

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2015 August 8; 4(3): 35-49



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WJCP covers a variety of clinical medical topics, including fetal diseases, inborn, newborn diseases, infant diseases, genetic diseases, diagnostic imaging, endoscopy, and evidence-based medicine and epidemiology. Priority publication will be given to articles concerning diagnosis and treatment of pediatric diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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World Journal of Clinical Pediatrics is now indexed in PubMed Central, PubMed and Digital Object Identifier.

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NAME OF JOURNAL

World Journal of Clinical Pediatrics

ISSN

ISSN 2219-2808 (online)

LAUNCH DATE

June 8, 2012

FREQUENCY

Quarterly

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8226 Regency Drive,
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PUBLICATION DATE

August 8, 2015

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Limited brain magnetic resonance imaging for evaluation of non-traumatic pediatric head emergencies

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Author contributions: Shah CC created the outline of the article and final edits; Parikh AK did the literature search and initial draft of the article.

Conflict-of-interest statement: Authors have no conflict of interests including but not limited to commercial, personal, political, intellectual, or religious interests.

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Received: January 28, 2015

Peer-review started: January 31, 2015

First decision: March 6, 2015

Revised: April 1, 2015

Accepted: May 7, 2015

Article in press: May 8, 2015

Published online: August 8, 2015

fast spin echo (SSFSE) and sagittal SSFSE can be performed in under 5 min of scan time. This approach may provide more information than a non-contrast head computed tomography (CT) in non-traumatic pediatric head emergency, avoid ionizing radiation from CT scan and stratify patients who need more detailed brain MRI. Research studies are required to provide evidence for feasibility of such an approach.

Key words: Magnetic resonance imaging; Head; Brain; Pediatric head emergency; Computed tomography; Pediatric; Emergency

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Core tip: Limited brain magnetic resonance imaging (MRI) consisting of axial fluid attenuated inversion recovery, axial diffusion weighted imaging, coronal single shot fast spin echo (SSFSE) and sagittal SSFSE can be performed in under 5 min of scan time. This approach may provide more information than a non-contrast head computed tomography (CT) in non-traumatic pediatric head emergency, avoid ionizing radiation from CT scan and stratify patients who need more detailed brain MRI. Research studies are required to provide evidence for feasibility of such an approach.

Shah CC, Parikh AK. Limited brain magnetic resonance imaging for evaluation of non-traumatic pediatric head emergencies. *World J Clin Pediatr* 2015; 4(3): 35-37 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v4/i3/35.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v4.i3.35>

Abstract

Limited brain magnetic resonance imaging (MRI) consisting of axial fluid attenuated inversion recovery, axial diffusion weighted imaging, coronal single shot

CURRENT SITUATION

Multitude of various indications exists for non-traumatic head imaging in the emergency department among children, most common of which is headache. Other

common indications include seizures, syncope, ataxia, or a focal neurologic deficit. For many of these reasons, a non-contrast head computed tomography (CT) is often performed. While quite useful in eliminating or diagnosing life-threatening conditions, if negative, CT will not be helpful in providing a specific diagnosis. In contrast, a limited brain magnetic resonance imaging (MRI) may be more efficient, cost-effective, diagnostic and safer alternative to non-contrast head CT in non-traumatic pediatric head emergencies.

Huda *et al.*^[1] estimated the organ-absorbed dose in head CT ranges from 30 mGy in neonates to 40 mGy in adults. More importantly, the effective dose for a head CT in a neonate was approximately four times higher than in an adult (0.9 mSv).

Pearce *et al.*^[2] found a correlation between head CT scans and an increased risk, albeit small, for the development of leukemia and brain tumors. In concert with the ALARA principle, it is now ever more prudent to attempt to limit the use of ionizing radiation and if possible, eliminate it altogether.

CHANGING SCENARIO

Previously, accessibility and efficiency have always been touted as being reasons for performing a head CT versus a MRI. However, newer MRI technologies have developed which allow for faster image acquisition. More institutions now employ more MRI scanners running on an around the clock basis allowing for more availability in performing urgent/stat exams.

Even though MRI examinations are faster than they ever have been, they cannot currently match the speed of CT. Because of this, sedation or general anesthesia is often employed in children to obtain quality MRI examinations. In our institution, sedation or general anesthesia is typically given to children after the first few months of life to age 6-8 years. A feed and sleep technique is typically employed for infants under 1 mo of age with a swaddling and sleep method used for infants under 6 mo. Between the ages of 6-8 years, programs that recreate the MR examination in a mock setting can be used to decrease the requirement of sedation/general anesthesia during the actual exam. Children older than 8 years of age are typically able to cooperate and hold still during the MR examination and thus do not require sedation/general anesthesia.

SUGGESTED APPROACH

Limited brain MRI of the head may prove superior to CT in eliminating life-threatening conditions and targeting children who would benefit from a more detailed MRI evaluation. The limited brain MRI that we suggest may consist of axial fluid attenuated inversion recovery (FLAIR) sequence, axial diffusion weighted imaging (DWI) sequence and T2-weighted images using single shot fast spin echo (SSFSE) pulse sequence images

in the coronal and sagittal planes. Total MRI scan time would be around 5 min.

Hemorrhage, infarction, hydrocephalus and a large tumor would easily be diagnosed *via* limited brain MR examinations. Such a finding may require a complete detailed MRI. A normal limited brain MRI would not need further imaging, particularly for a common indication such as a headache.

POSSIBLE HURDLES

However, there are few hurdles with a limited brain MR approach to emergent ED head imaging. While accessibility to MR exams is better than ever before, it lags considerably behind CT. This difference is immense among community and rural based hospitals. Further, even if the MR equipment is available, the trained staff available to manage and operate the scanners is very limited, especially after regular working hours.

RECOMMENDATIONS

A retrospective study is required for preliminary evaluation. Such a retrospective study would look at only FLAIR, DWI and T2 sequences of brain MRI done through referral from pediatric emergency. The study design would blind the radiologist from patient identifier and MRI report. Only these few sequences would be provided for review. The blinded researcher report would be then compared with the MRI report generated at the time of examination. Number of cases where clinically important findings would have been missed by this approach would be determined. List of insignificant and significant findings that might have been missed would be generated; If the outcome of the retrospective study suggested above provides support to this suggested approach, similar retrospective studies from multiple centers would be needed; If such multiple retrospective studies provide enough evidence to promote this suggested approach, prospective study will be needed; Cross training CT and MRI technologist may increase the availability of MRI personnel after regular working hours; A separate limited billing code would be required to bill such limited MRI study. Cost of such limited brain MRI without contrast would be comparable to or slightly more than a non-contrast head CT.

CONCLUSION

Limited brain MRI consisting of axial FLAIR, axial DWI, coronal SSFSE and sagittal SSFSE can be performed in under 5 min of scan time. This approach may provide more information than a non-contrast head CT in non-traumatic pediatric head emergency, avoid ionizing radiation from CT scan and stratify patients who need more detailed brain MRI. Research studies suggested above may help provide evidence for feasibility of such an approach.

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Howe NL, Ronckers CM, Rajaraman P, Sir Craft AW, Parker L, Berrington de González A. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet* 2012; **380**: 499-505 [PMID: 22681860 DOI: 10.1016/S0140-6736(12)60815-0]

P- Reviewer: Gonzalez-Granado LI, Saburi A **S- Editor:** Ji FF
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Blunted perception of dyspnea in asthmatic children: A potential misleading criterion

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Author contributions: All authors contributed to this work.

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

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Received: March 23, 2015
Peer-review started: March 25, 2015
First decision: April 10, 2015
Revised: May 2, 2015
Accepted: June 15, 2015
Article in press: June 16, 2015
Published online: August 8, 2015

Abstract

Dyspnea (or breathlessness) is a symptom describing a perceived experience of breathing discomfort. Children's awareness of dyspnea is variable and there is only a poor correlation between the objective respiratory distress measurements and the subjectively awareness of dyspnea. Those who do not perceive dyspnea may not be motivated to comply with their daily prophylactic

treatment. Since dyspnea is the main symptom of asthma, and disease management is based largely on the description of symptoms between clinic visits, unreliable symptom report may mislead decision-making for long-term treatment of asthma. Thus, therapeutic decisions should not be taken solely on patients' perception and description of dyspnea.

Key words: Breathlessness; Respiratory distress; Tachypnea; Asthma; Symptom

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Core tip: Children's awareness of dyspnea is variable and there is only a poor correlation between the objective respiratory distress measurements and the subjectively awareness of dyspnea. Children with asthma vary in their perception of dyspnea for the same degree of bronchoconstriction. Therapeutic decisions should not be taken solely on patients' perception and description of dyspnea.

Douros K, Boutopoulou B, Priftis KN. Blunted perception of dyspnea in asthmatic children: A potential misleading criterion. *World J Clin Pediatr* 2015; 4(3): 38-40 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v4/i3/38.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v4.i3.38>

INTRODUCTION

Dyspnea (or breathlessness) is a symptom describing a perceived experience of breathing discomfort and is considered a warning sign to a critical threat to homeostasis. It urges to adaptive responses intended to minimize the work of breathing, such as resting or taking the necessary medicines^[1]. Since dyspnea is a subjectively perceived abnormal sensation it is quite distinct from the objective signs of respiratory

distress, such as tachypnea, retractions and use of accessory muscles. Dyspnea is a common symptom of cardiopulmonary disorders. However, its intensity is not related solely to the severity of the underlying disease but it is also affected from psychological factors^[2]. In particular, anxiety in asthmatic children is positively associated with symptom perception during times when children's asthma is mild^[3]. In addition, dyspnea may also occur in healthy individuals, *e.g.*, during intense emotional states and heavy labor or exercise^[4].

Our knowledge on the pathophysiological pathways underlying dyspnea still remains incomplete. Specific dyspnea receptors have not been found so far and, since a clear beginning of the nervous sensory transduction pathway is missing, it is not yet feasible to clarify the neurophysiology of dyspnea and depict it as a well-defined model, such as the ones that exist for vision, hearing, or pain. However, the general principle of peripheral sensory information from the respiratory system, traveling through an intact afferent pathway and triggering regions of the cerebral cortex to produce the perception of dyspnea, does seem to exist.

DYSPNEA PERCEPTION AND LUNG FUNCTION IN ASTHMATIC CHILDREN

Despite the number of methods that have been developed in order to have accurate quantitative estimates of the degree of dyspnea and reproducible follow-up of patients, the incorporation of a real life method in everyday clinical practice still remains elusive. Among the plenitude of invented dyspnea scales, the most commonly encountered in medical literature, is the Borg scale and its modifications^[5]. The majority of dyspnea scales have been extensively used and studied in adults. However, their applicability is often questionable and, simplicity is always prerequisite in order to be used in children. Such scales can be used only on the assumption that the child's ability to organize objects in order - something that it is generally achieved after the age of 7 years - has reached an operational stage^[6].

But is the perception of dyspnea so critical as to affect clinical management and outcomes of asthmatic children? Male *et al*^[7] tried to investigate the relation of poor perception of breathlessness with severe asthma attacks in children. They retrospectively studied 27 children admitted to hospital with asthma exacerbation all of whom had recordings of breathlessness scores as well as oxygen saturation, clinical score, and FEV₁, at 5, 10, 24, 48, and 72 h after admission. They found that the more severely affected (hypoxic) children had a trend towards feeling less breathless at admission. These children also experienced a smaller decrease in dyspnea score for a similar improvement in FEV₁, than children presenting without hypoxia. van Gent *et al*^[8] in a cross sectional study, measured dyspnea in two groups of "diagnosed" and "undiagnosed" asthmatic children. Subjects in

the first group were already diagnosed with asthma, whereas in the second group asthma was actually diagnosed during the recruitment phase of the study. All children underwent hypertonic saline testing for bronchial hyperresponsiveness. The authors observed that children with "undiagnosed" asthma had worse perception of dyspnea than children with "diagnosed" asthma. Nuijsink *et al*^[9] studied the perception of bronchoconstriction during methacholine bronchoprovocation challenge in children with moderately severe atopic asthma. They demonstrated that the more severe the airway hyper-reactivity, the less likely it was for patients to perceive bronchoconstriction. They also observed that children having low baseline FEV₁ values tended to use less beta-agonist bronchodilator as a "rescue medication". Panditi *et al*^[10] measured the perception of dyspnea in asthmatic children during exercise challenge testing on treadmill. There was only a weak relation of the children's reported dyspnea measurements following the exercise test with the change in FEV₁ before and after the challenge. Approximately half of the children had a repeat challenge a few weeks later in which the discrepancies from the first visit were so great that no relation could be established between the changes in dyspnea and the spirometric indices between visits. They further compared parents' independent perception of their children's dyspnea with the dyspnea perceived from the children themselves. Parents' perception of their child's dyspnea was not related to any of the lung function measurements.

What the above studies add to our knowledge regarding children's perception of dyspnea? Children's awareness of dyspnea is variable and there is only a poor correlation between the objective respiratory distress measurements and the subjectively awareness of dyspnea. Children with asthma vary in their perception of dyspnea for the same degree of bronchoconstriction. In general, children, especially those with undiagnosed asthma, may become tolerant to a certain degree of bronchoconstriction mainly because of adaptation related to frequent bronchoconstriction^[11]. Despite the absence of direct evidence proving correlation between poor perception of dyspnea with either severe persistent asthma or history of severe asthma attacks, the blunted sensation of dyspnea in many children may result in delayed diagnosis and/or under-treatment of the disease, and so puts them at risk of severe and even life threatening asthma attacks. Those who do not perceive dyspnea may not be motivated to comply with their daily prophylactic treatment. Children who underestimate their symptoms tend to seek medical help only at a late stage of their exacerbations. Moreover, poor perception contributes to the considerable number of children without proper diagnosis despite suffering from asthma. In this case, the absence of prophylactic treatment combined with poor alertness may result in the first clear presentation of their disease being a severe and possibly life threatening acute attack^[12]. Parents and caregivers appear to be even less accurate in detecting their child's

symptoms.

CONCLUSION

Since dyspnea is the main symptom of asthma, and disease management is based largely on the description of symptoms between clinic visits, unreliable symptom report may mislead decision-making for long-term treatment of asthma. Thus, therapeutic decisions should not be taken solely on patients' perception and description of dyspnea.

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P- Reviewer: Kolettis TM, Sijens PE, Teng RJ
S- Editor: Tian YL **L- Editor:** A **E- Editor:** Liu SQ



Prevention of neural tube defects with folic acid: The Chinese experience

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Author contributions: Ren AG solely contributed to this work.

Conflict-of-interest statement: The author declares no competing financial or no-financial conflict of interests.

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Received: March 25, 2015
Peer-review started: March 31, 2015
First decision: May 13, 2015
Revised: May 21, 2015
Accepted: June 18, 2015
Article in press: June 19, 2015
Published online: August 8, 2015

Abstract

Neural tube defects (NTDs) are a group of congenital malformations of the central nervous system that are caused by the closure failure of the embryonic neural tube by the 28th day of conception. Anencephaly and spina bifida are the two major subtypes. Fetuses with anencephaly are often stillborn or electively aborted

due to prenatal diagnosis, or they die shortly after birth. Most infants with spina bifida are live-born and, with proper surgical treatment, can survive into adulthood. However, these children often have life-long physical disabilities. China has one of the highest prevalence of NTDs in the world. Inadequate dietary folate intake is believed to be the main cause of the cluster. Unlike many other countries that use staple fortification with folic acid as the public health strategy to prevent NTDs, the Chinese government provides all women who have a rural household registration and who plan to become pregnant with folic acid supplements, free of charge, through a nation-wide program started in 2009. Two to three years after the initiation of the program, the folic acid supplementation rate increased to 85% in the areas of the highest NTD prevalence. The mean plasma folate level of women during early and mid-pregnancy doubled the level before the program was introduced. However, most women began taking folic acid supplements when they knew that they were pregnant. This is too late for the protection of the embryonic neural tube. In a post-program survey of the women who reported folic acid supplementation, less than a quarter of the women began taking supplements prior to pregnancy, indicating that the remaining three quarters of the fetuses remained unprotected during the time of neural tube formation. Therefore, staple food fortification with folic acid should be considered as a priority in the prevention of NTDs.

Key words: Neural tube defects; Folic acid; Folate; Supplementation; Fortification

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Core tip: Neural tube defects are severe congenital malformations of the central nervous system. The prevalence of these defects in China is among the highest in the world. Low intake of dietary folate is to be blamed. The provision of free-of-charge folic

acid supplements to all women who live in rural areas and plan to become pregnant has been implemented since 2009. However, fortification of staple foods with folic acid has not been planned. It is time to consider fortification since many pregnancies are unplanned and therefore it is difficult for a woman to take folic acid supplements from before pregnancy.

Ren AG. Prevention of neural tube defects with folic acid: The Chinese experience. *World J Clin Pediatr* 2015; 4(3): 41-44 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v4/i3/41.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v4.i3.41>

EMBRYONIC AND CLINICAL FEATURES OF NEURAL TUBE DEFECTS

Neural tube defects (NTDs) are a group of congenital malformations of the central nervous system that are caused by the failure of the embryonic neural tube to close by the 28th day of conception^[1,2]. Anencephaly and spina bifida are the two major subtypes of NTDs. A closure failure that occurs in the cranial region of the neural tube leads to anencephaly, which is characterized by the absence of the cranial vault and absent or markedly reduced cerebral hemispheres. Fetuses with anencephaly are often stillborn or electively aborted due to prenatal diagnosis, or they die shortly after birth. A closure defect occurring in the caudal region of the neural tube is referred to as spina bifida or meningomyelocele. This condition is characterized by bony defects in the spine through which the meninges and/or spinal cord tissue protrude to the body surface. Most infants with spina bifida are live-born and, with proper surgical treatment and management, can survive into adulthood. However, these children often have life-long physical disabilities, including leg paralysis, absence of control of urine and bowel, and learning difficulties. In addition, a large proportion of infants with spina bifida are complicated with hydrocephalus, which may lead to intellectual impairment and even premature death.

PREVALENCE OF NTD

NTDs are the second most common birth defect after congenital heart defects. It has been estimated that every year more than 320000 infants are born with NTDs worldwide^[3]. However, the prevalence of infants born with NTDs varies widely between countries and also within countries. In China, NTD epidemiology is characterized by a higher prevalence in the North than in the South and a higher prevalence in rural areas than in cities. A nationwide survey conducted in 1986-1987 showed an overall prevalence of 45.5 per 10000 births in the 15 northern provinces, compared with 11.3 per 10000 births in 12 Southern provinces^[4]. Of the northern provinces, Shanxi had the highest prevalence,

with 68.5 per 10000 births for males and 144 per 10000 births for females. During the same period, the prevalence of NTDs was 6 per 10000 births in the United States^[5]. Ireland is well known for its high prevalence of NTDs. East Ireland had a prevalence rate about 23 per 10000 births in 1986-1987^[6]. These data indicate that the prevalence of NTDs in Northern China is among the highest in the world. It has been estimated that around 100000 fetuses are affected annually in China. In recent years, the prevalence of NTDs in China has been declining consistently, but no national data are available to clarify how much of this trend is attributable to fewer NTD occurrences or to avoidance through pregnancy termination after prenatal diagnosis. This is because the national birth defects monitoring system includes only pregnancies of 28 wk' gestation or greater, thus not counting any pregnancies that are terminated before 28 wk' gestation. One study showed that more than two-thirds of NTD-affected pregnancies were terminated before 28 wk of gestation in the Shanxi rural population in early 2000s^[7]. This proportion is expected to be over 90% in urban populations. Surveillance data from 5 counties in Shanxi Province show that NTD prevalence declined from a peak of 120 per 10000 births in 2004 to 31.5 per 10000 births in 2014 (unpublished data). The latter remains much higher than the current prevalence of NTDs (5-7 per 10000 births) in the United States^[8].

DIETARY FOLATE INTAKE AND BLOOD FOLATE LEVELS OF WOMEN OF REPRODUCTIVE AGE

It has long been known that low blood folate during the periconceptional period is associated with an increased risk that a pregnancy will be affected by an NTD^[9]. Folate is the natural form of folic acid contained in food and in the body. Folic acid is the synthetic form that is used in supplements and fortified foods. Folate cannot be synthesized in the body and therefore can only be obtained from food. The typical diet of northern China is characterized by low amounts of fresh vegetables and fruits; this results in low blood folate. An investigation among women in Shanxi's rural population who were planning to become pregnant showed that the mean (\pm SD) and median (interquartile range) daily folate intake values were 114.3 ± 59.7 μ g/d and 102.8 (69.3-146.8) μ g/d, respectively. Virtually all (99%) of the women had an intake level below 320 μ g/d, the estimated average requirement for non-pregnant women, and only 1% and 7% of the women consumed 75% and 50%, respectively, of the recommended daily folate intake of 400 μ g for non-pregnant women^[10]. As a result of this low dietary folate intake, people living in the North have less than half the blood folate level of people living in the South. During early to mid-pregnancy, women living in the North had plasma and erythrocyte folate concentrations of 12.2 nmol/L and 440.0 nmol/L, respectively, compared to 33.5 nmol/L and 910.4 nmol/L,

respectively, for women living in the south^[11]. Low dietary folate intake and low blood folate concentration lead to a high risk of an NTD-affected pregnancy.

NATIONWIDE FOLIC ACID SUPPLEMENTATION PROGRAM

Although folate may be taken in naturally *via* the diet, folate intake from the diet alone cannot meet the needs of pregnant women and their growing fetuses. Folic acid supplements and consumption of folic acid-fortified cereals or staples are two alternatives to increase folate intake. In the late 1980s, a multicenter randomized controlled trial demonstrated that supplementation with 4 mg of daily folic acid during the periconceptional period could reduce the risk of NTD recurrence (*i.e.*, a subsequent NTD baby) by as much as 83%^[12]. A later randomized controlled trial conducted in Hungary showed that periconceptional supplementation with an 0.8 mg folic acid-containing multivitamin every day could prevent the first occurrence of NTDs^[13]. In the early 1990s, Peking University conducted a large-scale community interventional trial on the prevention of NTDs with folic acid with 247831 women of reproductive age, in collaboration with the Centers for Disease Control and Prevention of the United States. The results confirmed that periconceptional supplementation with only 0.4 mg of folic acid per day can reduce NTD risk by as much as 81%^[14]. However, science discoveries are not easy to translate into public health or clinical practice. For example, between 2002 and 2004, only 15% of pregnant women in Shanxi Province reported that they had ever taken folic acid supplements during the periconceptional period, and only one-third of these women took the supplements prior to pregnancy^[15]. To tackle this problem, the Chinese government launched a program that provides folic acid supplements, free of charge, to all women with a rural household registration who plan to become pregnant (estimated total number, 8 million) in 2009. The supplements are procured by provincial governments, but paid in total or in part by the central government. Local maternal health care workers are responsible for the distribution of the supplements. In 2011, the perinatal (28 gestational weeks to 4 wk of life) prevalence of NTDs decreased by 22.4% in rural areas compared to that in 2009^[16]. In 2011 and 2012, 2 to 3 years after the initiation of the supplementation program, the folic acid supplementation rate had increased to 85% in the areas of highest NTD prevalence^[17]. The mean plasma folate concentration of women during early and mid-pregnancy increased to 33.4 nmol/L (range, 18.7-58.4 nmol/L), double the level before the program was introduced^[18]. However, the proportion of women who began taking folic acid prior to pregnancy did not increase. In a post-program survey of the women who reported folic acid supplementation, 23.2% had begun taking supplements prior to pregnancy, compared to 27.3% in the pre-program survey in the

high NTD prevalence population^[17], indicating that many fetuses/embryos remained unprotected during the time of neural tube formation.

STAPLE FORTIFICATION WITH FOLIC ACID

The provision of folic acid supplements can be costly when manpower and the other logistical efforts involved in its distribution are taken into account. It is estimated that the Chinese central government needs 195 million RMB (about United States dollar 31 million) per year for supplement procurement. More important, many pregnancies are unplanned, meaning that supplementation with folic acid prior to pregnancy is impossible. On the other hand, staple fortification can supply folic acid "passively" to all women of reproductive age (and unintentionally to other segments of a population as well). Currently, about 80 countries have adopted or plan to implement staple fortification with folic acid^[19]. Reported NTD prevalence has been reduced by 28% in the United States^[8], by 46% in Canada^[20], and by 50% in Chile^[21] since fortification began. However, China has no plan to fortify staple foods in the foreseeable future. Perceived major barriers to the implementation of staple fortification include^[22]: (1) a lack of consensus in the scientific community; (2) the absence of a centralized production and distribution system for staples; (3) a lack of public awareness and acceptance; and (4) a lack of political will. The author hopes that these problems can be solved so that fortified flour and/or rice will become commercially available.

ROLE OF PEDIATRICIANS IN THE PREVENTION OF NTD

Since the recent change in China's family planning policy, more women wish to have a second baby. A proportion of these women are in their 30s or even 40s, meaning that they are at an increased risk of conceiving babies with down syndrome. In addition, advanced age is associated with a greater likelihood of obesity and diabetes, which are confirmed risk factors for NTD-affected pregnancies. This is an imminent challenge for the prevention of birth defects, including NTDs. In the battle to combat NTDs, physicians, including pediatricians, can play a critical role in every clinical encounter with women of reproductive age. For women who plan to have a second baby, pediatricians should advise them to take a 0.4-mg folic acid supplement daily beginning 3 mo prior to pregnancy or when there is a chance they may become pregnant. For women with a previous pregnancy affected by NTDs, it is recommended that they take 5 mg of folic acid daily, beginning from 3 mo before a pregnancy is planned. The ultimate goal is to protect each fetus from NTDs, which are preventable with folic acid.

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P- Reviewer: Classen CF, Sergi CM, Urganci N

S- Editor: Tian YL L- Editor: A E- Editor: Liu SQ



Observational Study

Response of levetiracetam in neonatal seizures

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Supported by Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (CREC Ref.), No. 2014.072.

Institutional review board statement: The study was reviewed and approved by the Chinese University of Hong Kong Institutional Review Board.

Informed consent statement: Since this is an observational study, no informed consent was obtained from the participants.

Conflict-of-interest statement: All authors declare no conflict of interests associated with the preparation of the manuscript.

Data sharing statement: No additional data available.

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Received: April 20, 2015
Peer-review started: April 24, 2015
First decision: May 13, 2015
Revised: May 25, 2015

Accepted: June 15, 2015

Article in press: June 16, 2015

Published online: August 8, 2015

Abstract

AIM: To review the clinical response to levetiracetam (LEV) in neonatal seizure management in intensive care unit.

METHODS: Medical records of neonates who received LEV from January 2009 to August 2014 were reviewed. Their demographic data, clinical characteristics, etiology, seizures, electroencephalograms, response to treatment and outcome were noted. Literature review of use of LEV in neonates were also performed *via* PubMed and EMBASE with keywords - "neonates", "seizures", "epilepsy" and "LEV" up to Sep 2014 and retrieved the publications. The response rate to LEV was compared.

RESULTS: Twelve neonates were identified during the study period. All patients received phenobarbitone loading prior to consideration of LEV. Seven (58%) and nine (75%) achieved seizure freedom 24 h and 72 h after LEV was added, both clinically and electrographically. No serious adverse effects were associated with LEV use. From the literature, there are total 144 neonates reported to have used LEV. The overall results suggested that LEV could control up to 90% of neonatal seizures.

CONCLUSION: LEV was found to be relatively safe and efficacious in treating neonatal seizures, but might not work well in the most severe hypoxic ischemic encephalopathy.

Key words: Levetiracetam; Phenobarbitone; Neonates; Seizures

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Core tip: Neonatal seizures are common, but there is lack of evidence to support use of anticonvulsants in this group of patients. Phenobarbitone remains the first line of treatment despite its limitations. The current study aims to review our experience of using levetiracetam (LEV) in management of neonatal seizures and to compare with the experience reported in the literature. We find that LEV is a relatively safe and feasible treatment option. Difficulties in performing studies were also discussed with the latest report of using bumetanide for treatment of neonatal seizures.

Yau MLY, Fung ELW, Ng PC. Response of levetiracetam in neonatal seizures. *World J Clin Pediatr* 2015; 4(3): 45-49 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v4/i3/45.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v4.i3.45>

INTRODUCTION

Seizures are common in the neonatal period. The incidence ranges from 2-4 in 1000 full term newborns and the prevalence is even higher in preterm babies. The etiologies are diverse, ranging from hypoxic-ischemic encephalopathy, encephalitis/meningitis, intraventricular hemorrhage, structural malformations, and metabolic or electrolyte disorders, *etc.* Phenobarbitone has been used since 1914 as the preferred first-line anticonvulsant in neonates. However, it has less than 50% efficacy in controlling neonatal seizures^[1]. In animal models, phenobarbitone has been shown to cause neuronal apoptosis, and in toddlers and infants, it is associated with negative cognitive side effects^[2].

Levetiracetam (LEV) is a pyrrolidine derivative, which acts through binding to and modulation of the synaptic vesicle protein SV2A. It is well tolerated with little drug-to-drug interactions. The most reported adverse effects are sedation and behavioral changes. However, its uses in neonates are still under investigation. This article aims to report our experience of using LEV in our neonatal intensive care unit especially those with hypoxic ischemic encephalopathy and compare with the reported cases.

MATERIALS AND METHODS

Infants were eligible if they received their first dose of LEV within the first four weeks of life between January 2009 to August 2014. These neonates were identified *via* the clinical data analysis and reporting system of the local health authority, which is an electronic database of the essential clinical information of all inpatients, including every single drug used. The medical records of all these infants were then retrieved. There was no loss of information in the records. Information on demographics (sex, gestational age, and Apgar score),

seizure onset, aetiology, neuroimaging, treatment, response and outcome were retrieved. The study was approved by the local clinical research ethics board (CREC 2014.072).

We then searched the PubMed and EMBASE in English with keywords - "neonates", "seizures", "epilepsy" and "LEV" up to Sep 2014 and retrieved the publications. Case series/reports with patients who started LEV in less than 28 d of life or less than 44 post-conceptual weeks were included.

RESULTS

The clinical characteristics of our patients are summarized in Table 1. There were six male and six female neonates identified during the study period. Gestational age ranged from 23 6/7 wk to 40 wk (mean: 34.9 wk, median 36 wk). One baby was extreme premature (less than 28 wk), five were premature neonates with gestational age between 28 to 36 wk and six were term babies. Etiologies of neonatal seizures include six neonates with hypoxic ischemic encephalopathy, three with meningitis/encephalitis, one had metabolic cause identified, one with presumed mitochondrial disease, and one had hypoglycemia whose seizures persisted even after hypoglycemia was corrected.

Utilization of LEV

All patients received phenobarbitone loading prior to consideration of LEV. LEV was offered if there was suboptimal response to initial anticonvulsants or if significant side effects were observed. All except one received intravenous LEV. The initial dosage ranged from 7.5-20 mg/kg, while the maintenance dosage ranged from 5-60 mg/kg per day. Seven (58%) and nine (75%) achieved seizure freedom 24 h and 72 h after LEV was added, both clinically and electrographically. We did not observe any cardiovascular complications (arrhythmia, hypotension), changes in blood counts, renal and liver function, *etc.*, after the introduction of LEV. Two babies died, one because of severe hypoxic ischemic encephalopathy and the other because of underlying metabolic disease. The remaining patients were discharged on LEV. Two patients were discharged with adjunctive phenobarbitone, while four were discharged with adjunctive topiramate as well. Six patients had discontinued LEV on subsequent follow up. The longest follow up was five years and five months.

DISCUSSION

There are various mechanisms that make the immature brain more excitable as compared to adult brain. These include overabundant excitatory glutamatergic neurons and paradoxical excitatory action of gamma-aminobutyric acid in the developing brain^[3]. Immature development of the neurotransmitter systems leads to difference in targets for conventional anticonvulsant to work. There is only one randomized controlled trial in

Table 1 Clinical characteristics of neonates receiving levetiracetam

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
Gestation (wk)	38	39	35	38	41	29	36	23 6/7	30	39	36	40
Apgar score (1 and 5 min)	9, 10	9, 10	9, 10	9, 10	8, 10	7, 9	0, 0	4, 6	0, 0	0, 0	0, 0	4, 7
Age of seizure onset (days of life)	19	10	8	1	1	0	0	3	0	0	0	0
Etiology	GBS meningitis	HSV encephalitis	Suspected mitochondrial	Hypoglycemia	Sulphite oxidase deficiency	<i>E. Coli</i> meningitis	HIE	HIE	HIE	HIE	HIE	HIE
Neuroimaging	Cystic encephalo-malacia	Cystic encephalo-malacia	Cystic encephalo-malacia	Normal	Cystic encephalo-malacia	Hydrocephalus with generalized atrophy	Cystic encephalo-malacia	Cystic encephalo-malacia	Peri-ventricular leukomalacia	Normal	Peri-ventricular leukomalacia	Diffuse cystic encephalo-malacia
Electrographic seizures	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Clinical status epilepticus	No	No	No	No	No	Yes	No	No	No	No	No	Yes
Hypothermia	-	-	-	-	-	-	No	No	No	Yes	Yes	Yes
Anticonvulsant order	PHB/MDZ/LEV	PHB/LEV	PHB/LEV	PHB/LEV	PHB/LEV	PHB/MDZ/THI/LEV	PHB/MDZ/LEV	PHB/MDZ/LEV	PHB/MDZ/LEV	PHB/MDZ/LEV	PHB/MDZ/LEV	PHB/MDZ/LEV/THI
LEV loading dose (mg/kg)	15	20	10	7.5	10	10	15	16	18	10	8	20
Mm maintenance (mg/kg per day)	27	40	20	60	20	30	36	5	36	20	15	40
Seizure after 24 h	No	No	No	No	No	Yes	Yes	No	Yes	Yes	No	Yes
Seizure after 72 h	No	No	No	No	No	No	No	No	Yes	Yes	No	Yes
Anticonvulsant at discharge	LEV	TPM/LEV	PHB/LEV	PHB/LEV	Not applicable	TPM/LEV	Not applicable	LEV	LEV/TPM	LEV	PHB/LEV	PHB/LEV
Outcome	Mild delay	Severe delay	Severe delay	Normal	Death	Severe delay	Death	Severe delay	Moderate delay	Mild delay	Severe delay	Severe delay

GBS: Group B streptococcus; HSV: Herpes simplex virus; HIE: Hypoxic ischemic encephalopathy; PHB: Phenobarbitone; MDZ: Midazolam; LEV: Levetiracetam; THI: Thiopentone; TPM: Topiramate.

neonatal epilepsy in which Painter *et al.*^[1] studied the effect of phenobarbitone compared to phenytoin in a randomized crossover study. Their efficacies were similar: 43% vs 45% respectively. In our series, nine babies (75%) were seizure free within 72 h after LEV was added. But only 50% of babies with hypoxic ischemic encephalopathy had their seizures controlled after addition of LEV.

From the literature, (Table 2) there are total 144 neonates reported to have used LEV. They were heterogeneous in terms of etiology, treatment dosage and reported responses. Among these cases, up to 132 cases achieved seizure freedom, either immediately after loading dose or within 72 h. The overall results suggested that LEV could control up to 90% of neonatal seizures. In those studies with individual etiology specified, the overall seizure control rate is also lower, around 71%. The data in premature babies (defined as less than 37 gestation weeks) is encouraging. There have been 52 premature babies reported and 40 of them had seizures controlled after adding LEV (77%). But we have to bear in mind the potential problems of publication bias towards positive treatment responses.

The side effect profile of LEV is relatively mild and well tolerated. There may be nonspecific behavioral changes in up to 21% of children. Its uses in young children and acute repetitive seizure setting, even at high doses, were found to be relatively safe and effective^[15]. This is consistent with our observations and those reported in case series. In our series, all neonates were cared in the neonatal intensive care unit during the period of study with close hemodynamic monitoring. There was no immediate additional ventilator or inotropic support required after LEV was given. There were also no disturbances in the blood counts or liver and renal function. As most of these infants were critically ill with multiple medications, it would be preferable to use a drug with minimal drug-drug interaction, which is also a potential advantage of LEV. LEV might prevent intubation if anesthetic agents could be avoided for seizure control.

Interestingly, recently there have been animal studies regarding any possible neuroprotective or neurotoxic effect of LEV on neonatal rats. Griesmaier *et al.*^[16] found that LEV *per se* did not induce neurotoxicity in the developing rodent brain, but it increases brain injury in rodents with hypoxic-ischemic brain injury under the normothermic conditions, but not hypothermic conditions. But Komur *et al.*^[17] found that LEV has neuroprotective effect on hypoxic ischemic injury in neonatal rats. Further studies are

Table 2 Literature review of levetiracetam use in neonates

Ref.	Year of publication	No. of patients	Drugs used before LEV	Outcome: Seizure	No. of patients with HIE	Seizure outcome in HIE patients	Dosage (loading) (mg/kg)	Dosage (maintenance) (mg/kg per day)	Remarks
Shoemaker <i>et al</i> ^[4]	2007	3	PHB/MDZ/fPHT	All seizure free	1	Seizure controlled within 17 min of oral bolus	60 (oral)	30	
Fürwentsches <i>et al</i> ^[5]	2010	6	PHB	All seizure free in 6 d	1	Seizure free	NA	10-50	Prospective
Ledet <i>et al</i> ^[6]	2010	1	PHB	Seizure free	0	NA	NA	40	
Ramantani <i>et al</i> ^[7]	2011	38	NA	30 seizure free at 1 wk	9	NA	10	45-60	Prospective
Khan <i>et al</i> ^[8]	2011	22	PHB or PHT	19 seizure cessation at 1 h and 22 seizure free by 72 h	12	11 seizure cessation at 1 h			
Abend <i>et al</i> ^[9]	2011	23	PHB or PHT	7 seizure terminated, 1 reduced seizure > 50%, 1 seizure terminated in > 24 h, 2 improvement in > 24 h, 8 no improvement, 1 unable to judge	8	2 seizure terminated, 2 reduced seizures > 50%, 1 improvement in > 24 h, 2 no improvement, 1 unable to judge	5-22	10-80	LEV as first drug in 4 cases
Aylward <i>et al</i> ^[10]	2011	1	fPHT	Partially responsive	0	NA	20	19	
Sharpe <i>et al</i> ^[11]	2012	18	PHB	6 seizure controlled	8	NA	20-40	5-10	
Rakshasbhuvankar <i>et al</i> ^[12]	2013	8	PHB/PHT/MDZ	6 "excellent", 1 partial, 1 ineffective	5	4 "excellent", 1 "partial"	5-10	10-35	
Khan <i>et al</i> ^[13]	2013	12	PHB	9 seizure stopped in 24 h	5	3 seizure stopped in 24 h, 1 no response, 1 NA	25-50	50	
Kirmiani ^[14]	2014	12	PHB	10 seizure free by 72 h	5	NA	25-50	25-50	

PHB: Phenobarbitone; PHT: Phenytoin; MDZ: Midazolam; fPHT: Fosphenytoin; NA: Not available or applicable; HIE: Hypoxic ischemic encephalopathy; LEV: Levetiracetam.

needed to clarify the exact effect of LEV in neonatal brains, either in normothermic or hypothermic conditions and its clinical implications.

Up to date, the pharmacokinetics of LEV in neonates remains unclear. There is a wide range of dosing reported in the literature, ranging from 10-60 mg/kg loading and 10 to 80 mg/kg as maintenance and the frequency of dosing is also uncertain. We used a median dose of 12.5 mg/kg. Merhar *et al*^[18] suggested that the half-life of LEV is 8.9 h, longer when compared to older children. But Sharpe *et al*^[11] suggested that the clearance is higher in neonates suggesting more frequent dosing may be required. Therefore the optimal dosing and frequency of LEV in neonates still remains to be defined.

There were a few limitations to our study. This is a retrospective case series with relatively few patients. Together with published series/reports so far, could only provide level IV evidence to support use of LEV in neonates. But in real life practice, it is pragmatic to consider off-label use of drugs after gaining initial experience in older children. In fact, LEV is increasingly used in algorithms in the management of phenobarbitone-resistant neonatal seizures^[19].

Secondly, neonatal seizures were known to have spontaneous cessation, which could partially contributed to the observed efficacy of LEV. As most patients were already treated with multiple anticonvulsants prior to addition of LEV, the efficacy of LEV might be difficult to be delineated from the con-interventions.

Problems in studying medical treatment are best illustrated by the recent report of Ronit Pressler and members of the treatment of Neonatal seizures with Medication Off-patent consortium in using bumetanide for treatment of neonatal seizures^[20]. In the study, 30 patients were screened for electrographic seizures associated with hypoxic ischemic encephalopathy and 14 patients were enrolled. But five of them had no further seizures during the baseline period, so were de facto treatment failures. There are concerns and debates about what should be chosen and included in assessing the efficacy endpoints. It is controversial whether we should also include long-term developmental outcome and development of epilepsy, *etc.*, in the evaluation.

The experience from our case series, together with the published literature so far, supports LEV is a relatively safe and feasible option in neonatal seizures. But it may not work as well in neonates with most severe hypoxic ischemic encephalopathy. Further work is needed to evaluate its possible neuroprotective/neurotoxic effect in neonatal brains, the optimal dosage and role in neonatal seizures, *etc.*

COMMENTS

Background

Neonatal seizures are common, but there is lack of evidence to support use of anticonvulsants in this group of patients. Phenobarbitone remains the first line of treatment despite its limitations. Studies have reported the use of levetiracetam (LEV) in this group of patients.

Research frontiers

LEV is a broad-spectrum anticonvulsant which is licensed to be used in infants > 4 wk of age. Its use in neonates is still under investigation. It is very difficult to conduct controlled trials in neonatal seizures. The current research hotspot is to review our experience of using LEV in management of neonatal seizures and to compare with the experience reported in the literature.

Innovations and breakthroughs

This current study reviewed that LEV could be safely administered in sick neonates and its efficacy might be limited in those with most severe hypoxic ischemic encephalopathy. The experience from literature review also supports the relative safety of the drug.

Applications

LEV is a relatively safe and feasible treatment option for neonatal seizures.

Terminology

Neonatal seizures are common. The etiologies are diverse, ranging from hypoxic-ischemic encephalopathy, encephalitis/meningitis, intraventricular hemorrhage, structural malformations, and metabolic or electrolyte disorders, etc. LEV is a relatively safe and feasible treatment option for neonatal seizures.

Peer-review

Few medicines studied and approved to treat this subset of patients, management difficult.

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P- Reviewer: Onakewhor JUE, Troncoso AR **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Liu SQ





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