 School related factors analysis of children with functional constipation and without constipation

Characteristics	Functional constipation (*n* = 78), *n* (%)	Without constipation (*n* = 573), *n* (%)	*P* value
Type of school			0.221[1]
Govt	50 (64.1)	396 (69.1)	
Non Govt	28 (35.9)	177 (30.9)	
Residential			0.091[1]
Yes	32 (41)	187 (32.6)	
No	46 (59)	386 (67.4)	
Long periods of school			0.013[1]
Yes	13 (16.7)	166 (29)	
No	65 (83.3)	407 (71)	
Unhygienic toilet			0.056[1]
Yes	19 (24.4)	93 (16.2)	
No	58 (75.6)	480 (83.8)	
Toilet number			0.013[1]
Adequate	64 (82.1)	523 (91.3)	
Inadequate	18 (17.9)	50 (8.7)	
Feeling embarrassed to use toilet			0.039[1]
Yes	9 (11.5)	31 (5.4)	
No	69 (88.5)	542 (94.6)	

[1]Chi-square test, *P* value < 0.05 considered as statistically significant.

was 1:3.5[14]. In India, Kondapalli *et al*[20] also found female predominance. In China pediatric population with functional constipation, ratio between male and female was 1:1.1[15]. Khanna *et al*[8] and Roma-Giannikou *et al*[22] also showed a male preponderance in functional constipation.

In the present study, mean age of children having functional constipation was 11.24 ± 3.54 years. Peralta-Palmezano *et al*[19] found mean age was 12.3 ± 2.7 years. In the present study, residential area (rural-urban) and religion had no significance association with constipation. But Rajindrajith[7], Udoh *et al*[17] and Kondapalli *et al*[20] found prevalence of constipation being higher in children living in urban areas.

Regarding bowel habits of functional constipated (78) children of present study, large diameter stool was found in 92.3%, painful bowel movements in 76.9%, incontinence in 2.6%, retentive posturing in 9% and defecation frequency daily was in 55.1% cases, 1 d interval in 3.8% cases, at 2 d interval in 15.4% cases, 3 d interval in 25.6% cases. Kondapalli *et al*[20] found, 58.4% of functional constipation children had retentive behavior in the form of abnormal posturing, fecal soiling was present in 44 % of children and 80.1% of children had stool frequency of < 3 per week.

Oswari *et al*[21], showed withholding behaviour in 68.3%, defecation of less than 3 times per week in 64.6% of subjects and passage of hard stools in 63.4% cases.

The most common symptoms associated with constipation, found were anorexia, nausea, abdominal pain, hard stool, blood with hard stool, alternate hard and loose stool, abdominal distension and fecal mass in left iliac fossa and these findings were analyzed between two groups and all were significantly higher in children with functional constipation group except abdominal distention.

Oswari *et al*[21], showed abdominal pain, loss of appetite and straining during defecation were associated with constipation. Kondapalli *et al*[20] also found, abdominal pain as the presenting complaint which was present in 30.6% of children, blood streaked stools in 10.8% children. About 26% of functional constipation children had abdominal pain in the study of Kokkonen *et al*[23]. Rajindrajith [7] showed, patients with functional constipation had more somatic symptoms than controls.

In the present study, school related factors like government or private school, residential or non-residential school, long periods of school, unhygienic toilet, toilet numbers, feeling embarrassed to use toilet were analyzed, and here children with long periods of school/home works, feel embarrassed to use toilet at school, and inadequate number toilet at school/dormitory had higher percentage of constipation and *P* value was significant on univariant analysis. But on regression analysis feeling embarrassed to use toilet at school and inadequate number of toilet at school/dormitory was found

Table 5 Family related factors analysis of children with functional constipation and without constipation

Characteristics	Functional constipation (*n* = 78), *n* (%)	Without constipation (*n* = 573), *n* (%)	*P* value
History of constipation in other sibling			0.001[1]
Yes	18 (23.1)	25 (4.4)	
No	60 (76.9)	548 (95.6)	
History of constipation in parents/grand parents			0.001[1]
Yes	17 (21.8)	27 (4.7)	
No	61 (78.2)	545 (95.1)	
Family size			0.296[1]
Only child	3 (3.8)	28 (4.9)	
2-3 child	46 (59)	284 (49.6)	
≥ 4 child	29 (37.2)	261 (45.5)	
Birth order			0.794[1]
Elder	29 (37.2)	209 (36.5)	
Youngest	27 (34.6)	182 (31.8)	
Other	22 (28.2)	182 (31.8)	
Mother's education			0.797[1]
Primary	59 (75.6)	426 (74.3)	
SSC	11 (14.1)	83(14.5)	
HSC	5(6.4)	28 (4.9)	
Honors	3 (3.8)	36 (6.3)	
Father's education			0.610[1]
Primary	53 (67.9)	392 (68.4)	
SSC	10 (12.8)	82 (14.3)	
HSC	9 (11.5)	43 (7.5)	
Honors	6 (7.7)	56 (9.8)	
Mother's occupation			0.831[1]
Employed	9 (11.5)	73 (12.7)	
Housewife	69 (88.5)	500 (87.3)	
Household income (taka/mo)			0.393[1]
< 30000	49 (62.8)	384 (67)	
30000-60000	23 (29.5)	131 (22.9)	
> 60000	6 (7.7)	58 (10.1)	
Family status			0.251[1]
Single	72 (92.3)	510 (89)	
Joint	6 (7.7)	63 (11)	

[1]Chi-square test, *P* value < 0.05 considered as statistically significant.

significant.

Children who feel embarrassed to use toilet at school and where toilet number inadequate, voluntarily hold the defecation reflex. The withholding behavior causes contraction of the external anal sphincter and gluteal and pelvic floor muscles. The fecal mass then moves out of the rectal ampulla and back into the rectosigmoid colon, where the stool becomes harder and larger[24].

Hasosah *et al*[14], showed cleanliness and the facilities of their school toilets and homework of > 3 h/d as risk factors of FC.

Table 6 Diet related factors analysis of children with functional constipation and without constipation

Characteristics	Functional constipation (*n* = 78), *n* (%)	Without constipation (*n* = 573), *n* (%)	*P* value
Cow's milk intake			0.469[1]
Yes	40 (51.3)	301 (52.5)	
No	38 (48.7)	272 (47.5)	
Fiber			0.002[1]
Adequate	45 (57.7)	428 (74.7)	
Inadequate	38 (42.3)	145 (25.3)	
Junk foods intake			0.341[1]
Yes	26 (33.3)	209 (36.5)	
No	52 (66.7)	364 (63.5)	
Fluid intake			0.001[1]
Adequate	37 (47.4)	424 (74)	
Inadequate	41 (52.6)	149 (26)	

[1]Chi-square test, *P* value < 0.05 considered as statistically significant.

Table 7 Physical activity related factors analysis of children with functional constipation and without constipation

Characteristics	Functional constipation (*n* = 78), *n* (%)	Without constipation (*n* = 573), *n* (%)	*P* value
Games			0.216[1]
Outdoor	49 (62.8)	0 (0)	
Indoor	29 (37.2)	160 (27.9)	
Physical disability	0 (0)	2 (0.3)	
Electronic screen time			0.001[1]
< 1 h	42 (53.8)	410 (71.6)	
1-2 h	12 (15.4)	87 (15.2)	
> 2 h	24 (30.8)	76 (13.2)	

[1]Chi-square test, *P* value < 0.05 considered as statistically significant.

In the present study, family related factors like, history of constipation in other siblings, history of constipation in parents/grandparents, family size, birth order, parents education, household income, single or joint family were analyzed but only children having history of constipation in other siblings and history of constipation in parents/grandparents were found significant in both univariate and regression analysis.

As family members share the same food and similar life style which may explain familial aggregation of constipation. But there is no scientific explanation for this, but some researchers suggested that there was a significant genetic and familial connection in patients with constipation that might have been exacerbated by environmental factors[25].

Rajindrajith[7] and Dehghani *et al*[26], showed positive family history of constipation as a risk factor for FC. Rajindrajith[7] and Oswari *et al*[21], also did not find any association with family size, birth order, parent's job. But Kilincaslan *et al*[27] found that maternal education (elementary) and employed mother were risk factors for FC. Kondapalli *et al*[20] found that 75% of constipated children belonged to nuclear family.

In the present study, diet related factors were analyzed. Here children with less fiber intake and inadequate fluid intake had higher percentage of constipation and p value was significant on univariate analysis. But on regression analysis only inadequate fluid intake was found significant

The normal stool consists of about 70% of water. Comparatively a small change of water content of stool lead to considerable change in consistency, inadequate fluid intake results in hard stool that can be difficult to pass[28,29].

Table 8 Binary logistic regression analysis for risk factors

Characteristics	*P* value	95%CI		Exp ß
		Lower	Upper	
Age	0.051	1.000	1.204	1.097
Sex	0.056	0.985	3.280	1.798
Long duration of school period	0.746	0.415	1.876	0.883
Inadequate number of toilet	0.013	1.214	5.120	2.493
Feeling embarrassed to use toilet	0.006	1.435	8.794	3.552
H/O affect sib	0.001	1.884	8.397	3.977
H/O affect parents/grandparents	0.018	1.172	5.629	2.569
Inadequate fiber intake	0.286	0.403	1.307	0.726
Inadequate fluid intake	0.016	1.135	3.426	1.972
Electronic screen time > 2 h/d	0.033	1.063	4.301	2.138

P value < 0.05 considered as statistically significant.

Wu *et al*[16] found that constipation was associated with lower intake of vegetables, fruits, soybean products, and eggs. Kondapalli *et al*[20] showed milk being consumed by 74.8% constipated children, vegetables and fruits intake were inadequate in 75% of children, junk foods in the form of fried items in 46% of children. de Araújo Sant'Anna *et al*[30] found dietary fiber intake was insufficient in all children and even lower in those with constipation. Olaru *et al*[31] showed that cow's milk intake was a risk factor for FC.

In the present study, physical activity related factors were analyzed and children who preferred electronic media more than 2 h/d had higher percentage of constipation and p value was significant on both univariate analysis and regression analysis. Olaru *et al*[31] found lack of exercise and television watching more than 3 h/d constitutes a risk factor in the occurrence of constipation. Children when watching television and mobile games, they frequently withheld the defecation urge, which initiate the vicious cycle of constipation.

CONCLUSION

Frequency of constipation and functional constipation was 19% and 11% respectively. Inadequate toilet number, family history of constipation, inadequate fluid intake, feeling embarrassed to use toilet at school, and electronic screen time for > 2 h/d were found as risk factors in the present study for functional constipation. A country wide study is recommended to find out actual burden and risk factors of functional constipation in Bangladeshi pediatric population.

ARTICLE HIGHLIGHTS

Research background

Constipation is a common problem in children and a frequent cause of hospital visit in both primary & specialized care, which needs proper evaluation & management. Presentation of constipation is variable among children. In Bangladesh there has been no published data regarding constipation in community among school aged children.

Research motivation

No published data or study regarding the magnitude and etiology of functional constipation till date in Bangladesh.

Research objectives

The present study has been undertaken to determine the magnitude of functional constipation and it's risk factors in community among Bangladeshi school children.

Research methods

This descriptive cross sectional study was conducted in different schools of Dhaka division, Bangladesh. All school aged children between 5-16 years of age who attended school were included in this study. Samples were collected randomly. Proper clinical history & physical examinations (without digital rectal exam-ination) & available investigations (if done previously) were recorded. Diagnosis of functional constipation was done by Rome IV criteria and was compared with children without constipation. Children with any red flag sign, known chronic disease or any findings suggestive of organic disease and on treatment of constipation were excluded. Statistical analysis of the results was done by using Windows based software device with Statistical Packages for Social Science 20. For all statistical tests, *P* value of less than 0.05 was considered as statistically significant.

Research results

Total study populations were 707 and male was 443 and female 264. Among them, 134 (19%) children had constipation. In constipated children, 78 children fulfilled the Rome IV criteria for functional constipation and it was 11% of total population. Mean age of children having functional constipation was 11.24 ± 3.54 years and Male female ratio was 1:1.78. Anorexia, nausea, abdominal pain, hard stool, blood with hard stool, alternate hard and loose stool and fecal mass in left iliac fossa were analyzed between two group and all were significantly higher in children with functional constipation group. Children of school, where toilet numbers were inadequate had 2.5 times more constipation risk in comparison to children of school with adequate toilet number (OR = 2.493, 95%CI: 1.214-5.120). Children who feel embarrassed to use toilet at school, had 3.6 times higher risk of constipation (OR = 3.552, 95%CI: 1.435-8.794). Here children with H/O affected sibs and parents/grandparents had 4 and 2.6 times more chance of constipation respectively in comparison to children without H/O affected sibs (OR = 3.977, 95%CI: 1.884-8.397) and parents/grandparents (OR = 2.569, 95%CI: 1.172-5.629). Children with inadequate fluid intake had 2 times more risk of constipation in comparison to children with adequate fluid intake (OR = 1.972, 95%CI: 1.135-3.426). Children who passed electronic screen time of > 2 h/d had 2 times more chance of constipation in comparison to children who passed electronic screen time < 2 h (OR = 2.138, 95%CI: 1.063-4.301).

Research conclusions

Frequency of constipation and functional constipation was 19% and 11% respectively. Inadequate toilet number, family history of constipation, inadequate fluid intake, feeling embarrassed to use toilet at school, and electronic screen time for > 2 h/d were found as risk factors in the present study for functional constipation. A country wide study is recommended to find out actual burden and risk factors of functional constipation in Bangladeshi pediatric population.

Research perspectives

Frequency of constipation in Bangladeshi school children; Frequency of functional constipation (FC) in Bangladeshi school children; Alternate hard and loose stool as one of the presentation of FC; Inadequate toilet number is risk factor for FC.

ACKNOWLEDGEMENTS

Dr. Mohammad Kamrul Hassan Shabuj, Associate Professor, Department of Neonatology, Bangabandhu Sheikh Mujib Medical University, Bangladesh.

FOOTNOTES

Author contributions: Benzamin M was the guarantor and designed the study; Rana M, Alam R, Hossen K, Yasmin A, Fathema K, Khadaga M, Aishy AS participated in data collection; Benzamin M and Alam R participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript; Mazumder MW, Rukunuzzaman M and Karim AS revised the article critically for important intellectual content.

Institutional review board statement: Prior to the commencement of this study, the thesis protocol was approved by the Institutional Review Board of BSMMU, Dhaka.

Informed consent statement: Written informed consent for publication was obtained from the parents.

Conflict-of-interest statement: The authors declare they have no conflict of interest.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE statement, and the manuscript was prepared and revised

according to the STROBE statement.

Country/Territory of origin: Bangladesh

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S-Editor: Zhang H
L-Editor: A
P-Editor: Zhang H

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World J Clin Pediatr 2022 March 9; 11(2): 173-195

DOI: 10.5409/wjcp.v11.i2.173

ISSN 2219-2808 (online)

SYSTEMATIC REVIEWS

Epidemiology and phenotypes of diabetes in children and adolescents in non-European-origin populations in or from Western Pacific region

Steven James, Jayanthi Maniam, Pik-To Cheung, Tatsuhiko Urakami, Julia von Oettingen, Supawadee Likitmaskul, Graham Ogle

Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Yao K

Received: April 30, 2021
Peer-review started: April 30, 2021
First decision: July 27, 2021
Revised: August 9, 2021
Accepted: January 5, 2022
Article in press: January 5, 2022
Published online: March 9, 2022

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Abstract

BACKGROUND

Type 1 diabetes (T1D) incidence varies substantially between countries/territories, with most studies indicating increasing incidence. In Western Pacific region (WPR), reported rates are much lower than European-origin populations. In contrast, there are reports of substantial numbers of young people with type 2 diabetes (T2D). A deeper understanding of T1D and T2D in the WPR may illuminate factors important in pathogenesis of these conditions. Furthermore, with varying resources and funding for diabetes treatment in this region, there is a need to more clearly determine the current burden of disease and also any gaps in knowledge.

AIM

To compile and summarise published epidemiologic and phenotypic data on

childhood diabetes in non-European populations in and from WPR.

METHODS

Research articles were systematically searched from PubMed (MEDLINE), Embase, Cochrane library, and gray literature. Primary outcome measures were incidence and prevalence, with secondary measures including phenotypic descriptions of diabetes, including diabetes type categorization, presence of diabetic ketoacidosis (DKA) at onset, autoantibody positivity, C-peptide levels, and human leucocyte antigen phenotype. Extracted data were collected using a customized template. Three hundred and thirty relevant records were identified from 16 countries/territories, with analysis conducted on 265 (80.3%) records published from the year 2000.

RESULTS

T1D incidence ranged from < 1-7.3/100000 individuals/year, rates were highest in emigrant/mixed populations and lowest in South-East Asia, with most countries/territories (71.4%) having no data since 1999. Incidence was increasing in all six countries/territories with data (annual increases 0.5%-14.2%, highest in China). Peak age-of-onset was 10-14 years, with a female case excess. Rate of DKA at onset varied from 19.3%-70%. Pancreatic autoantibodies at diagnosis were similar to European-origin populations, with glutamic acid decarboxylase-65 autoantibody frequency of 44.1%-64.5%, insulinoma-associated 2 autoantibody 43.5%-70.7%, and zinc transporter-8 autoantibody frequency 54.3% (one study). Fulminant T1D also occurs. T2D was not uncommon, with incidence in Japan and one Chinese study exceeding T1D rates. Monogenic forms also occurred in a number of countries.

CONCLUSION

T1D is less common, but generally has a classic phenotype. Some countries/ territories have rapidly increasing incidence. T2D is relatively common. Registries and studies are needed to fill many information gaps.

Key Words: Epidemiology; Phenotypes; Diabetes; Children; Adolescents; Western Pacific

Core Tip: This systematic review found type 1 diabetes (T1D) incidence was generally low in countries/territories in the Western Pacific region. However, incidence is rising in most countries where this has been studied. Many countries do not have data or data are quite old. Peak age-of-onset was in later childhood. Rates of diabetic ketoacidosis vary but can be quite high (up to 70%). Autoantibody status is generally like European-origin populations. Fulminant and slowly progressive forms of T1D also occur in the region. Of note, type 2 diabetes was sometimes more common in countries than T1D. Establishment of registers will facilitate incidence studies and also define prevalence and mortality, and assist in outcome assessment. Such data will inform quality of care improvements, health professional training, and assist advocacy.

Citation: James S, Maniam J, Cheung PT, Urakami T, von Oettingen J, Likitmaskul S, Ogle G. Epidemiology and phenotypes of diabetes in children and adolescents in non-European-origin populations in or from Western Pacific region. *World J Clin Pediatr* 2022; 11(2): 173-195

URL: https://www.wjgnet.com/2219-2808/full/v11/i2/173.htm

DOI: https://dx.doi.org/10.5409/wjcp.v11.i2.173

INTRODUCTION

A diagnosis of diabetes is particularly challenging in young people. An estimated 1.1 million children and adolescents aged < 20 years are estimated to have type 1 diabetes (T1D) globally, with the number with type 2 diabetes (T2D) unknown[1]. Published information on diabetes in this age group is from European origin populations, and yet over half of the global burden is from non-European origin populations.

The commonest form of diabetes in this age group is T1D but other forms do occur[2]. T1D incidence and prevalence varies substantially between countries/territories, with most studies indicating that incidence is increasing at an average of 3%-4%[3], but this appears to be tailoring off in some high-

income nations/territories[1].

Increasing incidence in countries/territories with previously low rates offer a chance to better understand the link between genetics and environment in T1D development, especially in countries/territories with little population admixture[1,4]. Additionally, some studies have shown differences in diabetes incidence among migrant populations relative to the native population, which gives further support to the role of environment in T1D causation[5,6].

In the Western Pacific region (WPR), early studies had reported T1D being very rare in young people [4,7], and subsequent reports have shown incidence rates much lower than most European-origin populations[4,8-10]. In contrast, there are reports of substantial numbers of young people with T2D in some countries in the WPR[11,12].

A deeper understanding of both the epidemiology and phenotypes/endotypes of T1D and T2D in non-European populations such as those in WPR may illuminate factors important in pathogenesis of these conditions. Furthermore, with varying resources and funding for diabetes treatment in this region, there is a need to more clearly determine the current burden of disease and also any gaps in knowledge in related epidemiology and phenotypes/endotypes[1].

The objective of this systematic review is to compile and summarise current published epidemiologic and phenotypic data on childhood diabetes in non-European populations in and from the Western Pacific. Primary outcome measures were incidence and prevalence of diabetes in people < 20 years of age. Secondary measures included diabetes type categorisation and phenotype/endotype features including presence of diabetic ketoacidosis (DKA) at diagnosis, pancreatic autoantibody positivity rates, C-peptide levels, and human leucocyte antigen (HLA) phenotypes.

MATERIALS AND METHODS

Population

Non-European populations in and recently emigrated from the WPR.

Inclusion/exclusion criteria

Any relevant published study conducted in one or more of the 37 countries/territories of the Western Pacific, as determined by the World Health Organization[13], extending from the Mongolian steppes in central Asia, east to the Pitcairn Islands in the Pacific Ocean and south to New Zealand. The included countries/territories were Australia, Brunei, Cambodia, Cook Islands, Democratic People's Republic of Korea, Federated States of Micronesia, Fiji, Guam, Hong Kong, Indonesia, Japan, Kiribati, Laos, Macau, Malaysia, Marshall Islands, Mongolia, Myanmar, Nauru, New Caledonia, New Zealand, Niue, North Korea, Palau, Papua New Guinea, South Korea, Samoa, Singapore, Solomon Islands, Taiwan, Thailand, Timor-Leste, Philippines, Tonga, Tuvalu, Vanuatu and Vietnam. Studies on recent emigrant populations from these countries/territories to others were also included.

Publications were included if they focused on incidence, prevalence, diabetes type, clinical presentation (presence/rate of DKA), pancreatic autoantibody status, and HLA phenotype. Studies that did not include data on at least one of these factors were excluded.

Data from Australia and New Zealand exclusively were only included if children and adolescents < 20 years of age identified as being an Aboriginal and/or Torres Strait Islander, or Maori, respectively.

Studies were of any study design and in any language. There was no restriction on publication date or type.

Types of outcome measures (primary and secondary)

Primary outcomes: Incidence and prevalence of T1D, T2D and other forms in children and youth < 20 years in and from the WPR.

Secondary outcomes: Phenotypic descriptions of childhood- and youth-onset diabetes, including diabetes type categorization, the presence of DKA at onset, autoantibody positivity, C-peptide levels, and HLA phenotype.

Search strategy for identification of studies

Research articles were systematically searched in the following databases: PubMed (MEDLINE), Embase, and the Cochrane library. The search terms below were developed for PubMed and then adapted for other databases. The MeSH terminologies include Diabetes Mellitus, Epidemiology, Diagnosis, Symptoms, and Clinical Chemistry. The search strategy was: (Diabetes Mellitus) AND (Epidemiology OR Diagnosis OR symptom OR antibod* OR autoantibod* OR Ketoacidosis OR clinical chemistry OR HLA) AND (Country) AND (child* OR adolesc*).

For Embase database, the search terminology for "Diabetes Mellitus" was replaced with "insulin dependent diabetes mellitus".

To search the gray literature, we searched the following: (1) ProQuest Dissertations and Theses Global for theses; (2) Citation searching, including reference list searching and forward citation searching in Google Scholar, Scopus and Web of Science Core Collection; and (3) Hand-searched paediatric diabetes conference abstracts not indexed in the above databases: International Society for Pediatric and Adolescent Diabetes (ISPAD, available in Pediatric Diabetes); Pediatric Endocrine Society (PES, available in Hormone Research in Children); European Society for Pediatric Endocrinology (ESPE, available in Hormone Research in Children); Asia Pacific Paediatric Endocrine Society (APPES, abstracts available in member's area).

For each database, the years searched included the earliest available online year of indexing up to December 2019.

Data extraction and synthesis

The Covidence systematic review platform (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org) was used to assist with data management. Two independent reviewers reviewed the titles and abstract of the identified studies for relevance. The same reviewers independently reviewed the full text of these studies in a first screen to assess if they met inclusion and exclusion criteria. The reasons for excluding articles were recorded in Covidence. Any disagreements or queries were discussed until a consensus was reached. Thereafter, a final list of studies was produced.

The extracted data was collected using a customized template in Microsoft Excel (Microsoft, Redmond, United States). The extracted data included the following: Country/territory, city/region, type of study, year of publication, time period of study, diagnosis criteria used, T1D incidence and/or prevalence, T2D studies, other forms of diabetes, age range distribution, sex distribution, DKA at diagnosis, pancreatic autoantibody test results, and HLA phenotype. Additional information about the derivation of each value was collected to help qualify the data. Descriptive analyses were performed using Excel. A qualitative comparison of the results across the collected variables is the main focus of this review.

A total of 14252 records were identified, downloaded to EndNote version X9 and screened by reading titles and abstracts. Of these, 2924 records were excluded based upon duplication, language, and contents of titles/abstracts indicating they did not meet inclusion criteria. The remaining 11328 full-text articles were assessed for eligibility; their reference lists and citations were searched, and an additional 105 papers identified. Of these records, 11104 did not meet review inclusion criteria, leaving 330 relevant records. The search process and outcomes are summarised in Figure 1.

The 330 papers were from 16 WPR countries/territories (Table 1), with 204 (62.1%) papers from three countries/territories only. These were from China (n = 72), Japan (n = 94) and South Korea (n = 38). Two-hundred and sixty-five (80.3%) of the 330 studies were published in or after the year 2000. Table 1 summarises the number of papers for each variable and other characteristics of the included studies.

RESULTS

T1D

Incidence: Table 2 summarises the 25 studies from ten WPR countries/territories that had information about T1D incidence with data from 2000 or afterwards. Six studies were from China, five from South Korea, two from Thailand and Taiwan, and one each from four other countries/territories. Most studies (n = 18) reported data for youth aged < 15 years, and only 16 had been published within the past decade.

Incidence ranged from < 1 to 7.3 *per* 100000 individuals per year. An incidence of < 1 *per* 100000 were reported in four countries: Fiji[14], Indonesia[15], Thailand[16,17] and Papua New Guinea[18]. However in Fiji, the rate in Indo-Fijians was 9.3 times higher than the rate in Native Fijians[14].

T1D rates of approximately two *per* 100000 were observed in Japan[19], three in South Korea[20,21], four in Hong Kong[22], five in Taiwan[23,24] and seven in mixed population immigrants in the United States[25]. In China, average T1D rates were variable, with rates ranging from 0.7 to 3.1[26-31].

Single-study data looking at changes in incidence rates over time was available from six countries/territories. In China, rates rose 7.4% *per* annum (pa) in Harbin from 1990-2000[26], 12.0% pa in Zhejiang from 2007-2013[32], 4.4% pa in Beijing from 1995-2010[28], and 14.2% pa in Shanghai from 1997-2011[31]. In South Korea, rates rose by 7.6% pa from 2001-2010[33]. In Hong Kong, data was presented from 2008-2017 in an abstract published in 2018[22], with full data published in 2020[34]. The annual increment between 2008-2017 was 3.5% pa, with authors noting that this was less than the increment of 4.3% in the period 1997-2007. In Taiwan, rates rose 8.7% every two years from 1999-2000 to 2009-2010[23]. In Thailand, incidence almost quadrupled between 1996 and 2005, however, the authors commented that increased diagnosis likely contributed to this[16]. However, in Japan, incidence barely changed from 2005-2010 with a 0.5% pa increase[19].

Table 1 Overview of the included studies (excluding publications with all data before 2000) (*n* = 265)

Country/territory	Total records	
	n	Proportion of total
Australia	10	3.8%
China	67	25.3%
Fiji	1	0.4%
Hong Kong, China	6	2.3%
Indonesia	5	1.9%
Japan	66	24.9%
Malaysia	5	1.9%
New Zealand	6	2.3%
Papua New Guinea	1	0.4%
Philippines	2	0.8%
Singapore	5	1.9%
South Korea	35	13.2%
Taiwan, China	20	7.5%
Thailand	21	7.9%
Tonga	1	0.4%
Vietnam	11	4.2%
Multiple countries/territories	3	1.1%

Subtypes of T1D: In Japan, three sub-groups of T1D have been identified: "abrupt-onset" form (65%), "slowly-progressive" form (30%) and "fulminant" form (5%)[35]. Childhood-onset slowly-progressive T1D is usually detected by urine-glucose screening at schools, or testing by chance, and has minimum symptoms of diabetes without showing ketosis. This type of diabetes is commonest in adolescent females, and has positive beta-cell associated antibodies in approximately 70% of the cases[35]. Fulminant T1D is more common in adults with T1D where it represents around 20% of Japanese cases [36], although in children, age-of-onset has been reported as biphasic with one peak < 5 years[37]. Aside from other Japanese reports[38-40], fulminant T1D has also been reported in China[41-43] and South Korea[44].

Prevalence: Five countries reported prevalence of T1D, with two papers from South Korea[20,45], and one each from Fiji[14], Japan[19] and Papua New Guinea[18]. There was a wide variation in rates, from South Korea with 52 (< 25 years)[45] and 21 (< 20 years)[20] *per* 100000, Japan 13.5 (< 15 years)[19], Fiji 5.9 (< 15 years)[14], and Papua New Guinea 0.28 (< 15 years)[18]. The Fiji study[14] reported rates by ethnicity, with T1D prevalence in Indo-Fijians being almost 10 times higher than the rate in native-Fijians (13.6 *vs* 1.4).

Age at diagnosis: Table 3 summarises the 20 studies from seven WPR countries that had information about either mean/median or peak age of diagnosis. Only eight studies reported peak age of diagnosis. One study from Japan[19] reported peak age of onset in girls at 10 years and boys at 13 years. The remaining nine papers reported five-year interval data with peak 10-14 years.

Gender ratio: Twenty-two papers from eight countries reported new-onset T1D cases by gender (Table 4). Ten of these reported rates according to respective population sizes and the remaining 12 just presented numbers for each gender. There was a female excess in almost all studies, with the male:female ratio ranging from 0.58-1.13. The mean ratio across the 22 papers was 0.81.

DKA at diagnosis: Twenty papers from seven countries reported on the rate of DKA at onset (Table 5). The rates varied from 19.3% in one Taiwanese study[46] to 75.3% in one study from Malaysia[47]. Only three studies had rates below 33%.

Autoantibodies at diagnosis: Table 6 lists the 15 studies from four countries that reported autoantibody testing. All studies had glutamic acid decarboxylase 65 autoantibody (GAD65) data, with average frequencies of 51.3% (China), 58.1% (Japan), 64.5% (Taiwan), and 62.7% (Thailand). The frequencies in

Table 2 Type 1 diabetes incidence under 20 years of age in/from Western Pacific region (excluding publications with all data before 2000)

Ref.	Country/territory	Study period	Incidence/100000	*n* (%)	Age range (yr)
Zhang *et al*[26], 2008	Harbin, China	1990-2000	0.7 (average)	103	< 15
Gong *et al*[28], 2015[1]	Beijing, China	1995-2010	1.7[2]	485	< 15
Shen *et al*[29], 2002	Shanghai, China	1997-2000	1.6	103	< 15
Gong *et al*[30], 2004	Beijing, China	1997-2000	1.0 (annual): 1997 (0.76); 2000 (1.21)	71	< 15
Zhao *et al*[31], 2014	Shanghai, China	1997-2011	3.1[2] (annual): 1997-2001 (1.5); 2007-2011 (5.5)	622	< 15
Wu *et al*[32], 2016	Zhejiang, China	2007-2013	2.0[2] (annual): 2007 (1.2); 2013 (2.5)	611	< 20
Ogle *et al*[14], 2016	Fiji	2001-2012	0.9 (overall): 2.1 (Indo-Fijian); 0.2 (Native-Fijian)	28	< 15
Huen *et al*[154], 2009	Hong Kong, China	1997-2007	2.4[2] < 15 yr, 2.0 [2] < 19 yr	335	< 19
Tung *et al*[22], 2018	Hong Kong, China	2008-2017	2.4 (annual)	498	< 18
Tung *et al*[34], 2020	Hong Kong, China	1997-2007; 2008-2017	2.1[2] (annual): 1997 (1.6); 2007 (2.3). 3.5[2] (annual): 2008 (4.0); 2017 (4.5)	498	< 18
Pulungan[15], 2013	Indonesia	2010	0.03[3]	825	NS
Urakami *et al*[35], 2008	Japan	1974-2004	0.6[4]	54	< 15
Onda *et al*[19], 2017	Japan	2005-2010	2.3 (annual): 2005 (2.17); 2010 (2.23)	2326	< 15
Campbell-Stokes and Taylor [138], 2005	New Zealand	1999-2000	5.6 (Māori)	22	< 15
Ogle *et al*[18], 2001	Papua, New Guinea	1996-2000	0.1	8	< 15
Lee[141], 2014	South Korea	1995-2000 and 2012	1995-2000 (1.4); 2012 (2.9)	217	< 15
Lee *et al*[33], 2015	South Korea	2001-2010	2.0 (annual): 2001 (1.3); 2010 (2.7)	239	< 15
Song *et al*[20], 2016	South Korea	2011-2013	3.3	2346	< 20
Kim *et all*[21], 2015	South Korea	1995-2000 and 2012-2014	1995-2000 (1.4); 2012-2014 (3.2)	706	< 15
Hong *et al*[149], 2013	South Korea	2001-2010	2.0 (annual)	239	< 15
Lin *et al*[23], 2014	Taiwan, China	1999-2010	4.6 (annual): 1999-2000 (3.6); 2009-2010 (5.9)	1280	< 15
Lu *et al*[24], 2014	Taiwan, China	2003-2008	5.3	1306	< 15
Panamonta *et al*[16], 2011	Thailand	1996-2005	0.6	340	< 15
Patarakijvanich *et al*[17], 2008	Thailand	1997-2005	0.7	116	< 15
The Writing Group for SEARCH[25]	United States-Asian and Pacific Islander immigrants	2002-2003	7.3	56	< 20

[1]These data were partially published in 2013 also (Gong *et al*[27]).
[2]Standardised rate.
[3]Degree of ascertainment not stated.
[4]Urine glucose screening test.
NS: Not stated.

South Korea, Phillipines and Singapore were 53.0%, 44.1%, and 41.5%, respectively. Nine studies reported on insulinoma-associated 2 autoantibody (IA-2), with average prevalence of 43.5% (China), 70.7% (Taiwan) and 54.9% (Thailand). However, rates for islet autoantibody (ICA) were variable, ranging from 4 to 68.8%. Only one study (from Thailand[48]) reported zinc transporter 8 autoantibody (ZnT8) results, with 54.3% of cases positive.

C-peptide at diagnosis: Nineteen studies (from China, India, Japan, South Korea, Singapore, Taiwan and Thailand)[37,41,44,46,48-62], reported C-peptide results. C-peptide levels were generally low, consistent with classic T1D. Kim *et al*[44] in South Korea found that C-peptide values were lower in

Table 3 Age of diagnosis of type 1 diabetes patients in/from the Western Pacific region (excluding publications with all data before 2000)

Ref.	Country/territory	*n*	Mean ± SD/median (IQR) age of diagnosis (yr)	Age range (yr)	Peak age of diagnosis (yr)
Gong *et al*[28], 2015	Beijing, China	485	NS	< 15	10-14
Huo *et al*[155], 2018	Beijing, China and Shantou, China	515	11 (7-14)	< 21	10-14
Weng *et al*[156], 2018	China (13 areas)[1]	1239	NS	< 15	10-14
Huen *et al*[154], 2009	Hong Kong, China	335 (< 19); 293 (< 15)	NS	< 19	10-14
Tung *et al*[22], 2018	Hong Kong, China	498	10.5 (± 4.2)	< 18	NS
Onda *et al*[19], 2017	Japan	2326	NS	< 15	13 (boys); 10 (girls)
Lee *et al*[157], 2006	Singapore	211	7.9 (± 4.0)	< 17	NS
Kim *et al*[21], 2012	South Korea	110	10.6 (± 0.9)	< 18	NS
Kim and Kim[158], 2012	South Korea	113	9.26 (± 0.99)	< 18	NS
Hong *et al*[149], 2013	South Korea	239	NS	< 15	10-14
Lee *et al*[141], 2014	South Korea	217	NS	< 15	10-14
Kim *et al*[159], 2016	South Korea	706	NS	< 15	10-14
Lee *et al*[160], 2017	South Korea	361	8.9 (± 4.0)	< 20	NS
Lo *et al*[46], 2004	Taiwan, China	165	7.3 (± 4.1)	< 18	NS
Ting *et al*[61], 2007	Taiwan, China	304	7.9 (± 3.8)	< 20	NS
Panamonta *et al*[161], 2000	Thailand	77	NS	< 15	10-14
Likitmaskul *et al*[79], 2006	Thailand	195	9.2 (± 2.5)	< 19	NS
Patarakijvanich *et al*[17], 2008	Thailand	116	NS	< 15	11-14
Panamonta *et al*[16], 2011	Thailand	340	NS	< 15	10-14
Khwanhatai *et al*[162], 2018	Thailand	229	7.71 (± 3.3)	< 18	NS

[1]Harbin, Shenyang, Beijing, Shanghai, Nanjing, Jinan, Wuhan, Changsha, Guangzhou, Chengdu, Xi'an, Lanzhou and Yinchuan.
NS: Not stated.

fulminant versus autoimmune and idiopathic T1D. Lo *et al*[46] in Taiwan found that C-peptide levels were lower in subjects diagnosed younger. Finally, also in Taiwan, Ting *et al*[61] reported lower C-peptide levels in subjects who had DKA at diagnosis.

HLA status: Twelve studies reported HLA phenotype data, from China[49,63-67], Japan[68,69], South Korea[70,71], Taiwan[72] and Thailand[73]. Nine papers found an association between T1D and HLA-DRB1[49,63,67,69-72,74]. However, alleles contributing to T1D association differ among WPR countries. In China, several studies reported DRB1*0301[49,63,64] conferred the strongest risk for T1D, whereas in Japan, risk is conferred mainly from DRB1*0901 and *0802[69,74], with a contribution also from DRB1*0405[74] and *0404[69]. DRB1*0901 was strongly associated with early onset in preschool children in Japan with type 1A diabetes[68]. One study in a Japanese population reported that DRB1*0301 and *0302 were absent in T1D patients[74]. In South Korea, T1D risk was strongly associated with DRB1*0301,*0405 and *09012 alleles[70].

There were also significant findings for DQB1, with unique alleles contributing to T1D risk in various countries[49,65,66,69,73] and within different parts of China[49,66]. DQB1*0201 conferred the strongest risk and DQB1*0601 and *0602 were protective specifically amongst the Chinese Han population[66]. In Guangdong, T1D risk was linked with higher frequencies of DQB1*0303, *0401 and *0402 but DQB1*0301 was found to be protective[49]. DQB1*0601 and *0602 were associated with risk of type 1B in Japan [69]. In Thailand, higher frequencies of DQB1*0201,*0202 and *0302 were found in children with T1D.

Table 4 Gender ratio of type 1 diabetes patients in/from the Western Pacific region (excluding publications with all data before 2000)

Ref.	Country/territory	Ratio (M:F)	Age range (yr)
Xin *et al*[163], 2010	Shenyang, China	0.77	< 15
Gong *et al*[27], 2013	Beijing, China	0.58[1] (1995-2002); 0.74[1] (2003-2010)	< 15
Zhao *et al*[31], 2014	Shanghai, China	0.97[1]	< 15
Gong *et al*[28], 2015	Beijing, China	0.70[1]	< 15
Wu *et al*[32], 2016	Zhejiang, China	0.78[1]	< 20
Tao *et al*[164], 2017	Kunming, China	1.13	< 15
Huo *et al*[155], 2018	Beijing, China and Shantou, China	0.77	< 21
Weng *et al*[156], 2018	China (13 areas)[2]	0.78[1]	< 15
Huen *et al*[154], 2009	Hong Kong, China	0.76	< 19
Tung *et al*[22], 2018	Hong Kong, China	0.75	< 18
Onda *et al*[19], 2017	Japan	0.76[1]	< 15
Lee *et al*[157], 2006	Singapore	0.77	< 17
Hong *et al*[149], 2012	South Korea	0.86[1]	< 15
Lee *et al*[141], 2014	South Korea	0.84[1]	< 15
Kim *et al*[159], 2016	South Korea	0.80[1]	< 15
Song *et al*[20], 2016	South Korea	0.89	< 20
Lee *et al*[160], 2017	South Korea	0.86	< 20
Lo *et al*[46], 2004	Taiwan, China	0.70	< 18
Ting *et al*[61], 2007	Taiwan, China	0.94	< 20
Lu *et al*[24], 2014	Taiwan, China	0.78[1]	< 15
Patarakujvanich *et al*[165], 2001	Thailand	1.0	< 15
Panamonta *et al*[16], 2011	Thailand	0.65	< 15

[1]Ratio of T1D incidence.
[2]Harbin, Shenyang, Beijing, Shanghai, Nanjing, Jinan, Wuhan, Changsha, Guangzhou, Chengdu, Xi'an, Lanzhou and Yinchuan.
M: Male; F: Female.

There are also some reports of DQA alleles susceptible to T1D in China[49,64].

T2D

Incidence: Table 7 summarises the 14 studies from seven WPR countries that had information about T2D incidence. The studies from Australia and New Zealand on indigenous/regional origin populations, and also Asian/Pacific emigrants to the United States, showed high rates. The rates from four other countries/territories including China, Hong Kong, Japan and South Korea ranged from 0.43 to 2.63 *per* 100000 individuals. Rapid increases in incidence were seen in China[75] and Hong Kong[22], with data being published in 2021 showing a rate of 3.42[76]. In Fiji, the rate for Indo-Fijians was 20 times higher than the rate for Native Fijians[14]. The mixed population of Asian and Pacific Islanders emigrants to the United States recorded the highest T2D incidence rate (12.2 *per* 100000)[77].

Prevalence: Four countries reported population prevalence of T2D, with one paper each from China [11], Fiji[14], South Korea[45] and Taiwan[78]. There was a wide variation in rates, from South Korea with 249 *per* 100000 < 24 years[45], China 96.8 *per* 100000 < 18 years[11], Taiwan with 70 (males) and 80 (females) *per* 100000 (0-19 years)[78], and Fiji 2.4 *per* 100000 (< 15 years)[14]. The South Korea study[45] reported that between 2002 to 2013, T2D prevalence increased 2.35 fold; the 5-9 and 10-14 year age groups showed remarkable increases (2.59 and 2.54 fold respectively), although the age group 20-24 years had the highest prevalence. Similarly, the Taiwan study[78] reported a 33% increase from 2000 to 2008.

In Thailand, a multi-centre report in 2006 found that 18.6% of diabetes cases < 18 years were T2D[79]. A more recent report from Thailand showed clinic prevalence increasing from 10%-15% in 1995-2003 to 35%-40% in 2009-2014[80].

Table 5 Diabetic ketoacidosis at diagnosis with type 1 diabetes in/from the Western Pacific region (excluding publications with all data before 2000)

Ref.	Country/territory	% with DKA	*n*	Age range (yr)
Huen *et al*[154], 2009	Hong Kong, China	60.0	335	< 19
Tung *et al*[22], 2018	Hong Kong, China	41.0	498	< 18
Jalaludin and Harun[47], 2005	Malaysia	75.3	55	< 13
Fuziah *et al*[166], 2008	Malaysia	57.1	166	< 20
Gunn *et al*[167], 2017	New Zealand	28.7 (overall); 23.7[1]; 34.3[2]	38[1]; 35[2]	< 15
Lee *et al*[157], 2006	Singapore	53.0	211	< 17
Park *et al*[168], 2011	South Korea	55.0	23	NS
Kim *et al*[158], 2012	South Korea	36.4	110	< 18
Kim *et al*[169], 2013	South Korea	32.0	100	< 18
Kim and Kim[170], 2014	South Korea	39.0	113	< 18
Kim *et al*[21], 2015	South Korea	39.7	706	< 15
Lee *et al*[160], 2017	South Korea	56.5	361	< 13
Lo *et al*[46], 2004	Taiwan, China	19.3	165	< 17
Ting *et al*[61], 2007	Taiwan, China	65.1	304	< 19
Tung *et al*[62], 2009	Taiwan, China	67.0	157	< 19
Chen *et al*[171], 2017	Taiwan, China	66.2 (overall): 87.0; 55.0	52; 94	< 6; 6-18
Likitmaskul *et al*[172], 2003	Thailand	55.0; 78.0	94; 28	6-18; < 15
Patjamontri and Santiprabjob[173], 2012	Thailand	40.8	49	< 15
Jaruratanasirikul *et al*[80], 2017	Thailand	70.0	99	< 15
Trisorus *et al*[48], 2018	Thailand	63.0	81	< 15

[1]Māori.
[2]Pacific Islanders.
DKA: Diabetic ketoacidosis.

Other types of diabetes

Monogenic causes: There are numerous reports of single gene defects causing diabetes in China, Japan, Vietnam, Thailand, Singapore, South Korea and Fiji. These include reports of gene mutations resulting in permanent and transient neonatal diabetes mellitus and diabetes with onset later in childhood.

Most reports were case studies[81-102]. Larger studies that conducted genetic testing on neonatal diabetes cases were undertaken in China[103] and Vietnam[104-106]. Cao *et al*[103] reported a total of 25 cases with neonatal period onset. 72.0% cases (n = 18) were permanent (five with *KCNJ11* gene mutations, one *ABCC8* mutation, two *EIF2AK3*, one each with *INS*, *GLIS3* and *SLC19A* and seven without any known mutation) and seven cases (28%) with transient diabetes (two with ABCC8 mutation, one paternal UPD6q24, and four without mutations). In Vietnam, Craig *et al*[104] identified 13 neonatal cases that had gene mutations of *KCNJ11* (n = 3), *ABCC8* (n = 4), *INS* (n = 2) and uniparental disomy of chromosome 6q24 (n = 1) and three others without any mutations. Also in Vietnam, Can *et al* [105] genetically confirmed 16 neonatal cases with gene mutations of *KCNJ11* (n = 6), *ABCC8* (n = 5), *INS* (n = 2) and abnormality in chromosome 6q24 (n = 3). Finally, Ngoc *et al*[106] reported 38 cases (28 permanent and 10 transient) with monogenic diabetes, 31% with mutations of *ABCC8*, 29% *KCNJ11*, 16% *INS*, 16% chromosome 6q24, 3% FOXP3, 3% EIF2B1, and 2% EIF2AK3.

Successful switching from insulin to sulfonylurea treatment was observed in cases with KCNJ11 V59M/C42R and ABCC8 mutations[82,83,88,102,107,108].

In addition, there are various reports of diabetes occurring as part of a known syndrome: DEND syndrome (developmental delay, epilepsy, and neonatal diabetes syndrome)[82,90,109], Wolfram syndrome[110-113], Prader-Willi syndrome[114], Wolcott-Rallison syndrome[81] and Kearns-Sayre syndrome[115].

There were reports of maturity-onset diabetes of the young (MODY) among children and adolescents < 20 years from China[116-122] and Japan[123-131], with this condition also seen in Hong Kong[120, 132].

Table 6 Autoantibodies studies in children and youth with type 1 diabetes in/from the Western Pacific region (excluding publications with all data before 2000)

Ref.	Country/territory	*n*	Age range (yr)	% positive for GAD65	% positive for IA-2	% positive for IAA	% positive for ZnT8A	% positive for ICA
Huang[174], 2004	Guangdong, China	34	7-12	44.1	35.3			17.6
Li *et al*[175], 2008	Changsha, China	35; 51	0-9; 10-14	60.0; 64.7	62.8; 33.3			
Baoerhan and Maimaiti [176], 2015	Urumqi, China.	94	< 15	45.0	62.0			76.0
Urakami *et al*[35], 2008	Japan	48	6-15	70.8				68.8
Iwabuchi *et al*[177], 2013	Japan	43	Children	44.0				
Habu *et al*[134], 2013	Japan	48	< 19	59.5	68.1			
Mabulac[178], 2013	Philippines	68	Paediatric	44.1				
Lee *et al*[59], 2001	Singapore	41	< 15	41.5				41.5
Kim and Kim[170], 2014	South Korea	113	< 18	53.0		26.0		4.0
Chen *et al*[179], 2001	Taiwan, China	70	< 17	54.3				
Tung *et al*[62], 2009	Taiwan, China	157	12-18	73.0	76.0	21.0		
Cheng *et al*[146], 2018	Taiwan, China	750	< 20	66.3	65.3	35.7		
Santiprabhob *et al*[180], 2007	Thailand	51	< 15	63.0	61.0			
Patjamontri *et al*[173], 2012	Thailand	90	< 20	50.0	58.0			
Trisorus *et al*[48], 2018	Thailand	81	< 15	75.3	45.7		54.3	

GAD65: Glutamic acid decarboxylase 65 autoantibody; IA-2: Insulinoma-associated 2 autoantibody; IAA: Insulin autoantibody; ZnT8A: Zinc transporter 8 autoantibodies; ICA: Islet autoantibody.

DISCUSSION

This systematic review examined all published information on diabetes in young people in and from the 37 countries/territories in the WPR, excluding European-origin populations. Three hundred and thirty papers were relevant for the review. The analysis demonstrates both differences and commonality compared to observations in European-origin populations.

T1D

T1D incidence is dependent on both genetic and environmental factors[2,133]. HLA haplotype variations are the main genetic driver, although some other genes also play significant roles[2,133]. The specific environmental factors are less well understood[2,134].

T1D is most common in European-origin and some Arab-origin populations, with annual incidences ranging from 13-60 *per* 100000 population < 15 years[1,135]. In contrast, this systematic review demonstrates that all published WPR rates are much lower, although data since 2000 are available for only ten countries as well as one migrant population. A review by Park[136] in 2006 proposed a lower incidence of high-risk HLA alleles as with respect to identical DR-DQ haplotypes, the association and transmission to diabetic offspring were similar for Asians and Caucasians.

Reported incidence is even lower in non-Chinese-origin South-East Asian and Pacific countries (Thailand, Indonesia, Papua New Guinea, and Fiji), than in Eastern Asian nations (China, Hong Kong, Japan, South Korea and Taiwan), although lack of ascertainment may underestimate the true incidence rate in Thailand, Indonesia and Papua New Guinea, as some cases may die at onset misdiagnosed with another condition[16,18,137]. However, it must be noted that in Fiji, incidence < 15 years was nine times higher in Indo-Fijians compared to Native Fijians[14] and the incidence in New Zealand Maori was 4.5 times lower than in European-origin children[138]. In addition, incidence is similarly low in Bangladesh which is adjacent to South East Asia[139].

The highest incidence seen was in South- and Western-Asian- and Pacific Island-origin children who had emigrated to the United States, although the rate remained less than a third of that in non-Hispanic white children[25]. Finally, in a study of all-age T1D incidence in Australia in 2013, incidence in the

Table 7 Type 2 diabetes incidence in non-European populations in/from the Western Pacific region (excluding publications with all data before 2000)

Ref.	Country/territory	Study period	*n*	Incidence/100000	Age range (yr)
Craig *et al*[181], 2007	Australia Torres Straits Islands	2001-2006	23	12.7	< 19
Tran *et al*[182], 2014	Australia, Torres Straits Islands	2001-2008	31	20.7	< 19
Haynes *et al*[183], 2016	Australia, Torres Straits Islands	1990-2012	76	12.6	< 17
Wu *et al*[75], 2017	Zhejiang, China	2007-2013	392	1.73 (overall): 0.62 (2007); 3.62 (2013)	< 20
Ogle *et al*[14], 2016	Fiji	2001-2012	13; 11; 1; 1	0.43 (overall): 1.17[1]; 0.06[2]; 0.70[3]	< 15
Huen *et al*[154], 2009	Hong Kong, China	1997-2007	198	1.2	< 19
Tung *et al*[22], 2018; Tung *et al* [76], 2021	Hong Kong, China	2008-2017; 2008-2017	391; 391	1.9 (3.42)	< 18
Urakami *et al*[184], 2005	Japan	1974-2002	232	2.63 (overall): 1.73 (< 1980); 2.76 (> 1981)	< 16
Urakami *et al*[148], 2018	Japan	1975-2015	301	2.6	< 16
Campbell-Stokes and Taylor [138], 2005	New Zealand	1999-2000	7[4]	1.78	< 15
Jefferies *et al*[185], 2012	New Zealand	1995-2007	43[4,5]	3.4	< 15
Sjardin *et al*[186], 2018	New Zealand	1995-2015	34[4]	3.3 (overall): 3.4 (1995-2007); 4.0 (2008-2015)	< 15
			47[5]	3.6 (overall): 3.4 (1995-2007); 4.0 (2008-2015)	
Hong *et al*[149], 2013	South Korea	2001-2010	89	0.76	< 15
Liu *et al*[77], 2009	United States-Asian and Pacific Islander immigrants	2002-2003	73	12.2	< 15

[1]Indo-Fijian.
[2]Native-Fijian.
[3]Fijian of European descent.
[4]Māori.
[5]Pacific Islanders.

Aboriginal population was only 70% of that in the non-indigenous population[140], despite the extensive admixture between the two populations. Therefore, in these populations, changes in environment that could potentially increase incidence do not appear to fully overcome the impact of varying genetic susceptibility.

In the absence of large-scale immigration, genetic factors will remain essentially constant. Therefore, any changes in incidence will be due to changing environmental factors. Incidence in European-origin populations has increased by 3%-4% pa in many European-origin populations[135], although this is tailing off now in some countries[3]. There is some evidence that the rate of increase is higher in some lower-incidence countries[3].

The four studies from China[26,30-32] show that T1D incidence is rising quickly (from 4.4%-14.2% pa). South Korea[141] and Taiwan[23] also had high rates of increase at 7.6% and 8.7% pa respectively. However, the rate of rise was slowing in Hong Kong[22] and was virtually zero in Japan[19]. This may be due to evolving environmental factors which then approach a peak effect, as has been seen with slowing or peaking rates in some high-incidence countries[3].

Slowly-progressive diabetes that is clearly T1D is well described from Japan[35], and fulminant T1D (which occurs more in adults and in younger children) is well reported from Japan[36-40], China[41-43] and South Korea[44].

These distinct subtypes, as opposed to acute-onset T1D, do not have exact correlates in European-origin populations, although it is possible that to some extent these represent the more general heterogeneity of T1D, which is being increasingly recognised[142]. For instance, onset is more rapid in younger European-origin populations[143]. A study done in Western Asia and also in a European-origin population that used identical methodology to assess genotype, phenotype and endotype could help illuminate this and add to global knowledge of T1D pathogenesis.

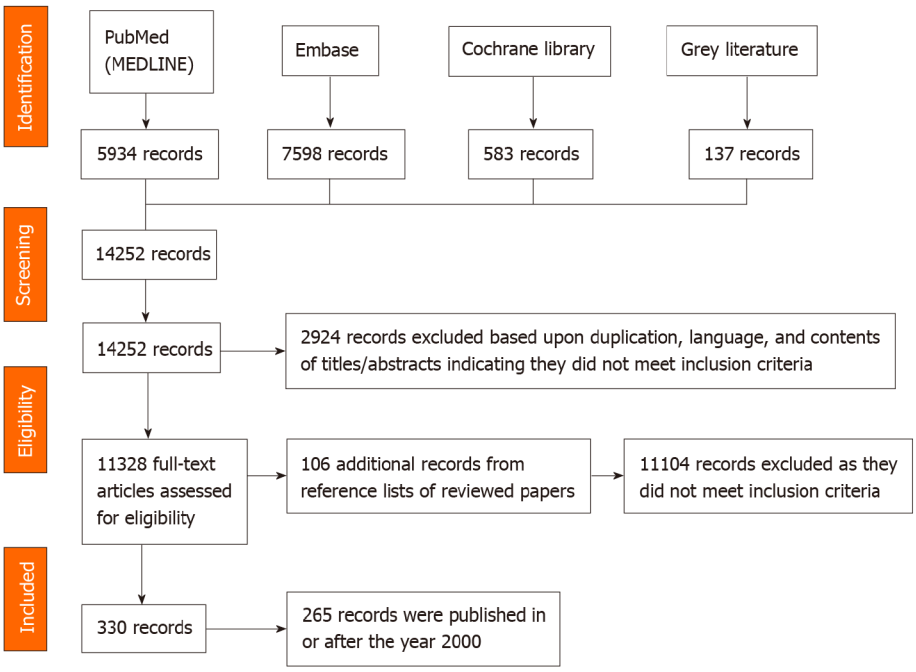

Figure 1 PRISMA flow diagram for searches and screening of articles included in the systematic review.

Prevalence data from non-European origin populations in WPR are limited to five countries. Prevalence is dependent upon past incidence and mortality. We did not find any publications on mortality in these populations.

The age of onset of T1D cases, with peak age 10-14 years, is consistent with European-origin populations.

Nearly all studies found a female excess of cases. In high-incidence countries, T1D is slightly more common in males[2]. In contrast, as in this review, a female excess is more common in lower-incidence countries[144].

Pancreatic autoantibody rates varied across studies. This could be due to various factors including study group age, duration of diabetes at the time of measurement, assay variations, and diagnostic uncertainty. Most GAD-65 and IA2 autoantibody rates were consistent with European-origin data. Only one study in this review, from Thailand[48] measured ZnT8 autoantibodies. Positivity was high at 54.3% in new-onset cases, with 16% of all new-onset cases having ZnT8 but not GAD-65 or iA2 autoantibodies. A recent study from Japan found that ZnT8 positivity was most common < 10 years[145]. With respect to change in autoantibodies over time, Cheng *et al*[146] found that in Taiwan, the rate of GAD-65 and/or IA-2 autoantibodies were 89.4% in the first year after diagnosis but fell to 36.7% after nine years.

The rate of DKA at diagnosis in most studies was higher than in high-incidence countries[147]. Usher-Smith *et al*[147] found that lower-incidence countries generally had higher DKA rates, presumably due to decreased awareness. Less-resourced health systems also had higher DKA rates, and this factor may also be impacting rates in some WPR countries.

T1D HLA associations showed some variation compared to European-origin populations, with also some differences across the region.

T2D

Our review underscores the limited data on T2D in non-European youth from the WPR region, with six studies in indigenous populations conducted in Australia and New Zealand, and single studies from China, Hong Kong, Japan, South Korea and Fiji, as well as one study on emigrant Asian/Pacific youth to the United States. However, a clear finding is that T2D incidence exceeded the T1D rates in some countries, and unlike T1D were comparable to rates in European-origin populations. For instance, the incidence of T2D, detected by urine-glucose screening at schools in Tokyo, was higher compared with that of T1D (2.5-3.0/100000/year *vs* 2-2.5/100000/year, particularly among junior high school children aged 13-15 years (6.5/100000/year)[148]. On the other hand, the incidence of T2D in school children was increasing during 1975-1982, but there was decreased tendency in recent years. Lifestyle changes might contribute to improved incidence of T2D in Japanese school children. In contrast to this, the most recent data from South Korea[149], China[75] and Hong Kong[22,76] showed that incidence was increasing sharply.

While not addressed in detail in this review, several studies noted the phenotypic heterogeneity of T2D when compared to European-origin populations. While obesity or morbid obesity are a

Table 8 Recommendations for further research and interventions

No.	
1	Establishment registers of diabetes in young people in all countries, and, where necessary, in distinct geographic/ethnic regions within countries
2	Ongoing incidence, prevalence, and mortality studies for both T1D and T2D in all countries
3	Phenotype, endotype and genotype studies in youth with any type of diabetes
4	Education campaigns aimed at increasing awareness of the signs and symptoms of T1D and reducing rates of DKA at onset
5	Public health measures aimed at reducing incidence of T2D in young people
6	In-country/territory advocacy efforts, informed by updated and new epidemiological research, aimed at improving quality of care
7	Regional coordination and dissemination of data and research skills

DKA: Diabetic ketoacidosis; T1D: Type 1 diabetes; T2D: Type 2 diabetes.

predominant feature in European origin youth with T2D, in Japan, for example, 10%-15% of youth with T2D are non-obese, with milder insulin resistance and substantial insulin secretion failure, in the absence of autoimmunity[148]. The genetic background likely plays a role[148], although more HLA and non-HLA genetic data are needed to further explore and support this hypothesis.

Overall, the high and, in some countries, increasing rates of T2D in the WPR region are concerning given their known and substantial risk of long-term complications and premature morbidity and mortality[150]. There is an urgent need for more and complete epidemiologic and phenotype data in youth with T2D from across the entire WPR in order to better understand and subsequently develop adequate and effective strategies that address T2D in youth as a public health concern.

Other types

Monogenic forms of diabetes were reported from various countries. Such disorders can present in the neonatal period or later in life. Genetic testing confirms diagnosis and helps identify selective forms responsive to alternate treatment: Most KCNJ11 and some ABCC8 mutations respond to oral sulphonylureas and so insulin can be discontinued, and also thiamine treatment is of benefit in SLC19A mutations (thiamine-resistant megaloblastic anaemia)[151]. In all monogenic cases, genetic counselling is indicated if desired by the family.

CONCLUSIONS

Given the population and number of countries in this region, many gaps in knowledge remain. A number of countries in WPR, including populous nations such as Indonesia, Philippines, and Vietnam, as well as a number of others, have no or minimal information published. Keeping this in mind as a major limitation, T1D with onset in childhood and adolescence is substantially less common in WPR than in European-origin populations, and incidence appears to be lower in South-East Asia than in Eastern Asia. The female preponderance differs from European-origin populations but is in line with the lower incidence rates. As incidence is rapidly increasing across the region, sex distribution will be informative to monitor. Age-of-onset, pancreatic autoantibody positivity rates and, at least across a large part of the WPR region HLA risk associations are similar to European-origin populations. Rates of DKA at onset are concerningly high across the region, consistent with published risk factors.

Data on youth-onset T2D are limited across WPR, with representations from only a handful of countries. Incidences are concerningly high and exceed those of T1D in some countries. Furthermore, rates are increasing.

Other forms of diabetes occur including various monogenic forms that also occur in European-origin and other populations.

Incidence studies are needed from all countries. A high ascertainment is needed, and it is preferable to have at least two overlapping data sources so a 'capture-recapture' method can be used[152]. Given the geographic size and ethnic diversity in some WPR countries, it is quite possible that T1D and T2D rates vary within countries as well. Establishment of registers will facilitate such incidence studies and also define prevalence and mortality, and assist in assessment of outcomes. These data will then inform quality of care improvements and health professional training, and assist in advocacy to improve provision of care by the respective government health system. An example of such a register is the "Thai Type 1 Diabetes and Diabetes Diagnosed Before Age 30 Years Registry, Care and Network"[153]. Table 8 gives recommendations for further research and interventions.

ARTICLE HIGHLIGHTS

Research background

Type 1 diabetes (T1D) incidence varies, with most studies indicating increasing incidence. Reported rates are much lower in the Western Pacific region (WPR), than European-origin populations. Conversely, there are reports of substantial numbers of young people with type 2 diabetes (T2D).

Research motivation

A greater understanding of T1D and T2D in the WPR may highlight factors important in pathogenesis of these conditions. There is a need to determine the current burden of disease more clearly and also any gaps in knowledge, in view of varying funding and resources for diabetes treatment in this region.

Research objectives

To gather and summarise epidemiologic and phenotypic data on childhood diabetes in non-European populations in and from WPR.

Research methods

A comprehensive systematic search of available literature was undertaken.

Research results

There are both differences and similarities compared to observations in European-origin populations. T1D was found to be less common, but generally has a classic phenotype. Some countries/territories have rapidly increasing incidence. T2D is relatively common. There are, however, many information gaps.

Research conclusions

Given the population and number of countries in this region, many gaps in knowledge remain.

Research perspectives

Registries and studies are needed to fill many information gaps. Establishment of registers will facilitate incidence studies and also define prevalence and mortality, and assist in outcome assessment. Such data will inform quality of care improvements, health professional training, and assist advocacy.

FOOTNOTES

Author contributions: James S and Maniam J contributed equally to the manuscript; James S, Maniam J and Ogle G co-designed the study; all authors collected/extracted data and contributed to the manuscript.

Conflict-of-interest statement: No conflicts of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2020 Checklist, and the manuscript was prepared and revised according to the PRISMA 2020 Checklist.

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S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 March 9; 11(2): 196-205

DOI: 10.5409/wjcp.v11.i2.196

ISSN 2219-2808 (online)

META-ANALYSIS

Pediatric Anesthesia Emergence Delirium Scale: A diagnostic meta-analysis

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Specialty type: Anesthesiology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Bersot CD

Received: March 19, 2021
Peer-review started: March 19, 2021
First decision: May 14, 2021
Revised: May 27, 2021
Accepted: February 9, 2022
Article in press: February 9, 2022
Published online: March 9, 2022

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Abstract

BACKGROUND

Emergence delirium (EmD) is a troublesome motoric, emotional, and cognitive disturbance associated with morbidity. It is often misdiagnosed despite being present in a substantial proportion of children and adolescents during emergence from anesthesia.

AIM

To evaluate the summary diagnostic accuracy of Pediatric Anesthesia Emergence Delirium Scale (PAEDS) for EmD among children and adolescents.

METHODS

Two researchers electronically and hand searched the published literature from May 2004 to February 2021 that evaluated the diagnostic accuracy of PAEDS for EmD among children and adolescents, using appropriate terms. Two independent researchers extracted the diagnostic parameters and appraised the study quality with QUADAS-2. Overall, the diagnostic accuracy of the measures was calculated with the summary receiver operating characteristic curve (SROC), the summary sensitivity and specificity, and diagnostic odds ratio (DOR) for EmD. Various diagnostic cut-off points were evaluated for their diagnostic accuracy. Heterogeneity was analyzed by meta-regression.

RESULTS

Nine diagnostic accuracy studies of EmD that conformed to our selection criteria and PRISMA guidelines were included in the final analysis. There was no publication bias. The area under the SROC was 0.97 (95% confidence interval [CI]: 95%-98%). Summary sensitivity and specificity were 0.91 (95%CI: 0.81-0.96; I^2 =

92.93%) and 0.94 (95%CI: 0.89-0.97; I^2 = 87.44%), respectively. The summary DOR was 148.33 (95%CI: 48.32-455.32). The effect size for the subgroup analysis of PAEDS cut-off scores of < 10, ≥ 10, and ≥ 12 was 3.73, 2.19, and 2.93, respectively; they were not statistically significantly different. The setting of the study and reference standard were statistically significantly related to the sensitivity of PAEDS but not specificity.

CONCLUSION

The PAEDS is an accurate diagnostic measure for the diagnosis of EmD among children and adolescents. Further studies should document its clinical utility.

Key Words: Anesthesia; Children; Emergence delirium; Diagnostic accuracy; Measure; Meta-analysis

Core Tip: Emergence delirium (EmD) is a motoric, emotional, and cognitive condition that is often seen among children or adolescents during their recovery from anesthesia. This condition is present in a sizeable portion of this age group and could result in morbidity. Many psychometrically validated measures are available to identify this post-anesthesia emergent phenomenon; one such test is the Pediatric Anesthesia Emergence Delirium scale (PAEDS). This meta-analysis documents that the diagnostic accuracy parameters are excellent for this measure. PAEDS use can significantly help diagnose EmD in post-anesthesia settings among children and adolescents.

Citation: Russell PSS, Mammen PM, Shankar SR, Viswanathan SA, Rebekah G, Russell S, Earnest R, Chikkala SM. Pediatric Anesthesia Emergence Delirium Scale: A diagnostic meta-analysis. *World J Clin Pediatr* 2022; 11(2): 196-205

URL: https://www.wjgnet.com/2219-2808/full/v11/i2/196.htm

DOI: https://dx.doi.org/10.5409/wjcp.v11.i2.196

INTRODUCTION

Emergence delirium (EmD) is seen in up to 80% of children and adolescents in post anesthesia care units [1,2]. This troublesome motoric, mental, and cognitive disturbance is often missed or misdiagnosed[3]. It can last from under 0.5 h to 2 d, and potentially can result in significant morbidity including transient neurological deficits[1,4], longer hospital stays, and regression of milestones if not identified early in its presentation[5]. Fortunately, the use of psychometrically validated measures improves the early diagnosis and effective treatment of delirium in intensive care settings[6]. However, despite the existence of more than 20 measures for EmD, many of them have not been validated[7]. Among the validated and widely used measures for EmD are the WATCHA Scale, Cravero Scale, and Pediatric Anesthesia Emergence Delirium Scale (PAEDS)[7]; the latter scale has been recommended for use in the identification of EmD among children and adolescents[3,8]. Nonetheless, the diagnostic accuracy parameters of PAEDS in individual studies have ranged widely from a sensitivity of 64%-100% and specificity of 80%-98%[7,9]. These wide ranges of results warrant the analysis of the pooled diagnostic accuracy data of PAEDS for EmD. Hence, we conducted this meta-analysis of published data to evaluate the pooled global diagnostic accuracy of PAEDS, its specific diagnostic accuracy parameters of pooled sensitivity and specificity, the diagnostic accuracy of various PAEDS total cut-off points, and the effect of the setting of the use of PAEDS, sample size, age of the juveniles, and the reference standard on the effect size of sensitivity and specificity by meta-regression.

MATERIALS AND METHODS

Literature search

Two researchers (RE and SMC), independently and electronically, searched for the diagnostic accuracy studies of PAEDS in English in the Scopus, PubMed, and Cochrane Data published between May 2004 (from the time of development of PAEDS and publication of its first validation study) to February 2021 (date of last literature update for final analysis). The term "Pediatric Anesthesia Emergence Delirium Scale" was combined with "diagnostic accuracy" and "validation" as ("pediatrics"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "pediatric"[All Fields] OR "pediatric"[All Fields]) AND ("emergence delirium"[MeSH Terms] OR ("emergence"[All Fields] AND "delirium"[All

Fields]) OR "emergence delirium"[All Fields]) AND ("scale s"[All Fields] OR "scaled"[All Fields] OR "scaling"[All Fields] OR "scalings"[All Fields] OR "weights and measures"[MeSH Terms] OR ("weights"[All Fields] AND "measures"[All Fields]) OR "weights and measures"[All Fields] OR "scale"[All Fields] OR "scales"[All Fields]) AND ("diagnosis"[MeSH Terms] OR "diagnosis"[All Fields] OR "diagnostic"[All Fields] OR "diagnostical"[All Fields] OR "diagnostically"[All Fields] OR "diagnostics"[All Fields]) AND ("accuracies"[All Fields] OR "accuracy"[All Fields]); and ("paediatrics"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields]) AND ("emergence delirium"[MeSH Terms] OR ("emergence"[All Fields] AND "delirium"[All Fields]) OR "emergence delirium"[All Fields]) AND ("scale s"[All Fields] OR "scaled"[All Fields] OR "scaling"[All Fields] OR "scalings"[All Fields] OR "weights and measures"[MeSH Terms] OR ("weights"[All Fields] AND "measures"[All Fields]) OR "weights and measures"[All Fields] OR "scale"[All Fields] OR "scales"[All Fields]) AND ("valid"[All Fields] OR "validate"[All Fields] OR "validated"[All Fields] OR "validates"[All Fields] OR "validating"[All Fields] OR "validation"[All Fields] OR "validational"[All Fields] OR "validations"[All Fields] OR "validator"[All Fields] OR "validators"[All Fields] OR "validities"[All Fields] OR "validity"[All Fields]).

The electronic search did not incorporate any search filter to improve the retrieval of as many articles as possible. After a review of the identified titles and abstracts, those articles deemed potentially relevant were collected. We augmented our electronic search with a hand search for additional relevant articles in reference lists of collected articles and from conference abstracts.

Study selection, data extraction, and quality appraisal

Two other researchers (Mammen PM and Shankar SR) extracted the required details independently, resolved any difference in extraction by consultation with another researcher (PSSR), and entered the information as electronic data. They extracted the information including participants, index measure, comparative reference measure, and outcome of diagnostic accuracy details. To be included in the final meta-analysis, studies had to compare the ability of PAEDS as the index test and DSM IV/DSM-IV-TR/DSM 5/ICD-10 or clinical consensus/clinical observation as the reference standard (using clinical interview, semi-structured interview, or interviewing schedules) among children and adolescents (1-18 years). Those diagnostic accuracy studies of PAEDS to identify EmD only were included and studies on PAEDS in the context of other emergent conditions like emergent agitation and emergent pain were excluded. Finally, the study had to report sufficient data to construct 2 x 2 tables for calculating the true positive, false positive, false negative, and true negative values. Two researchers (SR and SAV) appraised the quality of the studies with Quality Assessment of Diagnostic-Accuracy Studies, version 2 (QUADAS-2); differences in appraisal were resolved by consensus with the third researcher (Russell PSS).

Statistical analysis

We constructed the true positive, false positive, false negative, and true negative values, for each included study using 2 × 2 tables. We calculated the area under the curve (AUC) using the summary receiver operating characteristic curve (SROC) to establish the global diagnostic accuracy for all PAEDS cut-offs together; we calculated the confidence and prediction contour for the SROC as well[10]. The pooled sensitivity and specificity were estimated. We calculated the pooled diagnostic odds ratio (DOR) as the diagnostic accuracy parameter for various PAEDS cut-off scores and presented it as a forest plot. An I^2 value of > 50 was considered as substantial heterogeneity. For exploring the heterogeneity and subgroup analysis, the effect of the setting of the use of PAEDS, sample size, reference standard, as well as age of children and adolescents (as independent variables) on the effect size of sensitivity and specificity (as dependent variables) was done using univariate meta-regression. In addition, as the heterogeneity was substantial, it was reasoned that the summary statistics might not represent the individual studies adequately. Therefore, as a *post hoc* test to parametrise the summary DOR, we conducted a leave-one-out cross validation. We calculated the 95% confidence interval (95%CI) when indicated. The analyses were done with the METANDI module of STATA (version 16). We conducted the leave-one-out cross validation using the software Open-Meta meta-analysis software (Brown University, Providence RI, United States)[11].

RESULTS

Literature search

Totally we identified 232 studies from all the data bases, and nine studies (K = 9; n = 1251) were included for the final meta-analysis[7,9,12-17]. Two studies were excluded as they did not satisfy the selection criteria[18,19]. Augmentation strategies of checking the cross references and conference abstracts did not supplement to the eligible article list. The PRISMA flowchart of studies for the final meta-analysis is represented in Figure 1.

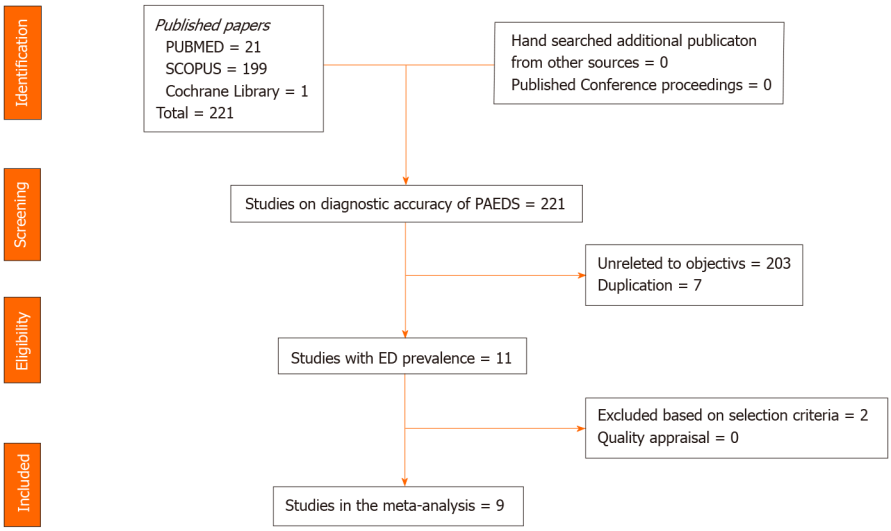

Figure 1 PRISMA flow chart of studies included in the diagnostic meta-analysis for Pediatric Anesthesia Emergence Delirium Scale.

The studies were conducted either in the out-patient (K = 2) or in-patient settings (K = 7) and the sample size varied from 90-260 participants. Four studies had children as participants and the remaining five had children as well as adolescents. Six studies had used a PAEDS cut-off of < 10, two studies ≥ 10, and two studies ≥ 12 for the diagnosis of EmD; except two studies, all had used clinical observation by trained professionals in identifying EmD as the reference standard (Table 1).

Publication bias and quality appraisal

The quality appraisal using QUADAS-2 is pictorially represented for individual studies and across studies in Figure 2A and 2B, respectively; the most common bias across studies was documenting the reference standards and applicability of the reference standards. The Deek's plot did not show publication bias [coefficient = 39.10 (95%CI: -6.05-84.25); P = 0.08] for the studies included in the final analysis as noted in Figure 3.

Diagnostic accuracy

The AUC for the HSROC was 0.97 (95%CI: 95%-98%) (Figure 4). The summary sensitivity and specificity (95%CI for sensitivity/specificity; I^2 for heterogeneity) for the PAEDS were 0.91 (95%CI: 0.81-0.96; I^2 = 92.93%) and 0.94 (95%CI: 0.89-0.97; I^2 = 87.44%), respectively, for diagnosing EmD. When we analyzed the sensitivity-specificity pair within studies, most of the studies had a higher specificity than sensitivity [8,12,15,16,18]. However, two studies each had a higher sensitivity than specificity[9,17] or equal sensitivity and specificity[13,14].

The summary DOR for all PAEDS cut-off scores together was 148.33 (95%CI: 48.32-455.32). With the leave-one-out cross validation, the individual studies significantly contributed to the summary DOR in a descending order from the study by Sikich *et al*[8] at the top [DOR = 152.23 (95%CI: 76.23-304.82)], followed by Bajwa *et al*[13] [DOR = 148.48 (95%CI: 82.18-268.27)], Bong *et al*[12] [DOR = 134.04 (95%CI: 66.53-270.02)], Somaini *et al*[17] [DOR = 133.30 (95%CI: 66.95-265.41)], Janssen *et al*[14] [DOR = 131.35 (95%CI: 64.70-266.64)], Locatelli *et al*[15] [DOR = 121.36 (95%CI: 59.72-249.32)], Simonsen *et al*[18] [DOR = 117 (95%CI: 76.23-304.82)], Joo *et al*[16] [DOR = 111.78 (95%CI: 62.25-200.73)], and finally Blankespoor *et al*[9] [DOR = 111.72 (95%CI: 63.47-196.65)].

The effect size for the subgroup analysis of PAEDS cut-off scores of < 10, ≥ 10 and ≥ 12 was 3.73, 2.19, and 2.93 respectively. Although the < 10 PEDS cut-off score had the largest effect size, the three studied cut-off scores were not statistically significantly different in their diagnostic accuracy; however, they were statistically significantly different when individual studies with varying cut-off PAEDS scores were studied (Figure 5).

Meta-regression

In the meta-regression, the setting of the study and reference standard used were statistically significantly related to the sensitivity of PAEDS and not to its specificity, but the age of the children and adolescents and the sample size of the studies were neither related to the sensitivity nor specificity (Figure 6).

Table 1 Data on methodology and epidemiology of included studies

Ref.	Sample size	Prevalence of EmD	Sn (%)	Sp (%)	Setting	Age (yr)	PEDS Cut-off	Reference standard
Sikich *et al*[8]	100	11%	64	86	OP	1.6-2	≥ 10	Dimenhydrinate treatment
Bong *et al*[12]	136	8.6%	85	96	OP	2-12	≥ 10	Clinical observation
Bajwa *et al*[13]	117	32%	100	95	IP	1-18	≥ 12	Clinical observation
Janssen *et al*[14]	154	16.9%	91	98	IP	1-17	≥ 8	DSM-IVinterview for delirium
Blankespoor *et al*[9]	144	16%	100	97	IP	1-18	≥ 8	Clinical observation
Locatelli *et al*[15]	260	25%	93	94	IP	1-3	≥ 9	Clinical observation
Joo *et al*[16]	90	25.5%	94	97	IP	2-5	≥ 16	Clinical observation
Somaini *et al*[17]	150	21%	96	80	IP	1-7	≥ 9	Clinical observation
Simonsen *et al*[18]	100	13.2%	86	100	IP	2 mo-16 yr	≥ 10	Clinical observation

Figure 2 Quality appraisal using the revised diagnostic accuracy studies (quality assessment of diagnostic accuracy studies-2) for individual studies (A) and average quality across studies (B). QUADAS-2: Quality assessment of diagnostic accuracy studies-2; PS: Patient selection - Describe methods of patient selection; IT: Index text -Describe the index test and how it was conducted and interpreted; RS: Reference standard - Describe the reference standard and how it was conducted and interpreted; FAT: Flow and timing; ACRS: Describe the applicability concerns about reference standard and how it was conducted and interpreted; ACPS: Describe the applicability concerns about patient selection and how it was conducted and interpreted; ACIT: Describe the applicability concerns about Index test and how it was conducted and interpreted; Low: Low bias; High: High bias UC: Unclear (if insufficient data were reported to permit our judgment).

DISCUSSION

Currently, the diagnostic methods for EmD are evolving, and there is more clarity in differentiating EmD from other emergent phenomena. This meta-analysis included only those studies where PAEDS was used as a diagnostic measure for EmD only. This meta-analysis on PAEDS supports the evidence obtained from previously documented diagnostic accuracy parameters based on individual studies that the measure can be used as an effective diagnostic measure for EmD among children and adolescents.

There was no publication bias. The quality appraisal showed that the most common bias across studies was documenting the reference standards and applicability of the reference standards. Overall, the studies were of moderate quality. The absence of very large studies, duplicated data sets, same study sample/population, and similar selection process of participants or same group of authors with similar interpretation of results has minimized the skewing of our summary findings.

The AUC-SROC for PAEDS in diagnosing EmD was 0.97. As this AUC is much above the random predictor value of 0.5, the classification of EmD by PAEDS is not by random chance of 50% or toss of a coin but instead the classification is because of the excellent inherent global diagnostic accuracy of PAEDS. Thus, PAEDS succeeds as a diagnostic test for pediatric EmD with the various diagnostic cut-off scores used currently.

The pooled sensitivity of PAEDS in our study was 91%, which is an excellent sensitivity meaning that 91/100 children with EmD were correctly identified. Similarly, the pooled specificity of PAEDS was 94%, which is an excellent specificity and it means that 94/100 healthy children were identified as not having EmD. Such excellent sensitivity and specificity again support the use of PAEDS as a diagnostic measure for EmD among the pediatric population. This pooled sensitivity and specificity are

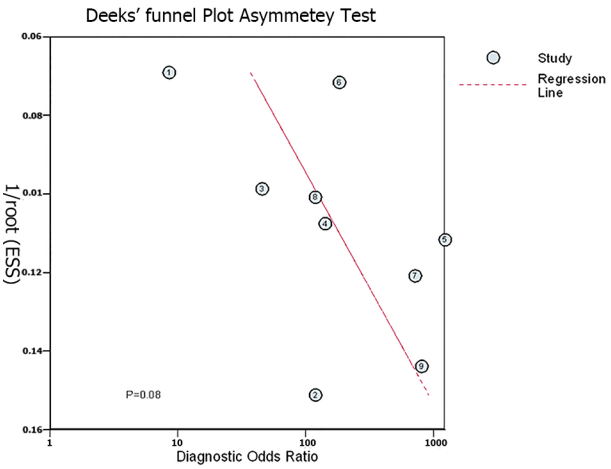

Figure 3 Deek's plot for publication bias among studies included in the diagnostic meta-analysis for Pediatric Anesthesia Emergence Delirium Scale.

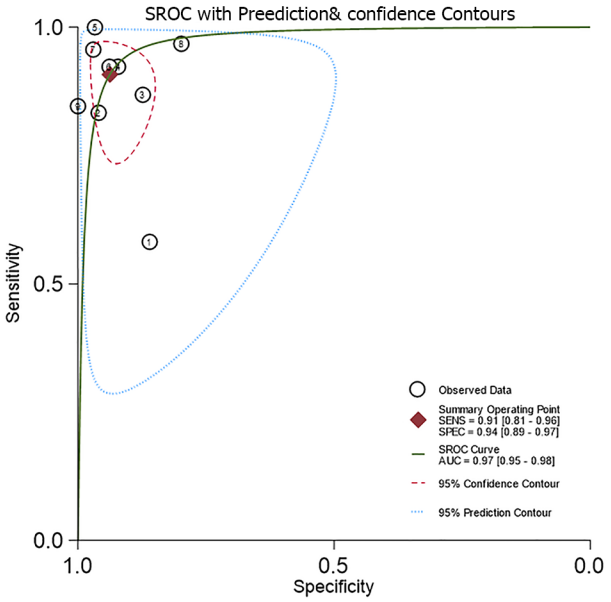

Figure 4 Diagnostic accuracy of the Pediatric Anesthesia Emergence Delirium Scale based on the summary receiver operating characteristic curve.

comparable with the data documented in individual diagnostic accuracy studies of PEDS[9,11,14-16].

The overall DOR calculated from sensitivity and specificity was 148. In theory, the DOR ranges in value from zero to infinity, with higher values indicating better discriminatory performance of the test. This binary classification is not dependent on the prevalence of EmD and hence can be applied in various pre-test probability contexts[20]. When the subgroup analysis of the DOR based on the PEDS cut-off scores was performed, although the lowest of the threshold scores more accurately diagnosed EmD, there was no statistically significant difference among them. However, when a range of cut-off scores, from > 8 to > 16, were used, the lowest score showed a statistically significant diagnostic accuracy than higher scores[9]. This speculatively could be because in higher PAEDS scores, the motoric combined with cognitive items possibly identify the symptoms of emergence agitation and emergence pain as well[20,21]; this hypothesis has to be further tested.

However, some of the above findings should be interpreted in the context of the study limitations and strengths. There was substantial heterogeneity in the diagnostic accuracy parameters of the PAEDS, which was partly explained by the setting of the occurrence of EmD and the reference standard used. The role of each individual study in the summary DOR was further explored with a range of 111-152, adding strength to the method of this meta-analysis. The PAEDS threshold effect has to be further studied with larger meta-analysis. Expecting heterogeneity to start with, the use of random effects models, exploring the heterogeneity by meta-regression, subgroup analysis, and the leave-one-out cross validation have strengthened the meta-analysis. Furthermore, in order not to compromise the diagnostic

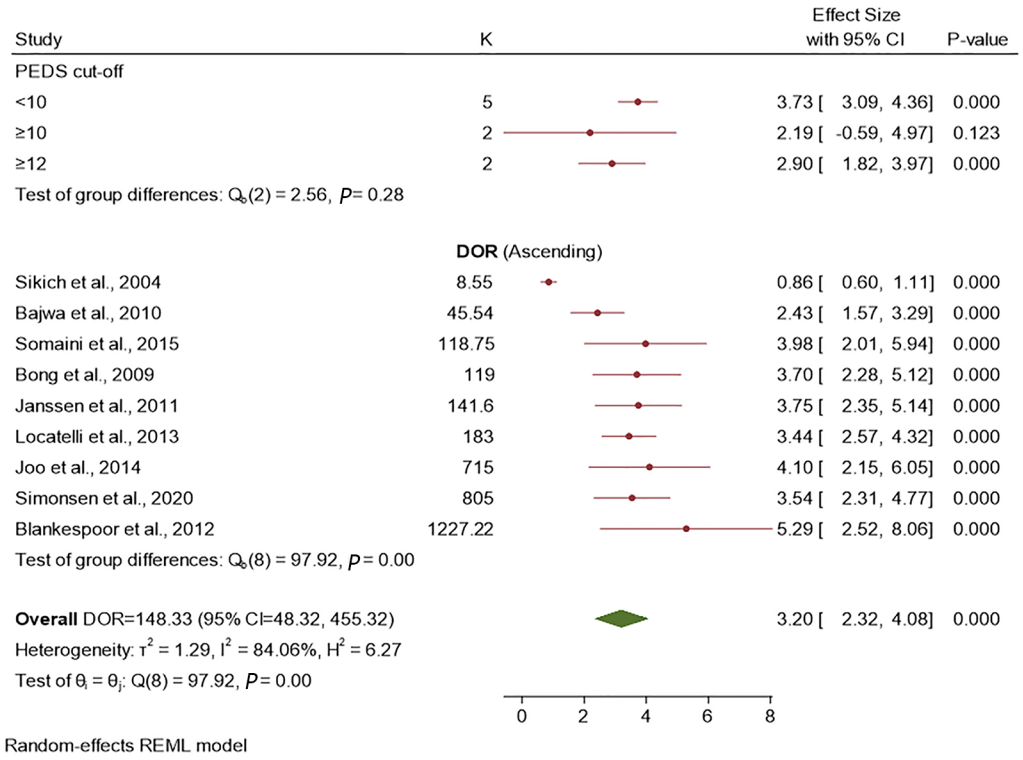

Figure 5 Forest plot for the diagnostic odds ratio presenting the subgroup analysis by cut-off scores and individual studies included in the diagnostic meta-analysis for Pediatric Anesthesia Emergence Delirium Scale.

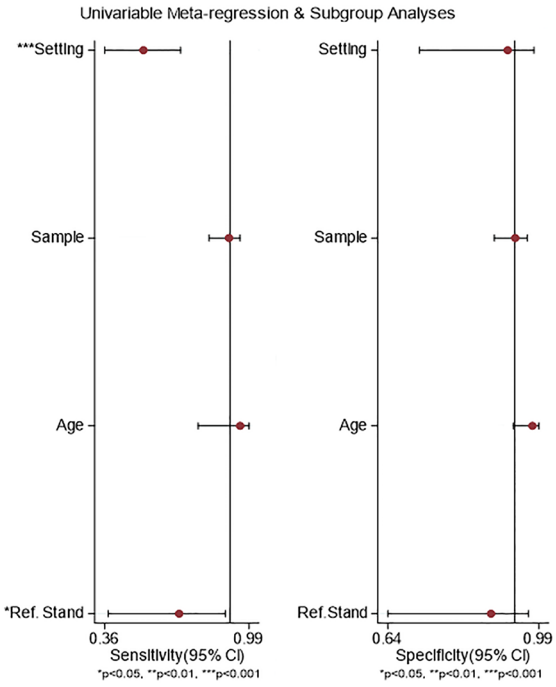

Figure 6 Meta-regression and subgroup analysis on sensitivity and specificity of Pediatric Anesthesia Emergence Delirium Scale.

accuracy of PAEDS for EmD from other post-anesthetic emergent problems like pain and agitation, we excluded those studies with such conditions in this meta-analysis.

From a clinical-utility perspective, PAEDS has the global and specific diagnostic accuracy characteristics to be used as a diagnostic measure for EmD among both children and adolescents. It has documented that integrated use of PAEDS in post-anesthesia care unit improves the identification of ED better than other measures[7]; our study encourages the integration of this measure for the diagnosis of ED.

CONCLUSION

In conclusion, PAEDS has excellent diagnostic accuracy for emergent delirium among children and adolescents.

ARTICLE HIGHLIGHTS

Research background

There are various measures to identify emergence delirium (EmD) among children and adolescents as they recover from anesthesia. Pediatric Anesthesia Emergence Delirium Scale (PAEDS) is one such measure and has been found to have varying accuracy for diagnosing EmD.

Research motivation

The diagnosis of EmD is often missed or misdiagnosed. This can result in significant morbidity. The widely used PAEDS across the world has been proven to have the ability of early identification of EmD.

Research objectives

The aims of this meta-analysis were to document the summary global and specific diagnostic accuracy parameters of PAEDS, diagnostic accuracy for various diagnostic threshold scores of the measure, and factors associated with these summary parameters of PAEDS in diagnosing EmD.

Research methods

Nine studies were included in the analysis following the PRISMA guidelines. We used the summary area under the receiver operating characteristic curve, with a random effects model, to summarize the global diagnostic accuracy of PAEDS along with its diagnostic odds ratio, sensitivity, and specificity.

Research results

The area under the SROC was 0.97 (95%CI: 95-98%). The summary sensitivity and specificity were 0.91 (95%CI: 0.81-0.96; I^2 = 92.93%) and 0.94 (95%CI: 0.89-0.97; I^2 = 87.44%), respectively. The summary DOR was 148.33 (95%CI: 48.32-455.32). The effect size for the subgroup analysis of PAEDS cut-off scores of < 10, ≥ 10, and ≥ 12 was 3.73, 2.19, and 2.93, respectively; they were not statistically significantly different. The setting of the study and reference standard were statistically significantly related to the sensitivity of PAEDS but not specificity.

Research conclusions

The authors have established the summary global diagnostic accuracy of PAEDS for EmD among children and adolescents.

Research perspectives

The PAEDS could be used for diagnosing EmD among children and adolescents. The specific diagnostic cut-off scores have to be further studied.

ACKNOWLEDGEMENTS

We acknowledge with gratitude Ms. Mary Pauline Paul and Mr. George Devadoss in coordinating the certification processes.

FOOTNOTES

Author contributions: Russell PSS and Mammen PM conceived and designed the study; Chikkala SM and Earnest R did the literature search and collected the data; Mammen PM and Shankar SR extracted the data; Viswanathan SA and Russell S appraised the quality of the studies; Mammen PM resolved the conflicts in data extraction and quality appraisal; Russell PSS and Rebekah G did the statistical analyses; all authors contributed to the writing and approval of the final manuscript.

Conflict-of-interest statement: All authors declare that there are no any conflicts of interest to disclose.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Ma YJ
L-Editor: Wang TQ
P-Editor: Cai YX

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World J Clin Pediatr 2022 March 9; 11(2): 206-214

DOI: 10.5409/wjcp.v11.i2.206

ISSN 2219-2808 (online)

META-ANALYSIS

Prevalence of intellectual disability in India: A meta-analysis

Paul Swamidhas Sudhakar Russell, Sahana Nagaraj, Ashvini Vengadavaradan, Sushila Russell, Priya Mary Mammen, Satya Raj Shankar, Shonima Aynipully Viswanathan, Richa Earnest, Swetha Madhuri Chikkala, Grace Rebekah

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Swai JD

Received: March 21, 2021
Peer-review started: March 21, 2021
First decision: May 6, 2021
Revised: May 18, 2021
Accepted: February 11, 2022
Article in press: February 11, 2022
Published online: March 9, 2022

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Abstract

BACKGROUND

Burden due to intellectual disability (ID) is only third to the depressive disorders and anxiety disorders in India. This national burden significantly contributes to the global burden of ID and hence one has to think globally and act locally to reduce this burden. At its best the collective prevalence of ID is in the form of narrative reviews. There is an urgent need to document the summary prevalence of ID to enhance further policymaking, national programs and resource allocation.

AIM

To establish the summary prevalence of ID during the past 60 years in India.

METHODS

Two researchers independently and electronically searched PubMed, Scopus, and the Cochrane library from January 1961 to December 2020 using appropriate search terms. Two other investigators extracted the study design, setting, participant characteristics, and measures used to identify ID. Two other researchers appraised the quality of the studies using the Joanna Briggs Institute critical appraisal format for Prevalence Studies. Funnel plot and Egger's regression test were used to ascertain the publication and small study effect on the prevalence. To evaluate the summary prevalence of ID, we used the random effects model with arcsine square-root transformation. Heterogeneity of $I^2 \geq 50\%$ was considered substantial and we determined the heterogeneity with meta-regression. The

analyses were performed using STATA (version 16).

RESULTS

Nineteen studies were included in the meta-analysis. There was publication bias; the trim-and-fill method was used to further ascertain bias. Concerns with control of confounders and the reliable measure of outcome were noted in the critical appraisal. The summary prevalence of ID was 2% [(95%CI: 2%, 3%); I^2 = 98%] and the adjusted summary prevalence was 1.4%. Meta-regression demonstrated that age of the participants was statistically significantly related to the prevalence; other factors did not influence the prevalence or heterogeneity.

CONCLUSION

The summary prevalence of ID in India was established to be 2% taking into consideration the individual prevalence studies over the last six decades. This knowledge should improve the existing disability and mental health policies, national programs and service delivery to reduce the national and global burden associated with ID.

Key Words: India; Intellectual disability; Prevalence; Children and adolescents; Meta-analysis

Core Tip: Intellectual disability (ID) is prevalent in India and earlier epidemiological studies on mental disorders have documented the lifetime prevalence of ID. However, the documented prevalence of ID in the country shows a wide range. The burden posed by ID is only third to the depressive disorders and anxiety disorders among mental disorders. The burden of ID in India significantly contributes to the global burden of ID; to decrease this we need to think globally and act locally in an evidence-based manner. To date, the prevalence of ID in India has been shown in narrative reviews. This suggests that the summary prevalence of ID in India has to be ascertained to help improve the existing disability and mental health policies, national programs and service delivery. This meta-analysis established that the summary lifetime prevalence of ID in India is 2%.

Citation: Russell PSS, Nagaraj S, Vengadavaradan A, Russell S, Mammen PM, Shankar SR, Viswanathan SA, Earnest R, Chikkala SM, Rebekah G. Prevalence of intellectual disability in India: A meta-analysis. *World J Clin Pediatr* 2022; 11(2): 206-214

URL: https://www.wjgnet.com/2219-2808/full/v11/i2/206.htm

DOI: https://dx.doi.org/10.5409/wjcp.v11.i2.206

INTRODUCTION

Intellectual disability (ID) contributes to 10.8% of the burden of mental disorders, measured by disability-adjusted life-years, in India. The burden caused by ID in India is only third to the depressive disorders and anxiety disorders[1]. Improving access to evidence-based mental health services for those with mental disorders is the best approach to address the burden of mental disorders in India[2]. However, the evidence based data for ID is difficult to build and most of the prevalence reviews for ID in India are narrative.

In narrative reviews, ID is prevalent in 1%-3.2% of the population in India depending on the definition of prevalence, study population, study design, and measures used to identify ID[3]. Among individual studies, the prevalence of ID in the country varied from 0.28%-20%[4,5]. This variation in prevalence is significant and does not help in planning precise policies, national programs and service delivery models for ID; the best way forward is to determine the summary prevalence of ID in India.

The summary prevalence of ID has not been documented in India and only an attempt to extrapolate from the 2002 Disability data report of the National Sample Survey Organization was made[6]. This meta-analysis documents the summary prevalence of ID in India for policy making and developing nation-wide clinical programs.

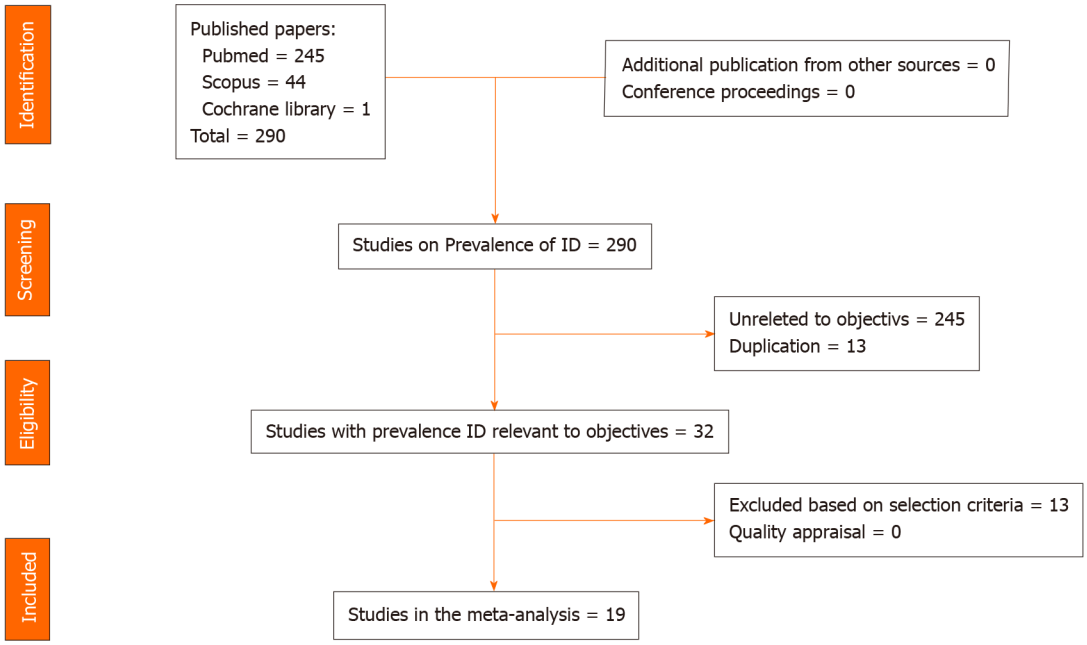

Figure 1 Preferred reporting items for systematic reviews and meta-analyses flow-chart for studies in the final meta-analysis.

MATERIALS AND METHODS

Literature search

Two researchers (Chikkala SM and Earnest R) independently and electronically searched for relevant published studies in PubMed, Scopus, and the Cochrane library over the past 60 years (January 1961 to December 2020). The search terms were as follows: "prevalence of intellectual disability in India", combined and included as: ("epidemiology"[MeSH Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms] OR "prevalance"[All Fields] OR "prevalences"[All Fields] OR "prevalence s"[All Fields] OR "prevalent"[All Fields] OR "prevalently"[All Fields] OR "prevalents"[All Fields]) AND ("intellectual disability"[MeSH Terms] OR ("intellectual"[All Fields] AND "disability"[All Fields]) OR "intellectual disability"[All Fields]) AND ("india"[MeSH Terms] OR "india"[All Fields] OR "india s"[All Fields] OR "indias"[All Fields]). In addition, a hand-search was conducted for any potential study for inclusion from cross references and conference publications.

Study selection and data extraction

The studies retrieved during the searches were screened for relevance, and those identified as being potentially eligible were fully assessed for inclusion/exclusion from the titles. Two researchers (Russell S and Shankar SR) individually extracted the required data from the studies selected from inclusion. Any difference in the data extracted between the researchers was resolved through consultation with a third researcher (Mammen PM). Details on the prevalence of ID, sampling method, sample size, participant characteristics; setting of the study, definition of ID (borderline intelligence was excluded) measures/criteria used for diagnosis of ID, from each study were extracted. To be included in the final analysis, the studies required all these details available for extraction. Those studies with age of participant above 18 years, hospital setting and participants with borderline intelligence but not ID, and studies carried out on special illness populations were excluded.

Quality appraisal and risk of bias

Two researchers (Nagaraj S and Vengadavaradan A) independently appraised the studies using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data for the quality of the studies included in the final analysis[7]; and any discrepancies in the critical appraisal was resolved by consensus through discussion with another researcher (Mammen PM). A contour-enhanced funnel plot was developed for publication bias and Egger's regression analysis was performed for the analysis of small study bias[8].

Statistical analysis

To evaluate the summary prevalence, we used the random effects model with arcsine square-root transformation; heterogeneity ($I^2 \geq 50\%$) was expected to be substantial in this prevalence meta-analysis and hence the transformation was used. As the contour-enhanced funnel plot and Egger's regression test demonstrated significant publication bias, as a post hoc test, the trim-and-fill technique was used to

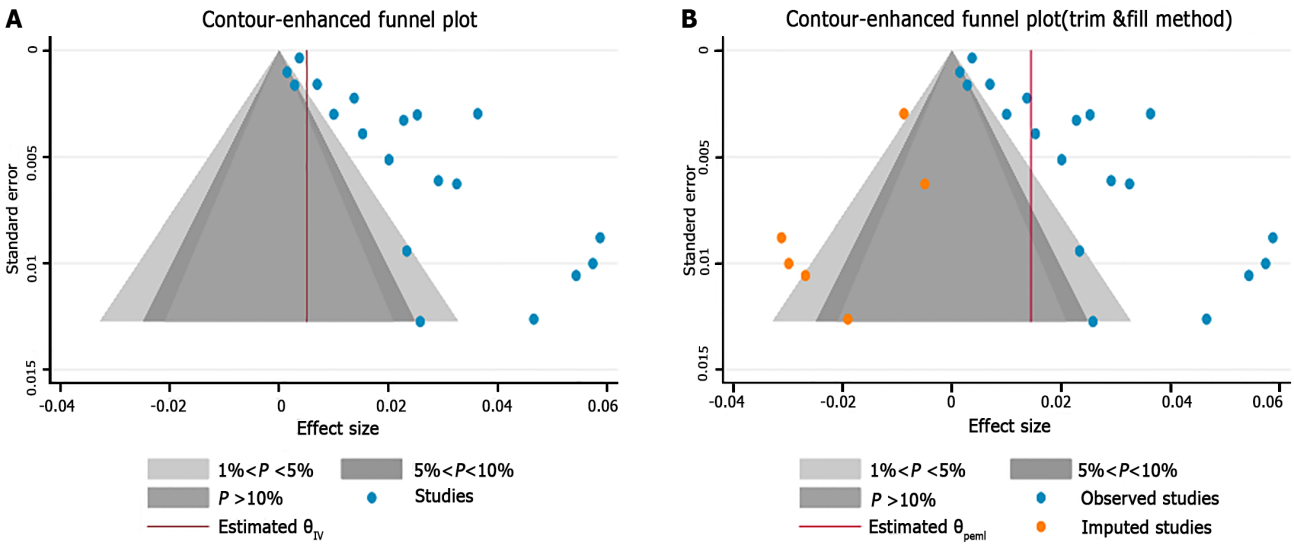

Figure 2 The contour-enhanced funnel plot (A) and trim-and-fill plot (B) for publication bias.

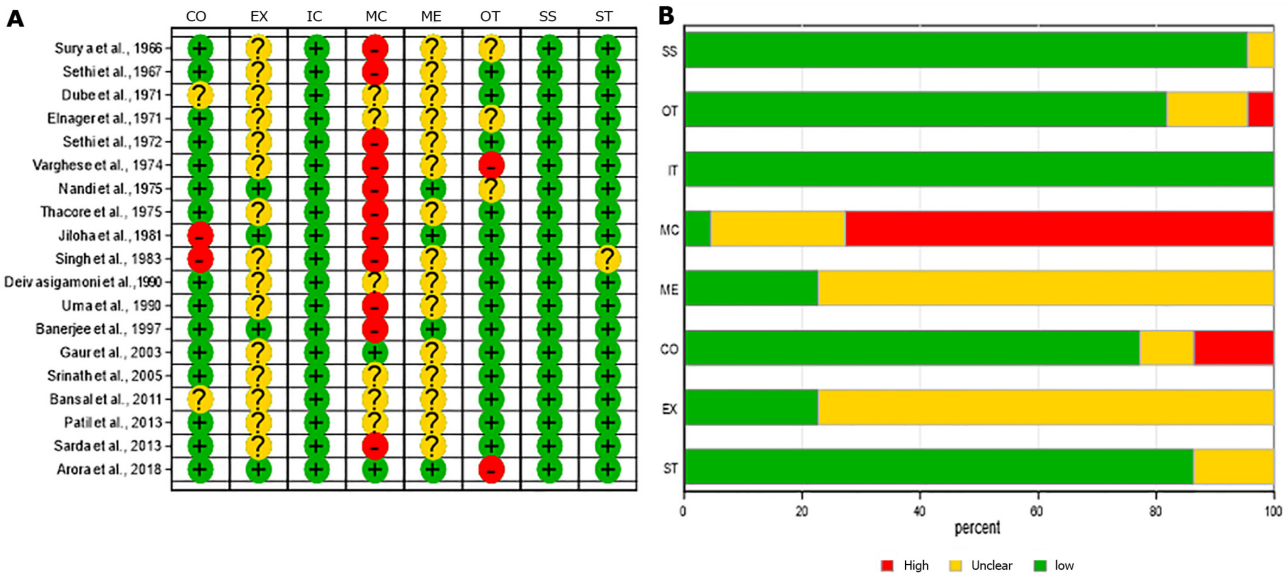

Figure 3 The Joanna Briggs Institute critical appraisal for prevalence meta-analysis for individual studies (A) and average quality across studies (B). IC: Were the criteria for inclusion in the sample clearly defined? SS: Were the study subjects and the setting described in detail? EX: Was the exposure measured in a valid and reliable way? ME: Were objective, standard criteria used for measurement of the condition? CO: Were confounding factors identified? MC: were strategies to deal with confounding factors stated? OT: Were the outcomes measured in a valid and reliable way? ST: Was appropriate statistical analysis used? High: High bias; No: Low bias; Unclear: Unclear bias; NA: Not applicable.

explore the nature of the bias[9]. We determined the heterogeneity with meta-regression. The analyses were carried out using the STATA (version 16) software package.

RESULTS

In total, we identified 290 studies from all the databases and 19 studies[10-28] were included in the final meta-analysis. Thirteen studies were excluded as they had either age group above 18 years and ID prevalence could not be calculated, a setting other than community or school, or the prevalence was studied in specific disease populations. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) details regarding the selection of studies for the final analysis are presented in Figure 1; the methodology and prevalence data are given in Table 1. The visual examination of the contour-enhanced funnel plot (Figure 2A) and the Egger's test [coefficient = 5.92 (standard error = 1.19), t = -5.0; P = 0.0001] revealed publication bias or a small study effect, respectively, on the prevalence of

Table 1 The methodological and prevalence details of included studies

Ref.	Area; setting	Age(yr)	Sampling, diagnostic method	Prevalence of ID (%)	Sample size
Surya *et al*[10]	Urban; community	0-15	Screening schedule + CI	0.7	2731
Sethi *et al*[11]	Urban; community	0-10	Comprehensive questionnaire + CI	5.74	541
Dube *et al*[12]	Mixed; community	44693	CI	0.37	8035
Elnagar *et al*[11]	Rural; community	0-14	CI + WHO ECH	0.86	635
Sethi *et al*[14]	Rural; community	0-10	Comprehensive questionnaire, CI	6.84	877
Verghese *et al*[15]	Urban; community	44663	Comprehensive questionnaire + ICD-9	2.01	747
Nandi *et al*[16]	Rural; community	0-11	Comprehensive questionnaire + WHO ECH	0.28	462
Thacore *et al*[17]	Urban; community	0-15	CI + DSM II	2.94	2696
Jiloha *et al*[18]	Rural; school	44693	Comprehensive questionnaire + ICD-9	5.87	715
Singh *et al*[19]	Urban; community	44575	CI + ICD-9	4.7	279
Deivasigamani *et al*[20]	Urban; school	44785	Rutter B + ICD 9	2.9	755
Uma *et al*[21]	Mixed; School	44624	PBCL (parent version)	2.91	155
Banerjee *et al*[22]	Urban; school	44783	CI + CBQ + ICD-9	5.4	460
Gaur *et al*[23]	Mixed; community	44726	CPMS + DISC + ICD-10 schedule	3.25	800
SriP-Editornath *et al*[24]	Mixed; community	0-16	CBCL + DISC + VSMS + CGAS + ICD-10	2.3	2064
Bansal *et al*[25]	Rural; community	44849	CPMS +ICD-10		
Patil *et al*[26]	Urban; community	44695	CI + DSM-IV	2.4	257
Sarda *et al*[27]	Mixed; school	44667	CBS + CBCL + DISC + ICD-10	0.99	1110
Arora *et al*[28]	Mixed; community		INCLEN Measures + DSM-IV-TR	3.6	3964

CI: Clinical Interview; CBQ: Children's Behaviour Questionnaire; CBCL: Child Behaviour Check List; CPMS: Indian Adaptation of CBCL; DSM: Diagnostic and Statistical Manual (edition IV and IV-TR); CGAS: Children's Global Assessment Scale; DISC: Diagnostic Interview Schedule for Children; ECH: WHO expert committee on mental health criteria; ICD: International Classification of Diseases (edition 9 and 10); INCLEN: The International Clinical Epidemiology Network; PBCL: Preschool Behaviour Check List; VSMS: Vineland Social Maturity Scale.

ID in India. The trim-and-fill method demonstrated that four more studies were required on the left side of the funnel to overcome this bias (Figure 2B). The JBI critical appraisal for each study and the average quality included in the final analysis are depicted in Figure 3. Concerns with control of confounders and reliable measurement of outcome were noted in the critical appraisal as common biases.

The summary prevalence of ID among children and adolescents in India was 2% [0.02 (95%CI: 0.02%, 0.03%); I^2 = 98%] and is presented as a forest plot (Figure 4). When the required six studies were included using the trim-and-fill method, the imputed prevalence of ID in India was 1.4%. The prevalence of ID has changed over the last 60-year period in India from 5% to 2%.

There was substantial heterogeneity in the meta-analysis; our meta-regression demonstrated that the heterogeneity between the prevalence studies was statistically significantly related to the age of the participants (children *vs* adolescents; coefficient =-0.019 (s.e) =0.009; P = 0.03), the area of residence or school, setting of the study in the community or school, and the diagnostic assessment used was not significantly related to the prevalence of ID.

DISCUSSION

This meta-analysis documents that the summary life-time prevalence of ID is 2% and the adjusted summary life-time prevalence is 1.4% in India. This prevalence is, thus, within the range of 1%-3% in the

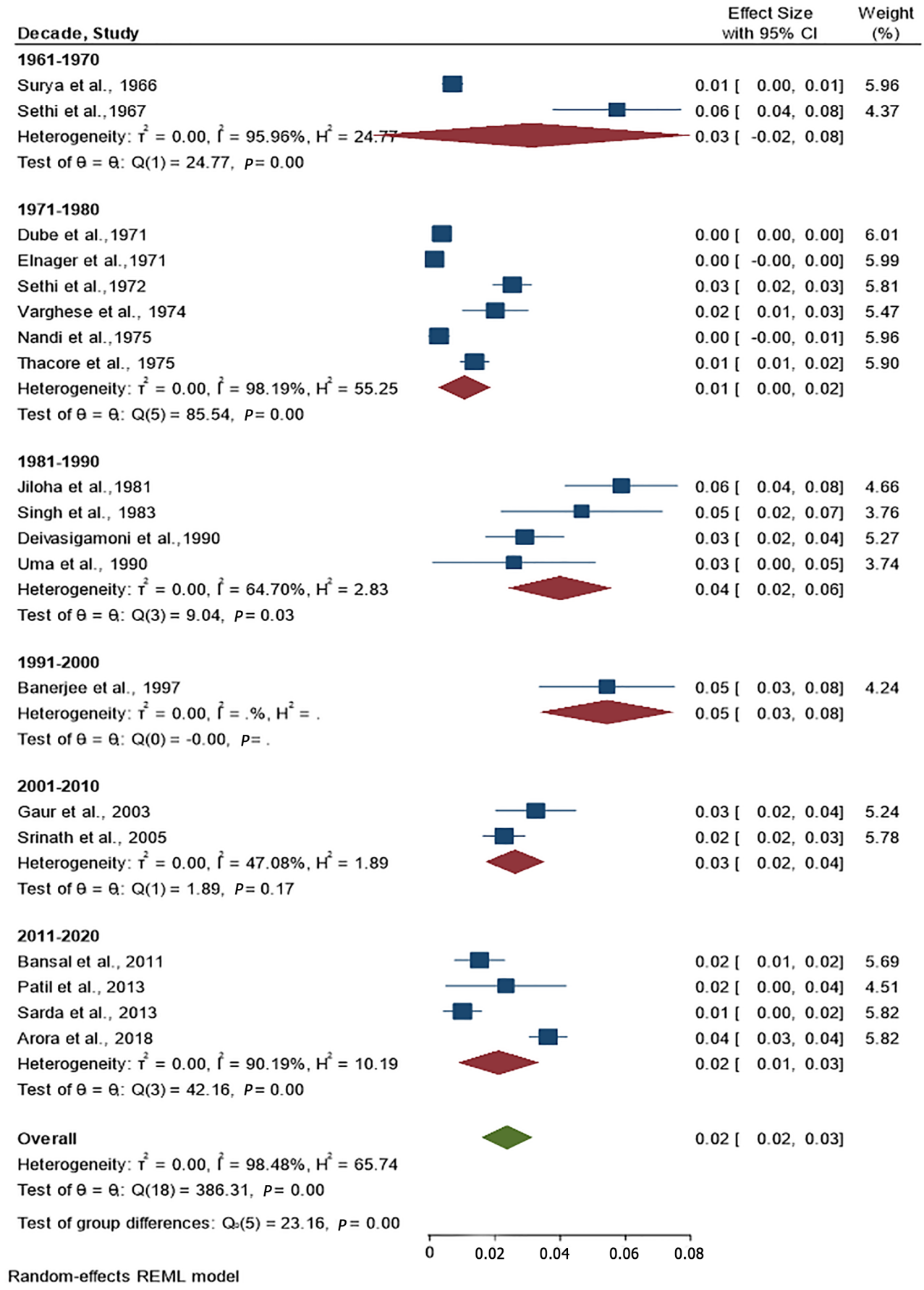

Figure 4 The forest plot for summary prevalence of intellectual disability in India.

narrative review[3] and the extrapolated data of 1.5% from the National Sample Survey Organization by the Ministry of Social Justice and Empowerment, Government of India[6]. With the above epidemiological insights, it is important to mitigate the burden with prevention and effective habilitation.

The lifetime prevalence of ID despite being small when compared with many other development disabilities of childhood[28], the burden caused by this disability is a significant 10.8% among mental disorders in India. The population size of India is so huge this burden adds to the global burden of ID; therefore, it has been suggested to enhance the disability programs to have sustainable burden reduction practices at the national level[29].

This meta-analysis was based on only published studies in the English language. Our funnel plot and test for the influence of small studies was significant and six more studies were required to prevent the publication and small study bias. However, we used the trim and fill method to impute the number of studies required to improve this meta-analysis and adjust the prevalence in our study. Thus, in this meta-analysis, the impact of four missing studies was simulated, and the original prevalence of 2% was revised to an adjusted prevalence of 1.4%.

From the utility perspective of this meta-analysis, it is important that the systematic survey we carried out as part of the meta-analysis shows there is a significant paucity of studies on the prevalence of ID in certain states of India. Moreover, the mental health programs at the national and state levels in India have to bridge the gap between identification and management need of those with ID, with focused polices, programs and capacity building. Although there has been noticeable progress in the policy, national program, and service programs, most of them are focused on the secondary and tertiary prevention of ID[3]. It has been documented that up to 25% of ID is preventable in India and 305 are acquired forms of ID[30]; this underscores the need for approaches such as the modified Finnish method in the context of identifying the aetiology of ID in India[31].

The findings of this study should be interpreted from the perspective of the lifetime prevalence of ID. We decided on this definition to build the systematic-survey, as ID is a lifetime condition, where the condition can be improved but cannot be reversed[32]. Secondly, although we searched for grey literature we did not search for unpublished data and thus could have limited the national data on this disorder.

CONCLUSION

In conclusion, the lifetime prevalence of ID in India is consistent with narrative reviews. Addressing the ID burden requires delivery of integrated disability and mental health care services at the community level. This summary lifetime prevalence should further enhance policymaking and resource allocation for ID in India.

ARTICLE HIGHLIGHTS

Research background

India has a population of more than one billion with a significant disability burden similar to other low- and middle-income countries. The summary prevalence of intellectual disability (ID) in India has not been established.

Research motivation

ID contributes to 10.8% of the burden due to mental disorders in India. This national burden significantly contributes to the global burden of ID and hence one has to think globally and act locally to reduce this burden. At its best the collective prevalence of ID is in the form of narrative reviews. There is an urgent need to document the summary prevalence of ID to enhance further policymaking, national programs and resource allocation.

Research objectives

The aim of the meta-analysis was to establish the summary prevalence of ID in India over the past 60 years.

Research methods

Nineteen studies were included in the meta-analysis following the PRISMA guidelines. To analyse the summary prevalence of ID, we used the random effects model with arcsine square-root transformation. Heterogeneity of $I^2 \geq 50\%$ was considered substantial and we determined the heterogeneity with meta-regression.

Research results

The summary prevalence of ID was 2% [(95%CI: 2%, 3%); I^2 = 98%] and the adjusted summary prevalence was 1.4%. Meta-regression demonstrated that age of the participants was statistically significantly related to the prevalence; other factors did not influence the prevalence or heterogeneity.

Research conclusions

The authors established the summary prevalence of ID in India as 2% taking into consideration the individual prevalence studies over the last 6 decades. This knowledge should improve the existing disability and mental health policies, national programs and service delivery models to mitigate the burden related to ID.

Research perspectives

Future research should focus on the role of the summary prevalence of ID in the reduction of burden due to this disability in India and globally.

FOOTNOTES

Author contributions: Russell PSS conceived and designed the study; Chikkala SM and Earnest R performed the literature search and collected data; Russell S and Shankar SR extracted data; Nagaraj S and Vengadavaradan A appraised the quality of studies; Mammen PM resolved the conflicts in data extraction and quality appraisal; Russell PSS, Viswanathan SA and Rebekah G carried out the statistical analyses; and all authors contributed to the writing and approval of the final manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: India

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S-Editor: Ma YJ
L-Editor: Webster JR
P-Editor: Cai YX

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ISSN 2219-2808 (online)

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2022 May 9; 11(3): 215-320

Published by Baishideng Publishing Group Inc

WJCP

World Journal of Clinical Pediatrics

Contents

Bimonthly Volume 11 Number 3 May 9, 2022

World Journal of Clinical Pediatrics

Bimonthly Volume 11 Number 3 May 9, 2022

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INDEXING/ABSTRACTING

The *WJCP* is now abstracted and indexed in PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Wen-Wen Qi*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Yu-Jie Ma.*

NAME OF JOURNAL
World Journal of Clinical Pediatrics

ISSN
ISSN 2219-2808 (online)

LAUNCH DATE
June 8, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Toru Watanabe, Elena Daniela Serban, Surjit Singh, Consolato M Sergi

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2219-2808/editorialboard.htm

PUBLICATION DATE
May 9, 2022

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

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https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 May 9; 11(3): 215-220

DOI: 10.5409/wjcp.v11.i3.215

ISSN 2219-2808 (online)

GUIDELINES

Preferred practice guidelines for retinopathy of prematurity screening during the COVID-19 pandemic

Anand Vinekar, Rajvardhan Azad, Mangat Ram Dogra, Subhadra Jalali, Pramod Bhende, Parijat Chandra, Narendran Venkatapathy, Sucheta Kulkarni

Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Lee SJ, South Korea

Received: March 1, 2021
Peer-review started: March 1, 2021
First decision: July 30, 2021
Revised: August 17, 2021
Accepted: March 16, 2022
Article in press: March 16, 2022
Published online: May 9, 2022

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Abstract

Retinopathy of prematurity (ROP) is the leading cause of preventable infant blindness in the world and predominantly affects babies who are born low birth weight and premature. India has the largest number of surviving preterm births born annually. ROP blindness can be largely prevented if there is a robust screening program which detects treatment requiring disease in time. ROP treatment must be provided within 48 h of reaching this threshold of treatment making it a relative emergency. During the severe acute respiratory syndrome-coronavirus disease 2019 pandemic in 2020 ROP screening was disrupted throughout the world due to lockdowns and restriction of movement of these infants, their families, specialists and healthcare workers. The Indian ROP Society issued guidelines for ROP screening and treatment in March 2020, which was aimed at preserving the chain-of-care despite the potential limitations and hazards during the (ongoing) pandemic. This preferred practice guideline is

summarized in this manuscript.

Key Words: Retinopathy of prematurity; Screening; Preferred practice; COVID-19; Pandemic; Indian retinopathy of prematurity society

Core Tip: Retinopathy of prematurity (ROP) is a relative emergency in ophthalmology because if it's screening and treatment is delayed it can result in permanent vision impairment or even blindness in at risk infants. During the coronavirus disease 2019 pandemic, the Indian ROP society formulated these preferred practice guidelines with the aim of reducing this risk.

Citation: Vinekar A, Azad R, Dogra MR, Jalali S, Bhende P, Chandra P, Venkatapathy N, Kulkarni S. Preferred practice guidelines for retinopathy of prematurity screening during the COVID-19 pandemic. *World J Clin Pediatr* 2022; 11(3): 215-220
URL: https://www.wjgnet.com/2219-2808/full/v11/i3/215.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i3.215

INTRODUCTION

The severe acute respiratory syndrome-coronavirus disease 2019 (COVID-19) pandemic that started in the last quarter of 2019 in China and spread thereafter reached epic proportions globally by early 2020 and is still ongoing in most regions of the world. This pandemic has become the greatest public health calamity in over a century or more. Lives and livelihood were lost globally and sadly the true quantum of loss and the impact on the future health and well-being of the human race is yet to be fully determined.

At the time of this submission, India had the second largest number of cases in the world. Like most parts of the world, the Government of India (GoI) mandated the first lockdown of all non-essential services between March 25, 2020 to April 14, 2020, which was followed by a series of continual lockdown periods with differing restrictions.

Like all other healthcare specialties, ophthalmology was impacted tremendously. While routine daycare surgeries were suspended initially only emergency services were offered. Since ophthalmology is a stand-alone specialty with very few life-threatening or relatively fewer eye emergencies, most ophthalmology set-ups were shut down. Aiming to strike a professional and ethical balance between controlling the spread of the virus and providing services for ophthalmic emergencies, the All India Ophthalmology Society (AIOS) developed.

A preferred practice pattern (PPP) based on consensus discussion between some of the leading ophthalmologists in India, major institutional representatives, and the AIOS leadership[1]. The PPP was initially for the specialty as a whole and was applicable to all practice settings including tertiary institutions, corporate and group practices, and individual eye clinics. Subsequently, sub-groups developed practice guidelines for eye-banking, glaucoma, vitreo-retina[2], and pediatric ophthalmology.

Retinopathy of prematurity (ROP), a bilateral vasoproliferative disease affecting the retinae of premature infants within a few weeks of birth is a relative Ophthalmic emergency. As this affects the vulnerable cohort of infants during their critical admission in the neonatal intensive care unit (NICU), ROP screening and often treatment requires to be made available in the NICU itself by the ROP team. Even in pre COVID times, ROP screening in India is not universal, with an acute shortage of trained specialists to carry out the screening[3,4]. The COVID lockdown restrictions of admissions into these NICUs, cessation of public transport, the shutdown of routine outpatient services added to the woes of ROP screening and treatment in an already fragile situation.

On March 24, 2020 a day prior to the national lockdown, the Indian ROP (IROP) society, a professional body of ROP specialists published the preferred guidelines for ROP screening on their website [5], and subsequently a summary was published in the vitreo-retinal diseases preferred practice guidelines[2]. These guidelines were circulated to all its members and subsequently were used in other countries with similar demographic profiles in the South and South-East Asian regions.

GUIDELINE METHOD

The Executive Founder members of the IROP contributed to the formation of the guidelines[3]. The

paper was then compiled and reviewed by the entire committee. In case there was any difference of opinion, a mutual consensus was reached by discussion amongst all the experts. The final version of the document was approved by all the authors.

Disclaimer by the authors

These guidelines are not sacrosanct and may be customized and modified depending on the regional situation in a particular district, state, or country. These guidelines are also not permanent and may be updated periodically depending on the prevailing condition, existing regulations and national and international scenario. These guidelines are not to be regarded as medico-legal advice.

The guidelines are summarized below and pertain to screening and treatment of ROP.

ROP screening criteria: (1) Who? This remains unchanged from the existing National ROP Operational Guidelines (2018)[6]. Eligible babies include: Those born ≤ 2000 g grams at birth/those born ≤ 34 wk of gestation; and outside the criteria if requested by the treating neonatologist; (2) When? We must strive to complete the first screening before the baby is 30 days old. If possible high-risk babies (< 1200 g and < 30 wk) may be screened earlier between 2-3 wk of life; (3) Where? In the NICU if admitted. In the NICU or Ophthalmic Office if discharged; and (4) How Often? With the aim of reducing the number of screening visits and restricting them to have the highest yield of detection of vision threatening ROP, the following modification to the screening schedule is suggested: Screening for ROP was initially restricted to the compliance of the below GoI guidelines. At the time of submission of this manuscript, these no longer are mandatory, but are included here for historical importance (Table 1).

CURRENT PREFERRED GUIDELINES-COMPLIANT WITH EXISTING RULES ON SOCIAL DISTANCING

Mother's with their infants waiting for screening must maintain social distance while undergoing dilatation, screening or counseling.

Mother must place the infant on a designated cot with a plastic/polythene sheet/large newspaper, uncovers the face of the infant and step away more than 6 feet. The screener walks to the baby and screens (using indirect ophthalmoscopy or a retinal camera).

Do not screen if the baby has conjunctivitis. ROP screening can be deferred until the infection is settled.

The assistant or nurse (wearing face mask) may handle the head only if needed during the screening.

After screening, screener must step back more than 6 feet. The mother then comes forward and picks up the baby and the ROP card with the findings documented.

The newspaper if used must be disposed in a yellow bin. The plastic/polythene sheet must be replaced or sanitized with an alcohol based sanitizer with a composition of, or similar to, a solution of liquid mixture of 1-Propanol and 2-Propanol (*e.g*. Sterillium or Bacillocid) before the next baby is screened.

Counseling the parents/other NICU staff must be done at a distance of 6 feet or more.

The designated cot must be sanitized using the above mentioned sanitizer. Other surfaces that may have been touched/handled by the physician/team/parent/must also be sanitized before the procedure is repeated for the next baby.

If an infant speculum is used during screening it should not be repeated unless sterilized before being re-used.

Eye drops used for dilating must be used carefully without touching the eye or eyelid and must be discarded at the end of the day or session.

The lens used for screening (20D or 28D) must be washed with water and soap and the rim should be cleaned with alcohol swabs. When a wide-field ROP camera is used, the lens tip should be cleaned with disposable alcohol swabs between each case.

Wherever possible, Personal Prophylaxis Equipment prescribed by the Indian Council of Medical Research must be used. The minimum protection that must be used by all members of the screening team are: Facial mask (preferably N95 grade), Head Cap, Eye protective glasses, Sterile gloves. However, these guidelines are constantly changing and the most updated recommendations must be followed.

Between each patient, hands must be washed and an alcohol based sanitizer as mentioned above must be used and allowed to dry before handling the patient.

The vehicle used for transporting the screening equipment are required to be sanitized every day before and after the screening sessions.

Tele-medicine must be encouraged. Tele-medicine platforms have been shown to be useful even in pre-COVID times[5,7].

To reduce the number of screening sessions, attempt must be made to pool infants of one district(s), region or center to maximize the efforts of the screening team.

Table 1 Mandatory questions that were required at the start of the pandemic in 2020

No.	Before screening, as the following 4 questions: (as *per* Govt guidelines in 2020)
1	International travel in last 4 wk
2	In quarantine period? (See stamp on hand or arm)
3	In isolation as some in family was COVID-19 positive or had contact with COVID positive patient
4	Fever, cough, cold

If yes to any of these 4, the parent/guardian must not enter the hospital and screening will not be performed. These are applicable to the physician, care giver, screening team and hospital staff as well fever is also checked at entry point with a non-contact thermometer (false negative if anti pyretic is taken).

Table 2 Suggested follow-up schedule for retinopathy of prematurity during the coronavirus disease 2019 pandemic

Finding in either eye with respect to zone	Next follow up	Comment
Immature retina in zone 3 and zone 2 anterior	3-4 wk or more	If the PMA is less than 34 wk/< 1500 grams/sick and admitted infant, consider a closer follow-up
Zone 3 and Zone 2 anterior disease	3-4 wk	Spontaneously regressing ROP can be watched
Zone 2 Posterior disease	2 wk	Unless associated with treatment requiring features (see below)
Zone 1 disease	1 wk or treat	Have a low threshold for treatment
Pre-plus	Consider early treatment or early follow-up if pupil does not dilate well and media is not clear	Individualize for each case based on the tempo of disease and PMA
Pre-plus	With good pupillary dilatation and clear media and other low risk features	Can delay the next screening by an additional 1 wk from the current guidelines

PMA: Post menstrual age; ROP: Retinopathy of prematurity.

Outreach specialists must be implored to take on a larger role to perform screening in centers that are in their proximity. Image based documentation and additional opinion from senior specialists must be encouraged.

Follow-up during ROP screening

Follow up visits are an integral part of ROP screening. On the average each infant requires 3-5 screening visits before the retinae are mature or the baby requires treatment. During the pandemic, the attempt was to reduce the number of follow-up visits without jeopardizing the ocular condition. The aim was to ensure that the most critical disease would not be missed and would be picked up at the appropriate time to avoid delayed treatment and is summarized in Table 2.

TREATMENT FOR ROP

The gold standard for ROP treatment is laser photoablation. Anti-Vascular endothelial growth factors injected intravitreally are also used in certain cases. The impact of delayed ROP screening and treatment has been reported from a tertiary care center more recently[8]. The aim of these guidelines was and are to prevent such a situation by optimizing the timing and modality of treatment and is summarized in Table 3.

Post treatment follow-up suggestions

Follow-up after treatment can be done by outreach specialists wherever feasible or by the treating physician's team if the former is not possible. The frequency of subsequent visits can be reduced and must be decided on case-to-case basis. Post intravitreal injection cases can be reviewed SOS/less frequently as normally followed in the initial phase. Recurrences can be addressed during the follow-up after the lock-down phase where possible.

Table 3 Suggested treatment guidelines for retinopathy of prematurity during the coronavirus disease 2019 pandemic

Disease	Comment
Type 1 ROP (ETROP)[9]	Treat as soon as you possible, preferably on the day that screening was done. Laser recommended
AROP[10]	Treat as soon as possible. Laser if disease is amenable. Intravitreal injections can be used, but caution to be exercised since follow-up may be a critical issue with travel restrictions for the family
Less than Type 1 ROP. Stage 2 with pre plus, stage 3 with no or early plus, high risk for APROP (but not yet full fledged), borderline Zone 1 disease/poor pupil dilatation, unclear media with pre-plus	Given the difficulty to closely follow-up consider treatment a 'little earlier' than classical Type 1 ROP
Stage 4A and 4B ROP[10]	Surgery must be performed as soon as treating ROP specialist feels it is required with adequate precautions taken while providing anesthesia
Stage 5 ROP[10]	Surgery is not urgent. Case-to-case based decision must be considered

ROP: Retinopathy of prematurity; AROP: Aggressive retinopathy of prematurity.

CONCLUSION

ROP is considered a relative emergency in Ophthalmology and as ROP specialists we understand our duty and responsibility towards mitigating the risk of blindness in infants who are at risk of this disease.

However, these are not normal times. In this unprecedented time, it is imperative that we also do everything possible to minimize the risk of COVID-19 (Corona Virus) transmission to our patients and our staff while simultaneously engaging in treating and preventing vision loss in our babies.

These guidelines are not designed to be ideal. In a restrictive time that the country is facing due to the *force de majeur* condition that we have encountered, it is important to understand that 'in good faith' and 'to the best of our ability' should be the driving dictum of the ROP care. Our aim should be to reduce and mitigate blindness without risking the lives of our patients and our health care givers.

FOOTNOTES

Author contributions: All authors read and approved the final manuscript.

Conflict-of-interest statement: No conflict-of-interest for any author.

Country/Territory of origin: India

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S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

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World Journal of Clinical Pediatrics

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World J Clin Pediatr 2022 May 9; 11(3): 221-238

DOI: 10.5409/wjcp.v11.i3.221

ISSN 2219-2808 (online)

REVIEW

Advances in pediatric non-alcoholic fatty liver disease: From genetics to lipidomics

Simona Riccio, Rosa Melone, Caterina Vitulano, Pierfrancesco Guida, Ivan Maddaluno, Stefano Guarino, Pierluigi Marzuillo, Emanuele Miraglia del Giudice, Anna Di Sessa

Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Zhou J, Singapore

Received: June 30, 2021
Peer-review started: June 30, 2021
First decision: July 30, 2021
Revised: August 5, 2021
Accepted: April 2, 2022
Article in press: April 2, 2022
Published online: May 9, 2022

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Abstract

As a result of the obesity epidemic, non-alcoholic fatty liver disease (NAFLD) represents a global medical concern in childhood with a closely related increased cardiometabolic risk. Knowledge on NAFLD pathophysiology has been largely expanded over the last decades. Besides the well-known key NAFLD genes (including the I148M variant of the *PNPLA3* gene, the E167K allele of the *TM6SF2*, the *GCKR* gene, the *MBOAT7-TMC4* rs641738 variant, and the rs72613567:TA variant in the *HSD17B13* gene), an intriguing pathogenic role has also been demonstrated for the gut microbiota. More interestingly, evidence has added new factors involved in the "multiple hits" theory. In particular, omics determinants have been highlighted as potential innovative markers for NAFLD diagnosis and treatment. In fact, different branches of omics including metabolomics, lipidomics (in particular sphingolipids and ceramides), transcriptomics (including micro RNAs), epigenomics (such as DNA methylation), proteomics, and glycomics represent the most attractive pathogenic elements in NAFLD development, by providing insightful perspectives in this field. In this perspective, we aimed to provide a comprehensive overview of NAFLD pathophysiology in children, from the oldest pathogenic elements (including genetics) to the newest intriguing perspectives (such as omics branches).

Key Words: Fatty; Liver; Genetics; Lipidomics; Pediatric

Core Tip: A large body of evidence supported a complex non-alcoholic fatty liver disease (NAFLD) physiopathology with several factors involved in this tangled puzzle. Considering the cardiometabolic burden of NAFLD even in childhood, a better knowledge of NAFLD physiopathology is fundamental for novel therapeutic strategies.

Citation: Riccio S, Melone R, Vitulano C, Guida P, Maddaluno I, Guarino S, Marzuillo P, Miraglia del Giudice E, Di Sessa A. Advances in pediatric non-alcoholic fatty liver disease: From genetics to lipidomics. *World J Clin Pediatr* 2022; 11(3): 221-238
URL: https://www.wjgnet.com/2219-2808/full/v11/i3/221.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i3.221

INTRODUCTION

Due to the increasing rate in pediatric obesity worldwide, non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease in childhood[1,2]. Current pediatric estimates report a prevalence of 3%-10% in the general population, while a dramatic increase (up to 50%) has been observed in children and adolescents with obesity[2]. Owing to its strong relationship with the metabolic syndrome (MetS) and insulin resistance (IR), both metabolic and cardiovascular risks are increased in children with NAFLD[2-4].

Hepatic fat accumulation represents the hallmark of the disease, that includes a wide spectrum of progressive forms ranging from simple steatosis through non-alcoholic steatohepatitis (NASH) to fibrosis and cirrhosis[5]. Lipolysis of adipose tissue and *de novo* hepatic lipogenesis are the main biological pathogenic processes contributing to fatty liver and IR[3,6]. Taken together, they result in an increased flux of free fatty acids to the liver and skeletal muscle that might activate lipotoxic pathways responsible for more progressive forms of hepatocellular injury. Interestingly, recent studies have highlighted not only the role of lipotoxicity but also of fatty acid composition as central players in NAFLD[7-9].

Pathophysiological hypotheses of NAFLD have been resumed in the "multiple hits" theory, by assuming the role of genetics, microbial, metabolic, and environmental factors through a complex interplay[1,2,10-12].

Key genetic factors for NAFLD are represented by the I148M variant of the *PNPLA3* gene[13], the E167K allele of the *TM6SF2*[14,15], the *MBOAT7-TMC4* rs641738 variant[16], and the rs72613567:TA variant in the *HSD17B13* gene[17] (Table 1).

Recently, advances in the understanding of NAFLD pathogenesis have reported the role of specific lipid classes (in particular sphingolipids and ceramides) and their correlation also with IR, by underscoring the strength of the tangled link between NAFLD and IR[9,18-21].

For this reason, we aimed to provide a comprehensive overview from the oldest to the newest pathophysiological evidence on pediatric NAFLD.

NAFLD PATHOGENESIS: THE "MULTIPLE HITS" THEORY

One of the most recurrent questions regarding NAFLD concerns the potential progression to more severe forms in certain subjects. This seems to be relevant as hepatic inflammation or fibrosis determine the long-term prognosis of the disease, while simple steatosis does not seem to worsen the outcome[22,23], although some studies would seem to weaken this assumption[24,25].

In an attempt to explain NAFLD pathogenesis, Day *et al*[26] first proposed the ''two hit'' model theory, suggesting that after a first hit (*i.e.*, hepatic steatosis), another hit (*e.g.*, gut-derived endotoxin) contributed to NASH development. Later, a more complex model called the "multiple parallel hits model"[23] in which multiple factors (including genetics, obesity, insulin resistance, metabolic and environmental determinants) act together to induce NAFLD development and progression in genetically predisposed or high-risk individuals was proposed. In particular, increased lipid storage, lipogenesis, and adipokine synthesis in adipose and liver tissue, may act as stress signals for the endoplasmic reticulum (ER) with subsequent hepatocellular damage[27]. In addition, certain genes (such as *PNPLA3, TM6SF2, GCKR, MBOAT7*, and *HSD17B13*) have been strongly related to NAFLD susceptibility.

Genetics

PNPLA3: The *PNPLA3* gene, discovered by Hobbs and colleagues in 2008, has been largely accepted as the most important genetic determinant in NAFLD development. *PNPLA3* is located on chromosome 22

Table 1 Main genes and changes in methylation found in human epigenomics studies in non-alcoholic fatty liver disease

Gene	Changes	Methods	Ref.
FGFR2	Hypomethylation	Bisulfite pyrosequencing and liver biopsy	Zhang *et al*[112]
MAT1A	Hypomethylation	Bisulfite pyrosequencing and liver biopsy	Zhang *et al*[112]
CASP1	Hypomethylation	Bisulfite pyrosequencing and liver biopsy	Zhang *et al*[108]
MTND6	Hypomethylation	Methylation-specific PCR and liver biopsy	Pirola *et al*[109]
PARVB	Hypomethylation	Targeted-bisulfite sequencing and liver biopsy	Kitamoto *et al*[111]
PNPLA3	Hypomethylation	Targeted-bisulfite sequencing and liver biopsy	Kitamoto *et al*[111]
PPARα	Hypomethylation	Bisulfite pyrosequencing and liver biopsy	Zeybel *et al*[112]
TGFβ1	Hypomethylation	Bisulfite pyrosequencing and liver biopsy	Zeybel *et al*[112]
Collagen 1A1	Hypomethylation	Bisulfite pyrosequencing and liver biopsy	Zeybel *et al*[112]
PDGFα	Hypomethylation	Bisulfite pyrosequencing and liver biopsy	Zeybel *et al*[112]
PPARGC1A	Hypomethylation	Methylation-specific PCR and liver biopsy	Sookoian *et al*[113]
cg08309687 (LINC00649)	Hypomethylation	Illumina BeadChip for array analyses	Ma *et al*[114]
NPC1L1	Methylation	Illumina human methylation 450 Beadchip and liver biopsy	Mwinyi *et al*[116]
STARD	Methylation	Illumina human methylation 450 Beadchip and liver biopsy	Mwinyi *et al*[116]
GRHL	Methylation	Illumina human methylation 450 Beadchip and liver biopsy	Mwinyi *et al*[116]

PCR: Polymerase chain reaction.

and belongs to the patatin-like phospholipase family. Its expression seems to be influenced by several factors, including diet, obesity, insulin and glucose levels, and gene mutation[28]. *PNPLA3* encodes for a protein called adiponutrin, an enzyme found in liver and adipose tissue that appears to confer susceptibility to increased liver fat levels and liver inflammation[29]. The discovery of *PNPLA3* has brought new insights into the understanding of fatty liver, specifically lipid remodeling in intracellular droplets has been identified as a common mechanism underlying disease progression independent of environmental triggers. In particular, *PNPLA3* is involved in the remodeling of triglycerides, phospholipids, and retinyl ester release, acting as a lipase on lipid droplets[30]. Adiponutrin is an enzyme with retinyl-palmitate lipase function that, in response to insulin, has been shown to be responsible for the release of retinol from lipid droplets in hepatic stellate cells *in vitro* and *ex vivo*[31]. It is induced by diet and IR[32] and exhibits lipolytic activity on triglycerides[33].

Several studies have investigated the major pathogenic role of the *PNPLA3* rs738409 (*PNPLA3* I148M) single nucleotide polymorphism (SNP) in NAFLD development. It is a non-synonymous variant in which there is a cytosine to guanosine change leading to an amino acid substitution of isoleucine to methionine at amino acid position 148 of the coding sequence, in the active site of the enzyme (I148M). This amino acid substitution affects the function of the enzyme (loss of-function), leading to intrahepatic triglyceride accumulation and consequent development of microvesicular steatosis. On the other hand, adiponutrin might exhibit a gain of lipogenic function, which could further lead to hepatic fatty acid accumulation[34]. The I148M variant, due to the altered enzymatic activity, determines an altered lipid remodeling, with accumulation of polyunsaturated fatty acids in diacylglycerol and triglycerides, and a parallel depletion in phospholipids[30]. Several studies have reported that the *PNPLA3* SNP resulted in decreased retinol metabolism and decreased hepatic protein levels of retinol dehydrogenase 16, which correlate with fibrosis severity[31].

There is strong evidence in the literature for an association between the *PNPLA3* 148M allele and NAFLD in both adults and children. In 2008, Romeo *et al*[29] first reported the association between the *PNPLA3* gene polymorphism (rs738409C/G) and NAFLD in a multiethnic cohort of Hispanic, African American, and European American adults.

Similarly, a large body of evidence supported the role of this gene in NAFLD development in children. Santoro *et al*[35], in a multiethnic group of 85 obese youths with magnetic resonance imaging (MRI)-detected steatosis, demonstrated that the prevalence of the G allele was higher in subjects with hepatic steatosis. Another study investigating 1048 obese Italian children, reported that children carrying the 148M allele showed higher aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, in particular homozygous 148M carriers with a high level of abdominal fat (expressed as Waist/Height ratio greater than 0.62) had a higher odds ratio (OR) for developing pathological ALT. Thus, it was observed for the first time that the extent of *PNPLA3* association with liver enzymes was determined by the amount of abdominal fat[36].

Romeo *et al*[37], in a 2010 study of 475 obese/overweight children and adolescents with steatosis evaluated by liver ultrasound, reported that the I148M variant of the *PNPLA3* gene was associated with increased ALT/AST levels in obese children and adolescents, suggesting that it conferred a genetic susceptibility to liver damage at an early age.

In addition, it has been demonstrated that the frequency of the *PNPLA3* risk allele rs738409 was lower in African Americans, by suggesting some protection from hepatic steatosis in obese African American youths[38]. In a 2018 study, Hudert *et al*[39] in a cohort of Berlin adolescents aged 10-17 years with NAFLD observed that the *PNPLA3* rs 73844078G variant was significantly associated with the severity of steatosis, with an increased risk of progression to fibrosis.

The association between *PNPLA3* gene and the other major genetic variants of NAFLD was also evaluated. Viitasalo *et al*[40] demonstrated higher serum ALT levels in children carrying the risk alleles for the polymorphisms *PNPLA3, MBOAT7* and *TM6SF2*. Grandone *et al*[15] reported that homozygous subjects for the PNPLA3 148M allele carrying the rare variant of TM6SF2 showed an OR of 12.2 (confidence interval 3.8-39.6, $P = 0.000001$) to have hypertransaminasemia compared with the remaining patients. Of interest, an Italian pediatric study also confirmed the combined effect of the 3 major risk variants (*PNPLA3, TM6F2* and *MBOAT7*) on NAFLD risk[16].

Besides, the interaction of the *PNPLA3* 148M allele with environmental risk factors for NAFLD such as obesity, nutrients (including carbohydrate and polyunsaturated fatty acids), physical activity, and sedentary behaviors have been demonstrated in children with NAFLD[41-45]. Dai *et al*[28], in a meta-analysis, reported a strong influence of the *PNPLA3* rs738409 polymorphism not only on fatty liver but also on histological damage.

More recently, compelling evidence has also supported an intriguing role of this gene in reducing the estimated glomerular filtration rate independently of common renal and metabolic factors both in adults and children[46-49]. This gene seems to promote both fibrogenesis and glomerulosclerosis through the activation of renal pericytes in which the 148M allele is highly expressed[47,48].

Considering its detrimental effect on renal function in childhood[46-48], these findings demonstrated that the *PNPLA3* gene acts not only as one of the major genetic player in NAFLD development but also as a harmful factor beyond the liver[46-48].

***GCKR*:** Several studies reported that variations at the *GCKR* gene locus are associated with NAFLD and appear to influence hepatic fat accumulation. The GCKR protein has an inhibitory action on the activity of the enzyme glucokinase that regulates the hepatic storage and disposal of glucose. In particular, *GCKR* forms an inactive complex with the enzyme glucokinase and transports it from the cytoplasm to the nucleus, thus controlling both activity and intracellular localization of this key enzyme of glucose metabolism[49].

Fructose-6-phosphate (F6P) enhances GCKR-mediated inhibition. By controlling glucose influx into hepatocytes, *GCKR* regulates *de novo* lipogenesis. The mechanism responsible for liver injury is probably due to the lack of inhibition of glucokinase enzymatic activity by F6P and consequently uncontrolled lipogenesis[50].

GCKR gene polymorphisms (rs780094 and rs1260326) have been identified that appear to be important in the pathogenesis of NAFLD. In particular, Beer *et al*[51] and Valenti *et al*[52] reported that in the association with NAFLD and consequently in the accumulation of hepatic fat, the common missense loss-of-function *GCKR* mutation (rs1260326 C>T) encoding for the P446L protein variant plays an important pathogenic role. The P446L variant blocks the inhibitory activity of GCKR on the enzyme glucokinase, resulting in a steady increase in hepatic glucokinase and glucose uptake by the liver. Hepatic glycolysis associated with the minor allele P446L results in lower levels of both glucose and insulin, but leads to increased levels of malonyl-CoA which in turn blocks fatty acid oxidation through inhibition of carnitine-palmytoyltransferase-1 and acts as a substrate for lipogenesis, thus promoting hepatic fat accumulation[53]. The *GCKR* rs780094 C>T variant has been found to be associated with increased intrahepatic fat accumulation and progressive forms of NAFLD[54,55].

A pediatric study involving 70 obese adolescents demonstrated that the *GCKR* rs780094 C>T variant was associated with NAFLD and decreased levels of *GCKR* protein, while the *GCKR* rs780094C>T and rs1260326C>T variants were associated with fibrosis and decreased levels of GCKR protein[39]. Lin *et al*[56], in a study examining 797 obese Taiwanese children, reported that the *GCKR* rs780094T variant was associated with an increased risk of NAFLD, by further demonstrating that the *GCKR* and *PNPLA3* variants were common NAFLD risk genetic factors in obese individuals. In fact, several studies have also reported a combined effect of the *PNPLA3* and *GCKR* SNPs as NAFLD risk polymorphisms. In particular, Santoro *et al*[57] in a study of 455 obese children and adolescents reported that the *GCKR* rs1260326 variant was associated with hepatic fat accumulation along with large levels of very-low-density lipoprotein (VLDL) and triglycerides, further demonstrating that *GCKR* and *PNPLA3* synergistically act to convey susceptibility to fatty liver in obese youths.

More recent studies confirmed the strong association of the three major genetic variants such as *TM6SF2* rs58542926, *PNPLA3*rs738409, and *GCKR* rs1260326 with NAFLD in obese children and adolescents[58].

***TM6SF2*:** *TM6SF2* is responsible for the regulation of lipid metabolism in the liver[59]. In particular,

TM6SF2 gene contributes to the secretion of VLDL from the liver[60]. As suggested by recent evidence [61], *TM6SF2* is a polytopic membrane protein acting as a lipid transporter. It is predominantly expressed in the liver, small intestine, and kidney. *TM6SF2* encodes a 351 amino acid protein with 7-10 predicted transmembrane domains[60]. Sliz *et al*[62] reported an association of the *TM6SF2* rs58542926-T allele with lower-risk lipoprotein lipid profile and lower levels of glycerol and glycoprotein acetylation. Specifically, the authors reported that the *TM6SF2* variant was associated with lower concentrations of all lipoprotein particle subclasses [including VLDL and low-density lipoprotein (LDL)]. In addition, there was an inverse association between this variant and total serum triglycerides and triglycerides in all lipoprotein subclasses, including high-density lipoprotein (HDL) subclasses. Finally, the *TM6SF2* rs58542926-T allele did not appear to affect apolipoprotein A-I concentration, whereas it was associated with lower apolipoprotein B concentration. Furthermore, it was also found to impair the secretory pathway leading to hepatic lipid accumulation and reduced levels of circulating lipids and lipoproteins.

In the last few years, a single nucleotide rs58542926 C>T polymorphism giving rise to the E167K *TM6SF2* variant was noted in the complex puzzle of NAFLD pathophysiology[34]. It was associated with increased liver fat content, NASH, advanced liver fibrosis, and cirrhosis[63]. This variant is characterized by an adenine-guanine substitution in nucleotide 499 that replaces glutamate at residue 167 with lysine (c.499A > G; p.Glu167Lys) leading to a loss of function in hepatic secretion of VLDL[61].

Another study on two large histologically characterized adult cohorts (including steatosis, steatohepatitis, fibrosis and cirrhosis) reported an association of the *TM6SF2* gene with advanced liver fibrosis, regardless of the *PNPLA3* genotype presence[64]. This association was also independently validated in another large European cohort[65].

Thus, *TM6SF2* might be considered as a regulator of liver fat metabolism with the opposite effects on triglyceride-rich lipoprotein secretion and hepatic lipid droplet content[34].

Chen *et al*[59] in a recent meta-analysis, on associations of TM6SF2 polymorphisms with chronic liver disease, suggested that rs58542926 polymorphism may be significantly associated with chronic liver disease in both Asians and Caucasians. In addition, Holmen *et al*[66] showed in a longitudinal adult Norwegian study an association of the E167K TM6SF2 variant with lower total cholesterol levels resulting in a reduced risk of myocardial infarction. Accordingly, Dongiovanni *et al*[65] showed an effect of this polymorphism on reducing the risk of carotid atherosclerosis in adults.

The effect of this polymorphism on ALT and cholesterol levels has also been confirmed in children and adolescents. Grandone *et al*[15] demonstrated in a cohort of 1010 obese Caucasian children and adolescents that the TM6SF2 167K allele in carriers was associated with hepatic steatosis, higher ALT levels and lower total cholesterol, LDL-cholesterol, triglycerides and non-high density lipoproteins. In addition, subjects homozygous for the *PNPLA3* 148M allele carrying the rare variant of *TM6SF2* showed an OR of 12.2 for presenting hypertransaminasemia compared with the remaining patients. Thus, the effect of *PNPLA3* and *TM6SF2* alleles appeared to be additive in determining pediatric NAFLD. As previously demonstrated in adults, the authors found that the TMS6SF2 E167K variant predisposed to NAFLD in obese children, with a relevant beneficial effect on cardiovascular risk[15].

It is noteworthy that recent data also showed a protective effect of the *TM6SF2* gene on renal function both in adults and children through the reduction of lipotoxicity[47,67].

In conclusion, the discovery of the E167K variant adds another piece not only in the complex pathophysiology of NAFLD but also in the larger context of NAFLD-related cardiometabolic risk.

***MBOAT7*:** The pathogenic role of this gene in NAFLD susceptibility has been largely studied both in adults and children. Findings demonstrated its effect in increasing not only the risk (and the severity) of NAFLD but also of other chronic liver diseases (*e.g.* hepatitis B and C virus-related). *MBOAT7* encodes lysophosphatidylinositol acyltransferase, involved in the inflammation cascade through the regulation of arachidonic acid levels and leukotriene synthesis in neutrophils. A combined effect of this gene with the major NAFLD risk polymorphisms (such as *PNPLA3* and *TM6SF2*) has also been highlighted in adult and pediatric studies[16]. Similar to renal effects observed for *PNPLA3* and *TM6SF2*, a role for this gene in kidney dysfunction has also been demonstrated[47].

***HSD17B13*:** The 17β-hydroxysteroid dehydrogenases (HSD17Bs) encompasses a large family of 15 members involved in various metabolic processes such as the metabolism of steroid hormones, cholesterol, fatty acids, and bile acids[68]. In 2008, Horiguchi identified *HSD17B13* as a novel lipid droplet (LD) associated protein. The human *HSD17B13* gene is located on chromosome 4 (4q22.1) and its expression is highly restricted to the liver, particularly in hepatocytes[69]. The human *HSD17B13* gene encodes a 300 amino acid protein, hydroxyl-steroid 17-beta dehydrogenase 13, a liver-specific LD-associated protein which is localized to lipid droplets[70].

To date, the physiological function of *HSD17B13* remains largely unclear. *HSD17B13* appears to have a role in estradiol metabolism and enzymatic activity against bioactive lipid mediators, such as leukotriene B4, that are involved in lipid-mediated inflammation[71].

In a 2019 study, Ma *et al*[72] reported that HSD17B13 exerts retinol dehydrogenase activity *in vitro*, which is closely linked to lipid droplets. Indeed, it was observed that *HSD17B13* catalyzes the oxidation of retinol to retinaldehyde, the rate-limiting step in all-trans retinoic acid biosynthesis.

The fact that *HSD17B13* is highly abundant in the liver and selectively expressed on the lipid droplet surface suggests a potential critical effect in lipid droplet function, as supported by growing data demonstrating the key role of the *HSD17B13* gene in hepatic lipid homeostasis and NAFLD pathogenesis[73].

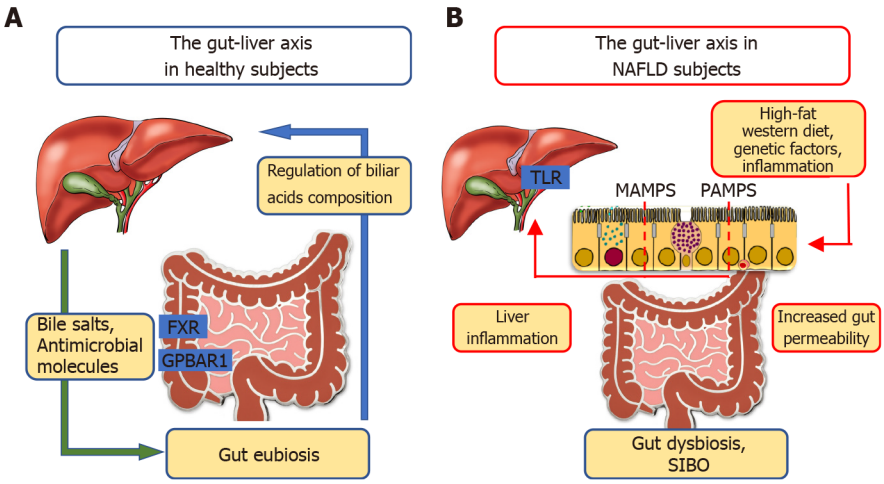
In contrast, inactivating variants in the *HSD17B13* gene have recently been linked with a reduced risk of chronic liver disease in several studies[63]. In 2018, Abul-Husn *et al*[71] reported that a loss-of-function variation in the *HSD17B13* (rs72613567:TA) gene resulting in a truncated protein confers protection against chronic liver damage and attenuates the progression of NAFLD and alcoholic liver disease (ALD) in European Americans through reduced enzymatic activity against several proinflammatory lipid species. Sookoian *et al*[74] in an exome-wide association study, confirmed that the *HSD17B13* rs72613567 variant had an influence on the susceptibility and histological severity of NAFLD. Furthermore, Pirola *et al*[75] observed a lower risk of progressive NASH in subjects carrying the rs72613567:TA variant compared to non-carriers. However, the exact role of *HSD17B13* in the NAFLD pathophysiology remains largely uncharacterized. Recently, interesting studies on the inactivation of *HSD17B13* in mice and the identification of an enzymatic active site that metabolizes retinol have been reported[76,77], but pathophysiological evidence on human models is still limited[74,78]. The rs72613567: TA *HSD17B13* variant seems to affect liver by modulating hepatic retinol metabolism and by reducing stellate cell activity[78]. Another study, examining a large adult population, reported a protective role of this variant against various liver diseases such as cirrhosis, and hepatocellular carcinoma (HCC). In particular, *HSD17B13* rs72613567 was associated with reduced inflammation and fibrosis, and milder disease severity of NAFLD. Thus, *HSD17B13* rs72613567 represents an important protective factor in distinct liver diseases (including ALD, cirrhosis, and HCC) and seems to be associated with milder histological progression of NAFLD[79,80]. In 2019, Yang *et al*[81] in a multicenter European study of a total of 3315 patients with or without HCC but with chronic liver disease, reported that the *HSD17B13* loss-of-function variant rs72613567 is protective of HCC development in patients with ALD. Taken together, these findings suggested the potential therapeutic role of the *HSD17B13* inhibition[79] in patients at high risk for liver diseases. The rs72613567 variant also appears to interact with PNPLA3 I148M through the additional *HSD17B13* TA alleles that reduce the effect of the additional *PNPLA3* I148M alleles on serum ALT levels. It also mitigated liver damage in individuals genetically predisposed to hepatic steatosis by *PNPLA3* I148M[71]. The protective effect of the rs72613567:TA *HSD17B13* variant in reducing liver damage has also been observed in children[17]. By analyzing a large cohort of Italian obese children, carriers of the *HSD17B13* variant showed lower NAFLD risk than noncarriers. It is noteworthy that this variant was found to protect against liver damage even among patients stratified on the basis of the number of the steatogenic alleles of the three major NAFLD risk polymorphisms (such as *PNPLA3, TM6SF2,* and *MBOAT7*genes). More interestingly, recent pediatric evidence[47,48,82] showed a similar protective effect of this gene also on renal function, by supposing its role in retinol metabolism through modulation of both inflammation and fibrogenesis. Another variant (rs143404524) in the *HSD17B13* gene, resulting in a truncated protein has also been associated with a reduced risk of chronic liver disease in the adult population[83]. Finally, it has also been demonstrated that the rs62305723 variant of the *HSD17B13* gene, a missense variant that confers loss of enzyme activity was associated with decreased steatohepatitis[72]. In conclusion, the *HSD17B13* gene represents a well-known genetic factor with a protective role against liver damage both in adults and children[68] that might be considered an important pharmacological target for NAFLD treatment [17,84].

NAFLD AND THE "GUT-LIVER AXIS"

Recently, compelling evidence has supported the close and interdependent relationship between the liver and gut axis in the pathogenesis of numerous chronic liver diseases such as chronic hepatitis B and C, ALD, NAFLD, NASH, development of liver cirrhosis, and HCC (Figure 1).

Bäckhed *et al*[85] for the first time described the role of gut microbiota in the context of NAFLD and obesity, taking part in the processes of absorption and storage of energy but also in the production of triglycerides, responsible for the infiltration of hepatocytes.

Crosstalk between the liver and gut occurs by means of the biliary tract, portal vein and systemic mediators[86]. The liver contributes to the maintenance of gut eubiosis through the transport of bile salts and antimicrobial molecules to the intestinal lumen. Conversely, the gut regulates bile acids (BAs) composition. In addition, BAs using farnesoid X receptor (FXR) in the enterocytes and G protein-coupled bile acid receptor 1 (also known as TGR5) are involved in the regulation of glucose and lipid metabolism, anti-inflammatory immune responses and host energy expenditure[87-91]. Furthermore, the gut through secretion of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide influences the pancreas in regulating both insulin and glucagon secretion[92]. Moreover, GLP-1 interaction with its receptor (also located on the hepatocytes) results in reduced hepatic fat deposition and IR. Finally, it promotes energy expenditure and peripheral utilization of triglycerides for energy production[93].



DOI:10.5409/wjcp.v11i3.221

Figure 1 The role of the gut-liver axis in non-alcoholic fatty liver disease. A: In healthy patients, the liver through the transport of bile salts and antimicrobial molecules to the intestinal lumen contributes to the maintenance of gut eubiosis. Conversely, the gut regulates bile acids (BAs) composition. BAs using farnesoid X receptor in the enterocytes and G protein-coupled bile acid receptor 1 are involved in the regulation of glucose and lipid metabolism, anti-inflammatory immune responses and host energy expenditure; B: In subjects with non-alcoholic fatty liver disease, altered gut microbial composition (dysbiosis), small intestinal bacterial overgrowth, and increased intestinal permeability (resulting from different factors including high-fat Western diet, genetic, inflammation) promote the influx of microbial-associated molecular patterns or pathogen-associated molecular patterns into the portal system reaching the liver. These molecular patterns are able to induce inflammatory responses mediated by the activation of pattern recognition receptors, like toll-like receptor, in Kupffer cells and hepatic stellate cells, leading to liver inflammation and fibrosis.

BAs synthesis is regulated by two hepatic methods: the enterohepatic circulation (with a subsequent negative feedback loop on the expression of CYP7A1) and FGF19, (derived from the activation of FXR by BAs in the ileum and has an inhibitory effect on *CYP7A1* gene[94]).

Impaired FXR-FGF19 signaling and elevated circulating BA levels were described both in children and adults with NAFLD. However, experimental therapeutic interventions targeting BA signaling with FXR agonists (obeticholic acid) have produced contradictory results[95].

Some differences were reported in the composition of gut microbiota (*i.e.* dysbiosis) in healthy controls than in subjects with simple fatty liver disease (FLD) and NASH[96]. In fact, many pediatric studies have reported a decreased gut microbiota alpha diversity, measured with the Shannon index[45, 97-99].

In 2006, Turnbaugh *et al*[100] found that the ratio of *Firmicutes* to *Bacteroidetes* increased in obese mice, suggesting a putative role for *Firmicutes* as a group of obesity-related microbiomes.

Loomba *et al*[101] in an elegant study showed that NAFLD patients exhibited more *Gram-negative* and fewer *Gram-positive bacteria* compared to healthy subjects, with an increase in *Proteobacteria* and a decrease in *Firmicutes* in more progressive NAFLD forms.

Michail *et al*[102] noted that children with NAFLD had more abundant *Gammaproteobacteria* and *Prevotella* compared to obese children without NAFLD and healthy controls. In addition, no difference in *Firmicutes* and *Bacteroidetes* or their ratio was observed between the groups.

Del Chierico *et al*[97] in a complex study with an integrated meta-omics-based approach found a significant increment of *Actinobacteria* and a decrease of *Bacteroidetes* in NAFLD patients compared to healthy controls.

Stanislawski *et al*[102] examined 107 adolescents with MRI-detected hepatic steatosis and found that *Bilophila* was positively correlated with hepatic fat fraction (HFF), while *Oscillospira* and *Bacteroides* showed different patterns in relation to HFF.

Schwimmer *et al*[99] in a prospective, observational, cross-sectional study of 87 children with biopsy-proven NAFLD and 37 obese children without NAFLD noted that a high abundance of *Prevotella copri* was associated with more severe fibrosis.

In a metagenomic study of gut microbiota by Zhao *et al*[103] conducted in 58 children and adolescents with NAFLD diagnosed by magnetic resonance spectroscopy, the authors found no significant differences in terms of alpha diversity among the study groups (NAFLD children, obese children without NAFLD and healthy controls). However, *Proteobacteria* were found to be more represented in NAFLD children than in the control group, while *Bacteroidates* (*Alistipes*) were significantly reduced.

Finally, Kravetz *et al*[45] in a cross-sectional study including 73 obese children and adolescents with and without NAFLD, in which HFF was determined by MRI, the NAFLD group showed a higher *Firmicutes* to *Bacteroidetes* ratio and lower levels of *Bacteroidetes*, *Prevotella*, *Gemmiger* and *Oscillospira*.

Altered gut microbial composition and increased intestinal permeability are linked to several factors (*e.g.* high-fat Western diet, chronic alcohol consumption, and genetic factors) and promote the influx of microbial-associated molecular patterns or pathogen-associated molecular patterns into the portal

system reaching the liver. These molecular patterns are responsible for inflammatory responses mediated by the activation of pattern recognition receptors, like Toll-like receptor, in Kupffer cells and hepatic stellate cells, leading to liver injury and fibrosis[86,104-106].

Potential gut-microbiome-targeted therapies in hepatic diseases are represented by probiotics, prebiotics, antibiotics, fecal microbial transplantation and bacteriophages, but larger validation studies are needed[107].

ROLE OF "OMICS" IN NAFLD

Epigenomics

Several authors have studied the role of epigenetic modifications in the natural history of NAFLD. The main epigenomic modification studied in NAFLD is DNA methylation.

A recent systematic review[108] included twelve studies on DNA methylation and FLD of which two assessed global DNA methylation, five assessed DNA methylation for specific candidate genes and the remaining four used the EWAS approach. The review suggested no consistent associations with FLD in the studies of global DNA methylation evaluated in hepatic tissue samples by quantifying the methyl-cytosine (5-mC) present in the genome. One of the two studies assessing global DNA methylation found mitochondrial encoded NADH dehydrogenase 6 hypermethylation in the liver of NASH patients compared to those with simple steatosis, and this methylation was significantly associated with NAFLD activity score[109]. On the other hand, another study reported that global liver methylation based on genome-wide methylation arrays was not associated with NAFLD or NASH, but NASH was associated with long-interspersed nuclear element hypomethylation compared to simple steatosis or normal liver [110]. More, studies using a candidate gene approach found that NAFLD was associated with hypomethylation at *FGFR2*, *MAT1A*, *CASP1* and *PARVB* genes and hypermethylation at *PNPLA3*[111], *PPARα*, *TGFβ1*, *Collagen 1A1* and *PDGFα* genes[112]. Furthermore, PPARGC1A methylation status was significantly associated with NAFLD[113]. The epigenome-wide DNA methylation studies reported different associations of distinct methylation compounds with NAFLD[114,115]. Finally, a single study reported the role of methylation in NAFLD in the expression of three genes (*NPC1L1*, *STARD* and *GRHL*) involved in lipoprotein particle composition[116].

A recent and interesting prospective cohort study analyzed epigenome-wide DNA methylation data of 785 newborns and 344 10-year-old children in relation to liver fat fraction (measured by MRI) at 10 years. No differential DNA methylation at age 10 years in newborns or 10-year-old children were found [117].

Despite some causative evidence, little is still known about the relationship between these changes in hepatic epigenome and their repercussion in the bloodstream. As a result, the contribution of epigenomics in the non-invasive diagnosis of NAFLD is still very limited but promising.

Transcriptomics

A growing body of data is derived from micro RNAs (miRNAs), highly conserved noncoding small RNAs, involved in gene expression modulation at the post-transcriptional level (Table 2). MiRNAs are resistant to degradation as well as to several freeze–thaw cycles, suggesting their potential role as ideal biomarkers for use in clinical practice.

Several studies highlighted the association between miR-122 and the severity of steatosis[118]. A reduced hepatic expression of miR-122 was described[119,120], whereas miR-122 levels were upregulated in serum[120].

A systematic review reported 34 miRNAs associated with FLD. Among these, miR-122, miR-34a, miR-192, miR-21 and miR-99a were associated with FLD in two or more independent studies[108].

Specifically, circulating miR-122 and miR-192 not only reflected both histological and molecular processes occurring in the liver, but have also been considered to be able to differentiate simple steatosis from NASH[121].

A cross-sectional validation study disclosed that 15 specific circulating miRNAs were significantly deregulated in prepubertal obesity, including the decreased miR-221 and miR-28 -3p, and increased concentrations in plasma of miR-486-5p, miR-486-3p, miR-142-3p, miR-130b, and miR-423-5p[122].

Can *et al*[123] showed a significant association between circulating miR-370, miR-33, miR-378, miR-27, miR-335, miR-143 and miR-758 values, and childhood obesity. Low levels of miR-335, miR-143 and miR-758, and high levels of miR-27, miR-378, miR-33 and miR-370 may have been responsible for elevated triglycerides and LDL-C levels, and a low level of HDL-C in obese subjects.

An interesting work by Cui *et al*[124] highlighted the specific role of three miRNAs, miR-486, miR-146b and miR-15b, by demonstrating their increased circulating expression in obese children and adult patients with type 2 diabetes mellitus (T2DM). In particular, miR-486 was implicated in accelerating preadipocyte proliferation and myotube glucose intolerance, miR-146b and miR-15b were engaged in the suppression of high concentration glucose-induced pancreatic insulin secretion, and they all contributed to the pathological processes of obesity and T2DM.

Table 2 Main findings of human transcriptomics studies and microRNAs in non-alcoholic fatty liver disease

Ref.	Study design	Population (*n*)	Main findings
Yamada *et al*[118]	Cross-sectional study	403 male subjects (median age 68.2 ± 10.3 yr); 48 NAFLD subjects (median age 66.2 ± 9.1 yr); 221 female patients (median age 65.5 ± 9.6 yr); 44 women with NAFLD (median age 65.0 ± 8.93 yr). Hepatic steatosis was assessed by ultrasound	Increased serum levels of miR-21, miR-34a, miR-122, and miR-451 were found in NAFLD patients
Cheung *et al*[119]	Cross-sectional study	50 patients with NASH (median age 52.5 yr) and 25 normal controls (median age 40.3 yr). NAFLD was suspected if abnormal liver enzymes or radiological evidence of a fatty liver and negative study for other common causes of liver disease and absence of clinically significant alcohol consumption	miR-34a and miR-146b were overexpressed in the liver of NASH patients, while miR-122 was underexpressed; miR-451 was not significantly different among the two groups
Pirola *et al*[120]	Case-control study	48 control patients (median age 47.8 ± 6.81 yr); 16 patients with simple steatosis (median age 51.5 ± 6.81 yr); 16 patients with NASH (median age 49.1 ± 8.6 yr). NAFLD was proven by biopsy	Increased levels of miR-122, miR-19a, miR-192, miR-19b, miR-125b, and miR-375 in serum either in SS or NASH patients were found. Reduced miR-122 levels in the liver of NASH patients were detected
Prats-Puig *et al*[122]	Cross-sectional study	10 lean children (median age 9.9 ± 1 yr), 5 obese children (median age 8.8 ± 1.8 yr)	Increased miR-486-5p, miR-486-3p, miR-142-3p, miR-130b, miR-423-5p, miR-532-5p, miR140-5p, miR-16-1, miR-222, miR-363, and miR-122; decreased miR-221, miR-28–3p, miR-125b, and miR-328 in obese children
Can *et al*[123]	Case-control study	86 non obese children (median age 14.44 ± 1.62 yr); 45 obese children (median age 14.71 ± 1.76 yr)	Reduced miR-335, miR-143, miR-758 and increased miR-27, miR-378, and miR-370 in the serum of obese children were detected
Cui *et al*[124]	Cross-sectional study	535 obese patients (median age 61.0 ± 10.4 yr); 106 OW patients (median age 59.6 ± 11.0 yr); 101 patients with T2D (median age 57.5 ± 12.2 yr); 82 with NGT (median age 49.3 ± 7.73 yr); 146 normal controls (median age 60.4 ± 11.1 yr)	miR-486, miR-146b and miR-15b were increased in the serum of obese children and T2D patients
Iacomino *et al*[125]	Cross-sectional study	189 children (median age 12.0 ± 1.6 yr) and 94 OW/Ob children (median age 12.3 ± 1.8 yr)	Increased miR-551a and miR-501-5p and reduced miR-10b-5p, miR-191-3p, miR-215-5p, and miR-874-3p levels in the serum of OW/Ob children were found

NASH: Non-alcoholic steatohepatitis; miR: MicroRNA; NAFLD: Non-alcoholic fatty liver disease; SS: Simple steatosis; T2D: Type 2 diabetes; NGT: Normal glucose tolerance controls; OW/Ob: overweight/obese.

Iacomino *et al*[125] in a pilot study (FAMILY Study) conducted in 149 overweight/obese and 159 normal weight children and adolescents demonstrated a panel of miRNAs differentially expressed in these two groups (miR-551a and miR-501-5p were upregulated; miR-10b-5p, miR-191-3p, miR-215-5p, and miR-874-3p were downregulated).

In a transcriptomic study by Sheldon *et al*[126] a new candidate marker for distinguishing steatosis from NASH was proposed, the soluble factor FCER2, produced from NOCTH2 activation in B cells, whose expression was increased in NASH patients.

Finally, in a recent study interleukin-32 was found as the most significantly upregulated transcript in advanced NAFLD and NASH, being linked to lipid accumulation and disease severity[127].

Although many studies have been investigating the role of miRNAs in the pathogenesis of NAFLD in view of their potential use as non-invasive biomarkers, results are still controversial and scarce. However, the innovative role of transcriptomics in the non-invasive diagnosis of NAFLD contributes to the new "omics" path of NAFLD.

Proteomics

To date, few studies on proteomic analysis in NAFLD have been performed, probably due to technical limitations in the correct detection and identification of proteins and to the changing quantification of blood proteins[128].

Among these proteins, the caspase-generated cytokeratin-18 (CK-18) fragments have been proposed as a noninvasive alternative biomarker of NASH. CK-18 showed a relatively good specificity for NAFLD, NASH and fibrosis but limited overall sensitivity[129].

Another protein being studied is the soluble intercellular adhesion molecule-1, with promising results also in NASH detection[130].

The mitochondrial enzyme carbamoyl-phosphate synthase 1 and the heat shock protein family A member 5 have been indicated as potential tools to stratify the different phenotypes associated with liver disease severity[131-133].

In a recent study by Malecki *et al*[134], a proteome analysis in a group of 30 children (16 with a previous NAFLD diagnosis by ultrasound) identified a total of 297 proteins. Thirty-seven distinct proteins (responsible for inflammation, stress response, and regulation of these processes) were identified. Up-regulated proteins included afamin, retinol-binding protein-4, complement components,

and hemopexin, while serum protease inhibitors, clusterin, immunoglobulin chains, and vitamin D binding protein were found in the down-regulated group[134].

Bălănescu *et al*[135] confirmed the role of the heat shock protein-90 (Hsp90) isoforms as biomarkers for NAFLD in obese and overweight children. While the Hsp90β isoform was higher, the Hsp90α isoform was lower in overweight and obese NAFLD patients.

Hence, proteomics represents one of the most challenging fields that might contribute to the development of new noninvasive targeted tools for NAFLD diagnosis and treatment. See Table 3.

Glycomics

Most of the glycomics studies in NAFLD have tried to identify glycans or glycoproteins that can serve as blood biomarkers for differentiating between NAFLD and NASH or for detection of the presence of liver fibrosis and its stage.

Changes in glycosylation represent a potential good marker of liver damage due to the hepatic production of several serum glycoproteins[136].

The findings of these studies demonstrated that higher concentrations of fucosylated, sialylated and agalactosylated glycans were observed in NAFLD and its progressive forms. Circulating sialic acid levels were also positively associated with metabolic syndrome and with NAFLD[128].

Furthermore, changes in fucosylation were observed in other inflammatory conditions, such as in chronic pancreatitis, Crohn's disease, rheumatoid arthritis and sickle cell disease[137].

Finally, hypogalactosylation (especially of IgG) was also associated with some autoimmune diseases and inflammatory pathways[138].

The first glycomic analysis in a pediatric NAFLD population was conducted by Blomme *et al*[136]. In agreement with adult findings, B cells were found to play a dominant role in the N-glycan alterations of pediatric NASH patients. Serum protein N-glycosylation patterns of 51 pediatric NAFLD patients were assessed with deoxyribonucleic acid sequencer-assisted fluorophore-assisted capillary electrophoresis and compared with histology. Analysis of the N-glycans on IgG confirmed the under-galactosylation status typical of chronic inflammatory conditions.

Metabolomics and lipidomics

To date, both metabolomics and lipidomics represent the most investigated omics branches in NAFLD with promising results for the development of new targeted strategies (Figure 2). Of interest, robust and extensive changes were observed both in the hepatic as well as in the circulating lipidome, which have led to the development of numerous diagnostic models for NAFLD and the identification of novel therapeutic targets. Many studies have reported several diagnostic models based on metabolomics, lipidomics alone or combined with other biochemical and clinical parameters for the diagnosis and staging of NAFLD.

Lipidomic studies have described specific changes in hepatic lipidome in patients with NAFLD. The hepatic concentrations of triacylglycerols, saturated fatty acids (SFAs and specifically of palmitic acid, C16:0 and stearate acid, C18:0), free cholesterol, sphingolipids, glycerophospholipids and eicosanoids increase, whereas ω-3 polyunsaturated fatty acids (PUFAs) and specialized proresolving mediators of PUFAs decrease. Monounsaturated fatty acids, lysophosphatidylcholine (LPC) and ceramide are also increased[21].

SFAs accumulation is associated with liver disease severity. They work in two different ways: on the hepatocytes stimulating proinflammatory cytokine secretion, enhancing oxidative stress, inducing apoptosis and on nonparenchymal liver cells stimulating secretion of proinflammatory and profibrotic cytokines (Kupffer cells) and induce proinflammatory M1 polarization of macrophages. Finally, SFAs stimulate the secretion of chemokines from hepatic stellate cells that recruit more macrophages in the liver[128].

LPC also stimulates ER stress, causes mitochondrial dysfunction and increases apoptosis[139]. Increased activity of the enzyme phospholipase A2 that catalyzes the formation of LPC from PC, leads to the rapid depletion of PC which affects hepatocyte membrane integrity and results in hepatocyte apoptosis, high release of lipotoxic lipids and increased inflammation. Additionally, PC deficiency reduces VLDL secretion resulting in higher intrahepatic lipid degradation and the formation of toxic intermediates[140].

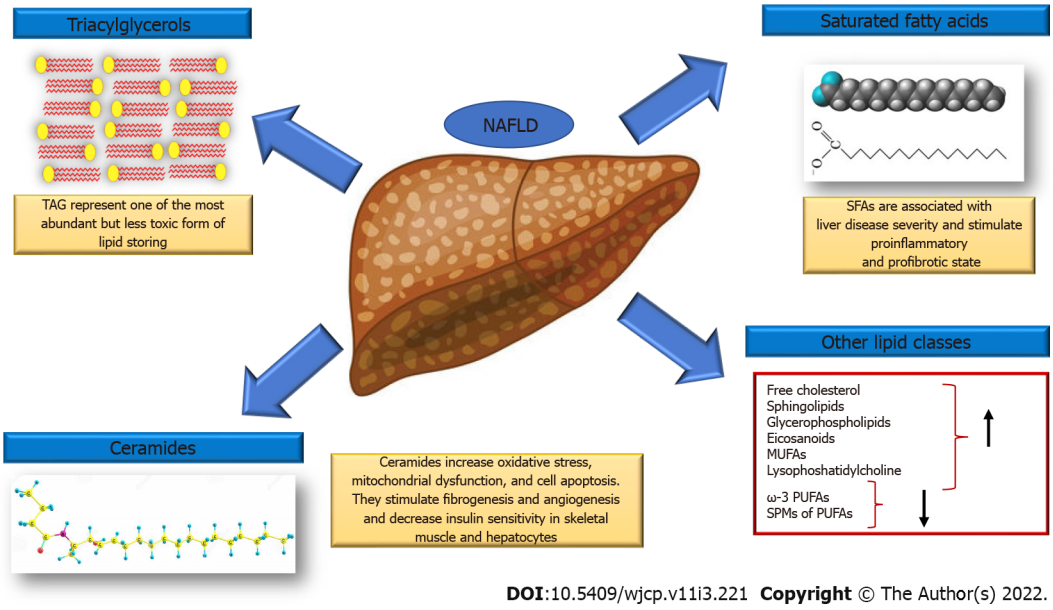
Ceramides correlate positively with hepatic disease severity[141]. These lipids have been found to decrease insulin sensitivity in skeletal muscle and hepatocytes[142] and are involved in increased oxidative stress, mitochondrial dysfunction, and cell apoptosis[142,143]. Finally, ceramide stimulates fibrogenesis and angiogenesis by increasing extracellular matrix deposition and the secretion of pro-angiogenic factors by hepatic stellate cells[144].

The attractive omics field might greatly contribute to improving not only knowledge on NAFLD pathophysiology but also its management.

Table 3 Main results of human proteomics studies in non-alcoholic fatty liver disease

Ref.	Study design	Population (*n*)	Main findings
Cusi *et al*[129]	Case-control study	300 subjects with NAFLD (median age 52 ± 1 yr) and 124 without NAFLD (median age 51 ± 1 yr). NAFLD was proven by MRS, biopsy, or US	Increased plasma CK-18 in steatosis, inflammation, and fibrosis
Sookoian *et al* [130]	Cross-sectional study	101 subjects with simple steatosis (median age 52.3 yr) and 60 NASH patients (median age 54.6 yr). NAFLD was proven by biopsy	sICAM-1 is able to differentiate between patients with simple steatosis and NASH
Rodriguez-Suarez *et al* [131]	Cross-sectional study	18 controls, 6 obese patients with NAFLD, 6 obese patients with early stage of NASH. Liver disease diagnosis was by biopsy	CPS1 could stratify different phenotypes associated with liver disease severity
Małecki *et al* [134]	Cross-sectional study	30 children (mean age 10.62 yr), 16 children with NAFLD (mean age 11.06 yr). NAFLD was proven by US	Afamin, retinol-binding protein-4, complement components, and hemopexin were upregulated; serum protease inhibitors, clusterin, immunoglobulin chains, vitamin D binding protein were down-regulated
Bălănescu *et al* [135]	Cross-sectional study	68 overweight and obese children (mean age 10 yr) and 10 healthy controls. NAFLD was proven by US or elevated alanine transaminase levels	HSP-90 isoforms could be used as NAFLD biomarkers in obese and overweight patients

NASH: Non-alcoholic steatohepatitis; miR: MicroRNA; NAFLD: Non-alcoholic fatty liver disease; MRS: Magnetic resonance spectroscopy; US: Ultrasound; CK-18: Cytokeratin-18; sICAM-1: Soluble intercellular adhesion molecule-1; CPS1: Carbamoyl-phosphate synthase 1; HSP-90: Heat shock protein-90.



DOI:10.5409/wjcp.v11i3.221

Figure 2 Main changes in hepatic lipid composition in non-alcoholic fatty liver disease. In non-alcoholic fatty liver disease subjects, hepatic concentrations of triacylglycerols, saturated fatty acids, free cholesterol, sphingolipids, glycerophospholipids and eicosanoids are increased, whereas ω-3 polyunsaturated fatty acids (PUFAs) and specialized proresolving mediators of PUFAs are decreased. Monounsaturated fatty acids, lysophosphatidylcholine and ceramide are also increased in the liver of these subjects.

CONCLUSION

Given the global relentless spread of childhood obesity, NAFLD and its cardiometabolic burden (including MetS, IR, cardiovascular disease, prediabetes, and type 2 diabetes) in childhood represent a major health challenge for clinicians[145]. Moreover, the close relationship of NAFLD with the metabolic milieu has recently been highlighted in the new definition of NAFLD as metabolic associated fatty liver disease[146,147].

To date, diet and lifestyle interventions remain the cornerstone of NAFLD treatment. Over the last few years, promising approaches have been proposed, but larger validation studies are required. In particular, omics represents the most intriguing strategy in this field, due to its potential effectiveness in preventing NAFLD as a noninvasive diagnostic and therapeutic tool.

Further novel therapeutic insights for this insidious disease might be provided only by advances in the knowledge of NAFLD pathophysiology.

FOOTNOTES

Author contributions: Riccio S and Di Sessa A wrote the manuscript; Miraglia del Giudice E, Di Sessa A, and Marzuillo P conceived the manuscript; Guarino S, Miraglia del Giudice E, Di Sessa A, and Marzuillo P supervised the manuscript drafting; Riccio S, Melone R, Vitulano C, Guida P, and Maddaluno I reviewed the literature data; Riccio S prepared the tables. Each author contributed important intellectual content during manuscript drafting or revision.

Conflict-of-interest statement: There is no conflict of interest.

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S-Editor: Zhang H
L-Editor: Webster JR
P-Editor: Zhang H

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World Journal of Clinical Pediatrics

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World J Clin Pediatr 2022 May 9; 11(3): 239-252

DOI: 10.5409/wjcp.v11.i3.239

ISSN 2219-2808 (online)

MINIREVIEWS

Management of sleep disorders among children and adolescents with neurodevelopmental disorders: A practical guide for clinicians

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Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Xiao CF, China

Received: March 23, 2021
Peer-review started: March 23, 2021
First decision: July 27, 2021
Revised: August 9, 2021
Accepted: March 25, 2022
Article in press: March 25, 2022
Published online: May 9, 2022

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Abstract

There is a complex relationship between sleep disorders and childhood neurodevelopmental, emotional, behavioral and intellectual disorders (NDEBID). NDEBID include several conditions such as attention deficit/hyperactivity disorder, autism spectrum disorder, cerebral palsy, epilepsy and learning (intellectual) disorders. Up to 75% of children and young people (CYP) with NDEBID are known to experience different types of insomnia, compared to 3% to 36% in normally developing population. Sleep disorders affect 15% to 19% of adolescents with no disability, in comparison with 26% to 36% among CYP with moderate learning disability (LD) and 44% among those with severe LD. Chronic sleep deprivation is associated with significant risks of behavioural problems, impaired cognitive development and learning abilities, poor memory, mood disorders and school problems. It also increases the risk of other health outcomes, such as obesity and metabolic consequences, significantly impacting on the wellbeing of other family members. This narrative review of the extant literature provides a brief overview of sleep physiology, aetiology, classification and prevalence of sleep disorders among CYP with NDEBIDs. It outlines various strategies for the management, including parenting training/psychoeducation, use of cognitive-behavioral strategies and pharmacotherapy. Practical management including assessment, investigations, care plan formulation and follow-up are outlined in a flow chart.

Key Words: Sleep; Emotional; Behavioural difficulties; Neurodevelopmental disorders; Pharmacotherapy; Non-pharmacologic interventions; Cognitive therapy; Melatonin; Adolescents; Psychoeducation

Core Tip: Up to 75% of children and young people with neurodevelopmental, emotional, behavioural and intellectual disorders (NDEBID) are known to experience different types of insomnia, associated with significant behavioral, emotional, cognitive and academic impairments, as well as negative impact on the wellbeing of other family members. This paper provides a brief overview of sleep physiology, aetiology, classification and prevalence of sleep disorders among children and adolescents with NDEBIDs. It outlines different strategies for the management of sleep disorders, including parenting training/psychoeducation, the use of cognitive-behavioural strategies and pharmacotherapy. Practical management including clinical assessment, investigations, care plan formulation and follow-up are outlined.

Citation: Ogundele MO, Yemula C. Management of sleep disorders among children and adolescents with neurodevelopmental disorders: A practical guide for clinicians. *World J Clin Pediatr* 2022; 11(3): 239-252
URL: https://www.wjgnet.com/2219-2808/full/v11/i3/239.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i3.239

INTRODUCTION

Sleep problems are common in children from preschool age to adolescence, especially among those who have recognizable neurodevelopmental (and related neurodisability), emotional, behavioural and intellectual disorders (NDEBID). The prevalence of sleep problems among typically developing children and adolescents ranges from 3% to 36%, while affecting up to three-quarters of children with NDEBIDs, depending on the diagnostic criteria used[1,2].

There is a complex relationship between sleep disorders and childhood NDEBID. Sleep deprivation is known to cause clinically elevated externalizing and internalizing behaviour disorders, including inattention, mood variability, disruptive and rule-breaking behaviours, and school problems[3]. It can also affect children's cognitive development and learning abilities, by exacerbating memory and concentration problems, and mood disorders[4,5]. There is clear evidence that various sleep disturbances among children and adolescents increase the risk of mental health disorders such as depression, suicidal and self-harm behaviours, as well as other psychiatric and health outcomes including obesity and metabolic disorders[6]. It can negatively impact the cardiovascular, immune and metabolic systems, including growth disorders[7].

Sleep disorders in children also significantly affect the wellbeing of other family members. Among a cohort of 156 care-givers of children aged 1.5 to 10 years with insomnia, 47% of primary caregivers had clinically significant parenting stress associated with bedtime resistance, daytime sleepiness, parent history of sleep problems, parent history of psychiatric conditions, and child externalizing behaviour[8].

Management of sleep problems is important for long-term mental health and optimization of functioning, prevention of deficits in daily functioning and for halting the progression of psychiatric pathology of affected children and young people (CYP) into adulthood[4,9]. However, healthcare professionals have insufficient training on sleep disorders[10].

This narrative literature review presents important themes identified from search of electronic databases including PubMed, PubMed Medical Central, OVID, EMBASE, PsycINFO and Cochrane databases up to October 2020, using combinations of keywords including 'melatonin', 'ASD', 'developmental disorder', 'ADHD', 'sleep disorder' and 'children'.

It provides a brief overview of the research evidence on the diagnosis and management of sleep disorders among CYP with NDEBID conditions such as attention deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), cerebral palsy (CP), epilepsy and learning (intellectual) disorders.

SLEEP PHYSIOLOGY

Definitions and classifications of sleep disorders

Various definitions of sleep disorders have been used in sleep studies in terms of age, frequency, severity, and duration of symptoms and sample populations[6]. Some studies define insomnia vaguely as parental report of difficulty falling and/or staying asleep[3]. Furthermore, there is considerable variability in children's sleep duration.

Both the 5th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[11] and the 3rd edition of the International Classification of Sleep disorders (ICSD-3)[12] are the key reference standards for the diagnosis of sleep disorders. Paediatric insomnia has been defined as "repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite age-appropriate time and opportunity for sleep and results in daytime functional impairment for the child and/or family"[6]. The ICSD-3 classification includes 6 categories (Table 1).

Why is sleep important?

Sleep is essential to refresh and rejuvenate the body and mind. An average person spends a third of their life sleeping (122 d every year). It is a good practice to emphasise the benefits of sleep to provide a positive message to children, parents, and carers. Table 2 illustrates positive effects of adequate sleep and negative consequences of insomnia.

How much sleep is ideal for children and adolescents?

There is a wide variation about sleep requirement dependent on the child's age. It is important for health professionals to discuss and provide parents/carers and children written information about sleep duration as in Table 3.

Aetiology and pathogenesis of sleep disorders

The aetiology of sleep disturbances in CYP with NDEBID is heterogeneous and often disease specific. The diagnosis and management of sleep disorders in this population are complex, and little high-quality data exist to guide a consistent approach to therapy[13]. Three main causes of insomnia are biologic, behavioural (including environmental) and psycho-medical[14]. Table 1 shows common causes and examples of sleep disorders.

Chronic sleep deprivation, insomnia, and delayed sleep phase disorder are the commonest sleep disorders in childhood[9]. Other common sleep problems in children with NDEBIDs include difficulty falling asleep, difficulty maintaining sleep, and early morning awakenings[15].

SLEEP DISORDERS AND NDEBID

What are NDEBID?

Childhood NDEBID such as ADHD, tic disorder/Tourettes syndrome, developmental delay, development coordination disorder are commonly managed by Community Child Health Paediatricians, working within integrated teams involving the education, social care and voluntary sectors[16]. Neurodisability describes a group of congenital or acquired long-term conditions that are attributed to disturbance of the brain and or neuromuscular system and create functional limitations in sensory, motor, speech, language, cognition or behaviour. The estimated prevalence of NDEBID reported in developed countries varies widely, ranging up to 15%, depending on the diverse methodologies and definitions used[17,18].

Prevalence of sleep disorders in NDEBID

Sleep disorders in ASD: ASD is an heterogenous group of neurodevelopmental disorders (NDD) caused by a combination of genetic variation with complex interactions with environmental factors.

Some studies have found that sleep disturbance is the second most common physical co-morbidity in children with ASD, with prevalence estimated to be between 33% and 81%[15,19,20]. Sleep disturbances in CYP with ASD are significantly associated with severity of autism symptoms and deterioration in daytime challenging behaviour including physical aggression, irritability, inattention, and hyperactivity [20-22].

The causes of poor sleep in CYP with ASD are multifactorial and include disturbances in neurotransmitters that promote sleep, including serotonin and melatonin, abnormal sensitization to environmental stimuli, behavioural insomnia and delayed sleep phase syndromes (DSPSs), rapid eye movement sleep behaviour disorders, decreased time in bed, increased proportion of stage 1 sleep, as well as coexisting psychiatric symptoms, such as anxiety, depression, and epilepsy[23-25]. The core behavioural deficits associated with ASD could impair the establishment of sound bedtime behaviours and routines. The parents may also struggle with arranging the sleep environment to promote sleep and conveying sleep expectations effectively, while trying to deal with multiple other priorities and stressors[15].

Recent meta-analysis of 38 published studies on various non-pharmacological strategies for management of sleep disorders among CYP with ASD has shown conclusively that no single intervention is reliably effective in managing all the wide range of sleep problems seen in this group of individuals[26]. A recent clinical guideline from the American Academy of Neurology (AAN) concluded that behavioural strategies should be offered as first-line treatment approach for sleep disturbance in CYP with autism, either alone or in combination with pharmacologic treatment with melatonin [with or without cognitive behavioural therapy (CBT)][27].

Table 1 Showing majority of sleep disorders can be grouped into 6 main categories

Category	Description		Conditions and causes, some examples
Insomnias	Inability to fall asleep or stay asleep		Environmental: Poor sleep hygiene, bedroom noise, bright light. Behavioural insomnia of childhood (sleep onset/limit setting/combined). Psychiatric, trauma and substance misuse: Anxiety, depression, OCD, PTSD, abuse or neglect, bullying, drug and substance misuse. Medical: Pain (headaches, joint pains), lung problems (asthma, cystic fibrosis), skin (eczema, allergies), neuromuscular, obesity, medication side effects
Sleep related breathing disorders	Breathing difficulties during sleep		Obstructive sleep apnoea. Central sleep apnoea
Central disorders of hypersomnolence	Excessively sleepy		Narcolepsy
Circadian rhythm sleep-wake disorders	Sleep times are out of alignment		Delayed sleep phase syndrome. Jet lag
Parasomnias	Unwanted events or experiences that occur at the time of falling asleep, sleeping or waking up	During NREM sleep	Confusional arousals. Sleep terrors. Sleep-walking
		During REM sleep	Nightmares
		Others	Enuresis
Sleep related movement disorders	Unusual body movements during sleep		Bruxism. Restless legs syndrome. Periodic limb movement disorder. Rhythmic movement disorder (head banging, body rocking)

OCD: Obsessive-compulsive disorder; PTSD: Post traumatic stress disorder; NREM: Non-rapid eye movement; REM: Rapid-eye-movement.

Table 2 Showing positive effects and negative consequences

Positive effects of adequate and good quality sleep	Negative consequences of lack of adequate and good quality sleep
Promotes growth. Strengthens immunity. Helps cell growth and body repair. Consolidates memory (https://www.sleepscotland.org/support/gateway-to-good-sleep/why-is-sleep-important/). Promotes learning and cognitive development[69]. Maintains physical health and emotional wellbeing	Increased association with excess weight gain and obesity [69]. Impairs immune function. Affects physical coordination. Affects ability to learn new information and problem solve. Affects mood and emotional regulation and increases risk of mental health problems *e.g.*, mood or anxiety disorder, suicidal ideation

Table 3 Showing National Sleep Foundation's sleep duration recommendations (https://www.sleepfoundation.org/press-release/national-sleep-foundation-recommends-new-sleep-times)

Age of the child	Recommended	May be appropriate	Not recommended
Pre-schoolers (3-5 yr)	10-13 h	8-14 h	Less than 8 h or more than 14 h
School-aged children (6-13 yr)	9-11 h	7-12 h	Less than 7 h or more than 12 h
Teenagers (14-17 yr)	8-10 h	7-11 h	Less than 7 h or more than 11 h

Sleep disorders in ADHD: ADHD affects approximately 5% of CYP worldwide[28]. The brain regions, such as dorsolateral and ventrolateral prefrontal and dorsal anterior cingulate cortices, implicated in ADHD pathophysiology, are known to be sensitive to sleep deprivation. Genetics studies have also pointed to the involvement of the catecholaminergic system in both ADHD and sleep regulation[29].

Common sleep problems affecting up to 70% of paediatric ADHD patients include behaviourally based insomnia (limit-setting disorder), bedtime resistance, latency of sleep onset, dim light melatonin onset delay, decreased duration of sleep, increased number of overnight awakenings, daytime somnolence, sleep-disordered breathing, and restless legs syndrome (RLS)/periodic limb movement disorder (PLMD)[30,31]. They may also have sleep disturbances due to co-morbid psychiatric disorders or ADHD medications such as delayed sleep onset and shortened sleep duration[32,33]. In a study of 195 children with ADHD aged 5 to 13 years, sleep problem was observed to be variable over a 12-mo period in 60% of the children and transient in most cases but it was more persistent in a sub-group (10%) of the children[34].

Table 4 Below illustrates some useful resources

Users	Resources	Free access	Website links
Parents and carers	CEREBRA-Sleep Advice service	Free access	https://cerebra.org.uk/get-advice-support/sleep-advice-service/
	Sleep for better day ahead-leaflet	Free access	https://www.qvh.nhs.uk/wp-content/uploads/2020/08/Sleep-for-a-better-day-ahead-0127.pdf
	Sleep hygiene in children and young people: Information for families-leaflet	Free access	https://media.gosh.nhs.uk/documents/Sleep_hygiene_F1851_FINAL_Jun20.pdf
	Encouraging good sleep habits in children with learning disabilities-leaflet	Free access	https://www.oxfordhealth.nhs.uk/wp-content/uploads/2014/05/Good-sleep-habits-for-children-with-Learning-Difficulties.pdf
	Sleep problems and sleep disorders in school aged children	Free access	https://www.sleephealthfoundation.org.au/sleep-problemsand-sleep-disorders-in-school-aged-children.html
	Further useful facts sheets and resources-website	Free access	https://www.sleephealthfoundation.org.au/fact-sheets.html
	Other websites	Free access	https://www.nhs.uk/live-well/sleep-and-tiredness/healthy-sleep-tips-for-children/; https://www.sleepscotland.org/
Adolescents	How to sleep well and stay healthy-A guide for teenagers. This is an interactive guide with animations, sounds and external links to useful educational video clips	Free access	https://books.apple.com/gb/book/how-to-sleep-well-and-stay-healthy-a-guide-for-teenagers/id1397176909
	Sleep tips for teenagers	Free access	https://www.nhs.uk/live-well/sleep-and-tiredness/sleep-tips-for-teenagers/
Children	Sleep poster: Interactive pdf for children and parents/carers	Free access	https://www.cambscommunityservices.nhs.uk/docs/default-source/Luton---NDD-Webpages/Sleep/sleep-poster76ddec06f4f66239b188ff0000d24525.pdf?sfvrsn=2
	I see the animals sleeping: A bedtime story-an app	Free on Google play, App store and Kindle store	http://school.sleepeducation.com/childrensapps.aspx
	The animal sleep: A bedtime book for biomes-an app	Free on Google play, App store and Kindle store	http://school.sleepeducation.com/childrensapps.aspx; https://www.youtube.com/watch?v=zLQ3bkn8Gu8

ADHD is most commonly treated using psychostimulants, with potential side-effects including sleep disorders. Use of psychostimulants may however improve some aspects of sleep in ADHD children[2].

Moderate to severe sleep problems have been associated with increasing ADHD severity and poorer child quality of life (QoL), daily functioning and caregiver mental health, increased likelihood of missed/being late for school, and the caregivers being late for work[30]. Disorders of sleeping pattern is associated with inattention, problematic behaviour, progressive psychopathology, and attenuated emotional regulation, all of which can mimic the symptoms of ADHD. It is therefore necessary for the clinician to assess for sleep problems before confirming a diagnosis of ADHD[33].

The management of sleep disorders in ADHD children include recommendation of good sleep hygiene and other behavioural interventions as the first-line treatment option[33]. There is ample evidence for the effectiveness of behavioural interventions from several studies. Sixty-seven percent of parents of children with ADHD reported complete resolution, with improved child QoL, daily functioning and parental anxiety, five months after randomization into two groups of either brief (1 session, n = 13) or extended (2-3 sessions, n = 14) behavioural sleep programme[30]. Similar findings as well as improvement of ADHD symptoms have been reported[35].

Other strategies include modifying the dose regimens, formulation, or use of alternative to stimulants such non-stimulant atomoxetine and alpha agonists guanfacine or clonidine, and melatonin[32]. Combined strategy of behaviour modification techniques with use of stimulant medication have been reported to yield sustained improvement in ADHD symptoms, sleep duration, and QoL in a randomized controlled trial (RCT) of 244 children with ADHD[36].

There is lack of robust and reliable evidence for prescribing drugs for behavioural insomnia in children with ADHD. A systematic review of 12 studies, mostly of low quality, was recently reported for the pharmacological treatment of insomnia in CYP with ADHD[37]. The strongest evidence from published literature supports the use of melatonin in reducing sleep-onset delay, but the evidence for

other medications is weaker, with reported significant advancement of sleep onset by 26.9 ± 47.8 min and advancement of dim light melatonin onset by 44.4 ± 67.9 min, when compared to placebo[33,38]. From a recent systematic review of 12 studies including RCTs and observational studies, clonidine, melatonin and L-Theanine demonstrated positive responses in sleep-onset latency and total sleep duration while zolpidem, eszopiclone and guanfacine failed to show significant efficacy when compared with placebo. Zolpidem was associated with neuropsychiatric adverse effects[37].

Sleep disorder in epilepsy and other chronic disabilities: Insomnia, especially maintenance insomnia, is widely prevalent in epilepsy and other chronic conditions. Some expert opinions and a few small studies have presented inconclusive findings suggesting that melatonin either lowers or increases seizure thresholds[39].

MANAGEMENT OF SLEEP DISORDER IN CYP WITH NDEBID

Published clinical guidelines

The American Academy of Pediatrics published a consensus document on pharmacologic management of insomnia in 2006, which focused mainly on future research recommendations[40]. The Sleep Committee of the Autism Treatment Network later developed an expert consensus practice pathway in 2012, which documented best practices for screening, identification, and treatment for sleep problems in people with autism[41].

Other recommendations and clinical guidance have been published more recently for the management of chronic insomnia in children associated with NDD in children including Autism, CP, and genetic syndromes like Rett syndrome, Angelman syndrome, Williams syndrome, and Smith-Magenis syndrome, mostly based on consensus opinions[13]. A consensus statement has been produced by multidisciplinary professional associations in Spain[7]. A clinical practice guideline has recently been published by the AAN for management of insomnia and disrupted sleep behaviour in CYP with autism [27]. An evidence-based sleep management clinical guidance and flow chart designed by the authors is included as Supplementary Material.

Clinical assessment and triage

The diagnosis of sleep disorders in CYP is essentially clinical, based on the information provided by the parents/caregivers and the child and from detailed clinical examination[7]. In view of the high prevalence of sleep problems among CYP, it has been suggested that clinicians need to ensure that questions about sleep are incorporated into their routine health assessment of children, and try to distinguish sleep disturbances from normal age-related changes[42,43].

A clear and comprehensive history that includes all the relevant family, social, academic and lifestyle information is essential to provide an accurate differential diagnosis. History should include the sleep/wake schedule, sleeping environment and bedtime routines, abnormal movements or behaviour during sleep, daytime effects of sleep deprivation, and sleep onset latency (SOL) (which need to be differentiated from delayed circadian rhythm)[1,42]. Clinical assessment should also evaluate the primary and secondary contributing factors and maladaptive behaviours related to sleep[42]. Common parameters to be documented include: (1) Sleep-onset latency; (2) Number and duration of night wakings; and (3) Sleep efficiency (total time of sleep divided by the total time in bed). Box 2 outlines common items to be included in a detailed clinical assessment in Supplementary Material.

Previously rarely reported sleep disorders among children with NDEBID such as narcolepsy and nocturnal epilepsy should be explored, as they have been identified to be commoner than previously thought[44]. Use of validated sleep problems questionnaires including BEARS screening tool and Children's Sleep Habit Questionnaire is recommended to supplement the clinical assessments.

Detailed clinical assessment should lead to formulation of a sleep disorder diagnosis or consideration of potential differential diagnosis (see Table 1) and exclude other physical explanations for insomnia including obesity, tonsillar hypertrophy, facial dysmorphism, nasal septal deviation, craniofacial abnormalities, hypotonia, chronic rhinitis or other physical illness or discomfort (for example, reflux, ear or toothache, bedwetting, constipation or eczema).

This assessment should lead to the formulation of a sleep plan with the parents or carers. A sleep plan should include specific behavioural interventions which address the identified sleep problems and help restore a regular sleep pattern. This plan needs to be reviewed regularly until a regular sleep pattern is established.

Investigations

Clinical assessment should be supplemented by sleep diary over a 2-wk period. Diagnostic tools such as validated questionnaires, sleep diary and actigraphy are essential to properly detect sleep disorders at early stages[9].

Actigraphy monitors body motion, sleep and wake patterns in individuals. It can measure the total sleep time (TST), sleep efficiency, wake after sleep onset, and SOL, help to determine sleep patterns and document response to treatment in the patient's normal sleep environment[7].

Major indications for polysomnography include strong clinical suspicion of sleep-related breathing disorder, atypical parasomnia, PLMD, clinically unconfirmed RLS or nocturnal seizures when the clinical history and conventional encephalography are inconclusive.

Differential diagnosis

Detailed assessment should lead to formulation of a sleep disorder diagnosis or consideration of potential differential diagnosis including as follows.

RLS and PLMD: Common causes of childhood onset RLS include familial predisposition and systemic iron deficiency. Treatment options include iron supplementation and Gabapentin (researched mainly in adults). PLMD is a sleep disorder that is associated with periodic and repetitive movements of legs and less often arms during sleep. These include bending of toes, foot or ankle, kicking or jerking of legs. There is conflicting evidence on using iron therapy for RLS and PLMD in children[45]. Dopamine agonists and anticonvulsants have not been trialled in children.

Parasomnias: Arousal parasomnias such as confusional arousals are often triggered by sleep apnoea, RLS, or acid reflux. They often respond to specific treatment of these disorders. Parasomnias should be managed with reassurance and safety measures, using benzodiazepines sparingly for severe, potentially dangerous cases. Low dose clonazepam at bedtime may help resolve sleep walking and confusional arousals[46].

Obstructive sleep apnoea: Obstructive sleep apnoea (OSA) affects about 2 percent of children and any suspicion should trigger a referral to the ENT surgeons. Adeno-tonsillar hypertrophy, cranio-facial anomalies, and obesity are common predisposing factors. Mild symptoms of OSA often responds to management with a combination of nasal corticosteroids and a leukotriene antagonist. Moderate to severe OSA would require surgery (adeno-tonsillectomy), positive airway pressure breathing devices or weight reduction as required[47].

DSPS: DSPS is common and can be treated with chronotherapy, light therapy and potentially melatonin as long as the patient is motivated.

COMPREHENSIVE MANAGEMENT STRATEGIES

Most authors and professional guidelines have consistently emphasized the role of effective sleep hygiene strategies, parent and care-giver education and training and behavioral interventions as first line in the management of childhood sleep disorders, with pharmacotherapeutic treatment only considered if sleep hygiene strategies alone have failed[13,48]. The flow chart shows a recommended sleep management guidance based on the published evidence in Supplementary Material.

NON-PHARMACOLOGICAL/BEHAVIOURAL INTERVENTIONS

Non-pharmacological treatment options include sleep hygiene, behavioural interventions, parent education/training programmes, alternative therapies (such as massage therapy, aromatherapy, nutrients and multivitamin or iron supplementation) and CBT for older children and adolescents[9,26,42]. There is sufficient evidence to support the recommendation of these cognitive-behavioral strategies as the most effective approach in the management of paediatric insomnia[7,49].

The most common behavioural interventions are different types of extinction ranging from complete (total removal of reinforcement to reduce a behaviour) to various forms of graduated extinction, bedtime fading/positive routines (including positive bedtime routines, delaying the child's bedtime to match when he/she is currently falling asleep, and stimulus control techniques) and scheduled awakenings (deliberately waking and then soothing a child back to sleep 15-30 min before their typical spontaneous nocturnal awakening) (definitions and practical tips are listed in Box 4 in Supplementary Material).

Previous literature reviews have shown strong empirical evidence for the effectiveness of behavioural interventions based on learning principles when implemented in the short- or medium-term, but long-term evidence for their efficacy is limited. It is not yet possible to postulate any long-term conclusions about the effects of these treatments over time. A recent review confirmed a significant overall effect with small to medium effect size on different sleep outcomes among typically developing children of all ages, but limited evidence is available for CYP with NDEBIDs. For example, there were no clinically significant improvements for any of the studied sleep outcome measures for two trials involving children with autism or Down syndrome[6]. A meta-analysis of 16 controlled trials found small to large

Table 5 Showing drugs used to treat insomnia[17]

Pharmaceutical	Class	Mechanism of action	Half life (h)	Site of metabolism	Peak concentration	Interactions	Effect on sleep
Diphenhydramine	Antihistamine	H1 agonist. Crosses blood-brain barrier	4-6	Hepatic	Fast absorption. Fast onset of action. Peak at 2-4 h	CNS depressants	Reduces latency. May decrease quality
Hydroxyzine	Antihistamine	H1 agonist. Crosses blood-brain barrier	6-24	Hepatic	Fast absorption. Fast onset of action. Peak at 2-4 h	CNS depressants	Reduces latency. May decrease quality
Melatonin	Neuro-hormone	Hypnotic	90% excreted in 4	Hepatic	30-60 min	Unknown	Reduces latency. Maximum circadian effect
Clonazepam	Benzodiazepine	Central GABA receptors	30-40	CYP 450 3A oxidation	60-240 min	Fluoxetine	Suppresses slow-wave sleep. Reduces arousal
Flurazepam	Benzodiazepine	Central GABA receptors	2-100	CYP 450 3A oxidation	30 min to 13 h	Fluoxetine	Suppresses slow-wave sleep. Reduces arousal
Zolpidem	Z-drug	Benzodiazepine-like	2.5-3	CYP 450 3A oxidation	90 min		Reduces latency. Weak effect on sleep architecture
Clonidine	Alpha agonist	Inhibits noradrenaline release	6-24	50%-80% in urine	Fast absorption 100% bioavailability. Onset of action: 1 h. Peak effect: 2-4 h		Reduce REM. Reduces slow-wave sleep

REM: Rapid-eye-movement; CYP: Children and young people.

effect sizes for a number of sleep outcomes including SOL, number of night wakings, duration of night wakings, and sleep efficacy among typically developing children. Two studies conducted with special needs populations also showed no evidence of significant improvements[6].

A recent trial of sleep clinics offered by specialists' advice to parents over the phone and in one to one sessions, based on Behavioural non-medication social prescribing, led to CYP gaining an extra 2.4 h sleep per night, significant improvement in their mental state, time taken to get to sleep falling by more than half, and improved QoL and wellbeing of the parents and carers (NHS England, 2019). The RCT of melatonin in children with NDD and impaired sleep (MENDS) study showed that about 40% of the initial cohort of CYP with NDD did not need to proceed to randomization for melatonin treatment as they responded to one-month parent-led behavioural sleep hygiene strategies[50].

Parent-training and psychoeducation

Psychoeducation is considered a fundamental part of managing sleep problems/disorders in children and adolescents and can contribute towards better understanding of their condition, self-management strategies, partnership working, and improved compliance, resulting in positive outcomes. Table 4 below illustrates some useful resources for parents and adolescents.

Good sleep hygiene

Sleep hygiene involves proven practical strategies that parents and adolescents can implement to attain more optimal sleeping patterns. These include modifiable daytime, bedtime, and night-time practices such as diet, exercises and sleeping environment[42]. There is insufficient data to support sleep hygiene strategies as an evidence-based, stand-alone treatment[9]. Parents can also use reward charts, objects of reference such as applying parents pyjamas or perfume on teddy bear, pink or white noise (or music), night or daytime indicators such as Glo-clock or side lamps[10]. Box 1 shows tips for effective sleep hygiene in Supplementary Material.

Neurofeedback to improve sleep onset insomnia

Some authors have suggested that that Sensory-Motor Rhythm and Slow-Cortical Potential neurofeedback may have positive effect on the normalization of sleep onset insomnia, especially in children with ADHD[51].

Pharmacological treatments

Many hypnotics are widely prescribed for the management of paediatric insomnia, mostly as off-label prescriptions, with limited research evidence to determine the efficacy and safety of their use in the

medium and long term basis (Table 5)[37].

Antihistamines (alimemazine, promethazine, diphenhydramine, hydroxyzine): Antihistamine agents, including hydroxyzine or diphenhydramine, represent the most widely prescribed sedatives in the paediatric population, despite the lack of research evidence to back up their use. There is a risk of paradoxical reaction with some antihistamines. A single, small RCT of diphenhydramine reported small effect size efficacy in sleep outcomes (8-10 min improvement in sleep latency and duration) after a 1 wk trial[52].

Clonidine: Clonidine is a central alpha2-adrenergic receptor agonist, with a half-life of 6-24 h. The mechanism of its sedative effect is unclear but it has been a favorite agent employed in the treatment of sleep disorders among children with NDD despite little evidence in literature regarding its efficacy[10]. Clonidine, melatonin and L-theanine showed some improvements in SOL and TST for children with ADHD, while zolpidem, eszopiclone and guanfacine did not reveal any improvement when compared with placebo[37].

Limited evidence supports the use of alpha-agonists such as clonidine to improve SOL, especially in ADHD subjects. In a United States National survey, alpha agonists were the most commonly prescribed insomnia medication for children with ADHD (81%)[29].

Z-drugs: Only few studies have been carried out in CYP regarding use of zolpidem, zaleplon, and eszopiclone, with contrasting results[42]. In a recent study, children taking eszopiclone or zolpidem experienced more frequent undesirable effects compared with melatonin or placebo[52].

Benzodiazepines like clonazepam and flurazepam: Benzodiazepines are not recommended for routine management of sleep disorders in children but may have a place for treatment of transient insomnia, especially if associated with daytime anxiety[42]. Clonazepam may be used for severe parasomnia/night terrors with specialist advice from a tertiary sleep centre[10].

Tricyclic antidepressants: Tricyclic antidepressants are frequently used in adults with insomnia but not recommended in children because of their poor safety profile. Trazodone and mirtazapine have potential use in the paediatric population but their wider application require further studies[42]. Trazodone may be considered in children with Angelman syndrome with specialist advice from a tertiary sleep centre[10].

Selective serotonin reuptake inhibitors: Use of selective serotonin reuptake inhibitors such as sertraline may be considered for disabling bedtime anxiety. Benzodiazepines and tricyclic antidepressants are not recommended in children[10].

ALTERNATIVE THERAPIES

Many parents self-manage with a wide range of herbal and other counter formulations for relieving sleep disturbances, including use of Valerian, Lavender, Chamomile and Kava. In the absence of research-based evidence, their use remains largely based on empirical tradition[7].

BRIGHT LIGHT THERAPY

Sleep-onset insomnia associated with late melatonin onset is one of the common causes of chronic sleep disorders in childhood. Studies have shown that melatonin or bright light therapy (BLT) is effective in treating these sleep problems, both decreasing sleep latency and advancing dim-light melatonin onset (effects on sleep onset was stronger for melatonin[53].

Fargason *et al*[54] reported the efficacy of 2-wk trial of 30-min morning 10000-lux BLT commencing 3 h after mid-sleep period among a group of adult ADHD patients. BLT significantly advanced the phase of dim light melatonin onset by 31 min mean time SEM, and mid-sleep time by 57 min, associated with significantly decreased ADHD rating scale total scores (P = 0.027 and 0.044) and hyperactive-impulsivity sub-scores (P = 0.014 and 0.013) respectively. There was however no evidence of significant effects in TST, sleep efficiency, wake after sleep onset, or proportion of wakefulness during sleep.

MELATONIN

What is melatonin

Melatonin is an endogenous neurohormone produced by the pineal gland, with its secretion being regulated by the hypothalamic suprachiasmatic nucleus, which controls the circadian physiological

rhythms in response to the ambient 24 h light-dark cycle, for example, controlling sleep/wake blood pressure, body temperature and metabolism[39]. The circadian cycle of high levels of melatonin secretion at night and low levels during the day begins in infants at the age of 3 mo. Melatonin helps in maintaining and synchronizing the circadian rhythm through its daily pattern of secretion[39]. Its rate of secretion generally declines after the first 12 mo as the pineal gland remains static in size while the pituitary gland continues to grow with age[55]. Melatonin has a chronobiotic effect, and acts by its circadian phase-shifting effect, but a less established hypnotic and sleep-promoting effect. Melatonin is also reported to have some immunomodulating properties and is not recommended in children with immune and lymphoproliferative disorders, and in those taking immunosuppressants[56].

Circadin (slow-release melatonin) is currently only licensed for patients with primary insomnia aged 55 and over, and its widespread use for the treatment of sleep disorders especially in the paediatric population is practically "off-label"[57]. The European Medicines Agency has recently granted paediatric-use authorisations for a brand of melatonin (Slenyto), which is available in age-appropriate forms as small tablets[58]. Box 2 shows list of licensed melatonin products in Supplementary Material.

Side effects of melatonin treatment are known to be relatively uncommon and mild in nature[59]. While melatonin is generally considered to be safe in the short term, its long-term safety is yet to be extensively researched. There is limited evidence to suggest that exogenous melatonin suppresses the hypothalamic-pituitary-gonadal axis, due to the observation that endogenous levels of melatonin were elevated in 7 male patients with gonadotropin-releasing hormone deficiency. Sudden termination of melatonin treatment might potentially lead to sleep phase shift in the absence of effective behavioural sleep hygiene implementation. CYP with NDEBID managed with melatonin would require regular follow-up by clinicians to re-evaluate insomnia and determine if continuation of melatonin is still necessary[39].

Use of melatonin for paediatric insomnia and NDEBID

A number of studies and review articles have demonstrated the effectiveness of melatonin treatment in children with NDEBID. Studies have documented significantly shorter sleep onset latencies with melatonin treatment, especially in children with autism. Ayyash *et al*[60] reported a cohort of children with NDEBID (including intellectual disability; autism and ADHD) and sleep disturbances, with 69% of them responding to either low or moderate doses of melatonin (2.5-6 mg), with significantly increased total hours of sleep per night, decreased sleep onset delay and decreased number of awakenings (all: P = 0.001), identified with the use of sleep diaries. Only 9% of them benefited from any dose above 6 mg.

A recent systematic review and meta-analysis of thirteen randomized controlled trials showed that melatonin significantly improved TST compared with placebo [mean difference (MD) = 48.26 min]. In 11 studies (n = 581), SOL improved significantly with melatonin use (MD = -28.97). However, the overall quality of the evidence is limited due to study heterogeneity and inconsistency[61].

Limitations of melatonin effectiveness

There is limited availability of high quality published evidence on the management of sleep disorders among children with NDEBIDs[62]. Despite the widespread use of melatonin for the management of sleep disturbances in children with NDEBIDs, there is limited evidence on effective dosage and lack of documentation on type-specific efficacy on different categories of sleep problems. There is no evidence that extended-release melatonin confers advantage over immediate release. There is convincing evidence that melatonin decreases SOL and increases TST but does not decrease night awakenings. From a systematic review of 19 RCTs, melatonin was shown to significantly improve sleep latency (median 28 min; range: 11-51 min), sleep duration (median 33 min; range: 14-68 min), and wake time after sleep onset (range: 12-43 min), but did not significantly reduce the number of sleep interruptions per night (range: 0-2.7)[52].

Decreased CYP1A2 activity, either genetically determined or from use of certain concomitant medication, can slow down melatonin metabolism, with loss of day-night time variation and loss of effectiveness[63]. Limited studies have shown reduced activities of cytochrome P450 enzyme, CYP1A2 in the liver, with slow metabolization of exogenous melatonin is almost exclusively responsible for the loss of response to treatment. In patients with loss of response to melatonin, a period of melatonin clearance for up to 3 wk and a considerable dose reduction has been advised[64].

The initial MENDS trial was based on a cohort of children who failed to fall asleep within 1 h of lights out or who slept for less than 6 h of continuously[65]. The efficacy of melatonin is likely going to be less significant for children who are able to sleep more than 6 h at night. The overall effectiveness of melatonin compared to placebo was also modest, increasing TST by 22.43 min and reduced SOL by (-37.49 min) using sleep diary or (-45.34 min) by actigraphy. Using a definition of one hour as the minimum clinically worthwhile difference after the intervention, the upper limit of the confidence interval for increased TST did not reach the level of clinical significance. The children fell asleep slightly faster but they gained little additional sleep duration on melatonin. Overall behaviour rating and family functioning outcomes showed no significant improvement[50]. It is also worth considering some potential and reported side effects associated with melatonin use. There are some areas of uncertainties including long-term effects on puberty development and immune system[66].

Melatonin 1 mg/mL oral solution (Colonis Pharma Ltd) contains propylene glycol excipients which may be potentially problematic when used in children[3]. These are generally safe for children above the age of 5 to 6 years, unless they are requiring very high doses[58].

COMBINED TREATMENT MODALITIES

Only limited studies have assessed the efficacy combining behavioural and pharmacological therapies. The combination of controlled-release melatonin over 12 wk and four sessions of cognitive-behavioural therapy among a group of ASD children aged 4-10 years, revealed a better efficacy compared to other treatment modalities, fewer participant dropouts and higher rate of clinically significant response to treatment[67].

A similar small Canadian study among 27 ADHD children reported the effect size of the combined sleep hygiene and melatonin intervention was 1.7 after 90 d of treatment, compared to 0.6 on average for either sleep hygiene or melatonin alone. However, the decreased sleep latency and improved sleep had no demonstrable effect on ADHD symptoms[68].

CONCLUSION

Sleep difficulties and sleep disorders are more prevalent in children and adolescents with NDEBID. They can result in a significant impact on the child's cognitive development, behaviour, physical and mental health. This can also affect peer and family relationships.

It is important for clinicians to evaluate for sleep disorders when assessing children and adolescents with cognitive, behavioural, and emotional problems. Assessment can include screening tools such as BEARS questionnaire, Child Sleep Habit Questionnaire, a 2-wk sleep diary and relevant physical examination in order to identify sleep schedule and duration and any underlying potential sleep disorders. Parents/carers should be provided with sleep/psychoeducation. Sleep hygiene measures and also specific behavioural interventions where appropriate should be offered as first line management for sleep disorders such as behavioural insomnia and certain parasomnias. Management of DSPS involves a combination of strategies including, chronotherapy, light therapy and melatonin. In children and adolescents with NDD and insomnia, use of melatonin should be carefully considered only following an unsuccessful trial of sleep hygiene and behavioural measures and emphasis should remain on continuing the appropriate sleep hygiene measures. Referrals should be made to appropriate specialist/sleep centre for further evaluation and management of sleep disorders, including OSA, PLMD and narcolepsy.

FOOTNOTES

Author contributions: Ogundele MO conceived the idea, performed the literature review and prepared part of the manuscript; Yemula C reviewed the literature and prepared rest of the manuscript.

Conflict-of-interest statement: The authors declare no conflict of interest for this article.

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 May 9; 11(3): 253-269

DOI: 10.5409/wjcp.v11.i3.253

ISSN 2219-2808 (online)

MINIREVIEWS

Food allergy in children—the current status and the way forward

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Specialty type: Allergy

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Gomez-Torrijos E, Spain

Received: April 6, 2021
Peer-review started: April 6, 2021
First decision: July 6, 2021
Revised: July 16, 2021
Accepted: March 16, 2022
Article in press: March 16, 2022
Published online: May 9, 2022

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Abstract

Food allergy in children is a major health concern, and its prevalence is rising. It is often over-diagnosed by parents, resulting occasionally in unnecessary exclusion of some important food. It also causes stress, anxiety, and even depression in parents and affects the family's quality of life. Current diagnostic tests are useful when interpreted in the context of the clinical history, although cross-sensitivity and inability to predict the severity of the allergic reactions remain major limitations. Although the oral food challenge is the current gold standard for making the diagnosis, it is only available to a small number of patients because of its requirement in time and medical personnel. New diagnostic methods have recently emerged, such as the Component Resolved Diagnostics and the Basophil Activation Test, but their use is still limited, and the latter lacks standardisation. Currently, there is no definite treatment available to induce life-long natural tolerance and cure for food allergy. Presently available treatments only aim to decrease the occurrence of anaphylaxis by enabling the child to tolerate small amounts of the offending food, usually taken by accident. New evidence supports the early introduction of the allergenic food to infants to decrease the incidence of food allergy. If standardised and widely implemented, this may result in decreasing the prevalence of food allergy.

Key Words: Oral food challenge; Oral immunotherapy; Allergens; Anaphylaxis; Desensitisation; Immunoglobulin E; Eosinophilic gastrointestinal diseases; Histamine; Mast cells; Basophil activation test

Core Tip: Food allergy in children is a potentially serious condition with an increasing prevalence. Current diagnostic tests are useful when interpreted in the context of the clinical history. The oral food challenge is the current gold standard for making the diagnosis, but its use is limited. New diagnostic methods have recently emerged. Currently, there is no definite treatment to induce life-long natural tolerance and cure for this condition, and available treatments only aim to decrease the occurrence of anaphylaxis. New evidence supports the early introduction of the allergenic food to infants to decrease the incidence of food allergy.

Citation: Elghoudi A, Narchi H. Food allergy in children—the current status and the way forward. *World J Clin Pediatr* 2022; 11(3): 253-269
URL: https://www.wjgnet.com/2219-2808/full/v11/i3/253.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i3.253

INTRODUCTION

Reactions to foods, including allergies, have been known for many centuries. "What is food to one man may be fierce poison to others", was quoted by Lucretius (99-55 BC). In the 1920s and 30s, food intolerance was blamed for many disorders and became a common concern amongst parents in the 1980s. Not surprisingly, it was associated with a steady increase in the diagnosis of food allergy[1]. This was caused by an increase in the prevalence of atopic conditions as a result of different environmental and genetic factors and also by an increase in public awareness. Immunoglobulin (IgE)-mediated food allergy is a global health concern that affects millions of individuals, disrupting many aspects of their lives[2,3].

The condition may cause stress, fear, anxiety in affected children and their parents alike. It also negatively impacts the nutritional status of children with either proven or merely suspected food allergy by resulting in food restriction, elimination, or complete avoidance of particular important food. Stigma, bullying at school, regulation from normal social life, such as attending parties and dining out, also have a significant impact on the child and the family. As for parents, holiday planning becomes a nightmare, similar to when the child goes to school for the first time or moves to a university campus and becomes independent.

The worldwide prevalence of food allergy is estimated to be around 4% of children and 1% of adults, with an increased prevalence in the past two decades[2,4,5]. Differences in reported prevalence are because food allergy is not fully understood, and some of the adverse reactions to food are not allergic. Although in the Western world it is believed that approximately 25% of adults suffer from a food allergy, when accurately diagnosed by testing and oral food challenge (OFC), its true prevalence is found to be much lower, closer to 8% in young children and less than 4% in adults.

This review will revisit the definition, prevalence, and clinical presentation and evaluate the current management of food allergies in children, focusing essentially on the most common IgE-mediated food allergy.

DEFINITION

Different terminologies in food allergy are a source of confusion, with terms such as allergy, hypersensitivity, pseudo-allergy, and intolerance often being incorrectly used interchangeably. At first, a food allergy may sound to parents, and even some professionals, like a single simple disease. However, in reality, it is far more complex.

Adverse reactions to food are defined as an abnormal response related to the ingestion of that food. They can be classified as food intolerance or food allergy based on the pathophysiological mechanism of the reaction[6]. The vast majority of food allergic reactions reported by parents and the general population are, in fact, food intolerances.

The most acceptable and widely used definition of food allergy states that it is an adverse immune response to food proteins that occurs in a susceptible host[2]. Its manifestations are not dose-dependent but are reproducible[6]. Furthermore, food allergy is not one single distinct condition but a spectrum of clinicopathological disorders[7]. In addition to the classic fast (IgE-mediated) food allergy, other Hypersensitivity diseases cover medical problems such as acute allergic hives, allergic gastrointestinal diseases, *e.g.*, eosinophilic esophagitis, acute flare-up of eczema, and oral food pollen syndrome.

As a result, the manifestations of food allergy are very broad and entirely depend on the underlying immune mechanism involved and the affected target organ(s), resulting in a wide spectrum of manifestations commonly involving, alone or in combination, the skin, the respiratory and cardiovascular systems. Thus, diagnostic tools for food allergy, such as the skin prick test and the specific IgE test, have

limitations caused by cross-reactivity and the inability to predict the severity of the allergic reaction; their results must, therefore, always be interpreted in the context of the clinical symptoms to make an accurate disease assessment and, hence, a diagnosis.

In contrast to food allergy, food intolerance is defined as a non-immune reaction to food[2]. It encompasses adverse responses to food, caused by the inherent properties of that particular food (*i.e.*, contamination with a toxin or pathogen, presence of a pharmacologically active component such as caffeine, alcohol, monosodium glutamate), or more commonly caused by an abnormal response of the host, for instance, enzyme deficiencies such as lactase (lactose intolerance), or metabolic disorders (galactosemia, congenital fructose intolerance), or food aversion (due to psychological issues). The clinical manifestations tend to be dose-dependent and are not consistently reproducible.

EPIDEMIOLOGY

Accurate ascertainment of the prevalence of food allergy facilitates the planning of allergy services. Unfortunately, accurate prevalence statistics are notoriously difficult to obtain. The reasons include the existence of various definitions and methods of reporting food allergy and the pleiomorphic manifestations of food allergy with various degrees of severity. In addition, some reports may have also included confounding factors by either investigating specific populations, focusing on specific foods, or using different methodologies. Furthermore, there are wide geographic variations, diet exposures, differences according to age, race, ethnicity, and many other factors. Additionally, the presence of multiple food allergies in children is not often accounted for in prevalence studies.

Methods of reporting food allergy

The methods of reporting food allergy, either self-reported by the individual child, parents, or even by adult patients, lead to different prevalence estimates, as self-reported food allergy rates are notoriously higher than those confirmed by medically supervised OFCs[8].

Offending food and geographical variations

Food allergies disproportionately affect persons in industrialised or Western countries and are more common in children than adults. There is a relatively short list of foods that account for the majority of the more serious manifestations of food allergy, namely peanut, tree nuts, fish, shellfish, egg, milk, wheat, soy, and seeds[4,9,10]. A survey by the World Allergy Organization of 89 member countries using widely different methodologies reported wide variations in prevalence data revealing that prevalence rates for those < 5 years of age were lowest in Thailand and Iceland and highest in Canada, Finland, and Australia[11]. A birth cohort study from 9 European countries where 12049 infants were followed until the age of two years, and using OFC to confirm the diagnosis of food allergy, found an adjusted mean incidence of egg allergy of 1.23% (95%CI: 0.98% - 1.51%), with the highest rate in the United Kingdom (2.18%) and the lowest in Greece (0.07%)[12]. However, the prevalence rates of milk allergy were lower (0.54%; 95%CI: 0.41% - 0.70%), with the highest rates in The Netherlands and United Kingdom (1%) and the lowest rates in Lithuania, Germany, and Greece (< 0.3%)[12,13].

In a meta-analysis of food allergy by history alone, the prevalence of fish allergy was 0%-7% and shellfish allergy 0%-10.3%, whereas, when food challenges were used instead for the definition, the prevalence of fish allergy (0% to 0.3%) was similar worldwide, with shellfish allergy prevalence (0% to 0.9%) being higher in the Southeast Asia region[14]. A systematic review and meta-analysis of 36 studies from Europe and the United States on the prevalence of tree nut allergy showed a prevalence rate < 2% for oral challenge confirmed allergy and 0.05% to 4.9% for possible allergy. Hazelnut was the most common tree nut allergy in Europe, and walnut and cashew were the most common in the United States [15]. Some of the highest rates of food allergy, diagnosed by an OFC, were reported from Australia, where > 10% of one-year-old infants had challenge-proven IgE-mediated food allergy to one of the common allergenic foods of infancy. The prevalence of any sensitisation to peanut was 8.9% (95%CI: 7.9-10.0); raw egg white, 16.5% (95%CI: 15.1-17.9); sesame, 2.5% (95%CI: 2.0-3.1); cow's milk, 5.6% (95%CI: 3.2-8.0); and shellfish, 0.9% (95%CI: 0.6-1.5). The prevalence of challenge-proven peanut allergy was 3.0% (95%CI: 2.4-3.8); raw egg allergy, 8.9% (95%CI: 7.8-10.0); and sesame allergy, 0.8% (95%CI: 0.5-1.1) [16,17].

Ethnicity

A systematic review aiming to address potential racial and ethnic disparities showed that black persons, mainly children, had increased food sensitisation or food allergy. However, these results were tempered by the heterogeneity of the different reports and also by some inherent limitations of some of the included studies[18]. The rate of increase in self-reported paediatric food allergy was greater in non-Hispanic black subjects (2.1% per decade) compared with non-Hispanic white subjects (1% per decade) [19]. In a high-risk inner-city cohort of children, 74% black and 18% Hispanic, a very high rate of food allergy (9.9%) was reported[20]. African American children have higher odds than white children of having an allergy to wheat, soy, corn, fish, and shellfish. However, they had similar rates of peanut,

milk, and egg allergy; and lower rates of tree nut allergy, but they also had higher rates of anaphylaxis and emergency department visits[21]. In the United Kingdom, between 1990 and 2004, there was an increase, from 26.8% to 50.3%, in the proportion of non-white patients with peanut allergy (but not egg allergy). However, the proportion of black subjects attending the clinic had not changed during that period[22]. In New York City schools, no difference was found in food allergy rates between black and white children[23].

Multiple food allergies

An electronic household survey in the USA estimated that 8% of children have a food allergy, with 2.4% having multiple food allergies and 3% having experienced severe reactions[5].

It is, therefore, clear that different reports of prevalence are influenced by many factors, alone or in combination, such as race, ethnicity, country, geographical location, and offending allergens, as well as many other factors such as parents' education, development of health care and the reporting systems. Therefore, disparities need to be better characterised. They might reflect differing awareness of food allergy and access to health care, racial/ethnic or socioeconomic influences on childhood feeding practices, or true differences in prevalence[24].

PATHOPHYSIOLOGY AND MEDIATORS OF FOOD ALLERGY

The immune system plays an integral role in maintaining tolerance to innocuous antigens.

The primary exposure

IgE-mediated food allergies occur as a result of dysregulation in the immune system, which maintains a state of tolerance by preventing benign food antigens from being incorrectly identified as pathogens. Oral tolerance to food is defined as the trans-mucosal crossing of food antigens, processing by non-activated dendritic cells and the control of the inhibitory cytokines mediators as interleukin (IL) 10, by the cells taking the first role in the primary allergen exposure where the unknown protein particles taken by antigen-presenting cells to the lymphoid tissue proximal to the site of exposure. Usually, the process gives the all-clear to the new food protein through T regulatory cells and inhibiting Th2 cells production. It will also result in increased IgA and IgG_4 production with a decrease in IgE production. In addition, there is also an immune suppression of eosinophils, basophils, and mast cells effector cells responsible for causing symptoms. In such a scenario, the innocent food protein will be given the "all clear" by default by the balanced and non-incorrectly triggered immune system.

Sensitisation is defined when food-specific IgE is detectable in the blood. This immunological response is fundamental in the development of type 1 hypersensitivity reaction, and it is primed by the transfer of food protein across the deranged digestive tract membrane and leads to an unnecessary release of inflammatory cytokines, which activate dendritic cells, which will, in turn, trigger naïve T cells into acquiring a Th2 phenotype. The latter will promote inflammatory signals which induce food antigen-specific B cells to produce food antigen-specific IgE. Sensitisation, therefore, is the mistaken identification of a benign food antigen as a pathogen. The specific IgE to that particular protein binds to the surface receptors of mast cells, basophils, macrophages, and other antigen-presenting cells, priming the immune system to an allergic reaction should a second exposure occur to that specific allergen.

A second exposure to the allergen results in the burst of mast cells, leading to the release of histamine, which is one of the most important preformed mediators responsible for the symptomatology of both mild allergic reactions and anaphylaxis. When histamine is secreted from mast cells and resemblance cells, its effect immediately manifests through fades within a few minutes. Histamine causes all the signs and symptoms seen in mild and severe allergic reactions, such as an increased capillary leak, hives, tachycardia and drop in blood pressure.

Other inflammatory mediators such as prostaglandin D2, platelet-activating factor, and leukotrienes also contribute to the allergic reaction.

In summary, the five components of the immune system, the epithelium, innate immune cells, T cells, B cells, and effector cells (mast cells, eosinophils, and basophils), can either promote tolerance to food antigens or sensitisation to them, which will then lead to allergic manifestations.

The role of Epithelial Barriers

The role of the intestinal epithelial cells in the central regulatory mechanism controlling the absorption of ingested antigens is important. It helps maintain tolerance by preventing the unnecessary entry of antigens and thus avoiding the secondary production of inflammatory cytokines.

Antigens cannot freely pass an intact epithelial barrier but are often transported through mechanisms of net movement of particles present beneath the cells through several very specialised cells[25].

In the absence of pro-inflammatory or danger signals, food antigens recognised by specialised antigen-presenting cells will further promote the maintenance of tolerance through the release of mediators such as IL 10 and transforming growth factor-beta (TGF-β), which will promote the development of regulatory T cells[26-28].

The role of T Cells

The relevant cytokine and other mediators released by a nonspecific line of defence cells such as natural killer cells, macrophages, neutrophils, mast cells, dendritic. Cells, mast cells, and basophils all help by playing a role in tolerance production and the generation of T regulatory cells[26-28]. Moreover, products from the dendritic cells permit a complicated exchange process in the gastrointestinal lining to produce an inhibitory effect by binding the effector particles to CTLA-4[29,30]. In addition, inflammatory mediators such as IL-10 released T regulatory cells can also have an inhibitory effect on effector cells[31].Th2 cells periodically move from the local lymphoid glands into the thin layer lining of the exposed surface of the gastrointestinal tract, where inflammatory mediators such as IL5 and IL13 stimulate the process of B cell activation, leading to the development of the body action towards certain foods. At the same time, naïve T cells transform into helper -and the release of IL-9, which eventually result in the development of allergic reaction and an increase in the histamine secreting cells[32].

TYPES OF FOOD ALLERGY

Oral tolerance refers to a systemic immune non-responsiveness to antigens first encountered by the oral route. A failure to develop this homeostatic process in persons who are genetically and probably environmentally predisposed to atopy can result in the development of food allergy[33]. Based on the immunological mechanism involved, food allergies may be classified into three types[1-3,7,34,35].

IgE-mediated food allergy

This is the best-known and well-characterised type of food allergy. It is the most common food allergy in the Western world, with the highest prevalence in children below three years of age (6%-8%)[6]. There has been a steady increase in this type of food allergy and food induced-anaphylaxis in the Western world[36,37].

These allergic reactions are immediate, reproducible, and caused by food-specific IgE, which can usually be detected by *in vivo* or vitro tests to confirm the food allergy diagnosis[6]. These food-specific IgEs bind to high-affinity receptors for the Fc region of IgE (Fc□RI) on basophils, mast cells, dendritic cells, and Langerhans cells in the gut, skin, or through the respiratory system. When exposed to the offending food, the specific food antigen is recognised by two or more specific IgE bound to the Fc□RI, resulting in a cross-link of the receptor and activation of mast-cells to release histamine and other mediators. These released chemical mediators will cause vasodilation, hives, angioedema, low blood pressure, smooth muscle constriction, consequent bronchospasm, diarrhoea, and vomiting[38].

Food allergy-associated anaphylaxis is an IgE-mediated reaction. In a previously sensitised person with food-specific IgE on mast cells and basophils, the food allergen is ingested and absorbed into the local tissue, then cross-links with IgE resulting in immediate release of preformed mediators[2,39,40]. This immune response is rapid; the onset of symptoms typically occurs within 5 to 60 min after exposure to the food. An anaphylactic reaction affects multiple organ systems and may rapidly develop severe symptoms (*e.g.*, hypotension or respiratory collapse) and even death[41].

Although cutaneous manifestations such as hives and pruritus are the most common, they are absent in 20% of anaphylaxis persons. Thus, a high index of suspicion is required when other signs and symptoms such as cough, wheezing, laryngeal oedema, vomiting, diarrhoea, and hypotension are present. IgE-mediated food allergy is rarely associated with fatal anaphylaxis in children and adolescents. Recent data have linked cow's milk protein to several severe anaphylactic reactions, including a deadly anaphylactic reaction to baked milk following an OFC test.

Several devastating incidences of food allergy, which unfortunately results in fatality either at take away restaurants, school or even following supervised food challenges, made the issue of food allergy a major concern for parents, the public, school, and health authorities.

Up to one-third of the population now believes that they have food allergies, a much higher estimate than the actual prevalence based on physician diagnosis (5% of adults and 8% of children)[42].

The most common foods incriminated in IgE mediated food allergy are milk, egg, peanuts, tree nuts, seafood, soy, wheat, and seeds. Sesame has recently been emerging as a typical new food allergen in the Middle East and Europe[43].

Food pollen syndrome or Oral allergy syndrome: A unique and interesting form of IgE-mediated food allergy is a pollen-associated type of food allergy due to the cross-reactivity of epitopes shared between allergen molecules in certain pollens and some vegetables and fruits[44]. Here, the primary sensitisation occurs to pollen allergen, with the initial symptoms being allergic rhinitis. However, upon further exposure to that particular fruit or vegetable which shares epitopes or components with pollens responsible for the primary sensitisation, other symptoms then develop in addition to allergic rhinoconjunctivitis such as itching, redness and oedema of the lips, numbness in lips and tongue, itching, and swelling in the throat[44,45]. Pollen food syndrome (PFS) usually does not lead to anaphylaxis. Its symptoms can usually be avoided by either peeling the skin of the fruit or vegetables or by boiling them. Rinsing the mouth with water usually eases the symptoms. PFS is commonly misdiagnosed as a

true food allergy, with children being prescribed unnecessarily an adrenaline autoinjector[46,47].

Non-IgE food allergy

These are immunologic reactions to food that occur without demonstrable food-specific IgE antibodies in the skin or the serum and can therefore have several pathogenic mechanisms[48]. The non-IgE-mediated disease consists of a wide range of gastrointestinal conditions, generally of slow onset and with signs and symptoms very similar to other common conditions, especially in the first year of life, such as colic, gastroesophageal reflux, diarrhoea, and eczema, making it difficult to recognise.

This type of food allergy has been increasing worldwide. It encompasses eosinophilic oesophagitis (EoE), Non-eosinophilic gastrointestinal disorders (Non-EoE-EGID), food protein-induced enterocolitis (FPIES), and food protein-induced allergic proctocolitis (FPIAP). While EoE, Non-EoE-EGID, FPIAP are chronic, FPIES is always an acute disease. Although T cells may play a central role in non-IgE mediated food allergy and EoE, the pathogenesis of FPIES and FPIAP remains less clear[49,50]. Non-IgE mediated food allergies are usually managed by joint care between the paediatric allergist and the gastroenterologist.

Mixed IgE-cell-mediated food allergy

This occurs when both IgE and immune cells are involved in the reaction. Mixed and non-IgE-mediated food allergies, such as EoE, eosinophilic gastroenteritis (EG), and atopic dermatitis (AD), have a more prolonged onset and manifest primarily in the gastrointestinal tract and skin[51]. Infants and young children with EoE may present with feeding dysfunction and failure to thrive, whereas older children and adults often manifest vomiting, abdominal pain, dysphagia, and food impaction. EoE is diagnosed by oesophageal biopsy, demonstrating the presence of > 15 eosinophils per high-powered field. It is not uncommon in patients with EoE to have other allergic diseases, such as allergic rhinitis and IgE-mediated food allergy. Food allergens and possibly aeroallergens seem to play causative roles in the immunopathology of EoE, and food-avoidance diets are often effective in inducing clinical and histologic improvement. When eosinophils are found distal to the oesophagus in the gastrointestinal tract, the diagnosis of EG is then made. Symptoms of EG vary depending on the portion of the gastrointestinal tract involved and may include abdominal pain, nausea, diarrhoea, malabsorption, and weight loss. Unlike EoE, food-avoidance diets offer little or no benefit in EG[52].

AD also has features of mixed IgE- and non-IgE-mediated food allergy. The presentation includes a chronic pruritic rash distributed on flexor surfaces such as the antecubital and popliteal fossa, wrists, ankles, and neck. In approximately 35% of children with AD (typically young children with severe AD), food allergens may exacerbate their rash, causing increasing erythema and pruritus over a few hours if only IgE-mediated or over days if non-IgE mediated. Milk, soy, egg, wheat, and peanut are the most common culprit foods. Elimination of suspect foods often improves AD symptoms within a few weeks, whereas repeated exposure exacerbates symptoms[52].

Sensitivity to food chemicals: This is thought not to be a true allergy and is not immune-mediated. However, it is commonly described in food allergy as it shares similarities. It represents an adverse chemical reaction to either existing food chemicals such as amines, salicylates, natural food colourings and glutamate, or artificially added food chemicals such as sulfites, benzoates, and artificial food colourings. A small amount of these chemicals are well tolerated most of the time. Salicylates naturally exist in fruits, vegetables, nuts, and cereals and are also used to manufacture chewing gum, toothpaste, and mouthwashes. Amines such as histamine can occur naturally in food or are secondary to microbial contamination or fermentation. Histamine-associated symptoms include urticaria, angioedema, itching, rhinitis, conjunctivitis, abdominal cramps, palpitation, flushing, and headache[53]. Glutamate is an essential amino acid occurring naturally in many foods such as cheese, tomato, mushrooms, soy, and yeast extract. Monosodium glutamate MSG (E621) is commonly used in the manufacture of soaps, food and sauces, widely consumed in Asian restaurants. The "Chinese Restaurant Syndrome" is a condition caused by glutamate, widely used in Chinese food, and which manifests as headache, muscle tightness, nausea, tingling, flushing, and chest tightness.

A food additive is any substance not naturally present in that food, such as E 220, E 221, E 222 cited on some food labels. Sulfite is a very common food additive that exists in shrimps, beer, wine, dried grapes, and pizza dough and which may induce symptoms ranging from mild reactions to anaphylaxis. Food colourings can be found in tea, berries, and cinnamon, and, although they cause concern to the public, they rarely produce reactions. The exact mechanism of producing these reactions is not fully understood. Colourings have also been linked to hyperactivity in children, especially when combined with other food additives[54].

MANIFESTATIONS OF FOOD ALLERGY

We will focus exclusively on IgE-mediated food allergy, a type I hypersensitivity reaction that occurs

when ingestion of specific food triggers a response by preformed circulating IgE antibodies developed earlier against that same food[7,55].

When food molecules which have been wrongly appreciated as a pathogen in the atopic child, comes in contact with the lamina propria of the intestinal tract, it rapidly binds to basophils and mast cells, resulting in degranulation of these cells and the release of the inflammatory mediators such as histamine and tryptase[56]. These mediators are responsible for the signs and symptoms are seen in mild and severe food allergic reactions such as the development of urticarial rash, cough, hoarseness of voice, bronchospasm, hypotension, and collapse[57,58].

Cutaneous manifestations

They are the most common IgE-mediated food-allergic symptoms. Usually presents as redness of the skin, itchy rash, which commonly takes the form of papules or hives. When the inflammation involves the deeper layers of the skin, the skin manifestation is called angioedema. Hives can last for hours if not treated. Angioedema develops when the swelling extends below the skin's surface and fatty tissue. It usually presents eyelids, face, and lips swelling, causing significant discomfort. Eczema may develop or worsen in non-IgE-mediated food allergy, although pre-existing eczema can also worsen with IgE-mediated food allergy. The magnitude of the skin reactions in type 1 hypersensitivity food allergy is reflected by the surface area of the skin affected[59].

Respiratory manifestations

The entire respiratory tract from the nose to the mungs can be affected. Symptoms vary from runny nose, congested nose, sneezing, itchy nose to cough, stridor, wheeze, or breathing difficulty. Some children experience severe tightness in the throat and a feeling of impending death[7,58,60]. It has been reported that some patients who presented to the emergency room with anaphylaxis due to food allergy have been mistakenly diagnosed and treated as life-threatening asthma.

Gastrointestinal manifestations

Abdominal pain, vomiting, and diarrhoea are the cardinal gastrointestinal feature of IgE-mediated food-allergic reactions. These symptoms are usually quick in onset and could appear immediately following the exposure to the offending food up to 2 to 4 h later. Other problems such as constipation and failure to thrive are more common in non-IgE -mediated food allergy[7].

Cardiovascular and neurological manifestations

They are usually described as the most severe complications of IgE mediated food allergy. Children become pale dizzy with tachycardia and may experience a marked drop in their blood pressure, resulting in collapse. Cardiovascular involvement commonly goes hand in hand with skin or respiratory manifestation[7,57]. Death rates are very low but usually very tragic.

Anaphylaxis

This is a serious form of an IgE-mediated hypersensitivity allergic reaction involving more than one organ system, including the respiratory tract, gastrointestinal tract, and skin. It is rapid in onset and potentially fatal[41]. Even though it is rare, anaphylaxis can also present with only cardiovascular or neurological symptoms such as dizziness, weakness, tachycardia, hypotension, cardiovascular collapse, or unconsciousness[57]. The World Allergy Organization classified anaphylaxis into five grades The classification is based on the number of organ systems involved, the severity of the morbidity induced by the allergic reaction, subjective measurements such as the forced expiratory volume in 1 second (FEV1) and the response to treatment given. Grade1 describes mild morbidity; meanwhile, death is the outcome of grade 5[61] (Table 1). For simplicity, acute allergic reactions that involve skin such as urticarial rash, lips swelling, eye swelling, or abdominal pain and vomiting only are usually classified as mild to moderate. However, if one or more of the above symptoms are associated with cough, hoarseness of voice, stridor, wheeze, difficulty in breathing, pallor, or collapse, the reaction will be described as anaphylaxis. Anaphylaxis is life-threatening, but in most cases, it does not produce a severe outcome and rarely causes death. Despite the existence of many local and international guidelines for making its diagnosis, the diagnosis of anaphylaxis remains subjective to a greater extent. Biochemical testing such as serial measurements of serum tryptase during the acute presentation and at 1 h later has been introduced to help make an accurate diagnosis of anaphylaxis when in doubt.

The term biphasic reaction refers to a reaction that describes a second surge of histamine from degranulated mast cells after the initial symptoms of anaphylaxis settled. It is reported to occur in about 10% of patients who suffer an anaphylactic reaction. Hypotension is linked to severe morbidity and mortality when it happens, and its incidence is estimated to be 3% in the cases of anaphylaxis in children[62].

Risk factors for severe anaphylaxis

Risk factors most strongly associated with fatal or near-fatal anaphylaxis include the type of allergenic food, adolescence or young adulthood, the presence of concomitant asthma, and the delayed use of, or

Table 1 World Allergy Organization systemic allergic reaction grading system

System	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	One organ system involved (cutaneous, respiratory, ocular or others)	Two organ systems involved, or lower respiratory tract involvement, gastrointestinal involvement, or uterine cramping			
Cutaneous	Generalised pruritus, urticaria, flushinor a sensation of heat or warmth, or angioedema not involving laryngeal, tongue, or uvular tissues. Localised hives or angioedema alone are not considered anaphylaxis				
Respiratory	Upper respiratory tract symptoms: sneezing, rhinorrhea, nasal pruritus and nasal congestion, throat clearing, itchy throat, and coughing	Lower respiratory tract symptoms: wheezing, shortness of breath. And a drop of 40% in the forced expiratory volume in one second (FEV1) and which responds to bronchodilators	Symptoms of laryngeal, uvular, or tongue tissue oedema. With or without stridor. Or FEV1 drops by 40% with no response to bronchodilators	Respiratory failure	
Cardiovascular				Hypotension	
Gastrointestinal		Abdominal cramping, vomiting or diarrhoea			
Conjunctival	Conjunctival erythema, pruritus, or tearing				
Other	Nausea, metallic taste, or headache	Uterine cramping			Death

lack of access to, an epinephrine autoinjector[41,62]. Also, several factors, including exercise, viral infections, menses, emotional stress, and alcohol consumption, place some persons at increased risk by lowering the reaction threshold after exposure to an allergen.

ALLERGY HISTORY TAKING

A good history is crucial for making an accurate diagnosis of food allergy. The use of "allergy-focused clinical history" is universally recommended, as it considers all the events and history related to the allergic reaction. A thorough inquiry about the personal and family history of atopy is also required. At least 30 min should be allocated to the first allergy consultation. In the case of IgE-mediated food allergy, the record is usually good enough for reaching the diagnosis. The National Institute for Health and Care Excellence produced a document on the quality standards of food allergy services in the United Kingdom, highlighting the importance of history taking in diagnosing food allergy and formulating any further management of the allergic patient[63].

Similarly, the European Academy of Allergy and Clinical Immunology had an essential role in standardising the allergy-focused history to maximise its value as an important diagnostic tool. It also considers the patient's age to produce age-specific standardised account-taking formats for children and adults, to be used by paediatricians, physicians, family physicians, allergists, and dietitians[64]. In 2009 the Royal College of Paediatrics and Child Health published its allergy care pathway, a reference for taking an allergy-focused clinical history in paediatrics[65].

INVESTIGATIONS IN FOOD ALLERGY

A variety of *in vivo* and *in vitro diagnostics* have been developed to assist with diagnosing food allergy.

In vivo tests

Skin prick test: It is the most commonly used test when investigating food allergy in children and adults. Usually, it is performed during the first visit and can also be repeated later to compare the size of the wheal produced by the allergen in question. This would help predict any development of natural tolerance or decide to conduct an OFC, which would help advise on either the continuation of avoidance or instead, to allow food reintroduction.

The skin prick test (SPT) is conducted using standardised extracts from different foods and environmental allergens such as house dust mites, pollens and animal dander. A drop of the standardised allergen solution is usually put on the child's forearm or back, then scratched with a lancet or a pointed device, aiming to prick the skin through the placed drop of the solution. Two drops of saline (negative

control) and histamine (positive control) are used to validate the results; *i.e.*, a positive impact for normal saline or a negative effect on histamine would void the test results. While the former development could occur in individuals with dermographism, the latter could indicate that the child has received antihistamines within 24-72 h of the test. After pricking the skin, the solution left on the skin is wiped by tissue as it may irritate the skin and sometimes makes it difficult to measure the reaction produced after 15 min. SPT uses standardised solutions produced by several manufacturers. The assessment of the wheal or erythema is used to determine the positivity of the test, with a wheal of ≥ 3 mm indicating a possible clinical allergy[65]. Another criterion for interpretation is to compare the wheal produced by the allergen solution to the one developed by the positive control (histamine). The test is considered positive if the wheal diameter made by the antigen extract is equal to or larger than the positive control. Most importantly, the SPT result should always be interpreted in the context of the patient's clinical history. A positive skin test only identifies sensitisation to the particular allergen but does not necessarily indicate a clinical allergy.

SPT is very informative for the child and the parents. It serves as a visual aid to reinforce the need for compliance with the avoidance of particular food, and it is usually performed in the clinic. Cost is low, especially when compared to other tests such as Component resolved diagnostics (CRD), where the number of tests, and thus prices, increase significantly with the required multiple components. Urticarial rash and itching can cause discomfort. Conducting and interpreting the test can also be challenging in individuals with eczema. A systematic review and meta-analysis found that the sensitivity of SPT ranges from 68 to 100 %, with a specificity of 70 to 91 %[66].

Recognisable wheals have been observed in 3-month-old infants, and some clinicians perform the test in infants from any age. However, the wheel size increases with age from infancy to adulthood, reflecting the change in the immune response. SPT is generally a safe procedure and is easily interpreted by trained professional staff. Emergency equipment and drugs should be readily accessible in case of any systemic adverse reactions to the allergen solution[67].

In vitro tests

Allergen-specific IgE: The serum's measurement of specific IgE, commonly known as the RAST test, through enzyme-linked immunosorbent assay (ELISA) technique, is being used nowadays, instead of the old RAST. In the allergen-specific IgE (sIgE) test, the allergen extracts of the allergen of interest are chemically attached to plastic test tubes or put into multiple wells in sensitised test plates, where a tiny volume of the patient's serum is added. As a result, any amount of the sIgE to the allergen will stick to the tube. A radiolabeled anti-IgE is then added and, after incubation and washing, the radioactivity is measured. The result is expressed in numbers, with a standard reference. It is more expensive than SPT, and despite the length of time to obtain its results, sIgE to the widely used. It remains an excellent alternative to SPT in patients with severe eczema or if systemic antihistamines have been taken within 1-3 d before the SPT[68]. The Immuno solid-phase allergen chip test uses microchip technology to detect specific IgE antibodies in a tiny blood sample to 112 food and airborne allergens using the same ELISA technique. Results need to be carefully interpreted due to the possibility of cross-reactivity between food proteins.

The total serum IgE concentration has lost its importance as one of the diagnostic tools in food allergy. It is commonly raised in atopic children with eczema, parasitic infestations, and immunodeficiencies. Additionally, low levels cannot rule out the existence of IgE-mediated food allergy.

CRD: Food components testing emerged in the 1990s as a diagnostic test capable of measuring IgE antibodies to specific components contained in the allergen of interest. Contrary to the basic old concept that cow's milk and food plants each have a single protein, determining its allergenicity, it became evident that every food plant has a range of heterogeneous protein components that may differ in their heat and acid stability as in their allergenicity.

By having specific information about the allergenicity, and heat stability of a particular component to which a child is sensitised, a more specific individualised action plan can be drawn up, depending on whether or not the child can tolerate the cooked/baked form of that food (if sensitised only to a heat-labile component(s). It can also help decide if the child or parents need to carry an adrenaline autoinjector, as determined by the allergenicity of the sensitised element (s)[69]. Sensitisation to peanut lipid transfer proteins, such as peanut Ara h1 and Ara h2, both heat and proteolytic resistant, would produce severe systemic reactions. At the same time, sensitisation to the peanut Ara h8 component alone would only produce oral symptoms[69]. Some data showed that sensitisation to certain proteins is linked to prolonged allergy, as in the case of Gald1 and Gald2 epitopes of hen eggs[70].

Like other allergy diagnostics, CRD should not be solely used to diagnose food allergy and should only be requested by clinicians competent in interpreting its results. More than 4700 food components have been discovered, adding complexity to the test. CRD can also help diagnose PFS and distinguish it from true IgE-mediated food allergy; later, the primary sensitisation occurs to food proteins rather than pollens. The two conditions' management, severity, and outcome are very different.

Basophil activation test: SPT, sIgE, and CRD cannot accurately diagnose food allergy because they only test for sensitisation by detecting specific IgE to whole food protein or its components. Sensitisation

does not mean allergy and cross-reactivity are common, especially in children with atopic dermatitis. Also, some non-allergenic components, such as polysaccharides, can trigger the production of specific IgE of no clinical importance, as it cannot produce an allergic reaction. The role of basophils is similar to mast cells in IgE-mediated food allergy, with both sharing similar high-affinity IgE receptors where specific IgE antibodies attach to their surface. As with mast cells, the basophil degranulates when re-exposed to food allergens. Detecting and measuring the degranulation of basophils by flow cytometry allows testing for allergy rather than sensitisation, likening the basophil activation test (BAT) to a "food challenge in a test tube". BAT can compensate for SPT, sIgE, and CRD testing deficiency. BAT results were 92% in line with the double-blind placebo-controlled food challenge in one study. This method is becoming increasingly used, and several commercial forms are currently available. However, its use is still restricted to research laboratories and some centres. Large-high-quality studies to standardise BAT are still lacking[69]. If BAT can replace the OFC, it would be considered one of the major successes in allergology.

OFC: Blood tests or skin prick tests cannot accurately predict the severity of the allergic reaction. Double-blind placebo-controlled OFC is the standard gold test for diagnosing food allergies. It consists of the oral administration of incremental doses of the suspected allergen, *e.g.*, cow's milk or peanut. It requires a physician, a nurse, space, and rescue medications. OFC is commonly performed in-office or clinic settings, especially for low-risk challenges. High-risk challenges, such as previous anaphylaxis and FPIES, should always be conducted in a safe environment with full resuscitation facilities to treat anaphylaxis.

OFC is an ideal diagnostic test used to either confirm or rule out food allergy when the history of alleged allergic reaction to food is inconsistent with the SPT and blood tests or when the clinician or parents want to explore food alternatives in children with multiple food allergies. Most importantly, it is used before food reintroduction, when the latest SPT or sIgE show that they may grow out of their allergy, which might have caused anaphylaxis in the past. The natural history of some food allergies, such as milk, is that it always occurs in the first year of life, but most children grow out of it quickly. Home reintroducing food to parents who witnessed their child suffering from anaphylaxis is not a good option for them or the child. Thus, they may never reintroduce cow's milk even with their doctor's reassurance and even when the allergy markers suggest the development of natural tolerance to it.

Any regular antihistamines should be discontinued at least 48 h before the challenge. When performing the challenge, the dose should be gradually increased until a typical food serving appropriate for the child's age is consumed. The total weight or portion of the food can be divided into four or six portions. A negative challenge is valid if no symptoms are observed following exposure to the problematic food, in an amount equivalent to a standard serving. The medical team will observe the patient for symptoms for several hours after the challenge. The procedure should be delayed if the child is unwell with cold, flu symptoms, or suffering from an asthma exacerbation. The latter is especially important when a child with asthma had received a short-acting beta-agonist or beta-blockers earlier. It may increase the risk of allergic reactions and antagonises the effect of anaphylaxis rescue treatment. Ideally, the child and parents are located in a calm and relaxing area, preferably with a play specialist available. Usually, parents will be requested to bring the food for the challenge, but this depends on the hospital policy. The paediatric dietitian will liaise with the allergy nurse or the doctor to determine the weight and portion of the food needed for the challenge. Usually, the food is given to parents under the observation of the medical staff. The challenge should be called off if the child develops symptoms of allergy such as hives, vomiting, change in behaviour, cough, stridor, pallor, or any other suggestive manifestations. The clinician responsible for the challenge should be immediately informed and treatment provided instantly[70]. If the symptoms or signs are very subtle, not convincing, or thought to be just a skin irritation to the food rather than an allergic reaction, the same dose can be repeated. The child is regularly observed throughout the procedure, with sets of vital signs and examinations, and whenever a reaction is suspected. If the child passes the challenge, it is recommended to continue to consume the challenged food regularly to prevent re-sensitisation.

OFC is time and staff-intensive. A single food challenge may take up to 4 h, and occasionally the child may refuse to eat or drink the challenging food. It is acceptable to stop the procedure should the parents request it, even without a valid reason.

References are available for serum level of sIgE and the wheal size of SPT to typical food to help predict and increase the rate of successful OFC. Although these diagnostics cannot be wholly relied upon, they may encourage clinicians and reluctant parents to accept the OFC. Passing the OFC would enable parents to reintroduce certain essential foods such as milk, egg, and fish, which could have been avoided earlier. It also reduces the stress experienced by the family and helps improve their quality of life and the child's nutritional status. The success rate of passing OFC is estimated to be around sixty per cent, with the most commonly encountered reactions being mild to moderate and the occurrence of anaphylaxis being infrequent[71]. Such responses should not undermine the clinician from doing further OFC. Anecdotally, some allergists even state that if a clinician does not see reactions while doing OFC, they may not be challenging suitable patients.

TREATMENT OF FOOD ALLERGY

There is no approved medical treatment for food allergy that develops a permanent tolerance. Treatment remains primarily based on counselling the patients and their families to avoid offending food, such as carefully reading food labels, taking precautions when dining out in restaurants and parties or being mindful of mistakes caused by a language barrier when travelling abroad. Parents of children with a food allergy should have a written allergy action plan. This usually includes the name of the offending food(s), information on how to detect an allergic reaction, when and how to use the rescue medications such as an oral antihistamine or an adrenaline autoinjector device, and what to do next. A copy should also be given to school nurses.

Oral immunotherapy

There has been a significant increase in oral food immunotherapy trials, with the majority focusing on developing oral immunotherapy (OIT) for peanut, cow's milk, and hen egg allergy. These trials were based on the old concept that the continuous introduction of small amounts of allergenic food would induce tolerance over weeks or months. These protocols were designed to induce tolerance while ensuring children's safety[71]. In real life, food OIT is still not widely available for all children with food allergy, and its use is minimal due to the absence of formally OIT-approved protocols in most countries.

Palforzia is the first FDA-approved food allergy medication designed to treat peanut allergy. It is a peanut allergen extract that has shown success in double-blinded placebo-controlled trials, with 67.2% of Palforzia recipients tolerating 600 mg of peanut protein when challenged, compared to 4% of the placebo arm of the study. The treatment risks provoking anaphylaxis, especially during the initial dose-escalation phase. A significant limitation of this treatment is that it does not provide a definite cure, as treated patients will only be able to tolerate a limited portion of peanut by the end of the treatment. However, many clinicians, parents, and patients consider it a success and a life-saving treatment. More research is required to develop a treatment that can produce long-term natural tolerance without exposing the patients to the risks of severe side effects and anaphylaxis during treatment.

OIT duration usually extends over many months or years. Some suitable treatment protocols are currently under, hoping to enable the allergic child to consume a total age-proportional volume of milk by the end of the treatment. So far, only a few treatment protocols have the formal approval of accredited bodies. It has also been shown that in a standard allergy clinic setting, 79% of the children with peanut allergy tolerated the desensitisation protocol and maintained it afterwards by consuming a daily dose of peanut[72]. Other studies had shown that some participants, who were successfully desensitised earlier, developed later eosinophilic oesophagitis due to regularly consuming the allergenic food at a sub-allergenic dose subsequently improved when the treatment was later aborted[73]. Similar protocols have been created for cow's milk and hen egg-allergic children. Although most participants did not experience significant reactions, a small number developed anaphylaxis during the treatment. It remains unclear if OIT would eventually produce tolerance similar to when these children naturally grow out of their allergy or if it only induces transient desensitisation. Some treated patients lose tolerance once stopped taking the maintenance amount of the offending food. Thus, some consider this kind of treatment an additional risk rather than a therapy[74]. More work is required to provide safe and efficient protocols that can be applied to everyday practise by addressing the encountered short and long-term complications of the OIT. Moreover, different routes such as epicutaneous or sublingual are currently under study.

Adjuvants

Adjuvants are frequently added to vaccines to boost their immune response and reduce some undesirable reactions. Their role has been investigated in OIT to improve the duration of tolerance and reduce side effects. Aluminium salt is one of the most popular vaccine adjuvants used. However, its use in treating peanut allergy has been disappointing due to the side effects encountered, especially with subcutaneous peanut therapy[75].

Probiotics

Studies have confirmed the role of intestinal microbiota in supporting the early establishment of immune tolerance and reducing the risk of developing food allergies in early life. In the first few days of life, the newborn baby's gut becomes inoculated by bifidobacteria, lactobacilli, and other non-aerobic bacteria. Also, in breastfed infants, other bacteria such as streptococci, staphylococci, lactobacilli, and bifidobacteria colonise the gut. Interacting with the host gut, these bacteria play a beneficiary role in absorbing nutrients, interfering with pathogenic organisms' growth, are essential for developing immune tolerance to different antigens, including food antigens[76,77]. Most of the studies that looked at probiotics' function in food allergy have focused on their role in managing cow's milk allergy. A systematic review of nine trials involving 985 patients with cow's milk protein allergy has demonstrated moderately encouraging results with probiotics, showing that the use of Lactobacillus rhamnoses GG can help induce tolerance in infants with suspected cow's milk protein allergy[76,77].

Biologicals

Omalizumab is one of the most common biologicals investigated to enforce and speed up tolerance during oral food immunotherapy. In a double-blind placebo-controlled trial comparing it as a catalyst in the treatment of cow's protein milk allergy to a placebo in 57 participants aged between 7 to 32 years; no difference was found in the number of participants desensitised to the cow's milk protein in the two arms of the study. However, there was a marked reduction in the allergic reaction that needed resuscitation with adrenaline in the omalizumab arm[77].

Studies of omalizumab have been performed to improve the safety of OIT and find out if it could speed up a tolerance to cow's milk and peanut in food allergic individuals. In the cow's milk study, 92% of the participants could reach the maintenance dose, although almost half suffered moderate to severe reactions during the induction phase. In the peanut study, 88% of the participants tolerated the induction phase, with only 2% continuing to encounter allergic reactions, with some requiring adrenaline to treat anaphylaxis[78,79].

From the available evidence, omalizumab offers some benefits as a mono booster for desensitisation in food allergy, but its benefit remains limited. More work is required to support biologicals either as monotherapy or other adjuvants in desensitising food allergy.

The role of baked food

Strong hypotheses state that introducing baked food, such as biscuits or cake containing milk or egg, in children with cow's milk and egg allergy would expedite the development of natural tolerance to these foods of high nutritional value. The baked form of the food is usually less allergenic than the raw or lightly cooked form, as cooking at high temperature alters the conformational epitope of the food proteins, making them less allergenic to the sensitised child[80]. It has been estimated that almost two-thirds of children with cow's milk allergy can tolerate the baked milk in biscuits, and the egg in cakes, and in addition, the continued ingestion of the baked form of these foods, speeds up the natural tolerance. This observation has been noticed with both IgE-mediated and non-IgE-mediated allergies. Some researchers are unconvinced of the role of baked food in inducing natural tolerance. One argument is the short and naturally self-limiting duration of cow's milk and egg allergy, and the other is that those children who tolerate the baked form of milk and egg may have an allergy phenotype that enables them to tolerate the baked forms of the food, facilitating a rapid tolerance oduction[81]. The benefit of introducing baked milk or egg remains a success, not only because of the added nutritional value of these foods to the allergic child but also to help reduce parental stress and anxiety and develop food aversion to milk and egg in these children.

The

role of **the** ***early dietary introduction of potentially allergenic food in food allergy prevention***

Until now, infant and young children's feeding and nutrition international advisory boards, such as the World Health Organization and United Nations International Children's Emergency Fund, advise parents and professionals dealing with children to delay the introduction of the common allergenic foods such as peanut, egg and cow's milk to breastfed babies. These recommendations were introduced in the last few decades due to the remarkable rise in food allergy prevalence among children. Also, in an attempt to promote natural breastfeeding, the introduction of cow's milk was discouraged in breastfed babies in the first 6 to 12 mo of life.

Unfortunately, the opposite effect was witnessed, as the prevalence of food allergy in children continued to rise despite that conservative approach. This led the international food and allergy community to revise the current recommendations a prompted researchers to conduct multicentre clinical trials to compare the effect of the early introduction of allergenic food with the current recommendations. Learning Early About Peanut Allergy (LEAP), a study published in 2015, gave concrete evidence that early introduction of peanuts can significantly prevent the development of peanut allergy in many infants and very young children[82]. The LEAP study was a game-changer that overshadowed all the previous international guidelines and recommendations. More studies followed, investigating how the early introduction of egg and cow's milk resulted in similar outcomes. The introduction of the egg at the age of 4-6 mo helped reduce the development of egg allergy compared to those who had egg introduced at 10-12 mo[83]. Some countries, such as Canada, took the lead and started to change infants' feeding recommendations, with the early introduction of peanut butter for children with mild to moderate eczema, at 6 mo. For infants with severe eczema or severe egg allergy (< 1%), the introduction needs to be done under medical supervision along with a skin prick test done initially, followed by a home or hospital-graded introduction. The introduction should be avoided in case of high sensitisation, especially in those with a skin prick test of ≥ 8 mm wheal[84].

We hope to see significant changes in the current recommendation concerning the age of introducing weaning food and the introduction of certain foods -considered highly allergenic- below the age of 6 and 12 mo. The development of new weaning guidance can be a challenge, especially when it comes to the recommended age of introducing the different allergenic foods the amount and frequency of meals to be given. Alternatively, the new guidelines could be more pragmatic and leave it to parents and the baby's tolerance to dictate when and how to introduce these foods as it is in the proper form and consistency for the infant to swallow them.

Food allergy and parental anxiety

Food allergy in infants and young children causes significant stress and puts a heavy burden on parents. The psychological effects vary from anxiety and stress to depression. These manifestations were observed more often in mothers, peaking at certain stages in their children's lives, such as when they join nursery or school. While in other medical conditions, control is achievable by using medications and avoiding specific obvious triggers, with food allergy, the accidental exposure to a hidden ingredient could happen "anytime and anywhere", as described by some parents.

The allergenic food could be a component of a benign food fed to the child unknowingly, or eaten due to poor labelling or simply because another child shared his food with the atopic child. The stress is amplified if parents have witnessed their child suffering an anaphylactic reaction, which could affect the parents' entire life and undermine their sound ability to make the right decision in their daily lives. It may even interfere with providing the optimal treatment during anaphylaxis.

Physicians, allergy nurses and dietitians are encouraged to spend part of the allergy consultation practising good listening to the parents and inviting them to talk about what they feel and think about their child's allergy. Studies have addressed this issue by evaluating the stress produced, quality of life, and how normal activities (school, work, dining out, attending events, travel, and normal social life) have been affected. Some studies have recommended mandatory referral of these parents to the local psychological service for support and counselling. Psychological support and cognitive therapy would support these parents in finding a balance between keeping their child safe and enjoying a nearly everyday life[85].

Natural history and prognosis of food allergy

Most children with cow's milk and egg allergies grow out of their allergies even before school age[86]. However, tree nuts, peanut, fish, and shellfish allergies persist. Peanut is widely known for the aggressiveness of its allergic reaction. However, data in recent years have shown that severe morbidity and mortality have been linked to cow's milk and sesame. Figures of children with sesame allergy are growing worldwide for no apparent reason[43]. Tolerance induction is expected when the level of specific IgE antibody drops during every6 to 12-monthly monitoring, usually followed by home or hospital supervised reintroduction[6]. Interestingly, sometimes tolerance is diagnosed with the child accidentally ingesting the offending food, but to the parent's surprise, it does not cause any signs or symptoms.

CONCLUSION

There is a pressing need to develop new allergy tests that can accurately diagnose and predict the severity of any potential reaction. Future research is also needed to create simple and quick diagnostic tests to inform clinicians and parents when these children grow out of their food allergies.

No approved definite treatment can produce lifelong natural tolerance, and adrenaline autoinjector (AAI) remains the drug of choice in treating anaphylaxis. Studies showed some parents might underuse AAI due to a lack of empowerment knowledge of when and how to use the device. Data also showed worrying attitudes by teenagers towards the use of AAI related to their risk-taking behaviour. Further studies are still needed to elucidate other reasons for the underuse of AAI. Better training with audio-visual aids and psychological support for the patients and parents to find a balanced lifestyle is required. Adrenaline autoinjectors need to be made available in public places such as malls, bus stations, and schools, as the child's first-ever noticeable food allergy reaction could be a severe and life-threatening one.

More research into feeding recommendations with early introduction of allergenic food such as peanut, egg, and cow's milk is also needed.

FOOTNOTES

Author contributions: Elghoudi A and Narchi H wrote the paper, revised it, and approved the final submitted version.

Conflict-of-interest statement: The authors declare that the review article was written in the absence of any financial conflict of interest.

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S-Editor: Chang KL
L-Editor: A
P-Editor: Chang KL

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World Journal of Clinical Pediatrics

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World J Clin Pediatr 2022 May 9; 11(3): 270-288

DOI: 10.5409/wjcp.v11.i3.270

ISSN 2219-2808 (online)

MINIREVIEWS

Bleeding per rectum in pediatric population: A pictorial review

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Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Govindarajan KK, India

Received: June 27, 2021
Peer-review started: June 27, 2021
First decision: July 30, 2021
Revised: August 9, 2021
Accepted: March 16, 2022
Article in press: March 16, 2022
Published online: May 9, 2022

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Abstract

Bleeding per rectum in children can be seen in congenital as well as acquired conditions that may require medical or surgical management. The present review article is aimed to discuss the imaging findings of some common and uncommon causes of bleeding per rectum in children.

Key Words: Bleeding; Per rectum; Children; Imaging; Congenital

Core Tip: Bleeding per rectum in children can be seen in congenital as well as acquired conditions. The referring clinicians as well the radiologists must be aware of the various radiological findings of common and uncommon causes of bleeding per rectum in children discussed in the article.

Citation: Chandel K, Jain R, Bhatia A, Saxena AK, Sodhi KS. Bleeding per rectum in pediatric population: A pictorial review. *World J Clin Pediatr* 2022; 11(3): 270-288
URL: https://www.wjgnet.com/2219-2808/full/v11/i3/270.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i3.270

INTRODUCTION

Bleeding per rectum in children may be in the form of passage of either bright red or dark red blood (hematochezia) or black tarry stools (melena). It may occur due to congenital as well as acquired causes in the pediatric population which may require medical or surgical management.

The causes of bleeding per rectum in children across different age groups are summarized in Table 1. In the present review, we aim to discuss the imaging findings

Table 1 Causes of bleeding per rectum in children across different age groups

Up to 2 yr of age	2-5 yr	6-15 yr
Milk allergy	Polyps	Polyps
Necrotizing enterocolitis	Anal fissure	Anal fissure
Duplication cyst	Intussusception	Infectious enterocolitis
Polyps	Meckel diverticulum	Inflammatory bowel disease
Anal fissure	Infectious enterocolitis	Henoch-Schönlein purpura
Intussusception	Bleeding diathesis	Hemolytic-uremic syndrome
Hirschsprung disease related enterocolitis	Henoch-Schönlein purpura	Bleeding diathesis
Meckel diverticulum	Hemolytic-uremic syndrome	Angiodysplasia
Infectious enterocolitis	Angiodysplasia	Lymphonodular hyperplasia
Bleeding diathesis	Lymphonodular hyperplasia	Extrahepatic portal venous obstruction
	Extrahepatic portal venous obstruction	

of some common and uncommon causes of bleeding per rectum in children.

NECROTIZING ENTEROCOLITIS

Necrotizing enterocolitis (NEC) refers to acute severe inflammation of the bowel in the newborn. Its incidence ranges from 1%-5% in neonatal intensive care units[1,2]. Greater risk of NEC is noted in extreme preterm (less than 28 wk) and extremely low birth weight (birth weight less than 1000 g) babies [3]. Approximately 10% of NEC cases may be seen in term neonates with associated congenital heart diseases being the major risk factor for these patients[1,4-6].

Clinical findings vary with the severity of involvement, with feed intolerance, vomiting, hematochezia, and abdominal tenderness noted in the early stage. In advanced stages, it can lead to peritonitis, sepsis, and eventually shock.

Plain abdominal radiographs are the initial radiological investigation and the mainstay of diagnosis of NEC in an appropriate clinical setting. Both supine views and cross-table lateral views are preferred. The earliest and most common sign of NEC even before clinical findings is the loss of normal "mosaic" pattern of bowel gas in neonates along with tubular or rounded dilatation of the loops. This is seen in 90% of the neonates. The degree of dilatation and clinical severity are correlated[7]. Furthermore, persistent dilated bowel loops are an ominous sign, with the "fixed bowel loop sign" reflecting transmural bowel necrosis and imminent perforation".

In an appropriate clinical setting, the presence of intramural gas is considered a pathognomonic sign of NEC and is seen in 19%-98% of the cases[8-10] (Figure 1). Two patterns can be seen - a bubbly pattern (representing air in the submucosa) or a linear pattern of intramural gas (suggesting subserosal gas).

Portal venous gas (seen in approximately 30% of cases on X-ray) is seen as linear, branching radiolucent lines radiating from the region of the hilum towards the periphery[11,12]. It must be differentiated from pneumobilia where the gas is seen more centrally as compared to portal venous gas where it extends more peripherally[12].

In later stages, bowel perforation may occur and is seen as pneumoperitoneum which becomes an indication for surgical intervention[13] (Figure 2). Various signs have described free intraperitoneal gas in the abdomen, namely, Rigler sign (air lining the bowel wall), football sign, Cupola sign (air under the central diaphragm), inverted V sign (air outlining the lateral umbilical ligaments), *etc.* Cross table lateral views are especially valuable in detecting small amounts of interbowel gas, which is seen as a triangular lucency between the bowel walls.

Ultrasonography (USG) provides valuable information in patients with NEC in the form of bowel wall thickness and echogenicity, free intraperitoneal fluid and its character, peristalsis, and bowel wall perfusion. Few studies have shown USG to be more sensitive in depicting intramural and portal venous gas[14,15]. However, the major limitation is that it is operator dependent. Early stages of NEC show bowel wall thickening with loss of normal gut signature (the hypoechoic rim of the muscularis propria) with an increase in the wall echogenicity (Figure 3). This is accompanied by an increase in the Doppler color flow in the bowel wall in early stages. Later stages show thinning of the wall with reduced and later absent flow[14]. Free intraperitoneal fluid may be seen. The presence of low-level internal echoes/septations suggests perforation[12,13].

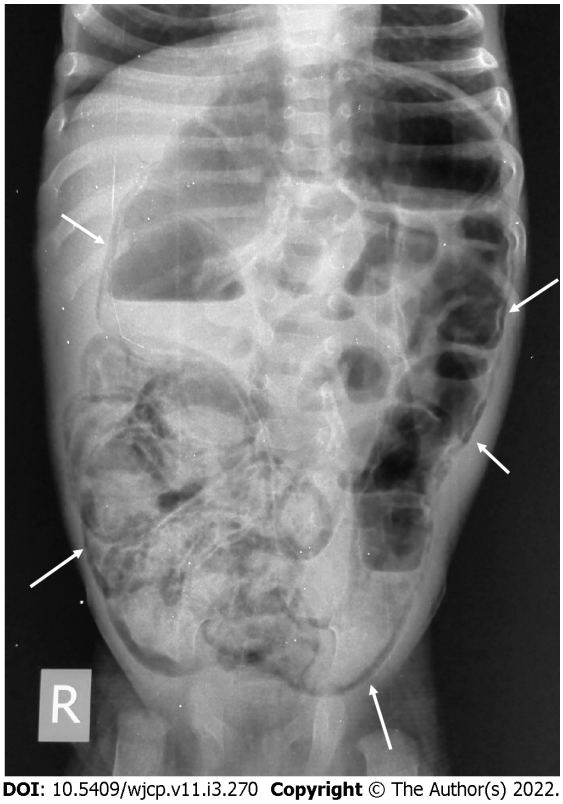

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Figure 1 Abdominal X-ray in an infant with necrotizing enterocolitis showing diffuse intramural air (arrows).

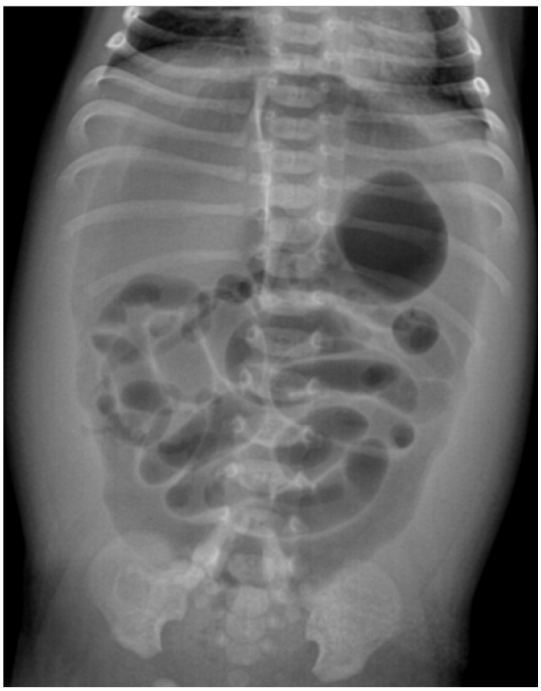

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Figure 2 Abdominal X-ray in an infant with necrotizing enterocolitis showing free air. The gas is seen outlining both sides of the bowel wall, *i.e.*, gas is seen within the bowel lumen as well as in the abdominal cavity. This sign is called Rigler sign and is suggestive of large amount of pneumoperitoneum.

MECKEL'S DIVERTICULUM

Meckel's diverticulum is a true diverticulum arising from the terminal ileum and is the result of persistence of the vitello-intestinal duct[16]. The lifetime risks of complications from Meckel's diverticulum are reported to be 6.4%[17], which include bleeding, diverticulitis, and intussusception.

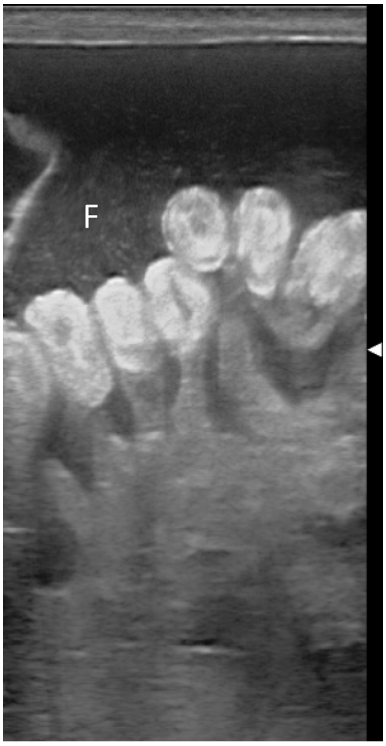

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Figure 3 Ultrasound in an infant with complicated necrotizing enterocolitis showing diffusely echogenic bowel walls. In addition, free fluid (F) with internal echoes is also seen.

The risk of bleeding is more common in children in than adults[18] and is due to the presence of ectopic gastric mucosa causing ulceration.

High-resolution USG shows a fluid-filled anechoic blind ending tubular structure in the right lower quadrant with a typical "gut signature". The other non-blinding end connects to a peristaltic bowel loop.

On $Tc^{99}m$ pertechnate scintigraphy, the ectopic gastric mucosa within the diverticulum appears as a focal area of increased tracer uptake in the right iliac fossa (sensitivity, 85%; specificity, 95%). Other scintigraphy techniques like Tc-99m labeled sulfur colloid scan and RBC scan can also localize the site of LGIB, but neither is specific for Meckel's diverticulum[19,20].

Complications of Meckel's diverticulum like diverticulitis, bowel obstruction, and in some cases intussusceptions are very well seen on computed tomography (CT)[21]. On CT, it appears as a fluid containing blind-ending pouch with variable mural thickness and adjacent fat stranding (Figure 4). Bowel obstruction can occur in Meckel's diverticulum secondary to intussusception, volvulus, the inclusion of diverticulum in the hernia, or foreign body impaction. Direct visualization of the diverticulum on computed tomography (CT) is difficult and features are similar to those caused by post-op adhesions, *i.e.,* dilated bowel loops with an abrupt change in caliber with the absence of soft tissue mass at the site of obstruction.

Surgical resection is the treatment of choice for symptomatic Meckel's diverticulum. However, management in asymptomatic incidentally detected diverticulum is controversial with some authors advocating conservative approaches owing to reduced lifetime risk of complications while others support early prophylactic diverticulectomy[17,18].

RECTAL POLYPS

Colorectal polyps are an important cause of lower gastrointestinal (GI) bleeding in children and adolescents with an estimated prevalence of 12% during pediatric colonoscopy for lower GI bleeding [22]. The majority of them are juvenile hamartomatous polyps[23] and an overwhelming majority of these are solitary and sporadic not associated with malignancy[24,25]. Most of these present as painless rectal bleeding[26]. Few of them may have lower abdominal pain. Most of these are located in the rectosigmoid and thus present as fresh red blood per rectum[27]. Multiple colonic polyps have been associated with polyposis syndromes.

On abdominal radiographs, they may appear as a rounded soft tissue mass in gas-filled bowel lumen. Barium enema may show polyps as a filling defect on the dependent wall[28]. Double contrast enema

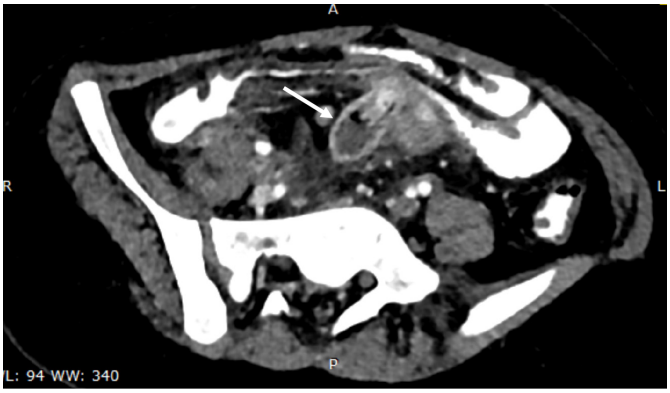

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Figure 4 Axial computed tomography image showing blind ending tubular structure (arrow) in the midline in the mesentery coursing towards adjacent ileal loop suggestive of Meckel's diverticulum. Inflammation is also seen in the surrounding mesentery.

(DCE) better outlines the polyps which may be seen as ring shadow with barium coated white rim. "Bowler hat sign" on double contrast air enema refers to the appearance of sessile polyp formed by a ring of barium at the base of the polyp surrounding a domed layer of barium coating the surface of the polyp[29]. "Mexican hat sign" is the analogous appearance of pedunculation on DCE formed by pair of concentric rings with outer and inner rings representing head and stalk of polyp[28].

CT colonography with the help of advanced graphic software creates two dimensional and three dimensional images along with volumetric data of the colon[30]. Being non-invasive, it provides a virtual endoluminal image of the polyps which are seen as projections (Figure 5). Bright lumen and dark lumen techniques in magnetic resonance (MR) colonography are used to visualize the colon. In bright lumen technique, polyps are seen as hypointense filling defects in the bright lumen. In dark lumen techniques, polyps appear as enhancing soft- tissue masses against the background of dark intraluminal air/water. Dark lumen techniques have better sensitivity than bright lumen techniques[31,32].

CROHN'S COLITIS

Inflammatory bowel disease is a chronic disease of the gastrointestinal tract consisting of two separate but related entities, namely, ulcerative colitis and Crohn's disease (CD). The manifestations of CD vary depending upon the extent of the disease with isolated colonic involvement presenting similarly to UC, whereas small bowel CD presents as fever, weight loss, and fatigue more commonly than UC[33]. Symptoms of inflammatory bowel disease wax and wane, resulting in "flares" and "remission", respectively. Up to 30% of children with CD present with growth failure[34].

Imaging has been used to assess parts of the bowel not accessible by direct endoscopic visualization, namely, the small bowel. Fluoroscopic techniques like small bowel enteroclysis and barium meal follow-through have largely been replaced by non-invasive techniques like CT and MR enterography, which provide both mucosal and extraluminal information as well as extraintestinal manifestations.

Double contrast barium enema allows to obtain greater details of the colonic mucosa and shows irregular thickening and distortion of the valvulae conniventes, widely separated bowel loops due to fibro-fatty mesenteric proliferation and pseudo-sacculations at the ulcer site. Severe cases produce transverse and longitudinal ulcers giving rise to cobblestone appearance. Chronic cases result in multiple strictures, sinus tracts, and fistulae, which can be readily demonstrated on contrast studies.

USG has a limited role and shows predominantly bowel wall thickening with loss of mural stratification, bowel wall hyperemia, reactive mesenteric lymphadenopathy, and ascites[35]. Other complications like abscess formation and bowel obstruction can also be demonstrated on USG.

CT helps in the simultaneous assessment of extraluminal and extraintestinal complications and has emerged as one of the primary imaging modalities. Common signs of active CD include bowel wall thickening (> 3 mm) and mucosal hyperenhancment[36,37]. These are the most common and sensitive findings of CD[38,39]. Increased vascularity in form of "comb sign" (Figure 6) refers to increased vascularity of the distal mesenteric arterial arcades and the vasa recta of the affected ascending colon and small bowel and is a sign of active inflammation[40]. Perienteric fat stranding and engorged vasa recta are the most specific signs of active CD on CT enterography[41]. Chronic CD produces "creeping fat sign" due to fibrofatty proliferation. Complications like strictures, bowel obstruction, fistula formation, and an intra-abdominal abscess can also be readily demonstrated.

MR enterography offers the advantage of radiation free modality and is of utmost importance in the pediatric population. It is specifically the modality of choice for better evaluation of perianal disease and better distinction of acute disease from chronic disease. Findings on MR enterography such as bowel

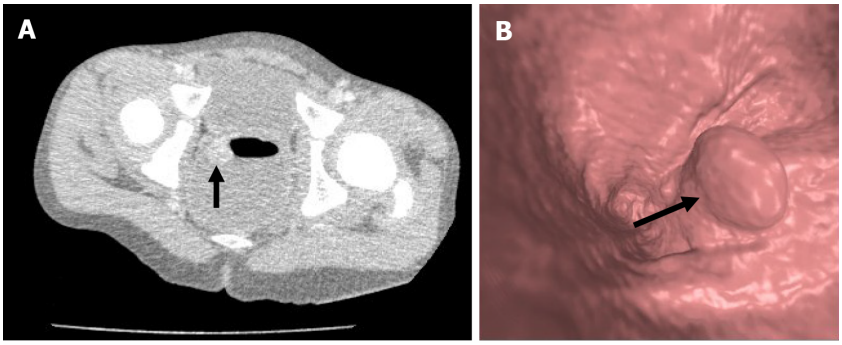

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Figure 5 Axial contrast enhanced computed tomography colonoscopy image. A: in a child with bleeding per rectum showing an enhancing polypoidal soft tissue (arrow) suggestive of a rectal polyp, as well as endoluminal colonoscopy image B: in another child showing a rectal polyp (arrow).

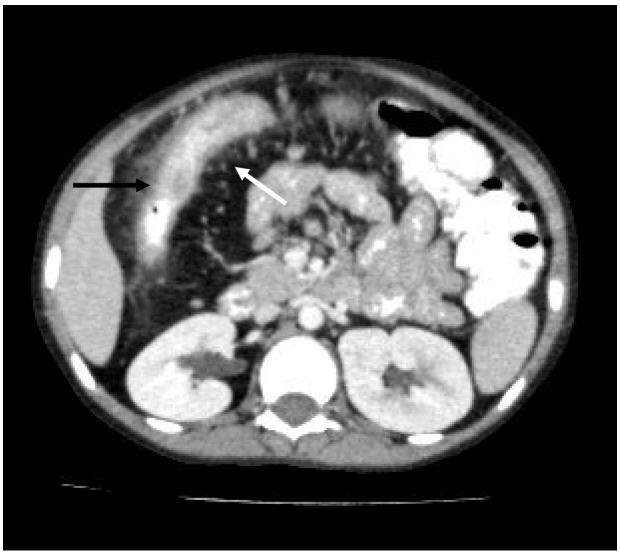

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Figure 6 Axial contrast enhanced computed tomography image in a child with Crohn's disease showing mesenteric fat proliferation with increased vascularity (white arrow) with mural thickening and enhancement in the adjacent bowel loop (black arrow).

wall thickening, mucosal hyperenhancement, mural stratification, and perienteric fat stranding denote active disease (Figure 7A and B). Chronic fibrotic CD shows hypointense signal on T2 weighted images. Diffusion weighted imaging is unique and shows restricted diffusion with low apparent diffusion coefficient values in active disease[42](Figure 7C). Strictures are better evaluated on MR enterography due to its dynamic bowel examination in time and CINE imaging[39]. Perianal fistulas and other entero-cutaneous fistulas appear as enhancing tracts best visualized on post- contrast fat-saturated T1 weighted sequences[43,44] (Figure 8).

MIDGUT VOLVULUS

Midgut volvulus occurs due to intestinal malrotation. In malrotation, due to abnormal 270^{0}counter-clock rotation of the midgut around the superior mesenteric artery (SMA) axis, an abnormally long, narrow mesenteric pedicle is present from the ligament of Trietz to the ileocaecal valve and is more susceptible for midgut volvulus. It usually presents with bilious vomiting due to proximal small bowel obstruction, but occasionally bloody stools may be seen secondary to intestinal ischemia.

Plain abdominal radiographs show a paucity of bowel gases beyond the stomach and the duodenum and colonic gas if present is seen in the left hemi-abdomen.

Upper GI contrast studies are the preferred imaging tests for a suspected case. Typical findings on fluoroscopy include a corkscrew appearance of the duodenum with it not crossing the midline and duodeno-jejunal (DJ) flexure present on the right, below the level of the pylorus and to the right of the left pedicle of L1 vertebra[45](Figure 9).

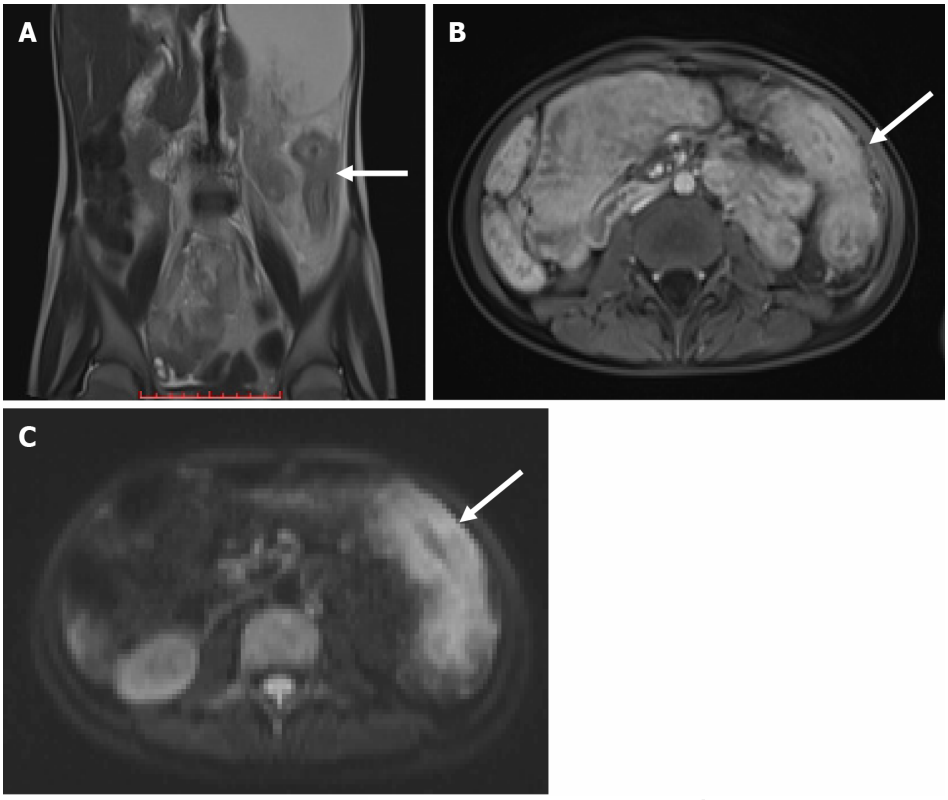

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Figure 7 Diffusion weighted imaging. A: Coronal T2 weighted magnetic resonance image showing long segment mural thickening in the descending colon (arrow in A) which is showing post contrast enhancement in post contrast T1 image (arrow in B) and intense diffusion restriction in diffusion weighted image (arrow in C) suggestive of active disease.

On USG, the superior mesenteric vein (SMV) is present to the left of the SMA[46]; however, the absence of this finding does not rule out malrotation[47,48]. On color Doppler images, twisting or wrapping of the SMV and the mesentery around the SMA in a clockwise direction is suggestive of whirlpool sign (Figure 10). It has a sensitivity, specificity, and positive predictive value of 92%, 100%, and 100%, respectively[46].

On CT and magnetic resonance imaging (MRI) at the site of volvulus, swirling of mesenteric vessels may be seen[49] (Figures 11 and 12). There is abnormally positioned duodenum, DJ flexure, cecum (in the left upper quadrant), and the large bowel (the majority of colonic loops in the right hemiabdomen) along with distention of the proximal duodenum and the stomach.

EXTRA-HEPATIC PORTAL VEIN OBSTRUCTION (EHPVO)

Extra-hepatic portal vein obstruction (EHPVO) is an important and common cause of non-cirrhotic portal hypertension (HTN). It is characterized by chronic thrombosis of the main portal vein, with or without intrahepatic portal vein, splenic vein, and SMV involvement with portal vein cavernoma formation. It is a disorder of children and young adults. In developing countries in the Asian region, it is the most common cause of portal HTN and upper GI bleeding in the pediatric population. Hypercoagulable state, infections, inflammation, portal venous anomalies, and perinatal umbilical vein catheterization are the most common etiologies; however, 70% of cases are idiopathic[50-52].

Clinically, these patients present with upper GI variceal bleeding with the associated feature of hypersplenism. Portal cavernous cholangiopathy (PCC) is seen in approximately 70%-100% of cases. Only 5%-28% of these are symptomatic due to biliary obstruction leading to intrahepatic biliary radical dilatation (IHBRD), choledocholithiasis, and hepatolithiasis[50,52]. Lower GI bleeding is rare with EHPVO (seen in 0.5%-10% of cases), but this is usually torrential and life-threatening. Anorectal varices (63%-95% of cases) and colopathy (approximately 54% of cases), secondary to increased portal venous pressure, are the two main causes for lower GI bleed in these patients[53]. Isolated inferior mesenteric vein portal hypertension secondary to EHPVO has been reported[54].

USG along with Doppler is usually the first investigation in a suspected case of EHPVO. The portal vein is not visualized and is replaced with multiple tortuous vascular channels suggestive of cavernoma formation. Depending on the extent of portal vein involvement, both intra- and extra-hepatic cavernoma

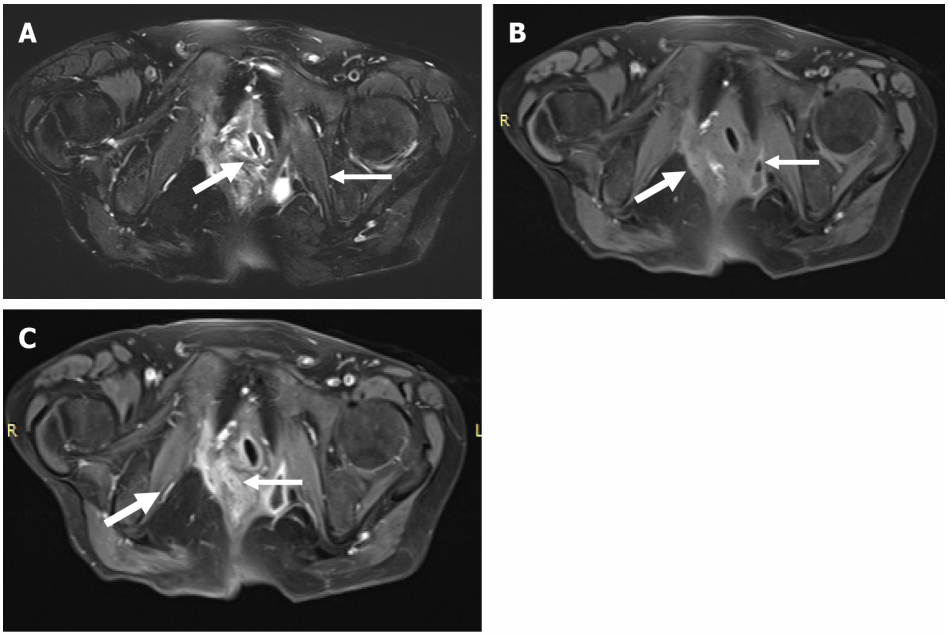

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Figure 8 Magnetic resonance image pelvis images in a child with Crohn's disease. A and B: T2 weighted fat suppressed and pre contrast T1 weighted images showing a fistulous tract (thick arrow in A and B) on the right side communicating with the rectum in the midline. In addition, a small collection (thin arrow in A and B) with air focus is seen in the left ischio-rectal fossa; C: Post contrast T1 weighted fat suppressed image showing enhancement of the tract (thick arrow) as well as peripheral enhancement of the collection (thin arrow).

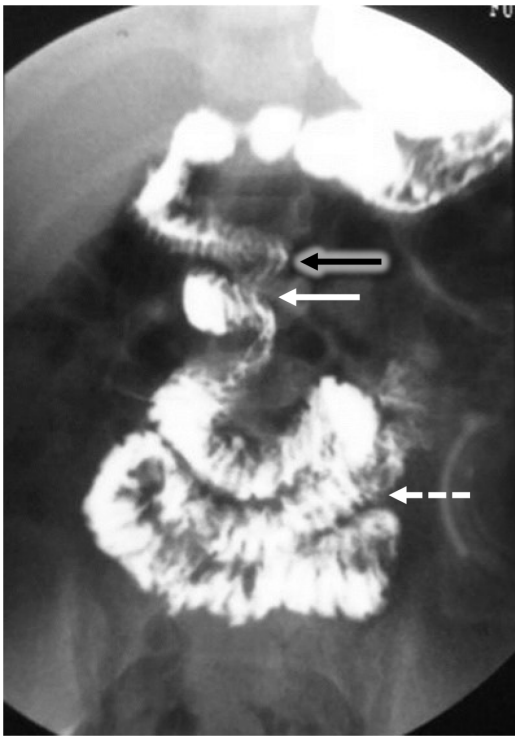

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Figure 9 Contrast study showing low lying duodenojejunal flexure (black arrow) with cork-screw appearance (solid white arrow) suggestive of malrotation with volvulus. The proximal jejunal loops (dashed white arrow) are seen in the midline and on the right side instead of the left side.

formation can be seen. Monophasic hepatopetal flow is noted in the collaterals. Pericholecystic collaterals are seen in approximately 30- 50% of cases. In patients with PCC, IHBRD, hepatolithiasis, and choledocholithiasis may be seen[50-52].

CT demonstrates vascular, biliary, and visceral changes. However, it is not routinely performed in children with EHPVO.

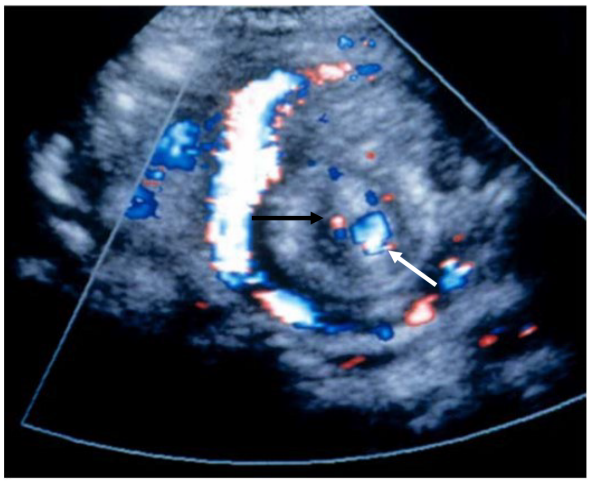

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Figure 10 Color Doppler image showing whirlpool sign due to rotation of the superior mesenteric vein (white arrow) along with bowel loops around the superior mesenteric artery (black arrow) suggestive of malrotation with midgut volvulus.

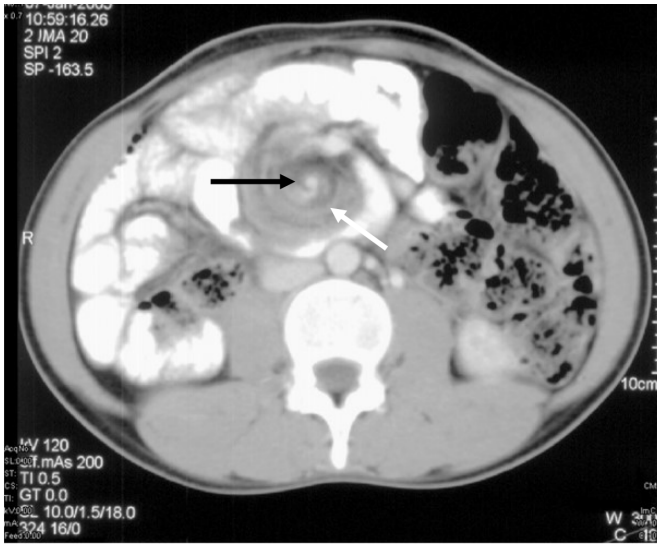

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Figure 11 Axial contrast enhanced computed tomography image showing whirlpool sign due to rotation of the superior mesenteric vein (white arrow) along with bowel loops around the superior mesenteric artery (black arrow) suggestive of malrotation with midgut volvulus.

Magnetic resonance cholangiopancreatography (MRCP) and MR portovenography provide valuable information regarding the biliary and splenoportal axis, respectively (Figure 13). MRI features suggestive of PCC include irregular wavy contour of bile ducts, biliary duct narrowing and strictures with or without dilatation, gall bladder and bile duct wall thickening, CBD angulation, hepatolithiasis and cholelithiasis, and choledocholithiasis. Paracholedochal and pericholecystic collaterals (Figure 14) are seen as enhancing tortuous collaterals causing smooth extrinsic impressions on bile duct[50,52]. MRI also demonstrates the presence of intra-splenic siderotic nodules (Gamna-Gandy bodies), which denotes long standing portal hypertension.

DUPLICATION CYST

Duplication cysts are a rare gastrointestinal tract developmental anomaly with an incidence of approximately 0.2% of all children and are most commonly seen in infancy. They may be contained within the gastrointestinal tract or lie outside to it and are usually seen on the mesenteric side. They are either cystic (80%) or tubular (20%). The ileum, esophagus, and colon are the common sites. Histologically, they show GI epithelial inner lining and smooth muscle outer layer. Presentation is variable and usually

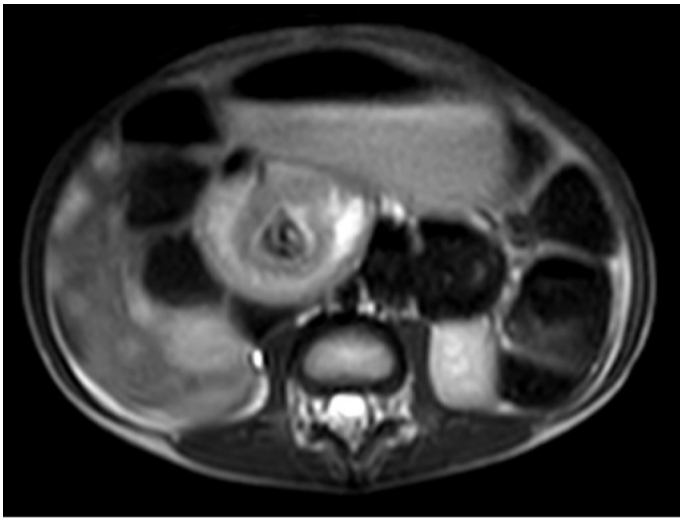

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Figure 12 Axial T2 weighted magnetic resonance image showing whirlpool sign suggestive of malrotation with midgut volvulus.

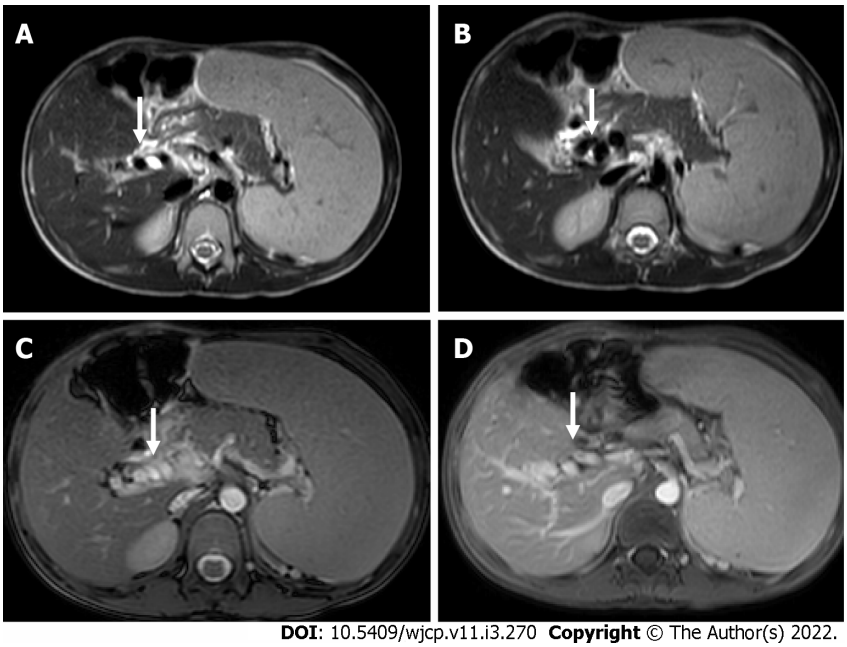

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Figure 13 A 7-year-old boy with extra-hepatic portal vein obstruction. A and B: Axial T2W images showing non visualized main portal vein with multiple collaterals (arrow) along the course of the portal vein; C and D: Axial BTFE and post-contrast T1 images show multiple collaterals (arrow) replacing the main portal vein at the porta. In addition, splenomegaly is also seen.

depends on location, size and mass effect, and complications. It may present as vomiting, abdominal distention, bleeding, abdominal mass, and increased urinary frequency and hesitancy. The cysts may be complicated by perforation and can act as a lead point for intussusception, volvulus, and bowel obstruction. GI bleeding occurs primarily because of ulceration of the gastric mucosa, intussusception, or pressure necrosis[55-58].

On USG, these are seen as well-defined anechoic lesions that demonstrate a classic gut signature (in about 50% of cases), *i.e.*, mucosal internal echogenic layer and muscular outer hypoechoic layer (Figure 15). This appearance is usually interrupted, due to non-uniform thickness[56]. USG appearance may vary in cases with hemorrhage. Barium contrast studies although not routinely used, may demonstrate a sub-mucosal filling defect with a mass effect on the gastrointestinal tract or rarely communicating with it[56].

On CT, a duplication cyst is seen as a well-defined non-enhancing mass with cystic attenuation adjacent to the GI tract (Figure 16). However, the central attenuation may vary, depending on hemorrhage or proteinaceous material, which usually show higher central attenuation[56] MRI will show a well-defined cystic lesion with heterogeneous signal density on TI weighted image and T2

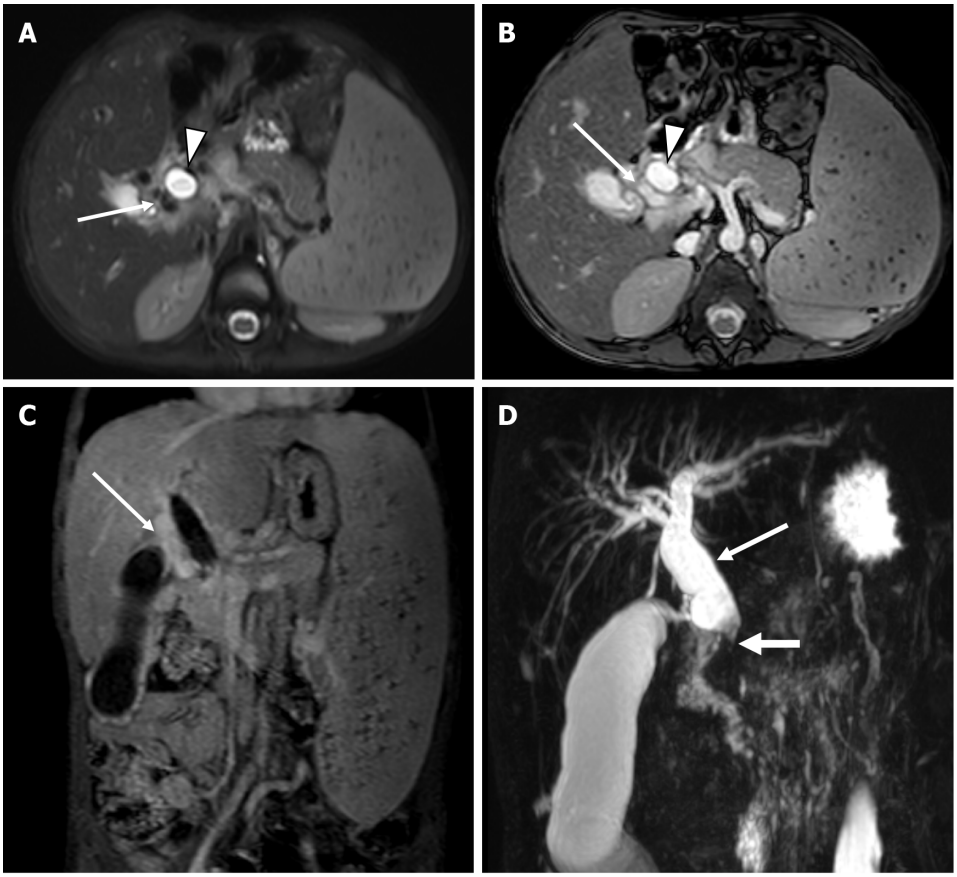

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Figure 14 Portal cavernoma cholangiopathy. A and B: Axial T2 weighted and axial BTFE magnetic resonance images show dilated CBD [arrowhead] with multiple pericholedochal collaterals [white arrow]; C: Coronal post-contrast T1 image shows multiple enhancing pericholedochal collaterals [white arrow]; D: Massive splenomegaly. Thick slab coronal magnetic resonance cholangiopancreatography image shows dilated and tortuous CBD (thin arrow) with abrupt cut-off at the lower end (thick arrow).

homogenous high signal intensity[55].

RECTAL HEMANGIOMA

Gastrointestinal hemangiomas are benign vascular tumors. They are most commonly seen in pediatric and young adults where they present as GI bleeding in about 80% of cases and are a cause of life-threatening anemia. Most commonly are seen in the small bowel. They are also seen in the colon and rectum. They may be seen as part of Klippel-Trénaunay, Maffucci, blue rubber bleb nevus syndrome, and disseminated neonatal hemangiomatosis. Histologically, they can be of cavernous, capillary, and mixed type with the cavernous variety being the most common subtype[59-61].

Plain radiograph being the first routine investigation may show phleboliths (evident in 50% of cases) along the course of the bowel. Extensive phleboliths are rare in young and this gives a clue for further investigations[59,60].

CT scan provides an intramural and extramural extension of the lesion. On CT, the involved bowel shows asymmetric bowel wall thickening with contrast enhancement. Phleboliths may or may not be seen[60] (Figure 17).

MRI shows rectal wall thickening, increased T2 signal intensity, and prominent perirectal serpiginous vascular channels. The perirectal vascular channels and atypical location help to differentiate rectal hemangiomas from hemorrhoids.

INTUSSUSCEPTION

Intussusception refers to telescoping of a bowel segment (intussusceptum) into the distal segment (intussuscipiens). It is among the most common abdominal emergencies in the pediatric age group with most cases (approximately 80%) occurring between 6 mo to 2 years of age[62-64]. It is also one of the

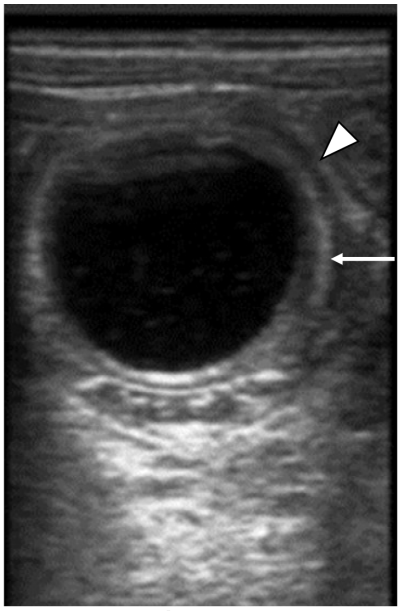

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Figure 15 Gray-scale ultrasonography image shows a well-defined anechoic lesion showing a classic gut signature with inner echogenic mucosa (arrow) and outer hypoechoic muscularis propria.

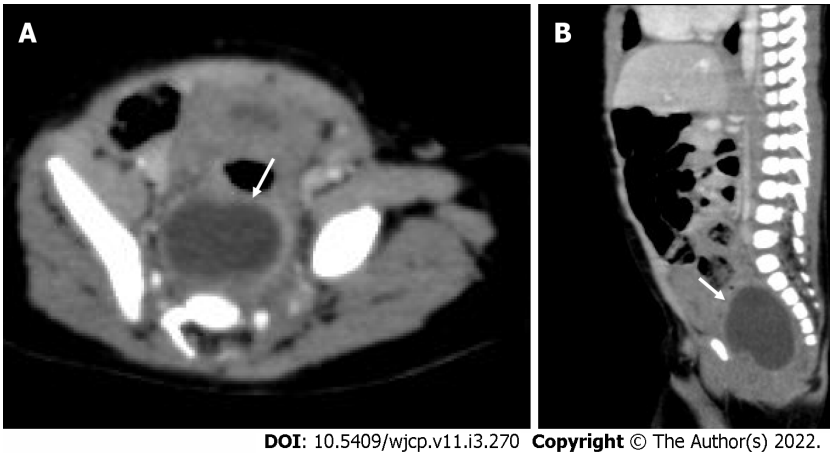

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Figure 16 Rectal duplication cyst. A and B: Axial and sagittal contrast enhanced computed tomography images show a well-defined cystic structure in the presacral space pushing the rectum (arrow) anteriorly.

most common causes of small bowel obstruction in infants[63]. The clinical triad of acute abdominal pain, palpable abdominal mass, and currant jelly stools/hematochezia is noted only in 50% of patients [62]. Ileo-colic is the most common type, where an ileum segment invaginates across IC junction into the colon for variable length[64].

Many radiographic signs of intussusception have been described, which include soft tissue density mass in the right upper quadrant, gasless abdomen, small bowel obstruction, and meniscus sign (Figure 18). X-rays usually are the initial investigation and are primarily used to look for obstruction and perforation and to rule out any other causes of pain abdomen. On barium enema, the meniscus sign and the coiled spring sign are the classic signs explained in intussusception[62].

Ultrasound has a high sensitivity (98%-100%) and specificity (88%-100%) for diagnosis of intussusception. Multiple concentric ring sign and crescent in doughnut sign are seen on axial scans (Figure 19). On longitudinal scans, sandwich and hayfork signs are explained[65](Figure 20). The intussuscipiens contains the entering limb and the returning limb of the intussusceptum, along with the mesentery. This gives variable ultrasound features depending on the length of the involved segment.

Most cases of intussusception are idiopathic. However, duplication cyst, polyps, tumor, or Meckel's diverticulum can act as a lead point and are more common in neonates or older children. USG is very sensitive in picking up and characterization of lead points[62,65](Figure 21).

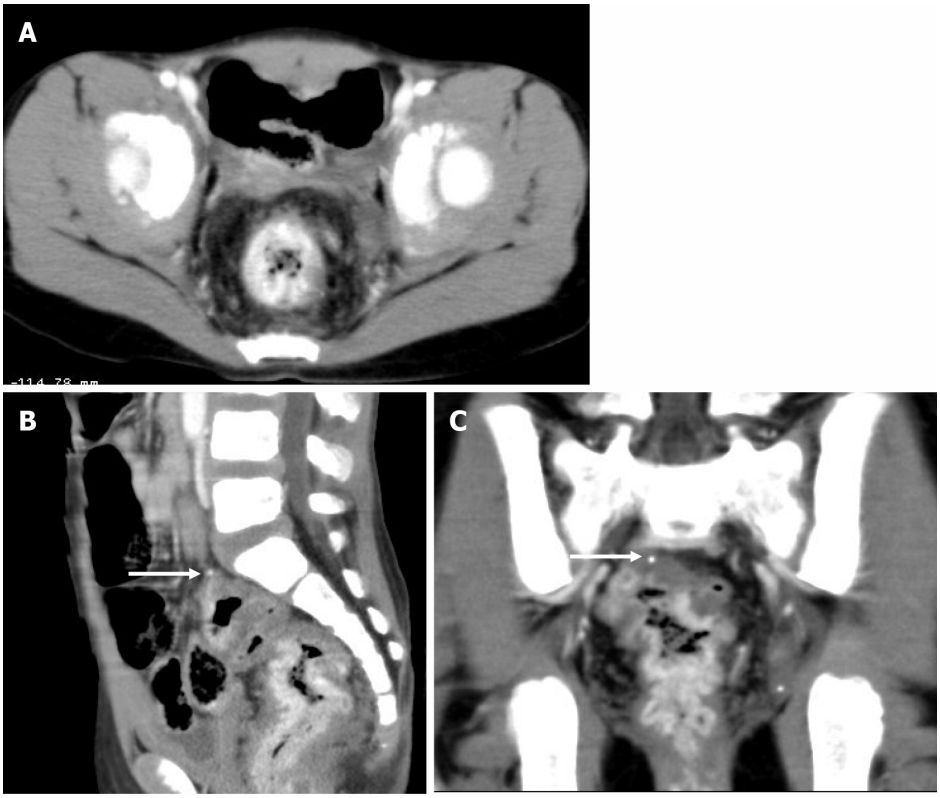

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Figure 17 An 8-year-old girl with bleeding per rectum. Axial (A), sagittal (B), and coronal (C) contrast enhanced computed tomography images showing diffuse rectal wall thickening with intense contrast enhancement. A tiny phlebolith is also seen (arrows in B and C). Findings are suggestive of rectal hemangioma.

Under real time fluoroscopy, uncomplicated ileocolonic and colocolonic intussusceptions can be reduced using barium enema, water-soluble contrast agents, and pneumatic reduction[62] (Figure 22).

CONCLUSION

To conclude, bleeding per rectum in children can occur due to a variety of medical and surgical causes across the different age groups. The referring clinicians as well as the radiologists must be aware of the various radiological findings of common and uncommon causes of bleeding per rectum in children, which may require medical and surgical management at the time of presentation.

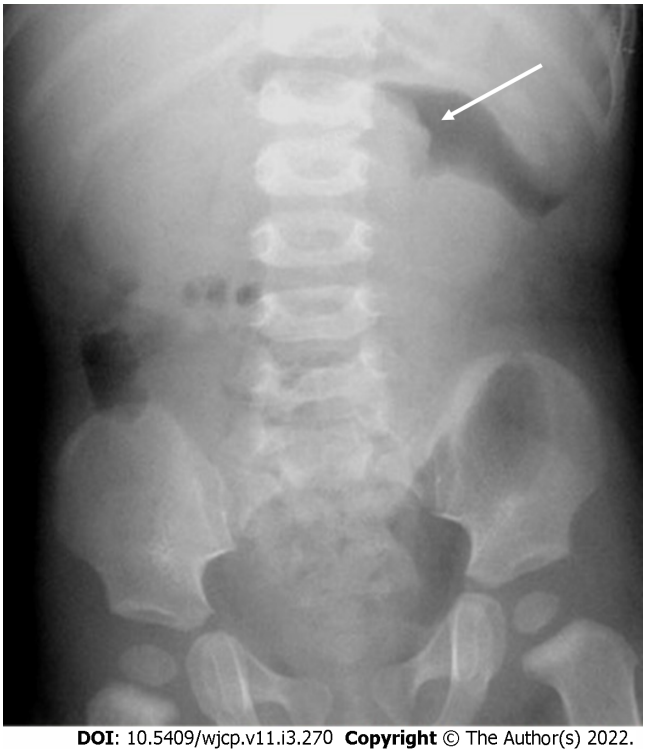

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Figure 18 Abdominal X-ray in a child with intussusception showing a gasless abdomen with meniscus of air outlining a soft tissue opacity (intussusceptum) in upper abdomen (arrow).

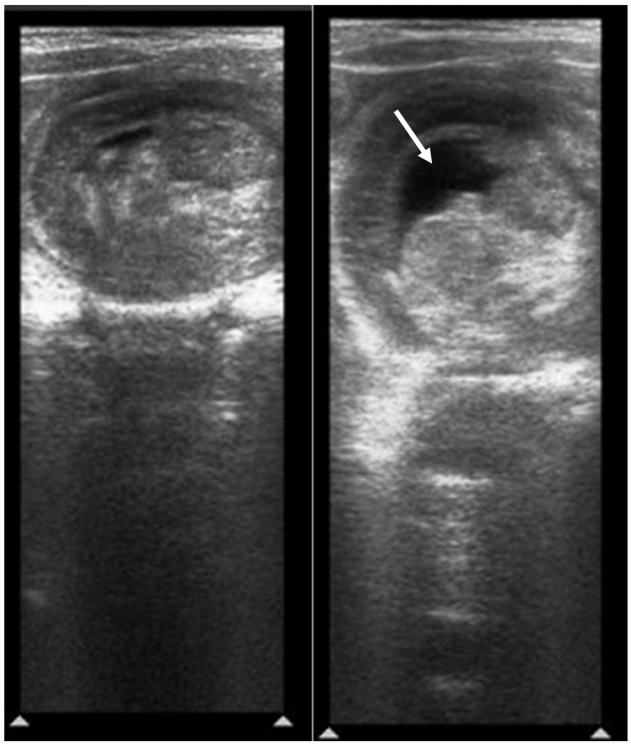

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Figure 19 Ultrasound image shows multiple concentric rings suggestive of intussusception. Minimal trapped fluid is also seen (arrow).

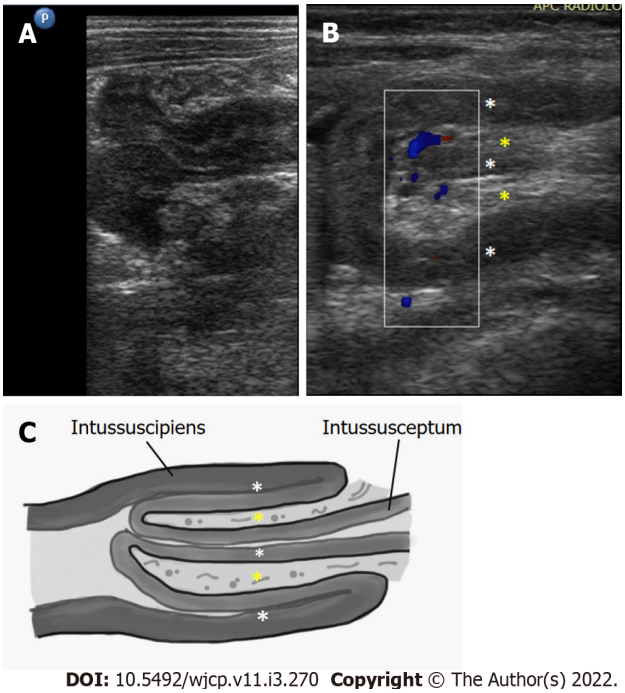

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Figure 20 Longitudinal ultrasound images of ileo-colic intussusception. A: Outer intussuscipiens and inner intussusceptum; B and C: Both show three hypoechoic lines (white asterixes) separating the two echogenic areas (yellow asterisks) giving sandwich sign/hay-fork sign. Longitudinal ultrasound images are important to delineate the length of the involved bowel segment.

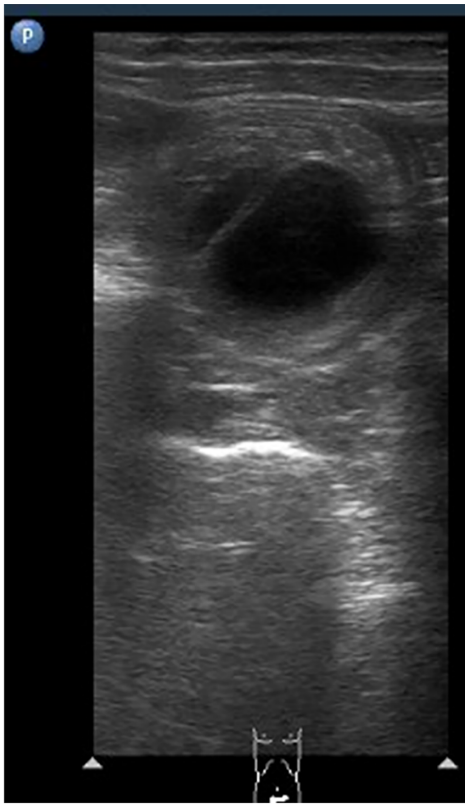

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Figure 21 Ultrasound image shows cystic structure at the apex of the intussusceptum as the pathological lead point. Differentials include duplication cyst and Meckel's diverticulum.

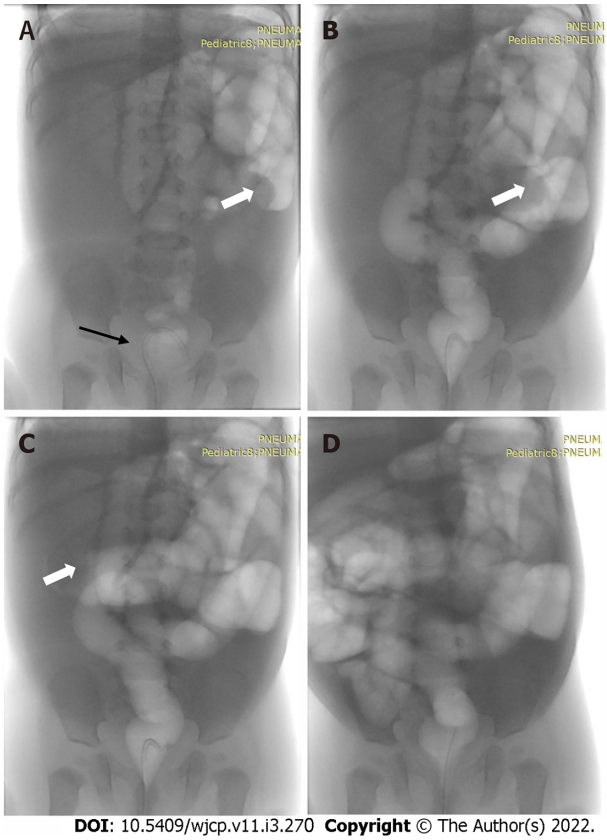

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Figure 22 Pneumatic reduction of intussusception under fluoroscopy. A: The patient is positioned supine with a feeding tube within the rectum (black arrow); B and C: The intussusceptum is seen in the left hypochondrium (open arrow) given by the meniscus sign; subsequent spots after air inflation show that the intussusceptum has moved proximally, as well as reflux of air in the small bowel after successful reduction (D) of the intussusception.

ACKNOWLEDGEMENTS

We thank Dr. Bhujade H, Assistant Professor, Department of Radiodiagnosis and Imaging, Postgraduate Institute of Medical Education and Research, Sector-12, Chandigarh, 160012, India for designing the diagrammatic image for Figure 20.

FOOTNOTES

Author contributions: Bhatia A, Saxena AK, and Sodhi KS designed the research study; Chandel K, Jain R, and Bhatia A performed the research; Chandel K, Jain R, and Bhatia A wrote the manuscript; Bhatia A, Saxena AK, and Sodhi KS edited the manuscript; all authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Country/Territory of origin: India

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S-Editor: Wang LL
L-Editor: Wang TQ
P-Editor: Qi WW

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 May 9; 11(3): 289-294

DOI: 10.5409/wjcp.v11.i3.289

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Observational Study

Turnaround times for molecular testing of pediatric viral cerebrospinal fluid samples in United Kingdom laboratories

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Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Gravina AG, Italy; Matowicka-Karna J, Poland

Received: June 21, 2021
Peer-review started: June 21, 2021
First decision: July 30, 2021
Revised: August 1, 2021
Accepted: March 26, 2022
Article in press: March 26, 2022
Published online: May 9, 2022

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Abstract

BACKGROUND

Rapid molecular testing has revolutionized the management of suspected viral meningitis and encephalitis by providing an etiological diagnosis in < 90 min with potential to improve outcomes and shorten inpatient stays. However, use of molecular assays can vary widely.

AIM

To evaluate current practice for molecular testing of pediatric cerebrospinal fluid (CSF) samples across the United Kingdom using a structured questionnaire.

METHODS

A structured telephone questionnaire survey was conducted between July and August 2020. Data was collected on the availability of viral CSF nucleic acid amplification testing (NAAT), criteria used for testing and turnaround times including the impact of the coronavirus disease 2019 pandemic.

RESULTS

Of 196/212 (92%) microbiology laboratories responded; 63/196 (32%) were excluded from final analysis as they had no on-site microbiology laboratory and outsourced their samples. Of 133 Laboratories included in the study, 47/133 (35%)

had onsite facilities for viral CSF NAAT. Hospitals currently undertaking onsite NAAT (n = 47) had much faster turnaround times with 39 centers (83%) providing results in ≤ 24 h as compared to those referring samples to neighboring laboratories (5/86; 6%).

CONCLUSION

Onsite/near-patient rapid NAAT (including polymerase chain reaction) is recommended wherever possible to optimize patient management in the acute setting.

Key Words: Cerebrospinal fluid; Nucleic acid amplification testing; Questionnaire survey; Turnaround times; Viral studies

Core Tip: Rapid diagnosis of viral meningitis in children through nucleic acid amplification testing (NAAT) of cerebrospinal fluid (CSF) can help in establishing a firm diagnosis, allowing early discontinuation of antibiotics and ensuring improved antibiotic stewardship. Turnaround times will be improved through availability of onsite NAAT facilities in the hospitals with inpatient pediatric units. All CSF samples in infants, irrespective of their white cell counts (actual/adjusted) should be offered NAAT, as viral meningitis due to enterovirus or human parechovirus can occur without pleocytosis.

Citation: Paul SP, Balakumar V, Kirubakaran A, Niharika J, Heaton PA, Turner PC. Turnaround times for molecular testing of pediatric viral cerebrospinal fluid samples in United Kingdom laboratories. *World J Clin Pediatr* 2022; 11(3): 289-294

URL: https://www.wjgnet.com/2219-2808/full/v11/i3/289.htm

DOI: https://dx.doi.org/10.5409/wjcp.v11.i3.289

INTRODUCTION

Timely diagnosis of meningitis is crucial to reduce mortality and long-term neurological disability[1,2]. The introduction of public health initiatives and immunization programs over the last 50 years have significantly decreased the incidence of bacterial meningitis in the United Kingdom[3]. In the United Kingdom, viral pathogens are the commonest cause of meningitis in both adult and pediatric populations[2]. The diagnosis of meningitis involves clinical assessment and a variety of laboratory investigations. Distinguishing between viral and bacterial causes can be challenging at initial presentation. For cases of suspected meningitis, in the absence of contraindications including coagulation disorders or raised intracranial pressure, a lumbar puncture should be performed[4,5]. Nucleic acid amplification testing (NAAT), predominantly through polymerase chain reaction (PCR) technology of the cerebrospinal fluid (CSF), is recognised as the gold standard for diagnosis in viral meningitis[6].

The aim of this study was to evaluate the use and availability of viral NAAT testing of CSF in microbiology laboratories across the United Kingdom.

MATERIALS AND METHODS

An electronic search of the National Health Service (NHS) database (http://www.nhs.uk/servicedirectories/pages/nhstrustlisting.aspx) was conducted to identify NHS trusts providing pediatric services across the United Kingdom (n = 212): England (n = 172), Scotland (n = 20), Wales (n = 12) and Northern Ireland (n = 8). Structured telephone surveys were conducted with either a Consultant Microbiologist (n = 3) or a Senior Biomedical Scientist (n = 193) in participating hospitals between July and August 2020. Twenty three of the 196 respondents submitted data *via* email citing data protection policy for their hospital. Sixteen laboratories did not respond, citing work pressures due to the coronavirus disease 2019 (COVID-19) pandemic, and were excluded from this study. The study was conducted and approved as an outcome audit. Ethical approval was considered not necessary as no confidential patient data was collected.

The survey consisted of a standardized questionnaire delivered by a single interviewer and the responses were collated electronically. The questionnaire asked the following details regarding NAAT of Paediatric CSF samples: (1) Whether the laboratory had onsite facilities to perform viral NAAT on CSF samples, type of assay used, criteria required to perform viral NAAT, the availability of point-of-

care (POC) testing, and the approximate turnaround time (TAT); (2) If the laboratory did not perform viral NAAT, they were asked where samples were sent, criteria required to perform testing, and the TAT for NAAT results; and (3) All the laboratories performing onsite testing were questioned about the impact of the COVID-19 pandemic on their ability to process CSF NAAT samples.

Statistical analysis was performed using standard Chi-squared analysis and a P value < 0.05 was considered to indicate significance.

RESULTS

In total, 196/212 hospitals (92%) responded to the questionnaire. Of those responding, 133 (68%) had an onsite microbiology laboratory within the same hospital site as the pediatric facility and were included in the study; 63 hospitals (32%) were covered by offsite microbiology services at a different hospital and were excluded from the study (Figure 1). More than one-third of onsite microbiology laboratories in the United Kingdom (n = 47) had facilities to perform viral CSF NAAT as well as cover neighboring onsite laboratories (n = 88) with no NAAT facilities. Other laboratories with no onsite microbiology laboratories (n = 63) outsourced samples elsewhere. The criteria used to perform viral NAAT amongst the 47 onsite laboratories were as follows: (1) Clinician request in 32% (n = 15); (2) Combination of CSF white blood cell count and clinician request in 28% (n = 13); (3) Performed on all samples if requested (referred to as "blanket testing") in 19% (n = 9); (4) Entirely dependent on CSF pleocytosis in 6% (n = 3); (5) Approval from a microbiologist in 4% (n = 2); and (6) Respondents unaware of the criteria for testing in 11% (n = 5).

The majority of microbiology laboratories (n = 86) that sent samples away did so on clinical request (n = 51; 59%). Other criteria included: CSF white cell counts (WCC) plus clinical request (n = 22; 26%), blanket testing (n = 8; 9%), and not known to respondent (n = 5; 6%). The TAT varied for CSF viral NAAT samples and is summarised in Table 1. The majority of laboratories (46 of 47) with onsite viral CSF NAAT facilities reported a sample processing time of ≤ 48 h, P < 0.00001. Four centers with onsite microbiology laboratories sent CSF samples to neighboring hospitals for more comprehensive NAAT targets as they offered limited facilities for viral PCR testing (only for enterovirus) performed through POC testing.

Onsite laboratories used a variety of assay kits to perform viral NAAT including BioFire® (n = 22), in-house kits (n = 8), various Multiplex PCR kits (n = 6), LightCycler® (n = 1), Altona diagnostics (n = 1), AusDiagnostics® (n = 3), EliTech® (n = 2), M2000 (n = 1) and kits not specified (n = 3). Most of the kits covered 4 common viruses: Enterovirus, Human parechovirus, Herpes simplex virus (HSV) 1 and 2. There were facilities for testing additional viruses such as Varicella zoster virus, Cytomegalovirus, Adenovirus, Human Herpes Virus-6, Epstein-Barr virus, which varied depending on the kit used.

The COVID-19 pandemic had minor effects on the turnaround time for viral CSF NAAT results for laboratories performing onsite tests (n = 4; 9%), primarily due to the sharing of PCR/NAAT machines for COVID-19 (severe acute respiratory syndrome coronavirus 2) analysis, as well as shortages of staff and/or manufacturer delays.

DISCUSSION

The diagnosis of pediatric meningitis can be fraught with difficulty, especially in neonates and infants. Although there are several suggestive clinical signs, there is no diagnostic isolated single finding or combination of features[7]. Clinical suspicion, with cytological and microscopic analysis of CSF samples are the mainstay of diagnosis; antibiotic treatment is often started empirically while these results are awaited.

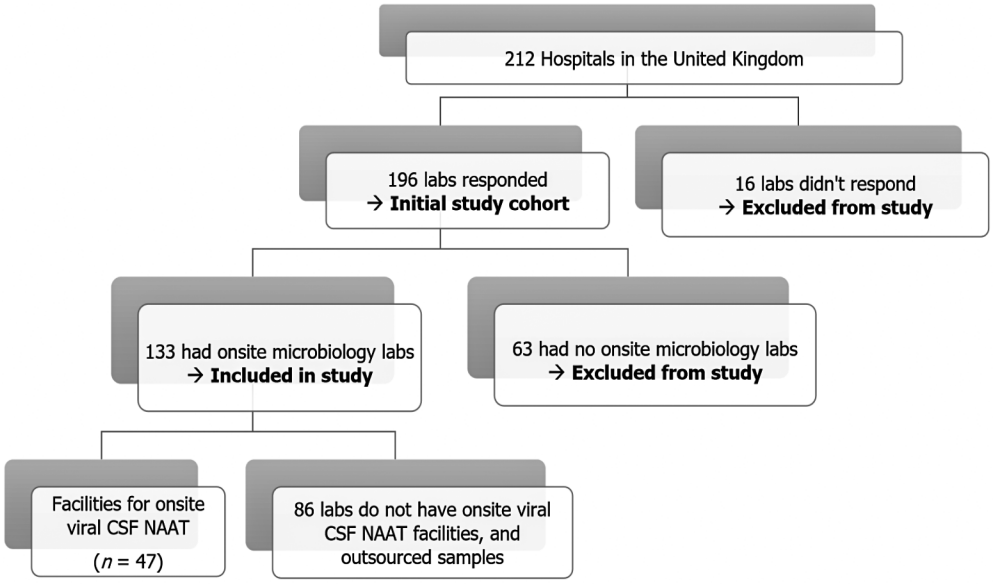
Enterovirus and Human Herpes Virus-6 (HHV-6) are the main pathogens causing viral meningitis in older neonates, infants and children. They usually have a favourable outcome, though neurological impairment has been observed, particularly following certain enterovirus strains such as D68 or human parechovirus[2]. HSV 1 and 2 infections typically cause severe encephalitis with serious sequelae if treatment with antivirals is delayed; evidence of these infections should be confirmed by NAAT as soon as possible.

The use of NAAT in the diagnosis of viral meningitis has been demonstrated to result in briefer parenteral antibiotic courses[5,8]. A positive CSF enterovirus result has also been associated with shorter lengths of hospital stay in infants with viral meningitis[5,9,10]. Most experts recommend that CSF PCR results for HHV-6 (due to potential for reactivation) should be interpreted with caution in the absence of readily attributable symptoms. A recent study reported that following detection of HHV-6 in 25 of 1005 children, five were subsequently diagnosed with either HHV-6 meningitis or meningoencephalitis based on HHV-6 detection in CSF, clinical presentation, and radiographic findings. These results led to early discontinuation of empirical acyclovir treatment in 12 children and appropriate initiation of ganciclovir therapy in 4 as a result of faster establishment of microbiological diagnosis[11]. NAAT remains an underutilised investigation: One observational study of 323 patients with a negative

Table 1 Turnaround times based on the presence of onsite laboratory nucleic acid amplification testing facilities

TAT (in hours)	Laboratories with onsite viral NAAT facilities (*n* = 47)	Laboratories without onsite viral NAAT facilities (*n* = 86)	*P* value
< 12	21	4	< 0.00001
12-24	18	1	< 0.00001
24-48	7	40	< 0.00001
48-72	0	23	NC
> 72	0	15	NC
Variable	1	3	NC

NC: Not calculated; NAAT: Nucleic acid amplification testing; TAT: Turnaround time.



DOI: 10.5495/wjcp .v11i3.289

Figure 1 Microbiology laboratories offering cerebrospinal fluid nucleic acid amplification testing. CSF: Cerebrospinal fluid; labs: Laboratories; NAAT: Nucleic acid amplification testing.

CSF gram stain reported that although PCR had the highest diagnostic yield it was only requested for 39.6% of patients[12].

The overwhelming majority of laboratories with onsite NAAT facilities (n = 47) reported a sample TAT of ≤ 24 h in 39/47 (89%), as compared to only 5/86 (6%) for samples sent elsewhere (P < 0.00001). The impact of transit times meant that only 52% (n = 45) of microbiology laboratories without NAAT facilities had a TAT of ≤ 48 h. Hopefully, as technology develops, turnaround times should improve, especially if POC tests become increasingly available. This has already been demonstrated as feasible for viral respiratory swab testing during the COVID-19 pandemic. A Canadian study using a model-based analysis of a retrospective cohort of all hospitalised children admitted with suspected enterovirus meningitis between November 2013 and 2017 demonstrated that same-day TAT of CSF enterovirus PCR was associated with a cost reduction of 342.83 Canadian dollar *per* patient in comparison to specimens sent to a reference laboratory. Further benefits such as decreased length of stay (LOS) and antibiotic therapy were also noted[13]. A retrospective study from the United States with 363 children who had HSV PCR tested on CSF samples demonstrated that the median duration of acyclovir therapy was significantly reduced in the group following implementation of a direct sample-to-answer assay technique (leading to faster TAT) as compared to laboratory-developed real-time PCR assay used in pre-implementation group [14.3 h *vs* 29.2 h (P < 0.01)] and marginal reduction in median LOS [4 d *vs* 5 d (P 0.23)][14].

There was also a wide variation in the acceptance criteria for performing NAAT analysis in the 133 centers with an onsite microbiology laboratory; the most popular approaches being based on clinician request (66/133, 50%) or a combination of CSF WCC with clinician request (35/133, 26%). Two recently published studies from the United Kingdom have suggested performing viral PCR testing of all CSF samples in infants, irrespective of their adjusted CSF WCC, has potential to reduce length of hospital

stay and antibiotic usage[5,9].

The COVID-19 pandemic had minimal effect on TAT with delay in sample analysis reported in 6% centers who had onsite testing facilities. Within the context of pediatrics, the cumulative effect of these delays can be lengthier hospital admissions, prolonged courses of parenteral antibiotics and diagnostic uncertainty.

CONCLUSION

Despite the widely documented benefits of using NAAT technology to aid the diagnosis and management of pediatric meningitis, onsite testing facilities for viral NAAT are limited in the United Kingdom. The lack of available NAAT facilities may have significant implications on patient outcomes, including increased LOS and duration of parenteral antibiotics. Early discontinuation of antibiotics in cases of viral meningitis should lead to improved antibiotic stewardship. Our study underlines the need for a national consensus on the role of PCR testing and emphasises the desirability of onsite PCR testing equipment for microbiology laboratories in the United Kingdom and elsewhere in the world.

ARTICLE HIGHLIGHTS

Research background

Viral pathogens are considered the major cause for meningitis worldwide. The use of nucleic acid amplification testing (NAAT), predominantly through polymerase chain reaction (PCR) in the diagnosis of meningitis has been demonstrated to result in faster turnaround times, shorter length of stay and briefer course of parenteral antibiotics.

Research motivation

NAAT remains an underutilized investigation and it is important to develop a national consensus on the role of PCR testing for diagnosing viral meningitis in children.

Research objectives

The aim of this study was to evaluate the use and availability of viral NAAT testing of cerebrospinal fluid (CSF) in microbiology laboratories across the United Kingdom.

Research methods

Structured telephone questionnaire survey was conducted to understand the availability of viral CSF NAAT in the United Kingdom with emphasis on the criteria used for testing and turnaround times including the impact of the coronavirus disease 2019 pandemic.

Research results

Onsite facilities for viral CSF NAAT was available in 35% centres with much faster turnaround times of ≤ 24 h as compared to those outsourcing to neighboring laboratories.

Research conclusions

Onsite/near-patient rapid NAAT [including polymerase chain reaction (PCR)] is recommended wherever possible to optimize patient management in the acute setting.

Research perspectives

Our study underlines the need for a national consensus on the role of NAAT and emphasizes the need for on-site PCR testing equipment for microbiology laboratories in the United Kingdom.

FOOTNOTES

Author contributions: Paul SP contributed to the Project concept, formulation of questionnaire survey, supervision, data analysis, manuscript revision, literature review and correspondence; Balakumar V, Kirubakaran A and Niharika J conducted interviews, data collection and analysis, prepared first draft; Heaton PA and Turner PC provided expert opinion, helped with formulation of questionnaire survey, edited manuscript.

Institutional review board statement: This is a national questionnaire survey and ethical approval wasn't considered necessary.

Conflict-of-interest statement: None for any of the authors.

Data sharing statement: All data has been included in the paper.

Country/Territory of origin: United Kingdom

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S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 May 9; 11(3): 295-306

DOI: 10.5409/wjcp.v11.i3.295

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Observational Study

Serologic, endoscopic and pathologic findings in pediatric celiac disease: A single center experience in a low/middle income country

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Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Han JM, China; Ma L, China

Received: October 11, 2021
Peer-review started: October 11, 2021
First decision: November 7, 2021
Revised: November 25, 2021
Accepted: April 2, 2022
Article in press: April 2, 2022
Published online: May 9, 2022

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Abstract

BACKGROUND

Studies in Africa, Asia, and Latin America are needed to provide a comprehensive picture of the global incidence of celiac disease (CD).

AIM

To describe the serology, endoscopic and histological findings in typical and atypical presentations of pediatric CD at a tertiary referral hospital in an African low/middle income country (LMIC).

METHODS

This observational study was conducted on 199 patients with CD from 2010 to 2019. The patients were divided into typical and atypical groups according to the presenting symptoms including 120 and 79 patients respectively. Serology, upper gastrointestinal endoscopy with duodenal biopsy were performed for patients who had symptoms suggestive of CD. The severity of the intestinal damage was graded according to the histo-pathologic Marsh-Oberhuber classification.

RESULTS

Chronic diarrhea was the main intestinal presentation in the typical group. Anemia was the most common extraintestinal symptom in both the typical and atypical group. Marsh-Oberhuber type 3b and 3c was significantly higher in the seropositive patients with a P value of 0.007. A significant correlation was observed between the histological grade of the biopsied duodenal mucosa and the clinical presentation ($P < 0.001$). Age was significantly higher in the atypical group (P value < 0.001).

CONCLUSION

Although typical CD was observed in 120 patients in this study, the clinical

variability of the condition was frequently observed. Age only was a significant predictor for the appearance of atypical CD. Therefore, CD presentations in LMIC are not different from industrialized countries.

Key Words: Typical; Atypical celiac disease; Celiac serology; Marsh-Oberhuber histopathology

Core Tip: This study included 199 patients diagnosed with celiac disease (CD) over a 10-year period from 2010 to 2019 and was conducted at our tertiary hospital. Age, sex, clinical presentation, serological tests, and endoscopic findings were evaluated. We used the Marsh-Oberhuber classification to define the histopathological findings of the duodenal biopsies. The histopathological evaluation of intestinal biopsies revealed a statistically significant correlation between the histological grade of biopsied duodenal mucosa and the clinical presentation ($P < 0.001$). Those typical and atypical CD are not different from industrialized countries regarding age, clinical presentations, serology and pathology.

Citation: Mansour HH, Mohsen NA, El-Shabrawi MH, Awad SM, Abd El-Kareem D. Serologic, endoscopic and pathologic findings in pediatric celiac disease: A single center experience in a low/middle income country. *World J Clin Pediatr* 2022; 11(3): 295-306
URL: https://www.wjgnet.com/2219-2808/full/v11/i3/295.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i3.295

INTRODUCTION

Celiac disease (CD) is an immune-mediated enteropathy caused by permanent sensitivity to gluten in genetically susceptible individuals. CD patients sustain an autoimmune reaction to the gliadin protein fraction of gluten[1]. The incidence of CD has been rising significantly in the second half of the 20th century and into the 21st century throughout the Western industrialized world. Population-based studies in Africa, Asia, and Latin America are needed to provide a comprehensive picture of the global incidence of CD[2].

CD is one of the most common causes of chronic malabsorption. This results from the injury to the small intestine with loss of absorptive surface area, reduction of digestive enzymes, and consequential impaired absorption of micronutrients, such as fat-soluble vitamins, iron, and potentially B_{12} and folic acid. Moreover, the inflammation exacerbates the symptoms of malabsorption by causing a net secretion of fluid that can result in diarrhea[3]. The clinical features of CD vary considerably. Typical or classic CD patients have predominant gastrointestinal manifestations, such as chronic diarrhea, abdominal distension, and failure to thrive. Typical CD is common in children diagnosed within the first 2 years of life. Many cases of CD present with predominant non-GI signs and symptoms, such as anemia, short stature, aphthous stomatitis, recurrent abdominal pain, pica, delayed puberty, osteopenia, and dental enamel hypoplasia and are called atypical or non-classic CD. The most common atypical presentations of CD are iron deficiency anemia unresponsive to iron therapy and short stature[4].

CD should be considered in the diagnosis of patients with an appropriate clinical history and patients from high-risk populations. Serological tests are used as initial tests for CD, and duodenal biopsies obtained during esophago-gastroduo-denoscopy (EGD) are considered the standard for diagnosis[5]. Endoscopy reveals grossly visible abnormalities in the proximal portion of the small intestine (scalloping of duodenal folds, mosaic mucosal pattern, and mucosal atrophy). The diagnosis is confirmed *via* histologic evaluation as per the Marsh-Oberhuber classification[6]. However, many recent studies have shown that the ingestion of uncontaminated oats is not only safe but can also improve the quality of the diet in most patients with CD or dermatitis herpetiformis. Other natural foods, such as vegetables, salads, pulses, fruits, nuts, meat, fish, poultry, cheese, eggs, and milk, can be consumed in a gluten free diet (GFD) without limitations[7].

This observational study aims to compare the serological, gastrointestinal endoscopic, and histopathologic findings in typical and atypical presentations of pediatric CD at a tertiary referral hospital in the capital city of Egypt; an African low/middle income country (LMIC). We also aimed to find whether these findings are different from presentations in industrialized countries.

MATERIALS AND METHODS

This hospital-based, cross-sectional observational study was conducted at Cairo University Children Hospital which is the largest pediatric tertiary hospital in the capital city of Egypt and one of the largest in the Middle East and North Africa (MENA) region. Data of the patients diagnosed with CD was collected in the period from January 2010 to December 2019. The study included 199 patients diagnosed with celiac disease; they were divided into two groups based upon the presenting symptoms: typical or classic CD (Group A) and atypical or non-classic CD patients (Group B). Patients with predominant GI features, such as chronic diarrhea, abdominal distension, and failure to thrive, were included in the typical CD group, whereas the patients with atypical intestinal or extraintestinal symptoms were included in the atypical CD group. The age of patients ranged from less than 1 year up to 18 years. Patients that were within the age group but on gluten-free diet, those within the age group without a history of gluten introduction before 6 mo, and those with other GIT pathology, such as inflammatory bowel disease (IBD) (*e.g.*, Crohn's disease) were excluded from the study. Detailed history was taken from each patient and/or care-takers with a special focus on the age of disease onset, history of diarrhea or constipation, abdominal distension, weight loss, anemia, bone pain, and neurological symptoms. Anthropometric measurements (height, weight and head circumference), and full systemic examination were performed.

Investigations of all patients included complete blood cell count, measurement and serum calcium and celiac serology (total immunoglobulin A, anti-tissue transglutaminase (anti-tTG) antibody IgA). EGD and duodenal biopsy were also performed. For the endoscopy to be accurate, the patients should have been on a gluten-containing diet. The patients were asked to fast (no food or drink) for 6-8 h before endoscopy. The amount and type of sedation are dependent on the patient's age, weight, and coexisting medical conditions. In the GI endoscopy laboratory of our tertiary hospital, UGI endoscopy was performed using pediatric-size flexible gastro-duodenoscopes with compatible biopsy forceps (standard gastroscope manufactured by KARL STORZ group (Tuttlingen, Germany). Four biopsies were obtained from the second and third part of the duodenum and one from the duodenal bulb. The endoscopic duodenal specimens were processed as formalin-fixed specimens embedded in paraffin blocks. The sections were cut with a thickness of 5 microns and stained with Hematoxylin and Eosin. The severity of the intestinal damage was graded by the pathologist as per the Marsh-Oberhuber classification[8]. After endoscopy was performed, the patient was transferred to a recovery room until any medication or sedation wears off. Most of the children were able to resume eating food within a few hours, after they fully recovered.

Diagnostic criteria for celiac disease patients in this study include (at least 4 of 5 or 3 of 4 if the HLA genotype is not performed)[9]

Typical symptoms of celiac disease: Chronic diarrhea, growth faltering and iron deficiency anemia.

Positivity of serum celiac disease IgA class autoantibodies at high titer: Both IgA class anti-tTG and endomyseal antibody (EMA) in IgA-sufficient subjects or IgG class anti-tTG and EMA in IgA deficient subjects. The finding of IgG class anti-deamidated gliadin peptide adds evidence to the diagnosis.

HLA-DQ2 or DQ8 genotypes: HLA-DQ2 positivity includes subjects with only half the heterodimer (HLA-DQB1*02 positive).

Celiac enteropathy at the small intestinal biopsy: Including Marsh-Oberhuber 3 Lesions, Marsh-Oberhuber 1-2 Lesions associated with positive celiac antibodies positive at low/high titer, or Marsh-Oberhuber 1-3 Lesions associated with IgA subepithelial deposits.

Response to the GFD: Data was statistically described in terms of mean ± SD, or frequencies (number of cases) and percentages when appropriate. Comparison of age between the study groups was done using Student *t* test for independent samples. For comparing categorical data, Chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Two-sided *P* values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, United States) release 22 for Microsoft Windows.

RESULTS

This observational study enrolled 199 patients diagnosed as CD according to clinical presentations, serology and histopathology at our tertiary referral hospital. Data of the patients diagnosed with CD was collected in the period from January 2010 to December 2019. They were further divided into two groups: typical CD and atypical CD groups. The typical group (Group A) included 120 cases of CD patients who had typical intestinal symptoms, whereas the atypical group (Group B) included 79 cases of celiac disease patients who had atypical intestinal or extraintestinal symptoms. The mean age was

3.74 ± 2.93 years in Group A (typical) and 5.74 ± 4.0 years in Group B (atypical), being significantly higher in the atypical group (*P* value < 0.001).

Overall, 51.7% (*n* = 62) males and 48.3% (*n* = 58) females presented with typical symptoms (Group A), whereas 51.9% (*n* = 41) males and 48.1% (*n* = 38) females presented with atypical symptoms (Group B) without statistically significant difference (*P* value was 0.9).

Chronic diarrhea (increased frequency and/or fluidity of the stool for more than 4 wk) was the main intestinal presentation in the typical group (99.2%) (*n* = 119) than in the atypical group (1.3%) (*n* = 1), whereas constipation (infrequent passage of stool or passage of hard stool) was more common in the atypical group (16.5%) (*n* = 13) than in the typical group (5.0%) (*n* = 6). Overall, 69.2% (*n* = 83) of the patients in the typical group and 41.8% (*n* = 33) in the atypical group presented with abdominal distention. Such symptoms were statistically significant as shown in Table 1.

Anemia (low hemoglobin level for age and sex) was the most common extraintestinal symptom in both the typical and atypical group (99.5%) (*n* = 198). There were 99.2% (*n* = 119) of the typical group cases discovered during patient follow-up and 100% (*n* = 79) of the atypical group cases presented with anemia. The type of anemia was determined by mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH). The most common type of anemia was microcytic hypochromic anemia, detected in 93.3% (*n* = 111/119) of the patients in the typical group and 93.7% (*n* = 74/79) in the atypical group. Normocytic normochromic anemia was detected in 5.9% (*n* = 7) of the patients in the typical group and 5.1% (*n* = 4) in the atypical group. Four cases of normocytic normochromic anemia were diagnosed as glucose-6-phpsphate dehydrogenase (G6PD) deficiency, two of them in the typical group and two in the atypical group. Macrocytic anemia was detected in two patients, one was typical and the other was atypical (Table 2).

Hypocalcemia was reported in 70.8% (*n* = 85) of the typical group cases and 65.8% (*n* = 52) of the atypical group cases. Delayed puberty was detected in 75% (*n* = 9/12) of the typical group cases and detected in 73.1% (*n* = 19/26) of the atypical group cases. Dermatitis was detected in 12.5% (*n* = 15) of the typical group cases and 7.6% (*n* = 6) of the atypical group cases.

Failure to thrive was common in the typical group, whereas short stature was common in the atypical group. Failure to thrive (weight < 5 percentile) was found in 67.5% (*n* = 81) of the typical group cases and 62% (*n* = 49) of the atypical group cases. Short stature (height < 5 percentile) was found in 61.7% (*n* = 74) of the typical group cases and 65.8% (*n* = 52) of the atypical group cases as shown in Table 1.

The majority of our patients had normal to high total IgA level (84.9%) (*n* = 169/199): 81.7% (*n* = 98) of the typical group and 89.9% (*n* = 71) of the atypical group. Low level of total IgA was observed in 18.3% (*n* = 22) of the typical group cases and 10.1% (*n* = 8) of the atypical group cases. Anti-tTG IgA was positive in 48.3% (*n* = 58) of the typical group cases and 60.8% (*n* = 48) of the atypical group cases (Table 3).

Histopathological evaluation of the intestinal biopsies (Figure 1) revealed Marsh-Oberhuber type 0 in 8 patients (4.0%), Marsh-Oberhuber type 1 in 18 (9.0%), Marsh-Oberhuber type 3a in 53 (26.6%), Marsh-Oberhuber type 3b in 56 (28.1%), Marsh-Oberhuber type 3c in 57 (28.6%), and Marsh-Oberhuber type 3b-c in 7 (3.5%). Marsh-Oberhuber type 3a was more common in the atypical group, whereas Marsh-Oberhuber type 3c was more common in the typical group. Marsh-Oberhuber type 3a was diagnosed in 24 patients (20.0%) in the typical group and 29 (36.7%) in the atypical group. The intestinal biopsies revealed Marsh-Oberhuber type 3c in 47 patients (39.2%) of the typical group and only 10 (12.7%) of the atypical group. The intestinal biopsies revealed Marsh-Oberhuber type 3b in 31 patients (25.8%) of the typical group and 25 (31.6%) of the atypical group. Marsh-Oberhuber type 3b-c was found in four patients (3.3%) of the typical group and three (3.8%) of the atypical group. No cases were classified as Marsh-Oberhuber type 2. Six patients (5%) of the typical group and two (2.5%) of the atypical group were classified as Marsh-Oberhuber type 0, whereas eight patients (6.7%) of the typical group and ten (12.7%) of the atypical group were classified as Marsh-Oberhuber type 1 (Table 4).

Marsh-Oberhuber type 0 was found only in seropositive patients. Total and subtotal villous atrophy (VA) (Marsh-Oberhuber type 3b and 3c) were more common in seropositive patients. Overall, 54% of the seronegative patients (*n* = 34) had Marsh-Oberhuber type 3b and 3c, whereas 67% of the seropositive patients (*n* = 71) had Marsh-Oberhuber type 3b-c, being significantly higher in the seropositive patients (*P* value = 0.007) (Table 5).

Among the seronegative patients, no cases were classified as Marsh-Oberhuber type 0 or type 2 based on their histological findings. In the seronegative patients with typical symptoms, 4 patients (10%) had Marsh-Oberhuber type 1, whereas 13 patients (32.5%), 13 patients (32.5%), 9 patients (22.5%), and 1 patient (2.5%) had Marsh-Oberhuber type 3a, 3b, 3c, and 3b-c, respectively. In the seronegative patients with atypical symptoms, four patients (17.4%) had Marsh-Oberhuber type 1, whereas eight patients (34.8%), ten patients (43.5%), and one patient (4.3%) had Marsh-Oberhuber type 3a, 3b, and 3c, respectively (Table 6).

In seropositive patients with typical symptoms 27 patients (46.6%) had Marsh-Oberhuber type 3c, in seropositive patients with atypical symptoms 15 patients (31.3%) had Marsh-Oberhuber type 3b with *P* value = 0.022 (Table 7).

Logistic regression analysis for the predictors of atypical CD, including all statistically significant items including age, diarrhea, constipation, abdominal distention, Marsh-Oberhuber type 3a, and Marsh-Oberhuber type 3c) was conducted. Age only was significant with a *P* value = 0.013 (as age

Table 1 Clinical presentation of typical and atypical celiac disease

Clinical presentations	Typical, *n* = 120		Atypical, *n* = 79		*P* value
	n	%	*n*	%	
Male	62	51.7	41	51.9	0.974
Female	58	48.3	38	48.1	
Chronic diarrhea	119	99.2	1	1.3	< 0.001
Abdominal distention	83	69.2	33	41.8	< 0.001
Constipation	6	5	13	16.5	0.007
Weight loss	81	67.5	49	62	0.427
Anemia	119	99.2	79	100	0.931
Short stature	74	61.7	52	65.8	0.552
Hypocalcemia	85	70.8	52	65.8	0.455
Depression	0	0	2	2.5	0.08
Skin lesion	20	16.7	11	13.9	0.764

Table 2 Type of anemia in typical and atypical celiac disease

	Microcytic hypochromic		Normocytic normochromic		Macrocytic hypochromic		*P* value
	n	%	*n*	%	*n*	%	0.931
Typical	111	93.3	7	5.9	1	0.8	
Atypical	74	93.7	4	5.1	1	1.3	

Table 3 Serological finding in both the typical and atypical groups

	Typical, *n* = 120		Atypical, *n* = 79		*P* value
	n	%	*n*	%	
Total IgA deficient	22	18.3	8	10.1	0.074
Anti-tTG IgA-positive	58	48.3	48	60.8	0.086
Anti-tTG IgA-negative	40	33.3	23	29.1	0.315

Ig: Immunoglobulin; Anti-tTG: Anti-tissue transglutaminase.

progresses, the predictors of atypical CD will increase).

DISCUSSION

This study included 199 patients diagnosed with CD over a 10-year period from January 2010 to December 2019 and was conducted at our tertiary hospital. Age, sex, clinical presentation, serological tests, and endoscopic findings were evaluated. We used the Marsh-Oberhuber classification to define the histopathological findings of the duodenal biopsies.

The mean age was 3.74 ± 2.93 years in Group A (typical) and 5.74 ± 4.0 years in Group B (atypical), being significantly higher in the atypical CD group than in the typical CD group ($P < 0.001$). The study conducted by Semwal *et al*[4] reported a mean age of 4.83 ± 3.05 years in the typical group and 7.71 ± 3.46 years in the atypical group, being significantly higher in the atypical group ($P < 0.001$). Dinler *et al*[10] reported a mean age of 6.2 ± 4.4 years in the typical group and 11.5 ± 3.4 years in the atypical group, being significantly higher in the atypical group ($P < 0.001$). Moreover, Kuloğlu *et al*[11]. reported that the age of children with typical type (7.5 ± 4.3 years) was significantly lower than that of those with atypical type (10.8 ± 4.3 years) ($P = 0.001$).

Table 4 Histological findings in the typical and atypical celiac disease group

Marsh-Oberhuber classification	Typical, *n* = 120		Atypical, *n* = 79		*P* value
	n	%	*n*	%	
0	6	5	2	2.5	0.386
1	8	6.7	10	12.7	0.149
2	0	0	0	0	
3a	24	20	29	36.7	0.009
3b	31	25.8	25	31.6	0.372
3c	47	39.2	10	12.7	< 0.001
3b-c	4	3.3	3	3.8	0.862

Table 5 Histological findings in the seropositive (normal IgA level+ positive anti-tTG IgA) and seronegative (normal IgA level + negative anti-tTG IgA) celiac disease

Marsh-Oberhuber grade	CD seronegative, *n* = 63		CD seropositive, *n* = 106		*P* value
	n	%	*n*	%	0.007
0	0	0	7	6.6	
1	8	12.7	8	7.5	
2	0	0	0	0	
3a	21	33.3	20	18.9	
3b	23	36.5	29	27.4	
3c	10	15.9	36	34	
3b-c	1	1.6	6	5.7	

CD: Celiac disease.

Table 6 Histological findings in the seronegative typical and atypical celiac disease group

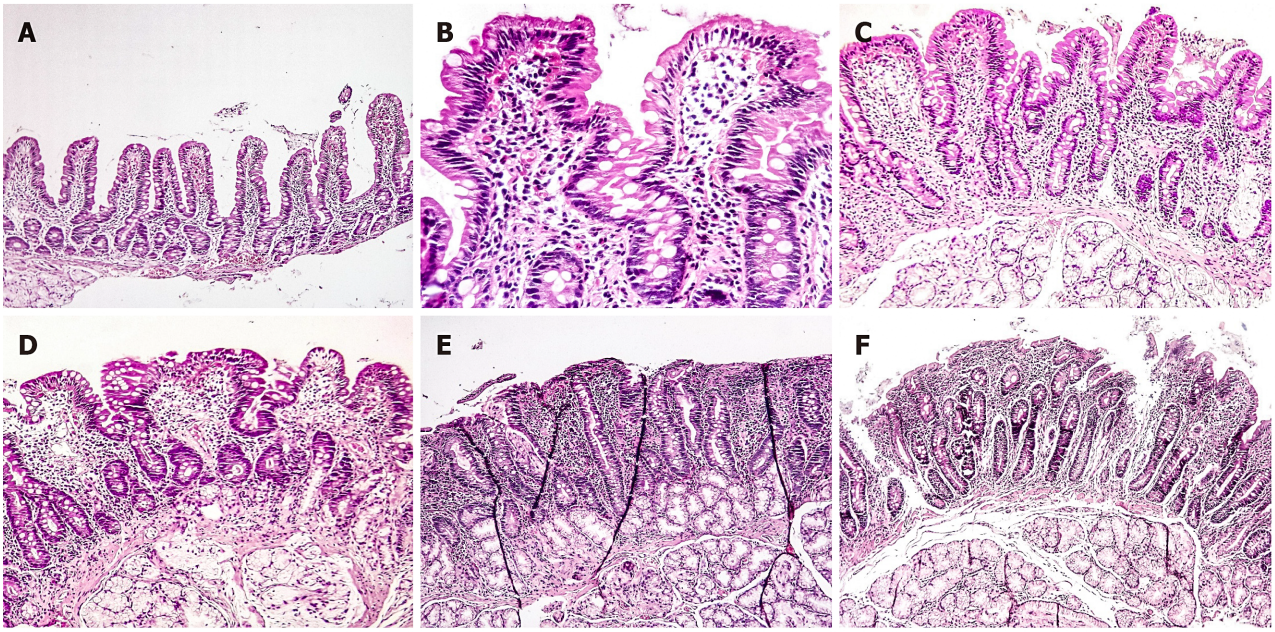
Marsh-Oberhuber classification	Typical, *n* = 40		Atypical, *n* = 23		*P* value
	n	%	N	%	0.315
0	0	0	0	0	
1	4	10	4	17.4	
2	0	0	0	0	
3a	13	32.5	8	34.8	
3b	13	32.5	10	43.5	
3c	9	22.5	1	4.3	
3b-c	1	2.5	0	0	

This difference is apparently due to the late diagnosis of the atypical cases because the typical presentations (diarrhea, abdominal distension) are usually noticed by the caretaker easily and therefore CD is diagnosed at an early age. Atypical presentations are diagnosed at a later age, due to the less awareness of the varied non-GI presentations of CD[4].

Of the studied cases, 51.7% (*n* = 103/199) were males and 48.2% (*n* = 96/199) were females, with a male/female ratio of 1.1:1. In the study conducted by Semwal *et al*[4], 48 males and 53 females had a male/female ratio of 1:1.1, whereas in the study of Dinler *et al*[10], 33 males and 54 females had a male/female ratio of 1:1.6. Kuloğlu *et al*[11] evaluated the features of 109 children with CD, in which the disease is known to be more frequent among females, with a male/female ratio of 1:1.5.

Table 7 Histological findings in the seropositive (106 patients) typical and atypical celiac disease group

Marsh-Oberhuber classification	Typical, *n* = 58		Atypical, *n* = 48		*P* value
	n	%	*n*	%	0.022
0	5	8.6	2	4.2	
1	3	5.2	5	10.4	
2	0	0	0	0	
3a	6	10.3	14	29.2	
3b	14	24.1	15	31.3	
3c	27	46.6	9	18.8	
3b-c	3	5.2	3	6.3	



DOI: 10.5492/wjcp.v11i3.295

Figure 1 Photomicrographs of duodenal mucosal biopsies. A: Preserved villi with increased intraepithelial lymphocytes (Marsh-Oberhuber type 1); B and C: Mild villous shortening and crypt hyperplasia with increased intraepithelial lymphocytes (Marsh-Oberhuber type 3a); D: Moderate villous atrophy and crypt hyperplasia with increased intraepithelial lymphocytes (Marsh-Oberhuber type 3b); E and F: Complete villous atrophy (Marsh-Oberhuber type 3c). Hematoxylin and eosin stained sections, original magnification ×40, ×200, ×100, ×100, ×100, ×100 respectively.

Anemia was the most common symptom (99.5%) (*n* = 198/199), followed by failure to thrive (65.3%) (*n* = 130/199), short stature (63.3%) (*n* = 126/199), chronic diarrhea (60.3%) (*n* = 120/199), and abdominal distention (58.3%) (*n* = 116/199).

In the study of Semwal *et al*[4], the most common symptom was anemia (54.5%) (*n* = 55/101) followed by chronic diarrhea (51.5%) (52/101) and short stature (50.5%) (51/101); in that of Dinler *et al*[10] chronic diarrhea (60.9%) (*n* = 53/87) followed by failure to thrive (49.4%) (*n* = 43/87), abdominal distention (41.3%) (*n* = 36/87), and short stature (33.3%) (*n* = 29/87); and in that of Kuloğlu *et al*[11], diarrhea (53.2%) (*n* = 58/109) followed by failure to thrive (45.9%) (*n* = 50/109), short stature (42.2%) (*n* = 46/109), and abdominal distention (26.6%) (*n* = 44/109).

Chronic diarrhea (*n* = 119/120) and abdominal distension (*n* = 83/120) were the most common presentations in the typical CD cases, whereas anemia (*n* = 79/79) and short stature (*n* = 52/79) were the most common presentations in the atypical CD cases. In the study of Semwal *et al*[4], chronic diarrhea (*n* = 52/55) and abdominal distention (*n* = 32/55) were the common presentations in the typical CD cases, whereas anemia (*n* = 36/46) and short stature (*n* = 29/46) were the most common presentations in the atypical CD cases. In the study of Dinler *et al*[10], chronic diarrhea (*n* = 53/55) and abdominal distention (*n* = 36/55) were the common presentations in the typical CD cases, whereas anemia (*n* = 10/32) and short stature (*n* = 20/32) were the most common presentations in the atypical CD cases. Moreover, in the study of Kuloğlu *et al*[11], chronic diarrhea (*n* = 58/66) and abdominal distention (*n* = 29/66) were the common presentations in the typical CD cases, whereas anemia (*n* = 23/41) and short stature (*n* =

22/41) were the most common presentations in the atypical CD cases.

In this study, the other common atypical presentations were constipation (9.5%) (*n* = 19/199), recurrent aphthous ulcers (5%) (*n* = 10/199), and bone changes in the form of rickets (10%) (*n* = 20/199). In the study conducted by Semwal *et al*[4], the most common atypical presentations were constipation (6.9%) (*n* = 7/101), recurrent aphthous ulcers (3.9%) (*n* = 4/101), and bone changes in the form of rickets (3.9%) (*n* = 4/101). Moreover, in the study conducted by Dinler *et al*[10], the most common atypical presentations were constipation (3.4%) (*n* = 3/87) and recurrent aphthous ulcers (2.2%) (*n* = 2/87), and in the study conducted by Kuloğlu *et al*[11], constipation (2.7%) (*n* = 3/109) and recurrent aphthous ulcers (1.8%) (*n* = 2/109).

Delayed puberty (14%) (*n* = 28/199), dermatitis (10.6%) (*n* = 21/199), and depression (1%) (*n* = 2/199). In the study of Semwal *et al*[4], delayed puberty (2.0%) (*n* = 2/101), chronic urticaria (1.0%) (*n* = 1/101), and depression (1.0%) (*n* = 1/101) were observed; in that of Dinler *et al*[10], chronic urticaria (1.1%) (*n* = 1/87) and delayed puberty (2.2%) (*n* = 2/87); and in that of Kuloğlu *et al*[11], delayed puberty (5.5%) (*n* = 6/109).

Anemia in CD is primarily caused by iron deficiency but also by the lack of other nutritional factors necessary for normal erythropoiesis, such as folic acid, vitamin B12, proteins, and copper[11]. Anemia was the most common presenting feature in the present study and was multifactorial. Based on the laboratory evaluation, anemia was prevalent in 198/199 patients (99.5%), with the microcytic hypochromic type being the most common in 185/198 patients (93.4%). In the study conducted by Berry *et al*[12], anemia was the most common presenting feature in their study and was multifactorial. Based on the laboratory evaluation, anemia was prevalent in 96/103 patients (93.2%), with iron deficiency anemia (IDA) being the most common in 84/103 patients (81.5%). In the study conducted by Dinler *et al*[10], iron deficiency with low iron stores was the most common presentation of anemia in both groups; IDA was found in 48/85 patients (56.5%). In the study conducted by Kuloğlu *et al*[11], iron deficiency anemia was a frequent finding in CD patients. It is seen in the majority of patients with one or more other findings and can also be the single finding of the disease. IDA was found in 80/98 patients (81.6%). Normocytic normochromic anemia was found in 5.6% of the patients (11 patients), one of them diagnosed with autoimmune hemolytic anemia and 4 cases (2%) diagnosed with G6PD deficiency. In the study conducted by Hosnut *et al*[13], the association between G6PD deficiency and CD was coincidental. The gene frequency of enzyme deficiency was 0.70 in the Mediterranean region. The prevalence of G6PD deficiency was high, reaching up to 10% in some ethnic populations in Turkey. Since G6PD deficiency is common in their country, the presence of CD and G6PD deficiency in their patients would be expected[13].

The prevalence of vitamin B12 deficiency is variable in different studies and ranges from 8 to 41% of the patients[14,15]. In this study, macrocytic hypochromic anemia was found in 2/199 patients (1%). One of them was diagnosed with megaloblastic anemia (vitamin B12 deficiency) by bone marrow biopsy (BMB). In the study conducted by Dinler *et al*[10] and Kuloğlu *et al*[11], vitamin B12 deficiency was observed in 3.4% (3/87) and 5.5% (6/109) of the child patients with CD, respectively. In the study conducted by Berry *et al*[12], Wierdsma *et al*[16], and McGowan *et al*[17], vitamin B12 deficiency was observed in 2.9% (3/103), 11% (5/50), and 19% (15/80) of the adult patients with CD, respectively. The mechanism of vitamin B12 deficiency in CD remains unclear. Various postulated mechanisms include ileal VA, pancreatic insufficiency in CD, autoimmune gastritis, small intestinal bacterial overgrowth, and decreased efficiency of mixing with transfer factors in the small intestine[12].

In this study, IgA deficiency was observed in 15% (*n* = 30/199) of the cases. In the study conducted by Kuloğlu *et al*[11], IgA deficiency was detected in 9.1% (*n* = 10/109) of the cases. The prevalence of CD in patients with selective IgA deficiency ranges from 10% to 30%[18]. Moreover, 53.3% (*n* = 106/199) of the cases had positive anti-tTG IgA. In the study conducted by Wolf *et al*[19], 76.4% (*n* = 404/529) of the patients had positive anti-tTG IgA.

In this study, we found a higher but non-significant proportion of patients with typical CD symptoms among the IgA anti-tTG-seronegative patients (63.5%) (*n* = 40/63) compared with the atypical CD seronegative cases (36.5%) (*n* = 23/63). In the study conducted on adults by Sugai *et al*[20], the proportion of patients with typical CD symptoms among the IgA anti-tTG-seronegative patients was 26.3% (*n* = 5/19) compared with the atypical CD seronegative cases (68.4%) (*n* = 13/19).

Furthermore, the histopathological evaluation of intestinal biopsies revealed total or subtotal VA (Marsh-Oberhuber type 3b and 3c) in 82/120 patients (68.3%) in the typical group and 38/79 (48%) in the atypical group. Partial VA (Marsh-Oberhuber type 3a) was observed in 24/120 patients (20%) in the typical group and 29/79 (36.7%) in the atypical group. The presence of total VA in the intestinal biopsies was significantly higher in the typical group than that in the atypical group ($P < 0.001$). In the study conducted by Dinler *et al*[10], the histopathological evaluation of intestinal biopsies revealed total or subtotal VA in 40/55 patients (72.7%) in the typical group and 12/32 (37.5%) in the atypical group. Partial VA was observed in 15/55 patients (27.3%) in the typical group and 20/32 (62.5%) in the atypical group. The presence of total or subtotal VA in the intestinal biopsies was significantly higher in the typical group than that in the atypical group ($P < 0.02$). Moreover, *Boskovica et al*[21] reported that the histopathological evaluation of intestinal biopsies revealed total or subtotal VA in 44/66 patients (66.6%) in the typical group and 24/37 (64.8%) in the atypical group. Partial VA was observed in 5/66 patients (7.5%) in the typical group and 1/37 (2.7%) in the atypical group.

Total and subtotal VA (Marsh-Oberhuber type 3b and 3c) were more common in the seropositive patients. Overall, 34/63 patients (54%) had Marsh-Oberhuber type 3b and 3c in the seronegative patients, whereas 71/106 patients (67%) had Marsh-Oberhuber type 3b and 3c in the seropositive patients, being significantly higher in the seropositive patients with a P value = 0.007.

In the study conducted on children by Hawamdeh *et al*[22], 40/51 seropositive patients (78.4%) had Marsh-Oberhuber type 3, whereas 9/30 seronegative patients (30%) had Marsh-Oberhuber type 3. A significant association between anti-tTG IgA titer and Marsh-Oberhuber grading was observed (P value 0.000). In the study of Donaldson *et al*[23], 3/26 seronegative patients (11.5%) had Marsh-Oberhuber type 3b and 3c, whereas 31/56 seropositive patients (55.3%) had Marsh-Oberhuber type 3b and 3c. IgA anti-tTG was significantly correlated with the Marsh-Oberhuber grades (P value 0.001). In the study conducted by Boskovica *et al*[21], the levels of tTG antibody were correlated significantly with Marsh-Oberhuber types in the entire population ($P < 0.0001$) and separately for typical ($P < 0.001$) and atypical ($P < 0.0001$) groups. In the study conducted on adults by Sugai *et al*[20], 7/19 seronegative patients (36.8%) had Marsh-Oberhuber type 3b and 3c, whereas 33/45 seropositive patients (73.3%) had Marsh-Oberhuber type 3b and 3c. In the study of *Dore et al*[24], severe duodenal mucosal damage (Marsh-Oberhuber type 2-3) was observed less frequently in patients with seronegative CD (n = 28/48) than in those with seropositive CD (n = 66/85) (58% *vs* 78%, P = 0.019).

In this study, 8/199 patients (4%) had Marsh-Oberhuber 0 and positive serology (potential CD): 6/120 patients had typical symptoms (5%) and 2/79 had atypical symptoms (2.5%). In the study conducted by Hawamdeh *et al*[22], 15/81 patients (18.5%) had Marsh-Oberhuber 0 and positive serology and were considered potential CD patients. In the study conducted by Boskovica *et al*[21], there were 12/37 patients with positive serology and Marsh-Oberhuber 0 (potential CD) (32.4%) had atypical CD symptoms and 11/66 (16.6%) had typical CD symptoms. In the present study, the histopathological evaluation of intestinal biopsies revealed Marsh-Oberhuber type 1 in 18/199 patients (9%), type 3a in 53/199 (26.6%), type 3b in 56/199 (28.1%), type 3c in 57/199 (28.6%), and type 3b-c in 7/199 (3.5%). Typical CD was more likely to have a significantly higher Marsh-Oberhuber grade based on the histological findings ($P < 0.001$). In the study conducted by Semwal *et al*[4], the histopathological evaluation of intestinal biopsies revealed Marsh-Oberhuber type 2 in 2/101 patients (2%), type 3a in 45/101 (44.6%), type 3b in 34/101 (33.7%), and type 3c in 20/101 (19.8%). Typical CD was more likely to have a significantly higher Marsh-Oberhuber grade based on the histological findings ($P < 0.001$).

In this study, the histopathological evaluation of intestinal biopsies revealed a statistically significant correlation between the histological grade of biopsied duodenal mucosa and the clinical presentation ($P < 0.001$). Dinler *et al*[10] and Semwal *et al*[4] also found that in children, total/subtotal VA was significantly higher in the typical group than in the atypical group. On the other hand, Brar *et al*[25] found that the degree of VA in the duodenal biopsies did not correlate with the mode of presentation, which might be due to the differences in the age of the study population since we studied children, while Brar *et al*[25] studied adult CD patients. Those typical and atypical CD in LMIC are not different from industrialized countries regarding age, clinical presentations, serology and pathology.

Limitations of our study: We didn't collect data about family history (as we focus on histopathology and clinical finding) and vomiting (as vomiting was not a common presentation in our patients and this was reported in Abu-Zekry[26]. We didn't collect data for laboratory test as anemia (hemoglobin, MCV, MCH) were taken through interpretation of result according to age and sex.

CONCLUSION

In conclusion, CD presentations in LMIC are not different from industrialized countries and late diagnosis is more common in atypical cases.

ARTICLE HIGHLIGHTS

Research background

Celiac disease (CD) is defined as an immune mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals. CD is one of the most common causes of chronic malabsorption. CD results from injury to the small intestine with loss of absorptive surface area, reduction of digestive enzymes, and consequential impaired absorption of micronutrients such as fat-soluble vitamins, iron, and potentially B12 and folic acid. Celiac disease presented with chronic diarrhea, failure to thrive and abdominal distention usually observed within the first 1-2 years of life. At the older age, atypical features such as anemia, short stature, bone disease and liver failure may occur. It should be considered in patients with an appropriate clinical history as well as in patients from high-risk populations. Serological tests are used as initial tests for CD and duodenal biopsies obtained during esophagogastroduodenoscopy (EGD) are considered the standard for diagnosis. The diagnosis of CD is based on the identification of histological lesions accompanied by clinical and serological consistent

data. On the basis of the presence of one or more of these elementary lesions the histopathology of CD is subdivided into different diagnostic categories according to Marsh classification.

Research motivation

Many cases of Celiac disease in our country with different clinical presentations motivate us to search for different histopathological examination in the disease sub-types.

Research objectives

To compare the serological, gastrointestinal endoscopic, and histopathologic findings in typical and atypical presentations of pediatric CD at a tertiary referral hospital in the capital city of Egypt; an African low/middle income country. We also aimed to find whether these findings are different from presentations industrialized countries.

Research methods

A hospital-based, cross-sectional observational study was conducted at Cairo University Children Hospital which is the largest pediatric tertiary hospital in the capital city of Egypt and one of the largest in the Middle East and North Africa (MENA) region. Data of the patients diagnosed with CD was collected in the period from 2010 to 2019. The study included 199 patients diagnosed with celiac disease; they were divided into two groups based upon the presenting symptoms: typical or classic CD (Group A) and atypical or non-classic CD patients (Group B).

Research results

Typical CD is more common than atypical, chronic diarrhea was common in typical group with *P* value < 0.001. sero-positive cases were 106 (typical 58, atypical 48cases). The most common histological finding in typical seropositive cases were March types 3c (27/58, 46.6%), The most common histological finding in atypical seropositive cases were March types 3b (15/48, 31.3%) (*P* value 0.022).

Research conclusions

CD clinical presentations in low/middle income country are not different from industrialized countries and late diagnosis is more common in atypical cases.

Research perspectives

Follow up of the CD cases and their prognosis, if there is changes in histological picture in future.

ACKNOWLEDGEMENTS

We would like to thank the parents and children for their cooperation in this study.

FOOTNOTES

Author contributions: El-Shabrawi MH, Mohsen NA, Abd El-Kareem D and Mansour HH contributed to the conception of the study, designed and executed the study, and wrote the final manuscript; El-Shabrawi MH contributed to the writing of the manuscript draft; Awad SM collected data and contributed to the writing of the manuscript; all authors read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the research ethics committee of Cairo university Institutional Review Board [(Approval No. 12-10-2019]).

Informed consent statement: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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S-Editor: Wang LL
L-Editor: A
P-Editor: Wang LL

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 May 9; 11(3): 307-320

DOI: 10.5409/wjcp.v11.i3.307

ISSN 2219-2808 (online)

SCIENTOMETRICS

Global research production in neonatal abstinence syndrome: A bibliometric analysis

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Specialty type: Substance abuse

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Dong Y, China

Received: March 19, 2021
Peer-review started: March 19, 2021
First decision: May 6, 2021
Revised: May 21, 2021
Accepted: March 16, 2022
Article in press: March 16, 2022
Published online: May 9, 2022

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Abstract

BACKGROUND

Recently, neonatal abstinence syndrome (NAS) emerged as a significant global concern with a dramatic increase in healthcare expenditures. The incidence of the NAS has increased notably in the past decade and emergence as a global public health problem.

AIM

To evaluate the development and trend of global NAS research from 1958 to 2019 by bibliometric analysis.

METHODS

Analyzed aspects included publication output per year, language, document types, journals, countries/territories, h-index, authors, and top research priorities. The VOSviewer was used to determine the top research priorities, and trends, and to present bibliometric networks concerning various dimensions, such as co-authorship, authors, and countries.

RESULTS

A total of 1738 articles were retrieved in the Scopus database from 1958 to 2019. It was found that the great majority of the total NAS documents (n = 1295) were original articles followed by reviews (n = 268) and letters (n = 48). The most productive countries in the NAS field were the United States (n = 833), Canada (n = 112), the United Kingdom (n = 111), and Germany (n = 77). Treatment and hospital outcomes in NAS, evidence-based nurse-driven interventions for the care of newborns with NAS, and a systematic reviews and network meta-analysis for therapeutic approaches of NAS were found in recent years (after 2010), compared with terms such as pathophysiology, mechanisms of NAS, and signs and symptoms in the early years.

CONCLUSION

Treatment and pediatric outcomes and the effectiveness of pharmacological treatment may be frontiers in the NAS field, and continued efforts from researchers are needed in those topics.

Key Words: Neonatal abstinence syndrome; Bibliometric; Scopus; VOSviewer; Visualization

Core Tip: This bibliometric study extracts data on Neonatal abstinence syndrome (NAS) research at a global level, aiming to provide the top-cited articles and top research priorities in NAS and to determine the most prolific countries, journals, and authors. This would enable scientists and clinicians interested in the NAS field to identify the most prevalent topics that have been used for increasing our understanding of NAS and provide a basis for future research. Treatment and pediatric outcomes and the effectiveness of pharmacological treatment may be frontiers in the NAS field, and continued efforts from researchers are needed on these topics.

Citation: Zyoud SH, Al-Jabi SW, Shahwan MJ, Jairoun AA. Global research production in neonatal abstinence syndrome: A bibliometric analysis. *World J Clin Pediatr* 2022; 11(3): 307-320
URL: https://www.wjgnet.com/2219-2808/full/v11/i3/307.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i3.307

INTRODUCTION

Neonatal abstinence syndrome (NAS) is a group of signs and symptoms that occur due to the sudden discontinuation of infants shortly after the birth of certain substances that were abused or used during pregnancy[1,2]. NAS can present with a broad range of signs and symptoms including restlessness, agitation, feeding intolerance, gastrointestinal disturbances, hypertonia, tremors, seizures, and respiratory distress[2-6].

Recently, NAS emerged as a significant global concern with a dramatic increase in healthcare expenditures[1,7-9]. The incidence of NAS has increased notably in the past decade and emergence as a global public health problem. The reported rise in antidepressant therapy during pregnancy, or the use of narcotic analgesics for pain relief in pregnant women, or the illicit use of opioids such as heroin and oxycodone[10] may play an important role in this aspect. The most clinically significant interventions in NAS management are appropriate to nonpharmacologic interventions[6,11] including promoting breastfeeding of infants when not contraindicated, rooming-in, positioning of the infant, bed type, and non-insertive acupuncture. Opioids such as morphine or methadone or buprenorphine are usually the first-line agent to treat the symptoms of withdrawal when pharmacological treatment is indicated. Although phenobarbital has been recognized as a second-line agent to be used in infants when opioids fail, clonidine may be used as a nonopioid adjunctive NAS therapy with minimal adverse effects and reduced treatment time[5,6,12,13].

Although several bibliometric analyses have been carried out on several topics related to substance abuse such as illicit drug addiction[14], cocaine intoxication[15], substance use disorders[16], drug and alcohol[17], and drug abuse and dependence[18-23], an extensive literature search did not reveal any bibliometric analysis on NAS. Therefore, this bibliometric study extracts data on NAS research at a global level, aiming to provide the top-cited articles and top research priorities in NAS and to determine the most prolific countries, journals, and authors. This would enable scientists and clinicians interested in the NAS field to identify the most prevalent topics that have been used for increasing our understanding of NAS and provide a basis for future research.

MATERIALS AND METHODS

Database used

To achieve the objectives of the current bibliometric study, we performed a generalized search using the database of Scopus (Elsevier's citation database). The search was performed on July 17, 2020. Because the first publication related to NAS was published in 1958, the timespan was set from 1958 to 2019. The final year (2020) was omitted from the study as, at the time of data collection, certain publications from that year might not have been indexed in databases and this year's data does not represent a complete year of publication in the field.

Search strategy

The search was thus conducted using the following search string: (TITLE-ABS (neonat*) OR TITLE-ABS (newborn) OR TITLE-ABS (birth) OR TITLE-ABS (infant) AND TITLE-ABS ("Abstinence Syndrome") OR TITLE-ABS ("Abstinence Symptom*") OR TITLE-ABS ("Substance Withdrawal") OR TITLE-ABS ("narcotic syndrome") OR TITLE-ABS ("narcotic Symptom*") OR TITLE-ABS ("Withdrawal Symptom*") OR TITLE-ABS ("Withdrawal Syndrome") OR TITLE-ABS ("drug Withdrawal") OR TITLE-ABS ("Passive Addiction") OR TITLE-ABS("opioid withdrawal") OR TITLE-ABS ("opioid syndrome") AND EXCLUDE (DOCTYPE) AND [EXCLUDE (PUBYEAR, 2020). Neonatal abstinence syndrome-related terms were selected for this string based on those identified in previous literature reviews[6,10,24-27]. The search strategy for the terms related to NAS was restricted to Title/Abstract to achieve greater accuracy in the results because many reported publications were not related to NAS (*i.e.*, false-positive data) if applied to other search fields such as keywords. The use of title/abstract search is recommended in bibliometric studies[15,28,29] in contrast to the title-abstract-keywords search query because it substantially increases specificity with minimum loss of sensitivity. The main explanation for the generation of false-positive results by keyword search is that Scopus considers keywords such as "Medline keywords", "EMTREE medical terms" and "EMTRE drug terms" as author and indexed keywords. In the absence of false-positive and false-negative findings, the method adopted in the current study was validated[30]. No language restrictions were applied. Thus, both English and non-English documents were used.

Data analysis and visualization

The data was organized and analyzed using Microsoft Office Excel 2010. Descriptive statistics were used for data analysis, using frequencies and percentages. The downloaded document included the title, abstract, publication date, journal information, authors, country, collaboration patterns, and citations as indicators for quantity and qualitative analysis. These indicators were identified according to previous bibliometric literature[31-33]. The VOSviewer version 1.6.14[34], a software package for analyzing and visualizing large bibliographic datasets, was used for content analysis to determine the top research priority topics, and trends, and to present bibliometric networks concerning various dimensions, such as co-authorship, authors, and countries. To map the network of terms co-occurrence in the title and abstract countries, collaboration co-authorship was extracted from downloaded bibliometric records. In terms with an occurrence frequency no less than 20 authors and countries who had at least five publications were chosen for visualisation. The number of publications related to a certain word is measured by the size of circles in VOSviewer maps and the distance between the two terms means the number of cooccurrences of the terms. Moreover, words that are similar to each other or have a certain color are more likely to deal with the same topic[34]. In addition, the terms co-occurrences were analyzed to distinguish topics used by the authors' overtime. Using the "link strength" indicator extracted from visualization maps, an international research collaboration among active countries was evaluated. The strength of the link is a measure of the strength of cooperation between any two countries in this field. The higher value of link strength means the thickness of the connecting line, which is considered the stronger research collaboration between certain countries in this field[34].

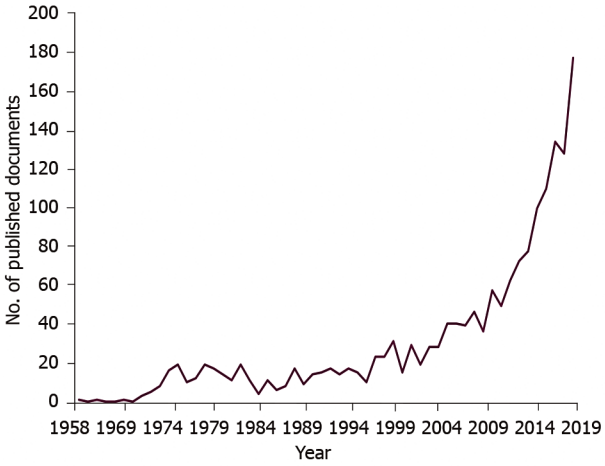
RESULTS

A total of 1738 articles were retrieved in the Scopus database from 1958 to 2019. It was found that the great majority of the total NAS documents (1295; 74.51%) were original articles followed by reviews (268; 15.42%) and letters (48; 2.76%). The yearly publication number of articles increased rapidly from 1958 to 2019 (Figure 1). Yearly articles increased from 2 in 1958 to 40 in 2007 and then to 177 in 2019. Twenty-three languages of publication were identified in the 1,738 articles retrieved. The four predominant languages were English (n = 1489; 85.67%), followed by German (n = 66; 3.80%), Spanish (n = 39; 2.24%), and French (n = 38; 2.13%).

There is a total of 111 countries/areas that make great contribution research publications in neonatal abstinence syndrome. Table 1 presents the 10 most productive countries in the NAS concerning total publications, h-index, as well as the collaboration pattern. The most productive countries in NAS field were the United States (n = 833; 47.93%), Canada (n = 112; 6.44%), the United Kingdom (n = 111; 6.39%)

Table 1 The top 10 countries contributed to publications in neonatal abstinence syndrome research (1958 to 2019)

SCR	Country	Number of documents (%)	h-index	No. of collaborated countries
1st	United States	833 (47.93)	71	38
2nd	Canada	112 (6.44)	29	14
3rd	United Kingdom	111 (6.39)	29	25
4th	Germany	77 (4.43)	17	23
5th	Italy	65 (3.74)	15	21
6th	Australia	63 (3.62)	26	7
7th	France	62 (3.57)	20	23
8th	Spain	59 (3.39)	18	22
9th	Austria	52 (2.99)	19	19
10th	the Netherlands	45 (2.59)	16	24



DOI: 10.5409/wjcp.v11i3.307

Figure 1 Annual number of articles published in neonatal abstinence syndrome.

and Germany (n = 77; 4.43%). The h-index of the total retrieved articles was 87. Among the most productive countries, the United States achieved the highest h-index value with 71, followed by the United Kingdom with 29, and Canada with 29. A network visualization map for country collaboration is shown in Figure 2 and demonstrates that the United States is the most important collaboration country. Of the 111 countries, 33 had at least five publications; the largest set of connected countries consists of 28 countries in 8 clusters. For research collaboration, the strongest was in the United States (total link strength = 111), followed by the United Kingdom (total link strength = 72), and Netherlands (total link strength = 70). For most countries, the link strength was less than 20, suggesting insufficient international research collaboration in this field[34].

Table 2 shows the 11 journals with more than 17 published papers with their impact factors. The journals publishing most papers are *Pediatrics* (n = 43), *Journal of Pediatrics* (n = 34), and *Journal of Perinatology* (n = 33).

Among the top contributive authors (Table 3), Jones Hendrée (42 publications) from the University of North Carolina at Chapel Hill (United States) was ranked first, followed by Fischer, Gabriele (29 publications) from the Medical University Vienna (Austria). Of note, 8 and 3 authors are from the United States and Austria, respectively, suggesting an important contributing role to these countries. A network visualization map for the authors' collaboration is shown in Figure 3. Of the 5305 authors, 118 had at least five publications; the largest set of connected authors consists of 70 authors in 11 clusters.

In VOSviewer, co-occurrence analysis for the title and abstract contents was used to produce the term co-occurrence network of NAS studies (Figure 4). In Figure 4, it can be seen that the top research priorities of NAS studies form five clusters, and the terms in the same cluster show superior connection in each of the research topics. These five clusters were as follows: Cluster 1 (blue) involved terms related to "treatment and hospital outcomes in NAS" such as "hospitalization, length, stay, hospital stay, discharge, neonate outcome"; Cluster 2 (yellow) involved terms related to "evidence-based nurse-

Table 2 The top 11 most productive journals on neonatal abstinence syndrome research from 1958 to 2019

SCR[1]	Journal	Frequency (%)	IF[2]
1st	*Pediatrics*	43 (2.47)	5.359
2nd	*Journal of Pediatrics*	34 (1.96)	3.700
3rd	*Journal of Perinatology*	33 (1.90)	1.967
4th	*Drug and Alcohol Dependence*	31 (1.78)	3.951
5th	*Addiction*	27 (1.55)	6.343
6th	*Advances in Neonatal Care*	23 (1.32)	1.405
6th	*American Journal of Obstetrics and Gynecology*	23 (1.32)	6.502
8th	*Acta Paediatrica*	22 (1.27)	2.111
9th	*Archives of Disease in Childhood Fetal and Neonatal Edition*	19 (1.09)	5.436
10th	*Journal of Addiction Medicine*	18 (1.04)	3.014
10th	*Pediatric Research*	18 (1.04)	2.747

[1]If some journals receive the same ranking number, a gap is left in the next ranking numbers.
[2]Impact factors based on Journal Citation Reports 2019 adapted from Clarivate Analytics which was published in 2020.
IF: Impact factors.

Table 3 The first twelve authors by record count in neonatal abstinence syndrome research

SCR[1]	Author name	Country	Number of documents (%)
1st	Jones HE	United States	42 (2.42)
2nd	Fischer G	Austria	29 (1.67)
3rd	Jansson LM	United States	28 (1.61)
3rd	Patrick SW	United States	28 (1.61)
5th	Finnegan LP	United States	24 (1.38)
5th	Kaltenbach K	United States	24 (1.38)
5th	Wachman EM	United States	24 (1.38)
8th	Davis JM	United States	17 (0.98)
9th	Jagsch R	Austria	14 (0.81)
10th	Huestis MA	United States	12 (0.69)
10th	Koren G	Israel	12 (0.69)
10th	Raith W	Austria	12 (0.69)

[1]If some authors receive the same ranking number, a gap is left in the next ranking numbers.

driven interventions for the care of newborns with NAS" such as "nurse, intervention, guideline, barrier, challenge"; Cluster 3 (red) involved terms related to "pathophysiology and mechanisms of NAS" such as "brain, onset, alteration, activity, administration, tolerance, analgesia, sedation, animal, rat"; Cluster 4 (purple) involved terms related to "systematic review and network meta-analysis for therapeutic approaches of NAS" such as "systematic review, meta-analysis, Medline, trial, search"; and Cluster 5 (green) involved terms related to "signs and symptoms" such as "jitteriness in neonates, meconium, irritability, prematurity". In the analysis of term co-occurrence (Figure 5), we also identified terms in the titles and abstracts related to NAS over time. Treatment and hospital outcomes in NAS, evidence-based nurse-driven interventions for the care of newborns with NAS, and a systematic reviews and network meta-analysis for therapeutic approaches of NAS were found in recent years (after 2010), compared with terms such as pathophysiology, mechanisms of NAS, and signs and symptoms in the early years (before 2010).

The top 20 cited publications in the field of NAS ranked by the total number of citations are shown in Table 4. The highest cited publication in the top 20 was cited 529 times and the lowest cited article 177

Table 4 The 20 Most-cited articles in neonatal abstinence syndrome based on the citation count

SCR	Ref.	Title	Year	Source title	Cited by
1st	Patrick *et al*[1]	Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009	2012	*JAMA - Journal of the American Medical Association*	529
2nd	Jones *et al*[43]	Neonatal abstinence syndrome after methadone or buprenorphine exposure	2010	*New England Journal of Medicine*	526
3rd	Hudak *et al*[40]	Neonatal drug withdrawal	2012	*Pediatrics*	443
4th	Finnegan *et al*[38]	Neonatal abstinence syndrome: assessment and management	1975	*Addictive diseases*	435
5th	Sanz *et al*[49]	Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: A database analysis	2005	*Lancet*	318
6th	Hughes *et al*[41]	Nicotine withdrawal *vs* other drug withdrawal syndromes: similarities and dissimilarities	1994	*Addiction*	253
7th	Patrick *et al*[9]	Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012	2015	*Journal of Perinatology*	251
8th	Levinson-Castiel *et al*[45]	Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants	2006	*Archives of Pediatrics and Adolescent Medicine*	238
9th	Costei *et al*[37]	Perinatal outcome following third trimester exposure to paroxetine	2002	*Archives of Pediatrics and Adolescent Medicine*	233
10th	Kocherlakota[2]	Neonatal abstinence syndrome	2014	*Pediatrics*	219
11th	Tolia *et al*[50]	Increasing incidence of the neonatal abstinence syndrome in United States neonatal ICUs	2015	*New England Journal of Medicine*	213
12th	American Academy of Pediatrics Committee on Drugs[36]	Neonatal drug withdrawal	1998	*Pediatrics*	212
13th	ACOG Committee on Health Care for Underserved Women and American Society of Addiction Medicine[35]	Committee opinion No. 524: Opioid abuse, dependence, and addiction in pregnancy	2012	*Obstetrics and Gynecology*	208
13th	Jones *et al*[42]	Buprenorphine *vs* methadone in the treatment of pregnant opioid-dependent patients: Effects on the neonatal abstinence syndrome	2005	*Drug and Alcohol Dependence*	208
15th	Wisner *et al*[51]	Pharmacologic treatment of depression during pregnancy	1999	*Journal of the American Medical Association*	200
16th	Zajecka *et al*[52]	Discontinuation symptoms after treatment with serotonin reuptake inhibitors: A literature review	1997	*Journal of Clinical Psychiatry*	197
17th	Nau *et al*[46]	Valproic acid and its metabolites: Placental transfer, neonatal pharmacokinetics, transfer *via* mother's milk and clinical status in neonates of epileptic mothers	1981	*Journal of Pharmacology and Experimental Therapeutics*	197
18th	Ryan *et al*[48]	Cocaine abuse in pregnancy: Effects on the fetus and newbornF	1987	*Neurotoxicology and Teratology*	181
19th	Lejeune *et al*[44]	Prospective multicenter observational study of 260 infants born to 259 opiate-dependent mothers on methadone or high-dose buprenophine substitution	2006	*Drug and Alcohol Dependence*	180
20th	Hadeed and Siegel[39]	Maternal cocaine use during pregnancy: Effect on the newborn infant	1989	*Pediatrics*	177
21st	Nordeng *et al*[47]	Neonatal withdrawal syndrome after in utero exposure to selective serotonin reuptake inhibitors	2001	*Acta Paediatrica,*	175

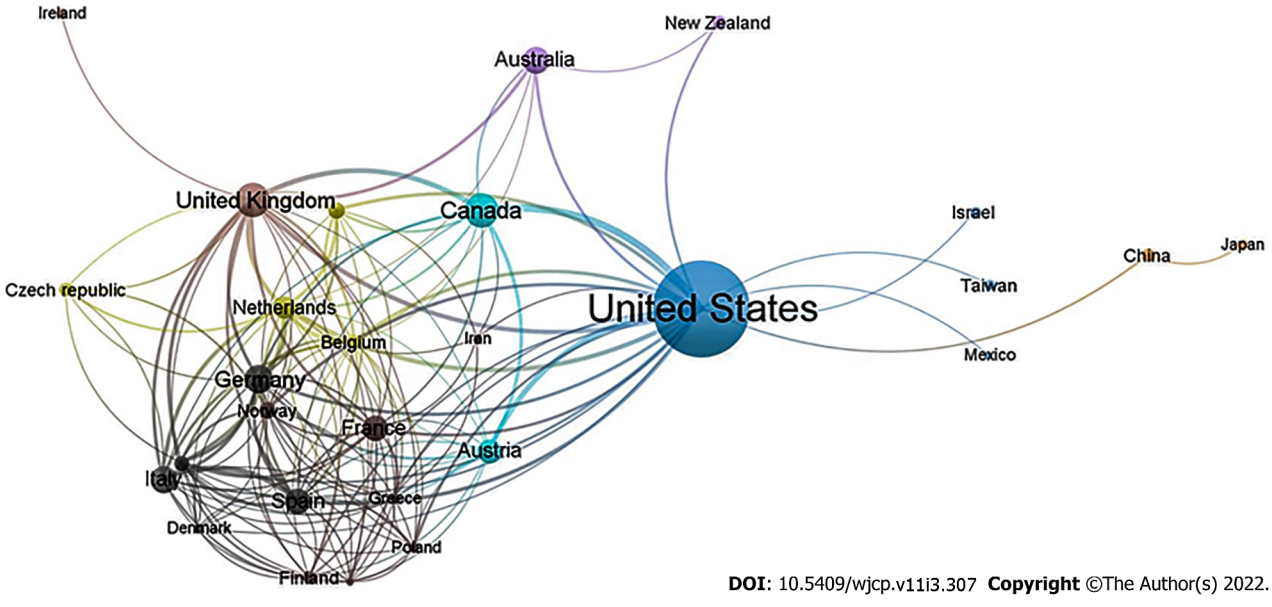
times[1,2,9,35-52]. Table 5 includes the most frequently encountered agents related to NAS literature. "Methadone" (n = 629) was the most commonly occurred in NAS literature, followed by "morphine" (n = 378), "buprenorphine" (n = 313), and "phenobarbital" (n = 275).

DISCUSSION

This study is set out with the aim of investigating the current situation of NAS research at a global level by analysing the related literature bibliometrically. In 2015, member states of the United Nations had

Table 5 List of most frequent drugs occurrences in neonatal abstinence syndrome literature

Drug	Number of publications
Methadone	629
Morphine	378
Buprenorphine	313
Phenobarbital	275
Diamorphine	212
Heroine	138
Cocaine	138
Clonidine	130
Diazepam	124
Alcohol	80
Cannabis	79
Chlorpromazine	76
Naloxone	62
Fentanyl	56



DOI: 10.5409/wjcp.v11i3.307

Figure 2 Network visualization map for countries collaboration among most productive countries. Of the 111 countries, 33 had at least five publications; the largest set of connected countries consists of 28 countries in 8 clusters.

signed and adopted Sustainable Development Goals (SDGs) to be achieved in 2030[53]. The third goal is dedicated to health and well-being. The fifth target of the third goal in the SDGs promotes the prevention and treatment of substance use disorders. Furthermore, the second target of the third goal promotes the health of the newborn and children by minimizing preventable deaths[54]. The current study will endorse the attainment of 2030 goals by shedding light on an important problem related to maternal and newborn health within the context of substance use disorders.

The current study is novel in describing the characteristics of research publications related to NAS across time, *via* bibliometric analysis, and determining the top research priorities in this field during six decades (1958-2019). Advances in the knowledge of NAS by determining the top research priorities for this complex health issue will help to improve future research for maternal and neonatal care.

Overall, the current study demonstrated an increase in the number of publications involving NAS over the period 1958–2019. In another way, the total number of publications related to NAS increased more than twofold from 437 before 2000 to 971 during the last decade (2010–2019). This was possible because of different explanations. First, research concerning substance abuse, with a focus on prevention

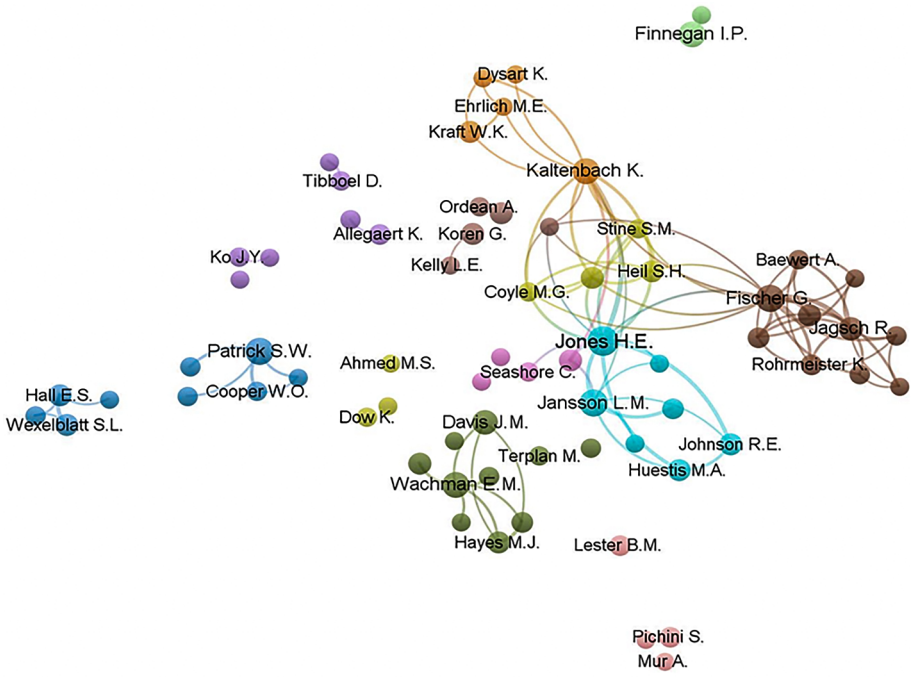


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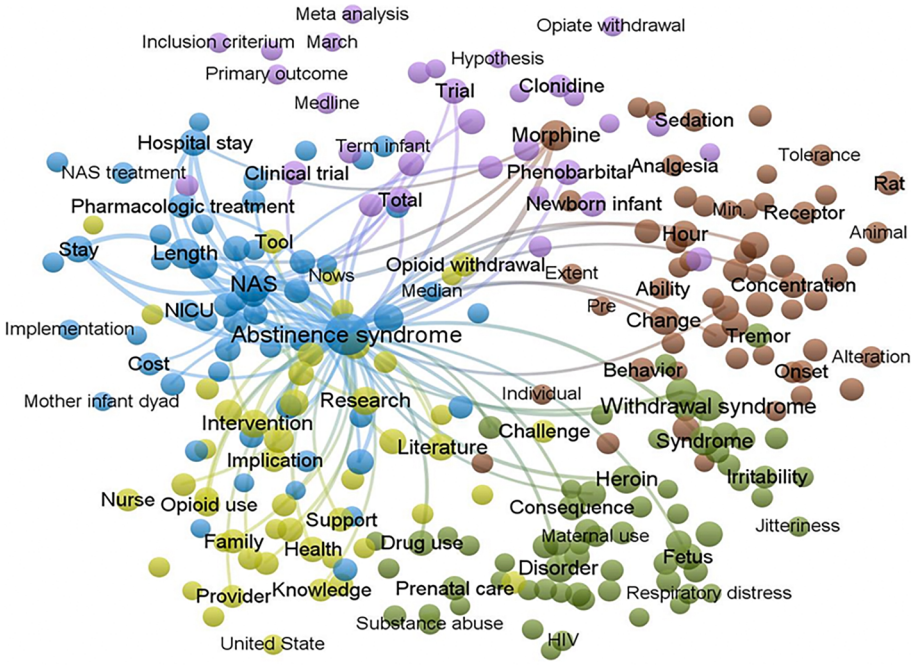
Figure 3 Co-authorship network among most productive authors with the threshold of minimum 5 publications. Of the 5305 authors, 118 had at least five publications; the largest set of connected authors consists of 70 authors in 11 clusters.



DOI: 10.5409/wjcp.v11i3.307

Figure 4 Terms co-occurrence network of neonatal abstinence syndrome studies. Of the 27233 terms, 436 terms occurred at least 20 times. For each of the 436 terms, a relevance score was calculated and used to select the 60% most relevant terms. The largest set of connected terms consists of 262 terms in five clusters.

and policy issues has become a rapidly emerging area in medical sciences and is recently reaching maturity. Second, this progress can be attributed largely to the trend of increasing maternal opiates and illicit drug use across the world. Third, the development of neonatal opioid withdrawal scale to measure opioid withdrawal signs and symptoms in the neonate. Fourth, the rapid growth of the global economy with the development of information technology has contributed to the progress of research to keep up this increasing trend.

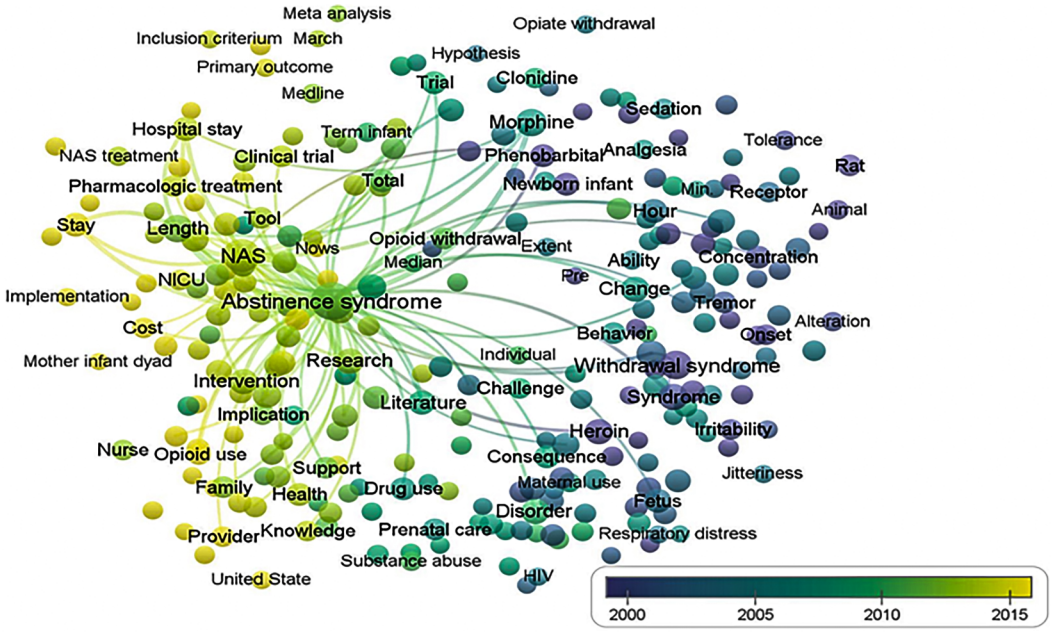


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Figure 5 Distribution of terms according to their time of appearance. The blue colored terms mean early appearance and yellow colored terms appeared later.

In this study, the United States was found to be the leader in NAS research. This result may be explained by the fact that the United States is the most prolific country for research in general by most bibliometric studies[31,55-57]. Moreover, the United States is one of the countries that attributed largely to the trend of increasing maternal cocaine, illicit drugs, and opiate use, and subsequently escalating numbers of deaths[58]. Additionally, the United States may be leading because of its size and economic strength and has a large research system including United States institutions, individual colleges, and hospitals[59]. Seven newborns were diagnosed with NAS for every 1,000 hospital stays for newborns, according to 2016 statistics[60]. This is around one baby in the United States diagnosed with NAS every 19 minutes, or almost 80 newborns diagnosed every day[60].

Clearly, the most commonly used keyword in NAS literature was "methadone," followed by "morphine", "buprenorphine", and "phenobarbital". It is interesting to note that three studies from the top 20 cited publications in the field of NAS were evaluating the efficacy and safety of methadone *vs* buprenorphine therapy for treating opioid-dependent pregnant patients[42-44].

The most cited publication in the field of NAS was published in 2012 in *JAMA - Journal of the American Medical Association,* conducted by Patrick *et al*[1], where the authors found an increase in maternal opiate use and incidence of NAS in the United States. The authors analyzed information on 7.4 million discharges from 4121 hospitals in 44 states, to measure the epidemiology and economic damage associated with NAS over the past decade. The authors reported that the number of mothers using opiates rose from 1.19 to 5.63 per 1000 hospital births per year between 2000 and 2009, and that it is estimated that aggregate hospital costs for NAS cases, adjusted for inflation, rose from $190 million to $720 million between 2000 and 2009. The second most cited publication was published in 2010 in *New England Journal of Medicine*, conducted by Jones *et al*[43] resulting from the collaboration between several countries (United States, Canada, and Austria). This study considered the use of buprenorphine as the first-line treatment option instead of methadone for the treatment of opioid dependency during pregnancy. Methadone therapy for heroin addiction began in New York City in 1964[61], and then became the standard therapy for treating opioid-dependent pregnant patients in both the developed and developing worlds[62]. Methadone therapy led to several adverse pregnancy events during withdrawal[63]. After that, marked progress has been made in the area of buprenorphine research as an alternative treatment for opioid dependence[43] which gives relative superiority for buprenorphine to be associated with a lower risk of NAS severity[64]. This finding also accords with our observations, which showed that top research priorities including treatment and pediatric outcomes, and the effectiveness of pharmacological treatment were found in recent years. Furthermore, top research priorities in the field of NAS are consistent with the findings highlighted in the most highly cited publications, which provide substantial and valuable findings that open the door for new areas of research investigation.

Despite the importance of this topic, there remains a paucity of evidence on several issues related to NAS[65-68]. The most significant knowledge gaps in NAS are the long-term outcomes and the international differences between treatments of drug-using mother/infant dyads. What happens to the children

afterward? How have they looked after? Some of the medications used to treat NAS (*e.g.*, methadone) are not sanctioned in countries outside the United States. Opioid-exposed infants are still at significantly higher risk of dying, of being abused, and of sliding towards an unpalatable life trajectory after discharge from the hospital. Further work is needed to highlight this missing information and note the urgent need to prioritize research and clinical care towards improving and ameliorating the impact of maternal drug use. More broadly, the emphasis on the need to conduct more research into pharmacological treatment neglects other aspects of care for infants, including rooming-in, breastfeeding, *etc.* The medications that are used to treat NAS are not innocuous, therefore, research is also needed to avoid pharmacological treatment, rather than to see which treatment is most effective in discharging the infants out of the hospital faster.

Strengths and limitations

This bibliometric study is the first comprehensive investigation to explore the distribution trends and top research priorities in the field of NAS. Additionally, another strength of the current study including a large literature database (*i.e.*, Scopus), benefits from a higher coverage than other databases[69,70], spanning multiple years of analysis to identify relevant NAS literature. Several limitations matching those observed in earlier bibliometric studies[31,71,72] should be noted. The main limitation of this study was the use of the Scopus database which expects that most perspectives of the publications in the field of NAS indexed in this database were analysed. Additionally, the current study used a comprehensive list of keywords based on those identified in previous literature reviews[6,10,24-27]; however, there is a possible slight chance that some keywords have been missed which may lead to false-negative results.

CONCLUSION

In conclusion, this bibliometric review defined the scientific research output in the field of NAS using bibliometric methods over the past 60 years, including publication numbers, countries, organizations, journals, top research priorities, and emerging trends. The findings from this study make several contributions to the current literature. First, this study confirmed the increase in the number of publications involving NAS over the period 1958–2019. Second, the United States, Canada, and the United Kingdom had the leading position in global research productivity in this field. Third, it was found that the comparative studies related to the safety and efficacy of methadone and buprenorphine in NAS were the mainstay of the top-cited studies. In the last treatment and pediatric outcomes, and the effectiveness of pharmacological treatment may be frontiers in the NAS field, and continued efforts from researchers are needed on these topics. This bibliometric study offers an objective and quantitative summary of the progress of research in the NAS field, which can serve as a significant guide and entry point for more scientific research. This information can be used to develop targeted interventions aimed to improve international cooperation between organizations and countries by applying useful initiatives and policies.

ARTICLE HIGHLIGHTS

Research background

Neonatal abstinence syndrome (NAS) has recently become a major global issue, resulting in a substantial rise in healthcare costs. The NAS has become a global public health epidemic in the last decade, with a rise in incidence.

Research motivation

Despite the fact that bibliometric studies have been conducted on a variety of topics related to substance abuse, such as illegal drug addiction, a thorough search of the literature revealed no bibliometric research on NAS.

Research objectives

Bibliometric analysis was used to assess the evolution and pattern of the global NAS research from 1958 to 2019.

Research methods

Yearly publication production, language, document types, journals, countries/territories, h-index, authors, and top research priorities were among the indicators examined. The VOSviewer was used to assess the top research priorities and patterns, as well as to present bibliometric networks on a variety of dimensions, including co-authorship, authors, and countries.

Research results

The current study is novel in that it uses bibliometric analysis to describe the characteristics of research publications relevant to NAS over time and determine the top research priorities in this field over six decades (1958-2019). Advances in NAS awareness will help to enhance future maternal and neonatal care research by identifying the top research priorities for this complex health problem.

Research conclusions

Treatment and pediatric outcome, as well as the efficacy of pharmacological treatment, may be frontiers in the NAS area, and researchers must continue to work on these topics.

Research perspectives

This will allow scientists and clinicians interested in the field of NAS to recognise the most common topics that have been used to improve our understanding of the disease and serve as a foundation for future study.

FOOTNOTES

Author contributions: Zyoud SH designed the study, collected the data, analyzed the data, made major contributions to the manuscript's existing literature search and interpretation, and drafted the manuscript; Al-Jabi SW, Jairoun AA, and Shahwan WM were involved in interpretation of the data, and made revisions to the initial draft; all authors provided a critical review and approved the final manuscript before submission.

Conflict-of-interest statement: The authors have no financial disclosures or conflicts of interest to declare.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: Palestine

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S-Editor: Ma YJ
L-Editor: A
P-Editor: Ma YJ

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ISSN 2219-2808 (online)

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2022 July 9; 11(4): 321-384

Published by Baishideng Publishing Group Inc

WJCP

World Journal of Clinical Pediatrics

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INDEXING/ABSTRACTING

The *WJCP* is now abstracted and indexed in PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Pediatrics

ISSN
ISSN 2219-2808 (online)

LAUNCH DATE
June 8, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Toru Watanabe, Consolato M Sergi, Elena Daniela Serban, Surjit Singh

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World J Clin Pediatr 2022 July 9; 11(4): 321-329

DOI: 10.5409/wjcp.v11.i4.321

ISSN 2219-2808 (online)

MINIREVIEWS

Hereditary fructose intolerance: A comprehensive review

Sumit Kumar Singh, Moinak Sen Sarma

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Barone M, Italy
A-Editor: Wang JL, United States

Received: November 27, 2021
Peer-review started: November 27, 2021
First decision: April 13, 2022
Revised: May 8, 2022
Accepted: June 20, 2022
Article in press: June 20, 2022
Published online: July 9, 2022

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Abstract

Hereditary fructose intolerance (HFI) is a rare autosomal recessive inherited disorder that occurs due to the mutation of enzyme aldolase B located on chromosome 9q22.3. A fructose load leads to the rapid accumulation of fructose 1-phosphate and manifests with its downstream effects. Most commonly children are affected with gastrointestinal symptoms, feeding issues, aversion to sweets and hypoglycemia. Liver manifestations include an asymptomatic increase of transaminases, steatohepatitis and rarely liver failure. Renal involvement usually occurs in the form of proximal renal tubular acidosis and may lead to chronic renal insufficiency. For confirmation, a genetic test is favored over the measurement of aldolase B activity in the liver biopsy specimen. The crux of HFI management lies in the absolute avoidance of foods containing fructose, sucrose, and sorbitol (FSS). There are many dilemmas regarding tolerance, dietary restriction and occurrence of steatohepatitis. Patients with HFI who adhere strictly to FSS free diet have an excellent prognosis with a normal lifespan. This review attempts to increase awareness and provide a comprehensive review of this rare but treatable disorder.

Key Words: Hereditary; Fructose; Intolerance; Children; Liver; Steatohepatitis; Aldolase

Core Tip: Hereditary Fructose Intolerance is a rare autosomal recessive inherited disorder due to the mutation of enzyme aldolase B. Awareness regarding its diverse manifestations is required to clinically suspect and diagnose this condition. Genetic testing clinches the diagnosis. Treatment is simple and involves only the dietary exclusion of fructose, sucrose and sorbitol. The prognosis is favourable. This review provides a comprehensive understanding of the disease.

Citation: Singh SK, Sarma MS. Hereditary fructose intolerance: A comprehensive review. *World J Clin Pediatr* 2022; 11(4): 321-329
URL: https://www.wjgnet.com/2219-2808/full/v11/i4/321.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i4.321

INTRODUCTION

Fructose is a monosaccharide found in honey, fruits and many vegetables consumed daily. It is also the component of the main sweetening agent, sucrose in the majority of sweets and syrups. Small amounts of fructose are also produced in the human brain *via* the polyol pathway[1]. After ingestion, fructose is absorbed from the intestine through glucose transport proteins (GLUT) 5 and 2[2]. Subsequent metabolism is carried out predominantly in the liver, kidney and small intestine by the enzymes fructokinase, aldolase B, and triokinase[3]. Hereditary fructose intolerance (HFI) is a pathological condition that occurs due to a deficiency of enzyme aldolase B[3]. It is characterized by hypoglycemia, lactic acidosis, hypophosphatemia, hyperuricemia, hypermagnesemia and hyperalanemia due to dysregulation of gluconeogenesis, glycogenolysis and decreased inorganic phosphate[4].

EPIDEMIOLOGY AND GENETICS

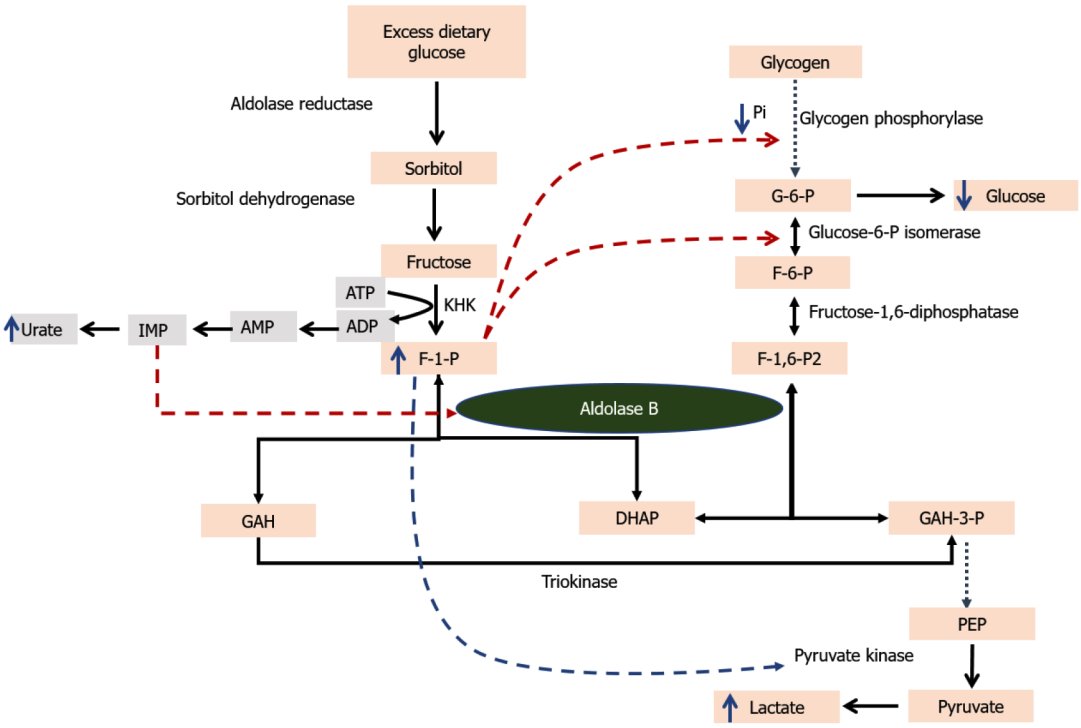
HFI is a rare autosomal recessive inherited disorder with an estimated population prevalence ranging from 1 in 20000 to 1 in 60000[5]. There is no sex predilection. The gene for the enzyme aldolase B (ALDOB) is located on chromosome 9q22.3. Mutational aberrations include simple missense mutations, deletions, frameshift mutations, and mutations at splicing sites. A systemic review was conducted to assess *ALDOB* gene variants among patients with HFI[6]. The prevalence of HFI was estimated from the carrier frequency of variants described in patients, as well as rare variants predicted as pathogenic by *in silico* tools. In silico predictive software allows assessing the effect of amino acid substitutions on the structure or function of a protein without conducting functional studies[7]. The application of in silico tools can significantly improve the detection of genes and variation[8]. The studies included in the systematic review described 1426 alleles involved in the pathogenesis of HFI, spread in 29 countries on four continents[6]. 68 variants in *ALDOB* were identified among patients with HFI distributed in different populations. These variants were detected in 85 different genotypic combinations. Most of the mutations described in patients with HFI are restricted to a single ethnic group. The commonest variants distributed worldwide that account for most of the identified cases are: NM_000035_3:c.178C>T, NP_000026.2:p.(Arg60Ter); NM_000035_3:c.360_363del, NP_000026.2:p.(Asn120LysfsTer32); NM_000035_3:c.448G>C, NP_000026.2:p.(Ala150Pro); NM_000035_3:c.524C>A, NP_000026.2:p.(Ala175Asp) and NM_000035_3:c.1005C>G, NP_000026.2:p.(Asn335Lys). The analyses showed that the variants p.(Ala150Pro) and p.(Ala175Asp) are the most frequent in patients, accounting for approximately 68% of the alleles. The p.(Ala150Pro) variant alone accounts for 53% of all alleles identified worldwide, and has a variable frequency between the different geographic regions.p.(Asn120LysfsTer32) variant is the third most frequent (4.6%)[9-11]. Five novel mutations, (c.324+1G>A, c.112+1delG, c.380-1G>A, c.677G>A, and c.689delA) have been reported from an Indian community[12].

PATHOGENESIS

It carries out the reversible conversion of fructose 1-phosphate (F-1P) to glyceraldehyde (GAH) and dihydroxyacetone phosphate (DHAP) as shown in (Figure 1). Aldolase B also plays a role in gluconeogenesis and glycolytic pathways as it catalyzes fructose 1,6-bisphosphate (F-1,6P2) conversion to DHAP and glyceraldehyde 3-phosphate (G3P) in a reversible manner (Figure 1). There are two other isoenzymes, aldolase A (predominantly expressed in skeletal muscle and red blood cells) and aldolase C (predominantly expressed in brain and smooth muscle) and both have a high affinity for F-1,6-P2 as a substrate[13]. The deficiency of aldolase A manifests mainly as recurrent rhabdomyolysis which may sometimes be accompanied by hemolysis and termed glycogen storage disorder type 12[14,15]. Aldolase C expression has been found to be associated with certain neuroendocrine tumors and is being studied as a marker of neuroendocrine tumors[16].

Metabolic consequences

In a patient with HFI, a fructose load leads to the rapid accumulation of F-1P which results in depletion of intracellular inorganic phosphate (Pi) and adenosine triphosphate (ATP). As a result, adenosine 5′-monophosphate (AMP) degradation is increased, and hence, inosine monophosphate (IMP) and urate



DOI: 10.5409/wjcp.v11.i4.321

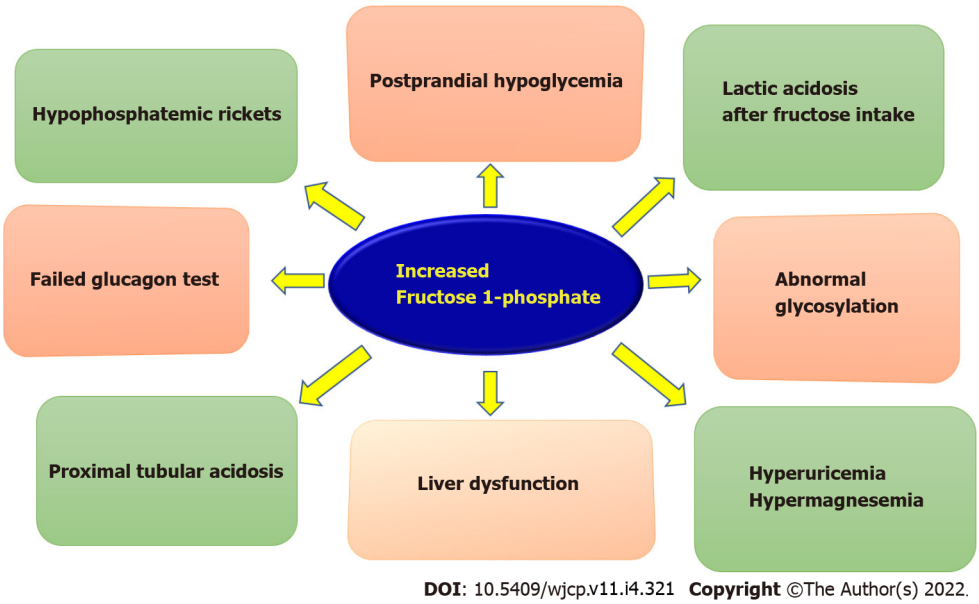
Figure 1 Illustrates the pathway of fructose metabolism. Fructose is converted by ketohexokinase to F-1P that acts as substrate for Aldolase B which forms dihydroxyacetone phosphate (DHAP) and glyceraldehyde (GAH) that enter the glycolytic/gluconeogenic pathways. Aldolase B also catalyzes the reversible conversion of F-1,6P2 to DHAP and GAH-3P. Accumulation of F-1P leads to inhibition of glucose -6 P isomerase and along with depletion of inorganic phosphate, inhibits glycogen phosphorylase (red broken line). Similarly, increased IMP inhibits any residual Aldolase B activity if present. F-1P also activated PK which promotes lactic acid production. ADP: Adenosine diphosphate; AMP: adenosine monophosphate; ATP: adenosine triphosphate; DHAP: dihydroxyacetone phosphate; F-6P: Fructose 6-phosphate; F-1P: Fructose 1-phosphate; F-1,6-P2: Fructose 1,6-biphosphate; G-6P: glucose 6-phosphate, GAH glyceraldehyde; GAH-3P: Glyceraldehyde 3-phosphate; IMP: inosine monophosphate; KHK: Ketohexokinase; PEP: Phosphoenolpyruvate; Pi: Inorganic phosphate; PK: Pyruvate kinase.

are generated rapidly resulting in hyperuricemia which is responsible for gout in patients with HFI (Figure 1). Increased IMP through specific inhibition of aldolase B creates a vicious cycle leading to a further increase in F-1P. Depletion of ATP also results in increased release of magnesium as well as impaired protein synthesis and ultrastructural lesions which are responsible for hepatic and renal dysfunction. The consequences of increased F-1P are shown in Figure 2.

Increased F-1P along with reduced Pi is also responsible for inhibition of glycogenolysis through impairment of glycogen phosphorylase. This fructose-induced hypoglycemia in HFI is not corrected by the administration of exogenous glucagon which again emphasizes the impaired glycogenolysis pathway. Further, the accumulation of F-1P impedes gluconeogenesis by inhibition of glucose-6-phosphate isomerase (G6PI) (Figure 1). Overall, when a patient with HFI is given a fructose load, it leads to hypoglycemia due to deranged gluconeogenesis and glycogenolysis. In addition, lactic acidosis occurs due to activation of glycolytic pathway through increased activity of pyruvate kinase by F-1P and inability of aldolase B to convert DHAP and G3P to F-1,6P2. Notably, the metabolic consequences of fructose load also occur after ingestion of sorbitol found in various syrups and those with high glycemic foods such as rice. Sorbitol, through polyol pathways, is responsible for the endogenous production of fructose (Figure 1)[1].

CLINICAL FEATURES

The genotype-phenotype correlation has not been identified in patients with HFI. Patients with HFI develop symptoms only when exposed to dietary fructose directly or indirectly through sucrose or sorbitol. The classical presentation is described as an infant, otherwise healthy, presenting with nausea, protracted vomiting, poor feeding and lethargy and sometimes with seizures following the introduction of weaning foods containing sugar or starch[17]. Li *et al*[18] reported four cases of neonatal and early infantile acute liver failure associated with multi-organ failure induced by sucrose-containing common infant formula in patients with undiagnosed HFI. All patients were appropriately grown, born at term after uncomplicated pregnancies and deliveries, and discharged within the first week of life. There was no known consanguinity. One patient had a family history of an older brother who died on day 28 of life with a similar illness, though a specific diagnosis could not be ascertained. Another patient had a



DOI: 10.5409/wjcp.v11.i4.321

Figure 2 Illustrates the consequences of hereditary fructose intolerance.

maternal half-sister who required a liver transplant for an indeterminate liver failure. Careful dietary history was obtained in all infants, though fructose exposure was unclear in two of the 4 cases due to unreliable history or unclear ingredient labelling, which delayed diagnosis. In all four cases, the newborn screen was normal. The diagnosis was confirmed by ALDOB gene sequencing. All infants were homozygous for the common c.448G>C (p.A150P) pathogenic variant[19]. Sometimes, it may present late in childhood or adulthood owing to the self-imposed strict dietary restriction of fructose-containing food items[19,20]. The child shows a strong aversion to sweets.

An intermittent dietary restriction can have a subtle presentation in the form of isolated hepatomegaly or intermittent elevations in transaminases[21]. Thus, a dietary history of fructose intake and the presence of fatty liver are important clues to suspect an underlying HFI in infants. Chronic liver disease in form of fatty liver, steatohepatitis and even cirrhosis may occur in patients with HFI who are fed regularly on a fructose-rich diet. Examination typically shows growth failure and hepatomegaly with or without jaundice. Renal involvement usually occurs in the form of proximal renal tubular acidosis and may lead to chronic renal insufficiency. Metabolic derangements include hypoglycemia, lactic acidosis, hypophosphatemia, hyperuricemia and hypermagnesemia[6]. HFI presenting as relapsing acute axonal neuropathy has also been reported recently, which improves after dietary fructose omission[22].

In contrast to the classical presentation of the above acute symptoms, some patients with residual enzymatic activity may remain asymptomatic or require a larger burden of fructose to become symptomatic. HFI can also remain masked in the presence of concomitant diseases. Aldag *et al*[23] reported an infant developing unexplained liver failure and metabolic dysfunction soon after a successful pyloromyotomy for hypertrophic pyloric stenosis and the diagnosis was confirmed by genetic testing. Similarly, Bobrus-Chociej reported that elevated transaminases and fatty liver may continue to prevail despite a compliant gluten-free diet in patients with celiac disease. In such a situation, a strong degree of suspicion for HFI is required[24].

Heterozygotes with HFI do not present with classical manifestations of HFI. It has been shown that there are significant but occult metabolic derangements in HFI heterozygous carriers. Randomized cross-over trials show that a high fructose diet (1.4 g/kg/d) increased postprandial plasma uric acid, insulin and hepatic insulin resistance index as compared to those on a low fructose diet (< 10 g/d). This analysis provides insight as to the extent of metabolic damages that can take place in homozygotes in whom these trials are deemed unethical[25]. There are several reports of gouty arthritis due to hyperuricemia in children with heterozygous mutation for HFI[26].

EVALUATION

A meticulous history revealing a clear correlation between exposure to dietary fructose and the onset of symptoms is the key to suspecting the possibility of underlying HFI. There are various pitfalls in the diagnosis of HFI. Kim *et al*[27] in their case series of 5 patients with subtle symptoms and aversion to sweets. They make a pertinent point that emphasis of classic teaching on infantile acute liver failure and biochemical derangements, such as hypoglycemia and hypophosphatemia, after the first exposure to

fructose may inadvertently increase the likelihood of missing cases of HFI characterized by other manifestations. Hence index of suspicion must be high and wide screening must be employed. HFI should be looked for in any patient with unexplained reasons for failing to thrive. HFI is also often misdiagnosed with other nongenetic and genetic conditions, including an eating disorder, recurrent hepatitis, and glycogen storage disease. Moreover, fructose intolerance may not be pathognomonic for HFI alone, given the description of rare patients with fruit-induced, food protein-induced enterocolitis syndrome. Furthermore, the lack of a specific and practical biomarker for HFI means that neither newborn screening nor biochemical testing can be used to establish the diagnosis. Compliance, discrimination and psychosocial issues may be specific problems in adolescence[28].

Detection of non-glucose-reducing substances in the urine sample while on a fructose-containing diet is a bedside screening test. The presence of reducing sugars (glucose/fructose/Lactose) in urine can be detected by Benedict's test[29]. While glucose can be detected in urine by glucose dipsticks, a positive Benedict's test in urine with a negative glucose dipstick test points to the presence of other reducing sugars like fructose/Lactose. Provocative fructose tolerance tests in young children are cumbersome and fraught with the dangers of hypoglycemia. Are there simpler biochemical ways to screen for HFI? Untreated HFI patients present abnormal transferrin (Tf) glycosylation patterns due to the inhibition of mannose-6-phosphate isomerase by fructose-1-phosphate. Hence, elevated serum carbohydrate-deficient Tf (CDT) may allow the prompt detection of HFI. The CDT values improve when an FSS-restrictive diet is followed. Cano *et al*[30] showed that by capillary zone electrophoresis method, asialoTf correlated with dietary intake of sucrose and that pentasialoTf + hexasialoTf negatively correlated with dietary intake of fructose in patients with HFI. Moreover, the tetrasialoTf/disialoTf ratio also differentiated treated HFI patients from healthy controls. However some patients with HFI have been initially misdiagnosed with type 1 congenital disorders of glycosylation[31].

Liver biopsy in patients with HFI shows macro vesicular steatosis with or without changes in inflammation and fibrosis[32]. For confirmation, a genetic test is favoured over the measurement of aldolase B activity in liver biopsy specimens as later is invasive and not widely available. Genetic testing has high sensitivity and specificity and includes single gene sequencing, multi-gene panels, and genomic testing [33].

DIFFERENTIAL DIAGNOSIS

Acute presentation of HFI mimics sepsis, acute infectious hepatitis, hemophagocytic lymphohistiocytosis and other metabolic diseases such as galactosemia, tyrosinemia, organic academia and urea cycle defect. In children presenting with hepatomegaly, fatty liver and raised transaminases, possibilities of Wilson disease, glycogen storage disorder, alpha-1 antitrypsin deficiency should be considered. Presentation as hypoglycemia, acidosis and hepatomegaly mimic fructose 1,6 bisphosphate deficiency, beta-ketothiolase deficiency, pyruvate carboxylase deficiency, congenital disorder of glycosylation, fatty acid oxidation defects and milder variants of respiratory chain defects. Predominant gastrointestinal symptoms and aversion to sweets distinguish HFI from the rest of the differential diagnoses.

TREATMENT

Being a complex metabolic disorder, management of HFI needs a multidisciplinary approach with the involvement of a pediatrician, clinical geneticist, dietician with experience in metabolic disorders, hepatologist and nephrologist. The crux of HFI management lies in the absolute avoidance of foods containing fructose, sucrose, and sorbitol (FSS). Patients presenting with an acute metabolic crisis should be admitted to an intensive care setting and initiated intravenous glucose (dextrose), treatment of metabolic acidosis, (if present) and supportive treatment. Strict avoidance of FSS in the diet along with supplementation of other sources of carbohydrate (glucose, corn-starch) results in rapid reversal of symptoms. At length repetitive counselling, clear instructions on dietary restrictions and continuous reinforcement are required to maintain long-term dietary compliance and precipitations of breakthrough events. Table 1 enlists the food items which should be avoided and which are permitted in patients with HFI. Patients with HFI on a strict FSS elimination diet can develop several nutritional deficiencies, especially vitamins mainly Vitamin C found predominantly in fruits and vitamin B complex. Thus, it is recommended to add multivitamin supplements to prevent the consequences of these deficiencies[34].

CONTROVERSIES IN MANAGEMENT

Diet

Although a strict FSS diet is recommended while treating HFI, there is no clarity as to whether small

Table 1 Food items to be avoided and permitted in hereditary fructose intolerance

Food category	Foods to be avoided	Foods permitted
Fruits	All fruits, fruit juices, fruit extracts, shakes, squashes	None
Cereals	Sweetened/sugar-coated cereals	All except sweetened/sugar coated cerelas
Vegetables	Sweet potatoes, peas, Zucchini	All others including potatos and onions
Breads	Any breads prepared with fructose/sucrose/sugar/sorbitol	Breads prepared without fructose, sucrose, sugar, or sorbitol
Deserts and sweeteners	All desserts/sweets prepared with sugar (cake, pie, ice cream, sherbet, sweetened lime soda)	Dietetic ice cream, dietetic puddings; natural yogurt
Poultry	Milk products added with sugar (sweetened curd/yogurt, fruit yogurt, milkshake, chocolate milk)	Milk without sugar, chicken, Turkey
Meat	Ham, bacon, hot dogs, processed meats; any other meat where sugar is used in processing	Beef, veal, lamb, pork; All Fish
Miscellaneous	Ketchup and other sauces/ condiments containing sugar, Honey, Jam, jelly, Candy, Cookies, Chocolates, , Carbonated beverages, medicinal syrups	Vegetable juices, coffee, tea, salt, pepper, broths/soups from permitted vegetables, eggs, nuts

amounts of fructose can be tolerated in the diet. At what permissible limit of fructose will liver and kidney damage not occur? Restriction of FSS may lead to growth failure even in clinically asymptomatic HFI patients. There is insufficient information about the long-term outcomes of minimal fructose ingestion. A recent study from Italy reported the ten years of follow-up of patients with HFI. Fatty liver (on sonography) persisted in 93.8% of patients despite being on FSS restricted diet of < 1.5 g/d (35). The authors also found that a significant proportion of patients continued to have raised transaminases (37.5%) even when dietary compliant. There are two reasons for the persisting liver abnormalities in patients with HFI. Firstly, fructose may be endogenously produced by the sorbitol-aldose reductase pathway, which can be activated after a glucose-enriched meal, nephrotoxic drugs or stressful conditions like sepsis and major surgery. Secondly, the permissible limits of fructose ingestion may not be safe in asymptomatic patients of HFI. The latter is supported by the determination of CDT by isoelectric focusing among the patients with HFI on an FSS-free diet by Di Dato *et al*[35]. They showed a significant correlation between the amount of fructose consumed and the percentage of disialoTf and tetrasialoTf/disialoTf ratio. The authors suggested that serum CDT profile could be considered a good tool to monitor FSS intake. In addition, CDT determination could be used to identify the maximum daily fructose tolerability of each HFI patient. However, the lack of widespread availability and high cost are the main barriers to the application of this tool.

Non-alcoholic fatty liver disease and HFI

As evident from the study by Di Dato *et al*[35], the majority of the patients with HFI despite being on an FSS-free diet continued to have fatty liver. In another cross-sectional study of 16 patients, non-alcoholic fatty liver disease (NAFLD) was found in 9 (56%) patients[32]. The importance lies in the fact that fatty liver may progress to steatohepatitis, hepatic fibrosis and cirrhosis. Moreover, there is an increased risk of type 2 diabetes and cardiovascular diseases[36,37]. The studies in ALDOB-KO mice as well as in patients with HFI have demonstrated that NAFLD may not be the result of direct lipogenic effects of fructose[38,39]. In addition, when ALDOB-KO mice were chronically exposed to small amounts of fructose in the chow (approximately 0.3%), they showed an increased accumulation of hepatic triglycerides, hepatic inflammation and signs of periportal fibrosis[38,40]. Notably, these ALDOB-KO mice also had increased intrahepatic F-1P concentrations[38]. Lanaspa *et al*[38] also showed the increased hepatic expression of enzymes was seen in de novo lipogenesis with an abundance of cytosolic glucokinase in ALDOB-KO mice. Thus, it can be speculated that the accumulation of F-1P in ALDOB-KO mice may stimulate hepatic glucose uptake, thereby enhancing the storage of glycogen and fat.

In the experimental model, almost all the metabolic abnormalities in the ALDOB-KO mice were ameliorated when supplemented with ketohexokinase (KHK), an enzyme involved in the phosphorylation of fructose[38]. Treatment with osthole, a natural KHK inhibitor also showed the same results[41]. Additionally, osthole treatment inhibited de novo lipogenesis in ALDOB KO mice. In humans, a loss of KHK results in essential fructosuria (OMIM #229800) which is a benign condition[42]. Hence, KHK inhibition may serve as a potential therapeutic target for the treatment of NAFLD in patients with HFI. Ghannem *et al*[43] have unusually reported epithelioid granulomas in association with liver adenomatosis and macrovesicular steatosis in an adult with HFI that yielded negative workup for tuberculosis, sarcoidosis and other infectious diseases. They postulated that the granulomas in the non-tumour liver sections may have developed from the inflammatory stress due to inflammatory hepatocellular adenomas.

Vaccines

There are considerable controversies about the safety concerns of vaccines that contain fructose, sucrose or sorbitol in HFI. Saborido-Fiaño *et al*[44,45] argue that the safe threshold of fructose was 2.4 mg/kg/dose and various oral rotavirus vaccines would not qualify for that category. This requires the need to revisit the vaccine content. The authors also cautioned against the use of Sars-Cov-2 vaccines in children affected with HFI. Urru *et al*[46] demonstrated the safety of these vaccines in adults.

PROGNOSIS

The data on long-term follow-up of patients with HFI is not available in the literature. However, In a recent study of HFI children with a mean follow-up of 10.3 ± 5.6 years, all of them were asymptomatic but had evidence of fatty liver in the majority and raised transaminases in some of them[26]. Interestingly, fructose intake in these children did not correlate with either of the two findings. The two case reports of HFI being diagnosed in adulthood because of self-imposed restriction to fructose in the diet since infancy may signify that the patients with HFI who adhere strictly to an FSS-free diet may have a good prognosis and normal lifespan[19,20]. On the other hand, when compliance is poor, renal and liver-related complications in the form of chronic renal insufficiency and hepatic fibrosis may ensue.

FUTURE RESEARCH

There is a need for data on the long-term outcome of HFI patients on an FSS-restricted diet to provide more insights into the consequences of NAFLD, cardiovascular disease and type 2 diabetes. Recent studies emphasized the role of F-1P in the hepatic fat accumulation of ALDOB-KO mice and the development of NAFLD. However, the exact role of endogenous fructose production (*via* the polyol pathway) in the accumulation of intrahepatic F-1P remains to be determined in animals as well as humans. Finally, clinical trials are required to show the benefit of KHK inhibition in the treatment of NAFLD in HFI patients.

CONCLUSION

HFI has diverse manifestations involving gastrointestinal, liver and renal issues. It mimics many metabolic conditions which present similarly. Other than genetics, there are no reliable laboratory markers that effectively diagnose this condition. A straight-forward FSS-free diet generally leads to a good long-term prognosis. There are however considerable controversies on the effect of dietary therapy on the liver, biochemistry, coexistence of steatosis and permissible levels of fructose in vaccines. Future research should be directed to basic sciences and long-term outcomes of this disease.

FOOTNOTES

Author contributions: Sarma MS conception, final drafting of the manuscript; Singh SK conception, primary drafting of the manuscript.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 July 9; 11(4): 330-340

DOI: 10.5409/wjcp.v11.i4.330

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Case Control Study

Effects of adherence to the Mediterranean diet in children and adolescents with irritable bowel syndrome

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Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Soares RLS, Brazil; Ulasoglu C, Turkey

Received: December 13, 2021
Peer-review started: December 13, 2021
First decision: March 24, 2022
Revised: March 24, 2022
Accepted: April 28, 2022
Article in press: April 28, 2022
Published online: July 9, 2022

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Abstract

BACKGROUND

Irritable bowel syndrome (IBS) is a highly prevalent gastrointestinal disorder in children and adults, which increased over the past twenty years. The Mediterranean diet is a well-known diet full of antioxidants and anti-inflammatory ingredients.

AIM

To evaluate the safety, tolerability, and effects of adherence to the Mediterranean diet on disease patterns in children and adolescents with IBS.

METHODS

This prospective, cross-sectional case-controlled study included 100 consecutive IBS patients diagnosed according to Rome IV criteria, aged 12-18 years. Patients

were subdivided into two groups (50 patients each); Group I received a Mediterranean diet, and Group II on their regular diet for six months. Besides IBS scores (IBS-SSS, IBS-QoL, and total score), different clinical and laboratory parameters were evaluated at the start and end of the study.

RESULTS

The Mediterranean diet was safe and well-tolerated in IBS patients. IBS children and adolescents with good adherence to the Mediterranean diet (KIDMED Score ≥ 8 points); group I showed significant improvement in IBS scores. IBS-SSS in the Mediterranean diet group was 237.2 ± 65 at the beginning of the study and decreased to 163.2 ± 33.8 at the end of the study ($P < 0.001$). It did not show a significant improvement in the group with a regular diet (248.3 ± 71.1 at the beginning of the study compared to 228.5 ± 54.3 at the study end with $P < 0.05$). The mean IBS-SSS in the Mediterranean diet group significantly improved compared with the group with a regular diet. Mean IBS-QoL in group I improved from 57.3 ± 12.9 at the start of the study to 72.4 ± 11.2 at the study end ($P < 0.001$) and significantly improved when compared to its level in group II at the study end (59.2 ± 12.7 with $P < 0.001$), while group II showed no significant improvement in IBS-QoL at the study end when compared to the beginning of the study (59.2 ± 11.7 with $P > 0.05$). The mean total IBS score in group I became 28.8 ± 11.2 at the end of our study compared to 24.1 ± 10.4 at the start ($P < 0.05$) and significantly improved when compared to its level in group II at the end of the study (22.1 ± 12.5 with $P < 0.05$), while in group II, non-significant improvement in the total score at the end of our study compared to its mean level at the start of the study (22.8 ± 13.5 with $P > 0.05$).

CONCLUSION

The Mediterranean diet was safe and associated with significant improvement in IBS scores in children and adolescent patients with IBS.

Key Words: Mediterranean diet; Irritable bowel syndrome; Children and adolescents; Safety; Tolerability

Core Tip: Diet is an essential factor in the pathogenesis and management of irritable bowel syndrome (IBS) patients. Studies involving different modalities of diets in IBS are lacking with contradictory results. The Mediterranean diet is a well-known balanced diet with anti-inflammatory properties. We prospectively studied 100 pediatric and adolescent patients with IBS, divided into two equal groups: group I received a Mediterranean diet, and group II had a regular diet for six months. Different clinical and laboratory parameters besides IBS scores were evaluated at the start and end of the study. The current study showed that the Mediterranean diet is a safe and effective low-cost new strategy in pediatric and adolescent patients with IBS.

Citation: Al-Biltagi M, El Amrousy D, El Ashry H, Maher S, Mohammed MA, Hasan S. Effects of adherence to the Mediterranean diet in children and adolescents with irritable bowel syndrome. *World J Clin Pediatr* 2022; 11(4): 330-340

URL: https://www.wjgnet.com/2219-2808/full/v11/i4/330.htm

DOI: https://dx.doi.org/10.5409/wjcp.v11.i4.330

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the highly prevalent gastrointestinal disorders in children and adults, which increased over the past twenty years. It has a significant effect on the lives of affected children and their families and poses a substantial burden on healthcare systems[1]. It is classified as one of the functional gastrointestinal disorders; characterized by varying degrees of abdominal pain or discomfort, abdominal distension, altered bowel habits, and flatulence, and can be divided into four subtypes; IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), IBS with mixed bowel habits (IBS-M) and IBS unsubtyped (IBS-U)[2].

IBS pathogenesis is a poorly recognized disorder. Many theories were proposed to explain its pathogenesis[3]. It could be related to low-grade inflammation of the bowel mucosa. Dysbiosis with dysregulation of brain-gut axis function and bacterial overgrowth are commonly seen in IBS and are accepted theories that can explain the occurrence of IBS. Immune activation and visceral hypersens-

itivity are possible pathogenetic mechanisms associated with disturbed gastrointestinal motility[4,5]. A possible mechanism is dysregulated neurotransmitters such as cholecystokinin, vasoactive intestinal peptides, and serotonin with the abnormal gut-brain axis[6]. Moreover, food allergy or vitamin deficiency may play a role[7,8].

A few potential therapeutic modalities are available to treat children with IBS, and fewer of them have shown some benefits. Additionally, most of the described pathophysiological mechanisms and treatment choices are adult studies. These have surfaced as challenges when dealing with pediatric IBS, and they need to be overcome for the effective management of children with IBS[9].

The Mediterranean diet is characterized by many vegetables, fruits, bread, and other forms of cereal, rice, beans, and nuts. It also includes virgin olive oil as the principal source of fat, moderate amounts of dairy products (basically cheese and yogurt), moderate amounts of fish, and red meat in low quantities. The value of this dietary model is related to being a balanced and diverse diet that can provide most of the recommended macronutrients in proper proportions. It is characterized by a low content of saturated fatty acids, high monounsaturated fatty acids, high amounts of fiber, complex carbohydrates, and essential antioxidants[10]. They play a crucial role in preventing cardiovascular and cerebrovascular diseases, diabetes, obesity, neurodegenerative illnesses, and cancer[11,12].

Data suggests that the Mediterranean diet might be beneficial in alleviating the functional gastrointestinal symptoms through increased fiber and antioxidant consumption and a low intake of saturated fats and oligosaccharides[13,14]. However, information about the compliance and efficacy of the Mediterranean diet in children and adolescents with IBS is lacking. We aimed to study the effects of the Mediterranean diet on the symptoms of IBS in children and adolescents.

MATERIALS AND METHODS

We designed the study to evaluate the Mediterranean diet's tolerability, safety, and potential efficacy in children and adolescent patients with IBS. After explaining the study design, goals, and rights, all patients/caregivers provided written consent or permission. We conducted the study according to the Helsinki Declaration of 1975. This prospective randomized, case-controlled study was carried out in the Pediatric and Gastroenterology departments, Tanta University Hospital, Egypt, between September 2020 and July 2021. We included one hundred consecutive children and adolescents with IBS diagnosed according to Rome IV criteria[15], aged 12-18 years old. We divided the patients into two groups (50 patients each); the group I received a Mediterranean diet with good adherence (KIDMED Score ≥ 8 points), and Group II received a regular diet. Allocation to the groups was done using simple randomization. The study was not blind as we need to do patient and family education about the Mediterranean diet.

Inclusion criteria

Patients aged 12–18 years were diagnosed with childhood irritable bowel syndrome according to ROME IV criteria[15].

Exclusion criteria

Exclusion criteria include recent changes in IBS therapy, gastrointestinal infection, history of gut surgery or radiation, celiac disease, overweight or underweight according to the centile curve[16], chronic diseases such as renal failure or diabetes mellitus, and patients not adherent to the dietary protocol.

Study intervention: During the study period (6 mo), the patients in group I had the Mediterranean diet as a sole intervention besides their regular treatment. Patients (and their caregivers) received one-to-one education and counseling by a dietitian trained in the Mediterranean diet during each visit. Before each visit, patients and their families completed a three-day food intake record to help assure compliance with the diet. We closely followed up with the patients with the study team, including the dietitian, research pediatrician, and research gastroenterologist, for questions and problem intervention during the study period.

All participants had complete history taking, including dietetic history, thorough clinical examination, and anthropometric measurements such as height, weight, and body mass index (BMI). All participants with IBS filled out the IBS symptoms severity score (IBSSSS) questionnaire[17]. IBSSSS consists of 5 items (severity and frequency of abdominal pain, bloating, satisfaction with bowel habits, and quality of life) collected by direct interview using the visual analog scale (VAS). We scored each item on a scale from 0–to 100. A score below 75 means that the patient is in remission. The mild, moderate, and severe boundary scores are 75–175, 175–300, and above 300. A decrease in the score of 50 or more was considered a significant improvement. The patients also had an IBS quality of life (IBSQoL) questionnaire[18]. Effectiveness, reliability, and sensitivity of IBSSSS to treatment are verified by IBSQoL, which has 34 items, using a 5-choice scale (0–4). We transformed the summed total score to a 100-scale ranging from 0 (lowest) to 100 (highest). A total score of IBS measured by a VAS of 100 scales is used to evaluate the real IBS symptoms' impact on the quality of life, which was done at the same

frequency as IBSSSS and IBSQoL scores.

The patients also had routine laboratory investigations such as complete blood count (CBC), erythrocyte sedimentation rate (ESR), serum calcium, random blood sugar, renal and hepatic functions, serum proteins, urine, and stool analysis. Fecal calprotectin was measured, and fecal blood in the stool was done in all included patients to exclude patients with inflammatory bowel disease. Follow-up visits were done at one, three, and six months. All IBS scores, laboratory parameters, and growth parameters (body weight, height, and BMI) were repeated at the end of our study.

KIDMED test: The Mediterranean diet quality index for children and teenagers (KIDMED test) is an instrument developed and validated by Serra-Majem *et al*[19]. It is used to evaluate the adherence of children and youths to the Mediterranean diet. The index ranges from 0 to 12. It is based on a 16-questions test that can be self-administered or conducted by interview (pediatrician, dietitian, *etc*.). Questions indicating a negative association concerning the Mediterranean diet are assigned a value of -1, and those with a positive aspect are given a value of +1. The total values from the processed test are categorized into three degrees: (1) ≥ 8, optimal adherence to the Mediterranean diet; (2) 4–7, adherence improvement is needed to adjust intake to Mediterranean patterns; and (3) ≤ 3, poor adherence to the Mediterranean diet[20].

The primary outcome of the current study was to assess the effects of adherence to the Mediterranean diet for six months on the IBS symptoms and severity score. The secondary outcome was to evaluate the safety and tolerability of the Mediterranean diet in children and adolescents with IBS.

Ethical considerations

This clinical study was conducted following the principles of the Declaration of Helsinki. At the beginning of the study, all subjects (and caregivers) were fully informed about the study objectives and their rights. They signed a written informed consent to participate in the study. The local Ethical Committee approved the study. The study is registered with the registration number PACTR-202008711997928. All authors had access to the study data and have reviewed and approved this final manuscript.

Statistical analysis

A sample size of 45 IBS patients in each group was required to achieve a power of more than 80 to detect a difference of 60 in the mean of the primary outcome point (IBSSSS) based on a previous study [21]. We recruited more than the estimated sample size, expecting a possible lack of adherence to the Mediterranean diet or withdrawal from the study, undermining our results. We collected and analyzed the data using SPSS version 17 (SPSS Inc., Chicago, IL, United States). We expressed the continuous data as mean ± SD. We used the paired *t*-test to compare the same group before and after treatment. An independent *t*-test was used for comparison between group 1 and group 2. We expressed the categorical variables as numbers and percentages and analyzed them using the Chi-square test. We used the Pearson correlation to evaluate the correlation between the Mediterranean diet with IBS scores. The statistical significance was defined as $P < 0.05$.

RESULTS

This study included 100 children and adolescent patients with IBS aged 12-18 years; divided into two groups included 50 patients. Group-I had 27 males and 23 females with a mean age of 15.5 ± 1.8 years, and group II had 26 males and 24 females with a mean age of 15.2 ± 1.5 years. Before the study, the average duration of IBS symptoms was 34.4 ± 9.1 mo in group I and 35.3 ± 9.8 mo in group II. We illustrated the demographic, growth parameters, clinical subtypes, IBS severity, treatment drugs, and IBS scores in both groups in Table 1. We found no significant differences between the two groups in all measured parameters at the start of our study.

Basic laboratory data in all patients done at start of our study (Table 2) with non-significant differences between both groups regarding serum albumin(4.1 ± 0.9 g/dL in Group-I and 4.3 ± 0.88 in Group-II with $P = 0.93$) ,serum triglycerides(120.7 ± 45.6 mg/dL in Group I and 112.9 ± 49.4 in Group-II with $P = 0.44$), serum cholesterol (154.0 ± 36.6 mg/dL in Group I and 163.6 ± 44.1 in Group II with $P = 0.35$),random blood glucose level (86.20 ± 20.20 mg/dL in Group I and 85.7 ± 9.70 in Group II with $P = 0.91$), hemoglobin level (13.10 ± 1.60 g/dL in Group-I and 13.6 ± 1.80 in Group II with $P = 0.47$). Fecal calprotectin was normal in both groups (12 ± 9.10 μg/g in group I and 11 ± 8.80 in Group II with p 0.52), and it was done to exclude patients with inflammatory bowel disease.

The Mediterranean diet was well tolerated in IBS patients. Only three patients could not tolerate it and were withdrawn from the study (one after one month and two patients after three months, replaced by other patients; Figure 1). No adverse events regarding the Mediterranean diet were reported as reflected by non-significant changes in growth parameters (height, weight, and BMI), laboratory parameters (serum albumin, triglycerides, cholesterol, glucose, and hemoglobin levels) at the end of our study when compared to the same parameters at the start of the research and when compared to group-

Table 1 Demographic data and clinical characteristics in irritable bowel syndrome patients' groups before the start of the Mediterranean diet

Variable	Group I (Mediterranean diet) (*n* = 50)	Group II (*n* = 50)	*P* value
Age (yr)	15.50 ± 1.80	15.2 ± 1.5	0.88[1]
Sex (M: F)	27:23	26:24	0.90[2]
Height (z-score)	0.04 ± 1	0.04 ± 1.00	0.66[1]
Weight (z-score)	0.14 ± 0.99	0.12 ± 0.89	0.83[1]
BMI (z-score)	0.18 ± 0.88	0.17 ± 1.02	0.77[1]
IBS subtypes			0.47[2]
IBS-C	22 (44 %)	21 (42 %)	
IBS-D	20 (40 %)	21 (42 %)	
IBS-M	4 (8 %)	5 (10 %)	
IBS-U	2 (4 %)	3 (6 %)	
IBS severity			0.55[2]
Mild	12 (24%)	14 (28 %)	
Moderate	33 (66%)	31 (62 %)	
Severe	5 (10%)	5 (10 %)	
Duration of IBS symptoms (mo)	34.40 ± 9.10	35.30 ± 9.80	0.58[1]
Treatment drugs[3]			0.66[1]
Gastroprokinetic	50	50	
Antidepressants	11	12	
Antacids	18	20	
Antibioticsprobiotics	924	723	
IBS-SSS	237.20 ± 65	248.30 ± 71.10	0.68[1]
IBS-QoL	57.30 ± 12.90	59.10 ± 11.70	0.71[1]
Total score	24.10 ± 10.40	22.80 ± 13.50	0.82[1]

[1]Independent *t*-test.
[2]Chi-square test.
[3]Treatment drugs for one month before starting the study and during the whole study period.
BMI: Body mass index; IBS: Irritable bowel syndrome; IBS-C: IBS constipation; IBS-D: IBS diarrhea; IBS-M: IBS mixed; IBS-U: IBS unsubtyped; IBS-SSS: IBS symptoms severity score questionnaire; IBS-QoL: IBS quality of life questionnaire.

Table 2 Laboratory data of all patients at the start of the study

Variable	Group I (Mediterranean diet) (*n* = 50)	Group II (*n* = 50)	*P* value
Albumin (g/dL)	4.10 ± 0.90	4.30 ± 0.88	0.93
Triglycerides (mg/dL)	120.70 ± 45.60	112.90 ± 49.40	0.44
Cholesterol (mg/dL)	154.00 ± 36.60	163.60 ± 44.10	0.35
Glucose (mg/dL)	86.20 ± 20.20	85.70 ± 9.70	0.91
Hemoglobin (g/dL)	13.10 ± 1.60	13.60 ± 1.80	0.47
Fecal calprotectin (μg/g) *n* < 50	12 ± 9.10	11 ± 8.80	0.52

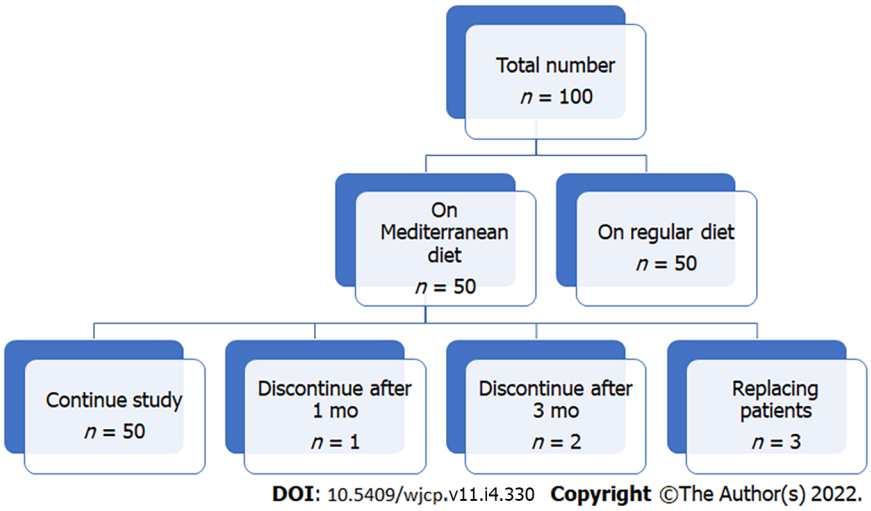
II at the end of our study (Table 3). At the end of our research, there was a significant improvement in all IBS scores in IBS patients who received a Mediterranean diet (group I) compared to such scores at the start of the study and when compared to group II at the end of the study (Table 3). The mean IBS-SSS in group-I became 163.20 ± 33.80 at the study end compared to 237.20 ± 65 at the start ($P < 0.001$), with

Table 3 Growth parameters, laboratory data, and irritable bowel syndrome scores in all patients at the start versus at the end of the study

Variables		Group I (Mediterranean diet) (n = 50)			Group II (n = 50)			P value[1]
		Start	End	P value	Start	End	P value	
Growthparameters	Height (z-score)	0.04 ± 1	0.04 ± 0.92	0.88	0.04 ± 1.00	0.04 ± 0.99	0.63	0.18
	Weight (z-score)	0.14 ± 0.99	0.13 ± 1.0	0.54	0.12 ± 0.89	0.12 ± 0.55	0.61	0.36
	BMI (z-score)	0.18 ± 0.88	0.17 ± 0.69	0.6	0.17 ± 1.02	0.16 ± 1.08	0.80	0.55
Laboratory data	Albumin (g/dL)	4.10 ± 0.90	4.3 ± 0.94	0.77	4.30 ± 0.88	4.50 ± 0.91	0.49	0.54
	Triglycerides (mg/dL)	120.7 0 ± 45.60	118.50 ± 47.10	0.90	112.90 ± 49.40	115.20 ± 50.40	0.51	0.65
	Cholesterol (mg/dL)	154 ± 36.60	155.80 ± 32.20	0.56	163.60 ± 44.1	168.10 ± 42.90	0.63	0.28
	Glucose (mg/dL)	86.2 ± 20.20	81.90 ± 24.50	0.27	85.7 ± 9.7	87.30 ± 11.20	0.28	0.73
	Hemoglobin (g/dL)	13.1 ± 1.60	14.00 ± 1.10	0.66	13.60 ± 1.80	13.20 ± 1.50	0.71	0.33
	Fecal calprotectin (μg/g) n < 50	12 ± 9.10	11.30 ± 9.90	0.81	11 ± 8.80	10.80 ± 9.20	0.88	0.62
IBS scores	IBS-SSS	237.20 ± 65	163.20 ± 33.80	0.001[1]	248.3 ± 71.1	228.50 ± 54.30	0.29	< 0.001[1]
	IBS-QoL	57.30 ± 12.9	72.40 ± 11.2	<0.001[1]	59.1 ± 11.7	59.20 ± 12.70	0.77	< 0.001[1]
	Total score	24.10 ± 10.4	28.80 ± 11.20	0.02[1]	22.8 ± 13.50	22.10 ± 12.50	0.94	0.03[1]

[1]P value is for group I *vs* group II at the end of the study.

BMI: Body mass index; IBS: Irritable bowel syndrome; IBS-SSS: IBS symptoms severity score questionnaire; IBS-QoL: IBS quality of life questionnaire.



DOI: 10.5409/wjcp.v11.i4.330

Figure 1 The flow chart of the study.

significant improvement when compared to group-II at the study end (228.50 ± 54.30) with P < 0.001, while in group-II, there was no substantial improvement in IBS-SSS at the study end compared to its mean level at the start of the study (228.50 ± 54.30 *vs*. 248.30 ± 71.10 with P = 0.29). Mean IBS-QoL in group-I became 72.40 ± 11.20 at the end of our study compared to 57.30 ± 12.90 at the start (P < 0.001) and significantly improved when compared to its level in group II at the end of the study (59.20 ± 12.70 with P < 0.001), while in group II, non-significant improvement in IBS-QoL at the end of our study compared to its mean level at the start of the study (59.20 ± 12.70 *vs* 59.10 ± 11.70 with P = 0.77). The mean total score in group I became 28.80 ± 11.20 at the end of our study compared to 24.10 ± 10.40 at the start (P = 0.02) and significantly improved when compared to its level in group II at the end of the study (22.10 ± 12.50) with P = 0.03, while in group II, non-significant improvement in the total score at the end of our study compared to its mean level at the start of the study (22.10 ± 12.50 *vs*. 22.80 ± 13.50 with P = 0.94). These changes reflect the Mediterranean diet's positive impact on the symptoms and lifestyle of IBS children and adolescents.

DISCUSSION

What should we eat? This question is one of the most frequently asked questions by patients with IBS and their caregivers. Many patients also seek dietary guidelines because the diet is considered safer than medical therapies. Treating IBS symptoms by modifying the patient's diet has been one of the most desirable therapeutic strategies for a long time. Unfortunately, the scarcity of high-quality evidence supporting a specific dietary intervention resulted in the unnecessary exclusion of diets despite lacking evidence of efficacy and safety, especially in pediatric age groups[22]. The current study found that the Mediterranean diet was safe and well-tolerated in IBS patients. Compared to the control group, good adherence to the Mediterranean diet resulted in significant improvement in IBS scores and IBS-QoL and total IBS scores. Many previous studies on children and adolescents showed a negative correlation between compliance with the Mediterranean diet and the development of various diverse pathological conditions, such as obesity, asthma, and recurrent cold[23,24].

Considering the potential association of adherence to the Mediterranean diet with the development of functional gastrointestinal disorders (FGIDs), much data from the adult population supports the beneficial effect of the Mediterranean diet on preventing the development of or lessening the gastrointestinal (GI) symptoms in patients with GI disorders, both functional (IBS, functional dyspepsia, gastroesophageal reflux) or organic (inflammatory bowel disease)[25]. Elmaliklis *et al*[26] showed that adherence to the Mediterranean diet (including functional foods containing probiotics, prebiotics, antioxidants, fiber, vitamins, minerals) was significantly lower in adult patients with various gastrointestinal disorders such as IBS, Crohn's disease, ulcerative colitis, and gastroesophageal reflux than in controls.

Another Southern Italian study by Zito *et al*[27] investigated the association between adherence to the Mediterranean diet and the onset of symptoms in adults with functional dyspepsia or IBS. They demonstrated a negative correlation between compliance with the Mediterranean diet and the development of gastrointestinal symptoms. They concluded that good adherence to the Mediterranean diet could prevent the development of gastrointestinal symptoms in adults. Moreover, they showed that patients with functional dyspepsia and IBS between 17 and 24 years had significantly poorer Mediterranean diet adherence than the age-matched controls. Interestingly, Strisciuglio *et al*[28] studied the adherence to the Mediterranean diet in children and adolescents suffering from inflammatory bowel disease with an age-matched population with FGIDs (gastroesophageal reflux and functional constipation). It was found that children/adolescents with inflammatory bowel syndrome had poorer adherence to the Mediterranean diet than those with FGIDs. However, there is no data on the association of Mediterranean diet adherence with the prevalence of FGIDs in children and adolescents.

In the current study, the Mediterranean diet was well tolerated in IBS patients; only three patients could not tolerate it and were withdrawn from the study (one after one month, two patients after three months, and replaced by other patients). No adverse events regarding the Mediterranean diet were reported as reflected by non-significant changes in growth parameters (height, weight, and BMI), laboratory parameters (serum albumin, triglycerides, cholesterol, glucose, and hemoglobin levels) at the end of our study when compared to the same parameters at the start of the research and when compared to group II at the end of our study.

Our study found positive effects of the Mediterranean diet in children and adolescents with IBS, with significant improvements in all IBS scores compared to the patients on the regular diet. These effects may be due to the specific components of the Mediterranean diet, which is characterized by a high intake of plant-based foods (vegetables, legumes, fruits, nuts, whole grain cereals), olive oil as the primary fat source, moderate amounts of dairy products (yogurt and cheese), and low or moderate cuts of fish and meat, with well-known antioxidant and anti-inflammatory properties[10]. Regular consumption of such products induces an accumulation of nitrate/nitrite/NO, polyunsaturated fatty acids (PUFA), and polyphenolic compounds, such as resveratrol, in the human body[12]. The most important dietary sources of NO_3^- for the human body include green vegetables such as spinach, lettuce, collard greens and radishes, beets, and meat. At the organ level, NO_2^--dependent vasorelaxation plays a role in hypoxic blood flow regulation and improves tissue microcirculation[29,30].

The Mediterranean diet traditionally includes an abundance of vegetables and fish; both contain a substantial amount of diverse PUFA (ω-3, 6, 9). Briefly, PUFAs are divided into three classes based on the position of the first double bond from the methyl carbon, labeled "ω": ω-3 (DHA-docosahexaenoic, EPA-eicosapentaenoic, and ALA-α-linolenic), ω-6 (LA-linoleic, GLA-γ-linolenic, and AA-arachidonic); and ω-9 (OA-oleic). Extensive studies have revealed that the protective effects of EPA and DHA could be mediated by forming reactive lipid molecules called Resolvins[31]. Resolvins (E1 and D1) have a well-known anti-inflammatory property by preventing polymorphonuclear neutrophil (PMN) activation and translocation into the tissue[32,33]. Resolvin E1 regulates cytokine/chemokine production[34] and inhibits TNFα-induced nuclear translocation of NF-kB[35]. Freeman *et al*[36] characterized several electrophilic oxo-derivatives of DHA and EPA, synthesized in activated macrophages *via* the cyclooxygenase-2 dependent pathway. Like Resolvins, these also possess strong anti-inflammatory properties.

Regular consumption of grape wine is an integral element of the Mediterranean diet. The anti-inflammatory benefits of grape wine could be attributed to its phenolic components. Polyphenolic compounds such as quercetin, resveratrol, or catechins are potent antioxidants; thus, one of the mechanisms of protection they provide might be the inhibition of oxidative stress[37]. Moreover, the effect of the Mediterranean diet on gut microbiota may be an additional factor. Previous studies demonstrated that good adherence to the Mediterranean diet was associated with lower *Escherichia coli* (*E. coli*) counts and a higher *Bifidobacteria* to *E. coli* ratio[38].

The strength of the current study is that it is the first report on the association between adherence to the Mediterranean diet and IBS symptoms in children and adolescents. The main limitation is the cross-sectional design, which allows the assessment of good associations but not conclusions on causality. The study was also from a single center, so the data cannot be generalized.

CONCLUSION

Results of the current study indicate that good adherence to the Mediterranean diet is safe and associated with significant improvement in IBS-score in children and adolescents. The mechanisms underlying this association and the causality between the Mediterranean diet and IBS need further clarification. If other studies with extensive metabolomic analysis and microbiome assessments confirm the current study's findings, this will complete the picture of the diet–health interaction and relationship. Until then, we should encourage children and adolescents to follow the Mediterranean diet to have a place among other measures in minimizing the symptoms.

ARTICLE HIGHLIGHTS

Research background

Irritable bowel syndrome (IBS) has a significant effect on the lives of affected children and their families and poses a substantial burden on healthcare systems. A few potential therapeutic modalities are available to treat children with IBS, and fewer of them have shown some benefits.

Research motivation

A few potential therapeutic modalities are available to treat children with IBS, and fewer of them have shown some benefits. The authors need to conduct more studies to help patients with IBS alleviate their symptoms.

Research objectives

The authors aimed to study the effects of the Mediterranean diet on the symptoms of IBS in children and adolescents.

Research methods

The authors studied one hundred consecutive IBS patients diagnosed according to Rome IV criteria, aged 12-18 years old. The authors divided the patients into two groups (50 patients each), the group I received a Mediterranean diet with good adherence (KIDMED Score ≥ 8 points), and Group II received a regular diet.

Research results

IBS children and adolescents with good adherence to the Mediterranean diet (KIDMED Score ≥ 8 points); group I showed significant improvement in IBS scores. IBS-SSS in the Mediterranean diet group was 237.2 ± 65 at the beginning of the study and decreased to 163.2 ± 33.8 at the end of the study ($P < 0.001$). It did not show a significant improvement in the group with a regular diet (248.3 ± 71.1 at the beginning of the study compared to 228.5 ± 54.3 at the study end with $P < 0.05$). The mean IBS-SSS in the Mediterranean diet group significantly improved compared with the group with a regular diet. Mean IBS-QoL in group I improved from 57.3 ± 12.9 at the start of the study to 72.4 ± 11.2 at the study end ($P < 0.001$) and significantly improved when compared to its level in group II at the study end (59.2 ± 12.7) with $P < 0.001$, while group II showed no significant improvement in IBS-QoL at the study end when compared to the beginning of the study (59.2 ± 11.7 with $P > 0.05$). The mean total IBS score in group I became 28.8 ± 11.2 at the end of our study compared to 24.1 ± 10.4 at the start ($P < 0.05$) and significantly improved when compared to its level in group II at the end of the study (22.1 ± 12.5) with $P < 0.05$, while in group II, non-significant improvement in the total score at the end of our study compared to its mean level at the start of the study (22.8 ± 13.5) with $P > 0.05$.

Research conclusions

Mediterranean diet was safe and associated with significant improvement in IBS scores in children and adolescent patients with IBS.

Research perspectives

The authors need to extend our study for a longer duration. We also need to investigate the effects of the Mediterranean diet on the various GIT functions, including bowel movement, stool consistency, and the impact on the gut microbiota.

ACKNOWLEDGEMENTS

We thank the anonymous referees and editors for their valuable suggestions.

FOOTNOTES

Author contributions: Hasan S, El-Amrousy D, and El-Ashry H performed the clinical part and collected the data; Maher S performed the laboratory part; Mohammed MA did the statistical analysis; Al-Biltagi M analyzed the data and wrote the manuscript; and All the authors revised and agreed on the final version of the manuscript.

Institutional review board statement: We performed to study according to the latest version of Helsinki's Declaration. The Research and Ethics Committee at the Ministry of Health, Kingdom of Bahrain, approved the study.

Informed consent statement: An informed written consent was signed by all subjects (and their caregivers).

Conflict-of-interest statement: None of the authors had potential undisclosed conflicts of interest.

Data sharing statement: Data are available upon reasonable request.

STROBE statement: The authors have read the STROBE statement, and the manuscript was prepared and revised according to the STROBE statement.

Country/Territory of origin: Egypt

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S-Editor: Ma YJ
L-Editor: A
P-Editor: Ma YJ

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World Journal of Clinical Pediatrics

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World J Clin Pediatr 2022 July 9; 11(4): 341-350

DOI: 10.5409/wjcp.v11.i4.341

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Retrospective Study

Prevalence, phenotype and medication for the pediatric inflammatory bowel disease population of a state in Southeastern Brazil

Adalberta Lima Martins, Renata de Sá Brito Fróes, Maria da Penha Zago-Gomes

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Day AS, New Zealand; Wen XL, China; Xiao Y, China
A-Editor: Elpek GO, Turkey

Received: January 7, 2022
Peer-review started: January 7, 2022
First decision: March 9, 2022
Revised: March 23, 2022
Accepted: June 3, 2022
Article in press: June 3, 2022
Published online: July 9, 2022

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Abstract

BACKGROUND

Inflammatory bowel disease (IBD) can lead to social and economic impacts worldwide. In Brazil, where its adult prevalence is increasing, the epidemiology of the pediatric population is not well known, although there is a documented increase in pediatric IBD incidence worldwide. Brazil has continental dimensions, and Espírito Santo is a state of southeastern Brazil, the region with the highest demographic densities and is the economically most important in the country.

AIM

To assess the prevalence, incidence, phenotype and medications in a Southeastern Brazilian pediatric population.

METHODS

Data were retrieved from the Public Medication-Dispensing System of the Department of Health in Espírito Santo state from documentation required to have access to highly expensive medication from August 1, 2012 to July 31, 2014. There were 1048 registered patients with IBD of all ages, and of these patients, the cases ≤ 17 years were selected. The data were obtained through the analysis of administrative requests for these medications and included medical reports, endoscopy exams, histopathology and imaging tests, which followed the Clinical Protocols and Therapeutic Guidelines of the Brazilian Government. Only confirmed cases of IBD were included in the study.

RESULTS

There were 55 pediatric patients/1048 registered patients (5.34%), with Crohn's disease (CD) representing 30/55 (55%), ulcerative colitis (UC) 24/55 (43.6%) and 1 unclassified IBD, a significant difference from adult patients (P = 0.004). The prevalence of IBD in pediatric patients was 5.02 cases/100.000 inhabitants; the incidence in 2014 was 1.36 cases/100.000 inhabitants. The mean age at diagnosis was 12.2 years (± 4.2). There were 7 children diagnosed up to 6 years old, 7 between 7 to 10 years old and 41 between 11 and ≤ 17 years old. There was no difference in the distribution of UC and CD between these age categories (P = 0.743). There was no difference in gender distribution in relation to adults. Children and adolescents with UC had a predominance of pancolitis, unlike adults (P = 0.001), and used aminosalicylates and immunomodulators for their treatment. Pediatric patients with CD did not present a difference in disease location but had a higher frequency of fistulizing behavior (P = 0.03) and perianal disease phenotype (P = 0.007) than adult patients. Patients with CD used more immunomodulators and biological therapy. Treatment with biological therapy was more frequently used in pediatric patients than in adults (P < 0.001).

CONCLUSION

Although the data from this study demonstrate that incidence and prevalence rates are low in southeastern Brazil, these data demonstrate the severity of IBD in pediatric patients, with the need for early diagnosis and therapy, avoiding serious damage.

Key Words: Inflammatory bowel disease; Pediatric; Prevalence; Phenotype; Brazil

Core Tip: In Brazil, where the prevalence of inflammatory bowel disease (IBD) in adults is increasing, the epidemiology of the pediatric population is not well known, although there is a documented increase in pediatric IBD incidence worldwide. Espírito Santo is a state of southeastern Brazil, the region with the highest demographic densities and that is the economically most important in the country. Our epidemiological data, including behavior and medication, evaluate the comparison between the pediatric and adult age groups. Therefore, this study has the potential to reinforce the need for adequate care of pediatric patients with IBD, with the potential to influence public health policies.

Citation: Martins AL, Fróes RSB, Zago-Gomes MP. Prevalence, phenotype and medication for the pediatric inflammatory bowel disease population of a state in Southeastern Brazil. *World J Clin Pediatr* 2022; 11(4): 341-350

URL: https://www.wjgnet.com/2219-2808/full/v11/i4/341.htm

DOI: https://dx.doi.org/10.5409/wjcp.v11.i4.341

INTRODUCTION

Inflammatory bowel disease (IBD) can lead to social and economic impacts worldwide. In Brazil, where its prevalence is increasing, the epidemiology of the pediatric population is not well known, although there is a documented increase in pediatric IBD incidence worldwide[1,2]. Represented by ulcerative colitis (UC), Crohn's disease (CD) and unclassified inflammatory bowel disease (U-IBD), these diseases have a chronic evolution, with more severe clinical manifestations and complex treatment when started in the pediatric age group[3,4]. IBD initiation in childhood and adolescence is described in up to 25% of patients[3,5].

The main signs and symptoms of IBD in the pediatric age range are diarrhea, abdominal pain and stunting, which can be confused with other diseases, causing a delay in diagnosis and inappropriate therapies. Considering the more aggressive phenotypes and worse therapeutic response in this age group, early recognition of the disease becomes extremely important[4-6].

There are still few epidemiological studies in the pediatric age group; however, this information is relevant as it can define characteristics specific to each region and provide improvements to the health system with programming of costs related to propaedeutics and treatment. In addition, early diagnosis and adequate therapy could provide better results, that is, deep remission, with better physical, social and school health quality[4].

Some epidemiological studies of IBD have been carried out in Brazil[7,8]; however, the majority were in reference centers for adult care, and other recent studies used the database of records of the "Sistema Único de Saúde (SUS)" which is Brazilian Health System[9,10]. Brazil has continental dimensions, but

there is no obligation to notify a case of IBD in the country, and there is no unified registry, although the Brazilian government provides medication for the treatment of IBD through the sector of the supply of high-cost drugs for chronic diseases, which all citizens are entitled to access. The aim of this study is to evaluate the epidemiology, phenotype and treatment of IBD in pediatric patients in the state of Espírito Santo, a state of Southeastern Brazil, the region with the highest demographic densities and most economic importance in the country, to contribute to possible improvements, both in the assistance and administrative areas of the health service.

MATERIALS AND METHODS

Study location and data collection

The study was conducted between August 1, 2012, and July 31, 2014, in the Public Medication Dispensing System of the Department of Health of Espírito Santo, sector for Pharmaceutical Assistance, which is responsible for dispensing medications for patients with IBD in the whole state.

This study evaluated patients with a confirmed diagnosis of IBD aged ≤ 17 years old from a total sample containing 1048 patients of all ages, with phenotype and treatment available, who received medications through the Federal Government and for whom the incidence and prevalence of IBD was determined in a previous study[9].

In medication-dispensing services, the evaluation is conducted by a gastroenterologist doctor, in this case, the author of the research, who was responsible for dispensing the medication for IBD. The data analyzed were obtained through the analysis of administrative requests of these medications and included personal identification documents, medical reports, endoscopy exams, histopathology and imaging tests, which followed the Clinical Protocols and Therapeutic Guidelines of the Brazilian Government[11,12].

As the study included patients aged 17 years, we chose to use the Montreal classification to establish the phenotype of IBD for CD and UC[13]. For the patients whose endoscopic examination, imaging, and histopathological and laboratory examinations associated with medical reports had difficulty in defining CD and UC, the terminology "unclassified inflammatory bowel disease" (U-IBD) was applied.

Dependent variables included the diagnosis, IBD classification, medications, new cases (diagnosis made less than 12 months before the time of the process of evaluation at the Pharmaceutical Assistance) and old cases (diagnosis older than 12 mo), distributed in assessment year 1 (August 1, 2012 to July 31, 2013) and year 2 (August 1, 2013 to July 31, 2014). Independent variables included age and sex.

Study limitations

The study was conducted with secondary data, and some information may not be complete. Not all patients with CD included in the study had an upper gastrointestinal endoscopy/biopsy, and magnetic resonance. Medical reports and few older documents have been damaged due to time, making it impossible to define the localization of the disease in some cases.

In Brazil, medications for IBD are expensive and provided by the Public Health care System for patients treated in the public and private systems. However, it is possible that some patients in the private system obtained their oral medications directly from drugstores without utilizing the public system.

Ethical considerations

This study was approved by the Ethics and Research Committee of the Nossa Senhora da Gloria Children's Hospital (CAAE 19602813.8.0000.5069) after obtaining authorization from the State Office for Pharmaceutical Assistance. The terms clarification and consent were waived because the data used were secondary data.

Statistical analysis

An Excel spreadsheet was used to collect all the data, and all patients aged ≤ 17 years of age when diagnosed were selected, building a new Excel table that was analyzed using SPSS Statistics 20.0 software. Data were tabulated and analyzed through descriptive analysis of frequencies, percentages, averages, and standard deviations (SD). To determine associations between categorical variables, a chi-square test was used, and Fisher's exact test was also used when appropriate. A P value of < 0.05 was considered statistically significant.

Data from the Brazilian Institute of Geography and Statistics (IBGE) were used to calculate prevalence and incidence based on the estimated census of 2014, in which the total estimated population of Espírito Santo was 3.885.049 inhabitants[14] and the population ≤ 17 years old was 1.095.669 inhabitants[15]. To calculate incidence, new cases arising in the second year of the study were used (August 1, 2013, to July 31, 2014), and prevalence was calculated as the number of children (≤ 17 years) who received dispensed IBD-related drug prescriptions during the study period that ended on July 31, 2014.

RESULTS

Incidence and prevalence

Out of a total sample of 1048 patients analyzed in medication-dispensing services at the Pharmaceutical Assistance in Espírito Santo who were diagnosed with IBD, 55 (5.24%) were diagnosed at ≤ 17 years old. There were predominance of CD 30/55 (54.5%), with UC 24/55 (43.6%) and 1 had a diagnosis of U-IBD, different from the sample of adult patients (P = 0.004).

In 2013, 33 patients were registered, and in 2014, 22 patients were registered, for a total of 55 cases. Of the 22 cases registered in 2014, 14 were new cases: 7 were CD and 7 were UC. The calculated prevalence and incidence are based on the estimated census of 2014[14,15]. The prevalence of IBD in pediatric patients in the state of Espírito Santo, Brazil, was 5.02 cases/100.000 inhabitants/year, while the incidence in 2014 (year) was 1.27 cases/100.000 inhabitants/year. The prevalence of CD was 2.73/100.000 inhabitants, and the incidence was 0.63 cases/100.000 inhabitants/year. The prevalence of UC was 2.19/100.000 inhabitants, and the incidence was the same as that of CD (0.63 cases/100.000 inhabitants).

Demographic characteristics

Seven children were diagnosed up to 6 years old, 7 were diagnosed between 7 to 10 years of age and 41 were diagnosed between 11 and 17 years of age, and there was no difference in the distribution of UC and CD between these age categories (P = 0.743), as summarized in Table 1. The distribution of sex is shown in Figure 1, but the difference was not significant (P = 0.357).

Disease Phenotype and Medication

The distribution of UC and CD phenotypes was compared with that in the adult group, and we observed the highest frequency of pancolitis in UC and perianal disease in CD in the group ≤ 17 years, as shown in Table 2. Perianal disease is more associated with fistulizing disease in CD, as shown in Figure 2. The distribution of biologics used in this group was compared with that in the adult group, and no significant difference was observed, as shown in Table 3.

Oral aminosalicylates (mesalazine/sulfasalazine) were the drugs most used in UC, and in CD, we observed a greater use of the immunomodulators than aminosalicylates, as shown in Figure 3.

DISCUSSION

This is the first epidemiological study of the incidence and regional prevalence of IBD in a pediatric/adolescent population in a state of our country based on searches at the National Center in Biotechnology Information. There is a documented increase in the incidence and prevalence of pediatric IBD worldwide, and although this information is of great value for the planning of the health system, the few existing studies present different methodologies, which makes a more reliable analysis difficult [3,16-20].

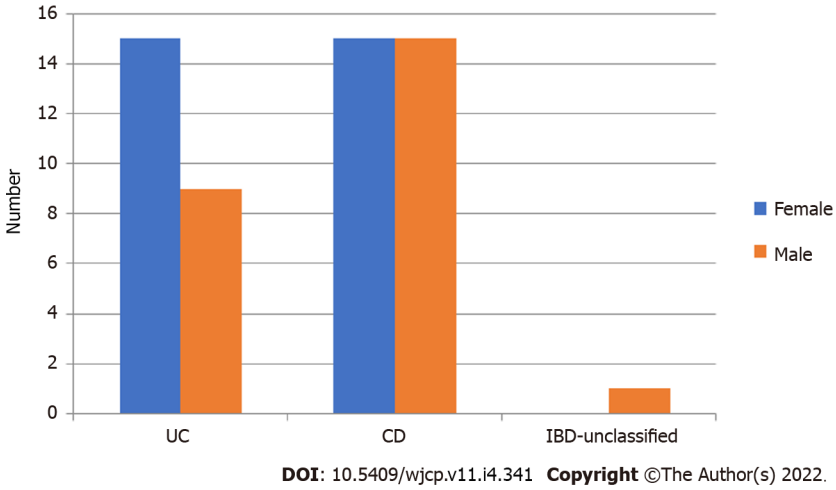
In this study, we observed that the prevalence of IBD ≤ 17 years in the state of Espírito Santo, southeastern Brazil, in 2014 was 5.02 cases/100.000 inhabitants/year (CD: 2.73/100.000 and UC: 2.19/100.000), higher than the prevalence of IBD in Mexico[18] in Central America in patients < 18 years old, with 0.18 cases/100.000 inhabitants, but much lower than other regions, as in the 2017 study by Ludvigsson *et al*[3], in Sweden that analyzed data between 1993 to 2010 and reported 75 cases/100.000 inhabitants (CD 29/100.000 and UC: 25/100.000) and the 2019 study by Jones *et al*[21] in Scotland that analyzed data from 2009 to 2018 and found prevalence in children under 17 of 106 cases/100.000 inhabitants. Roberts *et al*[22], 2020, in a systematic review of pediatric IBD in Europe, found few prevalence studies using national and regional data. The highest prevalence rates of CD were approximately 60/100.000 in Hungary from 2011 to 2013. Regarding UC, the highest prevalence was approximately 30/100.000 in 3 regions: Hungary, Sweden and Denmark[22]. In North America, in Canada (Manitoba), 1978-2007 study showed an increase in prevalence from 3.1 to 18.9/100.000 in CD and UC from 0.7 to 12.7/100.000 inhabitants in UC[23].

The incidence of pediatric IBD in this study was 1.36 cases/100000 inhabitants/year, with equivalent CD and UC values of 0.63/100,000. Our incidence was higher than that observed in Argentina (0.4/100.000)[17] and Mexico (0.04/100.000)[18] but lower than that in other areas of the world, as noted in the 2018 systematic review of the incidence of IBD in children/adolescents from Sýkora *et al*[16], from 1985 to 2018, which found that the highest annual pediatric incidences of IBD were 23/100.000 person/years in Europe (Finland), 15.2/100.000 in North America (Canada) and 11.4/100.000 in Asia/Middle East and Oceania. However, the highest pediatric CD incidence was 13.9/100.000 in North America (Canada), followed by 12.3/100000 in Europe (France). Regarding UC, the highest annual incidence was 15.0/100.000 in Europe (Finland) and 10.6/100.000 in North America (Canada)[16]. In the analysis of incidence and prevalence, we can conclude that we still have low rates.

Table 1 Demographic data from pediatric and adult patients diagnosed with inflammatory bowel disease in the state of Espírito Santo, from August 2012 to July 2014

Characteristics	Total amount		Age at diagnosis ≤ 17 yr		Age at diagnosis ≥ 18 yr		*P* value
	n	%	*n*	%	*n*	%	
	1.048	(100)	55	(5.24)	993	(94.76)	
Mean age at diagnosis (yr)	39.2	± 16.1	12,2	± 4.2	40,7	± 15.1	NA
Mean actual age (yr)	42.0	± 16.1	15,3	± 4.6	43,5	± 15.0	NA
Sex							
Male	433	(41.3)	25	(44.6)	408	(41.1)	0.522
Female	615	(58.7)	30	(55.4)	585	(58.9)	
IBD							
Crohn's disease	357	(34.1)	30	(54.5)	327	(32.9)	**0.004**
Ulcerative colitis	669	(63.2)	24	(43.7)	645	(65)	
Unclassified IBD	22	(2.1)	1	(1.8)	21	(2.1)	

Continuous values are expressed as mean ± SD and analyzed. Proportions are expressed in *n* (%) and analyzed by the chi-square test. NA: Not available; IBD: Inflammatory bowel disease..



DOI: 10.5409/wjcp.v11.i4.341

Figure 1 Distribution of inflammatory bowel diseases in the pediatric population regarding gender. UC: Ulcerative colitis; CD: Crohn's disease; IBD: Inflammatory bowel disease.

The frequency of IBD in the pediatric range in our region was 5.34%, below the global values (10% to 25%)[2,6]. Despite different methodologies, this study had a higher frequency than the West-Eastern European study in 2014 of children under 15 years of age, which presented a frequency of 3% (45/1560 patients)[19], and less than a study in Mexico in 2015, which showed that the frequency in pediatric patients under 18 years was 7.1% (32/479)[18].

In the distribution of IBDs, there was a slight predominance of CD (54.5%) compared to UC. Worldwide data are quite variable. A 2014 study by Burisch of West-Eastern Europe[19] found that Western Europe has an equivalent distribution between CD/UC, while Eastern Europe had a predominance of UC[19]. In Argentina[17], equivalence between CD and UC was observed. The study by Van Limbergem in the United Kingdom, 2008[6] observed a predominance of CD (66%) *vs*. UC (23.7%) in 416 pediatric patients < 17 years old. Buderus *et al*[20], 2015, found a predominance of CD (64%) in relation to UC (29%) in Germany, and Chaparro, 2018[24] also found a predominance of CD (61.5%) in Spain (2007-2017). In Mexico, the Yamamoto-Furusho study[18] observed a predominance of UC in 2015 (85%). We still have much diversity in the distribution of the disease.

In the study of the UC phenotype, pancolitis prevailed, similar to other pediatric studies worldwide [16-18,21,24]. In addition, our study showed a significant difference in relation to the adult group, with a higher frequency of extensive disease (pancolitis) in younger people.

Table 2 Phenotype data of pediatric and adult inflammatory bowel disease patients, in the state of Espírito Santo, from August 2012 to July 2014

Characteristics	Total amount		Age at diagnosis ≤ 17 yr old		Age at diagnosis ≥ 18 yr old		*P* value
	n	%	*n*	%	*n*	%	
	1.048	(100)	56	(5.34)	992	(94.66)	
Ulcerative Colitis	669	(63.2)	24	(42.9)	645	(65.0)	
Extension							
E1	198	(30.3)	3	(12.5)	195	(31.0)	**0.037**[1]
E2	247	(37.9)	6	(25.0)	241	(38.4)	0.183
E3	209	(32.0)	15	(62.5)	194	(30.8)	**0.001**
Crohn's disease	352	(34.1)	30	(55.4)	322	(32.9)	
Localization							
L1	11	(31.4)	5	(16.1)	408	(41.1)	0.194
L2	102	(28.9)	10	(32.3)	584	(58.9)	0.861
L3	109	(30.4)	11	(35.5)	92	(28.6)	0.698
L4	11	(30.4)	1	(1.8)	10	(1)	
L1+L4	8	(2.3)	1	(3.2)	7	(2.2)	
L3+L4	12	(3.4)	2	(6.5)	10	(3.1)	
Behavior							
B1	200	(56.5)	18	(60.0)	182	(56.3)	0.686
B2	76	(21.5)	1	(3.3)	75	(23.3)	**0.005**[1]
B3	75	(21.2)	11	(36.7)	64	(19.5)	**0.030**
Perianal disease	92	(25.9)	14	(46.6)	78	(24.1)	**0.007**

[1]Proportions are expressed in *n* (%) and analyzed using the Chi-square test and Fisher's exact test. L1: Ileal; L2: Colonic; L3: Ileocolonic; L4: Upper gastrointestinal; B1: Inflammatory; B2: Stricturing; B3: Fistulizing; NA: Not available.

Table 3 Data on the use of biological therapy in patients with inflammatory bowel disease pediatric and adults, in the state of Espírito Santo, August 2012 to July 2014

Biological	Total amount		Age at diagnosis ≤ 17 yr old		Age at diagnosis > 18 yr old		*P* value
	n	%	*n*	%	*n*	%	
	1.048	(100)	55	(5.24)	993	(94.76)	
IBD	187	(17.8)	19	(34.5)	168	(16.9)	***P* = 0.001**
CD	155	(43.5)	17	(56.7)	138	(42.2)	*P* = 0.126
UC	30	(4.5)	2	(8.3)	28	(4.3)	*P* = 0.353

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease.

In pediatric DC, the ileocolonic form predominated, as in other studies from Germany[20], Italy[25], Spain[24], Argentina[18] and Mexico[18]. Four patients had involvement of the upper intestinal tract (16%), similar to a study in Spain (15.4%)[24] but different from the results in Germany (53.6%)[20]. These differences may have occurred due to the limitations of the current study, as they were based on secondary data, and possibly, a smaller study of the upper gastrointestinal tract using imaging methods was performed.

Our study showed no significant difference in the location of CD in relation to adult patients.

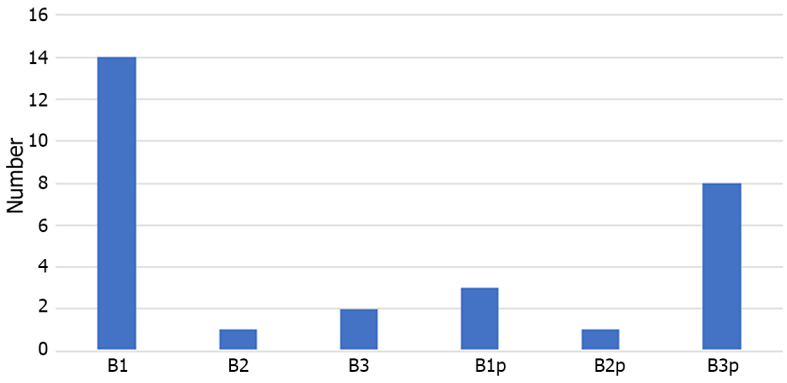


Figure 2 Distribution of the phenotype regarding the behavior of pediatric Crohn's disease patients in the state of Espírito Santo, from August 2012 to July 2014. B1: Inflammatory; B2: Stricturing; B3: Fistulizing; p: Perianal disease.

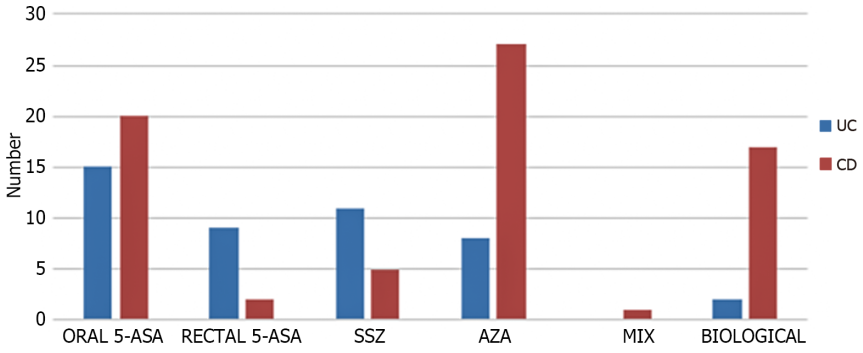


Figure 3 Distribution of medicines for pediatric age inflammatory bowel disease patients in the state of Espírito Santo, from August 2012 to July 2014. SSZ: Sulfasalazine; ASA: Mesalazine; AZA: Azathioprine; MTX: Methotrexate; BIOLOGICAL: Infliximab or adalimumab; UC: Ulcerative colitis; CD: Crohn's disease.

We observed a high frequency of perianal disease ("p") with 46.6% of pediatric/adolescent CD, which demonstrates the most serious behavior in this age group. Our data were higher than those of a Germany study[20] with 11.5% perianal disease, of a Canadian study[26] with 16% perianal disease in 2019, and of a Spanish study[24] with 16.4% perianal disease in 2018. When compared to the adult group, we observed the highest frequency of fistulizing behavior (B3) and perianal disease (p) in the pediatric age group, that is, more severe behavior in the youngest.

In the treatment of UC, oral aminosalicylates (mesalazine/sulfasalazine) were the most commonly used drugs, compatible with current therapeutic recommendations[27]. The use of corticoids was not evaluated in this study, as they are not dispensed by this state health care sector, and at the time of this study, biologics were not approved in our country for pediatric patients[11].

On the other hand, in CD, we observed a greater use of the immunomodulators when compared to aminosalicylates, according to guidelines[28]. Biological therapy was used in 56.7% (17/30) of pediatric patients with CD, compared with 42.2% of adult patients, but no significant difference was found (P = 0.126). We observed a higher use of biologic therapy in pediatric patients with Crohn's disease when compared to the 15% of the Hungarian study (2011-2013)[29] and 7.7% in the study from Poland (2012-2014)[30] We were able to observe that the use of medication in our region is consistent with the data from the literature recommendations[27,28], but we can see that pediatric patients with Crohn's disease used more frequent biologic therapy than those in another study.

CONCLUSION

In Brazil, where the incidence and prevalence of IBD are increasing in adults, it was observed that the prevalence and incidence in pediatric age are higher than those in other regions in Latin America, lower than those in Europe and North America, and in relation to the data worldwide, our pediatric IBD prevalence and incidence are still low. Children and adolescents with UC had a more extensive form (pancolitis) than adults, as in CD, and fistulizing forms (B3) and perianal diseases ("p") were more prevalent, which led to the high frequency of biological therapy in these patients with IBD before the age ≤ 17 years. These data, added to other epidemiological studies, demonstrate the severity of IBD in

the pediatric age group, with the need for early diagnosis and early intervention and correct use of specific therapy, avoiding serious secondary damage during the disease´s evolution.

Although we recognize the limitations of this study, as not all patients included had a complete imaging study (magnetic resonance imaging, an upper gastrointestinal endoscopy/biopsy) and secondary data based on documentation of the Public Health System was used, it is the first epidemiological pediatric IBD data published in the country. Although more studies are needed, this reports includes real-world data that can contribute to the planning of public health actions.

ARTICLE HIGHLIGHTS

Research background

Pediatric inflammatory bowel disease in a region of Brazil.

Research motivation

The pediatric inflammatory bowel disease data are practically unknown in Brazil and South America.

Research objectives

To determine the epidemiology of pediatric inflammatory bowel disease and its characteristics in Brazil and South America.

Research methods

The data were retrieved from the Public Medication-Dispensing System of the Department of Health in Espírito Santo state of Brazil.

Research results

The prevalence and incidence in pediatric ages are higher than those in other regions in Latin America. More severe disease was observed in the youngest patients. Pancolitis is more frequent in ulcerative colitis, and fistulizing and perianal disease are more frequent in Crohn's disease. Use of biological therapy was compared in the pediatric and adult groups.

Research conclusions

We have little data on inflammatory bowel disease in Latin America. We need to better understand the epidemiology, phenotype and medication used for the treatment of inflammatory bowel disease in each region.

Research perspectives

Obtain better therapeutic approaches and contribute to the planning of public health actions.

FOOTNOTES

Author contributions: Martins AL contributed to concept, design of the research, collection of the data, analysis, interpretation, and writing; Fróes RSB contributed to interpretation, writing and review; Zago-Gomes MP contributed to analyses study, statistical analysis, interpretation, and writing.

Institutional review board statement: This study was approved by the Ethics and Research Committee of the Nossa Senhora da Gloria Children's Hospital (CAAE 19602813.8.0000.5069) after obtaining authorization from the State Office for Pharmaceutical Assistance. The term of clarification and consent was waived because the data used is secondary data.

Informed consent statement: The terms of clarification and responsibility were not necessary because the information used were secondary data from Espírito Santo's State Health Department documents.

Conflict-of-interest statement: All the authors have no conflicts of interest to disclose related to the manuscript.

Data sharing statement: No additional data are available.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 July 9; 11(4): 351-359

DOI: 10.5409/wjcp.v11.i4.351

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Retrospective Study

Frequency of celiac disease and distribution of HLA-DQ2/DQ8 haplotypes among siblings of children with celiac disease

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D, D
Grade E (Poor): E

P-Reviewer: Alkhayyat M, United States; JAIN S, India
A-Editor: Nardi PD, Italy

Received: January 10, 2022
Peer-review started: January 10, 2022
First decision: March 8, 2022
Revised: March 18, 2022
Accepted: June 3, 2022
Article in press: June 3, 2022
Published online: July 9, 2022

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Abstract

BACKGROUND

Celiac disease (CD) is a multifactorial disease, but genetic factors play a major role in its etiology. It has been known that human leucocyte antigen (HLA)-DQ2/DQ8 haplotypes are one of the most important predisposing genetic factors. The risk of developing CD in first-degree relatives and especially siblings of celiac patients is quite high because of having the same HLA haplotypes.

AIM

To evaluate the frequency of CD and the distribution of the HLA-DQ2/DQ8 haplotypes in siblings of celiac patients.

METHODS

Patients with biopsy-proven CD and their siblings were included in the study; those who did not have HLA genotyping were excluded from the study. All siblings were on a gluten-containing diet. The HLA genotyping, tissue transglutaminase antibody IgA antibody test, and total IgA test were performed in all participants.

RESULTS

A total of 57 celiac patients and their 112 siblings were included in the study. The mean age of celiac patients and siblings were 10.30 ± 3.87 years and 9.90 ± 6.11 years, respectively. HLA-DQ2/DQ8 alleles were detected in 98.2% of patients with CD and 90.2% of siblings of celiac patients. HLA-DQ genotypes were present in all siblings diagnosed with CD. Tissue transglutaminase antibody IgA test was found to be positive in 16 siblings. CD was diagnosed in 12 siblings (10.7%) by intestinal biopsy.

CONCLUSION

The prevalence of CD was found to be 10.7% in siblings of celiac patients in our study. One-third of the siblings diagnosed with CD were asymptomatic. We detected HLA-DQ alleles in 98.2% of celiac patients and 100% in siblings diagnosed with CD. In addition, 1 of the 2 siblings was diagnosed with CD 1 year later and the other 4 years later. Therefore, we suggest that siblings of celiac patients should be followed up with clinical findings as well as HLA analysis and serological examination. Since the risk of developing CD is much higher in asymptomatic siblings, we recommend that siblings should be screened for CD even if they are asymptomatic.

Key Words: Celiac disease; Frequency; Genetic; HLA haplotypes; Intestinal biopsy; Siblings

Core Tip: Celiac disease (CD) is a multifactorial disease, but genetic factors play a major role in its etiology. Human leucocyte antigen-DQ2/DQ8 haplotypes are one of the most important predisposing genetic factors. We detected human leucocyte antigen-DQ alleles in 98.2% of celiac patients and 100% in siblings diagnosed with CD. Also, 1 of the 2 siblings was diagnosed with CD 1 year later and the other 4 years later. Siblings of celiac patients should be followed up with clinical findings and human leucocyte antigen analysis and serological examination. We recommend that siblings should be screened for CD even if they are asymptomatic.

Citation: Sahin Y, Mermer S. Frequency of celiac disease and distribution of HLA-DQ2/DQ8 haplotypes among siblings of children with celiac disease. *World J Clin Pediatr* 2022; 11(4): 351-359
URL: https://www.wjgnet.com/2219-2808/full/v11/i4/351.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i4.351

INTRODUCTION

Celiac disease (CD) is a systemic autoimmune disease triggered by gluten intake in genetically susceptible individuals characterized by various degrees of small intestinal damage[1]. It is a multifactorial disease, but genetic factors play a major role in its etiology. It has been known that human leucocyte antigen (HLA)-DQ2/DQ8 genotypes are one of the most important predisposing genetic factors[2-4].

The risk of developing CD in first-degree relatives and especially siblings of celiac patients is quite high due to having the same HLA genotypes and environmental triggers such as gut microbiome[5-8]. It has been reported that the risk of developing CD is higher in siblings of celiac patients compared to other first-degree relatives[9-11]. CD may be asymptomatic for years or even be diagnosed 10 years after the first symptom appears[12]. It has been reported that approximately half of the first-degree relatives of celiac patients newly diagnosed with CD are completely asymptomatic[2,8,10]. Early diagnosis of CD is very important for the prevention of long-term complications of CD such as osteoporosis, growth retardation, infertility, and malignancy.

Although there are many studies on the frequency of CD in first-degree relatives of celiac patients, the number of studies investigating the frequency of CD and the distribution of HLA-DQ2/DQ8 in siblings of celiac patients is rare[8,10,13,14]. The aim of our study was to evaluate the frequency of CD and the distribution of HLA-DQ2/DQ8 haplotypes in siblings of celiac patients.

MATERIALS AND METHODS

This study was carried out between February 2017 and June 2020. Patients with biopsy-proven CD and their siblings were included in the study; those who did not have HLA genotyping were excluded from the study. All siblings were on a gluten-containing diet. The current study was approved by the Local Ethics Committee (Toros University, Mersin, Turkey, 17.06.2020/41). The patient who was first diagnosed with CD was defined as an index case.

CD was diagnosed according to the European Society for Paediatric Gastroenterology, Hepatology and Nutrition 2012 guidelines[2]. In total, 57 celiac patients and their 112 siblings were included in the study. Three patients who did not have any siblings were not included in the study. The HLA genotyping, tissue transglutaminase antibody (tTG) IgA antibody test, and total IgA test were performed in all participants. tTG IgA antibody levels were measured by enzyme-linked immuno-

sorbent assay method (Diametra, Spello PG, Italy). The cutoff value for tTG IgA was 20 U/mL. Total IgA levels were measured by nephelometric method (Siemens Diagnostics, Marburg, Germany).

Gastroduodenoscopy and small intestinal biopsy were performed in all patients with tTG positivity. Four biopsies from the duodenum and at least one biopsy from the bulb were obtained. All intestinal biopsy specimens were evaluated according to the modified Marsh-Oberhuber classification[15] as follows: Marsh stage 0: normal mucosa; Marsh stage 1: increased intraepithelial lymphocytosis (> 40 lymphocytes per 100 epithelial cells); Marsh stage 2: increased intraepithelial lymphocytosis with crypt hyperplasia; Marsh stage 3a: increased intraepithelial lymphocytosis with crypt hyperplasia and partial villous atrophy; Marsh stage 3b: increased intraepithelial lymphocytosis with crypt hyperplasia and subtotal villous atrophy; and Marsh stage 3c: increased intraepithelial lymphocytosis with crypt hyperplasia and total villous atrophy. If the pathology result was compatible with Marsh stage 2 or stage 3, the patient was diagnosed with CD.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences software version 22.0 (SPSS Inc; Chicago, IL, United States). Frequency, percentage, and mean ± standard deviation were used as descriptive statistics. Independent sample *t*-test was used for nominal data. The Mann-Whitney *U* test was used to compare groups of numerical variables. χ^2 test was used for comparison of categorical variables.

RESULTS

A total of 57 celiac patients and their 112 siblings were included in the study. Of 112 siblings, 54 (48.20%) were female; 33 (57.89%) of the 57 celiac patients were female. The mean age of celiac patients and siblings were 10.30 ± 3.87 years and 9.90 ± 6.11 years, respectively (Table 1).

HLA-DQ2/DQ8 alleles were detected in 98.2% of patients with CD and 90.2% of siblings of celiac patients (Table 2). A total of 57 celiac patients (57.9%) had HLA-DQ2, 29.8% had HLA-DQ2/DQ8, and 10.5% had HLA-DQ8. Both alleles were found to be negative in 1.8% of them. HLA-DQ genotypes were present in all siblings diagnosed with CD (Table 3). tTG IgA test was found to be positive in 16 siblings. CD was diagnosed in 12 siblings by intestinal biopsy (Table 3). The pathology result of 10 siblings was compatible with Marsh stage 3. The prevalence of CD was found to be 10.7% in siblings of celiac patients in our study, and this rate was 22.7 times higher than the general population. Gastroduodenoscopy could not be performed in 4 of 16 siblings because of parental refusal. Out of 100 cases not diagnosed with CD, 59 had HLA-DQ2 positivity, 16 had HLA-DQ2/DQ8 positivity, 14 had HLA-DQ8 positivity, and 11 were negative for HLA-DQ2 and HLA-DQ8.

Seven of those twelve celiac patients had anemia, six of them had growth retardation, and four of them had no symptoms. HLA-DQ alleles were also positive in all 4 patients who refused to undergo gastroduodenoscopy. No IgA deficiency was detected in either group. Two siblings of three index cases were diagnosed with CD. The first sibling of the first index case was diagnosed 2 mo later, and the second sibling 1 year later (when looking at the second serology). The first sibling of the second index case was diagnosed with CD 4 years later (in the second serology examined with an interval of 2 years), and the second sibling was diagnosed with CD 4 mo after the first. The two siblings of the other index case were also diagnosed with CD within 3 mo.

DISCUSSION

The estimated prevalence of CD is 1% in the world, and this rate varies in different geographical regions [2,16]. The reason of that may be due to differences in genetic susceptibility and changes in dietary gluten intake.

With the identification of the major role of HLA-DQ2/DQ8 in genetically susceptible individuals, it has been reported that the negative detection of both HLA-DQ2 and HLA-DQ8 in first-degree relatives of celiac patients does not require further investigation for CD[17,18]. On the contrary, it has been reported that the risk of CD is higher in individuals with homozygous HLA-DQ2[19].

In the European Society for Paediatric Gastroenterology, Hepatology and Nutrition 2012 guidelines, HLA genotyping is recommended as the initial screening test for CD especially in risk groups such as first-degree relatives of celiac patients[2]. It has been shown that HLA-DQ analysis is helpful in predicting CD especially in first-degree relatives of celiac patients[20-22]. The absence of HLA-DQ2 and HLA-DQ8 most likely excludes CD, but celiac specific antibody tests are required to diagnose CD in the presence of those alleles[20]. While some authors have suggested that HLA analysis can be used in the diagnosis of CD, others have suggested that it is a good alternative for determining genetic predisposition[23,24].

Table 1 The demographic and laboratory characteristics of celiac patients and their siblings

	Celiac patients, *n* = 57	Siblings, *n* = 112	*P* value
Age (yr)	10.30 ± 3.87	9.90 ± 6.11	0.648
Sex (female/male)	33/24	54/58	0.234
Height (cm)	132.71 ± 20.29	130.27 ± 31.37	0.594
Weight (kg)	30.44 ± 12.82	33.22 ± 19.18	0.325
Hb (g/dL)	11.65 ± 3.87	12.71 ± 1.56	< 0.001
tTG IgA (U/mL)	108.65 ± 60.61	17.24 ± 41.14	< 0.001
Total IgA (mg/dL)	155.43 ± 78.44	124.33 ± 71.47	0.014

Hb: Hemoglobin; tTG: Tissue transglutaminase antibody.

Table 2 The distribution of human leucocyte antigen genotypes of celiac patients and their siblings

HLA genotypes	Celiac patients, *n* = 57 (100%)	Siblings, *n* = 112 (100%)
HLA-DQ2	33 (57.9)	68 (60.7)
HLA-DQ2/DQ8	17 (29.8)	18 (16.1)
HLA-DQ8	6 (10.5)	15 (13.4)
Both negative	1 (1.8)	11 (9.8)

HLA: Human leucocyte antigen.

Table 3 The laboratory and clinical data of siblings of celiac patients diagnosed with celiac disease

	Patient age at diagnosis (yr)	Symptoms	Hb (g/dL)	tTG (U/mL)	IgA (mg/dL)	HLA	Pathology
1	6	Failure to thrive, anemia	10.9	140	206	DQ2	Marsh 3a
2	8.5	-	13.4	94	87	DQ8	Marsh 3a
3	18	-	13.5	105	99	DQ2	Marsh 3a
4	4.3	Failure to thrive, anemia	10.4	46	33	DQ2	Marsh 3b
5	13.5	Failure to thrive, anemia	7.7	135	254	DQ2	Marsh 3b
6	5.5	Failure to thrive, anemia	11.7	35	66	DQ2	Marsh 3b
7	16.5	Anemia	11.7	41	86	DQ2	Marsh 3b
8	16	-	13.3	187	190	DQ2	Marsh 3b
9	14.5	-	14.3	37	179	DQ2/DQ8	Marsh 2
10	12	Anemia	11.9	46	122	DQ2/DQ8	Marsh 2
11	11.5	Failure to thrive	13.1	127	148	DQ2	Marsh 3a
12	10.5	Failure to thrive, anemia	10.9	34	70	DQ2	Marsh 3b

HLA: Human leucocyte antigen; Hb: Hemoglobin; tTG: Tissue transglutaminase antibody.

The prevalence of CD in siblings of celiac patients is 5.9%-18.3%[8,10,13,14,25]. As consistent with the literature, the prevalence of CD was found to be 10.7% in siblings of celiac patients in our study. Twelve siblings were diagnosed with CD by intestinal biopsy. Four siblings (25%) with positive tTG refused gastroduodenoscopy. In another study, the rate of those who did not accept biopsy (22.2%) was similar to our study[10]. The real prevalence of CD could not be estimated, as there were cases who refused the biopsy.

In a systematic review, it has been reported that the prevalence of CD in sisters of celiac patients is approximately two times higher than in brothers[25]. Contrary to this, the prevalence of CD was equal

in males and females in our study. The reason of that may be the study was cross-sectional, and 4 cases with positive serology did not accept endoscopy. For this reason, we may not have been able to fully determine the risk of CD. The other reason is that our study had a short follow-up period. Some seronegative individuals may be seropositive in the future and be diagnosed with CD.

In a multicenter study conducted in Europe, it was reported that 90% of celiac patients had the HLA-DQ2 genotype, and 5% to 10% of them had HLA-DQ8[26]. Those genotypes were found in 40%-65% of first-degree relatives of celiac patients and 18%-30% of the general population[10,11,27]. HLA-DQ8 positivity is higher in America, Asia, Chile, and Cuba compared to Europe[28-31]. In our study, 57.9% of celiac patients had HLA-DQ2, 29.8% had HLA-DQ2/DQ8, and 10.5% had HLA-DQ8. Both alleles were found to be negative in 1.8% of patients. HLA-DQ2/DQ8 ratios vary from region to region[26,28-31].

HLA analysis was performed on all siblings of celiac patients in the current study. HLA antigens were positive in 90.2% of siblings of celiac patients. As consistent with our study, HLA antigens were found to be positive in all siblings of celiac patients (100%) in another study conducted in our country [14].

In our study, out of 100 cases not diagnosed with CD, 59 had HLA-DQ2 positivity, 16 had HLA-DQ2/DQ8 positivity, 14 had HLA-DQ8 positivity, and 11 were negative for both HLA-DQ2 and HLA-Dq8. In a study with the same number of cases, 49 of 100 cases whose siblings of celiac patients were not diagnosed with CD had HLA-DQ2 positivity, 6 had HLA-DQ8 positivity, 2 had HLA-DQ2/DQ8 positivity, and 43 were negative for both HLA-DQ2 and HLA-DQ8[10]. The reason may be due to the HLA-DQ2/DQ8 ratios varying from region to region[26,28-31].

In the study by Bonamico *et al*[10], it was shown that the use of HLA genotyping as a first step can be used to exclude one-third of first-degree relatives, but it has been reported that patients negative for HLA-DQ2 and HLA-DQ8 can be overlooked. Also, it has been suggested that it may be more useful to evaluate the first-degree relatives of celiac patients together with tTG antibody test and HLA typing.

HLA antigens were detected in 94.7%-100% of siblings of celiac patients diagnosed with CD[10,14]. In parallel with the literature, HLA antigens were detected in all 12 siblings of celiac patients diagnosed with CD in our study.

It has been known that HLA-DQ alleles have a high prevalence among celiac patients[2,14,20,32,33]. Those alleles may determine susceptibility to CD in risk groups such as first-degree relatives of celiac patients[19]. It has been reported that the frequency of HLA-DQ2/DQ8 is high in risk groups such as first-degree relatives of celiac patients[2,34]. We found a high rate of positive HLA-DQ alleles in celiac patients and their siblings as compatible with the literature.

It has been reported that 30.0%-78.9% of siblings of celiac patients diagnosed with CD are asymptomatic[8,13,14,34]. As consistent with the literature, one-third of our patients were found to be asymptomatic. Since patients diagnosed with silent CD have a high prevalence, asymptomatic siblings of celiac patients should be screened for CD.

It has been suggested that HLA genotyping can be used to exclude 25%-33% of first-degree relatives from serological follow-up[10,23,35-37]. The absence of HLA-DQ alleles has a high negative predictive value for CD; positive results indicate only a genetic predisposition[38].

CD can occur at any age. A negative serological test once does not mean that there will be no CD in the future. Many studies have been conducted on serologically negative celiac patients[39-42]. In the study by Pittschieler *et al*[39], serological positivity was detected in 3 cases with HLA-DQ2 positivity after more than 10 years of follow-up, and then CD was diagnosed. In parallel with that study, CD was diagnosed in 1 of 2 cases with HLA-DQ2 positive 1 year later and the other 4 years later in our study. CD may be seen in any period of life. Since the follow-up period was short in our study, we think that other cases with positive HLA antigens may be diagnosed with CD in the future. Therefore, we recommend that cases in a high-risk group should be followed clinically and serologically.

In a Western cohort, only 0.5% of celiac patients were found to have HLA-DQ negativity[18]. In a recent study, it has been reported that HLA-DQ typing is insufficient to identify individuals susceptible to CD and could not be used to diagnose CD[43]. In another study conducted in Iran, HLA-DQ negativity was found to be 3.9%[44]. HLA-DQ2 and HLA-DQ8 were found to be negative in 5% of cases in another study[10]. In parallel with those studies, HLA-DQ antigens were found to be negative in 1.8% of celiac patients in our study. In those studies, it has been reported that the risk of developing CD is very low in cases with negative HLA-DQ. It has been suggested that cases negative for HLA-DQ2/DQ8 negative should be followed clinically and serologically every 2 years or 3 years[10]. For this reason, it has been suggested that HLA analysis would be more appropriate in cases where it is difficult to diagnose.

In a study conducted in healthy school children in our country, the prevalence of CD was found to be 0.47%[45]. In the current study, the prevalence of CD in siblings of celiac patients was found to be 10.7%. That is, we found that the prevalence was 22.7 times higher than in the general population.

One of the limitations of the study was that 15 celiac patients and their 28 siblings refused to participate in the study. If they did, the results would have been different, and the power of study would have been better. Another limitation was the short follow-up period. CD may develop over time in our serologically negative cases. For these reasons, we think that we were unable to estimate the real prevalence of CD.

CONCLUSION

In conclusion, the prevalence of CD was found to be 10.7% in siblings of celiac patients in our study, and this rate was 22.7 times higher than the general population. One-third of the siblings diagnosed with CD were asymptomatic. We detected HLA-DQ alleles in 98.2% of celiac patients and 100% in siblings diagnosed with CD. Thus, CD has been shown to be associated with HLA-DQ2 and HLA-DQ8 genotypes. In addition, 1 of the 2 siblings was diagnosed with CD 1 year later and the other 4 years later. Therefore, we suggest that siblings of celiac patients should be followed up with clinical findings as well as HLA analysis and serological examination. Since the risk of developing CD is much higher in asymptomatic siblings, we recommend that siblings should be screened for CD even if they are asymptomatic.

ARTICLE HIGHLIGHTS

Research background

Celiac disease (CD) is a systemic autoimmune disease triggered by gluten intake in genetically susceptible individuals. It is a multifactorial disease, but genetic factors play a major role in its etiology. It has been known that human leucocyte antigen (HLA)-DQ2/DQ8 genotypes are one of the most important predisposing genetic factors. The risk of developing CD in siblings of celiac patients is quite high because of having the same HLA genotypes and environmental triggers such as gut microbiome.

Research motivation

Although there are many studies on the frequency of CD in first-degree relatives of celiac patients, the number of studies investigating the frequency of CD and the distribution of HLA-DQ2/DQ8 in siblings of celiac patients is rare. Because of that, we aimed to evaluate the frequency of CD and the distribution of HLA-DQ2/DQ8 haplotypes in siblings of celiac patients.

Research objectives

To investigate the frequency of CD and the distribution of HLA-DQ2/DQ8 haplotypes in siblings of celiac patients.

Research methods

The current study was carried out between February 2017 and June 2020. Biopsy-proven celiac patients and their siblings were included in the study. CD was diagnosed according to the European Society for Paediatric Gastroenterology, Hepatology and Nutrition 2012 guidelines. In total, 57 celiac patients and their 112 siblings were included in the study. All siblings were on a gluten-containing diet. The HLA genotyping, tissue transglutaminase antibody IgA antibody test, and total IgA test were performed in all participants. Gastroduodenoscopy was performed in all patients with tissue transglutaminase antibody positivity. Four biopsies from the duodenum and at least one biopsy from the bulb were obtained. All intestinal biopsy specimens were evaluated according to the modified Marsh-Oberhuber classification.

Research results

HLA-DQ2/DQ8 alleles were detected in 98.2% of patients with CD and 90.2% of siblings of celiac patients. Tissue transglutaminase antibody IgA test was found to be positive in 16 siblings. CD was diagnosed in 12 siblings by intestinal biopsy. Seven of those twelve celiac patients had anemia, six of them had growth retardation, and four of them had no symptoms.

Research conclusions

The prevalence of CD was found to be 10.7% in siblings of celiac patients in our study, and this rate was 22.7 times higher than the general population. One-third of the siblings diagnosed with CD was asymptomatic. We detected HLA-DQ alleles in 98.2% of celiac patients and 100% in siblings diagnosed with CD. Thus, CD has been shown to be associated with HLA-DQ2 and HLA-DQ8 genotypes. In addition, 1 of the 2 siblings was diagnosed with CD 1 year later and the other 4 years later.

Research perspectives

According to the current study, we suggest that the siblings of celiac patients should be followed up with clinical findings as well as HLA analysis and serological examination. Since the risk of developing CD is much higher in asymptomatic siblings, we recommend that siblings should be screened for CD even if they are asymptomatic.

ACKNOWLEDGEMENTS

We would like to thank the pathologists, pediatricians and Derya Aydin Sahin for their help in the study.

FOOTNOTES

Author contributions: Sahin Y designed the study, analyzed the data, interpreted the data and wrote the manuscript; Mermer S designed the study and collected and analyzed the data; All authors had read and approved the final manuscript.

Institutional review board statement: The current study was approved by the Local Ethics Committee (Toros University, Mersin, Turkey, 17.06.2020/41).

Informed consent statement: Written informed consent was not obtained as the study is retrospective. However, the Local Ethics Committee approved the current study.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Data sharing statement: No additional data are available.

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S-Editor: Liu JH
L-Editor: Filipodia
P-Editor: Liu JH

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World Journal of Clinical Pediatrics

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World J Clin Pediatr 2022 July 9; 11(4): 360-368

DOI: 10.5409/wjcp.v11.i4.360

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Observational Study

Adipocytokine profile in children with Kawasaki disease at a mean follow-up period of 5.5 years: A study from North India

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Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Corso G, Italy; Maglio C, Sweden

Received: March 31, 2021
Peer-review started: March 31, 2021
First decision: July 30, 2021
Revised: August 21, 2021
Accepted: May 12, 2022
Article in press: May 12, 2022
Published online: July 9, 2022

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Abstract

BACKGROUND

Kawasaki disease (KD) is an acute self-limited vasculitis with a predilection for coronary arteries. Children with KD may have altered lipid metabolism and abnormal lipid profiles that may last for prolonged periods. However, there is a paucity of literature on the role of adipocytokines in KD.

AIM

To estimate the levels of adipocytokines (adiponectin, leptin and resistin) during the convalescent phase of KD.

METHODS

Twenty children, who had KD at least three years earlier, were enrolled in this study. In addition, 20 healthy controls were also enrolled. Clinical and laboratory profiles of patients were obtained from hospital records. Serum adiponectin, leptin and resistin levels were estimated by enzyme-linked immunosorbent assay.

RESULTS

Mean age of the patients in the study group was 10.15 ± 3 years and the male: female ratio was 1.5:1. Median serum resistin levels in patients with KD (27.77 ng/mL; [IQR: 18.66, 48.90]) were decreased compared to controls (21.20 ng/mL; [IQR: 14.80, 27.00]) (P = 0.04). Median serum leptin levels in cases and controls were 1.83 ng/mL; (IQR: 1.13, 3.80), and 1.10 ng/mL; (IQR: 0.41, 2.88), respectively (P = 0.09). Median serum adiponectin levels were similar in both cases (12.20 µg/mL; [IQR: 9.76, 17.97]) and controls (13.95 µg/mL; [IQR: 11.17, 22.58]); (P = 0.18). There was no significant difference in all 3 adipocytokines between children with (4/20) and without coronary artery abnormalities (16/20).

CONCLUSION

Serum resistin levels were significantly elevated in patients with KD during the convalescent phase compared to controls. Serum leptin levels appeared to be higher in patients with KD, although the difference was not statistically significant. Adiponectin levels were similar in both cases and controls. Raised resistin and leptin levels may partially explain lipid perturbations observed during the convalescent phase of KD.

Key Words: Adipocytokines; Adiponectin; Resistin; Leptin; Lipid metabolism; Kawasaki disease; Convalescent phase

Core Tip: The present study suggests that serum adipocytokine levels may impact lipid abnormalities observed during the convalescent phase of Kawasaki disease (KD). Serum resistin levels were significantly elevated in patients with KD during the convalescent phase compared to controls. Serum leptin levels appeared to be higher in patients with KD, although the difference was not statistically significant. Adiponectin levels were similar in both cases and controls.

Citation: Praharaj DL, Rawat A, Gupta A, Arora K, Pilania RK, Bhattad S, Singh S. Adipocytokine profile in children with Kawasaki disease at a mean follow-up period of 5.5 years: A study from North India. *World J Clin Pediatr* 2022; 11(4): 360-368
URL: https://www.wjgnet.com/2219-2808/full/v11/i4/360.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i4.360

INTRODUCTION

Kawasaki disease (KD) is a medium vessel vasculitis and the most common cause of acquired heart disease in children in most developed countries[1]. There are data to support that the incidence of KD is also rising in the developing world, including India[1]. Coronary artery abnormalities (CAAs) have been noted in 15%-25% of untreated children and treatment with intravenous immunoglobulin (IVIg) reduces this risk to 3%-5%[2]. Children with KD are known to have lipid abnormalities in the acute phase that may persist long after the initial episode of the disease[3-8]. It is known that serum lipid profiles may remain deranged for prolonged periods after the acute stage of the illness and this may contribute to the premature and accelerated atherosclerosis seen in patients with KD[9,10].

Adipocytokines play a significant role in lipid metabolism, inflammation and diseases associated with accelerated atherosclerosis[11-13]. Moreover, their levels may impact lipid abnormalities[11-14]. As some of the lipid abnormalities associated with KD persist during the convalescent phase, we hypothesized that the adipocytokine perturbations seen during the acute phase of KD, may also persist during follow-up. There is a paucity of literature on this subject[15-19], and the results are difficult to interpret. We, and others, have previously shown that children with KD in India have a different clinical phenotype compared to those reported in the developed world[20]. We have also shown that lipid abnormalities are seen in up to 25.9% of children with KD at a mean follow-up of 5 years[6,7]. We, therefore, conducted this study to determine whether adipocytokines are responsible for some of these lipid abnormalities.

MATERIALS AND METHODS

Patients and methods

The present study was a cross-sectional descriptive study conducted in the Paediatric Rheumatology Clinic, Advanced Paediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh. Our institute is a federally funded not-for-profit tertiary care centre catering to the population of North-West India. We follow the largest cohort of KD in India. Twenty consecutive cases of KD with at least 3 years of follow-up, and 20 healthy controls were enrolled in the present study. Children with acute KD and convalescent cases with less than 3 years of follow-up were excluded. The diagnosis of KD was based on the American Heart Association guidelines[21]. During the acute phase, children had received standard treatment *i.e.* IVIg 2 g/kg along with aspirin (initially in higher doses [30-50 mg/kg/d], followed by antiplatelet doses [3-5 mg/kg/d]). Written informed consent was obtained from the parents/guardians at study enrolment. Clinical records were reviewed. The study protocol was approved by the Institute Thesis Committee and Institute Ethics Committee. This

manuscript has been approved by the Departmental Review Board.

Evaluation of different adipocytokines

Collection of blood sample: Two milliliters of peripheral venous blood was collected from cases and controls in plain vials under aseptic conditions. Serum was extracted and collected in cryovials and immediately stored at-80°C. Hemolyzed and turbid samples were discarded.

Estimation of serum resistin: Serum resistin level was estimated using the AssayMax Human Resistin enzyme-linked immunosorbent assay (ELISA) kit designed for determining human resistin in plasma, serum, urine, saliva and cell culture samples as per the manufacturer's recommendations. Sensitivity of the assay was 0.2 ng/mL; intra-assay coefficient of variability (CV) was 4.5% and inter-assay CV was 7.0%. Absorbance was measured at 450 nm on a microplate ELISA reader (Infinite PRO 2000 TECAN Austria).

Estimation of serum adiponectin: Serum adiponectin level was estimated using the AssayMax Human Adiponectin ELISA kit designed for measuring human adiponectin in plasma, serum, urine, saliva and cell culture samples. Sensitivity of the assay was 0.7 ng/mL, intra-assay CV was 4.3% and inter-assay CV was 7.2%.

Estimation of serum leptin: Serum leptin level was similarly estimated using the DRG Human Leptin ELISA kit designed for determining human leptin in plasma and serum samples. Sensitivity of the assay was 1.0 ng/mL, intra-assay CV was 6%-7% and inter-assay CV was 8.5%-11.5%.

All 3 adipocytokines were measured in convalescent cases of KD and in healthy controls. Serum lipids were also estimated in 18 children in the study group during follow-up. Reference values for lipids in healthy Indian children were obtained from the study by Marwaha *et al*[22].

Statistical analysis

Data were collected on a pre-designed proforma and transferred to a Microsoft Office Excel sheet. Preliminary analysis was conducted by descriptive statistics, expressed as means (SD), medians (range) and proportions (centiles). A comparison of the study and control group with regard to levels of individual adipocytokines (*i.e.* leptin, resistin, and adiponectin) was performed using the Mann-Whitney test wherever data had skewed distribution and the Student's t test was used for normal distribution. Analysis was carried out using the Statistical Package for Social Sciences Version 20.0 for Windows.

RESULTS

Observation and results

The mean age of patients with KD and controls was 10.1 and 9.1 years, respectively. The male:female ratio in patients with KD was 1.5:1. Mean duration of follow-up in the cases was 5.5 years. No case of IVIg resistance was documented in this cohort. Four children (20%) had CAAs at first admission that resolved on follow-up of 6-8 wk. Eighteen of 20 cases had lipid estimations during follow-up. Lipid abnormalities noted in these children are shown in Table 1. No association was observed between the occurrence of CAAs and the presence of lipid abnormalities.

Median serum resistin levels in patients with KD (27.77 ng/mL; [IQR: 18.66, 48.90]) were increased compared to controls (21.20 ng/mL; [IQR: 14.80, 27.00]) (P = 0.04). Median serum leptin levels in cases and controls were 1.83 ng/mL; (IQR: 1.13, 3.80), and 1.10 ng/mL; (IQR: 0.41, 2.88), respectively (P = 0.09). Median serum adiponectin levels were similar in both cases (12.20 μg/mL; [IQR: 9.76, 17.97]) and controls (13.95 μg/mL; [IQR: 11.17, 22.58]); (P = 0.18) (Table 2). There was no significant difference in all 3 adipocytokines between children with CAAs (4/20) and without CAAs (16/20). We performed a correlation analysis of different lipid profiles with adipocytokines (Table 3). No significant correlation was observed between adipocytokines and lipid values. Body mass index (BMI) has also been shown to have a significant positive correlation with leptin levels. No significant correlation between BMI and resistin or adiponectin was observed.

DISCUSSION

KD is the most common cause of acquired heart disease in children in the developed world[1]. KD is being increasingly reported in several developing countries, including India[23]. Hospital-based studies at our centre have shown that the incidence of KD has risen significantly over the last 2 decades[23]. Whether, this increase represents a true increase in incidence, or an increased ascertainment of the disease as a result of heightened awareness, remains unknown. We, and others, have previously shown that KD in India has a different phenotype inasmuch as a higher proportion of older children are seen in

Table 1 Clinical and laboratory features of the study population

	Study group (*n* = 20)	Controls (*n* = 20)
Male:female ratio	1.5:1	1.5:1
Age at diagnosis < 5 yr	9	-
Age at diagnosis >5 yr	11	-
Mean age at enrolment (yr)	10.1	9.1
Mean duration of follow-up (yr)	5.5	-
Treatment received during the acute phase		-
IVIg (mg/dL)	20	
Aspirin (mg/dL)	20	
CAAs (mg/dL)	4/20	-
Lipid profile	mean ± SD	-
LDL (mg/dL)	74.73 ± 27.82	
TG (mg/dL)	118.72 ± 104.32	
VLDL (mg/dL)	16.96 ± 6.72	
HDL (mg/dL)	44.93 ± 11.40	
TC (mg/dL)	139.76 ± 27.16	
Body mass index (kg/m^2)	16.68 ± 3.25	-
Lipid profile (18/20)		-
High TC (mg/dL)	2	
High LDL (mg/dL)	2	
Low HDL (mg/dL)	6	
Borderline HDL (mg/dL)	11	
High TG (mg/dL)	4	
High VLDL (mg/dL)	0	

IVIg: Intravenous immunoglobulin; KD: Kawasaki disease; TC: Total cholesterol; LDL: Low density lipoprotein; HDL: High density lipoprotein; VLDL: Very low density lipoprotein; TG: Triglycerides, CAAs: Coronary artery abnormalities; SD: Standard deviation.

Table 2 Adipocytokine profile in patients with Kawasaki disease and healthy controls

	Study group (*n* = 20), Median (IQR)	Controls (*n* = 20), Median (IQR)	*P* value
Adiponectin (μg/mL)	12.20 (9.76, 17.97)	13.95 (11.17, 22.58)	0.18
Leptin (ng/mL)	1.83 (1.13, 3.80)	1.10 (0.41, 2.88)	0.09
Resistin (ng/mL)	27.77 (18.66, 48.90)	21.20 (14.80, 27.00)	0.04[a]

[a]*P* value < 0.05 was taken as significant. IQR: Interquartile range.

Indian cohorts[20,23,24]. Furthermore, periungual desquamation and thrombocytosis seem to appear earlier in children with KD in India[25].

Newburger and colleagues previously reported that KD was associated with significant abnormalities of lipid metabolism and derangement of serum lipid profiles[3]. In the first few d of the illness, mean plasma concentration of total cholesterol and HDL- cholesterol was profoundly depressed, whereas mean triglyceride level was very high. Total cholesterol values rapidly returned to normal and remained stable more than three months after the onset of illness. HDL-cholesterol concentration recovered more slowly after illness onset. Mean HDL-cholesterol level was significantly reduced, even after three years of illness onset. Lipid abnormalities in KD are in part attributable to concurrent reductions in lipoprotein lipase and hepatic lipase activities[4]. Several other authors have also reported

Table 3 Correlation of adipocytokines with different lipoproteins, body mass index and age of the patients with Kawasaki disease

Characteristics	Leptin		Adiponectin		Resistin	
	Correlation coefficient	*P* value	Correlation coefficient	*P* value	Correlation coefficient	*P* value
LDL (mg/dL)	0.030	0.90	-0.223	0.34	-0.003	0.99
TG (mg/dL)	0.076	0.75	-0.018	0.94	0.169	0.47
VLDL (mg/dL)	-0.076	0.75	0.330	0.15	0.105	0.65
HDL (mg/dL)	-0.037	0.87	0.505	0.47	0.470	0.03[a]
Total cholesterol (mg/dL)	0.033	0.89	-0.379	0.09	-0.217	0.35
BMI (kg/m^2)	0.574	0.02[a]	-0.334	0.20	-0.280	0.29
Age (yr)	0.379	0.09	-0.057	0.81	-0.128	0.59

[a]*P* value < 0.05 was taken as significant. LDL: Low density lipoprotein; TG: Triglycerides; VLDL: Very low density lipoprotein; HDL: High-density lipoprotein.

similar abnormalities in the lipid profile of children with KD[4,6,26]. We have shown that HDL-cholesterol was low in 6/18 and borderline in 11/18 patients with convalescent KD. Thus, 17/18 patients had abnormal HDL-cholesterol at follow-up. The persistence of low HDL-cholesterol for many years in our cohort suggests a long-lasting effect of KD on endothelial function, perhaps attributable to the diminished activity of lipoprotein lipase. Normal lipid levels in the general population have been studied in Indian children by Marwaha *et al* and these were used as historical reference standards in the present study[22].

Adipose tissue has long been considered an inert organ and a depot for energy storage. However, new advances have revealed that it is also an important endocrine organ that produces numerous adipocytokines[11]. Perturbations in adipocytokines are well known in obesity. These play a fundamental role in obesity-linked disorders such as diabetes mellitus and metabolic syndrome[12]. It is now well recognized that adipocytokines play a pivotal role in immune response and inflammation[13]. Studies have shown that adipokines may be important biomarkers for inflammation in chronic diseases [27,28]. While some adipocytokines can induce pro-inflammatory effects (*e.g.* leptin, resistin, IL-6, TNF-α), others have predominantly anti-inflammatory effects (*e.g.* adiponectin and IL-10)[14]. Therefore, analysis of specific adiponectin isoforms may be necessary to prove these diverse effects. An imbalance between pro-inflammatory and anti-inflammatory adipocytokines leads to persistent inflammation and may contribute to accelerated atherosclerosis. Low adiponectin, high resistin and high leptin levels have been reported to produce this phenomenon.

As children with KD have lipid abnormalities[6,26], it is plausible that a disturbed adipocytokine milieu may contribute to early development of atherosclerosis. This may, in turn, predispose children with KD to acute coronary events at a young age. Adiponectin, resistin and leptin are the most examined adipocytokines in disorders of lipid metabolism and we, therefore, conducted this study in the convalescent phase of KD. To the best of our knowledge, there are no published data on adipocytokine levels in children with KD from the Indian subcontinent.

Studies on adipocytokines profile in the follow-up of KD are sparse and have yielded conflicting results[5,9,19] (Tables 3 and 4). Fukunaga *et al*[19] reported low, medium molecular weight (MMW) and LMW adiponectin levels in convalescent cases of KD compared to controls. In the present study, serum resistin levels were significantly elevated in patients with KD during the convalescent phase compared to controls. Serum leptin levels appeared to be higher in patients with KD, although the difference was not statistically significant. Adiponectin levels were similar in both cases and controls. Cai *et al*[29] performed a meta-analysis to assess the association of adiponectin and resistin in patients with KD. These authors showed that while serum resistin levels in patients with KD were significantly higher compared with those in controls, adiponectin levels were similar in patients with KD and controls. Our results are also in accordance with these findings.

CONCLUSION

Our results suggest that serum adipocytokine levels may impact lipid abnormalities observed during the convalescent phase of KD. The strength of our study is that it is a single centre study wherein all children were diagnosed and treated by the senior author of this study (SS), thereby ensuring uniformity in sample recruitment. Furthermore, the diagnosis of KD was based on standard criteria (AHA 2004). One of the obvious weaknesses is the small sample size, but this was unavoidable as the study had to be completed in a given time frame for the dissertation of the first author (DP). It is

Table 4 Comparison of published literature on circulating adipocytokines in children with Kawasaki disease

Ref.	Number of cases/controls	Stage of disease	CAA	Resistin	Leptin	Adiponectin
Takeshita *et al*[30], 2006	Cases-20; Febrile controls-15; Healthy controls-15	Acute phase (day 4-6); Convalescent phase (day 25-39)	NA	-	-	Adiponectin levels were significantly reduced in the acute phase compared to the convalescent phase. No difference between the convalescent phase and controls.
Nozue *et al* [15], 2010	Cases-44; Controls-17	Acute	0	Increased during the acute phase and returned to normal after IVIg administration	Not assessed	Not assessed
Fukunaga *et al*[19], 2010	Acute phase KD-9; Convalescent phase KD-20; Controls-21	Both acute and convalescent (> 2 yr from KD onset); 6.72 ± 3.2 yr following KD (for convalescent cases)	NA	Not assessed	Not assessed	Total and HMW adiponectin levels were lower in acute KD compared to controls; MMW and LMW adiponectin levels decreased in convalescent cases compared to controls
Qi *et al*[31], 2012	Cases-40; Controls-15	Acute; Afebrile; Subacute phase	6	Significantly high in the acute stage of KD and decreased with the course of the disease; No difference between patients with KD in the afebrile and subacute phase compared with the controls		
Liu *et al* [16], 2012	KD-80; Controls-85	Acute	39	Increased compared to controls. No difference between KD with and without CAAs	No difference	Increased compared to controls. No difference between KD with and without CAAs
Kemmotsu *et al*[17], 2012	Cases-56; Healthy controls-30; Febrile controls-31	Acute	4	Markedly elevated in acute stage and returned to normal after IVIg administration. Non-responders to IVIg had very high resistin levels	No difference	No difference
Kim *et al* [18], 2014	Cases-40; Febrile controls-32; Healthy controls-15	Acute	12	Markedly elevated in the acute stage but did not predict development of CAAs	Not assessed	Not assessed
Zhang *et al* [32], 2018	Cases-80; Febrile controls-20; Healthy controls-20	Acute phase	24			Decreased compared to febrile controls. However, no difference compared with healthy controls
Zhang *et al* [33], 2021	Cases-42; Controls-20	Acute phase (1-10 d); Subacute phase (11-20 d); Convalescent phase (21-30 d)	18			Serum adiponectin was significantly lower compared to controls
Present study, 2021	KD convalescent phase-20; Controls-20	Convalescent; > 3 yr of follow-up; (mean 5.5 yr)	4	Elevated in patients with KD compared to controls	Trend towards higher levels of leptin in patients with KD compared to controls	No difference

CAAs: Coronary artery abnormalities; HMW: High molecular weight; IVIg: Intravenous immunoglobulin; KD: Kawasaki disease; LMW: Low molecular weight MMW: Medium molecular weight; NA: Not available.

suggested that the leads provided by our work should be applied in a larger and preferably multicentric study.

ARTICLE HIGHLIGHTS

Research background

Patients with Kawasaki disease (KD) may have abnormal lipid profiles that may last for prolonged periods. The reasons underlying the persistence of lipid abnormalities are unclear in patients with KD.

Research motivation

There is a paucity of literature on the role of adipocytokines and their effect on abnormal lipid metabolism in patients with KD.

Research objectives

To estimate the levels of adipocytokines (adiponectin, leptin and resistin) during the convalescent phase of KD.

Research methods

Serum adiponectin, leptin and resistin levels were estimated by enzyme-linked immunosorbent assay in patients with KD and controls.

Research results

The mean age of patients in the study group was 10.15 ± 3 years. Median serum resistin levels in patients with KD (27.77 ng/mL; [IQR: 18.66, 48.90]) were increased compared to controls (21.20 ng/mL; [IQR: 14.80, 27.00]) (P = 0.04). Median serum leptin levels and adiponectin levels in cases and controls were similar. There was no significant correlation between adipocytokines and the lipid profile in patients with KD. There was no significant difference in all 3 adipocytokines between children with CAAs and without CAAs.

Research conclusions

Our results suggest that serum adipocytokine levels may impact lipid abnormalities observed during the convalescent phase of KD.

Research perspectives

The leads provided by our work should be applied in a larger and preferably multicentric study to confirm these results.

FOOTNOTES

Author contributions: Praharaj DL, Rawat A, Gupta A and Singh S conceived and designed the research; Praharaj DL, Rawat A, Arora K, and Pilania RK collected data and performed the research; Praharaj DL, Arora K, Pilania RK, and Bhattad S were involved in writing the first draft; Praharaj DL, Rawat A and Arora K performed laboratory tests; Praharaj DL, Rawat A, Arora K, and Pilania RK analyzed the data; Gupta A, Pilania RK, Bhattad S and Singh S were involved in patient management; Praharaj DL, Rawat A, Gupta A, Arora K, Pilania RK, Bhattad S, Singh S reviewed the literature; Rawat A, Pilania RK, and Singh S edited the manuscript, performed critical revision at all stages and final approval of the manuscript; all the authors read and approved the final manuscript.

Institutional review board statement: The study protocol was approved by the Institute Thesis Committee and Institute Ethics Committee. The manuscript has been approved by the Departmental Review Board.

Informed consent statement: Written informed consent was obtained from the parents/guardians at study enrolment.

Conflict-of-interest statement: The authors declare no "conflicts of interest".

Data sharing statement: The data on the findings of this paper are all included in the tables.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: India

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S-Editor: Wang LL
L-Editor: Webster JR

P-Editor: Wang LL

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World Journal of Clinical Pediatrics

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World J Clin Pediatr 2022 July 9; 11(4): 369-374

DOI: 10.5409/wjcp.v11.i4.369

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Observational Study

Children with lysinuric protein intolerance: Experience from a lower middle income country

Syed Bilal Hashmi, Sibtain Ahmed

Specialty type: Pathology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Dai DL, China; Yang X, China
A-Editor: Liu X, China

Received: December 29, 2021
Peer-review started: December 29, 2021
First decision: March 16, 2022
Revised: March 21, 2022
Accepted: June 3, 2022
Article in press: June 3, 2022
Published online: July 9, 2022

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Abstract

BACKGROUND

Lysinuric protein intolerance (LPI) is an inborn error of metabolism consequential to recessive mutations in the *SLC7A7* gene. The metabolic imbalance in absorption and excretion of dibasic amino acids is considered the basis of LPI. The disease results from protein intolerance with signs and symptoms oscillating from cerebral impairment, respiratory involvement, renal failure and autoimmune complications.

AIM

To determine biochemical and clinical presentation of cases with biochemical picture suggestive of LPI in Pakistani children.

METHODS

The study was conducted at the Biochemical Genetic Lab, Department of Pathology and Laboratory Medicine, AKU Plasma, and urine amino acid quantification data from January 2013 to October 2018 was included in this study. The amino acids were analyzed by high performance liquid chromatography. Prestructured requisition forms were used to obtain the clinicopathological data. Statistical analysis was done by Microsoft Excel 2017.

RESULTS

A total of 6 patients were recognized. All the patients were male (100%). The mean age was 24 mo ± 10 d. All the patients had low plasma concentration of lysine, ornithine and arginine, whereas increased levels of lysine, ornithine and arginine in urine were observed in 2 patients. History of consanguineous marriage was present in all patients (100%). The most observed clinical symptom was feeding difficulty followed by failure to thrive (83.3%) and developmental delay (66.6%). Hepatomegaly was present in all patients (100%). No mutation analysis was done.

CONCLUSION
This study portrays the biochemical and clinical spectrum of LPI in Pakistan. Although clinical manifestations appeared in the first 2 years of life, most of them suffered a delay in undergoing diagnostic workup.

Key Words: Lysinuric protein intolerance; Consanguinity; Pakistan; Retrospective study

Core Tip: Lysinuric protein intolerance is an inherited biochemical disorder with just over 140 individuals worldwide. In this disorder, there is defective absorption and excretion of dibasic amino acids, such as lysine, arginine and ornithine. This is the first study from Pakistan, which has a high prevalence of inherited metabolic disorders. Only 4 previously reported cases were identified from South Asia. This study shows the biochemical pattern and clinical characteristics in patients with a suggestive diagnosis of lysinuric protein intolerance on biochemical workup.

Citation: Hashmi SB, Ahmed S. Children with lysinuric protein intolerance: Experience from a lower middle income country. *World J Clin Pediatr* 2022; 11(4): 369-374
URL: https://www.wjgnet.com/2219-2808/full/v11/i4/369.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i4.369

INTRODUCTION

Lysinuric protein intolerance (LPI) is a multi-organ congenital metabolic disorder. The recessive mutations of the *SLC7A7* gene located at chromosome 14q11.2 causes faulty transport of cationic amino acids of the epithelial cells, mainly at the basolateral membrane of the kidney and intestine[1]. This leads to an imbalance in absorption and excretion of cationic amino acids like lysine, ornithine and arginine. Hence their plasma levels are decreased, but urine levels are raised. The presence of the transport defect in the hepatocytes distinguishes LPI from other hyper-dibasic aminoacidurias[2]. There is co-occurrence of increased neutral amino acids (alanine, citrulline, glycine, proline and glutamine) on plasma amino acid testing[3,4].

The conventional presentation of LPI is after weaning from breast milk. It can present with upper and lower gastrointestinal symptoms, such as nausea, vomiting and diarrhea. Due to protein intolerance, most patients ultimately develop micronutrient and macronutrient deficiencies. Neurological manifestations such as hypotonia, lethargy, abnormal behavior, seizures and coma can result from episodic postprandial hyperammonemia[5,6]. This hyperammonemia is due to decreased levels of arginine and ornithine. The epitome of most of the symptoms is a secondary urea cycle defect. This combination of vague symptoms often causes a diagnostic delay[7], progressive disease and apprehension among caregivers. Clinical history and quantitative measurement of plasma and urine amino acids is required to reach the diagnosis. However, if a patient is on total parenteral nutrition, plasma amino acid profile may be falsely normal. The actual incidence of LPI in Pakistani population is unidentified. Therefore, this study was initiated to determine the clinicopathological spectrum of patients with a biochemical picture suggestive of LPI.

MATERIALS AND METHODS

The study was conducted at the Biochemical Genetic Lab, Department of Pathology and Laboratory Medicine, Aga Khan University Hospital, Karachi. Plasma amino acid (PAA) and urine amino acid (UAA) quantification data from January 2013 to October 2018 was included in the study.

The study was conducted in two phases. In the initial phase, a chemical pathologist reviewed PAA and UAA reports, and reports suggestive of LPI were outlined. In the subsequent phase, clinical details were retrieved from the history forms received with test requisition.

Biochemical analysis

First, 3-4 mL blood was taken in a lithium heparin tube for PAA quantification. Samples were centrifuged then delivered in dry ice to the Biochemical Genetic Lab. The samples were kept at -20 °C until analysis.

The amino acid level was measured by cation-exchange high performance liquid chromatography. To deproteinize the standard, the control and the samples, 10% sulfosalicylic acid was used. Norleucine was used as an internal standard. EZ chrome 3.31 was used to determine the results. Quality control and proficiency testing validation for amino acids were completed per the Clinical and Laboratory Standards Institution guidelines[8]. High and low levels of quality control samples were analyzed with each batch of 10 samples. The study commenced after receiving approval from the ethical review committee.

Data analysis

Statistical analysis was performed by Microsoft Excel 2017. Frequencies and percentages were generated for gender, consanguinity, clinical presentations and biochemical features of LPI.

RESULTS

Demographics

Over a span of 6 years, PAA estimation of 3057 patients was performed. Six patients were recruited in the study having PAA concentrations suggestive of LPI. All of them were males (100%). The mean age was 24 mo ± 10 d. Parental consanguinity was observed in all 6 (100%) patients (Figure 1).

Clinical and biochemical features

The most common clinical features recorded were feeding difficulty (6; 100%), failure to thrive (5; 83.3%) and developmental delay (4; 66.6%) as shown in Figure 2. Also, hepatosplenomegaly was observed in all patients (100%) and respiratory distress in 2 patients (33.3%). All the patients had decreased blood concentrations of lysine, ornithine and arginine (100%). The urinary concentrations of lysine, ornithine and arginine were increased in 2 patients (33.3%), while UAA was not undertaken for the remaining cases.

Follow-up and outcomes

Out of 6 patients, only 2 patients were followed up. They were put on a protein restricted natural diet along with L-citrulline and L-carnitine supplementation. The remaining patients refused any further diagnostic testing and treatment due to economic reasons.

DISCUSSION

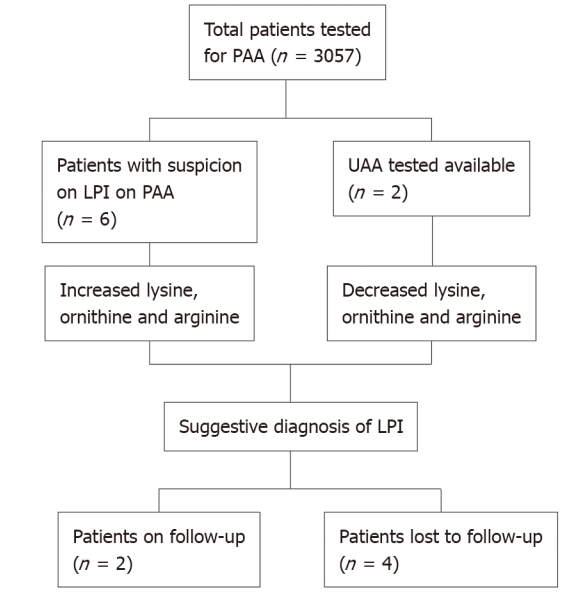
LPI is a rare disorder, and just over 140 individuals with LPI have been reported in the world, of which one-third are of Finnish origin[9]. There are no reported cases in Pakistan. An LPI patient usually presents with hepatosplenomegaly, impaired growth, protein intolerance and poor feeding. Long-term protein restriction and citrulline and nitrogen scavenging drugs are the drugs of choice. The prevention and treatment of the complications such as lung, renal and musculoskeletal system are also an important part of managing LPI. Being an autosomal recessive disorder, genetic counseling can form an important part of the management.

The cases reported in the current study presented after weaning with gastrointestinal disturbance, poor feeding, growth retardation and enlargement of the liver and spleen. Increased levels of lysine and arginine in the urine are diagnostic of LPI as was seen in our patients. Another method of making a definitive diagnosis of LPI is confirming the presence of the mutated *SLC7A7* gene by methods such as targeted mutation analysis and sequence analysis[1], which could not be done in this study.

A suspicion of LPI is aroused when a child shows an inability to digest proteins, whereas clinical findings include growth retardation, developmental delay and pulmonary and cerebral impairment. However, LPI may often be confused with other disorders such as hyperammonemia, lysosomal storage diseases, malabsorptive diseases and autoimmune disorders, such as systemic lupus erythematosus[10], which show similar clinical findings. Therefore, a confirmed diagnosis of LPI requires the combination of the above-mentioned signs along with positive laboratory findings.

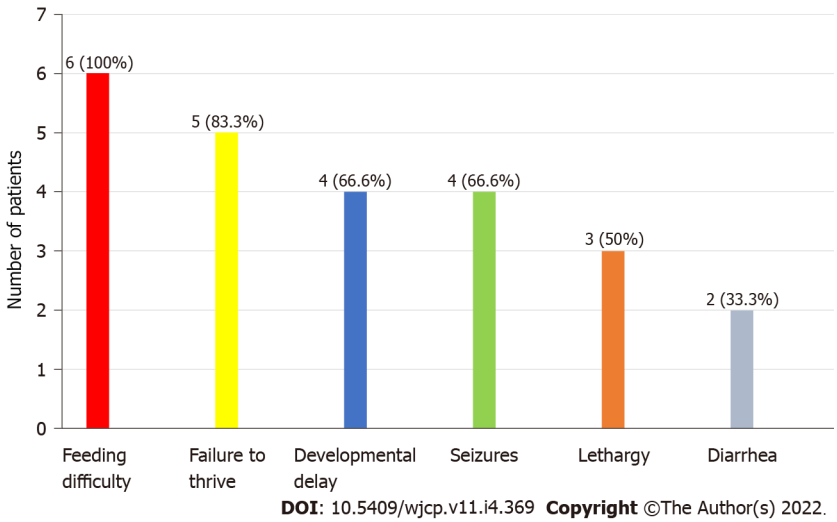
In addition to the small sample size from a single center, there are a few notable limitations of this study including the lack of gene sequencing for the confirmation of diagnosis and study population based on symptomatic cases following a high-risk screening. Gene sequencing for the disorder is not available in Pakistan, and additional cost of outsourcing the samples to laboratories abroad further leads to constraints for the confirmatory diagnosis.

Treatment of LPI includes protein restriction; compensation for the loss of lysine and arginine involves carnitine supplementation, as it has been found to be effective by having a lysine-sparing effect. Citrulline has also been found effective as a treatment option in LPI as it is converted to arginine in the body. In cases of an acute hyperammonemic crisis, pharmacologic treatment with arginine chloride, which blocks the production of ammonia, and a blend of medicines like sodium benzoate and



DOI: 10.5409/wjcp.v11.i4.369

Figure 1 Flow chart showing patients with lysinuric protein intolerance. PAA: Plasma amino acids; LPI: Lysinuric protein intolerance; UAA: Urine amino acid.



DOI: 10.5409/wjcp.v11.i4.369

Figure 2 Clinical features in patients with lysinuric protein intolerance (*n* = 6).

sodium phenylacetate has been suggested[10]. LPI is often associated with pulmonary and renal complications, and treatment of such complications with corticosteroids is found to be effective in some patients[1]. Therapy with bisphosphonates is currently under investigation as osteopenia leading to osteoporosis is a major feature[11].

Short stature, growth retardation and failure to thrive is usually observed in LPI patients due to protein malnutrition. Many studies have concluded that various amino acids and hormones influence the growth of these children. Awrich *et al*[12] reported that amino acids in combination such as citrulline with lysine and arginine with lysine had potent effects on growth and development of these children. A study also showed that an ample supply of arginine also helped in improving growth retardation in LPI [13]. The quality of life of these patients is dependent on lifelong monitoring and management of complications. The prognosis of a child with LPI varies on the involvement of lung and the successful resolution of its complications, with pulmonary involvement representing an increased fatal outcome [11]. Being an autosomal recessive disorder, an antenatal diagnosis of LPI can be made by the DNA analysis of fetal cells extracted by amniocentesis usually performed at 15-18 wk of gestation[10]. Table 1 shows the summary of studies from South Asia.

Table 1 Summary of studies on lysinuric protein intolerance in South Asia

Country	No. of cases	Ref.	Presenting symptoms	PAA findings	UAA findings	↑NH3
India	4	Bijarnia-Mahay *et al* [14], 2016	Neurodevelopmental symptoms	↓Lysine; ↓Ornithine; ↓ Arginine	↑Lysine; ↑Ornithine; ↑ Arginine	Yes
		Moosa *et al*[15], 2005	Neurodegenerative symptoms	↓Lysine; ↓Ornithine; ↓ Arginine	↑Lysine; ↑Ornithine; ↑ Arginine	Yes
		Deogaonkar *et al* [16], 2016	Skin pustules, decreased feeding, sepsis	Normal	↑Lysine; ↑Arginine	Yes
		Nalini *et al*[17], 2015	Failure to thrive, recurrent chest infections	↓Lysine; ↓Ornithine; ↓ Arginine	↑Lysine; ↑Ornithine; ↑ Arginine	Yes
Pakistan	6	This study, 2022	Feeding problems, failure to thrive, developmental delay	↓Lysine; ↓Ornithine; ↓ Arginine (in all patients)	↑Lysine; ↑Ornithine; ↑ Arginine (in 2 patients)	Yes

↑: Above the reference range; ↓: Blow the reference range; PAA: Plasma amino acids; UAA: Urine amino acids.

CONCLUSION

This study portrays the biochemical and clinical spectrum of LPI in Pakistani children. LPI is an inherited metabolic disorder. The treatment of which involves a protein-restricted diet and supplement of lysine, ornithine and citrulline. The clinical diagnosis of LPI can be delayed due to a combination of non-specific symptoms. In patients with hyperammonemia, LPI should be kept for differential diagnosis. There is need for wide spread local availability of PAA and UAA measurement to aid clinicians.

ARTICLE HIGHLIGHTS

Research background

Lysinuric protein intolerance (LPI) is an inherited metabolic disorder caused by alterations in the *SLC7A7* gene.

Research motivation

To create awareness among the clinical community and describe the spectrum of this rare disorder in Pakistan.

Research objectives

To present the biochemical and clinical presentation of cases with suggestive LPI in Pakistan.

Research methods

Descriptive cross sectional study.

Research results

Six cases with a suggestive diagnosis of LPI based on amino acid profiling were reported.

Research conclusions

Although clinical manifestations appeared in the first 2 years of life, a delay in diagnosis was evident.

Research perspectives

A high rate of inherited metabolic disorders in Pakistan is known.

FOOTNOTES

Author contributions: Ahmed S designed and conceived the idea, assisted in the write-up of the first draft and critically reviewed the manuscript; Hashmi SB performed the data collection, literature review and the majority of the write-up in the first draft.

Institutional review board statement: Study commenced after approval was obtained from the institutional ethics

committee (No. 2018-0553-894).

Conflict-of-interest statement: No conflict-of-interest to declare.

Data sharing statement: Dataset available from the corresponding author at ude.uka@demha.niatbis. Consent was not obtained as the presented data are anonymized and risk of identification is low.

Country/Territory of origin: Pakistan

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S-Editor: Zhang H
L-Editor: Filipodia CL
P-Editor: Zhang H

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World J Clin Pediatr 2022 July 9; 11(4): 375-384

DOI: 10.5409/wjcp.v11.i4.375

ISSN 2219-2808 (online)

SYSTEMATIC REVIEWS

Impact of sports participation on cardiovascular health markers of children and adolescents: Systematic review and meta-analysis

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Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Abdelbasset WK, Saudi Arabia
A-Editor: Yao QG, China

Received: July 29, 2021
Peer-review started: July 29, 2021
First decision: November 11, 2021
Revised: December 17, 2021
Accepted: May 26, 2022
Article in press: May 26, 2022
Published online: July 9, 2022

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Abstract

BACKGROUND

Cardiovascular diseases have a high prevalence in adults and their development begins in the first decades of life. On the other hand, sports participation in childhood and adolescence provides benefits which can delay the onset of these diseases.

AIM

To synthesize the available literature on the impact of sports participation on cardiovascular outcomes in children and adolescents.

METHODS

This systematic review was conducted on studies of children and adolescents (aged 8-18 years) who regularly practiced a sport and had reported cardiovascular outcomes (blood pressure and intima-media thickness) recorded. The Medline/PubMed, SciELO, Reference Citation Analysis (https://www.referencecitationanalysis.com/) and Bireme databases were searched.

RESULTS

In total, 3314 publications for blood pressure and 122 publications for intima-media thickness were identified in the databases. After exclusions (*e.g.*, duplicate articles, animal studies and those that did not meet the inclusion criteria), four publications for blood pressure (449 adolescents) and two publications for intima-media thickness were included (402 adolescents). For blood pressure, all publications were longitudinal in design (follow-up ranging from 12 wk to 12 mo) and involved adolescents aged from 8 years to 18 years of age. For intima-media thickness, both publications were longitudinal in design and involved adolescents aged from 11 years to 18 years of age.

CONCLUSION

Sports participation seems to promote benefits to cardiovascular structure and

function in adolescents. However, studies with adolescents are scarce and further research is needed to understand this phenomenon.

Key Words: Pediatrics; Adolescents; Sports; Blood pressure; Intima-media thickness

Core Tip: Obesity, poor diet and a sedentary lifestyle increases the risk for cardiovascular disease in adulthood. On the other hand, sports participation reduces blood pressure and children and adolescents engaged in sports tend to present better arterial thickness values. In this way, those who practice sports regularly may present better cardiovascular health. In this review we seek to characterize the results of sports practice in adolescence on aspects related to cardiovascular health.

Citation: Torres W, Maillane-Vanegas S, Urban JB, Fernandes RA. Impact of sports participation on cardiovascular health markers of children and adolescents: Systematic review and meta-analysis. *World J Clin Pediatr* 2022; 11(4): 375-384
URL: https://www.wjgnet.com/2219-2808/full/v11/i4/375.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i4.375

INTRODUCTION

Cardiovascular diseases are the main cause of death among adults[1,2] with arterial hypertension being the most prevalent[3]. Although arterial hypertension is frequently observed in adults, high blood pressure is its manifestation in children and adolescents. In fact, the prevalence of high blood pressure in early life has increased in recent years[4,5] which is concerning for health professionals as it predicts mortality related to cardiovascular diseases in adulthood[6,7].

Blood pressure monitoring is a simple and useful way to screen cardiovascular problems in clinical practice. In addition, measures of intima-media thickness (IMT) also constitute a relevant marker of cardiovascular health, being a non-invasive method used to screen atherosclerosis[8,9].

Although the occurrence of cardiovascular diseases in children and adolescents is low, habits assumed in early life are able to affect health outcomes later in life[8,10]. Increased time spent in sedentary behavior[11] and insufficient physical activity[12] are behaviors that contribute to the development of cardiovascular diseases including arterial thickening[13].

Physical activity is a relevant behavior with huge potential to affect pediatric health. In terms of cardiovascular health, regular engagement in physical exercise helps to prevent a large variety of cardiovascular diseases in adulthood[14-18], but the effects in children and adolescents are still under investigation. Similarly, the pathways by which routines of physical exercise are able to promote cardiovascular health have been widely investigated in pediatric and adult groups[19], however, relevant questions still remain, mainly in pediatric groups.

For example, there are limited data about the impact of sports participation on cardiovascular health during adolescence. This question is relevant because in the real world (different from exercise protocols performed in the laboratory), sports participation is the main manifestation of physical exercise in adolescence helping adolescents to reach moderate-to-vigorous physical activity recommendations[20-23].

However, in the literature it is unclear whether engagement in sports is beneficial to the cardiovascular system in apparently healthy adolescents. Most publications involving physical exercise and cardiovascular aspects in adolescents are focused on obese groups and the exercise protocols rarely consider sports participation[24]. Thus, the objective of this review is to synthesize the available literature on the impact of sports participation on cardiovascular outcomes (blood pressure and IMT) in children and adolescents.

MATERIALS AND METHODS

Search strategy

The present systematic review was conducted according to the Preferred reporting Items for Systematic Review and Meta-Analyses recommendations. The Problem was "sports participation and cardiovascular outcomes in adolescents", the Intervention was "engagement in sports", the Comparator was "cardiovascular outcomes in adolescents non-engaged in sports", and the Outcome was "blood pressure

and intima-media thickness".

The main outcome of this review was to identify changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) (mmHg) and femoral and carotid IMT (mm) attributed to sports participation in children and adolescents. Due to the limited number of publications, there was no stratification according to sports.

Literature search and selection

Two authors independently performed the literature search from March to July 2021 and studies published until June 2021 were accessed. The search was restricted to publications in the following electronic databases: Medline/PubMed (National Library of Medicine), SciELO, Reference Citation Analysis (https://www.referencecitationanalysis.com/) and BIREME (Latin American and Caribbean Center on Health Sciences information). The search strategy considered the combination of nine keywords (DeCS): *Children*, *adolescents*, *youth*, *teenagers*, *pediatrics*, *sports*, *sports participation*, *organized sports*, *blood pressure*, *intima-media thickness* and *vessel thickness*, as follows.

Blood pressure: ((((((Children) OR (Adolescents)) OR (Youth)) OR (Teenagers)) OR (Pediatrics)) AND (((Sports) OR (Sports participation)) OR (Organized sport))) AND (Blood pressure).

Intima-media thickness: ((((((Children) OR (Adolescents)) OR (Youth)) OR (Teenagers)) OR (Pediatrics)) AND (((Sports) OR (Sports participation)) OR (Organized sport))) AND ((Intima-Media Thickness) OR (Vessel Thickness)).

Inclusion criteria

In terms of language, only publications in English were considered. Data from reviews, expert opinions, case reports, editorials, rodent studies and computational studies were excluded. Cross-sectional studies were also excluded because the aim was to consider longitudinal studies that identified changes in blood pressure and IMT in adolescents engaged in sports. Finally, longitudinal studies that investigated adolescents (girls and boys) aged between 8 years and 18 years who were regularly engaged in any sport were considered eligible.

Data extraction

A standardized Cochrane Consumers and Communication Review Groups data extraction method was used, whereby the age of the participants, sample size, sex, sports participation definition and cardiovascular health marker outcomes (systolic blood pressure, diastolic blood pressure, carotid intima media thickness and femoral intima media thickness) were collated from each study.

Initially, two independent researchers (SMV and JBU) identified potential studies eligible for this review by screening titles and abstracts. Subsequently, the same reviewers observed the inclusion and exclusion criteria, assessed the full texts and extracted data from the included studies using a standardized extraction form. In case of discrepancy, another reviewer (WT) was available throughout the screening process to verify and resolve any issue.

Quality assessment

The Newcastle-Ottawa quality assessment scale was used, which adopts a star system to assess the quality of eight items in three different domains (selection, comparability and exposure). Each item can receive one star, except for the comparability domain (two stars). The total score of the instrument ranges from 0 to 9[25].

Statistical analysis

In cases where standard error of the mean (SEM) and mean values for the intervention or control group were available, the SD was calculated using the following formula: $SD = SEM \times \sqrt{n}$.

In cases where 95% confidence intervals (95%CI) were provided for the intervention or control group, the SD was calculated as follows: SD = $\sqrt{n}$ × (upper limit - lower limit)/t statistic).

The meta-analysis was performed using Review Manager software (Version 5, Cochrane Collaboration). Differences in means and 95%CI were calculated using a continuous random-effect model to incorporate heterogeneity among studies. If the number of available studies was small ($n \leq 3$), a fixed effect model was applied to estimate the between study heterogeneity.

Heterogeneity between studies was assessed using the chi square test expressed by means of inconsistency indices (I^2) (0%–25%: None, 26%–50%: Low, 51%–75%: Moderate, and 76%–100%: High). Statistical significance was set at $P < 0.05$.

Table 1 Blood pressure

Ref.	Title of paper	Aim/purpose	Total sample, *n* = 326	Sample age	Follow-up time	Sports	Main results	Quality assessment[1]
Cayres-Santos *et al*[29], 2020	Sports participation improves metabolic profile in adolescents: ABCD growth study	To analyze the impact of participation in sports with different CRF demands on changes in metabolic and cardiovascular markers in adolescents	184 adolescents (*n* = 122 engaged in sports and *n* = 62 not engaged in sports)	Between 11-18	12 mo	High CRF: Basketball, swimming, tennis, and track and field. Low CRF: Baseball, gymnastics, judo, karate, and kung fu	SBP increased in both sports with high [2.299 mmHg (95%CI: 0.142-4.456)) and low CRF [2.806 mmHg (95%CI: 0.261-5.351)]. DBP increased in sports with high [1.896 mmHg (95%CI: 0.499-3.293)], but not in sports with low CRF [0.948 mmHg (95%CI: -0.271 to 4.562)]	7
Cayres *et al* [30], 2018	Sport-based physical activity recommendations and modifications in C-reactive protein and arterial thickness	We analyzed the effects of 1 yr of engagement in ≥ 300 min/wk of organized sports on inflammatory levels and vascular structure in adolescents	89 adolescents (*n* = 15 sport practice and *n* = 74 non-sport practice)	Between 11-14	12 mo	Soccer, swimming, and others not shown	SBP did not change in the sports participation group [-0.309 mmHg (95%CI: -4.149 to 3.532)], but DBP did [-6.269 mmHg (95%CI: -9.313 to -3.224)]	7
Seabra *et al* [31], 2020	School-based soccer practice is an effective strategy to improve cardiovascular and metabolic risk factors in overweight children	We examined the effects of a 6-mo school-based soccer program on CV and metabolic risk factors in overweight children	40 overweight boys aged 8 to 12 yr (*n* = 20 soccer group and *n* = 20 control group)	Between 8–12	6 mo	Soccer	SBP did not change in the soccer group (2.7 mmHg), but DBP did (-4.0 mmHg)	9
Vasconcellos *et al*[26], 2021	Does Recreational Soccer Change Metabolic Syndrome Status in Obese Adolescents? A Pilot Study	To evaluate whether a soccer program (RSP) might lower risk factors related to MetS in obese adolescents	13 adolescents aged 13-17 yr (*n* = 6 soccer program and *n* = 7 control)	Between 12-17	12 wk	Soccer	SBP (-7.0 mmHg) and DBP (-3.0 mmHg) did not change significantly in the soccer group	8

[1]Quality Assessment according to Newcastle-Ottawa Scale (range 0 to 9) for cohort studies. ABCD Growth Study: Analysis of Behaviors of Children During Growth; CRF: Cardiorespiratory fitness; CV: Cardiovascular; MetS: Metabolic syndrome; RSP: Randomly assigned to experimental.

RESULTS

Study selection

The research team searched for publications considering two outcomes, the impact of sports participation on blood pressure and IMT.

A total of 3436 relevant studies were identified in the databases. The majority of the studies assessed blood pressure [*n* = 3314 (96.4%)], while 122 (3.6%) assessed intima media thickness. After removal of duplicates and screening of study titles and abstracts, 2307 studies remained. Following the final full-text screening process, 4 studies for systolic and diastolic blood pressure (*n* = 326) and 2 studies for intima media thickness (*n* = 273) were included in the meta-analysis. The study selection process is presented in Figure 1.

Study outcomes

The characteristics of participants included in each study are presented in Table 1 for blood pressure and Table 2 for intima media thickness issues. Comparisons between the two groups (sports participation and control groups) are shown in Figure 2.

Table 2 Arterial thickness

Ref.	Title of paper	Aim/purpose	Total sample, *n* = 273	Sample age	Follow-up time	Sports participation definition	Main results	Quality assessment[1]
Cayres-Santos *et al*[29], 2020	Sports participation improves metabolic profile in adolescents: ABCD growth study	To analyze the impact of participation in sports with different CRF demands on changes in metabolic and cardiovascular markers in adolescents	184 adolescents (*n* = 122 engaged in sports and *n* = 62 not engaged in sports)	Between 11-18	12 mo	High CRF: Basketball, swimming, tennis, and track and field. Low CRF: Baseball, gymnastics, judo, karate, and kung fu	Carotid IMT did not change in both sports with high [0.002 mm (95%CI: -0.018 to 0.023)] and low CRF [-0.001 mm (95%CI: -0.024 to 0.023)]. Femoral IMT did not change in both sports with high [0.013 mm (95%CI: -0.010 to 0.037)] and low CRF [-0.004 mm (95%CI: -0.024 to 0.033)]	8
Cayres *et al*[30], 2018	Sport-based physical activity recommendations and modific-ations in C-reactive protein and arterial thickness	We analyzed the effects of 1 yr of engagement in ≥ 300 min/wk of organized sports on inflammatory levels and vascular structure in adolescents	89 adolescents (*n* = 15 Sport practice and *n* = 74 non-sport practice)	Between 11-14	12 mo	Soccer, swimming, and others not shown	Carotid IMT did not change in the sports participation group [0.006 mm (95%CI: -0.013 to 0.024)], but Femoral IMT did [-0.043 mm (95%CI: -0.081 to -0.006)]	8

[1]Quality Assessment according to Newcastle-Ottawa Scale (range 0 to 9) for cohort studies. CRF: Cardiorespiratory fitness; IMT: Intima-media thickness.

Study characteristics and meta-analysis

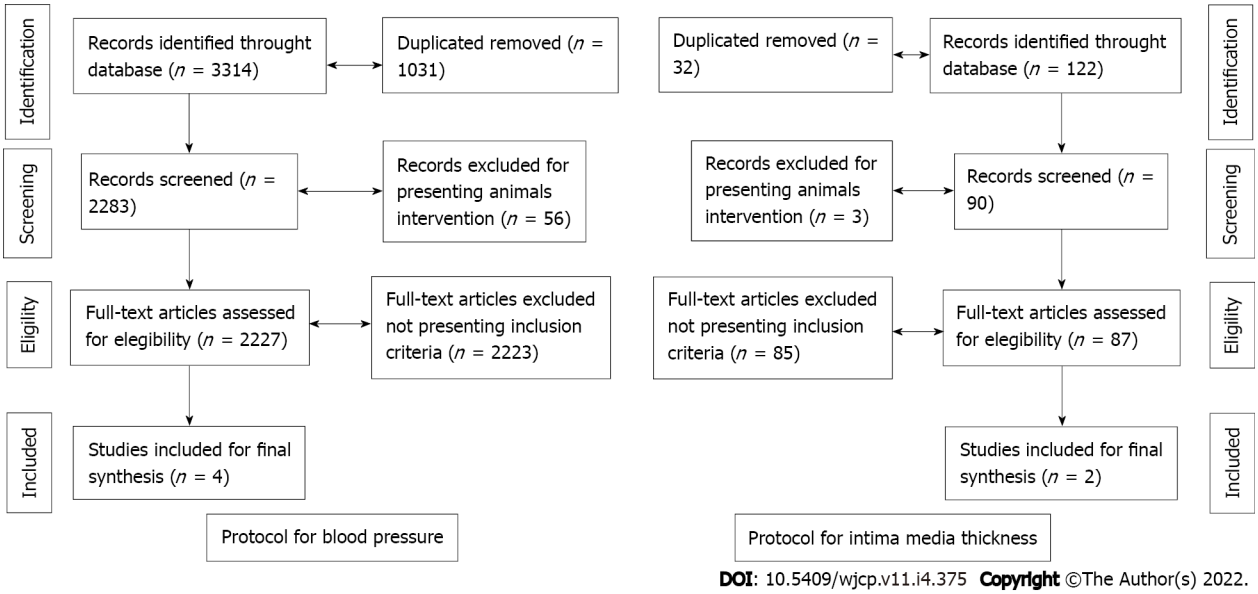
Blood pressure: The four publications included 326 adolescents aged from eight to 18 years (163 engaged in sports and 163 defined as control). All the studies had a longitudinal design and the findings are detailed in Table 1. The four publications varied according to the time of follow-up (ranging from 3 mo to 12 mo) and the sports considered included soccer, swimming, judo, karate, kung fu, gymnastics, basketball, track and field and baseball. All studies were published from 2018 to 2021.

In an individual way, studies did not show relevant changes through the follow-up for SBP and DBP. However, the meta-analysis model with the sum of all studies identified a decrease in DBP in favor of the sports participation group [-1.67 mmHg (95%CI: -2.90 to -0.43)].

IMT: The two papers included 402 adolescents aged from 11 years to 17 years. Both studies had a longitudinal design and the findings are detailed in Table 2. The studies were conducted between 2018 and 2020 and both recorded a 12-mo follow-up. No relevant changes were observed between sports participation and control groups in either the analysis of the individual results or in the meta-analysis model (Figure 2A and D).

Quality assessment

All 6 studies that met the inclusion criteria and from which data were extracted, presented a quality rating between good (Cayres-Santos 2020 and 2018) and high quality (Seabra 2020 and Vasconcellos). All studies clearly defined the objectives, the participants included, inclusion/exclusion criteria adopted, independent variables, outcome measures and exposure status (sport), along with training history. No studies reported investigators being blinded to participant sport/training exposures.



DOI: 10.5409/wjcp.v11.i4.375

Figure 1 Flowchart.

DISCUSSION

The aims of this review were to synthesize and analyze the available literature about the impact of sports participation on cardiovascular outcomes in children and adolescents, particularly blood pressure and intima media thickness.

For blood pressure, only four studies met the inclusion criteria. The limited number of longitudinal studies considering the impact of sports participation on cardiovascular health of pediatric groups highlights the absence of data assessing the impact of physical exercise in the real world mainly because sports participation is the most common manifestation of physical exercise in the pediatric groups[22]. Most of the literature available on this issue relies on exercise protocols carried out in research laboratories and limits application in non-laboratorial settings.

In terms of findings, sports participation seems to be related to lower DBP. In fact, the beneficial impact of physical exercise on blood pressure of obese children and adolescents seems relevant but is still unclear in non-obese groups[26]. In fact, the pathways linking physical exercise and reductions in blood pressure strongly rely on the presence of obesity mainly due to its pro-inflammatory role in the organism[26]. The four included manuscripts considered children and adolescents with and without obesity which demonstrates the potential of sports participation to affect blood pressure in non-obese children and adolescents. However, the reduced number of manuscripts limits further interpretations of the findings.

For intima media thickness, sports participation was not significantly related to any modifications. Among adults, the literature recognizes that physical exercise improves the morphometry of arteries (arterial diameter increases improving dilation capacity which leads to reduced wall thickness)[27]. Thus, regular engagement in physical exercise is pointed out as effective in primary and secondary prevention strategies to reduce arterial wall thickness and arterial stiffness, especially in at-risk populations[27,28]. However, in our study with pediatric groups, both studies were carried out by the same research team and only cohort studies were found (no randomized clinical trials) which also limits further interpretations.

Limitations

In terms of limitations, some aspects should be considered. First, our search was restricted only to the English language, not considering manuscripts published in different languages. Second, some relevant data in our meta-analysis (*e.g.*, standard deviation of the difference) were estimated by the authors and not provided by the authors of the publication considered in the meta-analysis. Third, the reduced number of publications limits further inferences about the findings.

CONCLUSION

In summary, although sports participation seems to be related to improvements in blood pressure (diastolic), the literature assessing the impact of sports participation on cardiovascular health in children

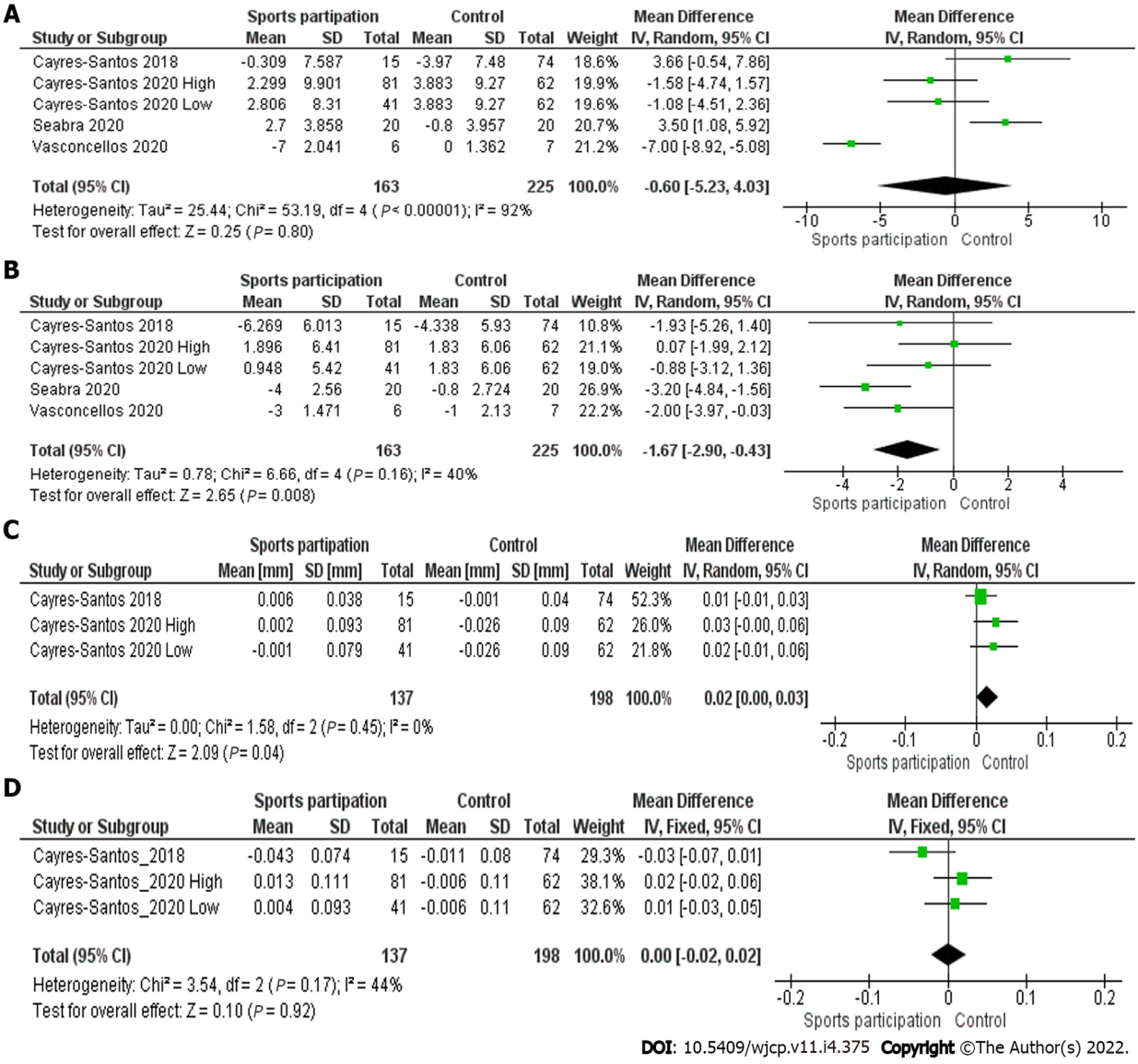


Figure 2 Sports participation *vs* control. A: Sports participation *vs* control for systolic blood pressure; B: Sports participation *vs* control for diastolic blood pressure; C: Sports participation *vs* control for carotid intima media thickness; D: Sports participation *vs* control for femoral intima media thickness.

and adolescents is extremely scarce.

ARTICLE HIGHLIGHTS

Research background

Adolescents are commonly engaged in sports but its impact on pediatric health is poorly explored in the literature.

Research motivation

There are many adolescents engaged in sports around the world and many organizations recommend sports participation as promoters of health among adolescents. However, little is known about its impacts on pediatric health.

Research objectives

To identify in the literature the potential benefits of sports participation on the cardiovascular health of children and adolescents.

Research methods
We ran a systematic review with meta-analysis.

Research results
Sports participation is related to blood pressure but not related to intima-media thickness. However, the amount of literature about the issue is extremely scarce.

Research conclusions
The literature assessing the impact of sports participation on cardiovascular health in children and adolescents is extremely scarce and it is unclear its impact on pediatric health.

Research perspectives
We hope these findings will be useful to motivate researchers to expand the amount of data about the impact of sports participation on the cardiovascular health of pediatric groups.

FOOTNOTES

Author contributions: Torres W, Maillane-Vanegas S, Urban JB and Fernandes RA were involved in the conception, data collection, performing the analysis and interpretation of data.

Supported by FAPESP, No. 2015/19710-3 and No. 2018/22593-7; FAPESP to Wésley Torres, No. 2018/09131-4; and CNPq, No. 2893293992696924.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: Brazil

ORCID number: Wesley Torres 0000-0001-6765-0516; Santiago Maillane-Vanegas 0000-0002-4780-6541; Jacqueline Bexiga Urban 0000-0002-4937-6776; Romulo Araujo Fernandes 0000-0003-1576-8090.

S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Fan JR

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ISSN 2219-2808 (online)

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2022 September 9; 11(5): 385-436

Published by Baishideng Publishing Group Inc

WJCP

World Journal of Clinical Pediatrics

Contents

Bimonthly Volume 11 Number 5 September 9, 2022

World Journal of Clinical Pediatrics

Bimonthly Volume 11 Number 5 September 9, 2022

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INDEXING/ABSTRACTING

The *WJCP* is now abstracted and indexed in PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Pediatrics

ISSN
ISSN 2219-2808 (online)

LAUNCH DATE
June 8, 2012

FREQUENCY
Bimonthly

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World J Clin Pediatr 2022 September 9; 11(5): 385-404

DOI: 10.5409/wjcp.v11.i5.385

ISSN 2219-2808 (online)

FRONTIER

Childhood constipation: Current status, challenges, and future perspectives

Shaman Rajindrajith, Niranga Manjuri Devanarayana, Marc A Benninga

Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Khayyat YM, Saudi Arabia; Shahini E, Italy; Tong WD, China

Received: November 6, 2021
Peer-review started: November 6, 2021
First decision: December 12, 2021
Revised: January 24, 2022
Accepted: July 6, 2022
Article in press: July 6, 2022
Published online: September 9, 2022

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Abstract

Constipation in children is a major health issue around the world, with a global prevalence of 9.5%. They present to clinicians with a myriad of clinical signs. The Rome IV symptom-based criteria are used to diagnose functional constipation. Functional constipation is also a huge financial burden for healthcare system and has a detrimental impact on health-related quality of life of children. There are various risk factors identified globally, including centrally connected factors such as child abuse, emotional and behavioral issues, and psychological stress. Constipation is also precipitated by a low-fiber diet, physical inactivity, and an altered intestinal microbiome. The main pathophysiological mechanism is stool withholding, while altered rectal function, anal sphincter, pelvic floor, and colonic dysfunction also play important roles. Clinical evaluation is critical in making a diagnosis, and most investigations are only required in refractory patients. In the treatment of childhood constipation, both nonpharmacological (education and demystification, dietary changes, toilet training, behavioral interventions, biofeedback, and pelvic floor physiotherapy), and pharmacological (osmotic and stimulant laxatives and novel drugs like prucalopride and lubiprostone) interventions are used. For children with refractory constipation, transanal irrigation, botulinum toxin, neuromodulation, and surgical treatments are reserved. While frequent use of probiotics is still in the experimental stage, healthy dietary habits, living a healthy lifestyle and limiting exposure to stressful events, are all beneficial preventive measures.

Key Words: Constipation; Children; Functional gastrointestinal disorders; Psychological stress; Treatment; Surgical interventions

Core Tip: Constipation is a public health problem. It has a high prevalence and a multitude of risk factors. The main pathophysiological mechanisms are stool withholding and colonic and anorectal dysfunction in younger and older children, respectively. Constipation is a clinical diagnosis based on the Rome IV criteria. Polyethylene glycol-based therapy is the mainstay in the management of constipation, while other osmotic and stimulant laxatives are used as adjunct therapies. Colonic washouts and surgical interventions are reserved for refractory constipation. A well-planned preventive strategy is useful in preventing functional constipation in children and would be able to reduce healthcare costs and improve health-related quality of life.

Citation: Rajindrajith S, Devanarayana NM, Benninga MA. Childhood constipation: Current status, challenges, and future perspectives. *World J Clin Pediatr* 2022; 11(5): 385-404
URL: https://www.wjgnet.com/2219-2808/full/v11/i5/385.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i5.385

INTRODUCTION

Childhood functional constipation (FC) is characterized by the presence of infrequent, and painful bowel motions, fecal incontinence, stool withholding behavior, and occasional passage of large diameter stools. Epidemiologically it amounts to a global health problem as developed and developing countries show a high prevalence[1]. Children with constipation suffer from a variety of symptoms unrelated to their gastrointestinal system and the disease detrimentally affects their quality of life, often unrecognized by the healthcare systems[2]. A large sum of public funds is also being spent on caring for children with constipation due to repeated hospital admissions, emergency room visits, and regular clinic visits because of recurrent exacerbations of their symptoms[3]. All these factors demand a fresh look at childhood constipation. Therefore, in this frontier article, we critically review the current literature to develop a new paradigm on epidemiology and risk factors, pathophysiology, investigations, and management of children with constipation.

Identifying children with constipation: The Rome criteria

Constipation had been defined using a large number of definitions. An unambiguous, universal definition was needed for epidemiological, pathophysiological, and clinical trials at the turn of the century. These demands paved the way to defining functional gastrointestinal disorders (FGIDs) in the Rome process. In 2006, Rome III criteria were established to diagnose childhood constipation. The duration of constipation was reduced from 3 mo used in Rome II criteria to 2 mo, clearly defining constipation in a more practical way[4]. Rome III criteria were more useful in clinical diagnosis of constipation in children and has a good construct validity. However, the inter- and intra-observer reliability of Rome criteria has been poor, indicating the necessity to develop more robust, clinically valuable criteria[5]. The Rome IV criteria were released in 2016[6] (Table 1). Apart from changing the duration of symptoms from 2 mo to 1 mo from onset to diagnosis, the other criteria remain as the same in Rome III. The change has not increased the number of children diagnosed with constipation, and both Rome III and Rome IV criteria were in excellent agreement[7]. However, the reduction of the duration of symptoms required to diagnose constipation is an important move as it is essential to start therapeutic interventions as early as possible to minimize both physiological and psychological consequences of late diagnosis and treatments.

Epidemiology

FC is a common FGID throughout childhood. In the last 2 decades, several systematic reviews reported that the prevalence of FC changes with the definition used, but prevalence does not change with age or sex and FC is found all over the world. The prevalence of FC is lower in Asian children compared to American and European children. Although the exact reason for this observation is not clear, it is possible that dietary, cultural factors, and social factors related to toilet training may play a role[1,8]. The relationship between socioeconomic status and FC is controversial. Several studies have reported that FC is not associated with low level of parental education, low family income, or maternal and paternal employment[9,10]. However, a Nigerian study reported a higher prevalence among children

Table 1 Rome IV diagnostic criterial for constipation in children

Diagnostic criteria must include at least 2 of the following features of constipation in a child with a development age of at least 4 yr with insufficient criteria to diagnose irritable bowel syndrome
Two or fever defecations in the toilet per week
History of retentive posturing or excessive volitional stool retention
History of painful or hard bowel motion
Presence of a large fecal mass in the rectum
History of large diameter stools which may obstruct the toilet
After appropriate evaluation, the fecal incontinence cannot be explained by another medical condition

with low social class[11]. Other important factors reported in epidemiological studies include positive family history and health problems among family members[9,10]. Recent studies using Rome IV criteria reported a significantly high prevalence of FC in infants and young children. A study from China noted that 7% of children aged 0-4 years were suffering from FC and among infants in Malaysia it was 1.1% [12,13]. A systematic review on FGIDs in infants and toddlers reported a prevalence of FC as 11.6% at the age of 3 mo according to Rome III criteria[14].

Risk factors for constipation

Several risk factors for FC have been identified. All these factors finally lead to anorectal dysfunction and fecal retention in the rectum and the colon leading to passage of infrequent, hard, and painful stools. It is understood that FC is a disorder of gut brain interactions. Therefore, the risk factors involving childhood FC is divided into two main categories namely, centrally mediated and gut related mechanisms.

CENTRAL RISK FACTORS

Stressful life event

Subtle perceived stressors, such as separation from best friend, failure in exam in school, being bullied at school, and change of school and home related stressors, such as divorce or separation of parents, loss of job of a parent, and severe illnesses in the family may precipitate FC[15]. Other home related risk factors reported were frequent domestic fights, marital disharmony, and sibling rivalry[16,17].

Abuse and child maltreatment

Psychological trauma associated with abuse and maltreatment is known to associate with FC. A study from Sri Lanka reported exposure to all three major forms of abuse (physical, emotional, and sexual) predispose children to develop FC[18]. It also showed that these children had more severe bowel symptoms and somatization. At the molecular level, abuse influences DNA methylation and lead to changes in epigenetic structure and mechanisms[19]. Stress generated during the period of exposure to abuse and psychological influences that last longer and changes in the epigenetic structure may contribute to permanent alterations in the dialogue between the brain and the large bowel leading to FC.

Other psychological and behavioral factors

Studying children with FC using the child behavior check list, several authors reported behavioral traits such as internalization and externalization are more frequent among these children[20,21]. FC is also associated with psychological maladjustment, anxiety, and depression[22-24]. Using the strength and difficulty questionnaire, Cagan-Appak and co-workers[25] noted emotional and peer problems to be more common among children with FC.

Parental rearing style and psychological state

The rearing style of parents is a significant factor during the early life of a child, particularly during the time of toilet training. Parents with high autonomy may try to train their children too strictly and parents with lower autonomy could neglect toilet training leading to fecal retention and constipation.

Studies have noted that parents of children with FC have strict and authoritative parenting styles and are over protective and have rigid attitudes[21,25,26]. In addition, FC in children is also associated with depression and anxiety of parents[25]. All these factors could negatively affect the developing minds of children, adversely affecting their brain-gut connections and lead to FC.

Toilet training

Poor toilet training is a major risk factor for the development of FC in toddlers. Toilet training/potty training should be started between 18-30 mo[27]. However, socioeconomic factors and cultural norms also play a significant role in determination of the timing. Indeed, a comparative study between children from Vietnam and Sweden reported that toilet training was started at 6 mo of age in 89% of Vietnamese children and was achieved in 98% of children by 24 mo, whereas only 5% of Swedish children had started training by 24 mo[28]. Some young children develop stool toileting refusal due to fear of defecation using the toilet or strained family dynamics which enhances withholding behavior [27].

PERIPHERAL RISK FACTORS

Diet

Several dietary factors have been identified as increasing the risk to develop FC. Fiber is an important component of the human diet. Several studies have shown an association between consumption of a diet low in fiber content, including fruits and vegetables, and FC in children[9,10,29]. An observational study noted an association between consumption of fast food and FC[30]. Cow's milk protein allergy is also considered as a potential risk factor for FC in children. Several studies have reported the association between consumption of cow's milk and FC[31-33]. In an elegant study, Borrelli *et al*[32] showed that children with cow's milk allergy-related constipation had increased rectal mast cell density and increased spatial interaction between mast cells and nerve fibers. In addition, anorectal motor abnormalities were found which may result in constipation. These abnormalities resolved on an elimination diet.

Physical activity

Physical activity is an integral part of day-to-day life and has a number of positive health benefits including improved cardiometabolic and bone health. Sedentary lifestyle has been associated with FC [30,34]. Likewise, others have also noted the beneficial effects of physical activity in preventing FC[35, 36].

Abnormal microbiota

The microbiome of the large intestine plays a crucial role in health and disease. Its concentration is estimated up to 10^{11}-10^{12} cell/g luminal content in the large bowel[37]. This large body of live organisms serves the human body with a variety of physiological functions including digestion and absorption, immunity, prevention of growth of pathogenic organisms, and production of multiple bioactive products. In addition, the microbiome significantly contributes to the stool bulk. de Meij and co-workers [38] reported increased Bacteroides (*B. fragilis, B. ovatus*) and Bifidobacteria (*B. longum*) in children with FC. Another study reported increased Bifidobacteria and Clostridia in children with FC[39]. In contrast a reduction of Bifidobacteria and Lactobacilli were noted in adults with FC[40]. When summarizing these data, it is not possible to clearly identify a pattern of organisms associated with FC. Therefore, there is no definitive evidence that the microbiome contributes significantly to predispose children to develop FC.

Pathophysiology

The etiology of FC in children is largely unknown. However, the understanding of the potential pathophysiological mechanisms is rapidly advancing with the aid of evolving novel technological advances, such as high resolution anorectal and colonic manometry and functional magnetic resonance imaging (fMRI) imaging. Growing evidence suggests that voluntary withholding, anorectal dysfunctions (altered sensation, increased compliance, anal achalasia, and dyssynergic defecation), colonic dysfunctions (altered electrophysiology and altered motility), and central mechanisms operating through the brain-gut-microbiota axis and hypothalamo-pituitary-adrenal axis contribute to the pathophysiological mechanisms.

STOOL WITHHOLDING

Stool withholding is the commonest pathophysiological mechanism for developing FC in young children. Faulty toilet training and painful defecation due to passage of hard and large fecal masses lead children to withhold stools. The rectal mucosa, which is designed to absorb water in stools, absorbs water in feces, and the fecal mass in the rectum becomes rock hard and difficult to evacuate. Occasional passage of the fecal mass causes pain in the perianal region, which further aggravates withholding. The rectal wall stretches due to the enlarging fecal mass and accommodates more fecal matter, sometimes leading to a megarectum, which further reduces the desire to pass stools, and augmenting symptoms

[41]. Stretched rectal walls may lose its normal contractility, which is necessary to propel feces. All these pathophysiological factors set up a vicious cycle of stool withholding, painful defecation, and alteration of rectal physiology.

ALTERED RECTAL COMPLIANCE

Increased rectal compliance was noted in children with long-standing fecal impaction. It is difficult to determine whether altered rectal compliance is a primary pathology leading to fecal impaction or secondary to bowel damage caused by prolonged fecal stasis. Children with higher rectal compliance have more severe symptoms, such as fecal incontinence[42]. However, it had been shown that increased rectal compliance has no relationship to the treatment success by noticing that children with high rectal compliance also recovered fully despite their abnormal physiology[42]. In addition, it is important to note that high rectal compliance persists in some children despite them being successfully treated and having no features of FC for many years[43].

ANAL SPHINCTER AND PELVIC FLOOR DYSFUNCTION

During the act of defecation, when the intra-rectal pressure rises to a critical point anal sphincters need to be relaxed to facilitate expulsion of feces. In a subset of children with FC, a paradoxical contraction of external anal sphincter was observed with an increase of intra-rectal pressure, widely known as dyssynergic defecation. Both conventional manometry and the novel three-dimensional high-resolution anorectal manometry have shown the existence of dyssynergic defecation due to dysfunction of the sphincter complex, puborectalis muscle, and internal anal sphincter achalasia[44]. Internal anal sphincter achalasia is a rare condition, which could present with refractory FC. The exact pathophysiological mechanism has not been delineated and the condition is thought to be due to altered intramuscular innervation leading to a dysfunctional anal sphincter[45].

COLONIC DYSFUNCTION

One of the main physiological functions of the colon is to store and propel fecal matter. Several pathological processes, such as neuropathies, myopathies, and reduction of the number of Intestinal Cells of Cajal, which are considered as the pacemaker cells of the large intestine, could contribute to poor colonic transit. Studies have shown that children with intractable constipation have slow colonic transit using nuclear transit studies[46]. Other methods, such as conventional and high-resolution colonic manometry studies, have shown the lack of high amplitude propagatory contractions, reduction in retrograde cyclic motor pattern, and failure to induce a meal response with cyclic motor pattern in children with constipation[47]. Accumulation of feces might lead to dilatation and elongation of the colon leading to premature termination of high amplitude propagatory contractions and the release of nitric oxide, which inhibits myenteric neurons inducing secondary colonic dysfunction[48].

IMPACT OF FC

Economic and burden on hospitals

Being one of the commonest FGIDs, FC has serious ramifications on existing healthcare systems across the world. Emergency room visits for fecal impaction and abdominal pain, regular clinic visits, regular medications (which could be needed for months), sophisticated investigations, such as anorectal and colonic manometry, and occasional surgical intervention in refractory cases, contribute to the cost. In addition. analysis of national emergency department data from the US showed that fecal impaction due to FC is an important reason to visit the emergency room[49]. In a birth cohort study of children younger than 5 years, FC was reported to have the highest number of first-time medical visits compared to other chronic gastrointestinal disorders, including abdominal pain and gastroesophageal reflux[50]. A study conducted in Victoria, Australia, noted that FC represented 6.7% of annual hospital admission with annual cost of 5.5 million Australian dollars[3]. Using a nationally representative household survey, the annual cost of managing FC in children in the US was noted to be 3.9 billion for urinary stone disease[51]. All these studies indicate the economic burden of FC on healthcare systems and on national healthcare expenditure.

QUALITY OF LIFE AND IMPACT ON EDUCATION

Health related quality of life (HRQoL) is an indirect measure of the impact of a disease in a given individual. It is calculated as a composite numerical figure, including several components such as social, emotional, physical, and school functions. HRQoL has also been identified as one of the secondary outcome measures in clinical trials of FC. Several studies have reported poor HRQoL in children with FC. In a case-controlled study, Youssef reported that children with FC have a lower HRQoL than children with severe organic diseases, such as inflammatory bowel disease or gastroesophageal reflux, indicating the magnitude of the problem[52]. A hospital-based, case-control study from China also reported poor physical, emotional, social, and school related quality of life in children with FC[53]. A recent systematic review and a meta-analysis has clearly emphasized the negative impact of FC on HRQoL in children[2]. There are multitude of reasons for this observation. Symptoms of FC, such as pain during defecation and lower abdominal discomfort due to fecal impaction, could be troublesome to children. Associated fecal incontinence (FI) also leads to significant embarrassment and shame. Finally, psychological comorbidities associated with FC, including emotional and behavioral issues, maladjustment, and abnormal personality traits, also could negatively affect the quality of life of children[20,22,23].

Clinical evaluation

A thorough history and a complete physical examination are sufficient to diagnose constipation. The main components of the clinical history are given in the Table 2. The modified Bristol Stool Scale Form can be used to identify the type of stools in children to facilitate the diagnosis[54]. A complete physical examination, specifically designed to spot general growth and dysmorphic syndromes that could be associated with constipation, should be undertaken as a part of clinical evaluation (Table 3). Alarm features that indicate possible organic diseases also will be revealed during clinical evaluation (Table 4). Presence of such features demands further evaluation of the child for possible organic disorders. In the majority of children with FC, it is not necessary for such investigations; however, a thorough understanding of anorectal physiology, neurophysiology, and morphology is essential when symptoms become refractory despite adequate medical interventions.

COMMON INVESTIGATIONS

Several reviews have summarized the value of plain abdominal radiograph in identifying FC[55,56]. According to these reviews and clinical experiences, a plain abdominal radiograph does not provide any useful insights for management. Similarly, most of the routine blood tests, such as thyroid function tests, screening for cow's milk allergy or celiac disease, and checking for electrolyte abnormalities (hypokalemia, hypercalcemia) are not very helpful in day-to-day management of FC[55].

COLONIC FUNCTION

Colonic transit time

Colonic transit studies measure the ability of the colon to propel fecal matter and are useful in assessing overall colonic motor function. Delayed colonic transit time (CTT) was noted in children with FC due to anorectal dysfunction as well as colonic dysfunction[57]. Currently CTT is utilized only to differentiate constipation associated fecal incontinence from functional nonretentive fecal incontinence when a clinical differentiation is not possible[56].

Colonic manometry

Colonic physiology in children with FC is poorly understood. High-resolution colonic manometry is a valuable method to study physiological function, including motor and propulsive activity of the colon. In the beginning, the fasting motility is recorded, and the gastrocolic reflexes are assessed after a meal. Bisacodyl is instilled into the colon only when high amplitude propagatory contractions are not identified after a meal. Absence of high amplitude propagatory contractions, generalized colonic hypomotility, absence of response stimulant laxatives, and lack of increase in the cyclic retrograde propagatory motor patterns after a test meal are characteristic features in children with FC indicating neuromuscular dysfunction. In addition, premature termination of the propagation of contractions possibly indicates the presence of a segmental dysmotility[58]. These observations are helpful in decision making in management, such as surgery of refractory cases. However, there are several limitations, including limited availability, need for general anesthesia, high initial cost, and lack of normal data in children.

Table 2 Clinical history-taking

Component and subcomponents
Onset of symptoms and duration of the disease
Bowel habits
Frequency of stools
Nature of the stools
Fecal incontinence
Blood in stools
Passage of meconium
Other associated symptoms
Withholding behavior
Somatic symptoms
Past medical and surgical history
Bowel surgeries
Medications
Neuromuscular diseases
Dietary history
Fiber continent in the diet
Frequency of junk food
Family history
Psychological history
Developmental history

ANORECTAL FUNCTION

Anorectal manometry

Anorectal manometry provides details on the length of the anal canal, rectal sensation, and squeeze sphincter pressures, rectoanal reflexes, and pressure changes in attempted balloon expulsion mimicking defecation. However, its main use is to exclude Hirschsprung disease in young children with constipation by demonstrating the absence of the rectoanal inhibitory reflex[55]. It is generally measured using either solid state or water perfused catheters.

Wireless motility capsule

The wireless motility capsule (WMC) is useful in measuring the transit through the different parts of the gastrointestinal transit. It is a non-invasive test that does not expose the patient to radiation. The pediatric studies using WMC, on the other hand are still in the early phase and have only been described as case studies[59]. The test is well tolerated up until the age of 8 years. WMC is beneficial in detecting the delayed colonic transit time in children with refractory constipation, and the results show a strong correlation with colonic transit time evaluated using radiopaque markers[60]. Therefore, the utility of WMC in children with FC should be investigated in future studies, particularly when FC is resistant to standard management strategies.

OTHER INVESTIGATIONS

Lower GI contrast studies in children are used to differentiate FC from Hirschsprung disease and assess the length of the aganglioinic segment in Hirschsprung disease. However, the test is insensitive, and once a transitional zone is detected, a biopsy is needed to confirm the diagnosis. Defecography is not useful in the day-to-day management of constipation in children as the procedure exposes children to a significant amount of radiation and rectoceles, and rectal intussusceptions are rare in children. Similarly endoscopy is also not recommended in children with FC[61]. Although the use of ultrasonography in diagnosing FC has been reported, further refinements of the technique are needed before it is used in

Table 3 Physical examination

Component and subcomponents
General examination
Assessment of growth
Assessment of development
Abdominal examination
Abdominal distension
Surgical scars
Palpable fecal masses
Perianal observation
Position of the anus
Perianal excoriation and dermatitis
Scars, fissures, and tags
Patulous anus
Neurological evaluation
Spine
Lower limb neurological assessment

Table 4 Red flag features and their clinical relevance

Features and subfeatures
Hirschsprung disease
Delayed passage of meconium
Positive family history
Ribbon like stools
Significant abdominal distension
Child sexual abuse
Extreme fear of anal examination
Scars in the perianal region
Fissures in children > 2 yr of age
Neurological abnormalities
Hair tuft/hemangioma/scars on spine
Abnormal anal and cremasteric reflex
Deficiencies in lower limb neurology
Developmental delay
Other organic disorders
Bilious vomiting
Blood in stools
Failure to thrive
Malposition of the thyroid gland

current clinical practice[62]. MRI of the spine is only indicated in children who show features of intractable constipation and features suggestive of spinal anomaly indicated by a tuft of hair, hemangiomas, or scars in the lower spine and neurological signs in lower limbs.

Management

Clinical management of constipation has several facets. The main approaches are non-pharmacological interventions (education and demystification, dietary adjustment, toilet training, behavioral interventions, use of biofeedback, and pelvic floor physiotherapy), pharmacological interventions (oral and/or rectal laxatives, including novel drugs such as prucalopride and lubiprostone), and surgical interventions (antegrade enema and bowel resection), and other novel modalities, such as neuromodulation (Figure 1). The majority respond to one or combination of above-mentioned therapeutic strategies. It is crucial to understand that untreated or poorly managed children with FC tend to have significant complications. Therefore, it is quite important to treat these children effectively at the early stages to relieve symptoms.

POOR PROGNOSTIC FACTORS

Presence of poor prognostic factors may interfere with treatment success. Table 5 provides the possible factors that could influence prognosis[55]. It is imperative that the clinician looks into these factors at the initial assessment and use these factors in decision making while determining therapeutic options.

CLEAN UP THE RECTUM AND COLON

The majority of children with FC have a large fecal mass in their rectum. Therefore, the first step in the management is to clean up the rectal fecal mass and the impacted colon as much as possible. This facilitates the passage of stools during the maintenance phase as the colon and rectum impacted with hard fecal matter may not respond to the drugs commonly used in the management of FC. In a comparative study, both polyethylene glycol (PEG, 1.5 g/kg) and enemas for 3-6 d were equally effective in disimpaction. Both modalities had similar frequency of adverse effects with the exception of fecal incontinence, which was significantly more common in the group receiving PEG[63]. However, the oral route is generally well tolerated in children and therefore should be the first line therapy when available. In children where medical therapy is not effective or the rectum is impacted with an enormous scybalous, manual evacuation of impacted feces in the rectum is recommended.

MAINTENANCE THERAPY

In the maintenance stage, children are encouraged to pass stools regularly while using laxatives for at least 2 mo. This is to keep stools soft and make defecations less painful and less frightening. After disimpaction, this is achieved by using both pharmacological and proven nonpharmacological interventions using a step-down model with gradual tailing off of laxatives. Once regular defecation pattern is established, children with FC are managed with regular use of toilet and a balanced diet with adequate fluid and fiber intake.

NONPHARMACOLOGICAL INTERVENTIONS

Toilet training

The majority (80%-100%) of young children with FC demonstrate features of stool withholding and most of the stool withholders (> 80%) refuse to pass stools in the toilet (stool toileting refusal)[64]. Parents should encourage their child to sit on the potty or toilet for 5 min after wakening and after lunch and dinner. They need to be instructed on proper seating method, how to keep legs and feet relaxed, how to relax the perineum, and how to strain to expel stools using a model toilet or a video. The process needs to be a conscious effort, and using mobile phones or tabs as rewards while sitting on the potty would be counterproductive. It is also imperative to counsel parents to reinforce the positive behavior of the child, especially when the child passes stools in the toilet/potty[65].

Behavioral and psychological intervention

There are many learned behavioral problems related to FC. They include toilet refusal, stress, and fear related to defecation. These behavior traits frequently lead to development and perpetuation of symptoms of FC. Therefore, in some children behavior therapy might be helpful in addition to medical treatment[66]. Novel therapeutic interventions, such as the use of principles of positive psychology, including resilience, optimism, and self-regulation providing a framework to achieve subjective well-being. These treatment modalities, when starting early in the disease process might be able to prevent the patient developing maladaptive coping habits, engage in high physical and psychological symptom

Table 5 Factors negatively affect the prognosis of functional constipation

Factor
Constipation during the 1st yr of life
Longer duration of symptoms before presentation
Low defecation frequency at presentation
Presence of fecal incontinence
Large diameter stools
Stool withholding
Nighttime urinary incontinence
Presence of fecal mass in abdomen/rectum
Prolonged colonic transit > 100 h
Failed balloon expulsion test

reporting, and exhibit poor, costly disease outcomes[67]. These new therapeutic modalities need to be explored in children with FC early in the disease process before bowel and psychological damage take place leading to poor long-term prognosis.

Dietary interventions

Fiber is an important dietary component with significant long term health benefits. The current recommendation from the American Health Foundation is to consume at least "age in years plus 5 g – 10 g" of fiber per day for children over 2 years[68]. Low fiber intake is a risk factor to develop FC in children[10]. In the last decades, 9 different fiber types have been tried as therapeutic agents for children with FC. They include cocoa husk, glucomannan, partially hydrolyzed guar gum, combination of acacia fiber, corn fiber, soy fiber, psyllium fiber, and fructose, galactooligosaccharides, and inulin-type fructose. A systematic review studying 10 randomized trials showed some beneficial effects of using fiber in treating children with FC. However, due to different types of fibers, different study designs, and small sample size, it is difficult to make strong recommendations[69]. Indeed, the ESPGHAN/NAPGHAN guideline recommends ensuring normal amount of dietary fiber intake for children with FC[55].

Probiotics

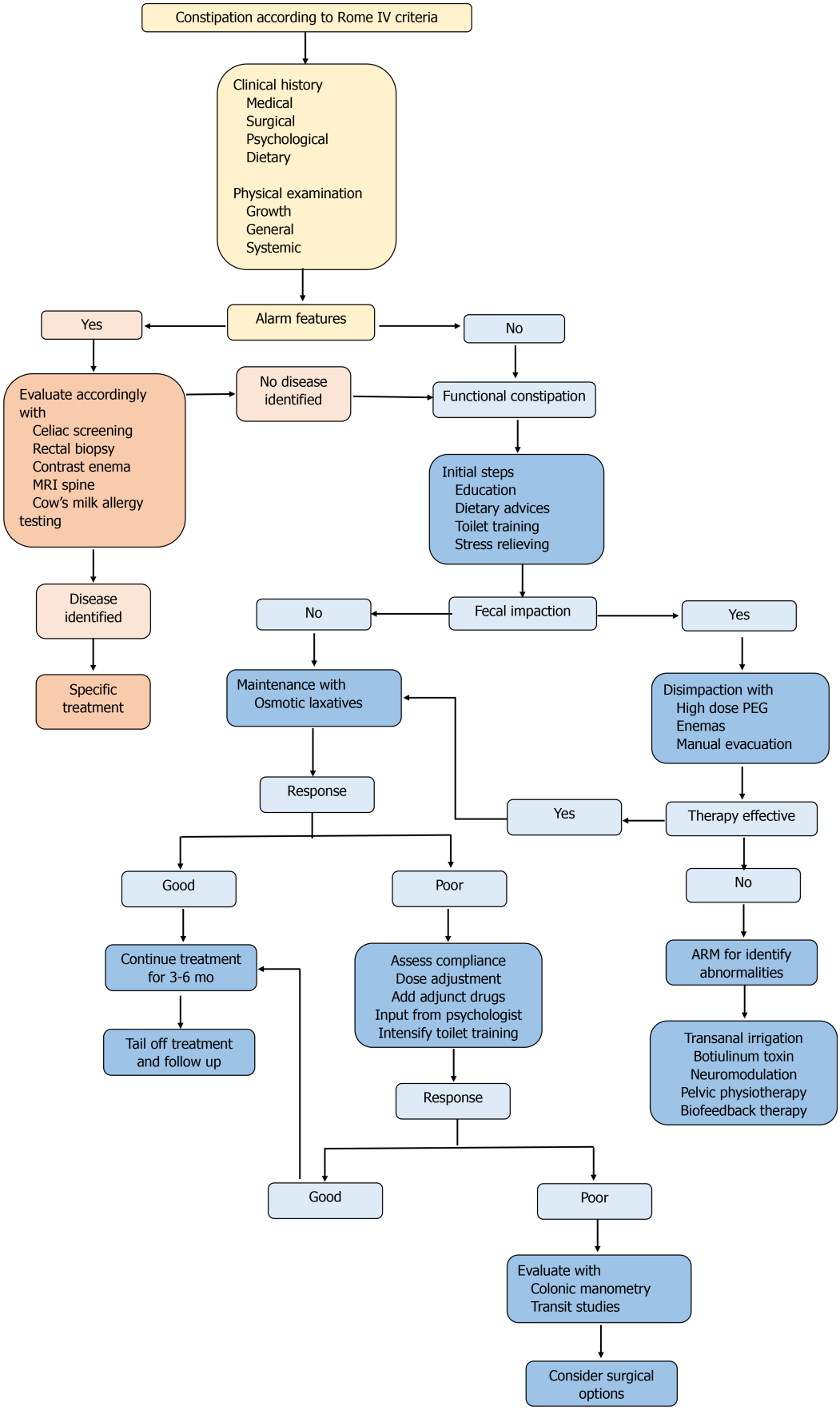
Dysbiosis is known to occur in children, although our knowledge of this important area is still in its infancy[38]. A systematic review published in 2017 assessed seven randomized controlled trials (RCTs) using probiotics for FC. In this systematic review the authors found that *Lactobacillus rhamnosus casei* Lcr35 is no more effective than a placebo in treating FC in children. None of the probiotics were effective in reducing frequency of fecal incontinence[70]. Other studies showed that *Lactobacillus rhamnosus* GG was not effective as adjunct therapy or with polyethylene glycol[71] in treating FC.

Other dietary modifications

Cow's milk protein allergy had been considered as a possible associated factor with FC. Two studies evaluated the clinical utility of cow's milk elimination diet in treating children with FC with variable results[72,73]. A recent trial conducted by Bourkheili *et al*[74], showed the efficacy of cow's milk elimination diet in children who did not respond to laxatives. However, the open-label nature of the study leads to a high degree of bias in their findings. The ESPGHAN-NASPGHAN guideline recommends cow's milk protein-free diet only in laxative resistant constipation and under the guidance of an expert[55]. Increasing water intake or hyperosmolar fluid has no significant effect on defecation frequency or improvement of consistency of stools[75]. The ESPGHAN-ESPGHAN guideline does not support the use of extra fluid intake in the treatment of FC[55]. Other studies of dietary interventions, such as Cassia Fistula emulsion and Descurainia Sophia seeds, showed high risk of bias and, therefore, could not recommended as therapeutic interventions[76,77].

Biofeedback and pelvic floor physiotherapy

Biofeedback gives a visual display of physiological monitoring of anorectal function while providing input by a therapist to retrain anorectal and perineal muscles. A systematic review concluded that biofeedback is not recommended for children with FC[78]. Similarly, the ESPGHAN-NASPGHAN guideline also does not recommend biofeedback as a therapeutic intervention for children with FC[55]. Pelvic floor physiotherapy uses motor relearning. The components of pelvic floor physiotherapy include supporting toilet training, increase awareness of sensation, and pelvic floor muscle training. A



DOI: 10.5409/wjcp.v11.i5.385

Figure 1 Management flow chart of childhood constipation.

pragmatic trial using the Dutch pelvic floor physiotherapy protocol compared pelvic floor physiotherapy plus standard medical care with standard medical care. The primary outcome of the study was defined as the absence of FC according to the 6 Rome III criteria. In this study 24 out of 26 (92.3%) children receiving pelvic floor physiotherapy with standard medical care showed treatment success compared to 17/27 (63.0%) who received standard medical care (adjusted OR 11.7; 95%CI 1.8-78.3; P = 0.011)[79]. However, there are several limitations in this trial, including lack of blinding, small sample size, and alteration and adjustment of the protocol during the trial. Potential benefits of pelvic floor physiotherapy as a therapeutic option for FC need further elaboration.

Pharmacological interventions

Pharmacological interventions are the mainstay of therapy for childhood FC. There are several therapeutic agents that can effectively and safely be used either alone or in combination.

OSMOTIC LAXATIVES

A Cochrane systematic review reported that polyethylene glycol (PEG) was found to be superior to placebo, lactulose, and milk of magnesia to improve stool frequency[80]. In addition, they showed that a high dose of (0.7 g/kg) PEG was more effective at increasing stool frequency than a low dose (0.3 g/kg). The common adverse effects of PEG include flatulence, abdominal pain, nausea, diarrhea, and headache. Another meta-analysis found that PEG is also more effective in disimpaction than non-PEG laxatives, such as lactulose, magnesium hydroxide, and liquid paraffin[81]. Based on the current evidence, PEG is the most suitable drug for both disimpaction and maintenance of FC in children.

There are no RCTs comparing lactulose with placebo. Two trials compared lactulose with liquid paraffin[82,83]. When pooling the data using a fixed-effect model, liquid paraffin was shown to be more effective than lactulose in increasing stool frequency[80]. Other trials comparing lactulose with partially hydrolyzed guar gum found no difference in clinical efficacy between those therapeutic modalities and lactulose[84]. Lactulose is recommended to use as the first line maintenance therapy when PEG is not available[55].

STIMULANT LAXATIVES AND FECAL SOFTENERS

Bisacodyl is a stimulant laxative. It has a local prokinetic effect and stimulates intestinal secretion. Bisacodyl is a useful adjunct drug to osmotic laxatives in treating children with FC[55]. Senna is a natural laxative made from the leaves and fruits of the senna plant and is another stimulant laxative that is frequently used in treating children with FC. In a retrospective chart review from the US, it was noted that senna was effective as a laxative in the treatment of FC, and only 15% of the patients reported significant side effects, including abdominal cramps and diarrhea. None of the patients had to stop the laxative due to adverse effects[85]. Sodium picosulphate is the other available stimulant laxative used in clinical practice. Mineral oil is a time-tested fecal softener and is only recommended as an add-on therapy in the maintenance phase when the response to osmotic laxatives is suboptimal[55].

NOVEL THERAPEUTIC OPTIONS

Several prosecretory agents have shown to be effective in treating constipation in adults. They include prucalopride, lubiprostone, linaclotide, and plecanatide. These agents stimulate secretory function of the intestine at various levels and improve stool consistency and stool volume, leading to increase bowel movements. Prucalopride is a highly affinity 5-HT4 receptor agonist with significant prokinetic properties. Studies in adults have shown beneficial effects of prucalopride in treating chronic constipation[86,87]. However, a large multicenter placebo-controlled randomized trial including 213 children (6-18 years) showed no significant difference in improvement in stool frequency and episodes of fecal incontinence between prucalopride and placebo[88]. Differences in mechanisms of constipation between children and adults, usage of different end points between studies (*e.g.*, inclusion of fecal incontinence in the pediatric study), and inclusion of a large number of children with refractory constipation may have contributed to the lack of response of prucalopride in childhood constipation.

Lubiprostone is a CIC-2 chloride channel activator and cystic fibrosis transmembrane conductance regulator. Studies in adults have shown clinical efficacy of lubiprostone in adults with chronic constipation, as well as IBS-C[89-91]. A large double-blind, placebo-controlled, multicenter study including more than 600 children with FC fulfilling the Rome IV criteria showed that 12 wk of lubiprostone treatment did not result in a statistically significant improvement in bowel movement frequency (to more than three times per week) in children with FC compared to placebo[92]. The reasons for not observing the desirable outcome of the trial may be similar to the prucalopride trial.

Linaclotide and plecanatide are guanylate cyclase C receptor agonists that promote secretion of fluid into the intestine. Although studies in adults show the efficacy of these two drugs in relieving constipation, no pediatric trials have been conducted. A retrospective chart review of 60 children with FC on linaclotide revealed that 45% had a positive response at 2.5 mo after starting the drug. However, about 1/3 of children on linaclotide had adverse events such as diarrhea, abdominal pain nausea, and bloating severe enough to stop treatment[93]. It is imperative to understand why these novel therapies are not working in children and find a way forward. Although the drugs make stools less hard and improve colonic motility by stimulating smooth muscles, none of these drugs address the main pathophysiological mechanisms of FC specially in younger children, *i.e.* stool withholding.

TRANSANAL IRRIGATION

Transanal irrigation systems irrigate the rectum and colon to clear accumulated feces. It is useful in children with constipation with severe recurrent fecal impaction resistant to conventional medical management. Three retrospective studies including children with constipation and FI (both organic and functional) have demonstrated improvement of FI when using transanal irrigation[94,95].

Surgical interventions

Surgical interventions are generally reserved for children whose symptoms are refractory to medical interventions. Around 10% of constipated children referred to a pediatric surgeon require some form of surgical intervention[96]. All these children need colonic and anorectal manometry and contrast enema of the lower bowel to delineate the physiological function and the anatomy before embarking into invasive surgical procedures.

ANTEGRADE CONTINENT ENEMA

In antegrade continent enema (ACE), a stoma is usually created to flush the colon from proximal to the distal direction using several surgical techniques. The initial procedure described was the Malone appendicocecostomy, where the appendix is brought out through the umbilicus, creating a conduit with a valve through which a catheter can be passed to irrigate the colon[97], or cecostomy, where a catheter is kept permanently. Novel techniques, such as creating a neoappendix using a colonic flap, laparoscopic-assisted cecostomy tube insertion, and inserting a percutaneous cecostomy button following interventional radiological procedures, have also been invented to establish the flushing mechanism [98]. A systematic review showed that both procedures (appendicostomy and cecostomy) are equally effective achieving continence (80% *vs* 70%, respectively)[99].

SURGICAL RESECTION AND STOMAS

Several surgical resection techniques have been described in the management of intractable constipation. They include segmental resection, including proctocolectomy with reservoir and ileoanal anastomosis, laparoscopic or open sigmoidectomy with or without ACE, laparoscopic low anterior resection, ileostomy, and colostomy[100]. However, there is no consensus on the definition of intractable constipation, and the type of surgical pathway that should follow. The decision that has to be taken after careful discussion between a motility specialist and pediatric surgeon. The physiological function of the colon needs to be carefully studied using contrast studies, transit studies, defecography and, when available, colonic manometry. However, complications, such as fecal incontinence, persistence of constipation following surgery, leaking from stomas, stoma prolapse, and small bowel obstructions, are known complications of these surgical interventions.

BOTULINUM TOXIN INJECTION

Botulinum toxin A is a neurotoxin, and acts as a muscle relaxant. When injected into intersphincteric area, botulinum toxin relaxes the internal anal sphincter and facilitates the passage of stools. The intervention is reported to be successful in the majority of children with constipation and only a few who received the first dose needed a second injection[58]. Minor complications such as pain, transient urinary and fecal incontinence are known to occur in some children. Large prospective placebo-controlled trials with a long follow-up are needed to evaluate the true effectiveness of this invasive and costly treatment.

NEUROMODULATION

Neuromodulation is an evolving therapeutic modality where a selective group of nerve fibers is electrically stimulated to alter the physiological function of a desired organ through neural activity. This can be achieved using transcutaneous stimulation of the posterior tibial nerve, transabdominal stimulation, and an electrode insertion surgically into the sacral foramen. Sacral neuromodulation improves colonic motility by increasing both antegrade and retrograde propagatory contractions[101,102]. Neuromodulation has been shown to be clinically effective (improving number of bowel motions and reducing frequency of fecal incontinence) in treating children with intractable constipation and slow transit constipation[103,104]. In addition, several systematic reviews have also shown the benefits of neuromodulation in children with constipation[105,106]. However, most of these studies are underpowered with a small number of patients, some were retrospective studies, and the majority had number of biases. In addition, there is no consensus on the frequency of stimulation or the duration of therapy. Therefore, it is difficult to draw firm conclusions in using neuromodulation as a treatment for chronic constipation in children.

Preventive measures

It is important to consider possible preventive measures that could be implemented for reducing incidence of FC in children. It is well known that stress, in any form, predisposes children to develop constipation. These events include minor home and school related events, child maltreatment, and exposure to civil unrest[107]. It is imperative to understand that most of these events are beyond the control of children. Teaching coping strategies with stress should be a part of modern school curricula, and through early psychological interventions, it may be possible to prevent constipation that is associated with psychological stress. In addition, identifying and addressing other psychological factors, such as anxiety, depression, internalization, and externalization, which are common in children with FC, need to be recognized and addressed early as primary or secondary preventive strategies[20,22,25,108]. Indrio and co-workers[109] provided evidence that prophylactic use of probiotics also would be able to prevent developing FC in young children with significant reduction in healthcare cost. The mechanisms of how probiotics play a role in prevention of FC is not entirely evident. However, it could possibly be through improvement of intestinal permeability, reduction of visceral sensitivity, changing mast cell density, and altering the cross talk between the brain and the gut through the brain-gut-microbiota axis. More research into this unexplored area with more convincing evidence would provide a potential window of opportunity to prevent constipation in the future. Improper or inadequate toilet training is a common risk factor for children to develop FC. Raising public awareness regarding the importance of timely toilet training would also help to reduce the prevalence of constipation. Additionally, educating parents and children about the importance of eating a balanced diet with the recommended amount of fiber and avoiding "junk food" is a critical step. Several studies have shown the association between sedentary lifestyle and constipation in children[30,34]. Therefore, encouraging physical activity in children would help in reducing the prevalence of FC. It is critical to recognize that, in today's competitive society, parents are compelled to work longer hours and spend less time with their children. Attention, attachment, appropriate parenting styles, and assisting children in developing desirable core lifestyles by setting a healthy example with proper dietary and physical activity patterns are also helpful in reducing the prevalence of FC.

Way forward into the future

It is evident that FC is a global public health problem with a significant physical, psychological, economic, and societal burden. Furthermore, at individual levels, chronic FC leads to physical and psychological consequences. The HRQoL of children is significantly affected due to both intestinal and extraintestinal symptoms of FC. Therefore, clinicians, and public health experts need to understand the gravity of the problem. Early aggressive, and effective medical therapy and other individualized non-pharmacological treatments need to be commenced as early as possible to prevent progressive bowel dysfunction and psychological consequences. Several therapeutic interventions may be used at the beginning of treatment, with gradual reduction of interventions as the child respond to treatment. Most of the novel investigations are only needed in children who do not respond to initial treatment. High resolution colonic and anorectal manometry are important investigations and will further improve the understanding of pathophysiology of chronic FC in children. In combination with a detailed clinical history and thorough physical examination, these novel investigation modalities reveals most of the pathophysiological processes that a clinician needs in decision making. The key drug in the medical management of FC in children will be PEG during for the foreseeable future. The other novel drugs will only be adjunct therapies. Researchers need to identify this reality, and novel drugs need to be tested in combination with PEG in randomized trials to improve the therapeutic armory. Surgical interventions are only needed in a minority of patients who are having severe and refractory constipation. Most of the described surgical interventions are studied in a non-randomized manner for several reasons. We believe more evidence is needed in major surgical procedures in the future to optimize the management of FC. Clinical validity of novel treatment options, such as pelvic floor physiotherapy and botulinum

toxin injection to the anal sphincter, need to be explored in well-designed randomized trails, as these treatments can be made available to many centers with collaborative training. Preventive measures should be explored widely across the world to minimize societal and economic burden of FC in children.

CONCLUSION

Childhood FC is a common health problem across the globe. The high prevalence is partly due to a multitude of risk factors which are highly prevalent among children. The aetiology of FC in children is not clearly understood. Stool withholding play a major role in developing FC in younger children while anorectal dysfunction, and colonic dysmotility significantly contribute to the development of FC in older children. FC is a clinical diagnosis established using the standard Rome IV criteria after a thorough clinical evaluation using clinical history and physical examination. Although commonly used most of the routine investigations are not helpful in diagnosing or day to day management. Anorectal, and colonic manometry are useful only in children who are refractory to conventional management strategies. The majority of children have fecal impaction when they present to a clinician. The first step in the management is to evacuate the rectal fecal mass either with oral PEG or enemas. The maintenance therapy using either osmotic laxatives alone or osmotic laxatives combined with stimulant laxatives aimed to prevent reaccumulation of fecal matter in the colon and the rectum. Although it may subject to variations, most children recover within 3-6 mo of therapy. Novel pharmacological interventions such as prucalopride, lubiprostone, and linaclotide need further clinical trials to prove their efficacy in children. The surgical options such as antegrade continent enema, creation of stomas, and bowel resection are only rarely needed in children and only reserved for refractory FC. It is imperative to understand that FC contributes to a significant healthcare expenditure, and reduction of HRQoL. Therefore, researchers should focus on developing preventive strategies to alleviate both the societal and healthcare burden of FC in children.

FOOTNOTES

Author contributions: Rajindrajith S developed the concept and wrote the initial manuscript; Devanarayana NM and Benninga MA edited the manuscript with significant intellectual contribution; All authors fulfilled the criteria for authorship established by the International Committee of Medical Journal Editors and verify the validity of the article.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Xing YX
L-Editor: Filipodia
P-Editor: Xing YX

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World Journal of Clinical Pediatrics

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World J Clin Pediatr 2022 September 9; 11(5): 405-407

DOI: 10.5409/wjcp.v11.i5.405

ISSN 2219-2808 (online)

FIELD OF VISION

Rational use of antibiotics in children with diabetic ketoacidosis needs attention

Xu Wang

Specialty type: Medicine, general and internal

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D, D
Grade E (Poor): 0

P-Reviewer: Cure E, Turkey; dildar S, Pakistan

Received: March 14, 2022
Peer-review started: March 14, 2022
First decision: May 11, 2022
Revised: June 20, 2022
Accepted: July 8, 2022
Article in press: July 8, 2022
Published online: September 9, 2022

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Abstract

Diabetic ketoacidosis (DKA) in children may lead to acute kidney injury (AKI). Among 45 children with DKA in our center, eight cases had AKI on admission, and in one child, his kidney function did not recover until 3 mo after discharge. This child was treated with antibiotics (cephalosporin), and we cannot rule out delayed AKI recovery due to the combined effects of the drug and the disease. Pediatricians should be concerned about the impact of nephrotoxic drug and disease interactions on children's kidney function, and need to follow up children with DKA and AKI to determine the development of AKI.

Key Words: Diabetic ketoacidosis; Acute kidney injury; Antibiotics; Nephrotoxic; Follow up

Core Tip: Pediatricians should pay attention to the prevention of further damage to kidney function in children with Diabetic ketoacidosis (DKA) and acute kidney injury (AKI), and it is necessary to rationally use PK model to achieve drug safety. It is of concern that children with DKA and AKI events must be followed up to determine the development of AKI. Risk factors that may further affect kidney function also need to be avoided.

Citation: Wang X. Rational use of antibiotics in children with diabetic ketoacidosis needs attention. *World J Clin Pediatr* 2022; 11(5): 405-407
URL: https://www.wjgnet.com/2219-2808/full/v11/i5/405.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i5.405

INTRODUCTION

Diabetic ketoacidosis (DKA) is a serious endocrine disease in children. DKA in children may present with obvious symptoms of dehydration, and even lead to acute kidney injury (AKI). We observed that among 45 children with DKA in our center, Children's Hospital of Nanjing Medical University, eight cases had AKI on admission, and 2 wk after DKA correction, seven cases had AKI recovery, and one case still had AKI on discharge. At follow-up 3 mo after discharge, the child's kidney function returned to normal. This child was treated with antibiotics (cephalosporin), and we cannot rule out delayed AKI recovery due to the combined effects of the drug and the disease It is suggested that most children with DKA have prerenal volumic reactive injury, and a few children with DKA may experience endogenous renal tubule injury leading to AKI, which may be caused by disease and drug interaction. This highlights the need for rational use of antibiotics in specific disease states.

Because of the limited research on pharmacokinetics, pharmacodynamics and drug-disease interactions in children, drug dose selection for children is extremely challenging. Antibiotic is a kind of drugs with potential kidney toxicity. In the absence of specific dose regimen of antibiotics for children, a simple linear relationship between body weight and drug pharmacokinetics was assumed based on experience, and the dose for children was inferred from adult data. However, in the case with DKA and AKI, the kidney function of children has been impaired, and therapy of antibiotics based on experience may result in overdosing or underdosing. Once the fragile kidney function of children is further impaired by antibiotics therapy, it may exacerbate pharmacokinetic changes, such as antibiotics accumulation, and increased nephrotoxicity. Therefore, pediatricians should be concerned about the impact of nephrotoxic drug and disease interactions on children's kidney function.

The concept of prevention for drug-related kidney injury is important. Detailed history and holistic assessment can help identify the risk of nephrotoxicity from antibiotic therapy. Antibiotic dosages can be determined based on therapeutic drug concentration monitoring (TDM)[1]. However, the limitation of pediatric TDM is that most antibiotic target concentrations are derived from adult patients rather than measured from pediatric data. Pharmacokinetic models (PK) that are used in adults can be extended to pediatric patients through comparative studies of antibiotic pharmacokinetics between children and adults[2]. For the use of nephrotoxic antibiotic, PK model can quantify the effect of kidney injury on drugs[3,4] and promote the optimal use of antibiotics in children with DKA and AKI.

The purpose of this vision is to emphasize that pediatricians should pay attention to the prevention of further damage to kidney function in children with DKA and AKI, and it is necessary to rationally use PK model to achieve drug safety. It is of concern that children with DKA and AKI events must be followed up to determine the development of AKI. Risk factors that may further affect kidney function also need to be avoided.

CONCLUSION

In conclusion, in our study, of the 8 children with DKA complicated with AKI, 7 case did not receive antibiotics and 1 received cephalosporin, and the cephalosporin treated child showed delayed recovery from AKI. The selection of antibiotics in children is more challenging in special disease states, and we emphasize that pediatricians should pay attention to the impact of potentially nephrotoxic drug and disease interactions on children's renal function. Among them, vancomycin and ceftriaxone can be regarded as representative drugs for exacerbating AKI in special disease states, which is worthy of academic attention. In addition, since most antibiotics have varying degrees of renal toxicity, we aim to stress the rational use of PK model to achieve drug safety.

FOOTNOTES

Author contributions: Wang X conceptualized and designed the study, and drafted and revised the manuscript.

Conflict-of-interest statement: All the authors declare that they have no competing interests.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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World Journal of Clinical Pediatrics

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World J Clin Pediatr 2022 September 9; 11(5): 408-418

DOI: 10.5409/wjcp.v11.i5.408

ISSN 2219-2808 (online)

MINIREVIEWS

Children with type 1 diabetes in COVID-19 pandemic: Difficulties and solutions

Yue Shi, Li-Qun Wu, Peng Wei, Ze-Huan Liao

Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): E

P-Reviewer: Abdelbasset WK, Saudi Arabia; Moshref RH, Saudi Arabia; Virarkar M, United States

Received: February 26, 2022
Peer-review started: February 26, 2022
First decision: April 17, 2022
Revised: June 1, 2022
Accepted: August 22, 2022
Article in press: August 22, 2022
Published online: September 9, 2022

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Abstract

Children/adolescents with type 1 diabetes (T1D) require holistic approach and continuous care. However, the coronavirus disease 2019 (COVID-19) pandemic has made challenges for the T1D children and their caregivers, professionals, and the healthcare system. This minireview aims to consolidate and discuss the difficulties and solutions of children with type 1 diabetes in the COVID-19 pandemic. T1D has been the most common type of diabetes in children and adolescents and the last decades has seen a rapid increase in the prevalence of T1D in youths worldwide, which deserves a public concern particularly in the COVID-19 pandemic. As reported in previous studies, T1D is a risk factor related to severe cases, while the virus may induce new-onset diabetes and serious complications. Moreover, restriction strategies influence medical availability and lifestyle, impact glycemic control and compilation management, and thus pose stress on families and health providers of youths with T1D, especially on those with certain fragile conditions. Therefore, special treatment plans are required for children provided by caregivers and the local health system. Latest health tools such as improved medical devices and telemedicine service, as well as a combined support may benefit in this period. This minireview emphasises that continued medical access and support are required to prevent deteriorated condition of children and adolescents with diabetes throughout this pandemic. Therefore, strategies are supposed to be formulated to mitigate the difficulties and stress among this group, particularly in the most at-risk population. Proposed solutions in this minireview may help individuals and the health system to overcome these

problems and help youths with T1D in better diabetes management during such emergency situations.

Key Words: Type 1 diabetes; Pediatrics; COVID-19 pandemic; Diabetes management; Glycemic control; Telemedicine

Core Tip: There are several reviews in the literature discussing the difficulties or solutions to the life of children with type 1 diabetes (T1D). However, this is the first review to collect and analyse the latest studies on which sub-groups of children with T1D are more likely to be influenced, how the coronavirus disease 2019 pandemic affects the treatment of children with T1D and the life of their caregivers, and what measures are supposed to be applied to deal with these dilemmas.

Citation: Shi Y, Wu LQ, Wei P, Liao ZH. Children with type 1 diabetes in COVID-19 pandemic: Difficulties and solutions. *World J Clin Pediatr* 2022; 11(5): 408-418
URL: https://www.wjgnet.com/2219-2808/full/v11/i5/408.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i5.408

INTRODUCTION

Type 1 diabetes (T1D) is a heterogeneous disorder characterized by destruction of pancreatic beta cells, culminating in absolute insulin deficiency. It accounts for 5- 10% of the total cases of diabetes worldwide corresponding to 21-42 million people, while type 2 diabetes (T2D), characterized by a combination of resistance to insulin action and inadequate compensatory insulin secretory response, is the more prevalent category[1]. Particularly, in children and adolescents, T1D has been the most prevalent type of diabetes and 15%-20% of newly diagnosed patients are under age 5. Children with T1D and their caregivers are faced with challenges from various aspects such as physiology, psychology, and development[2].

The coronavirus disease 2019 (COVID-19) has been regarded as a global pandemic since 2020, leading to strict control policy and interrupted health care services, which contribute to challenges such as disruption in follow-up visits, restricted availability of medicines, and changes in lifestyle, particularly for those with chronic illnesses such as T1D[3,4].

Although there have already been some attempts to help to address these dilemmas, a systematic review on this issue has not been carried out. Since there are a large number of children and adolescents with T1D, who have specific concerns during the ongoing pandemic, we review the existing literature, related websites, and relevant guidelines to form this minireview to help resolve key questions in this area.

T1D and its treatments

T1D is a frequent chronic diseases in infants and the most common endocrinal disease in children and adolescents[5]. To diagnose the diabetes syndrome, both the history and check results are clues: A family history of diabetes is important, while a history of previous early childhood deaths or miscarriages is relevant. Pointers in the examination include evidence of sensorineural hearing loss or vision defects or developmental delay. Useful investigations include autoantibodies to glutamic acid decarboxylase, islet cells, audiogram and visual evoked responses, and fasting insulin and C-peptide. Further specialized checks include an echocardiogram, bone marrow aspirate, skeletal survey, and genetic testing[6].

Diabetes management mandates adherence to insulin, balanced diet, regular physical activity, and self-monitoring of blood glucose to achieve good glycemic control and prevent the development of short-term and long-term complications[7]. Pediatric diabetes management needs continuous parental supervision and confronts the whole family in challenges in the daily life, including regular blood glucose monitoring, insulin application, dietary indications, *etc*[8]. To achieve a favorable control, it is necessary to monitor blood sugar on a regular basis in a day, while for the patients who have erratic glycemic control or intermittent hypoglycemia, it is recommended to monitor at least 4 times a day and an additional check should be performed when there are signs or symptoms related to hypoglycemia [8]. In addition, children and adolescents with T1D require multiple daily insulin injections: The major organizations recommend one to two basal insulin injections with at least three regular or rapid acting insulin injections[8].

Unsatisfying metabolic control may result in the acute complications of hypoglycemia and ketoacidosis, poor growth, and chronic microvascular and macrovascular complications. Due to the fact that children and adolescents are more sensitive to a lack of insulin than adults, the youths are at higher risk of a rapid and dramatic development of diabetic ketoacidosis. Episodes of severe hypoglycemia or ketoacidosis especially in young children are risk factors for structural brain abnormalities and impaired cognitive function[9].

Challenges of type 1 diabetes in children during COVID-19 pandemic

Risk of contracting COVID-19 in patients with T1D: Diabetes can affect the immune response to pathogens and thus make patients vulnerable to the infections[10,11]. Diabetic patients are exposed to a higher risk of being infected compared to the healthy group and the risk is even greater in T1D children than in those with T2D, which may be attributed to immune dysfunction, micro- and macro-angiopathies induced by hyperglycemia, and more needs for medical interventions in this group[12,13]. Analyses carried out in many countries revealed that people with diabetes hospitalized for COVID-19 have a greater chance to suffer more severe outcomes, including twice the risk of requiring intensive unit care and increased risk of death[14-19]. It can be attributed to free radical overproduction due to viral infection, which can burden the oxidative stress, leading to pulmonary oxidative injury and inflammation[20]. Furthermore, the virus causes glucose metabolism disorders, which may entangle the pre-existing diabetes in complications[21].

Effect of COVID-19 on development of T1D: Viral infections are associated with the development of pancreatic autoantibodies leading to T1D in genetically susceptible children, and coronavirus family was considered to be an incriminating pathogen[22]. Viral infections trigger autoimmune insulitis and pancreatic β-cell destruction by directly damaging β-cells, increasing the risk of autoantibody generation, and activating cytokine release and T cells[23]. According to previous surveys, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) binds to angiotensin-converting enzyme 2 receptors in the pancreas, consequently damaging islet cells and reduced insulin release[24]. During the COVID-19 pandemic, similar associations have been made for children[25,26].

The data in Figure 1 represent the situation in Western Greece. The median ages of the patients are 10.94 years old and 12.07 years old in pre-COVID-19 years and COVID-19 years, respectively.

Cautions against COVID-19 on complications of T1D: Chloroquine and hydroxychloroquine are increasingly administered to treat COVID-19. However, these drugs may increase the incidence of hypoglycemia in diabetes patients[27]. Chloroquine stimulates insulin secretion, glucose uptake, and glycogen synthase, while hydroxychloroquine decreases insulin degradation, increases intracellular insulin accumulation, and stimulates insulin-mediated glucose transport[27,28]. All these functions can lead to a low blood glucose level and therefore, patients with T1D who use these agents need should be monitored for hypoglycemia (Figure 2).

Risk of diabetic ketoacidosis: COVID-19 can increase the opportunity of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state even in people without previously diagnosed diabetes[29]. Meanwhile, patients with T1D are at a greater risk of developing DKA especially in youths, and there are reports of prevalence of severe DKA in COVID children with established T1D[21,30,31]. Moreover, researchers have found that delayed diagnosis of new-onset T1D can lead to severe DKA, which may be due to reduced clinical visit for fear of being infected by SARS-CoV2, less access to emergency departments, closure of non-COVID-19-related hospital services, preoccupied doctors, and potential changes in access to insulin or self-monitoring of blood glucose test strips[32,33]. Certain features of DKA overlap with viral illnesses in youths and pediatricians should pay attention to symptoms including polyuria, polydipsia, weight loss, and Kussmaul breathing, as well as a fruity odour in breath. Ultimately, the standard of care for DKA to apply intravenous insulin may lead to a dilemma in the present pandemic because it often requires ICU admission. However, beds may be occupied for COVID-19 patients[31,34].

Influence of restriction strategies on individual T1D management: Strict isolation measures interrupt access to routine health care and social activities, thus increasing stress and anxiety among children and adolescents with T1D and their caregivers[4]. Since T1D is dominantly affected by alterations in daily routine, isolation measures pose a negative effect in glycemic control. However, interestingly, several researchers have reported contrary results that there was no deterioration or even improvement in glycemic management (Table 1).

Factors that worsen glycemic control: Difficulties in access to medical care was particularly prevalent in families with a lower socio-economic condition[35,36]. The COVID-19 pandemic has led to an economic crisis, and those whose financial stability was already difficult were first to suffer[37]. Researchers found that minority children had a higher glycosylated hemoglobin (HbA1c) level both in the pre-pandemic and the lockdown period than white race[38-40]. Similarly, patients with medical aid had a notably higher HbA1c and increase in HbA1c during the lockdown than those with private insurance[38]. Other publications have also indicated that youth whose families are in a disadvantaged financial condition

Table 1 Pros and cons of various methods in different groups

Target group	Methods	Pros	Cons
Patients	Routine glycemic management	Provide a more convenient and comfortable alternative	
	Sick day management	Avoid glycemic fluctuations and subsequent risk of complications	Need regular education and more rigorous adherence
	Psychosocial aids	May help to vent out distress	
	Physical activities	May help to reduce stress and achieve a healthy BMI	May be hard to perform because of the restriction in outdoor activities
Caregivers	Channels for voice and guidance	Eliminate the sense of overload	
	Provision of multidisciplinary ways	Provide economically accessible information	
	Groups on social media	Share perceptions and help each other	
Medical providers	Collaboration and intervals	Improve patient care equality, provide the learning opportunities to establish a holistic view	
	Financial and social stressors inquiries	Affect family engagement with healthcare providers	
	Persistent efforts	May help to get desired outcomes	
Telemedicine users		May help to get diabetes reviews, self-management support, and timely professional intervention with the minimised risk of virus transmission	Have difficulty to perform a suitable physical examination, lack widespread availability, have obstacles to gain collaboration, cannot replace the in-clinic visits in several circumstances

BMI: Body mass index.

have poorer glucose control[38-40]. The reason can be ascribed to the fact that many of those are supported by various programs for regular supply of insulin and glucose meterstrips[41]. However, these medicine and devices may be unavailable because of closure of nodal healthcare facilities and local transport facilities during the lockdown. Sequentially, the limited availability and the fear of shortage of medical supply forced these children with T1D to reduce glucose monitoring, which caused more frequent hypo-/hyperglycemic excursions[42]. Moreover, consequent DKA may emerge with unavailability of any type of insulin or technology-related problems such as pump dysfunction[43].

Female gender was a risk factor for unfavorable glycaemic control due to more mental effect[44,45]. Glycemic control interacts with stress, which may directly disturb glucose regulation, or indirectly result in non-adherence to treatment and unhealthy daily routine[46]. Previous epidemiological publications reported that females are at a greater risk for psychological disorders and perceived stress is more prevalent among females compared with males in the lockdown[47]. Interestingly, one study indicated that the glycemic control of males was more adversely affected in this period, which may be ascribed to more changes in almost all aspects of lifestyle among boys compared to girls[36].

Factors that improve glycemic control: Glycemic level in the school age children had significantly improved during the lockdown period, which may be attributed to more supervision of insulin injections and overall health care from their parents[48]. On the contrary, the pubertal adolescents group showed an adverse trend, which may be attributed to a change in independence from the parents during this age and more pressure from peer and themselves[36].

Although children and adolescents performed less physical activity and engaged in more sedentary behavior during the lockdown which impeded glycemic control, the changes in eating habits seemed to play a more essential role in glycemic management[49]. Healthy diet is essential for glycemic control. Evidence revealed that hyperglycemia is a significant predictor of some viral infections including COVID-19 which can exacerbate the complications of diabetes mellitus (DM)[50]. According to the literature review, adequate intake of dietary protein, fiber, essential fatty acids, and some micronutrients especially vitamins D, C, and B12, folate, zinc and selenium are beneficial to the prevention and treatment of COVID-19 in diabetic patients through modulation of innate and adaptive immune responses or direct effects on virus enzymes or cell entrance[50]. Due to home confinement, parents may monitor their children's behavior throughout the day. Particularly, compared to those with a longer duration of the disease, children with newly diagnosed or less than a year diabetes got more benefit from improvement in eating behaviors, which may be partially ascribed by taking over diabetes control from their caregivers[51]. Furthermore, outside dining and junk food consumption are prone to be

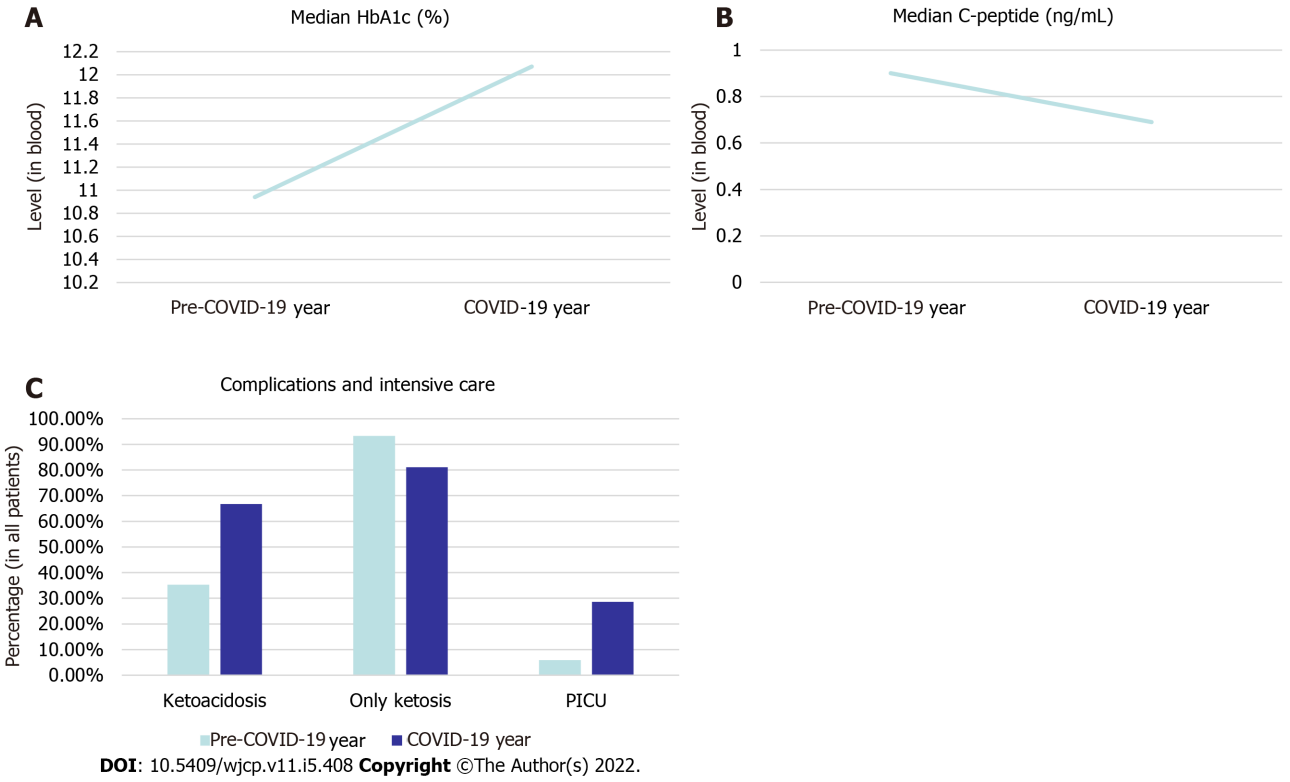

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Figure 1 Characteristics of children and adolescents diagnosed with type 1 diabetes mellitus during the coronavirus disease 2019 year and pre-coronavirus disease 2019 year. A: Median higher glycosylated hemoglobin; B: Median C-peptide; C: Complications and intensive care. HbA1c: Higher glycosylated hemoglobin; COVID-19: The coronavirus disease 2019; PICU: Pediatric intensive care unit.

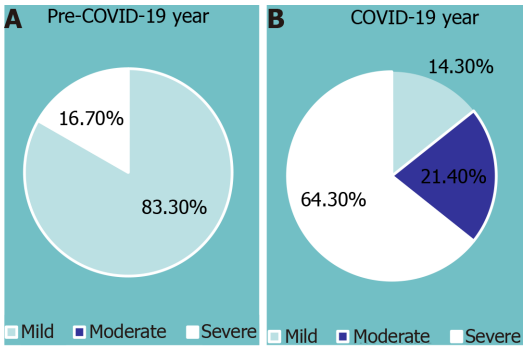

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Figure 2 Severity of diabetic ketoacidosis in children and adolescents diagnosed with type 1 diabetes mellitus during the coronavirus disease 2019 year and pre-coronavirus disease 2019 year. A: Pre-coronavirus disease 2019 (COVID-19) year; B: COVID-19 year. COVID-19: The coronavirus disease 2019.

limited due to the lockdown, which may have reduced opportunities to adopt or engage in the unhealthy dietary habits or weight control practices that have been frequently observed in youths with diabetes[43,52]. In addition, the isolation measures may have reduced or canceled activities and contexts typically linked to social situation with peers that usually challenge good diabetes management and lead to behaviors negatively influencing glycemic control[53]. However, in certain areas, because of strict lockdown and suspension of food supplies, regular supply of important components of their healthy diet plan may be not available, which obstructs medical nutrition therapy and deserves the concern of government[54].

Hard time for caregivers of T1D children: Before the pandemic, caregivers played a fundamental role in family diabetes control and short or long-term consequence resolving[55]. Pediatric T1D is a very fragile context, in which the pandemic can lead to emotional adaptation disorders[56]. In some families of children and adolescents with T1D, the school nurse provided most of the diabetes care. However, because of the sudden closure of school, parents who needed extra help may have less access to

adequate training[38]. The unavailability of medical appointments, the lack of information about the relationship between COVID-19 and T1D, the difficulty in obtaining specialized support, and the inability to provide quality food and supplies for diabetes during the pandemic may generate negative feelings and insecurity in these caregivers[57,58]. Ultimately, the emotional burden of caregivers might not only influence the parents' mental health, but also negatively affect blood sugar control of their children[59].

Challenges related to the healthcare system: Patients with T1DM require continuous access to healthcare services. However, the lockdown and closure of healthcare centers may deprive these patients of access to medical support for their daily disease management and complication treatment. In addition, emergency issues like hypoglycemia or DKA requiring hospitalization may be precipitated, while infections such as COVID-19 or any other cases, may also lead to glycemic fluctuations and increase the risk of hospitalization[43,60]. How to deal with all the factors mentioned above poses challenges for the healthcare system.

Possible solutions for the difficulties

Self-management: Patients with T1DM need to adhere to frequent glucose monitoring, proper dietary behaviors, adequate hydration, and dose titration of glucose-lowering medication. As signified in publications, the up-to-date medical devices and test methods may bring convenience to these procedures. For instance, continuous glucose monitoring (CGM) and fast glucose monitoring systems are proved to be useful[61]. Moreover, percentage time in range and other CGM-derived metrics are the substitutes of HbA1c in the absence of routine laboratory tests related to the pandemic, which are potential to monitor the glycemic control[62]. Meanwhile, transitioning to CGM indicates "fewer finger punctures and less pain" for children and caregivers can constantly monitor the insulin level with the device[63]. In addition, the insulin pump allows T1D patients to achieve a better control as it tracks the glucose level and injects a proper dose of insulin automatically, thus generating a more comfortable alternative compared to multiple daily insulin injections[64].

The importance of management in sick days should be highlighted to avoid glycemic fluctuations and subsequent risk of DKA or hypoglycemia. As mentioned in publications, when children with T1D are under stress and acute infections, less food intake and more stress hormones may affect glycemic control, therefore it should be cautioned about the rising risk of either hyperglycemia or hypoglycemia [65]. Moreover, patients are recommended to take symptomatic therapy to reduce fever[66]. Ultimately, regular education about diabetes-related symptoms may contribute to a faster diagnosis of T1D and reduce the prevalence of DKA in children and adolescents, along with more rigorous adherence to "sick-day rules" which are recommended to diagnosed T1D patients[67].

Mental outcomes of the COVID-19 pandemic should be taken into consideration in the further treatment plan for children and adolescents with T1D[56]. To vent out distress, the most common method was sharing problems with companions[68].

Physical activities: As recommended by the World Health Organization, young people are supposed to practice more than 1 h per day, doing moderate or vigorous intensity physical activity[69]. However, the physical activity level of T1D children was low before the lockdown and further reduced in the pandemic[36]. Therefore, innovative methods such as appropriate indoor exercises may be a potential way to maintain or lift physical activity levels during the restriction of outdoor activities[36]. For instance, taking online physical training which provides various indoor exercise selections could be a beneficial choice for teenagers.

Use of telemedicine: A move towards telemonitoring to provide healthcare services for patients with diabetes has been part of a long-term plan in the management of the disease[70]. Hopefully, the public health emergency of the COVID-19 pandemic has accelerated the process[71]. Telemedicine services means that digital services substitute for the routine care to offer reviews and self-management advice on diabetes[71]. Telemedicine consultation minimizes the risk of virus transmission by maintaining physical distancing, while remote monitoring of electronic data enables health-care workers to provide in-time support in patients with worsening condition based on available data, which may benefit clinical outcomes[72].

However, there are still limitations in telemedicine including unavailability to perform a suitable physical examination, obstacles in wide spread because of difficulty of Internet construction in certain regions and populations, and challenges in establishing harmonious relationship with patients or helping resolve behavior problems or making effective communication and gaining collaboration[73, 74]. In addition, it should be emphasized that in-clinic visits are indispensable in some care processes at a certain frequency. Meanwhile, patients with a more acute disease including DKA or hyperosmolar hyperglycemic state should not simply adapt the transition to telemedicine[75]. Moreover, insulin initiation in new-onset T1D is typically required in in-clinic attendance and face-to-face training. Therefore, in the future, telemedicine is not merely about keeping patients away from hospitals, but it is about knowing who should be asked to come to the clinic and when at the same time[71].

Relieving the stress of caregivers: There are several possible strategies that should be used to reduce the mental impact on caregivers[58]. To begin with, channels for these caregivers' voice and guidance on emotional self-relief should be provided to eliminate the sense of overloading[58]. In addition, the multidisciplinary ways which provide physical, psychological, and nutritional guidance for children and adolescents with T1D should be economically accessible[58]. Nevertheless, creating social media groups to promote peer interaction in communicating their perceptions and helping each other could be beneficial[58].

Responsibility of medical providers: The whole is greater than the sum of its parts. To provide efficient help, local support groups should coordinate with the hospital team for better T1D management[43]. Interdisciplinary collaboration *via* staff meetings or other forms at a regular basis improves patient care equality, allowing medical providers to learn from others and perform medical service from a more holistic view[74,76]. To connect with individual patients, clinics should ask families about stress on finance and society due to the pandemic, which may influence their coordination with medical providers as well[74].

Furthermore, it was reported that interventions of glycemic management employed during the first two cycles did not produce satisfying outcomes for any target. However, in the 3rd cycle of intervention, the screening and consultation rates increased[74]. Therefore, it should be highlighted that persistent efforts make sense.

Limitations

The minireview is based on the articles mostly reported in English, which limits the extrapolation of results across the globe. Moreover, in most of the research, assessments of glycemic control were only based on HbA1c instead of the home blood glucose levels due to a variety of reasons. Additionally, albeit the use of self-reported measures administered online overcomes the impossibility of conducting a traditional paper survey during the pandemic, it may lead to imprecise ratings of specific anthropometric and clinical data, and subjective perceptions and behaviors. Similarly, thoughts and feelings may not have been sincerely, accurately, or fully revealed[77]. Notwithstanding the above limitations, all studies provide an invaluable report about the difficulties met by youths with T1D and promising solutions.

CONCLUSION

T1D is one of the most common endocrine metabolic disorders around the world[78]. Children with T1D are imperiled by psychological issues, owing to the underlying disease and the complex management of diabetes[79]. As discussed in the minireview, children and adolescents with diabetes are vulnerable to the COVID-19 pandemic resulting in worsening healthcare and would need specific medical access in this period for health advice and support. In addition, they are encouraged to keep a healthy lifestyle whenever possible during these difficult times. In addition, emotional overload leads to exhaustion in youths with T1D diabetes and those who are responsible to take care of them. More than ever, the mental well-being of T1D children and adolescents and their caregivers should be prioritized, and coping strategies should be advocated[58]. Moreover, the COVID-19 pandemic is an opportunity for telemedicine development and puts it to the forefront of diabetes management. Besides distant management of diabetes, identifying the at-risk groups to provide in-person consultation and care is also the value of routine telemonitoring[71]. Ultimately, cooperation and continuous effort should be made among medical providers, families with T1D youths, and the whole society.

In summary, we can conclude that youths with T1D require continuous care and attention during the COVID-19 pandemic because of various issues as discussed above. Proposed solutions in this article may assist them to resolve these obstacles in diabetes management to reduce the risk of complications particularly DKA during such emergency situations. Furthermore, proper prospective studies need to be conducted to identify the challenges faced by youths with T1DM during lockdown and their influence on glycemic control and complications, which may help us to come to more precise solutions to improve the welfare of children and adolescents with T1D during such pandemic.

FOOTNOTES

Author contributions: Shi Y drafted the review and performed the majority of the writing; Wu LQ, Wei P, and Liao ZH contributed to the writing and editing of the manuscript; Liao ZH accepted the editor invitation, conceptualized the topic, and proofread the manuscript; both Wei P and Liao ZH provided supervision and approved the submission of this minireview.

Conflict-of-interest statement: All the authors declare no conflict of interest for this article.

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S-Editor: Wang LL
L-Editor: Wang TQ
P-Editor: Wang LL

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World Journal of Clinical Pediatrics

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World J Clin Pediatr 2022 September 9; 11(5): 419-428

DOI: 10.5409/wjcp.v11.i5.419

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Retrospective Study

Utilization of chest tube as an esophagus stent in pediatric caustic injuries: A retrospective study

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Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Govindarajan KK, India; Moshref RH, Saudi Arabia; Scriba MF, South Africa

Received: June 14, 2022
Peer-review started: June 14, 2022
First decision: June 27, 2022
Revised: July 17, 2022
Accepted: August 12, 2022
Article in press: August 12, 2022
Published online: September 9, 2022

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Abstract

BACKGROUND

The management of caustic esophageal burns in the pediatric population has changed over the years, while the most optimal management with regards to effectiveness, availability, and cost-beneficent stays controvertible.

AIM

To describe how to utilize a chest tube for esophageal stenting in pediatrics.

METHODS

Data regarding the etiology, treatment, and complications of caustic injury in pediatrics over 10 years was collected retrospectively. Furthermore, data regarding the patient's follow-up who underwent esophageal chest tube (ECT) were collected. The ECT was prepared by carving a narrowed section in the chest tube while maintaining the radiopaque section. The ECT will then be positioned from the cricopharyngeal and exited through the nostril and fixed on the patient's cheek.

RESULTS

During the period of our study, data from 57 patients with an average age of 2.5

years (range 1-12; SD = 1.7) were obtained. The results showed that 89% of esophageal injury was due to alkaline and 9.4% were caused by acidic agents. The treatment methods showed that 29 patients (50.8%) recovered with dilatation alone. In 16 patients (28.06%), the esophageal repair was performed by using the colon, and in 5 patients (8.7%), other surgical methods were used and in 7 patients (12.2%), the ECT stents were used. ECT was inserted in 7 cases with a mean age of 2 (range: 1.5-3) years who were classified as grade IIB or III. Grading was performed by endoscopy assessment on the first day. Antibiotics and corticosteroids were administrated as initial medical management for all patients. ECT implantation was done during the first 8 d for 5 out of 7 cases (mean: 3.8 d). For the 2 patients, ECT was used after 27 (patient 6) d and 83 (patient 7) d. The reason for late stenting in these patients was a postponed referral to our center, in which patient 7 even received 4 dilation episodes before visiting our center. ECT was removed after an average of 44 d in the first 5 patients, while in the other 2 patients (6 and 7) was 2 and 1 wk, respectively. There was no complication related to, or failure of, stent placement. It is worth mentioning that none of the 7 ECT cases required gastrostomy or jejunostomy.

CONCLUSION

The ECT method introduced in our study can be used as a broadly available, economic, and easy-use facility for esophageal stenting, particularly in developing countries and emergency departments which have limited access to modern equipment. Further multicenter studies with higher volume patients are required for further deployment of this method.

Key Words: Caustic injury; Pediatric; Esophageal stent; Facility; Emergency

Core Tip: Given that caustic ingestion is one of the most common incidents in clinical practice, especially among children, we believe that our new esophageal stent is not only an accessible device but also extremely cost-benefit relative to existing Self Expandable Metallic Stents and Self-expanding Plastic Stents. We hope that this new esophageal stent, which is a modified chest tube, will help all surgeons and emergency physicians manage patients with caustic ingestion in the future, especially for those working in developing countries and areas with lower equipment accessibility.

Citation: Salimi M, Hosseinpour H, Shahriarirad R, Esfandiari S, Pooresmaeel F, Sarejloo S, Foroutan H. Utilization of chest tube as an esophagus stent in pediatric caustic injuries: A retrospective study. *World J Clin Pediatr* 2022; 11(5): 419-428

URL: https://www.wjgnet.com/2219-2808/full/v11/i5/419.htm

DOI: https://dx.doi.org/10.5409/wjcp.v11.i5.419

INTRODUCTION

Esophageal injury followed by caustic agent ingestion, also known as erosive material ingestion, is among the most challenging and prevalent problems, particularly in developing countries[1,2]. Complications vary from an asymptomatic effect to drastic outcomes such as esophageal stricture or perforation, which can be potentially fatal[3-5]. The severity of injury also depends on the type of ingested substance as well as the amount and time of tissue exposure[6,7]. Esophageal stricture is considered to be the most prevalent complication in these cases[8,9].

Children and pediatrics are among the most frequent caustic ingestion victims, which occur either due to accidental or unintentional ingestion of erosive materials[6]. It has also been reported to be more prevalent among males[10]. Furthermore, this problem is most common in toddlers with a prevalence peak of 2 years old[11,12].

Acids and alkalis are the two basic types of erosive materials; however, alkaline materials are considered the most common erosive agents in these cases[3,13]. Almost 25% of caustic ingestion is followed by exposure to personal care products or household chemicals, such as detergent agents and bleaches[3,12]. The high morbidity and mortality rate followed by these injuries make them a serious challenging issue that requires initial management for all of these patients, including airway assessment, hemodynamic stabilization, and electrolyte replacement, followed by prescribing corticosteroids and antibiotics[14,15].

Using esophageal stenting to prevent or reduce future stricture formation is very controversial, with no pediatric-specific esophageal stents available or clear guidelines for their use.

The idea is to avoid contact with opposing sides to decrease adherence and following stricture formation. Even though this approach has been shown to decrease the rate of stricture formation, so far it has not been accepted as a routine clinical practice[16,17].

Some authors believed that esophageal stents are an effective method for preventing esophageal stricture in the first 48 h and also eliminating esophageal stricture recurrence followed by other dilation methods. Initial reports of outcomes following esophageal stenting described the use of a Silastic tube or polytetrafluoroethylene (PTFE) rod, both secured at the nose[18-20]. More recently, the use of self-expanding stents placed either endoscopically or under fluoroscopic guidance has been described. Plastic, metal, and biodegradable self-expanding stents have been used for esophageal strictures in children; however, the effectiveness, expensiveness, accessibility, and problems that these stents cause for the patients are still challenging issues[21-23].

Therefore, in this study, we aimed to introduce a new esophageal stenting method by utilizing a chest tube as an available and accessible device in emergency departments for patients suffering from caustic injuries. We also reviewed the etiology of caustic injury pediatrics in southern west Iran and the outcome of several patients treated with this Technique.

MATERIALS AND METHODS

Study design and participant selection

In this retrospective study, hospital records during ten years of patients aged under 18 years old who were admitted due to caustic chemical ingestion at the authors' affiliated hospital, which is a referral center for pediatric injuries, were collected. Data regarding the patient's characteristics, age, cause of the burn, degree of burn, treatment with antibiotics and steroids, use of gastrostomy and jejunostomy, number of dilatations and intervals, surgeries performed, and their complications (anastomotic leakage, esophageal rupture, adhesions, other early and late complications which were in associated to burns) was also gathered.

Various endoscopic grading is available and Zargar's classification is one of the most commonly used. In his study, Zargar *et al*[24] found all patients with grade 0, I and IIA burns recovered without sequelae. The majority of grade IIB and all survivors with grade III injury developed eventual esophageal or gastric cicatrization[24].

In our study esophageal stent was utilized in those with grades IIB and III.

The story and method of esophageal chest tube stenting

During several years of our clinical experiences, we found that esophageal stricture has developed frequently after caustic ingestion in those who have higher grades of corrosive injuries based on the endoscopically reports. We found that esophageal stents may prevent stricture significantly; however, the recently introduced self-expanding stents were so limited and expensive in our country; and many other low-income regions. Moreover, necrosis, ulceration, tissue hyperplasia, and fistula formation have been frequently reported by self-expandable metallic stents. After re-evaluating the patient's information, we found that esophageal stricture mostly developed in higher stages of injury (stage IIB and above). There were several recommendations from conservative management and medical therapy (such as steroids) to invasive methods; however, none of them had been proven. Therefore, we start to search for a costly and broadly available device. We consider the chest tube as an esophageal stent which may help; however, there were several concerns about it. The expected complication could be more similar to a plastic stent rather than a metal stent. Plastic stents are said to have lesser tissue hyperplasia but with a higher rate of stent migration and a lower tendency to sustain the significant radial force. Regarding the aforementioned concern, we used the radiopaque section of the chest tube to follow its place after insertion. Likewise, the external part of ECT exited the nose and fixed it to the patient's cheek using tape. Furthermore, we were afraid of the insertion procedure may lead to esophageal perforation, therefore, we placed it *via* endoscopy through a guide wire. Likewise, we didn't consider the injuries of stage IV due to its higher tendency for perforation. Moreover, we applied the anti-reflux medication and encourage the patient to elevate the head of their bed.

In this method, the esophageal chest tube (ECT) stent is inserted either in the first 48-72 h after a caustic injury or precisely after dilatation and is removed after 6-8 wk. In this technique, we utilize the ECT in three steps.

First, the chest tube's length is measured concerning age, weight, and the stature of each patient. We used different sizes of chest tubes based on the physician's preference according to the initial endoscopic evaluation. Sedative and analgesic medications were also applied. Afterward, a narrowed section is shaped by obliquely carving the chest tube and maintaining the radiopaque section, which will be positioned from the cricopharyngeal until the external section of the tube. After preparing the ECT, the tube will be inserted orally *via* endoscopy through a guide wire, with the narrow end positioned out of the mouth (Figure 1A). Following the ECT insertion, we aim to exit it through the nasal cannula, in which we use either a Nelaton or nasogastric tube. In this regard, we insert the tube through the nasal cannula so that it exits the mouth while keeping the proximal section out of the nose.

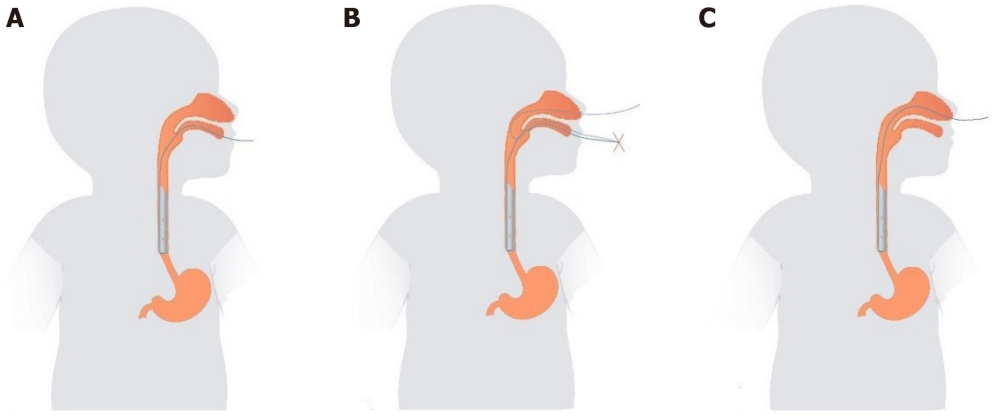

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Figure 1 Utilizing a chest tube as an esophageal stent in caustic injury in pediatrics. A: Insertion of esophageal chest tube (ECT) from cricopharyngeal until lower sphincter and exiting the external part from the mouth; B: Suturing the external part of the ECT to a Nelaton or nasogastric tube which has been passed through the nostrils; C: Exiting the external part of the ECT through the nostrils.

Subsequently, the end part of the tube is sutured to the distant narrow part of the ECT (Figure 1B). Therefore, by pulling onto the proximal part of the tube, it will act as a guide for the ECT to extract it through the nasal cannula (Figure 1C). Consequently, the ECT will exit the nose and be fixed to the patient's cheek using tape. (Figure 2). Also, by preserving the radiopaque section of the ECT, monitoring the position of the tube is possible through chest radiography. (Figure 3).

Follow-up evaluation

Then patients were evaluated for early complications such as pneumonia, pneumothorax, esophageal rupture, *etc*., or late complications such as esophageal stricture, gastroesophageal reflux, and the need for colon interposition.

RESULTS

During the period of our study, data from 57 patients with an average age of 2.5 years (range 1-12; SD = 1.7) were obtained. The results showed that 89% of esophageal injury was due to alkaline and 9.4% were caused by acidic agents. Table 1 demonstrates the etiology factors of the patients in our study.

The treatment methods showed that 29 patients (50.8%) recovered with dilatation alone. In 16 patients (28.06%), the esophageal repair was performed by using the colon, and in 5 patients (8.7%), other surgical methods were used and in 7 patients (12.2%), the ECT stents were used.

ECT was inserted in 7 cases with a mean age of 2 (range: 1.5-3) years who were classified as grade IIB or III. Grading was performed by endoscopy assessment on the first day. Antibiotics and corticosteroids were administrated as initial medical management for all patients. ECT implantation was done during the first 8 d for 5 out of 7 cases (mean: 3.8 d). For the 2 patients, ECT was used after 27 (patient 6) d and 83 (patient 7) d. The reason for late stenting in these patients was a postponed referral to our center, in which patient 7 even received 4 dilation episodes before visiting our center. ECT was removed after an average of 44 d in the first 5 patients, while in the other 2 patients (6 and 7) was 2 and 1 wk, respectively.

There was no complication related to, or failure of, stent placement. It is worth mentioning that none of the 7 ECT cases required gastrostomy or jejunostomy. Table 2 summarized information on patients managed with esophageal stenting using a chest tube.

DISCUSSION

Caustic injuries are considered one of the most prevalent, as well as preventable accidental injuries. Children are among the highest groups at risk of these injuries due to their curiosity and ability to reach objects without discerning their harm and potential dangers[25,26]. In 2009, the Kids' Inpatient Database of the United States reported 807 cases of caustic injuries. Our study was conducted in southwest Iran, in which 57 pediatric hospitalized patients with caustic injuries were collected for 10 years (1994-2003), demonstrating an annual rate of 5.7 cases/year. In similar studies in our province, Honar *et al*[27] reported 75 in 2006-2011 (12.5 case/year) and Dehghani *et al*[10] reported 41 cases from 2015-2016 (20.5 cases/year). This upsurge in the number of cases shows the significance of this matter and therefore, evaluating the etiology and applied management, along with choosing the proper therapeutic option for

Table 1 Etiological features of caustic injury among pediatrics in southern west Iran

Variable	Frequency, *n* = 57	Percentage (%)
Etiology		
Caustic Soda	47	83.3
Stove-top cleaner	3	5.7
Acid	3	5.7
Hydrochloric acid	2	3.7
Boiled water	2	3.7
Medical treatment		
Antibiotic Therapy	36	66.7
Corticosteroids	22	40.7
Advanced treatment		
Dilatation	29	50.8
Stent insertion	7	12
Colon interposition	16	28
Other surgical methods	5	8.7
Surgical treatment		
Gastrostomy	19	33.3
Jejunostomy	4	7.4
Complication		
No complication	39	69.6
Pneumothorax	11	19
Esophageal rupture	6	11.4

Table 2 Caustic injury pediatrics treated with esophageal stenting using a chest tube

Variable	Patient						
	1	2	3	4	5	6	7
Age (mo)	24	24	18	36	24	30	34
Grade	III	IIB	IIB	IIB	III	IIB	IIB
Etiology	Caustic soda	Hydrochloric acid	Acid	Acid	Caustic soda	Stove cleaner	Caustic soda
Time of esophageal chest tube insertion (after injury)	1	6	8	2	1	27	83
Esophageal chest tube duration	27	35	50	90	20	16	7
Replacement (Frequency)	1:14	-	2:12 and 22	2: 30 and 60	-	1: 9	1: 4
Surgical intervention	-	-	-	-	Colon Interposition	-	-
Duration of follow-up (mo)	23	22	16	6	35	15	14
Patient Satisfaction	Satisfied	Satisfied	Satisfied	Mild esophageal stenosis	Satisfied	Satisfied	Mild esophageal stenosis

these patients is necessary.

Among the contributing factors to this increasing number of cases per year may be the increased use, easy accessibility, and low cost of detergents and bleaches, especially in developing countries. Alkaline was considered the most corrosive agent in this study with an incidence of 89% (50 out of 57 cases), while acid agents consisted of 9.4% (5 out of 57 cases) of the etiologies in our study population. In a

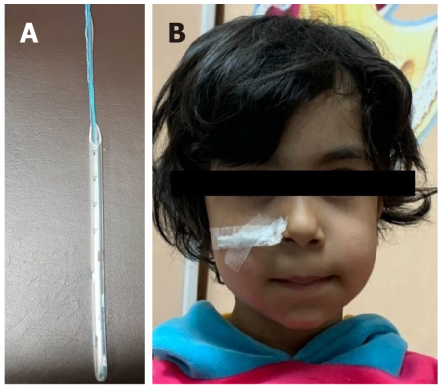

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Figure 2 Esophageal chest tube. A: Esophageal chest tube prepared for a 6-year-old boy with a caustic injury; B: Esophageal chest tube fixed for a 6-year-old boy with a caustic injury.

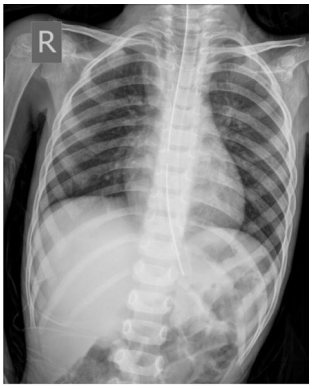

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Figure 3 Chest X-ray, Chest radiography demonstrating and esophageal chest tube inserted for a patient with a caustic injury.

similar study in our center, 64 hospitalized patients were reported to have had alkaline ingestion for 4 years[11]. Also, in a study conducted in Australia, 74% of caustic ingestion occurred by alkaline agents [28]. Acids, regarding their low viscosity and therefore rapid transfer to the stomach and also due to their nature cause coagulation necrosis, with eschar formation that may prevent further damage and limit the injury depth. Conversely, alkalis bind to tissue proteins and lead to liquefactive necrosis and saponification, and penetrate deeper into tissues, assisted by a higher viscosity and a longer contact time through the esophagus. On the other hand, children usually tend to swallow a larger amount of alkaline because alkalis are usually odorless and tasteless; although, acidic agents have a sour taste which makes children spit them out. Another point for our region (the south of Iran) is the excessive use of air conditioners followed by its cleaner that fundamentally and are made by NaOH which kept in beverage bottles without any warning label in addition to the low educational level of parents have led to increasing the occurrence of esophageal burn by caustic ingestion.

In caustic injury patients, a preliminary survey includes airway assessment as well as fluid and electrolyte balance[12]. We also administered antibiotics along with corticosteroids as medical management. Among the most imperative complications of esophageal burns is a stricture. Katz *et al*[9] reported esophageal stricture in more than 90% of patients with grade 3 and almost 30%-70% of grade 2B caustic injury. Malignant transformation to esophageal cancer is one of the following complications of esophageal stricture[29]. Studies have also reported that esophageal stricture is associated with hiatal hernia, reflux disease, dysphagia symptoms, and causing difficulties for esophageal reconstruction[30-32]. A study in 1992 evaluated the administration efficacy of antibiotic and systemic steroids simultaneously in caustic ingestion, which concluded that antibiotics with steroids might be useful in reducing strictures in patients with esophageal burns[33]. Controversially, a controlled randomized trial revealed the corticosteroids' ineffectiveness in preventing esophageal stricture in children with a caustic injury [34]. Therefore, novel therapeutic approaches for preventing or managing esophageal strictures that would enable a child to tolerate an oral diet in a more expeditious and less invasive manner would be highly desirable. Furthermore, the oblique cutting of the ECT facilitates feeding and also prevents unintentional aspiration.

In this report, we utilized the chest tube, as a broadly available and well-known equipment in all emergency departments, proposed as an esophageal stent for not only preventing esophageal stricture in the first 48 h but also after dilatation. Formerly, self-expanding plastic stents (SEPS) and fully covered self-expanding metal stents (FCSEMS) have been used for stenting, and each had its advantage and disadvantage. The success rate for SEPS showed 50% by Broto *et al*[21] and 75% for FCSEMS by Zhang *et al*[22].

Stent migration is another common complication that has been reported in 14% to 48% of cases, which has been related to the type of stent[35]. Metal stents that are fully covered with PTFE, polyurethane, or silicone have a higher chance of migration, compared with uncovered metal stents, which are held in place by hyper-granulation and mucosal ingrowth; nevertheless, these proliferations contribute to ulcers and struggle when removing the stent[36,37]. Self-expanding plastic stents are at greater risk of migration when compared with self-expanding metal stents, which are daunted in benign esophageal stenosis due to their high incidence of necrosis and ulceration, tissue hyperplasia, new stricture or fistula formation, and the tendency for the metal portion to embed within the esophageal wall[38,39]. Best *et al*[40] and Manfredi *et al*[39] reported high rates of mucosal ingrowth and hyper-granulation, causing difficulty in stent removal and stent-induced ulceration. Since the ECT is inserted from below the cricopharyngeal till the lower esophagus sphincter and also fixed from outside of the nose, this decreases the chance of migration compared to other methods of fixation using thread and suture. Furthermore, the stent material safeguards cell proliferation into the stent, resulting in easy removal of the ECT and less complication such as esophageal ulcers and hyper-granulation.

From an economic point of view, as one of the most important factors in management decision making particularly in developing countries, the proposed ECT can be an ideal choice due to its cost-effective aspects and in centers where other esophageal stents are unavailable.

Among the other advantages of the ECT is that the patient will be able to tolerate oral feeding with soft diets as well as liquids, so the foods are based on the inlet of the ECT, which is located in the cricopharyngeal area and allows a pathway to the stomach. However, since the ECT covers the total length of the esophagus to the lower sphincter, a risk of reflux should be considered which can be managed with proper anti-reflux medication.

Among the patients in our study, 5 were satisfied with their results, while two (patients 4 and 7) had mild esophageal stenosis. Among these two, patient 4 had ECT for 90 d. The exact duration in which stents should be used is still a matter of debate. The European Society for Gastrointestinal Endoscopy Recommendations for the Stenting of Benign Esophageal Strictures acknowledges this lack of data available and suggests the insertion of self-expanding metal and plastic stents for a minimum of 6-8 wk and no more than three mo[41]. Likewise, we recommend removing the ECT after 6-8 wk. Furthermore, patient 7 had ECT inserted 83 d after the injury, which had already caused chronic damage and stricture. It is also worth mentioning that ECT was inserted in one of the patients with grade I caustic injury, which was intended as prophylaxis for esophageal stenosis.

Endoscopic dilatation with a balloon has been the standard of treatment for benign esophageal strictures; nevertheless, the recurrence rate was reported to be 30%-40%[38]. Increasing the victims of caustic ingestion on one hand, and the high economic burden, on the other hand, made us use the ECT in early stenting, which is more economical, broadly available, and also regarding its high efficacy. In this study, we just want to report our experience in a referral center in a low-income country. Of course, there is an inevitable need to examine it during the trials. Also, we don't recommend this in the situation that another stent is available.

Limitations

Several caveats regarding our study deserve mention. First, this was a retrospective, single-institution series of esophageal stents deployed in a heterogeneous group of patients. Also, our series lack of control group and consists of a small sample size. This study was non-comparative and did not compare stenting to other therapeutic options. However, our study's main focus was utilizing an already existing device, the chest tube, as an esophageal stent for the early management of caustic injury pediatrics, especially in centers with limited equipment.

CONCLUSION

Caustic injury and its management are among the most challenging problems among pediatric surgeons. The availability, efficiency, and economic aspect of materials are important factors that should be taken into consideration in planning the therapeutic approach for these patients. In this study, we successfully report utilizing a chest tube, as an available device in almost every emergency department, as a method for esophageal stenting. This method should especially be considered in developing countries with limited utilities and also emergency departments and centers with restricted access to modern equipment.

ARTICLE HIGHLIGHTS

Research background

Using esophageal stenting for future stricture formation prevention is very controversial, with no clear guidelines for their use. The idea is to avoid contact with opposing sides to decrease adherence and following stricture formation. Even though this approach has been shown to decrease the rate of stricture formation.

Research Motivation

Different stents have been introduced so far, however, the effectiveness, expensiveness, accessibility, and problems that these stents cause for the patients are still challenging issues.

Research objectives

To introduce a new esophageal stenting method by utilizing a chest tube as an available and accessible device in emergency departments for patients suffering from caustic injuries.

Research methods

Collect demographic data of children with caustic injuries respectively, patients who had stage IIB and III of corrosive injuries were eligible for esophageal chest tube insertion.

Research results

Twenty-nine patients (50.8%) recovered with dilatation alone, 16 needed esophageal repair, and an esophageal chest tube (ECT) was inserted for 7 patients. None of the 7 ECT cases required gastrostomy or jejunostomy.

Research conclusions

We successfully report utilizing a chest tube, as an available device in almost every emergency department, as a method for esophageal stenting. This method is could be an alternative in developing countries with limited utilities as well as centers with restricted access to modern equipment.

Research perspectives

The chest tube has many advantages, it has a radiopaque line that could be used to monitor it, and patients could get an oral diet after stabilization. it is also costly and broadly available. By keeping the advantage and improving its problem, it could be used more efficiently. Moreover, it should be examined during different trials.

FOOTNOTES

Author contributions: Foroutan H designed and performed the research; Salimi M and Hosseinpour H designed the research and wrote the paper; Shahriarirad R designed the research and supervised the report; Esfandiari S designed the research and contributed to the analysis; Pooresmaeel F and Sarejloo S provided clinical advice.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Shiraz University of Medical Sciences.

Informed consent statement: Written informed consent was obtained from the patients' parent/guardian in our study. The purpose of this research was completely explained to the patient's parents/guardian and was assured that their information will be kept confidential by the researcher. The present study was approved by the Medical Ethics Committee of Shiraz University of Medical Sciences. Consent was obtained from the patient parent/guardian regarding the publication of this study.

Conflict-of-interest statement: All authors have no financial relationships to disclose.

Data sharing statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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S-Editor: Wang LL
L-Editor: A
P-Editor: Wang LL

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 September 9; 11(5): 429-436

DOI: 10.5409/wjcp.v11.i5.429

ISSN 2219-2808 (online)

CASE REPORT

Three novel homozygous *ITGB2* mutations among two patients with leukocyte adhesion defect type-1: Two case reports

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Specialty type: Genetics and heredity

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Shuang W, China; Zhao GH, China

Received: April 22, 2022
Peer-review started: April 22, 2022
First decision: May 31, 2022
Revised: June 10, 2022
Accepted: August 22, 2022
Article in press: August 22, 2022
Published online: September 9, 2022

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Abstract

BACKGROUND

A leukocyte adhesion defect (LAD) is a rare primary immunodeficiency disorder. LAD type 1 (LAD-1) is the most common, which is caused by *ITGB2* mutation resulting in dysfunction of β2 integrin, which impairs leukocyte adherence to the endothelium.

CASE SUMMARY

The first two cases of LAD-1 in Thailand presented with recurrent omphalitis, soft tissue infection, marked leukocytosis, and neutrophilia. One patient experienced delayed umbilical cord separation. Mutation analysis was performed by direct DNA sequencing of the *ITGB2* gene. The results revealed two novel homozygous missense mutations, c.920C>T (p.Leu307Pro) in exon 8 and c.758G>A (p.Arg-253His) in exon 7, and one novel homozygous nonsense mutation, c.262C>T (p.Gln88Ter) in exon 4, in the genomic DNA of the first and second patients, respectively. Heterozygous mutations were identified in the parents of both patients, suggesting a carrier status. The patients were administered intravenous antibiotics for infections with good clinical responses. Hematopoietic stem cell transplantation could not be performed due to the unavailability of matched donors. However, a significant decline in infections was observed after antibiotic prophylaxis. Several follow-up visits were conducted for both patients. They are currently 6 years old.

CONCLUSION
Molecular analysis is essential for definitive diagnosis, early treatment implementation, and prevention of LAD-1 in future pregnancy.

Key Words: Leukocyte adhesion defect; *ITGB2*; Omphalitis; Bacterial soft tissue infection; Molecular investigation; Case report

Core Tip: Leukocyte adhesion defect (LAD) is a rare autosomal recessive primary immunodeficiency disorder characterized by defects in the leukocyte recruitment cascade. LAD type 1, caused by a mutation in *ITGB2*, is the most common form. Here, we report the first two cases of LAD type 1 with a molecularly confirmed *ITGB2* mutation in Thailand. At the time of initial presentation, both patients had recurrent omphalitis, bacterial soft tissue infection, and marked leukocytosis. Molecular analysis revealed two missense variants and one nonsense mutation. Early identification of these patients by molecular analysis was proven essential for definitive diagnosis, proper antibiotic prophylaxis, and initiation of matched donor hematopoietic stem cell transplantation.

Citation: Suksawat Y, Pacharn P, Siripipattanamongkol N, Boonyawat B. Three novel homozygous *ITGB2* mutations among two patients with leukocyte adhesion defect type-1: Two case reports. *World J Clin Pediatr* 2022; 11(5): 429-436
URL: https://www.wjgnet.com/2219-2808/full/v11/i5/429.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i5.429

INTRODUCTION

Leukocyte adhesion defect (LAD) is a rare autosomal recessive primary immunodeficiency disorder affecting one in every 100000 individuals. A deficiency in the leukocyte adhesion cascade to the blood vessel wall is the pathogenesis of LAD and is classified into three types. LAD type 1 (LAD-1) (OMIM#116920), which is caused by a mutation in the *ITGB2* gene, is the most common form. The *ITGB2* gene (OMIM*600065) is located on 21q22.3 and encoded the common β subunit of the β2 integrin protein (CD18). Dysfunctional β2 integrin is the main defect in LAD-1 and is attributable to impaired neutrophil firm adhesion[1]. The hallmark characteristics are recurrent bacterial skin and soft tissue infections, omphalitis, and delayed umbilical cord separation. In addition, the absence of pus formation is a distinctive feature[2]. LAD-1 diagnosis can be confirmed by flow cytometric expression of CD18 and CD11 on leukocytes or *ITGB2* mutation analysis[2,3]. To date, more than 110 mutations have been identified[3]. Here, we report the first two cases of LAD-1 with molecularly confirmed *ITGB2* mutation in Thailand. The study protocol was approved by the Institutional Review Board of the Royal Thai Army.

CASE PRESENTATION

Chief complaints

Case 1: A 21-mo-old Burmese boy presented with prolonged fever and multiple whitish ulcers in the oropharynx (Patient #1, P1).

Case 2: A 9-d-old Thai girl presented with redness around the umbilical stump (Patient #2, P2).

History of present illness

Case 1: The patient had fever and dyspnea for 3 wk. Additionally, he had been previously treated in Myanmar and Laos; however, his clinical condition had deteriorated, and he was referred from a rural hospital near the Thai border. He was on the verge of respiratory failure due to acute upper airway obstruction. Emergency tracheostomy was performed, and pus with debris extending to the oropharynx, larynx, and epiglottis was discovered intraoperatively. *Streptococcus viridans* and *Staphylococcus epidermidis* were identified in the pus cultures. Although intravenous antibiotics were administered, healing of the wound was difficult. He was re-admitted several times with chronic wound infections around the tracheostomy site, *Pseudomonas aeruginosa* pneumonia, oral candidiasis, and cellulitis. Several organisms, including *Staphylococcus aureus, Staphylococcus epidermidis, Pseudomonas*

aeruginosa, *Salmonella gr.B*, and carbapenem-resistant Enterobacteriaceae *Klebsiella pneumoniae* were identified in pus cultures.

Case 2: At 9 d of age, she presented with fever and abdominal distension. Physical examination revealed minimal pus with redness around the umbilical stump (Figure 1). The patient was then diagnosed with omphalitis. Intravenous cloxacillin and metronidazole were administered; however, her clinical condition worsened. Omphalitis persisted until 4 wk of age. Pus culture revealed *Staphylococcus epidermidis*, *Escherichia coli*, and extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*. The intravenous antibiotics were switched to carbapenems, with some clinical improvement. She was re-admitted because of recurrent omphalitis at 6 wk of age. After administration of intravenous antibiotics for 3 d, her symptoms subsided. At 2 mo of age, she was referred to our university hospital for assessment of recurrent omphalitis.

History of past illness

Case 1: The patient had a delayed umbilical cord detachment 30 d after birth and delayed wound healing, resulting in difficult-to-treat omphalitis.

Case 2: The patient's umbilical cord was separated 20 d after birth.

Personal and family history

Case 1: The patient was born at term with an uneventful pregnancy and delivery history. The patient completed an extended immunization program based on his age. His sister had no health issues despite being the second child of consanguineous parents.

Case 2: The patient was born at term with an uneventful pregnancy and perinatal history. Her birth weight was 2650 g. BCG and HBV vaccines were administered after birth. She was the first child of a couple who had denied consanguinity.

Physical examination

Case 1: Physical examination of P1 revealed a weight of 9.5 kg (3rd percentile) and a height of 82 cm (25th–50th percentile). Multiple whitish ulcers were present on both lips and the oral cavity, and a BCG scar was observed on the left shoulder. Mild hepatosplenomegaly was observed.

Case 2: Physical examination of P2 revealed normal growth parameters. Periumbilical redness with a lack of pus formation was observed, and a BCG scar was observed on the left shoulder.

Laboratory examinations

Case 1: Complete blood count revealed leukocytosis (WBC 94600/mm^3) and neutrophil predominance (67166/mm^3), while anti-HIV was negative. Bone marrow aspiration revealed no evidence of hematological malignancy. His parents were asked for permission to conduct immunologic tests, but they denied due to financial concerns.

Case 2: Complete blood count showed significant leukocytosis (65300/mm^3) and neutrophilia (46800/mm^3). The lymphocyte populations determined using flow cytometry, serum immunoglobulin levels, and dihydrorhodamine 123 assays were normal.

Imaging examinations

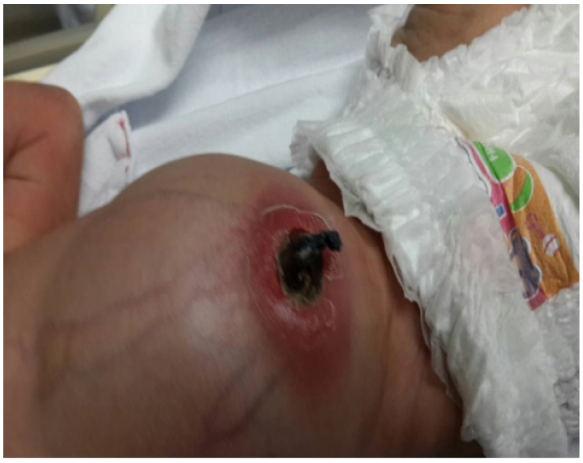
Case 1: Chest radiography showed patchy infiltration in both lower lungs. Computed tomography of the neck showed obstruction of the upper airway due to an infection involving the mucosa of the oropharynx, hypopharynx, glottic, and subglottic levels.

Case 2: Anatomical abnormalities of the umbilicus were excluded by abdominal ultrasound, which revealed neither a patent urachus nor an omphalomesenteric cyst.

The diagnosis of LAD-1 was suspected in both patients.

Further diagnostic work-up

After informed consent was obtained from the patients and their parents, genomic DNA was extracted from peripheral blood lymphocytes using commercially available kits, according to the manufacturer's protocol. Sixteen coding exons and exon-intron boundaries of the *ITGB2* gene were amplified by PCR using primers as described previously[4,5]. Each 50 μL PCR mixture contained 1.5 mmol/L $MgCl_2$, 200 μmol/L of each dNTP, 0.5 μmol/L of each primer, 100 to 200 ng of genomic DNA and 1.25 units of Taq DNA polymerase. The PCR conditions were as follows: Initial denaturation at 95°C for 5 min; 30 cycles of 95°C for 30 s, 62 °C to 64°C for 30 s, and 72°C for 45 s; and a final extension at 72°C for 5 min. All PCR products were purified and directly sequenced in both the forward and reverse directions. The reference sequences were NM_000211.5 and NP_000202.3 for *ITGB2* cDNA and β2 integrin amino acid positions, respectively.



DOI: 10.5409/wjcp.v11.i5.429

Figure 1 Sign of omphalitis in Patient 2.

Results

Homozygous of two novel "likely pathogenic" missense variants, c.920T>C (p.Leu307Pro) in exon 8 and c.758G>A (p.Arg-253His) in exon 7, and homozygous of a novel nonsense mutation, c.262C>T (p.Gln88Ter) in exon 4 of the *ITGB2* gene were identified in the genomic DNA of P1 and P2, respectively. Mutations were also characterized by the heterozygous state in both parents of P1 and P2, suggesting carrier status in the parents (Figure 2). The pathogenicity predictions for these mutations are summarized in Table 1.

Clinical and laboratory information, including *ITGB2* mutation analysis results for both patients, are summarized in Table 2.

FINAL DIAGNOSIS

The final diagnosis for both patients was LAD-1 with the carrier status in the parents.

TREATMENT

Case 1

Intravenous cloxacillin, ceftazidime, and amikacin were administered for chronic wound and soft tissue infections, resulting in good clinical responses.

Case 2

The use of intravenous gentamycin and ciprofloxacin for recurrent omphalitis improved her clinical outcome. She has not presented with omphalitis since that time.

OUTCOME AND FOLLOW-UP

Currently, hematopoietic stem cell transplantation cannot be performed because of the unavailability of matched donors. Sulfamethoxazole-trimethoprim with itraconazole prophylaxis was initiated and a significant decline in infection was noted. P1 developed a soft tissue infection around the tracheostomy, and P2 had occasional gastroenteritis and chronic otitis media in response to antibiotics. Several follow-up visits were conducted for both patients. They are currently six years old.

DISCUSSION

LAD-1 was first identified in 1979[6]. To date, more than 400 LAD-1 cases have been reported with the highest prevalence in Iran, the United States, and India in over 100 publications[7,8]. Our report is the first case series of LAD-1 diagnosed in Thailand. Patients with LAD-1 usually present in infancy with delayed umbilical cord separation, omphalitis, and skin infection in both mucosal and subcutaneous

Table 1 Pathogenicity prediction of mutation/variant (s) identified in the *ITGB2* gene in Patient 1 and Patient 2

Information/computation (in silico) predictive programs	c.920T>C (p.Leu307Pro) in exon 8	c.758G>A (p.Arg253His) in exon 7	c.262C>T (p.Gln88Ter) in exon 4
Human gene mutation database (HGMD)	Not identified	Not identified	Not identified
National center for biotechnology information (NCBI): dbSNP and ClinVar	Not identified	Uncertain significance rs200423927	Not identified
Exome aggregation consortium (ExAC) and 1000 genomes project	Not identified	ExAC 0.0002817 heterozygous (only)	Not identified
Mutation taster (http://www.mutationtaster.org/)	Disease causing	Disease causing	Disease causing
PolyPhen (http://genetics.bwh.harvard.edu/pph2/)	Probably damaging	Benign	-
SIFT (http://sift.jcvi.org/)	Damaging	Damaging	-
ACMG classification (2015)	Likely pathogenic (PM2, PM3, PP2, PP3)	Likely pathogenic (PM2, PM3, PP2, PP3)	Pathogenic (PVS1, PM2, PM3, PP3)

Table 2 Clinical, laboratory and molecular information in two patients with leukocyte adhesion defect type-1

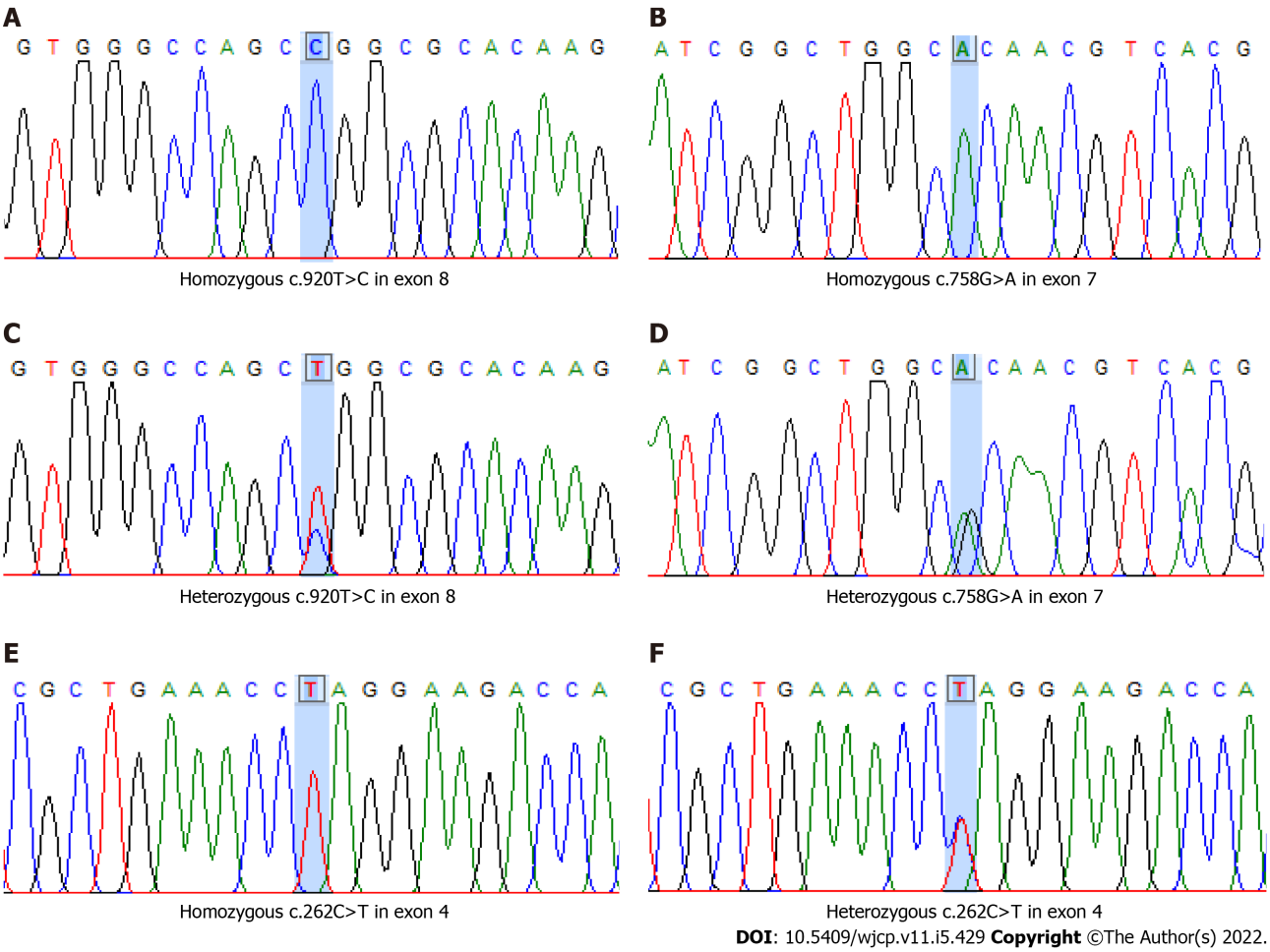
Clinical information	Patient 1	Patient 2
Age of onset	1 mo	9 d
Clinical characteristics	Omphalitis	Omphalitis
	Soft tissue infection	Gastroenteritis (occasional)
	Delayed wound healing	
	Pneumonia	
Delay separation of the umbilical cord	Yes	No
Family history of consanguineous marriage	Yes	No
Organisms	*Streptococcus viridans*	*Staphylococcus epidemidis*
	Staphylococcus epidermidis	*Escherichia coli*
	Staphylococcus aureus	*Klebsiella pneumonia, ESBL*
	Pseudomonas aeruginosa and others	
White blood cells (WBC)	94600/mm^3	65300/mm^3
Absolute neutrophil counts (ANC)	67166/mm^3	46800/mm^3
ITGB2 mutation	c.920T>C (p.Leu307Pro) in exon 8 and c.758G>A (p.Arg253His) in exon 7	c.262C>T (p.Gln88Ter) in exon 4
Outcome (at present)	Alive	Alive

ESBL: Extended-spectrum beta-lactamase.

tissues. LAD-1 is classified as mild (LAD-1$^+$), moderate (LAD-1$^-$), or severe (LAD-1^0) depending on CD18 expression in neutrophils. Although the CD18 expression study remains unavailable at our institution, our patients were suspected of having LAD-1^0 due to the early age of onset[3,7-9]. Both patients experienced omphalitis at the first presentation, which was also the most common initial manifestation among patients with LAD-1^0 in related studies[8,10,11]. However, delayed cord separation after three weeks was only observed in P1, suggesting that this clinical feature may not be an essential characteristic of LAD-1^0[8-10,12].

Other common infections that have been widely reported in related studies, including respiratory tract infection and sepsis[5-8,10], were not identified in P2, which could possibly be explained by early diagnosis and antibiotic prophylaxis in this patient. The spectra of infectious organisms in our patients were similar to those of other reported cohorts in which bacterial infections, including gram-positive cocci (Staphylococci or Streptococci) and gram-negative bacteria (*Pseudomonas aeruginosa* or *Klebsiella pneumoniae*) were predominantly identified[8,9,11]. Marked neutrophilic leukocytosis, which is the hallmark of LAD-1, was found in both patients.

The BCG vaccine is routinely prescribed for newborns as part of the national immunization program in Thailand. Vaccine-associated serious BCG infection has been reported among people with



DOI: 10.5409/wjcp.v11.i5.429

Figure 2 Direct DNA sequence analysis of the *ITGB2* gene. A and B: Homozygous c.920T>C (p.Leu307Pro) mutation in exon 8 and homozygous c.758G>A (p.Arg253His) mutation in exon 7 in the genomic DNA of Patient 1; C and D: Heterozygous c.920T>C mutation in exon 8 and heterozygous c.758G>A mutation in exon 7 of both parents in Patient 1; E: homozygous c.262C>T (p.Gln88Ter) mutation in exon 4 in the genomic DNA of Patient 2; F: heterozygous c.262C>T mutation in both paternal and maternal DNA.

immunodeficiency, particularly severe combined immunodeficiency and chronic granulomatous disease (CGD)[13]. Furthermore, we previously described a case of X-linked CGD with disseminated BCG infection[14]. According to the recent vaccination recommendations for primary immunodeficiency disease, live bacterial vaccines, such as BCG vaccine, are not recommended for patients with LAD[15]. Nevertheless, no BCG vaccine-related complications were reported among patients with LAD in the most recent systematic review[13], except for one reported Japanese girl with LAD-1 who had necrotizing ulcers after BCG vaccination[16]. This phenomenon is explained by a study in mice with abnormal integrins, CD11a and CD18, which were susceptible to *Mycobacterium tuberculosis* infection, indicating that adhesion molecules are essential for mycobacterial immunity[17]. Because BCG vaccination was administered to both patients at birth, BCG-related complications were monitored. To date, BCG-related complications have not been observed.

The diagnosis of LAD-1 is based on either the flow cytometric expression study of CD18 on leukocytes or molecular confirmation. Due to the unavailability of the CD18 expression study at our institution, molecular analysis by direct DNA sequencing of *ITGB2* was performed. Mutations in the *ITGB2* gene are heterogeneous, and missense mutations are the main cause of LAD-1 deficiency. Most mutations are located in the highly conserved domain, Von Willebrand Factor type A (VWFA), which consists of 240 amino acids encoded by exons 5 to 9 of the *ITGB2* gene. This domain is required for the enzymatic activity of the β2 integrin (CD18). Other mutations are scattered throughout the gene[3,4,7,8,10].

This study identified three novel mutations: two likely deleterious missense mutations and one deleterious nonsense mutation. The two missense variants, c.920C>T (p.Leu307Pro) in exon 8 and c.758G>A (p.Arg253His) in exon 7, which were identified in P1, are located in the VWFA domain, which is highly conserved in the β2 integrin protein. The c.920C>T variant has never been identified in either the Exome Aggregation Consortium (ExAC) or the 1000 Genomes Project population databases. c.758G>A is a rare variant identified in approximately 4 of 8632 individuals of East Asian ancestry according to the ExAC database and was identified only in the heterozygous state. Additionally, these

two homozygous missense mutations were not identified in the Thai Reference Exome variant database (1092 unrelated Thai individuals; T-Rex, https://trex.nbt.or.th/).

Most of the *in silico* analysis tools consistently predicted these two variants that may damage protein function (Table 1). Many missense pathogenic variants in nearby residues in the *ITGB2* gene have been reported to be associated with LAD-1[3]. These reasons support the possibility of "likely pathogenic" for both missense variants in Myanmar patient with LAD-1. Further *in vitro* studies may address the possible impact of amino acid substitutions on the function of β2 integrin. Unfortunately, functional studies cannot be performed at our institution. Two mutations were detected simultaneously in some of the previously reported patients[4]. One nonsense mutation, c.262C>T (p.Gln88Ter) in exon 4, which was identified in P2, leads to a premature stop at codon 88 which normally encodes for glutamine and results in loss of both active VWFA and cysteine rich domains of β2 integrin protein. This nonsense mutation has never been reported in the ExAC or 1000 Genomes Project databases. The VWFA domain is crucial for the structural association of a β-integrin subunits for heterodimer formation on the cell surface and functional activity. Any significant alterations in this region will definitely have a deleterious effect on the expression and function of β2 integrin and result in the LAD-1^0 phenotype among most patients with LAD-1[8,10]. Even though consanguineous marriage was denied by the parents of P2, consanguinity could not be excluded based on the identification of a novel nonsense mutation in the homozygous state in the patient and the heterozygous state in both parents.

LAD-1^{0}has an extremely poor prognosis, with the majority of patients dying within two years of life [7,12]. Early hematopoietic stem cell transplantation remains the treatment of choice, but this is unavailable for the majority of affected children in developing countries, including our patients. Thus, antibiotics used for prophylaxis and treatment of infections are the mainstay of treatment, while waiting for matched donors.

CONCLUSION

Herein, we report two classic cases of severe LAD-1. Early onset and recurrent omphalitis were common pathognomonic signs in our patients. A significant increase in white blood cell counts combined with neutrophilia should increase the awareness of LAD-1. Mutation analysis of the *ITGB2* gene remains the gold standard for the diagnosis of LAD-1. Three novel homozygous *ITGB2* mutations were identified in these patients. Molecular investigation is essential for definitive diagnosis, early treatment implementation, and prenatal diagnosis in future pregnancies.

ACKNOWLEDGEMENTS

The authors express their gratitude to the patients and their families who participated in this study. This study was supported by Phramongkutklao College of Medicine.

FOOTNOTES

Author contributions: Suksawat Y, Siripipattanamongkol N and Boonyawat B contributed to the drafting and writing of the case report manuscript and were involved in the clinical care of the patients; Boonyawat B extracted genomic DNA and performed genetic studies; Pacharn P supervised and edited the manuscript; all authors approved the final draft of the manuscript.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: Thailand

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S-Editor: Gong ZM
L-Editor: A
P-Editor: Gong ZM

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ISSN 2219-2808 (online)

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2022 November 9; 11(6): 437-484

Published by Baishideng Publishing Group Inc

World Journal of Clinical Pediatrics

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INDEXING/ABSTRACTING

The *WJCP* is now abstracted and indexed in PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Pediatrics

ISSN
ISSN 2219-2808 (online)

LAUNCH DATE
June 8, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Toru Watanabe, Consolato M Sergi, Elena Daniela Serban, Surjit Singh

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PUBLICATION DATE
November 9, 2022

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World J Clin Pediatr 2022 November 9; 11(6): 437-454

DOI: 10.5409/wjcp.v11.i6.437

ISSN 2219-2808 (online)

EDITORIAL

Cow's milk-induced gastrointestinal disorders: From infancy to adulthood

Mohammed Al-Beltagi, Nermin Kamal Saeed, Adel Salah Bediwy, Reem Elbeltagi

Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D, D
Grade E (Poor): 0

P-Reviewer: Li J, China; Margiotta G, Italy; Wen XL, China

Received: August 14, 2022
Peer-review started: August 14, 2022
First decision: August 29, 2022
Revised: September 1, 2022
Accepted: October 14, 2022
Article in press: October 14, 2022
Published online: November 9, 2022

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Abstract

Milk is related to many gastrointestinal disorders from the cradle to the grave due to the many milk ingredients that can trigger gastrointestinal discomfort and disorders. Cow's milk protein allergy (CMPA) is the most common food allergy, especially in infancy and childhood, which may persist into adulthood. There are three main types of CMPA; immunoglobulin E (IgE)-mediated CMPA, non-IgE-mediated CMPA, and mixed type. CMPA appears before the first birthday in almost all cases. Symptoms may start even during the neonatal period and can be severe enough to simulate neonatal sepsis. CMPA (often non-IgE mediated) can present with symptoms of gastroesophageal reflux, eosinophilic esophagitis, hemorrhagic gastritis, food protein-induced protein-losing enteropathy, and food protein-induced enterocolitis syndrome. Most CMPAs are benign and outgrown during childhood. CMPA is not as common in adults as in children, but when

present, it is usually severe with a protracted course. Lactose intolerance is a prevalent condition characterized by the development of many symptoms related to the consumption of foods containing lactose. Lactose intolerance has four typical types: Developmental, congenital, primary, and secondary. Lactose intolerance and CMPA may be the underlying pathophysiologic mechanisms for many functional gastrointestinal disorders in children and adults. They are also common in inflammatory bowel diseases. Milk consumption may have preventive or promoter effects on cancer development. Milk may also become a source of microbial infection in humans, causing a wide array of diseases, and may help increase the prevalence of antimicrobial resistance. This editorial summarizes the common milk-related disorders and their symptoms from childhood to adulthood.

Key Words: Cow's milk; Adults; Children; Functional gastrointestinal disorders; Cow's milk protein allergy; Lactose intolerance, Inflammatory bowel disease; Zoonosis

Core Tip: Milk has been a basic human food for hundreds of centuries with a high nutritional value. However, milk can cause various gastrointestinal disorders from early childhood to late adulthood, as many milk ingredients, such as lactose and cow's milk proteins, can trigger gastrointestinal discomfort and disorders. Cow's milk protein allergy and lactose intolerance are the most common milk-related disorders. However, milk consumption is related to many functional gastrointestinal disorders, inflammatory bowel disease, milk-related cancer, and milk-born zoonotic infections. Awareness of these disorders is crucial for physicians and patients to avoid unnecessary nutritional mismanagement.

Citation: Al-Beltagi M, Saeed NK, Bediwy AS, Elbeltagi R. Cow's milk-induced gastrointestinal disorders: From infancy to adulthood. *World J Clin Pediatr* 2022; 11(6): 437-454
URL: https://www.wjgnet.com/2219-2808/full/v11/i6/437.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i6.437

INTRODUCTION

Milk is a comprehensive dietary liquid containing adequate amounts of highly bioavailable nutrients humans need. Humans have consumed animal milk for about 10000 years and as baby food for about 8000 years, as evidenced by the dental remains of Neolithic humans, ancient clay pottery vessels, and ancient baby bottles[1]. Many gastrointestinal disorders humans suffer are related to dietary components, and diet modification could be an essential step in disease management. As milk is a critical component in the human diet, milk is related to many gastrointestinal disorders from the cradle to the grave[2]. Many milk ingredients, such as lactose and cow's milk proteins, can trigger gastrointestinal discomfort and disorders. Milk decreases gut bacterial diversity. Dairy and dairy products, such as yogurt and kefir, can modulate and alter the gut microbiota[3]. In addition to its effects on gut microbiota, cow's milk may make humans prone to many food-borne infectious diseases. In this editorial, we discuss the various cow's milk-induced gastrointestinal disorders from infancy to adulthood that will be highlighted in the topics of this special issue. Table 1 summarizes the various gastrointestinal effects of cow's milk on humans.

METHODS AND RESULTS

In this editorial, we conducted a comprehensive literature review by searching electronic databases such as PubMed, Embase, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature, Web of Science, Scopus, Library and Information Science Abstracts, and the National Library of Medicine catalog up to July 31, 2022, related to cow milk effects on the gastrointestinal tract in children and adults. Reference lists were inspected, and citation searches were performed on the included studies. We included open-access papers on English-language studies. Figure 1 shows the flow chart of the reviewed articles. We included 146 articles concerned with the various effects of cow's milk on humans, from birth to the elderly. We also cited high-quality articles in *Reference Citation Analysis* (https://www.referencecitationanalysis.com).

Table 1 The various gastrointestinal effects of cow's milk in humans

Items	Details
Cow's milk protein allergy	Pediatric onset: (1) IgE-mediated; (2) Non-IgE-mediated; and (3) Mixed type
	Adult onset: (1) Mostly IgE-mediated; and (2) Pregnancy-induced CMPA
	Pediatric onset with adulthood persistence
Lactose intolerance	Developmental
	Congenital (inherited)
	Primary (aging-induced)
	Secondary
Cow's milk-related functional gastrointestinal disorders	Functional dyspepsia
	Persistent regurgitation and gastroesophageal reflux
	Infant colic
	Functional constipation
	Irritable bowel syndrome
Cow's milk and inflammatory bowel diseases	Crohn's disease
Cow's milk-related gastrointestinal cancer	Anti-colorectal cancer
Milk-born gastrointestinal infections	*Mycobacterium avium*, *Mycobacterium bovis*, *Salmonella species*, brucellosis, streptococcal infections, "summer diarrhea", *Yersinia enterocolitica*, *diphtheria*, *Escherichia coli* (*E. coli*), *Campylobacter jejuni*, *Citrobacter species*, *Shiga toxin-producing E. coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Klebsiella species*

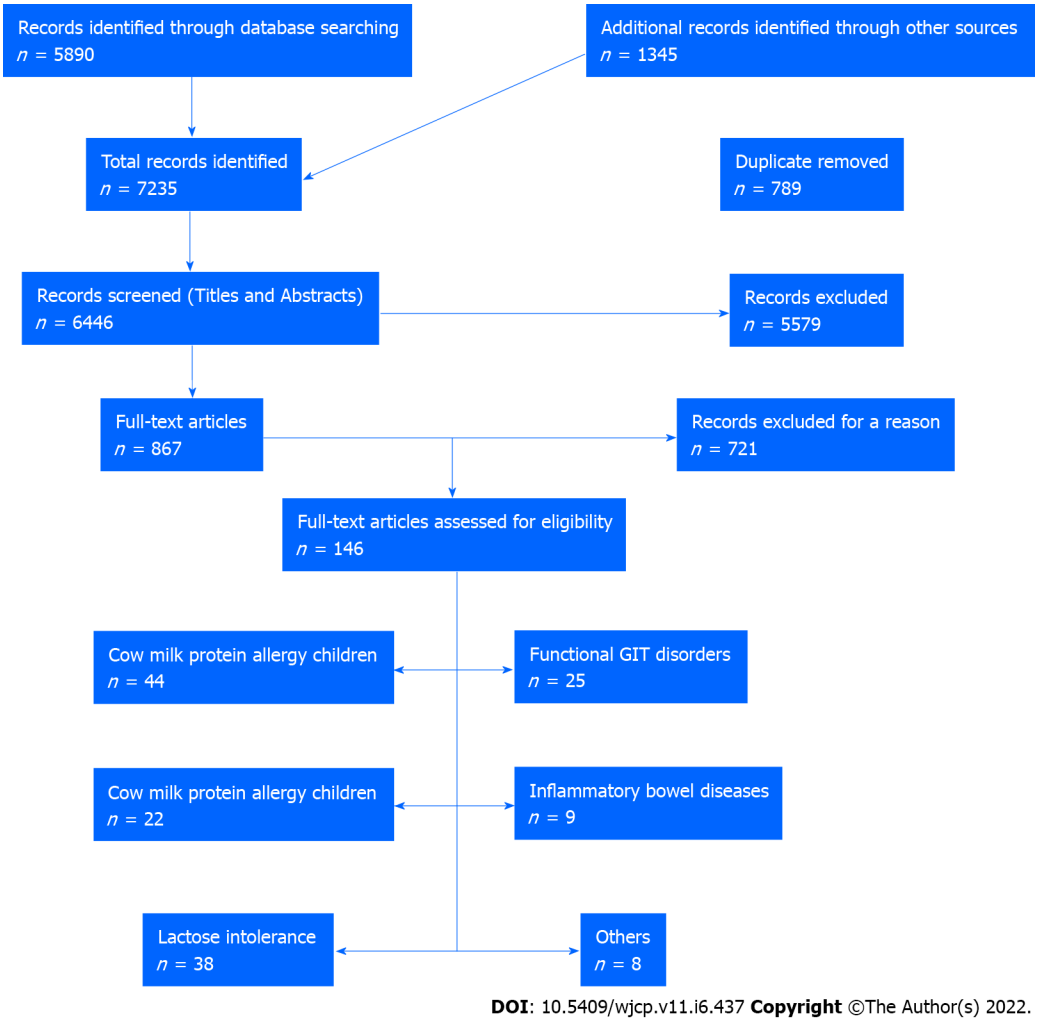
E. coli: *Escherichia coli*.

COW'S MILK PROTEIN ALLERGY

Cow's milk protein allergy (CMPA) is the most frequent food allergy, especially in infancy and childhood, but it can persist into adulthood. It is due to an abnormal immune response to CMP. It should be distinguished from the other adverse effects of cow's milk, such as lactose intolerance and infection-related disorders[4]. Both casein and whey (α-lactalbumin and β-lactoglobulin) proteins can cause allergic reactions. α-lactalbumin and casein are the most common cow's milk allergenic proteins, while β-lactoglobulin is associated with severe anaphylaxis[5]. In addition, β-lactoglobulin has a relative resistance to enzymatic degradation. Therefore, β-lactoglobulin could be implicated in non-immunoglobulin E (IgE)-immune-mediated CMPA with delayed gastrointestinal symptoms[6]. Besides cow's milk and dairy products, CMPs can be detected in some probiotics, oral polio vaccines, and lactulose. Some dry powder inhalers containing lactulose (such as Fluticasone/Salmeterol or Lanimavir) could be contaminated with CMPs. Some parenteral vaccines, such as the diphtheria-tetanus-pertussis vaccine, can be contaminated with CMP[7].

It should also be noted that cow's milk allergy is not only against cow's milk proteins but can also be triggered by other additives that could be added to modify cow's milk, such as artificial flavors or preservatives. Cross-reactivities with other mammals' milk (*e.g.*, goats and sheep) and raw beef are prevalent due to the composition of homologies of amino acids[8,9]. About 13%-20% of children with CMPA have a beef meat allergy. In addition, patients with beef meat allergies mostly have CMPA. Camel's milk proteins are unlikely to cross-react with cow's milk proteins due to phylogenetic differences, and consequently, camel's proteins cannot be recognized by circulating IgEs and monoclonal antibodies[10]. Even though soy milk is being used as a possible substitute for cow's milk in the case of CMPA, cross-reactivity between both occasionally exists due to cross-reactivity with bovine caseins and soybean protein p34[11].

There are three main types of CMPA: IgE-mediated CMPA, non-IgE-mediated CMPA, and mixed allergic reactions. The role of other kinds of immune-mediated reactions to CMP, especially those associated with IgG and IgA antibody isotypes, is presently controversial[12]. The rate of IgE-mediated CMPA decreases while other non-IgE-mediated CMPA increases with increasing age. High cow's milk-specific IgE levels are rare in adults[13]. CMPA may manifest as an isolated gut reaction or be associated with other systemic manifestations such as skin, respiratory, or cardiovascular manifestations. CMPA can affect any part of the gastrointestinal tract, from the mouth to the anus, and at any age, from newborn to the elderly[14].



DOI: 10.5409/wjcp.v11.i6.437

Figure 1 The flow chart of the included studies. GIT: Gastrointestinal tract.

CMPA in infancy and childhood

CMPA commonly occurs early in life, and almost all cases appear before the first birthday. The average age for CMPA to appear during childhood is 3.5 mo (ten days-to-ten months). The symptoms usually appear in the first week after the introduction of CMP (95% of cases). About 60% of patients developed symptoms with the first formula feeding[15].

Risk factors for CMPA include immature gastric acid production, defective intestinal and pancreatic enzymes, low vitamin D levels, and a deficit of regulatory T cells[16,17]. Other risk factors include male sex, parental atopy, maternal allergy, maternal smoking during pregnancy, amnionitis, maternal vaginitis, febrile infection during pregnancy, gestational diabetes, hypertension, stress, decreasing maternal age, and difficult delivery (early or threatened labor, malpresentation of the fetus, cesarean section, breech and instrumental delivery, low APGAR score). Post-natal risk factors include neonatal jaundice, Erythema toxicum neonatorum, antibiotic use in the first week of life, and indoor air contaminants such as mold and smoking[18,19]. Another important risk factor for CMPA during infancy is gut microbial dysbiosis. Gut microbiotas play a vital role in modifying intestinal regulatory T (Treg) cell responses to develop an oral tolerance that could protect against IgE-mediated CMPA and other types of food allergies[20]. On the other hand, non-IgE-mediated CMPA can induce gut microbial dysbiosis, affecting intestinal immune homeostasis and tolerance[21]. Tan *et al*[22] showed that *Lactobacillus rhamnosus* (*L. rhamnosus*) could help promote oral tolerance in children suffering from CMPA and assist with intestinal symptom recovery.

Sensitization can occur before and after birth, resulting in non-IgE mediated CMPA as indicated by the presence of CMP-specific tumor necrosis factor-α in the cord blood and the appearance of the symptoms shortly after birth[23]. The onset of symptoms in infancy and childhood usually develops within a week of cow's milk exposure, although symptoms may take many weeks (up to 24 and 36 wk). Most cases appear after cow's milk exposure (raw or formula milk), but some may appear after cow's milk-based foods. However, some exclusively breastfed infants may develop CMPA after exposure to CMP excreted in breast milk[24,25]. Most CMPAs are benign and outgrown during childhood. Non-IgE-mediated CMPA usually resolves more quickly than IgE-mediated allergy. Signs of persistence of

CMPA include the presence of acute manifestations, multiple food allergies, especially to eggs, concomitant bronchial asthma, allergic rhinitis, and reactivity to CMP in baked milk on exposure or first challenge[26,27].

Gastrointestinal symptoms of CMPA in infancy and children

Acute manifestations of IgE-mediated CMPA include nausea, vomiting, diarrhea, bloody stools, gastroesophageal reflux (GER), and colicky abdominal pain. The symptoms usually appear rapidly within minutes of exposure. Anaphylaxis may also manifest in young infants with angioedema of the lips, tongue, and palate, oral pruritus, pallor, and floppiness[28]. Symptoms may occur even during the neonatal period and can be so severe as to be misdiagnosed as neonatal sepsis[29]. Non-IgE-mediated CMPA is common (50% of pediatric CMPA) and is presented with faltering growth, frequent "spitting up", feeding problems, food refusal or aversion, pallor and tiredness, abdominal colic, upper digestive bleeding, gastroesophageal reflux with or without disease (GERD), abnormal stool habitus such as chronic diarrhea or constipation, blood and/or mucus in the stools, perianal redness, and skin manifestations such as atopic eczema[30,31].

CMPA (often non-IgE mediated) can present with symptoms of GERD, such as poor appetite, crying, fussiness, regurgitation, vomiting, and sleep disturbances. Oral milk elimination and rechallenge tests, esophageal pH impedance, and gastrointestinal endoscopy are advised for a correct clinical diagnosis, but they are not always achievable in all patients[32]. Eosinophilic esophagitis is an immune-mediated disease by Th2 interleukins affecting the esophagus with age-dependent symptoms such as GER, abdominal pain, and food impaction. Various allergens, including CMP can trigger it. Endoscopy shows characteristic features of mucosal eosinophilic infiltration of more than 15 eosinophils/high power field [33]. It can be treated with proton-pump inhibitors, but dietary treatment is the cornerstone of therapy after confirming the diagnosis with endoscopy and a 4- to 12-wk elimination test. The dietary approaches involve amino acid-based formula, allergy testing-based directed diet, or empirical six-food elimination diet (milk, soy, wheat, eggs, fish/seafood, and peanut/nuts)[34,35].

Hemorrhagic gastritis: Hemorrhagic gastritis is not common in infants with CMPA but is recorded in some cases. A possible cause is *in utero* CMP sensitization. It may be present with persistent vomiting and with subacute or chronic hematemesis. Occasionally, it may be present with subclinical hemorrhage. Endoscopy is usually needed to confirm the diagnosis. Nevertheless, etiological diagnosis is made according to clinical guidelines to diagnose CMPA with an elimination diet and rechallenge test. The outcome is usually favorable, with complete spontaneous resolution within one week after a period of bowel rest using either parenteral nutrition or amino acid formula[36,37]. Acute pancreatitis was recorded in one case with eosinophilic gastroenteritis due to CMPA[38].

Food protein-induced protein-losing enteropathy: Food protein-induced protein-losing enteropathy in infancy is a mixed IgE and non-IgE immune-mediated food allergy characterized by villous atrophy that leads to enteral loss of proteins, causing hypoproteinemia/hypoalbuminemia, diarrhea, edema, malabsorption, and poor weight gain. Laboratory work-up showed anemia, eosinophilia, hypoalbuminemia, raised fecal α1-antitrypsin (α1AT), raised specific-IgE, and positive allergy skin prick test (SPT) for milk proteins[39]. Hypoalbuminemia results from protein loss in the stool. α1AT is a part of the plasma protein not digested in the intestines and is not present in animal or plant food. The increased fecal α1AT is a good marker of protein loss through the digestive system[40]. A diagnosis relies mainly on the response to an elimination diet, with clinical improvement usually occurring within 3-4 d, but it may take weeks to resolve fully[41].

Food protein-induced enterocolitis syndrome: Food protein-induced enterocolitis syndrome (FPIES) is mainly a non-IgE-mediated disease caused mainly by CMP. It is caused by IgE-mediated mechanisms in 25% of cases, especially in patients with more protracted and persistent courses. Those with multiple allergies present with copious, repetitive vomiting, abdominal pain, and frequent diarrhea, causing acute dehydration with lethargy. Weight loss and failure to thrive occur in chronic conditions. FPIES is frequently misdiagnosed as acute viral gastroenteritis, sepsis, or surgical conditions, which delays the diagnosis for many months. FPIES occasionally results in symptoms similar to protein-induced protein-losing enteropathy and protein-induced proctocolitis[42,43]. The diagnosis is mainly clinical. However, open food challenges, milk-specific IgE, and SPTs can help diagnose FPIES. Milk-specific IgE is positive in about 25% of cases. Ondansetron may help in acute conditions. FPIES usually resolves by 3-5 years [44]. However, we still need future investigations and treatment guidelines to improve patient care for those with FPIES.

Food protein-induced allergic proctocolitis: Food protein-induced allergic proctocolitis (FPIAP) is a benign non-IgE-mediated delayed immune response to allergenic foods such as a cow or soymilk protein. It usually presents with a bloody mucoid stool in a well-appearing healthy infant aged one to four weeks. It occurs mainly in exclusively breastfed infants (60%) and resolves when the mother eliminates CMP and soy proteins from their diet[45]. As skin allergy tests and IgE are negative in infants with FPIAP, the diagnosis is usually made by exclusion and confirmed with an elimination/rechallenge test with CMP or soymilk protein[46]. The symptoms usually disappear within 1-3 d of the elimination

of the offending CMP or soy protein from the diet of breastfeeding mothers. However, it may take a longer time to resolve the symptoms. With a dairy-eliminated diet, the mother should be supported with a daily calcium intake of at least 800 mg and multivitamins as needed. Bottle-feeding babies may benefit from extensively hydrolyzed formulas or sometimes amino acid-based formulas. FPIAP is benign, and most cases resolve by the first birthday[47].

CMPA in adults

CMPA is not as common in adults as in children, but when present, it usually has a severe and protracted course. The symptoms can be elicited by traces of milk as small as 0.3 mg of CMPs[40]. Adults with CMPA have allergies to the same major allergenic milk proteins (casein and whey). However, they usually display robust immune responses, as illustrated by powerful SPTs and high IgE reactivity[48]. Even dermal or respiratory exposure to CMP can induce a severe form of CMPA, including anaphylaxis. Repeated exposure to CMP by food handling or inhalation of dairy products could induce cutaneous sensitization in adult patients with a personal history of atopy[49,50]. Hansen *et al*[51] showed that only 1%-3% of children with CMPA would continue to have CMPA as an adult, usually severe and life-threatening. Stöger and Wüthrich[52] showed that CMPA was more common in females (92%); 39% of them developed CMPA during or shortly after pregnancy. Casein was the predominant sensitizing allergen in 71%, while whey protein sensitization (alpha-lactalbumin and beta-lactoglobulin) was rare. He *et al*[53] demonstrated that A1 β-casein is the responsible component of casein that can induce CMPA, whereas A2 β-casein alleviates the acute gastrointestinal symptoms in Chinese adult patients with CMPA. The presence of other autoimmune diseases could increase the risk of CMPA. Kristjánsson *et al*[54] showed that 50% of adult patients with coeliac disease developed a mucosal inflammatory response similar to that of gluten with rectal CMP. Casein was the main allergic protein. About one-quarter of patients with irritable bowel syndrome (IBS) have food hypersensitivity, including CMPA[55].

Different factors can affect the prevalence of CMPA in adults, such as ethnic origin and geographical area. A study by Domínguez-García *et al*[56] on young adult students (18- to 25-year-olds) in a Mexican university showed that the prevalence of CMPA among them was 1/400 compared to 1/10 for lactose intolerance. A risk factor for developing CMPA in adulthood is the excessive intake of dairy products [57]. Sousa *et al*[58] reported a 24-year-old man who developed CMPA after excessive intake of hydrolyzed casein and whey CMPs for bodybuilding for two years. CMPA was confirmed by positive IgE against cow's milk α-lactalbumin, β-lactoglobulin, and casein extracts, suggesting that excessive CM intake may induce CMPA. On the other hand, adult patients with CMPA have lower IgG levels than controls[58]. The respiratory tract and skin are the main organs affected in adulthood CMPA in adults, while gastrointestinal and cardiovascular manifestations are less frequent than in childhood CMPA[59]. Due to the higher rate of lactose intolerance compared to CMPA in adults, some cases of CMPA are wrongly diagnosed as lactose intolerance due to the common symptoms. Lactose intolerance can be excluded by the negative hydrogen breath test for lactose, the positive cow's milk challenge and SPTs, and high IgE levels against CMP[60]. Therefore, cases with refractory lactose intolerance should be investigated for CMPA, as IgE-mediated sensitivity to CMP is a common comorbidity in patients with refractory lactose intolerance not responding to a lactose-free diet[61]. Although most CMPAs reported in adults are IgE-mediated, non-IgE-mediated CMPAs may also occur. For example, FPIES, which are non-IgE-mediated CMPAs, can also be observed in older children and adults[62,63]. IgG-mediated CMPAs were also reported by Anthoni *et al*[12]. They reported a significant association of high IgG levels with self-reported milk-provoked gastrointestinal symptoms, especially constipation, in the adult population. However, the serum IgG levels decrease with the increasing age of the affected patients[10].

Despite adulthood CMPA prevalence being about one-quarter of childhood CMPA, the adulthood type is more severe and more liable to complications and even death. CMPA is rarely implicated in the worsening of coexisting atopic dermatitis during adolescence and adulthood[64]. Recurrent acute pancreatitis was reported as a rare complication of IgE-mediated CMPA. de Diego Lorenzo *et al*[65] reported recurrent episodes of acute pancreatitis in a 23-year-old patient with characteristic abdominal pain and high serum pancreatic enzyme levels, confirmed by the presence of swelling and edema of the pancreas on the sonogram. The episodes were induced by milk consumption and associated with diarrhea and signs of generalized urticaria, such as conjunctival injection, facial erythema, and generalized pruritus. The blood showed eosinophilia and high serum levels of CMP-specific IgE and anti-beta-lactoglobulin IgE[66].

In addition, young adults with CMPA in infancy are at an increased risk of failing to reach their growth potential and height. Therefore, they are candidates for proper growth and nutritional monitoring and need appropriate dietary intervention[65]. They are more prone to reduced bone mass density and developing early osteoporosis. This effect could be reversed by milk desensitization, adequate calcium supplements, and optimal nutritional rules for these patients. Eliminating dairy products in treating adult patients with CMPA may increase the risk of gout and hyperuricemia, as milk consumption protects against gout[67].

LACTOSE INTOLERANCE

Lactose is a disaccharide composed of galactose linked to glucose that can be hydrolyzed in the small intestine brush border membrane by β-galactosidase (lactase enzyme). After infancy, lactase activity progressively decreases due to a gradual decrease in lactase synthesis ability. Therefore, adults do not tolerate large amounts of lactose[68]. Lactose intolerance is a common condition of food intolerance characterized by the development of many symptoms following the consumption of foods containing lactose, the primary milk sugar, due to absolute or relative deficiency of the lactase enzyme in the mucosal brush border of the small intestine. As a result of inadequate lactose digestion, the lactose reaches the colon undigested, where the gut microbiota ferments it, causing nonspecific symptoms such as abdominal pain, bloating, flatulence, and mushy to watery diarrhea. The symptoms usually develop within 30 min to a few hours after lactose ingestion. The severity of the symptoms correlates with the deficiency of the lactase enzyme. Therefore, nausea and vomiting may occur after consuming large amounts of lactose-containing foods such as dairy products[69-71].

There are four main types of lactose intolerance; developmental lactose intolerance, which occurs in premature babies as lactase enzyme production starts after 34 wk of gestation; congenital lactose intolerance, which is inherited from lactase deficiency due to a defect in the gene responsible for lactase synthesis; primary lactose intolerance, which results from the normal aging process and is the most common cause of lactose intolerance; and secondary lactose intolerance which results from damage of the brush border of the intestinal mucosa due to infection, inflammation, or trauma and improves with treatment of the cause[72]. Lactose intolerance can be isolated or part of a broader intolerance to variable saccharides, including monosaccharides, disaccharides, oligosaccharides, and polyols. It is crucial to determine whether lactose intolerance is isolated or compounded during the treatment to ensure successful therapy of a lactose-free diet[73].

The manifestations of lactose intolerance depend on many factors, in addition to the degree of lactase deficiency. These factors include the dose of ingested lactose; the osmolality of the food; the dietary fat content; gut motility and gastric emptying time; gut microbiota and its ability to ferment lactose; small intestinal bacterial overgrowth; water absorptive capacity of the colon; and the pain threshold due to sensitivity of the intestine to the generated gases and other fermented substrates due to lactose fermentation[73]. For example, a patient with lactose intolerance may tolerate up to 12 g of lactose (equivalent to a glass of milk); an amount between 12 and 18 g can be tolerated when mixed with other types of food; while an amount between 18 and 50 g starts to produce symptoms of lactose intolerance and the symptoms increase with increased the amount. Lactose over 50 g causes significant symptoms in most patients. However, the relation between the amount of ingested lactose and the severity of the symptoms needs more valid evidence[70]. These symptoms include abdominal distension, bloating, colic, abdominal pain, increased borborygmi, flatus, and osmotic diarrhea induced by lactose in dairy products. Nonspecific symptoms of lactose intolerance may include headaches, muscle pain, chronic fatigue, depression, and concentration problems[74].

Diagnosis of lactose intolerance

Diagnosis of lactose intolerance depends on self-reported symptoms, dietary challenges, and investigative testing, including physiological, genetic, and endoscopic testing. Physiologic testing depends on the evaluation of lactase activity by different methods. It is also essential to rule out secondary causes. When lactose intolerance is assumed, a trial of a lactose-free diet should be conducted for 2-4 wk with the elimination of all lactose sources, including hidden lactose sources. Then, lactose is reintroduced to the diet. If symptoms recover during the 2-4 wk period and reappear with lactose reintroduction, a lactose intolerance diagnosis can be made[75]. Indirect evidence of lactose malabsorption due to lactase deficiency includes measuring stool pH and reducing substances. Fecal pH of less than 6.0 may suggest lactose intolerance. However, this test is not recommended in infants less than two years of age due to the high rate of false negative results[76]. Fecal-reducing substances are another indirect tool to diagnose lactose (or other carbohydrates) maldigestion and malabsorption. Positive results may suggest an absence of the related enzyme[77]. However, false negative results could occur if the patient has not recently ingested lactose.

The lactose hydrogen breath test: The lactose hydrogen breath test is commonly done in suspected lactose-intolerant patients. The test depends on the principle that lactase deficiency causes lactose indigestion, which undergoes gut microbiota fermentation and subsequent hydrogen gas production. The patient ingests 25 to 50 g of lactose, and then the hydrogen gas is checked every 15 min for 3-6 h. The increasing hydrogen concentration in the breath by more than 20 ppm (parts per million) over baseline after lactose ingestion indicates hypolactasia. However, the test needs a long duration (3-6 h) with a risk of a false negative in 10% of cases[78]. A false negative test may be related to the presence of non-hydrogen-producing fermenting bacteria. In this situation, methane-producing bacteria may cause methane gas production in about one-third of the adult population and may have additional health consequences worse than excess hydrogen levels. Therefore, combined measuring of hydrogen and methane significantly improves the diagnosis of malabsorption syndromes, including lactose intolerance and small intestinal bacterial overgrowth, compared with a single hydrogen breath test[79].

The lactose tolerance test: The lactose tolerance test examines the ability to digest lactose to its components by checking the glucose level after administering 50 g of lactose orally. The blood glucose levels are checked before and after 30, 60, and 120 min of lactose intake. The absence of increased blood glucose levels after oral lactose intake indicates the inability of the body to digest lactose and hence possible lactase deficiency. However, this test is affected by other factors, such as gastric emptying time and mechanisms of glucose metabolism, and has lower sensitivity and specificity, with false positive and negative results in 20% of patients. Therefore, it is rarely performed. However, it can detect patients with lactose intolerance and a negative hydrogen breath test due to a lack of hydrogen gas-producing bacteria. Patients with diabetes mellitus are not candidates for this test as their blood sugar will increase even in the presence of lactose intolerance[80,81].

The gaxilose test: The gaxilose test is considered the new gold standard for lactose intolerance diagnosis. It uses gaxilose, a synthetic disaccharide formed of -O-β-D-galactopyranosyl-D-xylose that can be metabolized with lactase enzyme into galactose and xylose due to its structural similarity to lactose. Xylose is absorbed by the enterocyte, reaches the blood, and is then excreted in the urine. Therefore, the blood and urine levels of xylose will reflect the activity of the lactase enzyme available to metabolize gaxilose. However, this recent test needs more studies to confirm its efficacy, safety, sensitivity, and specificity[82-84].

Genetic tests: Genetic tests apply real-time polymerase chain reaction or sequencing of DNA extracted from buccal mucosa or venous blood to detect the genetic type of lactose intolerance. Determining the lactase enzyme activity on intestinal biopsies is done for other reasons to detect a primary or secondary cause of lactose intolerance. The patchy activity of lactase should be considered during the biopsy. Therefore, more than a single biopsy may be needed to achieve optimal test accuracy. The genetic test is a good predictor of lactase persistence or non-persistence in specific populations[85-87].

Lactose intolerance comorbidities

Lactose intolerance should not be considered an isolated disorder as it may trigger many other diseases. There are significant correlations between lactose intolerance and the prevalence of osteoporosis, mental status changes, and the existence of other food intolerances[74]. Infant colic is a common problem. Subclinical lactose intolerance could be an underlying pathophysiologic mechanism[88]. About one-third of patients with IBS have lactose intolerance as a part of their malabsorption syndrome. Therefore, a trial of a lactose-free diet is a common practice in managing IBS. Consequently, a hydrogen breath test is recommended in newly diagnosed patients with IBS to identify those who would benefit from a lactose-free diet[89]. At the same time, patients with inflammatory bowel disease (IBD) have a 2.7-fold increased risk of lactose intolerance, indicating the need to screen patients with IBD for lactose intolerance to avoid overlapping or confusing symptoms[90].

CMPA could be a comorbidity of lactose intolerance or the underlying cause as the CMP-immune mediated inflammation destroys the brush border of the intestinal mucosa that contains lactase enzyme, resulting in lactase deficiency and lactose intolerance. In addition, CMPA is commonly mistaken for lactose intolerance as both have common symptoms. Therefore, CMPA should be considered in lactose-free diet-refractory lactose intolerance. However, there are critical differences between cow's milk allergy and lactose intolerance which could limit misunderstandings in diagnosing these two conditions [60,91]. Grundmann *et al*[92] showed that 21.4% of patients with chronic pruritus had lactase deficiency, and 38.3% had an excellent anti-pruritic effect after four weeks of a lactose-free diet. Therefore, lactase deficiency could be an independent underlying cause of chronic pruritus. Hence, lactase deficiency screening is a reasonable diagnostic step in investigating chronic pruritus. A lactose-free diet should be tried if lactose intolerance is confirmed in patients with chronic pruritus[92]. Patients with systemic sclerosis have a 44% higher prevalence of lactose intolerance than those in control. Lactose intolerance occurs as a part of the malabsorption syndrome that results from gut inflammation as a feature of systemic inflammation associated with systemic sclerosis[93]. Other saccharides malabsorption, such as fructose malabsorption, is also common in patients with systemic sclerosis[94]. On the other hand, a cross-sectional study over ten years showed that patients with lactose intolerance might have a reduced risk of gastric and colon cancer[95].

Management of lactose intolerance

Management of lactose intolerance is sometimes tricky. First, we should confirm the diagnosis, detect secondary causes, and determine the amount of lactose the patient can tolerate. This step is crucial in the management, as complete lactose restriction is not advised. Usually, 12-15 g of daily lactose can be tolerated by most adult patients and up to 5 g by most children, especially when mixed with foods. We start with a lactose-restricted diet, then gradually reintroduce milk and milk products according to the person's tolerance to improve the symptoms and induce tolerance[96]. Mixing lactose with other foods causes slow lactose release in the small intestine and better tolerance. Some lactose-containing foods can be more easily tolerated than others. Yogurt is better tolerated as it contains partially hydrolyzed lactose. On the same track, high-fat-containing dairy products cause delayed gastric emptying and slow

lactose release, while skimmed milk can produce severe symptoms due to low fat and high lactose content[71,97].

Consistent and continuous gradual administration of lactose often improves the number and effectiveness of colonic bacteria metabolizing lactose, generating fewer symptoms[98]. Probiotics containing lactose-fermenting bacteria such as *Streptococcus thermophilus, L. reuteri*, *L. rhamnosus*, *L. acidophilus*, *L. bulgaricus*, and *Bifidobacterium longum* promote lactose digestion and help to improve gastrointestinal symptoms of lactose intolerance[99].

Therefore, lactose-free milk is usually unnecessary except when a large daily amount of milk is needed, such as during infancy or in severe cases when small doses produce marked symptoms of lactose intolerance. Milk alternatives such as coconut, almond, rice, or oat milk should not be used as the primary nutritional milk source for children below the age of five years. These types of milk should also be fortified with vitamin D. Soy milk, or any plant-based milk, is not recommended for infants below the age of one year. However, soy milk might be considered in infants older than six months if they cannot tolerate satisfactory amounts of cows' milk formula[100,101]. Children with lactose intolerance using lactose-free milk or plant-based formula are more likely to develop osteoporosis and decreased bone density due to a deficiency of calcium, vitamin D, riboflavin, and protein. They should be supplemented with adequate calcium and vitamin D intake to ensure optimal peak bone mass in childhood and adolescence. Adequate vitamin D and calcium intake can be achieved by increasing consumption of calcium-rich non-dairy foods such as fish, dark green leafy vegetables, tofu, seeds, and nuts, as well as getting enough sunlight exposure through daily walks and other outdoor activities[102,103].

If symptoms of lactose intolerance are still present despite adequate nutritional management, lactase enzyme supplements can be tried as an adjunct and not a replacement for dietary management. Enzyme replacement therapy may not completely alleviate symptoms, and it is hard to calculate the effective dose[96]. However, a recent study showed that oral lactase enzyme supplementation significantly lessened the clinical symptoms and diminished hydrogen breath excretion in subjects with lactose intolerance[104]. Breastfeeding mothers of infants with lactose intolerance do not need to have a low or free-lactose diet, as the lactose content of the breast milk has no relation to the lactose intake by the mother. On the other side, formula-fed infants benefit from a lactose-free formula with a trial of lactose-containing reintroduction food over 2-4 wk[105].

COW'S MILK-RELATED FUNCTIONAL GASTROINTESTINAL DISORDERS

Functional gastrointestinal disorders (FGIDs) are frequent disorders in infants, children, and adults, characterized by persistent and recurring gastrointestinal symptoms (*e.g.*, dysphagia, abdominal pain, dyspepsia, bloating, constipation, or diarrhea) in the absence of clear underlying pathological conditions. However, diet is an essential factor in the pathogenesis and management of FGIDs[106]. Functional dyspepsia is characterized by recurrent symptoms and signs of indigestion without apparent cause. The link between cow's milk and functional dyspepsia is not well established. Unfortunately, intolerance of dairy products is usually not one of the differential diagnoses of functional dyspepsia. In their study, Wortmann *et al*[107] showed that adult-type lactose intolerance was present in 44.7% of patients with functional dyspepsia. Mishkin *et al*[108] showed that the prevalence of lactose intolerance in patients with functional dyspepsia is affected by ethnic group and age, with a decreased prevalence between 25-55 years and an increase after 55 years.

Persistent regurgitation is a common nonspecific symptom of CMPA in infants. It usually presents with excessive crying, irritability, pain, respiratory symptoms, and feeding or sleep disturbance. CMPA was documented in up to 50% of infants with persistent GER, which could be just an association or CMPA-induced GER. The likelihood of CMPA increases in the presence of atopy and multiorgan symptoms such as failure to thrive, diarrhea, rectal bleeding, or atopic dermatitis[32,109,110]. A negative SPT does not rule out CMPA as it is IgE-and non-IgE-mediated. At the same time, clinical improvement with a cow's milk-free diet is not solid proof of immune system involvement. Therefore, esophageal pH impedance, oral food challenge, and endoscopy are recommended to reach a correct clinical diagnosis and classification, but they are not always possible in all infants[111]. We should consider using 2-4 wk of a protein hydrolysate or amino acid-based formula in a formula-fed infant or eliminating cow's milk in the maternal diet in breastfed infants[112]. However, there is not enough evidence to avoid drinking milk for GER. Patients with GER who tolerate cow's milk may continue to consume it. Avoidance of milk consumption should be avoided only if symptoms of GER increase with milk consumption[113]. Due to its acid-neutralizing properties, milk has long been used to treat the symptoms of peptic ulcers and GERD. However, the high calcium and protein content significantly increased acid production by 30% for every 250 mL of milk. In addition, patients with peptic ulcers are more vulnerable to the effects of milk on the gastric parietal cells[114]. As confirmed by an endoscopic study[115], patients with peptic ulcers who avoided a milk-based diet had better ulcer cicatrization results than those who consumed milk. However, patients with a peptic ulcer can consume a moderate amount of dairy products according to their tolerance to benefit from their high nutritional content[116].

Infant colic is a functional disorder characterized by full-force crying for a minimum of three hours per day for a minimum of three days per week in infants younger than five months. It is a worldwide disorder affecting many infants and families. The precise mechanisms are not well known. While it does not indicate the presence of disease, it occasionally represents an underlying severe disorder in a small percentage of infants who may require a medical assessment[117]. Cow's milk may precipitate infant colic through CMPA and lactose intolerance. Both conditions can induce colic through gut inflammation (as indicated by fecal calprotectin) and gut dysmotility and dysbiosis, with fewer Bifidobacilli inducing abnormal peristalsis and colicky pain[118]. Colic may arise as a delayed reaction within a few hours to days of CMP consumption. Infant colic may be one of the many symptoms of CMPA. A cohort of 100 infants with colic showed a positive challenge-proven CMPA in 44% of the infants during a cow's-milk challenge[119]. Moravej *et al*[120] showed that the SPT for CMP was positive in 2.6% of infants with colic who responded well to cow's milk elimination from the mothers' diet. Many infants with colic have transient lactose intolerance, causing excessive gas production. Lactase enzyme activity may be low in many infants during the first weeks of life and may take a few weeks to improve. Pretreatment of feeds with lactase can improve colic[121]. For breastfeeding colicky infants, a trial of dairy product exclusion by the mother for 2-4 wk could produce symptomatic improvement. For bottle-fed infants, a partially hydrolyzed formula with Galacto-Oligosaccharides/Fructo-Oligosaccharides and added β-palmitate might be beneficial in cases where CMPA is not suspected. The mother can also use a formula containing prebiotics and/or ferments or a lactose-reduced formula[122].

Functional constipation is a common disorder in children, negatively impacting their quality of life. Simeone *et al*[123] showed that 17.3% of children with functional constipation had evidence of CMPA and improved with a CMP elimination diet. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition-North American Society for Paediatric Gastroenterology, Hepatology and Nutrition advised that a CMP-free diet be tried only in cases of laxative-resistant constipation and only after consulting an expert. However, a literature review by Sopo *et al*[124] showed that 28% to 78% of children with functional constipation benefited from a CMP-free diet. The review results give solid scientific evidence for a causal relationship between functional constipation and CMPA. Therefore, they recommended a two-to-four-week restricted diet as a first-line diagnostic and therapeutic strategy in children with functional constipation[124]. The same result was also found in the literature review by Gelsomino *et al*[125]. They propose that a CMP-free diet should be considered a first-line treatment for functional constipation, at least in preschool children and children with a previous diagnosis of CMPA or a personal or family history of atopy.

IBS is one of the most common FGIDs with poorly understood mechanisms that affect a significant proportion of the population with a strong negative impact on the quality of life[126]. The lack of well-understood underlying pathophysiologic mechanisms makes choosing effective treatment strategies difficult. Clinicians commonly recommend a lactose-free diet to manage this syndrome[118]. Approximately one-third of patients with IBS have some degree of lactose intolerance, which could be present with diarrhea, gas, and bloating. Milk lactose irritates the already vulnerable intestines of people with IBS. However, a systematic review by Vaiopoulou *et al*[127] did not find convincing evidence to indicate an objective relationship between IBS and any recognized malabsorption syndrome involving lactose intolerance.

On the other hand, a significant portion of people with IBS and self-reported lactose intolerance and negative hydrogen breath testing were proved to be due to underlying immune-mediated reactions to CMP. Carroccio *et al*[55] in a study with retrospective and prospective phases, showed that a percentage of self-reported milk intolerance in patients with IBS was not related to lactose intolerance; instead, they clinically reacted when subjected to whole cow's milk, indicating CMPA. Patients with IBS and lactose intolerance had more severe symptoms and a higher degree of fatigue, anxiety, and depression[128, 129]. Therefore, we should consider that a significant minority of patients with IBS could benefit from a dairy elimination diet, especially in the presence of evidence of CMPA. More studies are necessary to identify the complex pathogenic mechanisms of FGIDs and to improve their management[130].

COW'S MILK AND IBDS

The relationship between cow's milk and IBD is cause and effect. There is much evidence of an increased prevalence of ulcerative colitis in children with a previous history of CMPA. Knoflach *et al* [131] found high IgG and IgM against CMP in patients with IBD than in controls, with a good correlation between disease activity and the levels of IgG and IgA against certain CMPs. In addition, Virta *et al*[132] found in two separate studies that a past history of CMPA increases the prevalence of pediatric IBD. In contrast, asthma increases the likelihood of Crohn's disease[132,133].

On the other hand, lactose malabsorption prevalence is significantly more common in patients with Crohn's disease affecting the small intestine than in patients with Crohn's disease affecting the colon or patients with ulcerative colitis. In IBD affecting the colon, lactose malabsorption prevalence is affected by other factors, such as ethnic risk determined by genetic factors. The degree of lactose malabsorption in Crohn's disease of the small intestine is also affected by bacterial overgrowth and small intestine

transit time, in addition to lactase enzyme activity[132].

Avoiding dairy products is common dogmatic advice given by many physicians to patients with IBD. However, Strisciuglio *et al*[134] showed that dietary CMP elimination has no substantial role in managing ulcerative colitis in non-sensitized children. Due to dairy product restrictions in patients with IBD (either due to unnecessary fear of the presence of CMPA or due to the occurrence of secondary lactose intolerance), there is an increased risk of inadequate intake of calcium, an essential element to prevent the decrease in bone mineral density, which consequently increases the risk of osteoporosis. Therefore, proper dietary management is crucial to prevent osteoporosis through education and adequate dietary management with low/free-lactose milk, fermented milk, plant-based milk supplemented with calcium and vitamin D, calcium-rich foods, and calcium supplements[135]. The exclusion of certain types of foods should be based on solid science. Indiscriminate exclusion of certain foods increases the risk of nutritional deficiencies. Lim *et al*[136] showed that the mean daily calcium, vitamin A, and zinc intake were significantly decreased in the food exclusion group. Milk was the most common restricted food, followed by dairy products, raw fish, deep-spicy foods, and ramen. Therefore, the magnitude of osteoporosis will be further increased by dairy product restriction, in addition to the effects of IBD itself[137].

Fermented milk using specific lactic acid bacteria could help avoid dairy product restrictions. Fermented milk with lactic acid-producing bacteria contains exopolysaccharides, peptides, and short-chain fatty acids that help to modulate intestinal lumen pH, help recovery of intestine mucosa, modulate the gut microbiota, and alleviate the inflammatory response by modifying the innate and adaptive immune system. As a result, bioactive compounds derived from fermented milk can alleviate the negative symptoms of IBD[138]. Consequently, the disease activity can be significantly reduced by the oral administration of specific probiotics containing *B. subtilis* JNFE0126. Zhang *et al*[139] showed that *B. subtilis*-containing fermented milk could decrease the intestinal mucosa inflammatory response, induce intestinal stem cell proliferation, and promote mucosal barrier reconstruction. *B. subtilis*-containing fermented milk helps to rebalance the gut mucosa through the enrichment of *Lactobacillus, Bacillus*, and *Alistipes* and decrease *Escherichia* and *Bacteroides* abundance.

COW'S MILK-RELATED GASTROINTESTINAL CANCER

Despite data from the geographic distribution of colon cancer showing increased milk consumption [140], a meta-analysis found that milk and whole milk products are associated with a lower risk of colorectal cancer[141]. The protective effects of milk and whole dairy products are related to the high calcium content of milk. Calcium is the primary anti-carcinogen, especially in doses equal to or higher than 1200 mg/d. Therefore, calcium supplementation is indicated in patients with a contraindication to milk intake[142]. Vitamin D is another milk ingredient that protects against colon cancer. However, Baron *et al*[143] showed that daily vitamin D3 (1000 IU), calcium (1200 mg), or supplementation with both after surgical removal of colorectal adenomas did not show significant risk reduction of recurrent colorectal adenomas over a follow-up period of three to five years.

MILK AND GASTROINTESTINAL INFECTIONS

As milk is a part of everyday human food from birth onwards, it may be a source of microbial infection in humans, causing many diseases. Milk is rich in sugars, lipids, and proteins, which are ideal media for the growth of a broad spectrum of organisms. Diseases produced by milk-borne organisms include *Mycobacterium avium, Mycobacterium bovis, Salmonella species,* brucellosis, streptococcal infections, "summer diarrhea", *Yersinia enterocolitica*, *diphtheria*, *Escherichia coli* (*E. coli*), *Campylobacter jejuni*, *Citrobacter species*, *Shiga toxin-producing E. coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Klebsiella species*[144]. Campylobacter species and Salmonella species are the most common identified etiological agents, while other zoonotic infections, particularly yersiniosis and listeriosis, are increasingly reported. Most infections were due to improperly treated cows' milk or dairy products and increasingly polluted "heat-treated" milk products. Milk pasteurization decreased infectious diseases and their high infant mortality rates by only 50%, even with concurrent medical and dairy hygiene advances, particularly in the less developed world[145]. Most of these infections presented with manifestations of gastroenteritis, food poisoning, and hepatosplenomegaly, in addition to systemic manifestations such as fever, muscle aches, severe headache, meningitis, sepsis, pneumonia, and renal failure. Raw milk consumption, a common practice by milk producers on their farms, is a significant risk factor for milk-transmitted infection, despite the other health benefits of drinking fresh milk over pasteurized milk. In addition, raw milk consumption increases the risk of horizontal gene transfer of antimicrobial resistance genes where the bovine strains may meet the human microbiota and change them into resistant pathogenic strains, a fundamental reason for increasing the prevalence of antimicrobial resistance[146].

CONCLUSION

Cow's milk induces various gastrointestinal and systemic manifestations from birth to the elderly with various underlying mechanisms. Cow's milk allergy is a common disorder, especially at pediatric age, with different presentations according to the site of major implication. However, when it is present in adulthood, it is usually severe. Eliminating the offending CMP from breastfeeding mothers' diets and using extensively hydrolyzed or amino acid-based formulas are the main lines of treatment in infancy and childhood. Avoiding dairy and dairy products is also conducted for adults with CMPA. Different types of lactose intolerance can occur with different presentations and prevalence according to age and ethnicity. It can be isolated or be a part of a broader intolerance to various saccharides. CMPA and lactose intolerance, in addition to milk-induced gut microbiota dysbiosis, are commonly associated with various FGIDs such as gastroesophageal reflux, peptic ulcers, infant colic, IBS, and constipation. Cow's milk consumption may be implicated in the pathogenesis of some cancers and the prevention of others. In addition, cow's milk is a significant source of many zoonotic infections that could affect human health. It may also play a role in the development of antimicrobial resistance. This special issue will cover these various topics in more detail. Physicians and patients should be well oriented with milk-related disorders to avoid unnecessary nutritional mismanagement.

ACKNOWLEDGEMENTS

We thank the anonymous referees for their valuable suggestions.

FOOTNOTES

Author contributions: Al-Beltagi M, Saeed NK, Bediwy AS, and Elbeltagi R collected the data and wrote and revised the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Wang JJ
L-Editor: Webster JR
P-Editor: Wang JJ

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 November 9; 11(6): 455-462

DOI: 10.5409/wjcp.v11.i6.455

ISSN 2219-2808 (online)

OPINION REVIEW

Tangled relationship between insulin resistance and microalbuminuria in children with obesity

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Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Geng TY, China; Liao Z, Singapore

Received: July 31, 2022
Peer-review started: July 31, 2022
First decision: September 5, 2022
Revised: September 19, 2022
Accepted: October 27, 2022
Article in press: October 27, 2022
Published online: November 9, 2022

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Abstract

Childhood obesity represents a complex disease with a well-known cardio-metabolic burden including fatty liver, type 2 diabetes, metabolic syndrome, and cardiovascular disease. From a pathogenic point of view, insulin resistance (IR) represents the key factor underlying the spectrum of these obesity consequences. As observed in adults, recent data supported the occurrence of microalbuminuria (MA) as marker of early kidney dysfunction and its potential link with cardio-metabolic factors also in children with obesity. In fact, a well-documented pathophysiological hypothesis both in adults and children supported an intimate correlation with the major feature of obesity such as IR through the influence of insulin on renal hemodynamics. Based on the clinical and prognostic relevance of this relationship in daily practice (including an increased risk of chronic kidney disease development overtime), more scientific attention needs to be paid to the evaluation of early kidney damage in children with obesity. In this paper, we attempt to address three debated questions regarding the intriguing liaison between IR and MA in children with obesity: (1) What is the prevalence of pediatric MA? (2) What is the state of art of MA in children with obesity? and (3) Is there a link between IR and MA in children with obesity?

Key Words: Kidney damage; Microalbuminuria; Insulin resistance; Children; Obesity

Core Tip: In addition to the well-known cardiometabolic consequences of obesity (including fatty liver, type 2 diabetes, metabolic syndrome, and cardiovascular disease), early kidney damage has been also demonstrated in children with obesity. As a consequence of the dysmetabolism, the occurrence of microalbuminuria as an early marker of kidney dysfunction has been widely described in these subjects and closely linked to insulin resistance. Given the lack of extensive pediatric data and the prognostic implications of this intriguing association, a better knowledge in this field is needed to counteract the intrinsic increased cardiometabolic risk of children with obesity.

Citation: Colasante AM, Bartiromo M, Nardolillo M, Guarino S, Marzuillo P, Mangoni di S Stefano GSRC, Miraglia del Giudice E, Di Sessa A. Tangled relationship between insulin resistance and microalbuminuria in children with obesity. *World J Clin Pediatr* 2022; 11(6): 455-462
URL: https://www.wjgnet.com/2219-2808/full/v11/i6/455.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i6.455

INTRODUCTION

Microalbuminuria (MA) has been largely recognized as an independent predictive and prognostic marker not only of renal dysfunction but also of cardiovascular morbidity and mortality[1-3] not only in adults with diabetes or obesity but also in healthy subjects[1]. MA is diagnosed when urinary albumin excretion (UAE) is 30-300 mg/24 h in a 24-h urine collection or 20-200 μg/min in a night time collection and ratio of urinary albumin to creatinine concentrations (UACR) is 30-300 mg/g or 3-30 mg/mmol in a first-morning urine sample random urine[2]. Estimates from cross-sectional studies found a prevalence of MA in healthy adult subjects of approximately 4%[3,4] (3.7% in males and 4.6% in females, respectively[4]) with a significant increase up to 6.2% in patients with obesity[4]. In particular, visceral obesity has been linked to MA, since the negative role of visceral adipose tissue on cardiovascular outcomes[5,6]. In this context, MA and obesity had a similar additive effect on the risk of death, independently of other common risk factors (*e.g.*, diabetes, smoking, hypertension)[7].

Owing to its clinical relevance as an early marker of glomerular damage preceding the onset of overt diabetic nephropathy by 10-14 years[8], MA prevalence has been studied also in adults with diabetes, ranging from 7.4% to 11.4%[3,4]. Given the beneficial influence of an optimal glycemic control on the entire spectrum of renal impairments diabetes-related (MA, nephropathy, micro- and macrovascular consequences), MA screening has been recommended in these subjects[9,10].

In contrast to robust evidence supporting the clinical significance of MA in morbid adults, pediatric data in this field are still very limited[1].

WHAT ABOUT PEDIATRIC MA?

The evaluation of MA in healthy children and adolescents represents a pitfall since its potential relationship with strenuous exercise or febrile illness[11].

Based on cross-sectional data from NHANES III[2], MA prevalence in the first years of life has been found to be approximately 5.7%-7.3% in boys and 12.7%-15.1% in girls[1]. The higher percentage of MA in girls than boys could be attributed to the lower muscle mass and urinary creatinine excretion resulting in higher UACR values.

Remarkably, some studies reported an increased prevalence of MA in normal weight adolescents than in those with obesity[12-14]. Higher albumin excretion rate (ACR) levels have been significantly associated with a lower body mass index standard deviation score[15] and a higher height *z*-score[16]. In fact, healthy adolescents with MA are commonly thin and tall[16] and in these subjects MA might be directly related to the increased physical activity of thin children.

More, an increase of MA has been found in small for gestational-age children[1] and in school-age children[13]. In particular, the microalbumin/creatinine ratio in spot urine of healthy children decreased with increasing age[16]. A positive correlation between ACR and pubertal development stage has been also reported[17].

Of note, glucose metabolism impairments [*e.g.*, insulin resistance (IR)], pro-atherosclerotic pathways (*e.g.*, obesity), and haemodynamic load (*e.g.*, hypertension) have been largely accepted as the main cardiometabolic risk factors for the onset of MA in childhood[1,13,18].

Certain pathophysiological mechanisms such as low-grade inflammation, diffuse vascular damage with endothelial dysfunction[19], and increased permeability of the glomerular basement membrane[20] have been implied in urinary albumin loss.

WHAT IS THE STATE OF ART OF MA IN CHILDREN WITH OBESITY?

Although there is a direct association between MA and metabolic syndrome in adults[21,22], no similar consensus has been currently reached in childhood[13,23,24] . As a consequence of pediatric obesity epidemic[21], MA has been described in these children but its relationship with metabolic milieu is still debating[25,26](Table 1).

In cross-sectional studies, MA prevalence in children and adolescents with obesity has been found to be approximately 6.4%[27]. Several clinical and cardiometabolic risk factors linked to MA in children and adolescents with obesity have been studied including age, sex, body mass index, waist circumference, triglycerides, high-density lipoprotein cholesterol, hypertension, and glycated hemoglobin (HbA1c)[28-30].

A large pediatric Korean study[23] demonstrated a significant association of MA with hyperglycemia [odds ratio (OR) 2.62, 95% confidence interval (CI): 1.09-6.30, $P < 0.001$] in normal weight children, while hypertension (OR 14.10, 95%CI: 1.12-177.98, $P < 0.001$) was found to be correlated to MA in children with obesity. Interestingly, HbA1c was associated with MA in both groups (OR 3.34, 95%CI: 1.09-10.17, $P < 0.001$, and OR 6.68, 95%CI: 1.87-23.95, $P < 0.001$, respectively)[21].

Nguyen *et al*[29] showed that overweight adolescents with impaired glucose tolerance, IR, and hypertension had MA, as previously demonstrated in adults[22,23]. From a pathogenic point of view, the increased intraglomerular capillary pressure consequent to the excess weight status might result in glomerular hyperfiltration. Consequently, it may potentially lead to MA through endothelial dysfunction triggered by specific "hits" as hypertension, impaired fasting glucose, diabetes mellitus, or smoking[31].

Lurbe *et al*[32] found that elevated urinary albumin excretion was correlated with higher waist circumference and insulin levels, by emphasizing the role of metabolic derangements in this relationship.

Cho and Kim[24] in a study on 1976 children and adolescents without diabetes mellitus, found a prevalence of MA in subjects with obesity of 3%. More, authors reported an association of HbA1c with MA regardless of weight status. In particular, a significant association of MA with hypertension was demonstrated in these patients, supporting the usefulness of MA as a marker of cardiovascular risk.

Another study[33] examined 105 pediatric patients with obesity divided into three groups as subjects with obesity only, subjects with obesity and metabolic syndrome, and subjects with obesity and type 2 diabetes. MA and increased levels of serum cystatin-C were found in patients with type 2 diabetes. In addition to glomerular damage IR-related, the tubule-interstitial injury might be further aggravated by glucose homeostasis dysregulation in patients with type 2 diabetes.

Burgert *et al*[34] reported a significant correlation of MA with post challenge alterations in glucose metabolism and insulin sensitivity loss in pediatric patients with obesity and normal glucose tolerance. In line with previous evidence[36], no association between metabolic syndrome and MA was reported, but results are affected by the lack of a control group.

Similarly, Bartz *et al*[35], in a study on 58 adolescents described an intriguing link between obesity-related IR (calculated through the euglycemic hyperinsulinemic clamp), and early MA onset. Indeed, insulin enhanced the effects of angiotensin II, contributing to hypertension, raised intraglomerular pressure, exacerbation of proteinuria, production of inflammatory cytokines, and apoptosis[36].

In contrast to the low prevalence of MA in the context of pediatric obesity reported in these studies, data on kidney function from adolescents with severe obesity reported a higher MA prevalence (17.3%) [37], suggesting a greater risk of chronic kidney disease for these patients.

In a study by Martin-Del-Campo *et al*[38] subjects with kidney alterations had higher body fat markers (including body mass index, waist circumference, fat percentage, subscapular skinfold, *etc.*) values and lower high-density lipoprotein cholesterol levels. Commonly, all these factors have been strongly associated with the development of kidney disease in adults[39-41]. In fact, fat deposition in the glomerulus may alter renal production of vasoactive and inflammatory mediators related to glomerular damages[42].

Also, in the study of Sanad and Gharib[43], MA was proposed as a marker of the endothelial dysfunction related to obesity and its metabolic consequences. Indeed, a positive correlation between MA and a worse cardiometabolic profile (including abdominal obesity, dyslipidemia, hypertension, IR, and impaired glucose tolerance) was demonstrated in children with obesity.

Similar evidence was provided by Savino *et al*[44]. Although no clinical evidence of kidney dysfunction was found in youths with obesity compared to healthy controls, MA was confirmed to be associated with hypertension, adiposity, and IR.

Csernus *et al*[45], found that children with obesity and glucose homeostasis abnormalities (including hyperinsulinemia and impaired glucose tolerance) and had a higher urinary albumin/creatinine ratio than normal weight children, supporting the central role of these factors in the development of kidney damage.

On the other hand, there is some contrasting evidence[29] reporting no association between MA and cardiometabolic risk factors in childhood obesity. To explain this, it could be supposed that a longer dysmetabolism (including duration of obesity and IR status) is required for renal dysfunction development.

Table 1 Main studies on microalbuminuria in children with obesity

Ref.	Study design	Population	Main findings
Savino *et al* [44]	Case Control	One hundred seven OB Caucasian prepubertal and pubertal children and adolescents of both sexes (M 52, F 55). Fifty normal weight Caucasian children as control group (M 26, F 24)	A modest significant difference was seen in AER values, which were higher in the OB group, even if mostly within normal range. AER showed a positive correlation with central adiposity, insulin resistance indexes and hypertension
Sanad and Gharib[43]	Cross – Sectional	One hundred fifty prepubertal obese children. Exclusion criteria: fever, infections, renal diseases, LES, endocrine disorders, albuminuria associated with urinary tract infections	There were significant positive correlations between MA and BMI, WC, systolic and diastolic BP, TG and LDL-c levels, insulin resistance and fasting glucose level. In contrast, there was a negative correlation between MA and HDL-c levels ($P < 0.01$). No significant correlations of MA with age and sex were found ($P > 0.05$)
Csernus *et al* [45]	Case-Control	Eighty-six obese children. Seventy-nine normal weight children as a control group. children with secondary obesity were excluded	OB children with obesity had a significantly higher U-ACR and U-BMCR as compared to the normal weight children. OB children with no more than one of cardiovascular risk factors (*e.g.*, hyperinsulinemia, fasting or post-prandial glucose, dyslipidemia and hypertension) had a significantly lower U-ACR than those with two or more features. U-ACR was positively correlated with body weight and with the fasting plasma glucose concentrations measured during the OGTT. U-ACR was increased in OB children with hypercholesterolemia. No association of U-ACR with TG and HDL-c levels was found
Goknar *et al* [30]	Case-Control	Eighty-four OB individuals aged 4-16 yr as study (case) group. Sixty-four normotensive healthy children as control group	No statistically significant differences were found in urine microalbumin/creatinine ($P = 0.740$)
Hirschler *et al* [12]	Retrospective Study	One thousand five hundred sixty-four children aged 5-14 yr, 220/1564 OB (14.1%), 300/1564 OW (19.2%), 1044/1564 (66.7%) normal weight, 318/1564 (20.3%) central OB	U-ACR decreased with increasing z-BMI for boys and girls. Median ACR and urinary albumin levels were significantly higher in normal weight children than in OW/OB children. Median ACR and urinary albumin levels was higher in OB girls than in OB boys
Radhakishun *et al*[28]	Retrospective	Four hundred eight OB children aged 3-19 yr, 50 % males	A low prevalence of MA (2.7%) was found. All subjects with MA were obese
Oz-Sig *et al* [33]	Retrospective	One hundred and five obese children (M 39) aged 4-18 yr. The cohort was divided into three groups as solely obese, with metabolic syndrome and with type 2 diabetes. MA was tested in 24 h collected urine (MA: 30-300 mg)	MA was significantly higher in type 2 diabetic group; statistical significance was reached in the group with metabolic syndrome and type 2 diabetic group. MA was not detected in the solely obese group
Lurbe *et al*[32]	Retrospective	One hundred and thirty-four OB children aged 9-18 yr. Obesity: *z* score > 2, Moderate obesity: *z* score 2-2.5. Severe obesity: *z* score > 2.5. UAE was measured in the first voiding urine of the morning	No differences between different groups of obesity degree were found. Increased UAE was linked to fasting Insulin HOMA Index, higher WC, and TG levels
Cho *et al*[15]	Retrospective	One thousand four hundred and fifty-nine adolescents aged 12-18 yr	MA was detected in 3.6% of subjects (53/1459). The Height *z* score of the MA group was greater than that of the NA group. The Weight z score of the MA group did not differ from that of NA group. The MA group had a lower BMI z score. MA group had higher HDL-c and lower TG levels. No significant differences in BP, fasting glucose, total cholesterol, and LDL levels were reported. UACR was associated with younger age, lower weight *z* score, lower BMI *z* score, lower W/Hr, but not with the height *z* score. UACR was associated with higher HDL level and lower TG values
Burgert *et al* [34]	Cohort Study	Two hundred seventy-seven children and adolescents	MA was found in 10.1 % of subjects (28/277). No significant differences between the two groups (MA e NA) in term of the anthropometrical and common cardiovascular risk factors were reported. Subjects with MA had higher plasma glucose and insulin levels during OGTT
Nguyen *et al* [29]	Cross Sectional	Two thousand five hundred fifteen adolescents aged 12-19 yr. 310/2515 children with BMI > 95 pc.	MA was detected in 8.9% of the study population. UACR girls was significantly higher in girls than in boys. MA was prevalent among NON-OW adolescents. Similarly, MA was prevalent among adolescents without abdominal obesity, and without insulin resistance
Martin-Del-Campo *et al* [38]	Cross Sectional	One hundred seventy-two children and adolescents aged 6-16 yr, 46/172 (27%) normal weight, 55/172 (32%) overweight, 71/172 (41%) obesity	MA was observed in children with OW (3.6%) and with OB (9.9%) more than in normal weight children

AER: Albumin excretion rate; BMI: Body mass index; HDL-c: High-density lipoprotein- cholesterol; LDL-c: Low-density lipoprotein- cholesterol; MA: Microalbuminuria; NA: Normal albuminuria; OB: obese; OGTT: Oral glucose tolerance test; OW: overweight; TG: Triglycerides;U-ACR: Urinary albumin/creatinine ratio; UAE: Urinary albumin excretion; U-BMCR: Urinary beta-2-microglobulin/creatinine ratio; WC: Waist circumference; W/Hr: waist-to-height ratio.

An Italian study[46] involved 901 children and adolescents subdivided according to estimated glomerular filtration (eGFR). Children with mild-low eGFR (< 20th percentile) and high eGFR (> 80th percentile) had an increased presence of cardio-metabolic risk factor. Between these, children with reduced eGFR levels had a worse cardio-metabolic profile. Considering this, authors suggested eGFR as a useful tool to identify children at greater cardiometabolic risk.

Similar findings were reported in another cross-sectional study examining 360 children with obesity [28]. Subjects with eGFR > 1 SD had higher systolic blood pressure, glucose, and insulin levels in response to oral glucose tolerance test. No significant association was demonstrated between MA (reported in 6.4% of subjects) and other cardiometabolic markers in children with obesity, although a lower insulinogenic index in subjects with MA was reported.

IR AND MA IN CHILDHOOD OBESITY: IS THERE A LINK?

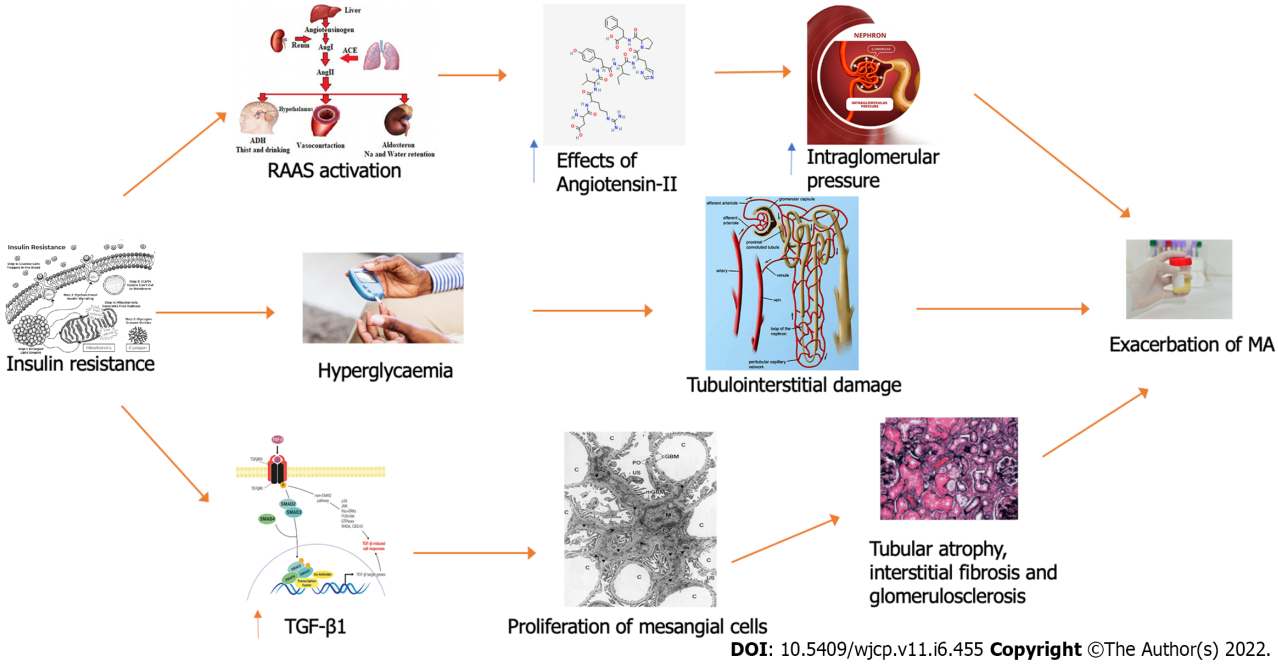
As observed adults[7,39], early renal damage (expressed as MA) has been demonstrated as a consequence of obesity in childhood[1,12,26]. Robust evidence has shown that MA represents a close reflection of the systemic vascular endothelial damage status[26,34,35]. In this tangled framework, a pivotal pathogenic role in the development of the underlying renal hemodynamic abnormalities has been widely recognized for IR[26,32,35] (Figure 1). As a consequence of a reduced insulin sensitivity, hyperinsulinemia- through the well-documented conflicting effects of insulin (both antinatriuretic and at tubular and glomerular level, respectively), acts as a key player in the tangled dysregulation of renal hemodynamics (including glomerular hyperperfusion, hyperfiltration, *etc*.) occurring in children with obesity[47,48]. To complicate matter, IR seems to mediate the intertwined relationship of MA with obesity and early renal impairment[35]. Classically, several different signaling pathways are involved in IR development and have been found to act also in the early stages of renal injury[26,34,35]. Therefore, MA represents an early predictive cardiometabolic risk marker as its close relationship with endothelial dysfunction reflecting both renal and systemic endovascular damage[26,34,35]. Although the current paucity of data examining the association of IR with MA in children with obesity, there is some pediatric evidence linking this latter to cardiometabolic risk factors[23,25,26,43]. IR represents a central player in Metabolic syndrome, in turn closely related to obesity, realizing a dangerous vicious circle[26,43,46]. In particular, the adiposity-related IR might lead to endothelial dysfunction with subsequent increased permeability responsible for the loss of albumin and other molecules involved in lipid accumulation and inflammation in the wall of vessels[26,43]. Taken together, these derangements might represent a potential pathophysiological explanation of kidney damage observed in children with obesity[26,43,47].

As the relevant prognostic implications of the relationship between MA and IR on the cardio-metabolic burden of children with obesity[49], this intriguing link deserves to be further strengthen in larger pediatric studies.

CONCLUSION

Within the spectrum of the pediatric obesity-related consequences, recent data have focused on the risk of early kidney damage in these children. Although still contrasting, a large body of evidence supported a complex relationship of MA with IR. Noteworthy, this latter represents an intriguing shared risk factor between obesity and early renal impairment.

Taking into account the adverse prognostic implications of the association of MA with IR not only on renal function but also on the general health status of children with obesity, we believe that MA evaluation should be included in the overall assessment of these patients as subjects with an intrinsic higher cardiometabolic risk.



DOI: 10.5409/wjcp.v11.i6.455

Figure 1 Pathophysiological link between microalbuminuria and insulin resistance. MA: Microalbuminuria; TGF-β1: Transforming growth factor-β1; RAAS: Renin-angiotensin-aldosterone system.

FOOTNOTES

Author contributions: Colasante AM and Di Sessa A wrote the manuscript; Miraglia del Giudice E, Di Sessa A and Marzuillo P conceived the manuscript; Miraglia del Giudice E, Di Sessa A, and Marzuillo P supervised the manuscript drafting; Nardolillo M, Bartiromo M, Guarino S and Mangoni di S Stefano GSRC reviewed the literature data; Colasante AM and Nardolillo M prepared the table and the figure; each author contributed important intellectual content during manuscript drafting or revision.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Gao CC
L-Editor: A
P-Editor: Zhang XD

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 November 9; 11(6): 463-484

DOI: 10.5409/wjcp.v11.i6.463

ISSN 2219-2808 (online)

SYSTEMATIC REVIEWS

Insulin pumps in children - a systematic review

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Specialty type: Endocrinology and metabolism

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Liao JX, China; Olsen MT, North Zealand

Received: July 8, 2022
Peer-review started: July 8, 2022
First decision: August 1, 2022
Revised: August 2, 2022
Accepted: September 21, 2022
Article in press: September 21, 2022
Published online: November 9, 2022

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Abstract

BACKGROUND

Insulin pump therapy is a real breakthrough in managing diabetes Mellitus, particularly in children. It can deliver a tiny amount of insulin and decreases the need for frequent needle injections. It also helps to maintain adequate and optimal glycemic control to reduce the risk of metabolic derangements in different tissues. Children are suitable candidates for pump therapy as they need a more freestyle and proper metabolic control to ensure adequate growth and development. Therefore, children and their caregivers should have proper education and training and understand the proper use of insulin pumps to achieve successful pump therapy. The pump therapy continuously improves to enhance its performance and increase its simulation of the human pancreas. Nonetheless, there is yet a long way to reach the desired goal.

AIM
To review discusses the history of pump development, its indications, types, proper use, special conditions that may enface the children and their families while using the pump, its general care, and its advantages and disadvantages.

METHODS
We conducted comprehensive literature searches of electronic databases until June 30, 2022, related to pump therapy in children and published in the English language.

RESULTS
We included 118 articles concerned with insulin pumps, 61 were reviews, systemic reviews, and meta-analyses, 47 were primary research studies with strong design, and ten were guidelines.

CONCLUSION
The insulin pump provides fewer needles and can provide very tiny insulin doses, a convenient and more flexible way to modify the needed insulin physiologically, like the human pancreas, and can offer adequate and optimal glycemic control to reduce the risk of metabolic derangements in different tissues.

Key Words: Insulin pump; Children; Diabetes mellitus; Keto-acidosis; Continuous glucose monitoring; Insulin therapy

Core Tip: The insulin pump is a significant step in proper diabetes management in the way to simulate the human pancreas. Insulin pumps undergo significant daily improvement every day to enhance their performance. The insulin pump is beneficial for children with type I diabetes mellitus. However, proper training and education of the children and their families are mandatory for the appropriate function of the insulin pumps. They should know how to use it properly and overcome the difficulties they may encounter and the different scenarios they may meet. The way still long to achieve our goals.

Citation: Al-Beltagi M, Saeed NK, Bediwy AS, Elbeltagi R. Insulin pumps in children - a systematic review. *World J Clin Pediatr* 2022; 11(6): 463-484
URL: https://www.wjgnet.com/2219-2808/full/v11/i6/463.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i6.463

INTRODUCTION

The insulin pump is a giant breakthrough in diabetes mellitus (DM) treatment. Treating diabetes with an insulin pump is the method most similar to the normal physiologic function of the pancreas. The pump delivers insulin in 2 different ways simulating the human pancreas. It delivers a continuous small insulin quantity as a "background insulin" to maintain the basal metabolic rate and bolus insulin doses when needed to metabolize the ingested food. The insulin pump is particularly needed in the management of type I DM. The insulin pump is continuously undergoing massive improvement. Nonetheless, there is yet a long way to reach the desired goal[1].

MATERIALS AND METHODS

This review aims to discuss the history of pump development, its indications, types, proper use, special conditions that may enface the children and their families while using the pump, its general care, and its advantages and disadvantages. In this narrative review, we conducted comprehensive literature searches of electronic databases, PubMed, Embase, Cochrane Library, Reference Citation Analysis (RCA), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, Scopus, Library and Information Science Abstracts (LISA), and the National Library of Medicine (NLM) catalog up until June 30, 2022, related to pump therapy in children. Reference lists were inspected, and citation searches were done on the included studies. We included open access papers for English-language studies concerned with insulin pump therapy and diabetes mellitus in children. We also reviewed many review articles concerned with pump therapy in children. We also reviewed the articles that are

available as abstracts only. We excluded articles with commercial backgrounds.

RESULTS

Figure 1 showed the flow chart of the reviewed articles. We included 118 articles concerned with insulin pumps, 61 were reviews, systemic reviews, and meta-analyses, 47 were primary research studies with strong design, and ten were guidelines.

DISCUSSION

For a long time, there is a need for proper management of children with diabetes. The result of this review showed that despite the many challenges that enface the use of insulin pumps in children, the advantages are far more than the challenges.

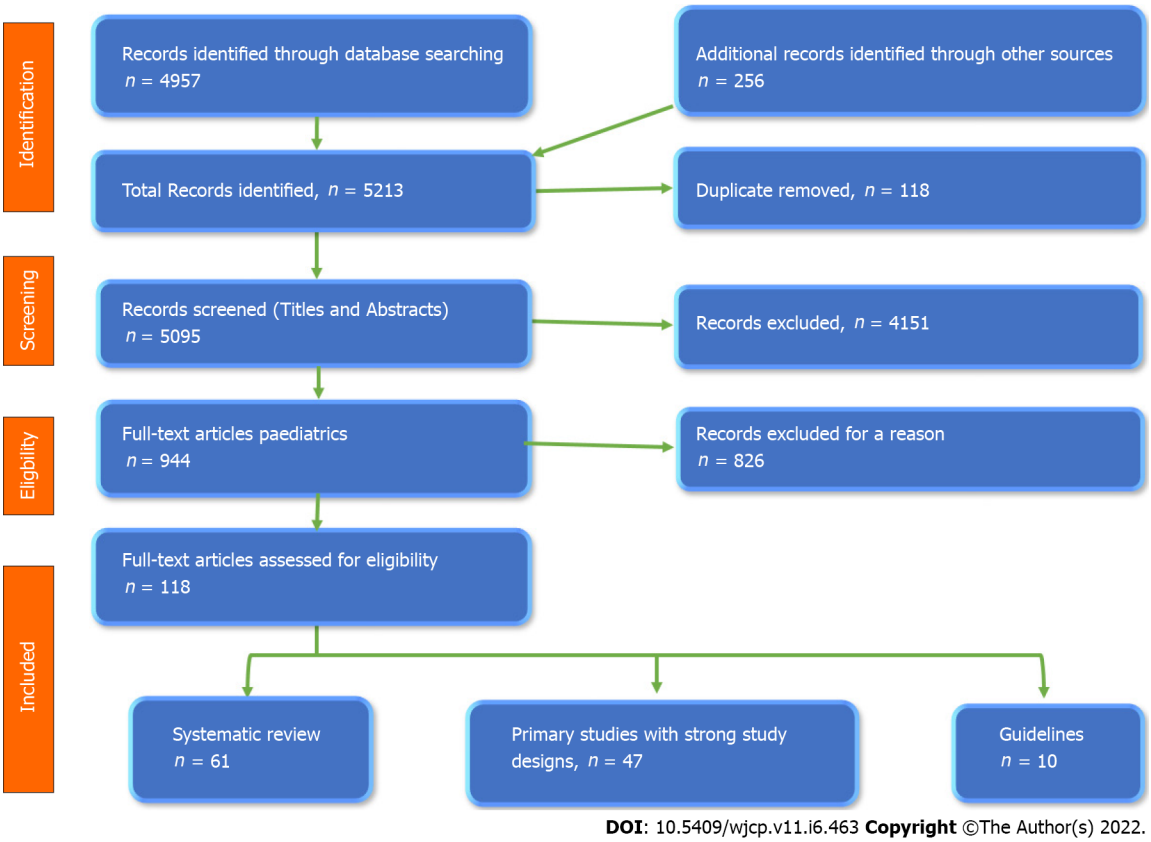
HISTORICAL BACKGROUND

Diabetes has been described in the Papyrus Ebers (c. 1550 BC), Ayurvedic medicine (5th/6th century BC), Greek medicine (1st century BC), and medieval Islamic medicine by Avicenna for a long time[2]. Oskar Minkowski and Joseph von Mering first linked diabetes to pancreatic illness in 1889. In 1910, Sir Edward Albert Sharpey-Shafer proposed that the missing pancreatic component be named insulin, after the Latin word Insula (island). Frederick Grant Banting and his colleagues discovered and refined insulin for clinical use in Toronto, Canada, between 1920 and 1922[3].

Leonard Thompson, a fourteen-year-old boy, was the first human to receive an insulin injection, controlling his high blood sugar within 24 h. Shortly after, Eli Lilly's medical company started mass insulin production from cattle and pigs to supply the needs of North America. After about 14 years, Harold Percival Himsworth differentiated type I Diabetes Mellitus from type II in 1936. In the same year, Novo Nordisk Pharmaceuticals developed long-acting insulin. By 1978, genetic engineering enabled the human being to have the first synthetic "human" insulin produced by E. coli bacteria. After four years, Eli Lilly made the human biosynthetic insulin commercially available for the first time with the brand name Humulin in 1982[4,5].

The first insulin pump was invented in 1963 by Arnold Kadish, who developed a prototype backpack pump to deliver insulin and glucagon. However, Dean Kamen developed the first wearable insulin infusion pump in 1973, which started to be produced commercially by AutoSyringe Inc in 1976[6]. In the same year, continuous subcutaneous insulin infusion was started successfully. The glucose-controlled insulin infusion system was developed by BioStar company to be the first step in the development of artificial pancreas development in the 1980s. During the same period, the first blood glucose home-based monitors were available to accurately monitor blood glucose levels at home. A few years later, the prefilled syringe-insulin pen delivery systems appeared, providing a safe and convenient insulin delivery method with accurate dosing[7]. In 1983, MiniMed released the first small-sized programmable insulin pump, followed by the soft-set infusion set in 1987, using a soft, flexible cannula to ensure customer comfort. In 1992, MiniMed redesigned the pump to be programmed to include meal bolus memory and daily insulin totals. Continuous upgrading of the pump continued to prolong blood glucose recording to 3 days in 1999. The same year showed constant upgrading of the pump to enable remote programming abilities to control, administer, and stop insulin delivery and to program multiple delivery patterns and different alert types, including vibration mode and child-block[8].

By 2000, the concept of implantable insulin pumps emerged to help patients with significantly uncontrolled diabetes. In 2003, the wireless "intelligent" insulin pump was introduced, which can automatically transmit a blood glucose value from a glucose meter to the insulin pump, which calculates the proper insulin dosages. In 2004, the pump was upgraded to notify and alarm diabetes patients of potentially severe high or low glucose fluctuations. In 2005, the system was upgraded to display updated real-time blood glucose values every five minutes, plus the alarming system for severe blood glucose fluctuations, which provided significant help to people with diabetes who need better glucose control[9]. In 2006, a real-time insulin pump system with a continuous glucose monitoring system became available, which was a significant step in developing a "closed-loop" insulin delivery system or what is called "artificial pancreas" trying to mimic some human pancreas functions. Updating the pump system continued over the years, so by 2012, the concept of next-generation artificial pancreas systems was elaborated. In 2018, Bekiari *et al*[11] showed that the artificial pancreas is "effective and safe" in treating people with type 1 diabetes[10,11].



DOI: 10.5409/wjcp.v11.i6.463

Figure 1 The flow chart of the study according to PRISMA 2009 guidelines.

INDICATIONS OF INSULIN PUMP

The Key target of diabetes management is to maintain adequate and optimal glycemic control to reduce the risk of metabolic derangements in different tissues. Although it may be a simple goal, it is not always easy to achieve in practice. There are currently two ways to deliver insulin: Multiple daily subcutaneous injections (conventional insulin therapy) or continuous subcutaneous insulin infusion, also identified as insulin pump therapy[12]. There are many difficulties with conventional insulin therapy, including the variable glycemic control with frequent occurrence of hypoglycemia, abnormal weight gain related to the insulin therapy, augmented by improper dosage calculation related to human error, and the lack of adherence to insulin therapy, especially with multidose regimens[13]. Using an insulin pump to manage DM depends on many factors, including the patient's desire, daily life routine, and knowledge and experience with the disease. More than 25% of patients with type I DM are currently using insulin pump therapy. It is especially indicated in the presence of high hemoglobin A1C, poor glycemic control with problematic hypoglycemia such as nocturnal hypoglycemia, recurrent hypoglycemia, activity-induced hypoglycemia, recurrent diabetic ketoacidosis, frequent hospitalization, large total daily dose, presence of progressive complications such as gastroparesis, inability to self-administer insulin (such as in pre-school or grade-school children), the need for more meal time flexibility, or the inability to predict food or meal intake (such as in infants or toddlers)[14]. Baretić *et al* [15] showed that nocturnal hypoglycemia is the main indication for insulin pumps in adults with type I DM, especially with limited affordability. Patients with type 2 Diabetes who fail to have adequate glycemic control with multidose insulin therapy may have better control with pump therapy, improving HbA1c, and limiting weight gain[16]. So, the insulin pump can be sued for type I and II DM in adults and children, especially for those who want more flexibility and proper mealtime adjustment. About 1/1000 of patients with DM are currently using insulin pumps, and their number is increasing; 90% have type I DM, while only 10% have type II. About 6% of adult patients with type I DM use it, while it reaches about 19% in children with type I DM[17].

TYPES OF INSULIN PUMPS

There are two main types of insulin pumps; the first type is a 'tethered' pump that uses a fine tube connecting the pump with a cannula (Figure 2A). The patient can wear the pump in a pocket or fasten it

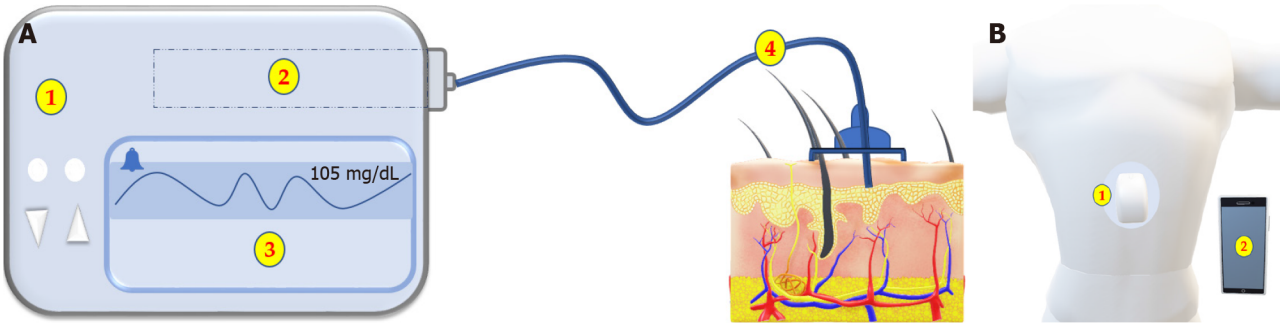


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Figure 2 shows the two main types of Insulin Pumps. A: Tethered pump formed of 1: Main pump. 2: Insulin Reservoir. 3: Monitor. 4: Infusion set; B: The patch pump formed of 1: A pump adherent to the skin with no or very short tube and 2: A wireless control unit.

to a belt and should change the tubing every 2-3 d. The patch pump (micro pump) is another type without tubing or may have a very short flexible plastic tube (cannula) inserted under the skin (Figure 2B). The pump usually adheres to the skin with an adhesive patch and is wirelessly controlled with a handheld controller unit[18]. The insulin pump is generally formed of the central pump unit connected to an insulin reservoir which usually holds between 176-300 units of short-acting insulin. Another new version of the insulin pump has a built-in Continuous Glucose Monitor (CGM). The pump is supplied with an alarm system activated when the blood glucose reaches a predetermined low or high level[19]. A SmartGuard Technology can be added to CGM to stop insulin supply for two hours if the user's blood glucose reaches a predetermined low level pre-settled without activating the alarm system. Some pumps use a hybrid closed-loop technology by using the SmartGuard technology to permit the users to select from increasing the levels of automation that best suit their needs. The auto mode enables automatic adjustment of the basal insulin delivery according to the glucose reading of the user's CGM sensor and recent insulin delivery[20].

There is also a bolus calculator, able to automatically calculate the doses and inform the person if they are too closely set together. However, in this mode, the user should enter the details of carbohydrate intake, confirm the mealtimes, and adjust the correction boluses. Some insulin pumps have an Insulin on board (IOB) feature so that the pump can calculate how much insulin remains active in the patient's body from the previous insulin bolus dose[21]. Some pumps are also waterproof to tolerate up to 12 feet underwater for about 24 h. This feature enables patients with diabetes to enjoy swimming with minimal risk of hypoglycemia. The vast advances in insulin pumps are related to significant software and artificial intelligence progress. For example, some pumps allow choosing an exercise set to change the person's glucose target[22] automatically. Most of the new versions of insulin pumps are compatible *via* Bluetooth with smartphones with different applications such as the Carelink Connect app, which allows family members or caregivers to access the patient's information and show all readings and permits notifications and alarms. People also can deliver insulin remotely using a smartphone-like Personal Diabetes Manager device. The suitable age for the pump use differs according to the pump type and version, in which the manufacturers determine the appropriate age of use according to each pump's features[23].

USE OF THE INSULIN PUMP

The children and their caregivers should understand the proper use of insulin pumps to achieve successful pump therapy. The children and their caregivers should have a comprehensive education program about diabetes management and insulin pump use before starting it. They should be able to adjust the blood glucose levels using multiple daily insulin injections and monitor blood glucose frequency at least four times daily during the last two months before the insulin pump therapy[24]. They should also learn to test ketones when the blood glucose level is more than 13.3 mmol/L (240 mg/dL) and recognize symptoms of ketoacidosis when present. Before using the pump, the children or their caregivers should know the suitable age for using it as predetermined by the manufacturers[25]. They should know whether the pump is waterproof, watertight, water-repellent, water-resistant, or not. If the pump is not, they should remove it before showering or swimming. If the pump is waterproof, they should know how many feet in-depth and how long. The patient also should know the maximum time the pump can be removed without affecting its performance, *e.g.*, one hour for the Aviva Combo insulin pump[26]. The child and his/her caregiver should know the number of insulin units the insulin cartridge can hold. However, they should know that the half-life of the insulin pods may not depend on how much insulin is used. The insulin the pump uses is fast-acting insulin because of its rapid onset and offset. Even fast-acting insulin takes some time for its action onset and offset. We should also note the

presence of significant individual variations in the onset, duration, and offset of the same type of insulin [27].

The patients and their caregivers should be aware of the lowest basal delivery rate the pump can deliver. They should understand the available basal (background) insulin patterns such as daily, weekend, exercise, and night shifts. They also should be aware of the insulin-to-carbohydrate ratio program feature. This mode helps the patient calculate an estimated insulin bolus dose to cover any carbohydrates the patient eats or drinks or improve high blood glucose[20]. The most important thing to properly using the insulin pump is calculating the total daily insulin dose, which equals the basal and the bolus insulin doses delivered each day. Total daily basal insulin is a continuous insulin infusion needed to metabolize hepatic glucose production over 24 h, while the total daily bolus insulin is the insulin units given on needs to control the meal-related glucose peaks over 24 h[28].

The pump's total daily insulin dose is 25% less than the current total daily insulin injection dose. To calculate the pump's total daily insulin dose, we usually take the average of the 25%-reduced current total daily insulin injection dose and the weight-based insulin daily dose, which equals the body weight multiplied by 0.5. The pump's total daily insulin dose is less than the current total daily insulin injection dose as the pump delivers the insulin more efficiently, and the insulin is more regularly absorbed than the intermittent daily injections[26]. 40%-50% of the pump's total daily insulin dose is delivered as a total daily basal insulin, while the other 50%-to-60% will be delivered as bolus doses related to the meal intake (Figure 3). The total daily basal insulin is delivered at an hourly rate. However, it can be programmed at different rates throughout the day according to daily activities and circumstances[29].

Meanwhile, the percentage of the total daily basal insulin from the pump's total daily insulin dose differs according to the age of the patients; 20% to 40% from the pump's total daily insulin dose in prepubertal and pubertal subjects, 30%-40% from puberty to adulthood, and 40% to 50% in adults. The rest of the pump's total daily insulin dose is divided into bolus doses according to the meals. The ratio of basal to bolus insulin is also dependent on the amount of carbohydrate diet, decreasing with a high carbohydrate diet[30].

Basal insulin is the insulin level required to balance gluconeogenesis and peripheral glucose utilization. Basal insulin keeps the blood sugar relatively constant without food intake. The pump delivers the basal insulin in a tiny quantity per hour to control the blood glucose levels over a predetermined period[31]. If a desired change in the basal insulin delivery is required, the adjustment should begin two to three hours before the expected change in the blood glucose to prevent significant fluctuations in its levels; so that the blood glucose level fluctuations are less than 30 mg/dL up or down, either during the day or at night. In the flat basal profile, the total daily basal insulin is divided equally over the day hours (divided by 24)[32]. However, the basal requirements show significant variation within the same person day-on-day, based on circadian rhythm, meal and activity levels, exercise, illness and stress, and the potential changes in the insulin absorption from the cannula. There are various types (4-6) of modified basal profiles. The patient usually starts with a flat basal profile; then, the profile is modified according to the patient's activity[33]. Some patients may need to increase the basal rate in the early morning to neutralize the Dawn phenomenon. Conversely, we may need to reduce the basal rate between mid-morning and mid-afternoon. Meanwhile, some patients may require an increase in the basal rate in the evening (dusk phenomenon) due to a reduction in physical activity later in the day (Figure 4)[34].

Suppose the patient has a fixed period of activity that occurs daily at the same time, such as walking or swimming, when there is a risk of hypoglycemia. In that case, the basal rate can be modified to accommodate these activities by reducing the basal rate 60-90 min before the expected activity. In a situation with an increased likelihood of hyperglycemia, such as during illness, the patients may increase the basal rate 30%-50% above the flat basal rate[35]. It should be noted that Blood insulin levels need 2-3 h to reach a steady state after a basal rate change. Consequently, the changes in the basal rate usually occur in blocks of hours. Most patients need to have multiple basal rates throughout the daytime. Basal rates modified to match the patient's activity are associated with improved outcomes [36]. Some insulin pumps can be programmed to suspend/stop insulin delivery from the pump for a particular time before, during exercise, or in hypoglycemia. To reach the proper basal profile, the patients need to check their blood sugar as frequently as eight times daily during the pump's first month. After getting the target profile, the frequency of checking is about four times daily. However, extra checks may be needed during times of exercise, traveling, illness, or the beeping of the pump alarm[17].

Bolus insulin is an intermittent insulin bolus infusion intended to parallel the rises in blood glucose related to food intake. It depends on personalized carbohydrate-insulin ratios, which are the amount of insulin needed to match the ingested carbohydrate in grams without causing hypo/hyperglycemia[37]. It is calculated by dividing 500 in adults or 300 in children by the total insulin daily dose. For example, if a child needs 45 insulin units as a daily dose, his carbohydrate-insulin ratio is 300/45 = 6.6. This means that the child needs one Insulin unit for every 6.6-gram carbohydrate. For a meal that contains 120 gm of carbohydrates, the child needs 18 insulin units to maintain the blood glucose levels within the normal range[38]. The insulin pump can deliver various forms of insulin bolus. There are three main types of bolus insulin; the typical bolus, the square-wave bolus, and the dual-wave bolus (Figure 5)[39]. In the typical bolus, the pump delivers the insulin immediately on top of the basal rate for three minutes. The

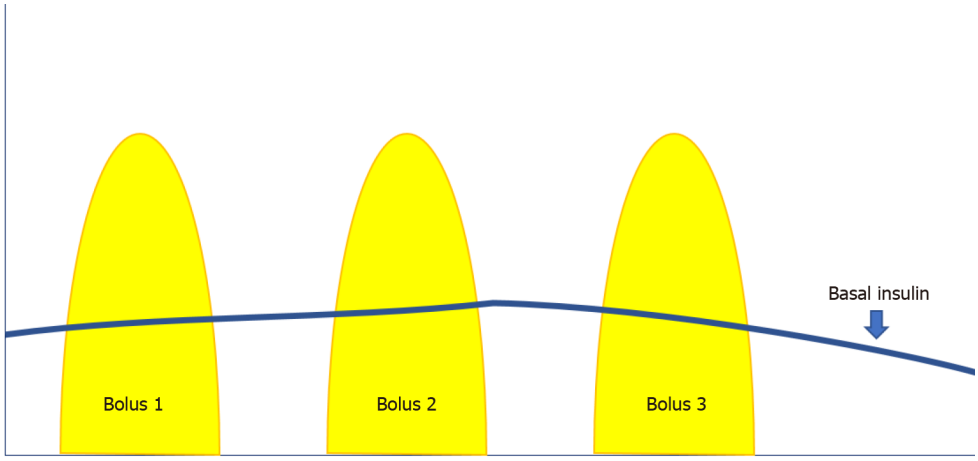

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Figure 3 Basal and bolus insulin. Basal insulin is delivered continuously in a small amount as a background to keep the blood glucose levels within the target between meals. The pump can be programmed to deliver at different rates within 24 h. Bolus insulin is a large amount delivered over a short period, which can be given at any time. The pre-meal bolus is given based on the number of carbohydrates in grams. The bolus can also be given to correct high blood glucose levels.

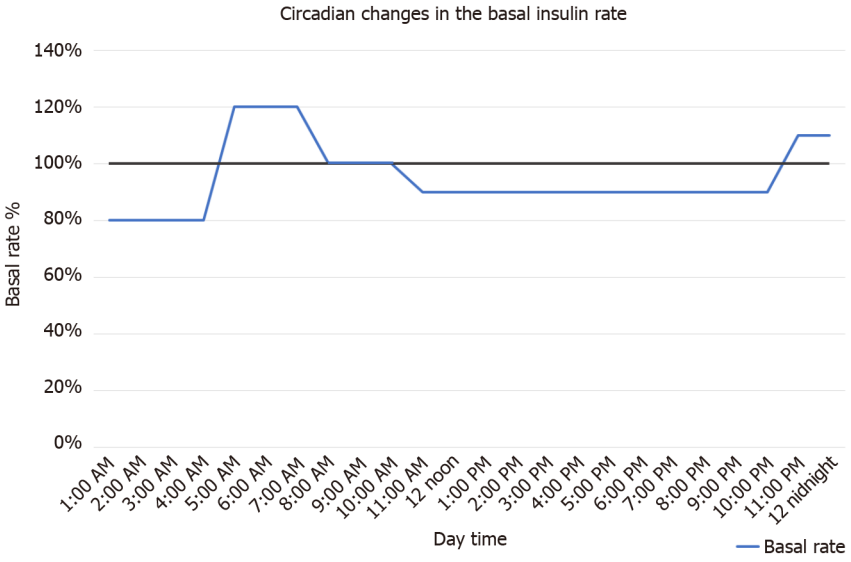

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Figure 4 Circadian changes in the basal insulin profile. An example of the circadian changes in the basal insulin profile. Between 12 midnight to 4:0 am, the basal rate is reduced by 20% to increase 20% between 4:0 am to 7:0 am, then will be 100% between 7:0 am to 10:0 am to be reduced by 10% between 10:0 am to 10:0 pm, then it increases again by 10% between 10:0 pm to 12 midnight.

extended bolus delivers the insulin over a longer period than the typical bolus (the insulin dose is not delivered at once). The square wave bolus is an extended bolus that delivers the insulin over a fixed extended duration (2-4 h)[40]. We usually need it when the food is ingested over a longer time, such as during social events, or delayed digestion, such as in gastroparesis. The dual-wave bolus delivers the insulin in two or more waves (dual or multi-waves], 30%-70% of the insulin bolus is delivered as the typical bolus, and the rest of the bolus is delivered over a predetermined fixed duration, such as 2-4 h (biphasic, dual, or multi-wave). The dual/multi-wave bolus is helpful with meals with high protein or fat content (*e.g.*, pizza, pasta, cheese, or fish) as protein and fat usually take longer to increase blood glucose levels than carbohydrates, which immediately affect blood glucose[41].

In the super bolus (Figure 6), the pump delivers the basal insulin for the next 1-4 h is added to the bolus, followed by temporarily suspending the basal insulin delivery for those hours (basal rate is 0% for the next 1-4 h) without stopping the pump. This super bolus is needed with a diet high in carbohydrates and low in protein and fat, such as white toast, jam, white rice, sugary drinks, jelly sweets, *etc.* However, if the post-meal blood sugar persists to be high after a super-bolus insulin dose, we should revise the insulin: carbohydrate ratio. If the post-meal blood sugar fluctuates, we should revise carbohydrate counting as it often shows a wide range of variations[42]. A comparison between the different types of insulin boluses is shown in Table 1.

Table 1 Comparison between the different types of insulin boluses

Bolus type	Normal	Extended	Dual wave	Super bolus
Indication	With most diets, 10-20 min before the meal	Rarely needed: With lengthy mealtime & gastroparesis	With low carb & high protein & fat (> 25 gm fat) meals	With high carbohydrate meal
Method of insulin delivery	Deliver insulin immediately	Deliver all the insulin in an extended fashion over a chosen duration which may be the meal length.	60%-70% of the bolus is delivered immediately, while 30%-40% is delivered over 2-4 h	The basal insulin units of the next 1-4 h are added to the bolus, followed by a temporary 0% of basal rate for that 1–4 h
When to test blood glucose	Before bolus and after 4 h	Before bolus, after the end of the bolus, & after 4 h	Before bolus, after the end of the bolus, & after 4 h	Before bolus, after one & 4 h after the bolus

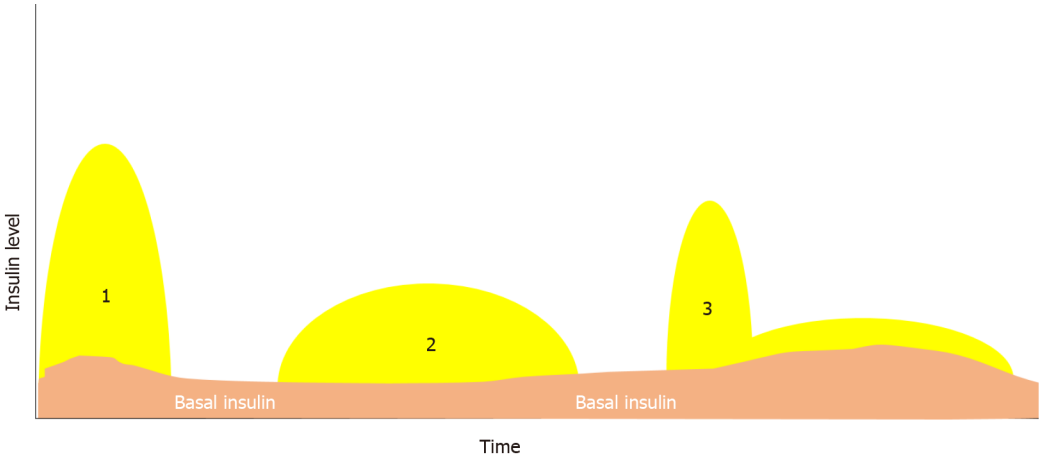

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Figure 5 The different insulin bolus types. 1: The typical bolus, 2: The extended bolus, 3: The dual bolus

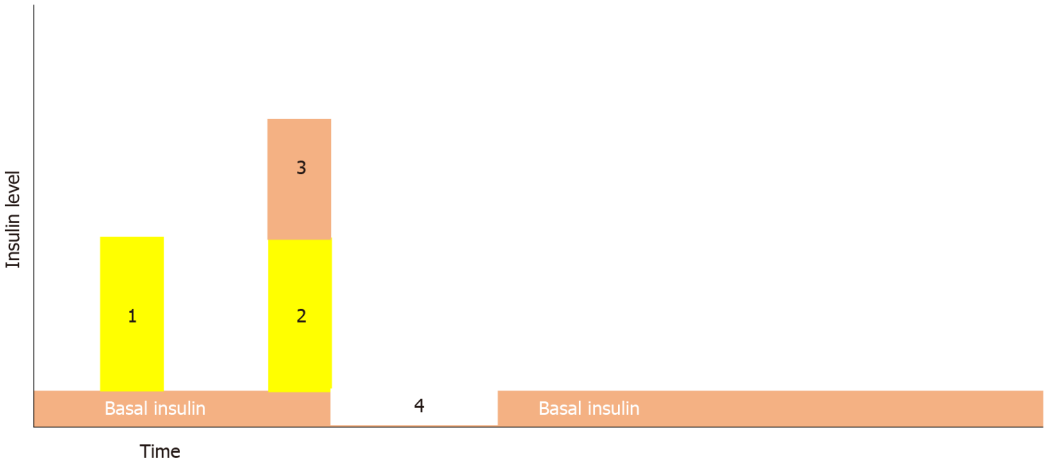

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Figure 6 Different types of insulin bolus. 1: Typical insulin bolus, 2 and 3 super bolus equal to the calculated bolus plus the basal insulin for the coming one to four hours, 4: The basal insulin rate will be 0% for the remaining four hours.

Correction bolus is the number of insulin units delivered by the pump when the blood glucose level is above the target range. It depends on the individual insulin sensitivity factor (ISF), which is the amount of decrease in blood glucose level for every one unit of rapid insulin. It calculates the correction bolus dose, which is the number of insulin units the patient needs to bring the blood glucose into the target range without inducing hypoglycemia[43]. To calculate ISF, we divide 100 by the average total daily insulin dosage over three or four days (TDD) to get the result in mmol/L (100 Rule) or divide 1800 by the average TDD to get the results in mg/dL (1800 Rule). So, when the average TDD is 75 Insulin Units, ISF will be 1.33. Thus, one unit of rapid-acting insulin would reduce the blood sugar by 1.33

mmol/L (24 mg/dL) across the next 2-4 h[43]. The following formula can calculate the correction dose: [(Current Blood Glucose – Target Blood Glucose)/ISF]. However, the Association of British Clinical Diabetologists advises routinely starting with the rule of 130 rather than the 100 rule [ISF = 130/TDD] to achieve the optimal ISF and estimate how much one unit of insulin will decrease the blood glucose level in mmol/L[44]. We should ensure the adequacy of ISF by testing the blood glucose after 4-5 h after the last insulin bolus dose. Carbohydrate was consumed more than three hours ago, and the patient can wait for 4-5 h until the next meal[43].

The caregivers and their child should adequately adjust the pump setting for the IOB and the active insulin time, which is the duration that an insulin dose continues to work after its delivery. Most pumps set this time to be four hours; however, it can be shortened or prolonged in the presence of hypo/hyperglycemia[26]. With short active insulin time, the pump includes the effects of the more recent insulin doses, omitting the impact of the insulin from the previous doses, thus increasing the risk of hypoglycemia[28]. On the other hand, long active insulin time causes overestimation of the insulin on board, and the pump gives smaller boluses which can cause hyperglycemia. Longer active insulin time than four hours is needed in cases with impaired renal functions, as the kidneys clear about 80% of the insulin. Those needing TDD less than or equal to 40 Units/day should reduce active insulin time. In comparison, those receiving a bolus dose of more than 10 Units or TDD of 60 Units/d or more should consider increasing active insulin time[45].

The caregivers and their child should recognize the accepted target blood glucose level, which is individualized according to the child's status and is comfortable with it. Some insulin pumps correct the blood glucose level to a single target level but give the correction bolus when a predefined threshold is reached[46]. Other pumps correct to a higher figure in a predefined target range, while others correct to the mid-target range. The target range usually lies between 4.5-5.5 mmol/L (80-100 mg/dL) (± one mmol/L). However, the target level is modified according to the presence of different factors. Those with high HbA1c need a higher target as the setpoint for hypoglycemic symptoms is higher than for more well-regulated patients with diabetes. They frequently have episodes of pseudohypoglycemia until they are used to lower glucose values[47]. Those with HbA1c > 10% should start with high target blood glucose between 9-10 mmol/L (160-180 mg/dL), then reduce the target level monthly until we reach the normal target blood glucose levels. This gradual decrease of the target is particularly indicated in the presence of diabetic retinopathy, which may deteriorate with the rapid lowering of blood glucose levels. To maintain the target glucose blood level, the caregivers and the children need to frequently test the blood glucose levels, especially in the presence of hypo/hyperglycemia, and to know which insulin doses need to be modified, the basal rate, or the bolus insulin[48].

When there is blood glucose variation (hypo/hyperglycemia) during the night, before breakfast, or when a meal is skipped or delayed, the basal rate of insulin needs to be adjusted. However, the insulin-to-carbohydrate ratio and ISF should be revised when the blood glucose variation (hypo/hyperglycemia) occurs within four hours of the bolus or meal or after giving a correction insulin bolus. To test the basal rate, we should eliminate the influence of other factors that could affect it by dividing the day into windows, testing the basal rate for each window on different days, and ensuring that the tested person follows his/her usual routine without strenuous activity before the test by 24 h and during the test period[49,50]. Hypoglycemia should not present during the last 12 h before testing, and the patients should be fasting for the tested period except for water. We use the standard basal rate during testing, stop testing with hypoglycemia (< 4 mmol/L or 72 mg/dL), and give a corrective bolus with hyperglycemia of more than 14 mmol/L (252 mg/dL). We should record blood glucose levels, basal rate, and carbohydrate intake. There are four main periods to test the basal rate: Morning testing from 7:00 am to 12:00 noon, after noon testing from 12:00 noon to 18:00, evening basal from 18:00 to 22:00, and overnight testing from 21:00 to 7:00 am[51]. Overnight testing is usually done first, followed by the other periods, each on different daily bases. First, we correct hypoglycemia; then, we correct hyperglycemia with a 10%-20% decrease or increase, *i.e.*, 0.025-0.05 unit/ hour one to hours before the expected change, to keep the blood glucose variation less than 1.5 mmol/L (28 mg/dL)[52].

For bolus adjustment, we try to keep the two-hours post-meals to be 1.6-3.2 mmol/L (29-58 mg/dL) higher than the pre-meal blood glucose levels. If the two-hours post-meal blood glucose level increases to less than 1.6 mmol/L (29 mg/dL), decrease the total bolus by 10%-20%. If the two-hour post-meal blood glucose level increases to more than 3.2 mmol/L (58 mg/dL), increase the total bolus by 10%-20%. Slattery *et al*[53] suggested that insulin administration 15-20 min before the meal will provide optimum postprandial glucose control. To adjust the correction bolus dose, adjust the insulin sensitivity factor by a 10%-20% increase or decrease to make the two-hours post-meal blood glucose level halfway to the target and reach the target by four-hours post-meal. If the patient uses continuous glucose monitoring (CGM), a retrospective analysis of the time associated with blood sugar fluctuations can help modify the basal rate[54]. Some pumps have a wizard to change the basal rate according to the blood sugar levels. However, CGM should be associated with an event diary to document the meal timing and the carbohydrate intake for accurate assessment. CGM is indicated with frequent or severe hypoglycemia, hypoglycemia unawareness such as in young children, suboptimal glycemic control, or monitoring of young children or beloved ones by family members or friends[55,56].

Suppose the patient needs to change the insulin pump therapy to subcutaneous insulin for any reason. In that case, we need to calculate the total daily basal insulin given by the pump and increase it by 20% for the first few days and by 30% in the following days to calculate how much long-acting basal subcutaneous insulin is needed. This dose can be administered as a single or divided dose depending on the type of long-acting insulin used[57,58]. The bolus pre-meal insulin and the corrective insulin doses are given as usual. The pump should continue working for two hours after starting the first long-acting insulin dose. Doing this shifting in the morning is recommended to avoid troubleshooting at night[59]. Alternatively, if we need to resume the pump therapy after subcutaneous therapy, we resume it two hours before the next long-acting insulin dose. Again, we need to reprogram the pump setting and temporarily reduce the basal insulin rate by about 30% for the next 24 h. Blood glucose levels should be checked one to two hours after starting pump therapy[18]. So this shift is better to be in the morning for easy monitoring. Suppose we want to shift the insulin therapy from continuous intravenous infusion to pump therapy. In that case, we can shift without waiting for the coming meal and discontinue the intravenous insulin infusion only 60 min after starting the pump therapy[60].

PUMP THERAPY IN SPECIAL SITUATIONS

Sports and exercise

Exercise has a long-term beneficial effect on blood glucose regulation regardless of the type of exercise. However, it has a short-term modification on the blood glucose level to be considered during the pump therapy—two significant difficulties enface children with type I diabetes who are willing to exercise regularly. The first problem is controlling the blood glucose level, and the second is the possible occurrence of hypoglycemia during or following exercise[61]. Aerobic exercise reduces blood glucose levels and enhances insulin sensitivity for 16 h following the exercise. On the other side, high-intensity aerobic exercise or that associated with high adrenaline could cause hyperglycemia. Resistance training or anaerobic exercise increases blood glucose levels and insulin resistance, which persist 6-8 h after exercise. Brief periods of anaerobic exercise activity (*e.g.*, short sprints or weight lifting) during moderate-intensity aerobic exercise may decrease the risk of hypoglycemia[62]. However, all types of physical exercises may increase the risk of nighttime and even the next day hypoglycemia, mainly when performed in the afternoon, independent of sex[63].

We can prevent the development of exercise-induced hypoglycemia by reducing the bolus or basal insulin, increasing carbohydrate intake, or adjusting the exercise regimen. The basal insulin can temporarily be reduced one to two hours before and throughout the exercise. The degree of basal rate reduction depends on the intensity of exercise, 30% in low-intensity, 50% in moderate-intensity, and up to 100% reduction in high-intensity exercise. If modification of the basal insulin is not feasible, a fast-acting carbohydrate (15-20 gm without bolus insulin dose) can be given immediately before the short, intense exercise. For more extended, moderately intense exercise, a solid snack with slow-release carbohydrates can be given. If an exercise is planned within two hours after a meal, the premeal-bolus insulin dose can be reduced by 25%-75% according to the exercise intensity[64]. If we are anticipating anaerobic exercise-induced hyperglycemia, we can give a 50% extra bolus dose 30-60 min before the exercise to antagonize the expected increase in the blood sugar. Alternatively, we can increase the basal rate by 10%-20%, 30-90 min before the exercise, and continue at this rate when post-exercise hypoglycemia persists. In the case of combined aerobic and anaerobic exercise, hypoglycemia is more frequent but less than pure aerobic exercise. Hypoglycemia can be prevented with a reduction of basal insulin by up to 50%. If these changes are impossible, we should consider the artificial pancreas. The artificial pancreas system appeared to get efficient and secure control of blood glucose levels during exercise and four hours later[65].

Troubleshooting hypoglycemia

If severe hypoglycemia is present, the patient should not stop the pump but keep it running and check blood glucose levels. When confirmed, the patient is advised to take 15 gm of fast-acting carbohydrates and to recheck blood glucose after 10-15 min. If hypoglycemia persists, another dose of fast-acting carbohydrates is given, and the basal insulin could be temporarily reduced by 10%-20%. As the insulin type used in pump therapy is short-acting, long-acting carbohydrate is not a valid option to treat hypoglycemia with pump therapy. Patients with type I DM on pump therapy should be well trained to recognize and manage the episodes of hypoglycemia they may encounter. The patients should not rely on the hypoglycemia symptoms. Pseudohypoglycemia may occur in patients with diabetes with the typical symptoms of hypoglycemia with blood glucose levels of more than 3.9 mmol/L (70 mg/dL)[66].

Disabling hypoglycemia occurs when repeated episodes of hypoglycemia result in persistent anxiety and impaired quality of life. It usually occurs with tight DM control and with an increasing duration of diabetes. Severe hypoglycemia is that associated with the patient's inability to self-treat with marked impairment of cognitive functions, contrary to non-severe hypoglycemia in which the patient can self-treat and mild cognitive function impairment. Therefore, all children and adolescents with type I DM should have annual screening for impaired hypoglycemia awareness using a valid screening tool such

as Gold Score or Clarke Score[67]. These tools can identify the increased risk of severe hypoglycemic events. CGM can detect when more than 10% of the reading is less than four mmol/L (72 mg/dL) or when there are more than three readings with less than three mmol/L (54 mg/dL) per week, which increases the risk of severe hypoglycemic events[68]. It is crucial to investigate the underlying cause of disabling hypoglycemia, such as cortisol, a Growth Hormone, Coeliac disease, insulin Antibodies, *etc*. If no reason is detected, we should start an intensive education program for the family and the child. Then we can update the pump to sensor augment pump {SAP} without low glucose suspend (LGS). If not improved, we can shift to SAP with LGS. Islet cell or pancreas transplant could be the last option[69]. The child should be reassessed every 3-6 mo.

Sick child

Children with diabetes and adequate metabolic control should not encounter more infections or illnesses than children without diabetes. However, when a child with type I DM gets sick, we should rule out the presence of uncontrolled or symptomatic hyperglycemia, ketoacidosis, dehydration, and hypoglycemia[70]. The most crucial point to be emphasized is never to stop insulin; it is a prevalent mistake that leads to the development of ketoacidosis. When a child with diabetes has vomiting, we should consider insulin deficiency till proven otherwise. Consequently, the insulin dose may need to be increased or decreased according to the blood glucose level and the presence or absence of ketosis. The blood glucose should be monitored more frequently, at least every 3–4 h, particularly during the night and occasionally every 1–2 h. we also need to monitor for ketosis[70]. We should not depend on urinary ketones' presence to diagnose ketoacidosis as there is a long time lag between the pump stoppage and appearance of the ketone bodies in the urine and the lack of association between the ketones in the urine and the ketones in the blood. Blood beta-hydroxybutyrate monitoring is beneficial in too young children or when urine collection is hard to get[71].

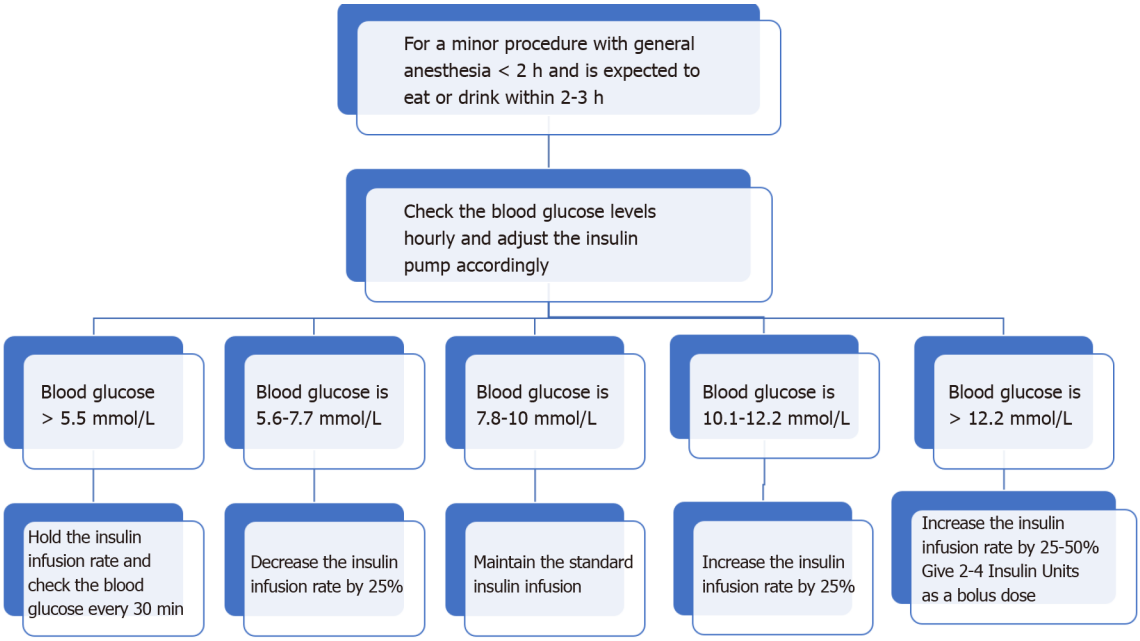
In the presence of hyperglycemia, we need to check for ketosis. If the urine ketones are absent or small or the blood ketones are less than 0.6 mmol/L (11 mg/dL), we give a pump correction bolus by drinking extra low-carbohydrate fluids and hourly checking of the blood glucose. If the blood glucose starts to decrease, then continue monitoring and accordingly decide to give another bolus dose or not. If the blood glucose fails to decrease after one hour from the corrective dose, then we supplement with a syringe or pen injection. Suppose the urine ketones are moderately or severely increased, or the blood ketones are equal to or more than 0.6 mmol/L (11 mg/dL). In that case, we should check for a pump delivery failure or a significant medical problem, *e.g*., severe infection. Accordingly, we can shift to insulin therapy by pen or syringe according to the severity of hyperglycemia and degree of ketonuria/ketonemia[70]. The pump should be checked for mechanical or catheter difficulties by replacing the insulin in the pump, the infusion set, and the cannula while continuing to give bolus doses with a pen or syringe until the hyperglycemia is controlled. Then, we must resume the pump therapy with a temporary basal rate of 120%, hourly blood glucose monitoring, and extra low-carbohydrate diet fluids[72].

If the child exhibits signs of diabetic ketoacidosis (DKA), the pump therapy should be discontinued due to the altered tissue perfusion in DKA, which impairs insulin absorption and affects the reliability of the pump therapy. The pump should be temporarily discontinued; the cannula should be removed, then follow the standard protocol to manage DKA. Once DKA is fixed, pump therapy is resumed at the patient's standard basal rate, but the patient should maintain intravenous insulin infusion till he receives a meal bolus[73]. Wang *et al*[74] showed that using nano-insulin pumps in children with DKA can quickly correct children's blood glucose and ketone body levels. If there is ketosis with low blood glucose, the child should drink extra high-carbohydrate fluids with continuous blood glucose monitoring. In case of persistent vomiting or failure of the previous attempt to control the disorder, the child should be hospitalized[75].

Insulin pump use in a hospitalized child

When hospitalized with a severe medical condition, children with type I DM need aggressive management of diabetes. Adequate and meticulous control of diabetes is associated with significant morbidity and mortality improvement in children and adults with diabetes[76]. However, intensive insulin therapy is associated with an increased hypoglycemia rate and complications without a significant mortality reduction. Therefore, continuous monitoring of the blood glucose level is crucial to prevent hypo/hyperglycemia[77]. Non-critically ill children hospitalized for elective and non-acute hospitalizations who can operate their insulin pumps are allowed to continue using them. Fasting prior to elective surgical procedure is allowed with proper adjustment of the basal insulin rate to prevent the development of hypoglycemia. However, if the children cannot operate their pump, they can transition to the basal-bolus regimen[78]. If the child is expected to go into a minor procedure with general anesthesia for less than two hours and is expected to eat or drink within 2-3 h, check the blood glucose levels hourly and adjust the insulin pump accordingly (Figure 7)[79].

It is acceptable that hospitalized patients continue to self-control their DM using an insulin pump except if they are unconscious, confused, or have severe pain, undergo major surgery or procedure under general anesthesia lasting more than two hours, or develop DKA. However, if children are hospitalized due to a critically ill condition or surgery that needs anesthesia for more than two hours



DOI: 10.5409/wjcp.v11.i6.463

Figure 7 A flow chart for a minor procedure with general anesthesia for less than two hours.

and will miss more than one meal, they need to shift to intravenous insulin therapy. The patients should remove the insulin pump and keep it safe to be resumed once the procedure finishes unless being critically ill. Frequent blood glucose monitoring (or CGM) offers safe insulin delivery control[80]. Care should be taken while doing specific procedures in the hospital to avoid damage to the insulin pump. The insulin pump should be covered by a lead apron while doing an X-ray, computerized tomography scan, cardiac catheterization, or insertion of a pacemaker/automatic implantable defibrillator. Ultrasonography can be done when needed, but the operator should avoid direct pointing the transducer to the pump. On the other hand, the pump should be removed while doing magnetic resonance imaging. Upper or lower gastrointestinal endoscopies do not require the removal of the pump[81].

Use of corticosteroid with pump therapy

As DM type I is an autoimmune disease, it is frequently associated with other autoimmune disorders, such as autoimmune thyroid disease[82]. Corticosteroids are frequently used in high doses to treat these autoimmune disorders such as asthma and inflammatory bowel diseases. Steroids usually increase insulin resistance, insulin requirement, and the risk of hyperglycemia. Hyperglycemia is predicted to occur approximately four to eight hours following oral steroids administration and sooner following intravenous steroids[83]. On the contrary, blood glucose levels may return to pre-steroid levels 24 h following intravenous steroids discontinuation. If oral steroids are withdrawn gradually over many weeks, glucose levels may decrease dose-dependently[84,85].

Interestingly, the daily timing of steroid-induced hyperglycemia depends on the type of steroid use. For example, prednisolone, usually given in the morning, induces hyperglycemia in the late morning and persists into the evening with a gradual fall of blood glucose back overnight, often reaching baseline levels the following morning[86]. Therefore, children on pump therapy need to increase the basal insulin rate to 130%-150% during the expected times of maximal hyperglycemia. However, we may occasionally need to increase the basal insulin rate to 200%-300% of the standard rate. Other management options are adjusting ICR or giving corrective insulin bolus when needed. Frequent blood glucose monitoring every 4 h should be done. Once steroid therapy is reduced or stopped, the insulin requirement can be decreased back to pre-steroid levels; therefore, readjusting insulin rates may be needed[87].

Improving insulin absorption at the insertion sites

Warming the injection site increases the blood flow, increasing the subcutaneous insulin absorption rate. Warming can be done by massaging or using special warming devices, which is particularly helpful in managing postprandial hyperglycemia[88,89]. Local application of recombinant human hyaluronidase increases the subcutaneous insulin dispersion and absorption rate at the injection site, conferring both ultrafast insulin absorption and action[90]. Using silicon microneedles integrated within the insulin pump trans-dermally delivers insulin efficiently, safely, and painlessly. It also helps decrease the insulin

pump size[91].

Insulin pump and school days

School life occupies an integral part of children's daily life. Consequently, children using an insulin pump should be able to manage it and have a good education about the proper use of the pump and the management of different problems that they may enface. This awareness is crucial for young children who may need continuous supervision of the pump data and settings, especially for carbohydrate intake, blood glucose monitoring, and insulin administration. The responsible teachers or the school healthcare worker should be well trained in the different scenarios the child using an insulin pump may encounter to allow rapid interference when needed. A clear school health plan to manage students with Type I DM should be available and practiced in recognizing and managing specific acute emergencies such as hypo/hyperglycemia with/without ketonemia[87].

Puberty in children using an insulin pump

Puberty is associated with increased sex hormone levels which increase the degree of insulin resistance and, consequently, increase the insulin requirement during puberty. Puberty is associated with higher hemoglobin A1c levels and rates of diabetes complications[92]. Adolescence is also associated with an increased risk of alcohol consumption and considerably increases the diabetes risk in young adulthood and makes diabetes control more difficult. Alcohol consumption in the evening increases the risk of hypoglycemia, especially at night and after the next breakfast, which needs frequent blood glucose monitoring, particularly at night and early morning[93,94].

Menstrual cycle in an adolescent female with Type I DM

Menses is associated with high fluctuations of the glycaemic control with an increased risk of hyperglycemia and increased insulin resistance during periovulation and early luteal phases (premenstrual period), possibly due to the rising oestradiol levels that occur before ovulation, which may need a temporary increase in the basal insulin rate[95]. On the contrary, when menses start, the progesterone level begins to drop, causing a sharp decline in the insulin requirement, which may increase the hypoglycemia risk steeply[96]. If the adolescent girl has a disturbed menstrual cycle and needs to use contraceptive pills to regulate the cycle, care should be taken while using them as an increase in the basal insulin requirement may occur, especially with high-dose contraceptive pills or with long-acting progesterone injections[97].

Traveling with an insulin pump

Despite traveling being a welcome retreat from our everyday life difficulties, it is associated with an extraordinary increase in daily activity, which could increase the risk of hypoglycemia and becomes a real challenge in patients with diabetes. It is particularly challenging in the presence of time zone differences > 3 h, significant variations in the basal rates, such as the marked Dawn phenomenon, recurrent or severe episodes of hypoglycemia, or reduced hypoglycemia awareness. The pump basal rate is reduced by 10%-20% during traveling for the first 24 h and gradually changes the pump timing setting to the new local time upon arrival at the destination by 2-3 h each day. This change should be associated with frequent blood glucose monitoring. Disconnecting the pump during take-off and landing is also essential to avoid pressure effects on the pump delivery mechanism[98].

GENERAL CARE FOR CHILDREN WITH DM WHO REQUIRE INSULIN PUMP THERAPY

Skin care and prevention of insertion site infection

Skin changes occur in one-third of patients with diabetes. Children with high glucose levels tend to have dry skin[99]. Therefore, they need adequate blood sugar control and proper skin hydration with specific lotions for diabetes following site change, especially in pump care. Itching is frequent at the insertion site; the child is advised to gently rub and avoid scratching the affected area to avoid skin breakage [100]. The insertion set should be applied to dry, unwet, non-broken skin. The insertion site should be rotated ideally every three days, over 6-10 sites, to long-term preserve skin integrity. Certain areas are advised more than others due to their superior insulin-absorptive capabilities, more comfort, and better convenience. The most common sites suitable for insertion are the abdomen (two-centimetre radius around and away from the navel), upper buttocks, upper thigh (medial and lateral areas, at least 5 cm away from hip or knee joints), upper buttocks (flank), upper arm, and rarely forearm (Figure 8A). The area with the least hair should be chosen as the hair decreases the longevity of the insertion site. Every site should take at least one week for recovery and should be away from the next site by at least one to two inches. Different patterns of insertion site rotations are demonstrated in Figure 8B[101].

Vaccination

Patients with DM, especially those requiring insulin pump therapy, need intense vaccination programs.

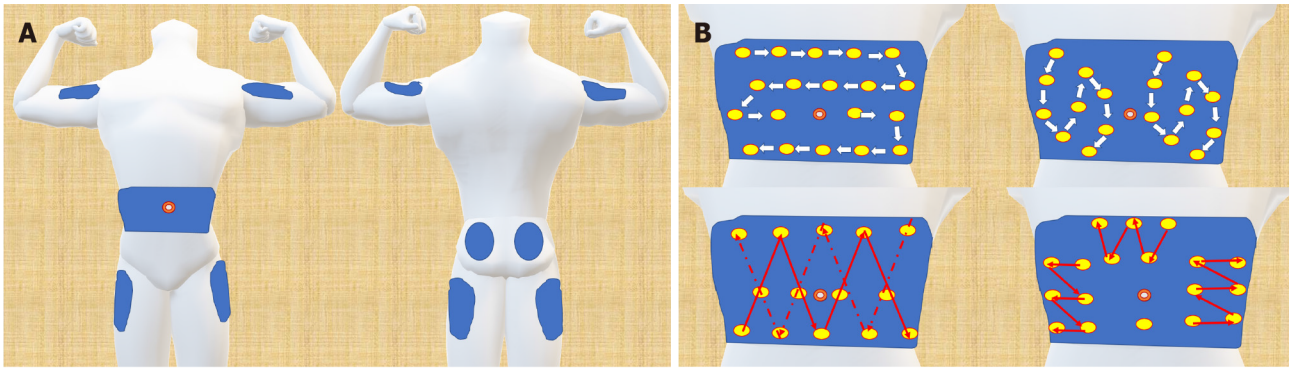


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Figure 8 Approved insertion sites and different types of insertion site rotation. A: There are four approved sites for the subcutaneous injection of insulin: Insulin Absorption Rate Fluctuation Depending on Injection Site; B: shows different types of insertion site rotation. Note that all the rotation patterns keep away from the umbilicus by at least one inch.

They should receive an annual flu vaccination. They also should consider having Streptococcus pneumoniae vaccines, and the coronavirus disease 2019 (COVID-19) vaccination is strongly recommended[102].

The use of insulin pumps in special situations such as traveling, swimming, bathing, imaging, and other procedures is summarized in Table 2.

ADVANTAGES OF INSULIN PUMP THERAPY

The insulin pump provides fewer needle injections as there is no need to inject insulin every time needed. It also can provide small insulin doses down to ten times less (0.05-0.1 Units) than an insulin pen or syringe, which is particularly useful in insulin-sensitive young children. Meanwhile, the insulin pump provides a convenient and more flexible way to modify the needed insulin more physiologically, relatively similar to the human pancreas[103]. Hence basal insulin can be programmed to match the person's activity, the changing daily requirement, hormonal changes, pubertal spurts, stress, illness, traveling, and any other situations. At the same time, insulin bolus can be delivered in different ways considering various conditions such as gastroparesis, malabsorption, or even to match the ingested foods. On the other hand, insulin delivery can be temporarily reduced or suspended in certain situations, such as hypoglycemia[32].

This incredible flexibility in the insulin delivery system and the marked less in blood glucose fluctuations allow a better quality of life. Using rapid-acting insulin delivered in a low volume tailored to the individual needs allows the insulin pump to overcome the variation in insulin absorption that is usually observed with long-acting insulin, resulting in more consistent and reliable insulin absorption and consequently less fluctuation of both insulin profile and blood glucose level[104]. This feature also helps to decrease the need for snacks, especially before exercise, consequently decreasing the rate of weight gain[105]. However, Boucher-Berry *et al*[106] found that lower bolus to basal insulin ratios increases the risk of excess weight gain. Hence, proper bolus and basal insulin dose adjustments are mandatory during insulin therapy. Pump therapy also improves the patient experience and satisfaction due to technology motivation and improved self-management. Pumps can also integrate easily with the new technology, so they can link easily with blood glucose measuring technology, bolus advisors, and wizards for diabetes management, forming a closed-loop system similar to an artificial pancreas which significantly improves the patient's quality of life[107].

DISADVANTAGES OF INSULIN PUMP THERAPY

There are some disadvantages to insulin pump therapy that may limit its use. Being worn all the time (24 h a day/7 days a week), even during sleep, showering, and sports, with continuous reminders of being diabetic, can influence body image and self-confidence. Luckily, numerous accessories are accessible to make wearing the pump hidden and convenient[108]. Because insulin pumps use only rapid-acting insulin without a long-acting insulin depot, there is a high risk of rapid development of DKA with technical failure or interruption of insulin flow such as air in the tubing, a damaged infusion set, or infection at the insertion site. Therefore, the patient should monitor blood glucose levels more frequently, at least four times daily, and a specialized well-trained interdisciplinary care team should be accessible in case of emergency. The pump also should not be disconnected for a long time (short-acting

Table 2 Special situations with insulin pumps

Situation		Management
Air travel		The patient should have a note from the physician about the need for the pump before traveling
		The patient should inform the security about the pump before passing through the security checkpoint with an X-ray detector
		All the suppliers and the accessories should be carried in a separate bag for easy inspection
		The metal detectors and whole-body scanners do not damage the device
Shower and bathing		A warm shower is associated with more rapid insulin absorption than usual, increasing the risk of hypoglycemia
		A warm bath (*e.g.*, hot tub or sauna) can expose insulin to high temperatures, which could be spoiled when exposed for an extended period
		High temperatures can also damage the pump, so it is crucial to check the owner manual for temperature specifications about ideal operating temperatures for the pump
		Knowing the type of the pump as waterproof, watertight, water-repellent, and water-resistant is essential
		If the insulin pump is not water waterproof, it is better to disconnect the pump and keep it in a dry place
Swimming		Knowing the type of the pump as waterproof, watertight, water-repellent, and water-resistant is essential
		If the pump is waterproof, they should know how many feet in-depth and how long
		The patient also should know the maximum time the pump can be removed without affecting its performance, *e.g.*, one hour for the Aviva Combo insulin pump
		Some pumps can be worn while swimming. It will be adjusted to deliver a specific basal rate throughout the swimming
		If the pump is not compatible with swimming according to the manufacturer's guidelines, the pump can be removed, leaving the cannula attached in place and covered with a dressing and a cap
		If the pump is removed for more than one hour, testing the blood glucose using a glucometer is advised with the recommended amount of carbohydrates and insulin intake, and continue swimming
Contact sports		All types of sports, including martial arts and those with possible body contact, are permitted if there are no other systemic contraindications
		Contact sports may increase the risk of dislodgement of the pump cannula
		Ensure adequate hydration during any exercise
		The pump can be removed for up to one hour
		After one hour, testing the blood sugar using a glucometer is advised with the recommended amount of carbohydrates and insulin intake, and continue sports
Imaging	**X-ray**	Radiation can provoke electrical currents in the electric circuit, impairing the pump function
		The pump should be removed when possible
		Safe to keep on an insulin pump in position if the x-ray beam is less than 3 seconds at a time and if a lead apron protects the pump
	Dental X-ray	The patient should ensure that the pump is covered by the lead apron he wears
	Ultrasound	The ultrasound beam should not directly point at the pump or the insertion site
	CT-scan and Fluoroscopy	The pump should be removed when possible
		If unable to remove the pump, relocate it to another area away from the anatomic examination site and cover it with a lead apron
		Switch off the pump during the examination and set a reminder timer to reoperate the pump just after finishing the radiological procedure
		After finishing the procedure, the pump should be checked for any possible malfunction with frequent blood glucose monitoring
	MRI	The MRI magnetic field is strong enough to magnetize the pump's motor and thus damage it
		The pump should be removed and kept outside the MRI room whenever possible
		If it is impossible to remove the pump and the patient uses a metal cannula or an Omnipod, he/she must remove it before entering the room and insert a new cannula after finishing the test
		If the pump is accidentally exposed to an MRI field, it should be stopped and disconnected immediately and checked by the maintenance team for any malfunction before resuming its use

Insulin pump renewal	The pump is renewed if there is evidence of clinical benefits over the past four years
	The pump is renewed after warranty expiration to obtain the safest result. However, it can still be used but with an increased risk of malfunction
The transition from Pediatric to the adult pump user	The child pump users can shift to MDT between 12-18 yr of age. However, they can continue using the pump as an adult
	They need at least three monthly follow-up appointments to ensure the adequacy of MDT with a smooth transition to the adult clinic
	Pediatric pump users can take a holiday off from the pump therapy. During this holiday, they can receive MDT as a training period and are not considered as a pump therapy failure
	Strong cooperation between the pediatric and the adult pump therapy clinic is needed to ensure a smooth transition of the adolescent to an adult pump or MDT user

CT: Computed tomography; MDT: Multidose therapy; MRI: Magnetic resonance imaging.

insulin). This limitation could affect the child's daily activities, such as swimming. However, many pump types are waterproof and fit for swimming[109].

Insulin pump setup occasionally is complicated and difficult to proceed with compared to pen or syringe use. Therefore, adequate training and education are mandatory for both the child and the caregiver. It also needs a high level of motivation, understanding, and education to achieve the best benefit of the pump and avoid complications. In addition, the insertion set, including the infusion set and cannula, requires to be replaced every 2-3 d. In addition, the infusion set may be prone to incorrect priming, air bubbles, tubing breakdown, and kinking or slippage of the cannula, which can interrupt insulin delivery[110].

Infection of the insertion site occurs in 17% of patients on insulin pumps over a period of three years, especially when the infusion set is left for longer than it should[111]. Risk factors for insertion site infections include large insulin doses, poor patient selection, inadequate patient education, lack of hygienic measures, infrequent changes of the infusion set as requested by the manufacturer, and incorrect cannula insertion[112]. Staphylococcal or streptococcal bacterial infections are the most common infection at the insertion site, followed by *Rhizomucor pusillus* fungal cellulitis[113]. Occasionally the infection may progress to cellulitis or collect into an abscess requiring surgical drainage. Primary tuberculous infection of the insulin injection site is rare but reported complications of insulin therapy[114]. Changing the insertion set should be done according to the manufacturer's guidelines or pump educator to diminish the chance of infection. It is also imperative that the patient follow proper hygienic measures, especially washing the hands and periodically changing the site to decrease infection chances. The cost of the pump is not only limited to the device but also running costs for accessories, cartridge syringes, batteries, skin preparation items, cannulas, and infusion sets, which are significantly higher than the regular insulin pens and syringes. Because insulin is a lifesaving essential medicine, every effort should be made to minimize the cost to the patient and his family[115].

DISCONTINUATION OF INSULIN PUMP THERAPY

About 3% of the pump user discontinue pump therapy within one year. The most frequent causes, according to Wong *et al*[116], include difficulties in pump insertion/adhesive (60%), interference with sports activities (42%), discomfort with wearing the pump (38%), interference with intimacy (34%), pump dysfunction (28%), and problematic hyperglycemia (28%). Beato-Víbora *et al*[117] 2015 showed that pump therapy improves glycaemic control and hypoglycemia awareness, decreases hypoglycemia frequency, and can be sustained for many years. However, 5% of the users discontinued the pump therapy due to a lack of clinical advantage, technical problems, safety issues, or user choice.

The pump therapy should be discontinued for recurrent DKA as it affects the local absorption of insulin due to altered tissue perfusion. It should also be discontinued when there is a pump failure or mismanagement, inadequate blood glucose monitoring (less than four times/day), recurrent injection site infection, intentional overdosing, failure to meet the objective of pump therapy, or with the parents' or the child's wishes. Pump therapy should be discontinued if the patient becomes unconscious, confused, and unable to self-management, such as severe pain or illness. It should also be discontinued if the patient goes for major surgery with general anesthesia for more than two hours[118]. Limitation of the study: some of the included articles were in favor of using insulin pumps which may carry the risk of bias. However, we tried to include most of the available studies to minimize the risk of bias.

CONCLUSION

The insulin pump is a giant breakthrough in DM management, especially in the pediatric age. The insulin pump provides fewer needles and can provide very tiny insulin doses. It provides a convenient and more flexible way to modify the needed insulin physiologically, like the human pancreas. It can offer adequate and optimal glycemic control to reduce the risk of metabolic derangements in different tissues. However, there are some disadvantages to insulin pump therapy that do not necessarily prevent its use. It should be discontinued with recurrent diabetic ketoacidosis.

ARTICLE HIGHLIGHTS

Research background

The insulin pump is a giant breakthrough in diabetes mellitus (DM) treatment. Treating diabetes with an insulin pump is the method most similar to the normal physiologic function of the pancreas.

Research Motivation

We are motivated to write this manuscript to decrease the gap in understanding of insulin pump use among children health care professionals, parents, and children with diabetes mellitus who need intensive insulin therapy.

Research objectives

To identify all the existing evidence-based research for the proper use of insulin pumps among children with diabetes Mellitus and to increase awareness among these patients and their families.

Research Methods

We conducted comprehensive literature searches of electronic databases until June 30, 2022, related to pump therapy in children and published in the English language. The selected articles were subsequently explored to identify the most recent evidence-based research and existing guidelines for the proper use of insulin pumps in children.

Research Results

We identified 118 articles concerned with insulin pumps, 61 were reviews, systemic reviews, and meta-analyses, 47 were primary research studies with strong design, and ten were guidelines. These articles covered the different aspects of insulin pump use in children with diabetes mellitus.

Research conclusions

The insulin pump is a giant breakthrough in pediatric DM management. It provides fewer needles and can provide very tiny insulin doses with a convenient and flexible way to modify the needed insulin physiologically, like the human pancreas. It can offer adequate and optimal glycemic control to reduce the risk of metabolic derangements in different tissues.

Research perspectives

Continuous modification and upgrading of the insulin pump are expected to proceed. These modifications will probably help to make insulin pumps more physiologic and similar to the human pancreas.

ACKNOWLEDGEMENTS

We thank the anonymous referees for their valuable suggestions.

FOOTNOTES

Author contributions: Al-Biltagi M, Saeed NK, Bediwy AS, and Elbeltagi R collected the data and wrote and revised the manuscript.

Conflict-of-interest statement: All authors declare no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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