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The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

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EDITORIAL

New exploration on pathogenesis and early diagnosis of gestational diabetes

Hua Bai

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Abstract

Gestational diabetes mellitus (GDM) refers to varying degrees of abnormal glucose metabolism that occur during pregnancy and excludes patients previously diagnosed with diabetes. GDM is a unique among the four subtypes of diabetes classified by the international World Health Organization standards. Although GDM patients constitute a small proportion of the total number of diabetes cases, the incidence of GDM has risen significantly over the past decade, posing substantial risk to pregnant women and infants. Therefore, it warrants considerable attention. The pathogenesis of GDM is generally considered to resemble that of type II diabetes, though it may have distinct characteristics. Analyzing blood biochemical proteins in the context of GDM can help elucidate its pathogenesis, thereby facilitating more effective prevention and management strategies. This article reviews this critical clinical issue to enhance the medical community's sufficient understanding of GDM.

Key Words: Gestational diabetes mellitus; Pathogenesis; Proteomics; RBP4; ANGPTL8

Core Tip: Pancreas β cellular damage and tissue insulin resistance are key to the pathogenesis of gestational diabetes mellitus (GDM). Once beta cell dysfunction begins, hyperglycemia, insulin resistance, and further beta cell dysfunction are likely to enter a vicious cycle. Introducing advanced biotechnology such as proteomics for basic research on GDM is a good attempt. RBP4 and ANGPTL8 proteins may play a role in the pathogenesis of GDM, but there is insufficient evidence to diagnose GDM by detecting the two proteins.

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INTRODUCTION

In this editorial, we comment on a retrospective research paper by Cao *et al*[1], published in the latest issue of the *World Journal of Clinical Cases*. The authors used quantitative proteomics to detect differential protein expression in the blood of patients with gestational diabetes mellitus (GDM). Their goal was to explore the pathogenesis and characteristics of GDM and to identify potential biomarkers to predict its occurrence. Proteomics is the study of protein composition and its changes in cells, tissues, or organisms. This research includes analyzing protein expression levels, post-translational modifications, and protein-protein interactions[2]. The pathogenesis of GDM may involve abnormalities in lipid metabolism, activation of the coagulation cascade, the complement system, and various inflammatory response factors. Numerous proteins are also implicated. The author tested 47 proteins and found that two had significantly increased expression and certain specificity. These two proteins may have significant implications for the early diagnosis and understanding of GDM pathogenesis. Proteomics is a central focus of life sciences in the post genomic era. Complex post-translational modifications, subcellular localization or migration, and protein-protein interactions are challenging to determine at the mRNA level, necessitating the development of high-throughput and high-sensitivity research technologies. Proteomics techniques have filled these gaps. Techniques such as two dimensional gel electrophoresis, isoelectric focusing, biological mass spectrometry and non-gel technologies are all related to proteomics. In clinical practice, these technologies typically involve comparing and analyzing the protein mass spectrometry profiles in the serum of patients with the disease under study. Identifying differential proteins and using analysis software like Biomarker Pattern to establish relevant classification tree models are essential steps in this process[3]. The team conducting this study on GDM achieved promising results using these analytical techniques. This represents a positive step for the application of proteomics in interdisciplinary diseases within clinical medicine and obstetrics and gynecology.

THE COMPLEXITY AND DIVERSITY OF DIABETES PATHOGENESIS

Diabetes is a polygenic, genetically heterogeneous disease caused by a combination of genetic and environmental factors. Type I diabetes mellitus typically has a genetic abnormality background, where the destruction of pancreatic islets β-cells leads to absolute insulin deficiency, often mediated by abnormal immune factors. Type II diabetes mellitus (T2DM) is characterized by insulin resistance and an absolute or relative insufficiency of insulin secretion, primarily due to environmental factors such as excessive nutrition, obesity, insufficient physical activity, aging, long-term stress, and exposure to chemical toxins. Genetic factors also play a secondary role in T2DM, increasing genetic susceptibility and affecting certain aspects of glucose metabolism, though they are not necessary for the onset of the disease. Insulin resistance is now believed to be a hallmark of T2DM and is likely the initiating factor in its development. Both lipid overload and chronic inflammation can cause insulin resistance. Increased adipocyte levels in patients elevate the levels of free fatty acids and their metabolites in the blood and within pancreatic islet β-cells and muscle cells, inhibiting insulin signal transduction. Additionally, the inactivation of inflammatory proteins produced by macrophages can improve diet induced diabetes, while dietary fat promotes pathological insulin resistance through chronic inflammation[4]. Excessive adipocytes attract macrophages and secrete inflammatory signaling molecules such as TNF-α and IL-6, which block insulin signal transduction in skeletal muscle through JNK. These mechanisms overlap and interact, leading to insulin resistance.

The dysfunction of pancreaticislet β cells is crucial in the pathogenesis of T2DM. Defective β-cells lead to abnormal insulin secretion in terms of both quality and quantity, as well as disrupted insulin secretion patterns. The pathogenesis of T2DM progresses from impaired fasting glucose and impaired glucose tolerance to the appearance of clinical symptoms. Genetic abnormalities typically determine the initial factors causing structural and functional abnormalities of β-cells. These involve gene such as *HLA*, *CTLA4*, *GCK*, *PTPN22*, *INS*, and *IL-2RA*. Genome-wide association studies of T2DM have identified hundreds of genetic variants in non-coding and β-cell regulatory genomic regions. Walker *et al*[5] focused on β-cell hub gene and transcription factor RFX6, finding that multilayer genetic risks converge on RFX6-mediated networks, reducing insulin secretion. Other important factors influencing T2DM pathogenesis include abnormal mitochondrial function, disrupted tricarboxylic acid (TCA) cycle, abnormal triglyceride/free fatty acid cycle, oxidative stress of endoplasmic reticulum, chronic inflammation of islets, deposition of fat and other harmful substances in islets, low differentiation and transdifferentiation of β-cells, and abnormal endocrine hormone levels in patients. Additionally, the brain-centered glucose regulation system can lower blood glucose levels through both insulin-dependent and insulin-independent mechanisms. Reduced glucose availability also significantly impacts diabetes pathogenesis[6]. The dysfunction of pancreatic islet α-cells, deficiency of incretin secretion, and abnormal intestinal flora structure and function are also related to T2DM pathogenesis.

EXPLORING THE MECHANISM OF GDM

High-risk pregnant women prone to GDM are typically older, have positive urine glucose tests, obese, have a family history of diabetes, and experience persistent mental stress. The diagnosis of GDM requires an oral glucose tolerance test between 24 and 28 weeks of pregnancy. Women diagnosed with diabetes before pregnancy are considered to have diabetes complicated by pregnancy, which is beyond the scope of this discussion. Since the occurrence of GDM is similar to that of T2DM, understanding the pathogenesis of T2DM can provide significant insights into the pathogenesis of GDM. Although glucose metabolism in GDM patients may return to normal after delivery, a small number of patients can develop permanent diabetes. During early pregnancy, as gestational age increases, the fetus's demand for nutrients rises. Concurrently, estrogen and progesterone increase the mother's glucose utilization, causing her plasma glucose levels to decrease as pregnancy progresses[7]. In the second and third trimesters, anti-insulin substances in pregnant women increase, and the sensitivity of these chemicals decreases with advancing gestational age. Hormones such as estrogen, progesterone, leptin, cortisol, placental prolactin, and placental growth hormone collectively promote insulin resistance [8]. To maintain normal glucose metabolism, the demand for insulin must increase accordingly. If a pregnant woman has limited insulin secretion, GDM may occur if physiological changes during pregnancy cannot compensate and blood sugar levels rise. Chen *et al*[9] found that TET3 dysfunction in oocytes caused maternal inheritance of glucose intolerance, and defects or abnormalities in the glucokinase gene may be related to the pathogenesis of GDM.

Pregnancy can cause latent diabetes to manifest, lead to the development of GDM in women without prior diabetes, and exacerbate pre-existing diabetes. Cao *et al*[1] identified 215 differentially expressed proteins in GDM patients. Of these, the isotopic tags for relative and absolute quantification (iTRAQ) ratios of 47 proteins were significantly different, being greater than 1.50 or less than 0.67. Compared to healthy women, 31 proteins had increased expression in GDM pregnancies, while 16 proteins had decreased expression. The researchers divided the subjects into GDM and normal control groups according to IADPSG diagnostic criteria and used bioinformatics analysis to identify the key proteins and signaling pathways related to GDM. Venkatesh *et al*[10] retrospectively analyzed 1560822 cases of GDM in United States and found an increased frequency of various adverse pregnancy outcomes in these women. Specifically, there was a significant increase in the incidence of pre-eclampsia, premature delivery, and admission to the neonatal intensive care unit. Differences in adverse outcomes persisted across different racial groups. The impact of GDM on both mother and fetus depends on the quality of diabetes control. Poor blood sugar control significantly increases the risk of complications for both mother and fetus. Paolino *et al*[11] found that babies born to mothers with GDM had increased birth weight and C-peptide levels. Regardless of dietary regulation or insulin therapy, the number of Treg cells in the placentas of women with GDM decreased. They suggested that RANK signaling in thymic epithelium and natural Treg cells is central to pregnancy immunity and metabolic maternal adaptation. Human pregnancy is associated with progressive insulin resistance, which may manifest as dominant GDM if not compensated.

The changes in glucose metabolism during pregnancy are complex, and the potential mechanisms of GDM include abnormal endocrine hormones in the uterus, disrupted TCA cycle, oxidative stress in endoplasmic reticulum, fat overload and expansion, chronic immune inflammation, abnormal gluconeogenesis and oxidative stress, chronic damage to islet structure and deposition of harmful substances, and the inability of pancreatic β-cells to compensate for chronic energy demands, eventually leading to insulin resistance[1]. β-cell injury and tissue insulin resistance are central to the pathogenesis of GDM. When β cells lose the ability to accurately perceive blood glucose concentrations or cannot release sufficient insulin, β cell dysfunction occurs. Insulin resistance exacerbates this dysfunction, reducing insulin-stimulated glucose uptake and further leading to hyperglycemia. In response, β-cells must produce extra insulin. Insulin resistance often results from the failure of insulin signal transduction, leading to inadequate translocation of glucose transporter 4 to the plasma membrane. Once β-cell dysfunction begins, a vicious cycle of hyperglycemia, insulin resistance, and further β-cell dysfunction is likely to ensue.

THE ROLE OF RBP4 AND ANGPTL8 PROTEINS IN THE PATHOGENESIS OF GDM

RBP4 and ANGPTL8 are proteins synthesized by the liver and adipose tissue. Serum RBP4 levels are usually closely related to body weight and glucose sensitivity, with RBP4 affecting insulin function by regulating fat metabolism. There is a strong correlation between RBP4 levels and decreased blood flow-regulated vasodilation, increased urinary albumin excretion rate, and retinopathy, suggesting that serum RBP4 Levels can serve as a reference index for complications of type 2 diabetes. Wu *et al*[12] conducted a case-control study on 332 patients with GDM and 664 matched controls. After adjusting the multivariate model of potential risk factors, the OR for the extreme quartile of serum RBP4 level was 2.26, indicating that each standard deviation increment of RBP4 was associated with a 1.39 times higher risk of GDM. ANGPTL8 is involved in the regulation of lipid metabolism and triglyceride homeostasis, playing a role in the upstream or internal regulation of protein processing and lipoprotein metabolism. Abdeltawab *et al*[13] found that, compared with healthy pregnant women, levels of miRNA-223 and ANGPTL8 were significantly increased in women with GDM. MiRNA-223 and ANGPTL8 were also significantly correlated with each other and with total cholesterol and triglycerides. These findings support the hypothesis that miRNA-223 and ANGPTL8 are involved in the pathogenesis of GDM, suggesting that ANGPTL8 may be used for early diagnosis of the condition.

The scholars of the above study also found[1] a significant increase in RBP4 and ANGPTL8 proteins in the blood of pregnant women with GDM. The expression levels of RBP4 and ANGPTL8 proteins in the serum of these pregnant women were detected by ELISA, consistent with the results of mass spectrometry experiments, indicating certain sensitivity. Since both proteins are associated with insulin resistance, it is speculated that they are closely related to the

pathogenesis of GDM. Some researchers believe that the level of ANGPTL8 in early pregnancy is significantly and independently correlated with the risk of developing GDM at 24-28 weeks of pregnancy. Combining ANGPTL8 levels with conventional risk factors can improve the predictive ability for GDM[14,15]. GDM affects about 14% of pregnant women worldwide. According to IADPSG diagnostic criteria, the International Diabetes Federation estimates that there are currently 18 million GDM patients, and this number is expected to rise with the obesity epidemic. Approximately 80% of pregnant women with diabetes have GDM, while less than 20% have pre-existing diabetes[16]. Pregnancy is a state of high metabolic activity, making the maintenance of glucose homeostasis crucial. When pancreatic β-cells cannot compensate for the chronic energy demands, leading to insulin resistance, hyperglycemia, and abnormal glucose supply to the growing fetus, GDM may occur[17]. RBP4 and ANGPTL8 may play a combined role in the pathogenesis of GDM, but there is still insufficient evidence to diagnose GDM solely by detecting these two proteins. Further research is needed to establish their diagnostic value.

CONCLUSION

Modern medicine emphasizes both precision and personalization, and research on GDM holds significant clinical and theoretical value. Damage to pancreatic islets β-cells and insulin resistance in tissue cells are key to the pathophysiology of GDM. Only through in-depth research on the pathogenesis of GDM can we hope to ultimately overcome this disease. Introducing advanced biotechnologies, such as proteomics, for basic research on GDM is a promising approach. In the future, it will be essential to collect more blood samples from GDM patients and track several relatively specific proteins to continue this line of research. This will enable a deeper understanding of GDM and the development of more effective diagnostic and therapeutic strategies.

FOOTNOTES

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EDITORIAL

Navigating medial patellotibial ligament reconstruction: Clinical perspectives and surgical strategies

Juan Pablo Zicaro, Ignacio Garcia-Mansilla

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Abstract

The surgical approach for patellar instability usually refers to reconstruction of the medial patellofemoral ligament associated with an osteotomy of the tibial tuberosity or a trochleoplasty when required. The medial patellotibial ligament and the medial patellomeniscal ligament are secondary stabilizers of the patella. Despite this, both the medial patellotibial and patellofemoral ligaments aid in patellar rotation and tilt when the knee is flexed beyond 45°. The medial patellotibial ligament plays a particularly important role in the final stages of stretching in extension and between 40 degrees to 90 degrees of flexion. The clinical relevance and surgical indications for medial patellotibial ligament reconstruction associated with medial patellofemoral ligament reconstruction are still controversial. This editorial explores the surgical indications and clinical results for medial patellotibial ligament reconstruction to improve readers' understanding of this technique, especially because reported clinical outcomes have remained sparse.

Key Words: Medial patellotibial ligament; Patellar instability; Reconstruction; Surgical

Core Tip: Though the medial patellotibial ligament reconstruction technique was described in 1922, its indication remains limited. Surgical indications are still not precisely delineated. Regardless, it is a viable option for young patients experiencing recurrent patellar instability with osseous abnormalities or patients facing severe instabilities in both extension and flexion.

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INTRODUCTION

Patellar dislocations account for 2% to 3% of all knee injuries and are frequently observed in young and athletic patients [1,2]. Surgery becomes necessary in cases of recurrent instability to restore patellar stability. When addressing patellar instability, several parameters must be considered to determine the appropriate type of surgery, including patellar height, tibial tuberosity - trochlear groove (TT/TG) distance, and the rotations of the hip and ankle. Additionally, the medial patellar complex plays a critical role as a patellar stabilizer[3,4]. This structure consists of a primary stabilizer, the medial patellofemoral ligament (MPFL), and two secondary restraints, the medial patellotibial ligament (MPTL) and the medial patellomeniscal ligament (MPML). While the MPFL is the primary stabilizer and has been extensively studied in terms of postoperative outcomes, recent years have seen a growing recognition of the MPTL's role in cases of severe instability. In this editorial, our aim is to emphasize the role and relevance of the MPTL in patellar stability.

ANATOMY OF THE MPTL

There is significant anatomical variability in the literature regarding the presence of the MPTL[4-6]. The MPTL and MPML are located within the second layer of the knee, as originally described by Warren and Marshall[7]. Both the MPTL and MPML have variable insertion points on the patella or tibia. Kaleka *et al*[5] reported a mean MPTL length of 46 mm (SD 8.8 mm), with the origin and insertion points being larger than the body of the ligament. Regarding patellar insertion, Hinckel *et al*[2] defined it as 3.6 mm proximal to the distal border of the patella. However, they noted different anatomical variations in the patellar insertion between the MPTL and MPML. While most specimens showed a combined patellar insertion, the MPML was proximal to the MPTL in three cases and the MPTL was proximal to the MPML in one case. The mean tibial insertion for the MPTL was 13.7 mm (ranging from 5 mm to 22 mm) distal to the joint line and medial to patellar tendon insertion.

BIOMECHANICS

There is consensus in the literature regarding the importance of the MPFL as the primary medial stabilizer of the patella [3,4,8]. In 1993, one of the earliest studies on MPTL biomechanics[9] indicated that it contributes less than 5% to total medial restraining forces. In 2006, Panagiotopoulos *et al*[9,10] used a similar method and sequentially sectioned the medial patellar ligaments at 30 degrees of flexion. They found that the MPTL contributed 13% to patellar stabilization, while the MPML contributed 24%. In 2012, Philippot *et al*[11] determined that the MPTL contributed 46%, 72%, and 92% to patellar shift, tilt, and rotation respectively, between 30 degrees and 90 degrees of flexion. These findings suggest that the MPTL plays a significant role in patellar stability at higher degrees of flexion. Regarding stiffness, strength and rupture, Hinckel *et al*[2] compared the characteristics of the MPFL with those of the MPTL and found that the MPTL was stiffer and exhibited less deformation at the maximum tensile strength (MTS), but showed no differences in force, energy at MTS, or energy for complete rupture.

CLINICAL RELEVANCE

Although the MPTL and the MPML are traditionally considered secondary stabilizers of patellar stability, their role in maintaining patellofemoral joint stability is increasingly recognized[1,4]. Their primary function occurs in the final phase of extension, where they counteract the proximal lateral traction of the quadriceps. They also become taut at higher degrees of flexion, playing a significant role in restricting lateral translation of the patella. Furthermore, the MPTL and MPML are essential for preserving proper patellar tracking, helping to maintain normal patellar tilt and rotation. Recent proposals suggest that reconstructing the MPFL in conjunction with the MPTL may offer an effective solution for enhancing patellar stability, particularly near full extension.

SURGICAL INDICATIONS

There is considerable controversy regarding the specific surgical indications for MPTL reconstruction (MPTL-R)[2,4,8,12]. Among the initial reports, Zaffagnini *et al*[12] suggested performing an isolated MPTL-R in conjunction with distal

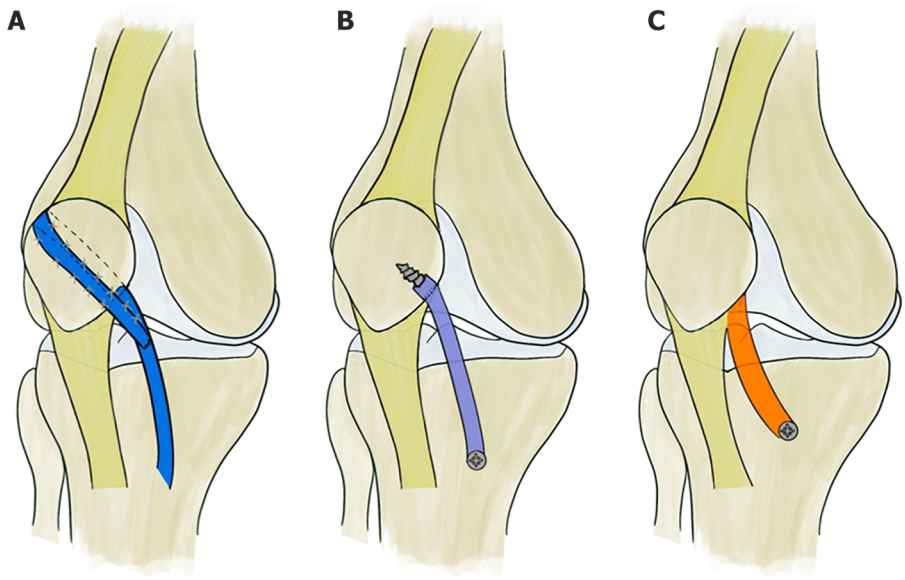

Figure 1 Surgical techniques. A: Semitendinosus tenodesis; B: Medial patellotibial ligament reconstruction; C: Medial transfer of the medial patellar tendon.

realignment or trochleoplasty for patients with recurrent patellar instability. More recently, Hinckel *et al*[2] outlined specific indications for MPTL-R, including subluxation in extension, instability in flexion, knee hyperextension with ligamentous laxity, and skeletal immaturity with associated risk factors. Most authors concur that MPTL-R, whether performed in isolation or in combination with MPFL reconstruction (MPFL-R), can provide additional stability to the patella, especially in cases where anatomical factors such as TT/TG, patellar height, or trochlear dysplasia cannot be addressed, such as in skeletally immature patients[4,8,13,14].

SURGICAL TECHNIQUES

Semitendinosus tenodesis

One of the most renowned techniques in MPTL-R is semitendinosus tenodesis[15-17], initially introduced by Galeazzi in 1922. This method was modified by Fiume in 1954[18], incorporating lateral retinacular release and medial retinacular reefing. Subsequently, in 1972, Baker *et al*[19] further refined this technique by creating an oblique tunnel across the patella along the line of the tenodesis, facilitating the passage of the semitendinosus tendon from the medial to the lateral side (Figure 1A).

MPTL reconstruction

An alternative to tenodesis is MPTL-R[20,21]. In such instances, patellar fixation is accomplished through a tunnel, resembling the technique delineated by Galeazzi. Concurrently, tibial fixation involves the utilization of either an anchor or a tenodesis screw (Figure 1B).

Medial transfer of the medial patellar tendon

Some authors, such as Rillmann *et al*[22] and Zaffagnini *et al*[12] have utilized the medial segment of the patellar tendon along with a bone block sourced from the tibial tuberosity. In contrast, Myers *et al*[23] and Oliva *et al*[24] solely employed the patellar tendon (Figure 1C).

OUTCOMES

There is still limited data available, with only a few published series reporting on the outcomes of MPTL-R. Zaffagnini *et al*[12] indicated isolated MPTL-R using the medial third of the patellar tendon, relocating the distal insertion next to the medial collateral ligament, with 10% of cases associated with distal realignment and 21% with trochleoplasty. Out of 32 patients with a mean follow-up of 6.1 years, they reported a 14% failure rate. In contrast to these results, Ambra *et al*[25] performed a biomechanical study comparing MPFL-R and MPTL-R and concluded that isolated MPTL-R fails to restore lateral patellar stability when compared to MPFL-R.

The combination of MPFL-R and MPTL-R has shown more promising outcomes. Leite *et al*[13] found that MPFL-R combined with MPTL-R in skeletally immature patients with additional uncorrected anatomical patellofemoral abnormalities leads to acceptable clinical outcomes within a minimum of 5 years follow-up, although it has a high failure rate of 24.1%. The addition of MPTL-R to the MPFL may result in decreased patellar laxity on physical exams, as

demonstrated by improved patellar glide, patellar tilt test, and reduced subluxation in extension. Finally, Abbaszadeh *et al*[4] in a systematic review and meta-analysis evaluated five prospective series and found it to be an effective method for patients with patella alta or trochlea dysplasia, where no bony procedures such as TTO and trochleoplasty could be performed. However, none of the studies were comparative with isolated MPFL or combined with bony procedures.

CONCLUSION

In conclusion, MPTL-R remains a relatively underexplored area in the literature, with limited published series reporting outcomes. Current studies suggest that MPTL-R, whether performed in isolation or in combination with MPFL-R, can provide additional patellar stability, particularly in cases where anatomical factors cannot be addressed. While isolated MPTL-R has shown some success, it may not fully restore lateral patellar stability compared to MPFL-R. Further research is necessary to gain better understanding of the role of MPTL-R in patellar stability and to refine surgical indications.

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FOOTNOTES

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EDITORIAL

Advancement in utilization of magnetic resonance imaging and biomarkers in the understanding of schizophrenia

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Abstract

Historically, psychiatric diagnoses have been made based on patient's reported symptoms applying the criteria from diagnostic and statistical manual of mental disorders. The utilization of neuroimaging or biomarkers to make the diagnosis and manage psychiatric disorders remains a distant goal. There have been several studies that examine brain imaging in psychiatric disorders, but more work is needed to elucidate the complexities of the human brain. In this editorial, we examine two articles by Xu *et al* and Stoyanov *et al*, that show developments in the direction of using neuroimaging to examine the brains of people with schizophrenia and depression. Xu *et al* used magnetic resonance imaging to examine the brain structure of patients with schizophrenia, in addition to examining neurotransmitter levels as biomarkers. Stoyanov *et al* used functional magnetic resonance imaging to look at modulation of different neural circuits by diagnostic-specific scales in patients with schizophrenia and depression. These two studies provide crucial evidence in advancing our understanding of the brain in prevalent psychiatric disorders.

Key Words: Schizophrenia; Magnetic resonance imaging; Biomarkers; Neurotransmitters; Psychiatric disorders

Core Tip: Schizophrenia is a serious psychiatric condition that has life-long implications for the individual as well as their family. The underlying psychopathology is still unclear and evolving. With advancements in the field of neuroimaging and neurotransmitters the understanding of the disorder is gradually improving, however, a lot of work is still needed in this area. In this editorial article we briefly discuss what we already know and how recently published articles help to advance our knowledge about schizophrenia.

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INTRODUCTION

Schizophrenia is a complex neuropsychiatric condition that has a long-lasting impact on an individual's functioning in all areas. Schizophrenia is associated with high unemployment rates, poor dietary habits, increased rates of smoking, and comorbid substance use that contribute to a reduced life expectancy of 13-15 years[1]. Our understanding of schizophrenia has come a long way from Emil Kraepelin's distinguishment of dementia praecox (schizophrenia) to manic-depressive psychosis in 1893, to Eugen Bleuler coining the term schizophrenia (previously known as dementia praecox) in 1908, to the current Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) classification in 2013. The DSM-5 criteria for schizophrenia include positive symptoms such as delusions, hallucinations; disorganized speech, grossly disorganized or catatonic behavior and negative symptoms such as decreased motivation and diminished expressiveness; two or more of these must persist for a period of one month or longer[1]. Additionally, cognitive symptoms of schizophrenia include deficits in working memory, executive function, and information processing.

NEUROIMAGING AND NEUROTRANSMITTERS IMPLICATED IN SCHIZOPHRENIA

During Kraepelin and Bleuler's time, they did not have access to our current capabilities of the neuroimaging modalities. However, even with today's imaging tools for exploring the brain, the underlying psychopathology of schizophrenia is still not fully understood. Structural alterations associated with schizophrenia have been examined widely. Some of the consistent findings across various studies include smaller total brain volume, enlarged ventricles, and reduced hippocampal and thalamic volumes[2]. A meta-analysis utilizing magnetic resonance imaging (MRI) of over 4000 patients determined that patients with schizophrenia had widespread thinner cortex and smaller brain surface area[3]. Another meta-analysis of 317 studies inclusive of over 18000 patients, compared medicated and non-medicated individuals and determined that medicated schizophrenia patients had decreased intracranial and total brain volume, while medication-naive patients had increased volume reductions in the caudate nucleus and thalamus[4]. They also found that advanced gray matter reduction was associated with a longer duration of illness and a higher dose of antipsychotic medication at the time of scanning[4]. In addition to structural changes in schizophrenia, researchers have also used functional MRIs to show support for both hypofrontality, decreased prefrontal cortex activity, and hyperfrontality, increased prefrontal cortex activity[5,6]. Patients with hypofrontality were more likely to experience negative symptoms of schizophrenia, while patients with hyperfrontality were more likely to experience positive symptoms[6,7].

The two main neurotransmitters implicated in schizophrenia are dopamine and glutamate. Dopamine was first suspected to play a role in schizophrenia after recreational amphetamines induced psychotic symptoms that had similarities to schizophrenia[8]. Numerous methods including animal studies, post-mortem research, clinical effects of drugs that either block or accentuate dopaminergic neurotransmission, and positive emission tomography studies all show indirect evidence that increased dopamine signaling is associated with schizophrenia[9]. A meta-analysis of 21 studies found that patients with schizophrenia had greater elevation of dopaminergic functioning in the dorsal striatum when compared with controls[10]. However, antipsychotics that block dopamine receptors effectively treat the positive symptoms of schizophrenia, but are not nearly as effective at treating the negative symptoms[8]. Further research is needed to elucidate the psychopathology behind the negative symptoms of schizophrenia to provide more effective treatment.

Glutamate is an excitatory neurotransmitter which has 2 receptors- ionotropic and metabotropic. Ionotropic N-methyl-D-aspartate (NMDA) receptors have been the primary focus of the underlying role of glutamatergic transmission in schizophrenia. Various animal models have shown that administration of NMDA antagonists such as ketamine and phencyclidine can induce symptoms of schizophrenia[9,11]. Several post-mortem studies targeting structural alterations of glutamate neurons have found reductions in dendrite arborization, spine density, and synaptophysin expression across frontal and temporal regions suggesting indirect evidence of role of glutamate in schizophrenia[9]. Moreover, recent research has shown evidence suggesting that the glutamatergic projections from the cortical brainstem communicate with the dopaminergic pathways and are associated with the positive symptoms of schizophrenia. Hypofunctional NMDA receptors can cause inhibition of the mesocortical dopamine pathway which may result in limited dopamine release in the prefrontal cortex with subsequent development of negative and cognitive symptoms[9]. One study showed that the

results of the Positive and Negative Syndrome Scale (PANSS) were not associated with glutamine variability in the medial frontal cortex or glutamate variability in the basal ganglia[12].

Although extensive research has been conducted on the dopamine and glutamate systems independently of one another, neither one alone explains the full spectrum of schizophrenia. It is theorized that schizophrenia may be caused by the interactions of the dopamine and glutamate systems and therefore the most effective treatments will target both [13].

REVIEW OF THE STUDIES

In this article we review 2 studies published in the journal by Xu *et al*[14] and Stoyanov *et al*[15] that look at interdisciplinary connectivity and validation of schizophrenia. The studies focus on imaging modalities and quantitative measurements of neurotransmitters to show how the brain reacts and responds to certain stimuli in individuals diagnosed with schizophrenia. With improvements in imaging modalities, there continues to be an evolving understanding of the brain that spans all the way from neurotransmitters to the gyri.

In one of the studies that this article reviews, Xu *et al*[14] enrolled 97 patients with schizophrenia and 100 control patients to examine brain anatomical and neurotransmitter differences. This study aims to fill the gap in the understanding of the biological and anatomical differences between positive and negative symptoms of schizophrenia. First, fasting venous blood was drawn from subjects to examine the levels of dopamine, glutamate, and Gamma-aminobutyric acid (GABA). MRIs of patient's brains examined several craniocerebral measurements which included the distance between the midline of the brain to the inferior fornix, the vertical and horizontal distance between the corpus callosum and the inferior part of the fornix, the distance between the middle fornix, and the area of the ventricles. They further divided the case group into positive or negative symptom groups based on the results of the PANSS. They examined neurotransmitter levels and craniocerebral measurements between patients with positive or negative symptoms of schizophrenia.

There were many significant findings in this study. In terms of neurotransmitters, the patients in the case group had significantly higher dopamine levels and significantly lower glutamate and GABA levels compared to patients in the control group. Additionally, patients with positive schizophrenia symptoms had significantly higher levels of dopamine, glutamate, and GABA than those with negative symptoms. In terms of the MRI results examining brain anatomical characteristics, patients in the case group had significantly greater vertical and horizontal distances between the corpus callosum and the inferior part of the fornix and a larger ventricle area than patients in the control group. There were no significant differences in brain structural characteristics between the positive and negative symptom groups. Unfortunately, this study is limited by the number of participants and would have benefited from examining other neurotransmitters such as serotonin and acetylcholine.

Increased dopamine levels contributing to the pathology of schizophrenia has been a long-supported theory. Additionally, some studies support that patients with schizophrenia have differences in brain anatomy compared to healthy controls when analyzed at the group level[16]. It is well known that antipsychotics are less effective for patients with negative symptoms of schizophrenia, however, the biological differences between the negative and positive symptoms of schizophrenia must be further investigated[17]. The results of Xu *et al*[14] provide possible targets to develop improved treatment methods for the negative symptoms of schizophrenia.

In the other study, Stoyanov *et al*[15] looked at various brain networks that were activated during responses to various items in 27 patients with Schizophrenia and 33 patients with major depressive disorder (MDD). As per this study, clinical diagnostic scales identified five independent brain signals displayed on the functional magnetic resonance imaging paradigm. These components included specific locations of the brain that are activated and utilized in patients with schizophrenia and MDD. Research is still ongoing to examine the active brain regions in patients with Schizophrenia. MRI continues to be utilized in this growing field as we know that diminished brain volume occurs with the first break. The study consisted of three distinct conditions with depressive, paranoid, and neutral items and a resting condition representing a standard block. Every block contained four textual statements, paranoid and depressive sections stemming from von Zerssen subscales of depression and paranoia, whereas the neutral section was based on a general questionnaire of likes and interests.

The study by Stoyanov *et al*[15] displayed several significant findings in the two groups of patients while they performed the task with depressive, paranoia-specific, and neutral stimuli. One significant finding is that the component (C) 14 area in the brain within the right superior and middle temporal gyri, left middle and inferior frontal gyri, and right anterior insula was shared between all three groups of patients. Therefore, C14 is limited in the differential diagnostic algorithm between schizophrenia and MDD. The frontal motor/Language and parietal areas of the brain were shared between the MDD and schizophrenic patient groups. One specific component, C38, which entails the brain's prefrontal region, was linked to the paranoid-specific section. C22 and C36, which included areas within the posterior cingulate and precuneus, lingual and fusiform gyrus, and parahippocampal gyrus, are linked to the depression-specific items in schizophrenia as compared to the MDD patients. This study furthers our understanding of the anatomical validation between neuroimaging, neuroanatomy, and neurophysiology for common psychiatric disorders affecting our population. Another recent study by Iliuta *et al*[18] showed a reduction in brain volume in patients with schizophrenia. Still, it did not demonstrate specific connectivity to brain regions like Stoyanov *et al*[15] showed, especially in paranoid schizophrenia.

CONCLUSION

These two studies encourage clinicians in psychiatry to go beyond the traditional methods and to provide objective measures in the understanding of schizophrenia. They provide future directions for distinguishing the biological differences between positive and negative symptoms of schizophrenia. However, we are not yet able to use imaging or neurotransmitters to assess diagnoses, prognosis, or which treatment may be most effective on an individual level. The differences in brain anatomy can overlap between patients with schizophrenia and controls, so we cannot yet rely on MRI findings alone to diagnose schizophrenia. These studies have certain limitations, including but not limited to the number of participants and the question of other confounding factors. The presence of other neurotransmitter involvement, such as the serotonin and cholinergic systems in schizophrenia are still evolving and warrants further investigation. There were also specific items used to assess the responses in patients, which is another limitation. These items are not standardized tools that have been seen used more broadly in psychiatry outside of the focus of these studies. It would be beneficial to use more standardized items and protocols with questionnaires to show better replicability of the results.

FOOTNOTES

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EDITORIAL

Machine learning applications in healthcare clinical practice and research

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Abstract

Machine learning (ML) is a type of artificial intelligence that assists computers in the acquisition of knowledge through data analysis, thus creating machines that can complete tasks otherwise requiring human intelligence. Among its various applications, it has proven groundbreaking in healthcare as well, both in clinical practice and research. In this editorial, we succinctly introduce ML applications and present a study, featured in the latest issue of the *World Journal of Clinical Cases*. The authors of this study conducted an analysis using both multiple linear regression (MLR) and ML methods to investigate the significant factors that may impact the estimated glomerular filtration rate in healthy women with and without non-alcoholic fatty liver disease (NAFLD). Their results implicated age as the most important determining factor in both groups, followed by lactic dehydrogenase, uric acid, forced expiratory volume in one second, and albumin. In addition, for the NAFLD- group, the 5th and 6th most important impact factors were thyroid-stimulating hormone and systolic blood pressure, as compared to plasma calcium and body fat for the NAFLD+ group. However, the study's distinctive contribution lies in its adoption of ML methodologies, showcasing their superiority over traditional statistical approaches (herein MLR), thereby highlighting the potential of ML to represent an invaluable advanced adjunct tool in clinical practice and research.

Key Words: Machine; Learning; Artificial; Intelligence; Clinical; Practice; Research; Glomerular filtration rate; Non-alcoholic fatty liver disease; Medicine

Core Tip: Across numerous diverse industries, machine learning (ML) is revolutionizing healthcare as well. It has demonstrated the potential to aid in disease diagnosis, treatment planning, decision-making, and outcome prediction, as well as improve clinical trial design and their success rates, often surpassing traditional methods. We highlight a study, published in the *World Journal of Clinical Cases*, where ML techniques proved superior to traditional statistical methods in analyzing factors affecting the estimated glomerular filtration rate in healthy women with and without non-alcoholic fatty liver disease.

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INTRODUCTION

Machine learning (ML) is a type of artificial intelligence that assists computers in the acquisition of knowledge through data analysis, thus creating machines that can complete tasks otherwise requiring human intelligence. It encompasses various techniques, among which are neural networks, decision trees, support vector machines, and ensemble algorithms, to name a few[1]. ML allows the generation of predictions or assessments without the need for explicit programming[2]. By using algorithms to analyze and find patterns in large datasets, it enables the development of models that can make accurate predictions or identify insights[3]. These models are trained using supervised (labelled data) or unsupervised (unlabeled data) learning, a hybrid form of the two using both labelled and unlabeled data (semi-supervised learning), and reinforcement learning (based on reward or penalty)[2], and they can improve over time with additional data and feedback.

Unsurprisingly, considering its immense, endless capabilities, ML has demonstrated revolutionary applications across numerous diverse sectors, from robotics[4] to finance[5,6], and from business[7] to cybersecurity[8] and healthcare[9-11]. Some of the largest applications of ML in healthcare include the analysis of medical images[12], natural language processing in electronic health records[13], and using human genetics in disease prediction and disease etiology identification[14].

ML ALGORITHMS

ML algorithms can assist healthcare professionals in diagnosing diseases, developing personalized treatment plans, aiding in decision-making[15], and predicting patient outcomes. ML models such as convolutional neural networks (CNNs) or recurrent neural networks (RNNs) are an important part of ML's significant role in healthcare. Both CNNs and RNNs automate feature extraction and pattern recognition, enabling faster, more accurate diagnoses and predictions compared to traditional methods, thus transforming clinical decision-making. CNNs use layers of filters to automatically learn and extract important features from medical images. Convolutions capture spatial hierarchies, allowing CNNs to identify edges, textures, and patterns indicative of medical conditions. Based on these patterns learnt from vast amounts of training data, eventually CNNs become capable of differentiating between healthy tissue and abnormalities, therefore assisting in tasks like detecting tumors or classifying diseases. On the other hand, RNNs excel in predictive analytics by analyzing sequential data. RNNs maintain memory of previous inputs, making them ideal for predicting disease progression or patient outcomes. In healthcare, by analyzing trends in patient data (*i.e.*, vital signs and laboratory results), RNNs may be used to predict events (*i.e.*, hospital readmission).

Recent developments have shown that the utilization of big data and ML has the potential to generate algorithms demonstrating comparable performance to that of human physicians[16], including tasks such as determining the presence of tumors on radiological and/or other kinds of medical imaging[15,17]. Some examples of applications in medicine that have even gained United States Food and Drug Administration approval include different types of software that may detect cardiac rhythm disorders or heart failure or rapidly and accurately assess radiological images such as X-rays and computed tomography scans for the identification of several conditions, including strokes, fractures, tumors, intracranial hemorrhage, aortic dissection, pneumothorax, suspected uncontained intra-abdominal gas, and lung nodules[18].

To further illustrate their capabilities, ML methods have even proven efficient with tasks such as the utilization of magnetic resonance imaging scans to assist with preoperative tumor staging[19], thereby demonstrating their potential to break the barrier of disease diagnosis and influence advanced decision-making by enabling more accurate treatment options as well (*i.e.*, surgical planning and timing of chemoradiation)[20]. On a similar note, ML methods are often applied to analyze and interpret complex data obtained through hyperspectral imaging, an advanced imaging technique that captures and processes information from multiple spectral bands across the electromagnetic spectrum. In healthcare and medical diagnostics, this advanced technique can provide detailed information that can improve disease diagnosis

and treatment by analyzing tissue characteristics non-invasively. For example, ML methods combined with hyperspectral imaging have been successfully employed in detecting skin cancer and in the early detection of esophageal cancer[21,22]. In addition, the ability of ML algorithms to indirectly extrapolate information from previously available datasets has proven capable of allowing opportunistic screening and early diagnosis of diseases, thus allowing for optimized patient outcomes, and synchronously opening new horizons into research opportunities[23,24]. Similarly, within the realm of research, ML has been employed to scrutinize extensive datasets and spot intricate patterns that would otherwise pose challenges for human interpretation, thus leading to significant advancements in various fields (*i.e.*, genetics and pharmaceutical exploration)[15].

On a similar note, ML has exhibited the capacity to augment the design of clinical trials and enhance their success rate through diverse means, such as employing predictive models to be able to uphold optimal statistical power with smaller sample sizes[25,26]. To elaborate on the role of ML in clinical trials, statistics, and research, it is essential to recognize that while ML models should not be considered a panacea compared to traditional statistical methods[27], they are increasingly augmenting or replacing traditional approaches in classifying and predicting health outcomes[28]. For example, ML methods have been used in comparison with traditional statistical methods, where they seemed to outperform conventional logistic regression models in the prediction of abnormal carotid intima-media thickness in patients with type 2 diabetes[29].

To further illustrate the impact of ML advancements in structuring clinical studies and inferring insights that may prove useful for clinical practice while also exploring ML methods' abilities to outperform traditional statistical methods, we discuss the recent study by Chen *et al*[30], featured in the latest issue of the *World Journal of Clinical Cases*. The authors of this study conducted an analysis, using both multiple linear regression (MLR) and ML methods, to investigate the significant factors that may impact the estimated glomerular filtration rate (eGFR) in healthy women with and without non-alcoholic fatty liver disease (NAFLD).

NAFLD is a prevalent etiology of chronic liver disease on a global scale and encompasses a range of conditions that are distinguished by the presence of hepatic steatosis, with no other identifiable factors (such as excessive alcohol consumption) contributing to the buildup of fat in the liver. NAFLD may range from the benign non-alcoholic fatty liver to the more severe non-alcoholic steatohepatitis, while it even holds the potential to advance to fibrosis, cirrhosis, and even neoplastic conditions (namely hepatocellular carcinoma)[31]. Evidently, NAFLD carries significant health, economic, and social repercussions[32] and therefore seems to be a significant health concern warranting increasing attention in healthcare. The correlation between NAFLD and various other disorders has received great interest in recent years, with chronic kidney disease (CKD) emerging as a significant connection, both in terms of prevalence and significance[33,34]. Notably, around one-third of NAFLD patients exhibit renal function impairment[35]. The eGFR serves as a valuable and direct indicator of renal filtration function, frequently utilized in clinical settings for diagnosing CKD and evaluating renal function[36]. The eGFR is closely linked to various risk factors [including hypertension, obesity, liver enzymes, lipid levels, uric acid (UA), and hemoglobin] associated with NAFLD in apparently healthy populations. Furthermore, the influence of NAFLD on eGFR may be influenced by age, a significant risk factor for kidney disease, given that eGFR calculation incorporates age as one of its key parameters[37]. However, the majority of studies focusing on the above matters have relied on traditional statistical analysis methods, with limited research utilizing ML approaches. Only recently, Cao *et al*[38] employed ML to identify NAFLD-related genes as diagnostic markers in CKD patients with NAFLD, highlighting the potential of ML in this context.

Thus, Chen *et al*'s recent study[30] represents a significant effort to address the research gap in the use of ML techniques to investigate risk factors affecting eGFR in NAFLD patients. Specifically, the authors of this retrospective study employed a combination of traditional statistical methods (MLR) and three ML techniques (stochastic gradient boosting, extreme gradient boosting, and elastic net) to analyze a large and diverse dataset covering over 100 biological indicators and identify key factors influencing eGFR in healthy Chinese women, both with and without NAFLD (NAFLD+ and NAFLD-). The study found that ML methods surpassed MLR in performance. Age emerged as the most crucial factor influencing eGFR in both NAFLD- and NAFLD+ groups, followed by lactic dehydrogenase (LDH), UA, forced expiratory volume in one second (FEV1), and albumin (Alb). In the NAFLD- group, thyroid-stimulating hormone (TSH) and systolic blood pressure (SBP) were ranked as the 5th and 6th most significant factors, whereas plasma calcium (Ca) and body fat (BF) were identified as the 5th and 6th key factors in the NAFLD+ group.

The study's findings align well with existing literature while simultaneously building upon it. It's unsurprising that age emerged as the primary determinant for eGFR, given the well-documented decline in renal function with advancing age [37]. Notably, elevated LDH levels have been identified as a predictive marker for renal failure[39], and elevated UA levels can compromise renal function, potentially leading to CKD through various pathways[40]. Additionally, FEV1, a useful indicator of pulmonary function, also appears relevant, as obstructive lung function has been associated with an increased risk of renal impairment[41]. Alb levels have also been consistently linked with renal function across several studies[42]. TSH has been shown to influence renal function, warranting regular monitoring in patients with hypothyroidism[43] and demonstrating improvement with appropriate treatment[44]. Furthermore, increased SBP is a well-established independent risk factor for CKD and end-stage renal disease[45,46]. Finally, low serum Ca levels have been implicated as an independent factor for CKD progression[47] and linked to poor renal outcomes[48], while BF has also been shown to negatively impact renal function, aiding in CKD progression, and has been recommended as a surveillance marker for renal impairment[49].

The study's findings have noteworthy implications for understanding the relationship between NAFLD and renal function and shed light on the importance of the various factors found to significantly affect eGFR in NAFLD+ and NAFLD- patients. Considering that the study participants represent a healthy cohort, these insights could potentially facilitate early detection and management of renal diseases in at-risk populations, thereby playing a crucial role in population screening. The ML approach employed in the study seems to have improved the robustness and reliability of

the results. By utilizing three distinct ML methods that provided valuable insights and surpassed the traditional MLR model in, the study highlights the potential of advanced analytics in medical research.

As acknowledged by the authors, the study presents certain limitations, including its exclusive focus on healthy Chinese women and its cross-sectional design. To enhance the study's broader applicability and generalizability, conducting longitudinal research and expanding the methodology to encompass both men and women from diverse ethnic backgrounds would be desirable. Furthermore, expanding the research beyond healthy populations to explore how various factors influence eGFR across different clinical conditions and diseases could yield invaluable insights. Additionally, given that grades 1 to 3 were collectively defined as fatty liver based on ultrasound findings in this study, conducting subgroup analyses to explore the factors influencing eGFR across different grades of fatty liver could provide interesting results as well.

CONCLUSION

Overall, the current study presents a useful contribution to the understanding of factors affecting eGFR in healthy women with and without NAFLD. The use of ML techniques and the demonstration of its superiority compared to traditional statistics add the most novel dimension to the present study, potentially paving the way for ML to become an invaluable advanced adjunct tool in clinical practice and research. Nonetheless, despite its promising potential, integrating ML into clinical practice and research requires awareness and caution as it also presents challenges, including the necessity for robust validation, interpretability of models, and data privacy concerns. To provide additional context, robust validation is necessary because ML models must be tested carefully on diverse, high-quality datasets to confirm their accuracy, generalizability, and reliability in real-world medical scenarios. Without proper validation, inaccurate predictions could lead to erroneous decisions. Interpretability is another key concern. The decision-making processes of many ML models, especially DL models, are difficult for clinicians to understand and therefore adopt their results in clinical practice. To build trust and enable acceptance in clinical practice, ML models must provide clear, explainable outputs that physicians can interpret and justify. Finally, data privacy is critical. Medical datasets contain sensitive patient information, and integrating ML requires secure handling, adhering to appropriate regulations. Ensuring data security while maintaining access to large, comprehensive datasets for training models is a delicate balance that needs careful management.

FOOTNOTES

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EDITORIAL

Searching for new drugs to treat Alzheimer's disease dementia through multiple pathways

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Abstract

Dementia is a group of diseases, including Alzheimer's disease (AD), vascular dementia, Lewy body dementia, frontotemporal dementia, Parkinson's disease dementia, metabolic dementia and toxic dementia. The treatment of dementia mainly includes symptomatic treatment by controlling the primary disease and accompanying symptoms, nutritional support therapy for repairing nerve cells, psychological auxiliary treatment, and treatment that improves cognitive function through drugs. Among them, drug therapy to improve cognitive function is important. This review focuses on introducing and commenting on some recent progress in exploring drugs to improve cognitive function, especially the new progress in drug treatment for AD. We mainly discuss the opportunities and challenges in finding and developing new therapeutic drugs from the aspects of acetylcholinesterase, N-methyl-D-aspartate glutamate receptor, amyloid protein, tau protein and chronic immune inflammation.

Key Words: Alzheimer's disease; Dementia; Cholinesterase inhibitor; Beta amyloid; Tau protein

Core Tip: The therapeutic targets for acetylcholinesterase (AChE), N-methyl-D-aspartate glutamate receptor, amyloid (Aβ) protein, tau protein and immune inflammation are still the main direction of developing Alzheimer's disease (AD) drugs. Several classical AChE inhibitors are worth keeping. Although there are many experimental research results on antibodies against Aβ or tau protein, there are few successful clinical trials of drugs. The development of new drugs for chronic immune inflammation to treat AD is still in the animal experimental stage. It is necessary to establish a multi-target-oriented precision treatment system for many key links and aspects involved in the pathogenesis of AD.

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INTRODUCTION

In this editorial, we comment on progress in the drug treatment for Alzheimer's disease (AD). AD is a degenerative dementia that disrupts neurocognitive function. The underlying pathogenesis of AD is complex and is thus difficult to address through a single drug or intervention[1]. The effective treatment of AD faces many challenges, and current drugs essentially treat symptoms, assisting in the restoration of cognitive function and controlling abnormal behavior while retarding disease progression and associated deterioration. Despite decades-long research and development of drugs for AD, few have been officially approved for clinical use. The primary reasons are that the key factors triggering AD onset are still unclear, the targeting of single factors or molecules, poor drug bioavailability, poor penetration of the blood–brain barrier, and difficulties associated with nerve cell regeneration and functional recovery[2]. Although a comprehensive understanding of the molecular mechanisms underlying AD onset is as yet unavailable, some of the signaling pathways and several important molecules involved in AD pathogenesis have been identified. The amyloid (Aβ) hypothesis is the most widely accepted molecular explanation. However, recent large-scale clinical phase 3 trials of monoclonal antibodies targeting Aβ have all ended in failure, indicating the complexity and difficulty of treating AD, while clinical research on drugs targeting tau protein is not optimistic, indicating that the road to developing AD drugs is long[3]. Due to the significant difficulties encountered in conventional research and traditional drug treatment, there is an increasing demand for innovative ideas in the development of drugs for treating AD.

Molecular docking can provide useful biological information for the design of new inhibitors, reducing the time needed for chemical synthesis and the cost of biological testing. It also allows simulations of the mechanism of drug action and the prediction of therapeutic doses, as well as the discovery and verification of novel targets and optimization of the pharmacokinetic characteristics of drugs[4]. There have been many animal experiments conducted on the treatment of AD by controlling neuroinflammation, especially in the development of novel drugs targeting the NLRP3 (NOD-like receptor thermal protein domain associated protein 3) inflammasome, but there is still a long way to go in clinical drug trials[5]. The development of nanotechnology provides the possibility of solving some limitations associated with the delivery of active candidate drugs, and has also been used in the development of drugs for AD. In recent years, replacement therapy has attracted significant attention, and traditional Chinese medicine (TCM) or neurotrophic supplements have been demonstrated to be effective in treating AD[6]. The following is a brief analysis of some recent advances in AD drug research.

DRUGS FOR TREATING AD BY BLOCKING ACETYLCHOLINESTERASE

Reduced levels of acetylcholine (ACh) are associated with cognitive impairment and abnormal behavior, and the onset of AD is closely related to a lack of ACh in the brain. Inhibition of acetylcholinesterase (AChE) activity increases the effective amount of ACh, thus reducing the progression of cognitive impairment. The first AChE inhibitor approved by the US Food and Drug Administration (FDA) for the treatment of AD was tacrine, which has subsequently been withdrawn due to its many side effects. At present, donepezil, rivastigmine and galanthamine are AChE inhibitors approved by the FDA that are used to treat AD, with good clinical efficacy. These compounds bind reversibly to AChE, inhibiting its activity and thus increasing ACh levels[7]. Donepezil, a derivative of indone benzyl piperidine, is a long-acting cholinesterase inhibitor with reversible selective deacetylation in the central nervous system. As an AChE inhibitor, donepezil is 10 times more effective than tacrine, and its selectivity for AChE is about 750 times that of butyrylcholinesterase. Donepezil binds to the A chain through Van der Waals forces, π–σ, π–π, and alkyl bonds. In addition, the phenyl nucleus of indacone interacts *via* π–π bonds with Trp286 in the active center of AChE, inactivating the enzyme. Donepezil has been shown to be effective in improving memory, reducing hallucinations, and enhancing attention[8].

Lismin is a carbamate derivative, which can irreversibly bind to AChE and inactivate it, thus indirectly leading to the increase of ACh concentration. Because of its preferential selectivity to hippocampus and cortex, it shows that it can increase the level of synaptic neurotransmitters and improve the function of cholinergic receptors. The use of lismin patches has a better therapeutic effect[9]. Galanthamine has higher selectivity for AChE. It forms π–alkyl and π–π bonds

with the length of 4.7–4.8 with Trp286 on two AChE chains through cyclohexene-2-alcohol and benzene ring, and also binds to the A chain of the enzyme through oxygen atoms and hydrogen bonds of methoxy group. Besides acting on AChE, it also acts through the allosteric regulation of nicotine receptor, which regulates the release of glutamic acid, serotonin and γ-aminobutyric acid, and has a beneficial effect on relieving dementia symptoms[10]. Huperzine A is a reversible cholinesterase inhibitor, which can improve the associative learning, graphic recognition and memory recovery of AD patients. The above Ach inhibitors have been widely used in clinic and achieved different degrees of effect, but these drugs have many side effects, and there is still a big gap in reversing the progress of AD and completely controlling the symptoms of AD.

NMDA RECEPTOR ANTAGONISTS AND SOME NEUROPROTECTIVE AGENTS

Memantine is an antagonist of the N-methyl-D-aspartate glutamate (NMDA) receptor. As early as 2003, some European countries had approved the use of memantine for clinical treatment of AD. Multiple phase 3 clinical trials of metatron treatment for dementia have been completed in other countries and industries around the world; all of which have confirmed its effectiveness in treating AD. Meijingang can inhibit glutamate function and increase dopamine transmission at the same time. Glutamate is an excitatory neurotransmitter that is closely related to the onset of AD, while dopamine is a neurotransmitter that can increase pleasure experiences and improve cognitive function. Meijingang mainly treats dementia by increasing attention and improving episodic memory. For patients with ineffective use of cholinesterase inhibitors, it is recommended to switch to memantine or combine cholinesterase inhibitors with memantine[11].

Sodium oligomannate is an acidic oligosaccharide compound extracted from marine plant brown algae, independently developed by China and approved for clinical use. This drug has shown certain therapeutic effects in treating mild to moderate AD by controlling brain neuroinflammation caused by intestinal microbiota imbalance[12]. Dexmedetomidine (Precedex) is a selective antagonist of 2 adrenergic receptors, which has undergone phase 1 clinical trials for AD treatment, with the final efficacy to be determined. Trehalose is a nonreducing disaccharide and serves as a target for rapamycin kinase complex 1 independent autophagy inducer. It protects neurons by inducing autophagy and clearing Aβ protein aggregates. Recently, clinical trials have used trehalose to treat dementia[13].

Increasing evidence shows that chronic neuroimmune inflammation plays a role in the pathogenesis and progress of AD. Chronic inflammation can lead to the activation of microglia, which can produce cytokines, chemokines and reactive oxygen species, which cause damage to neurons and lead to the development of cognitive symptoms. The activation of inflammatory corpuscles of NLRP3 may play an important role in the pathogenesis of some AD patients. Diacetyl-p-phenylenediamine (DAPPD) has the ability to regulate the function of microglia, inhibit neuroinflammation and alleviate cognitive defects. In the transgenic mouse model of AD, Park *et al*[14] found that DAPPD can control the occurrence and deterioration of AD by affecting the nuclear factor B1 signal transduction pathway and inhibiting the activation of NLRP3 inflammatory corpuscles. Progesterone (PG) has a unique neuroprotective effect. Some researchers have found that PG can significantly inhibit the activation of NLRP3 inflammatory corpuscles induced by Aβ, suggesting that the neuroprotective mechanism of NLRP3-caspase-1 inflammatory corpuscles regulated by PG may be a potential therapeutic target to improve the pathophysiological process of AD[15]. Stavudine (D4T) is a nucleoside reverse transcriptase inhibitor, which can block the assembly of inflammatory corpuscles of NLRP3. Rosa *et al*[16] found that D4T can reduce the production of interleukin-18 and caspase-1, reduce the phagocytosis of Aβ, and stimulate Aβ autophagy of macrophages. These effects can be shown by downregulation of extracellular signal-regulated protein kinases 1 and 2 and protein kinase B phosphorylation, showing that D4T can reduce the activation of inflammatory corpuscles of NLRP3.

DRUGS AND ANTIBODIES FOR THE TREATMENT OF AD

The oligomerization of beta Aβ and its interaction with various nerve cells lead to some pathophysiological abnormalities in the brain of AD patients, including mitochondrial dysfunction, tau phosphorylation, activation of immune inflammatory factors, dysregulation of calcium metabolism, and enhanced activity of glycogen synthase kinase 3β (GSK-3β). According to the amyloid cascade theory, the main factor causing AD is the aggregation of Aβ, followed by the formation of senile plaques, which damage nerve cells and brain function. If we want to prevent AD or its development, it is mainly achieved by reducing the production of Aβ, preventing Aβ aggregation, and increasing Aβ clearance[17]. There are two types of vaccine research: (1) Active immunization; and (2) passive immunization. The goal of active immunization is to develop an A42 vaccine that targets the formation of amyloid plaques. The three key enzymes involved in processing amyloid precursor protein have become drug targets for the development and treatment of AD. Drugs such as β-secretase inhibitors, γ-secretase inhibitors and α-secretase promoters have emerged successively. Among this large class of chemical reagents, drugs that have entered clinical trials include elenbecestat, umibecestat, verubecestat, ataabecestat and semagacestat[18].

In addition, immunotherapy can stimulate the immune system to produce autoantibodies or use exogenous antibodies to achieve the above treatment ideas. They are Aβ aggregation inhibitors and some relatively specific monoclonal antibodies. Drugs that have undergone clinical trials include aducanumab, AN-1792, solanezumab, lecanemab, donanemab, ABvac40, *etc.* AN-1792 is the first Aβ vaccine, but its efficacy in later clinical trials has been unsatisfactory, and ABvac40 is the first active vaccine targeting the C terminus of the Aβ 40 peptide. Anti Aβ 40 antibodies can prevent and treat the production and aggregation of toxic substances of Aβ 40. Although the neurotoxicity of Aβ 40 is lower than

that of Aβ 42, this drug is currently undergoing phase 3 clinical trials[19]. Phase 3 clinical trials are the final confirmation of drug safety and efficacy, requiring ~600 or more participants and lasting > 5 years, with at least 80% of patients successful. Aducanumab was approved by the US FDA for clinical use in 2021. It is currently the only monoclonal antibody drug officially approved for the treatment of AD. The drug can cross the blood–brain barrier and bind to amyloid protein, thereby helping to degrade and clear excess Aβ in the brain, which can improve cognitive function in AD patients. However, there is significant debate in the academic community regarding aducanumab, mainly due to its unstable therapeutic efficacy and significant side effects[20]. The above-mentioned drugs that entered large-scale clinical trials in phase 2 or 3 were rarely successful, which led clinical scientists to reflect on whether the presence of Aβ aggregates and tau protein fibers is the main risk of AD in drug research and development, and whether the mainstream neuropsychiatric theory of AD is misleading.

DRUGS AND ANTIBODIES DESIGNED FOR TAU PROTEIN

In the past 10 years, the viewpoint that tau protein causes AD has attracted more attention, and the tau protein superphosphate theory has emerged. When tau is hyperphosphorylated, it can produce neurofibrillary tangles, damage the normal function of neurons, and accelerate their degeneration, leading to AD. Because the correlation between tau pathology and cognitive impairment is stronger than that of Aβ lesions, targeting tau is expected to be more effective than clearing Aβ. In the past, anti-tau protein therapy was mainly based on inhibiting related kinases, or inhibiting tau aggregation, or stabilizing microtubules, but these methods were either too toxic or ineffective, and most of them had stopped. At present, the main direction of targeted therapy of tau protein in clinical trials is immunotherapy, which is said to be effective in many clinical studies[21]. Active immunization against tau protein in the treatment of AD is represented by anti-tau vaccine (AADvac1) and phosphorylated tau (ACI-35). AADvac1 antibody can prevent tau oligomerization, mainly by binding the six amino acid sequence HXPGGG of tau protein to prevent microtubule synthesis. ACI-35 targets the pSer396/404 epitope of tau protein and has been clinically tested in AD patients to evaluate the tolerance and immunogenicity of ACI-35246. At present, the clinical trial drugs targeting tau protein by passive immunization are RG7345, BMS-986168, C2N-8E12, RO 7105705, LY3303560 and INJ-63733657260, *etc.* These drugs act on different sites of tau protein, for example: (1) RG7345 can recognize tau protein phosphorylated at Ser422 site; and (2) C2N-8E12 can recognize amino acids 25-30 of tau protein. They are all in clinical trials ranging from phase 1 to 3, and the curative effect is uneven[22]. Cyclin-dependent kinase 5, GSK3 and mitogen-activated protein kinase are all key enzymes that control tau protein phosphorylation. At present, there have been some studies on these related signal proteins[23].

The combination of multiple therapies may be more effective in treating AD than using a single drug, because the onset of AD has complex pathophysiological mechanisms and there may be a synergistic relationship between Aβ and tau. In phase 2 clinical trials, the anti-Aβ antibody bapineuzumab can reduce the phosphorylation level of tau protein in the cerebrospinal fluid of AD patients. However, in phase 3 clinical trials, bapineuzumab had no effect on the neuropathology of tau protein. This result suggests that clearing Aβ during active or passive immunity cannot fully reduce tau levels to alter disease progression[24]. Many drug research paths are winding. For example, encouraging results have been achieved in animal studies using methylene blue derivatives, but their clinical research data is not ideal; curcumin, limited by its bioavailability, has not yet been proven to have therapeutic effects on human tau like degeneration; MK-8719 can increase the level of O-GlcNA acylation protein, showing promising application prospects, but its phase 2 clinical trial has not yet reached a definite conclusion[25]. Overall, both active and passive immunization strategies have their own advantages, and the combination of tau and Aβ targeted immunotherapy through antibody engineering may significantly improve efficacy. The cost of drug treatment is also a problem that needs to be seriously considered. We hope that some AD patients in underdeveloped areas can also get effective treatment.

TCM REPLACEMENT THERAPY AND DRUG ADJUVANT THERAPY

Some drugs developed and refined from TCM also play a certain role in the prevention and treatment of AD. *Ginkgo biloba* extract has the effects of promoting blood circulation, removing blood stasis, dredging channels and activating collaterals. It was originally used to treat vascular dementia, and later it was found to be effective in treating AD. Ginseng has the effects of invigorating qi and blood, calming the nerves and improving intelligence; *Astragalus* has the effects of enhancing immunity and reducing blood viscosity; *Polygonatum sibiricum* has the functions of nourishing kidney, replenishing essence, nourishing heart and calming nerves; *Gastrodia elata* has the function of calming the liver and calming the wind; *Lycium barbarum* has the function of nourishing liver and kidney, *etc.* The combination of the above TCMs alone or in combination shows the effect of improving cognitive function. *Cannabis* plants contain cannabinoids, and cannabinoids contain δ-9-tetrahydrocannabinol and cannabidiol, both of which have anti-inflammatory and neuroprotective effects, and can improve cognitive function and assist in the treatment of AD[26]. In fact, huperzine A is also a natural plant alkaloid extracted from *Huperzia serrata*, a Chinese patent medicine plant. Later, it was confirmed by western medicine that it has the activity of inhibiting AChE, thus showing the efficacy of treating AD.

The route of administration and drug absorption effect in AD drug therapy are also a research issue worthy of attention. Due to the natural obstacle of the blood–brain barrier, the effect of some drugs for treating AD is reduced or even clinical trials fail. However, nanoparticles are helpful for the delivery of such drugs. Nanoparticles can improve biocompatibility, prolong half-life, transport macromolecules, cross the blood–brain barrier and reach the central nervous system, showing good targeting ability[27]. AD patients are often accompanied by mental disorders, or symptoms such as

depression and anxiety. The treatment for these symptoms is important to improve the quality of life of patients, and there are many drugs to choose from. However, these drugs are not the scope of this article. For the treatment of advanced AD patients, drug therapy may be more important than nondrug therapy. There are many combinations of drug therapy and nondrug therapy, and there is no recognized best combination at present. It should be emphasized that any patient advocates comprehensive treatment and makes a special treatment plan for each patient.

CONCLUSION

Due to the complex and numerous factors that affect the onset of AD, it is necessary to comprehensively analyze and identify the goals of control. The establishment of multitarget targeted precision therapy systems is a joint action aimed at key nodes of multiple signaling pathways involved in the pathogenesis of AD. Inhibition of cholinesterase activity, blockade of NMDA receptors, antibody targeting of Aβ and tau proteins, substitution therapy with TCM, and improvement of drug absorption are all current directions for drug treatment of AD[28]. The fact that a single treatment method or drug may not be effective does not mean that this treatment method or drug should be abandoned, but rather that serious improvement or seeking combination therapy is needed. The clinical characteristics and pathophysiology of AD patients are different. Typical randomized controlled trials need to be conducted on a large scale to obtain reliability. Tracking big data can improve the accuracy of measurement results. The development of AD drugs is going through a new stage from natural randomness to more rigorous and efficient[29]. The best treatment for AD is definitely comprehensive therapy, which combines various drugs, cognitive function training, nursing assistance, and community organizations to form the so-called dementia processing unit and is receiving attention[30]. If patients are found to exhibit symptoms related to dementia, it is necessary to seek medical attention in a timely manner, as early diagnosis and reasonable treatment can improve quality of life, among which drug therapy remains the main method for treating AD.

FOOTNOTES

Author contributions: Bai H was responsible for design, conception, writing and modifying the paper, collecting references, discussing related issues, and replying to the reviewer comments; Feng XF was responsible for collecting references and discussing related issues; all of the authors read and approved the final version of the manuscript to be published.

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ORIGINAL ARTICLE

Observational Study

Practice patterns among ophthalmic surgeons in treating concomitant oculoplastic conditions in preoperative period: A questionnaire-based study

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Abstract

BACKGROUND

Addressing oculoplastic conditions in the preoperative period ensures both the safety and functional success of any ophthalmic procedure. Some oculoplastic conditions, like nasolacrimal duct obstruction, have been extensively studied, whereas others, like eyelid malposition and thyroid eye disease, have received minimal or no research.

AIM

To investigate the current practice patterns among ophthalmologists while treating concomitant oculoplastic conditions before any subspecialty ophthalmic intervention.

METHODS

A cross-sectional survey was disseminated among ophthalmologists all over India. The survey included questions related to pre-operative evaluation, anaesthetic and surgical techniques preferred, post-operative care, the use of adjunctive therapies, and patient follow-up patterns.

RESULTS
A total of 180 ophthalmologists responded to the survey. Most practitioners (89%) felt that the ROPLAS test was sufficient during pre-operative evaluation before any subspecialty surgery was advised. The most common surgical techniques employed were lacrimal drainage procedures (Dacryocystorhinostomy) (63.3%), eyelid malposition repair (36.9%), and ptosis repair (58.7%). Post-operatively, 47.7 % of respondents emphasized that at least a 4-week gap should be maintained after lacrimal drainage procedures and eyelid surgeries. Sixty-seven percent of ophthalmologists felt that topical anaesthetic procedures should be preferred while performing ocular surgeries in thyroid eye disease patients.

CONCLUSION
Approximately 50% of ophthalmologists handle prevalent oculoplastic issues themselves, seeking the expertise of an oculoplastic surgeon under particular conditions. Many ophthalmologists still favor using ROPLAS as a preliminary screening method before proceeding with cataract surgery. Eyelid conditions and thyroid eye disease are not as commonly addressed before subspecialty procedures compared to issues like nasolacrimal duct obstruction and periocular infections.

Key Words: Oculoplasty; Ophthalmic plastic surgery; Nasolacrimal duct obstruction; Practice patterns; Survey

Core Tip: The study among Indian ophthalmologists reveals reliance on ROPLAS test for preoperative evaluation. Lacrimal drainage procedures dominate surgical interventions, with postoperative care emphasizing a 4-week gap. Topical anaesthesia is preferred for thyroid eye disease surgeries. While many manage oculoplastic issues independently, collaboration with oculoplastic surgeons occurs in complex cases. Nasolacrimal duct obstruction and periocular infections receive more attention compared to eyelid malpositions and thyroid eye disease preoperatively. The findings underscore the importance of comprehensive evaluation and highlight potential areas for practice improvement, including enhancing evaluation methods for less studied conditions and promoting interdisciplinary collaboration for optimal patient care.

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INTRODUCTION

The prevalence of patients with oculoplastic diseases in general ophthalmologists' clinics varies from 1.4% to 7.4% of all new patients presenting for eye care[1,2]. The management of coexisting oculoplastic conditions during the preoperative period varies widely among ophthalmic surgeons and remains an area of diverse practice patterns among surgeons. Routine screening for symptoms and examination of the lacrimal system before cataract surgery is performed worldwide [3-6]. Oculoplastic anomalies, ranging from nasolacrimal duct obstructions, eyelid malposition, periocular infections, thyroid eye disease, *etc.*, can significantly impact surgical planning for any ophthalmic subspecialty practices in addition to cataract surgery[1]. The postoperative outcomes of these surgeries also have an impact on patient satisfaction as well as on the reputation of the ophthalmic surgeon. There is a lacuna in the existing literature regarding the management of common oculoplasty disorders by comprehensive ophthalmologists and exclusive subspecialty surgeons in India. Therefore, this questionnaire-based study explores the prevailing practice patterns among ophthalmic surgeons when confronted with concomitant oculoplastic conditions, particularly before any surgical planning for cataracts or other subspecialty. By analyzing the varied approaches, the study hopes to shed light on the common practices, potential gaps in treatment, and avenues for standardized care.

MATERIALS AND METHODS

A cross-sectional questionnaire-based study was designed. A total of 180 ophthalmic surgeons, encompassing a mix of early, mid, and late-career professionals, were selected randomly from various institutions and private practices across the country. The 22-question survey questionnaire was meticulously crafted, containing both closed and open-ended questions, to glean insights into their diagnostic, therapeutic, and decision-making strategies. It covered topics such as common oculoplastic conditions encountered, preferred management techniques, and factors influencing treatment choices in treating these conditions. The entire questionnaire was validated by an in-house pilot study in the tertiary eye care institute. The data was collected during the period of three months, from 1st April to 30th June 2023. Communication

was primarily *via* WhatsApp, supplemented by email, with three reminders sent at one-week intervals. The ethical approval of the institute was obtained, and all participants provided informed consent before participating in the study. Data from Google sheets was analysed using Excel and STATA 14.0. Participation was voluntary and anonymous. Statistics showcased the preferred surgical methods, with responses presented as frequencies, percentages, and means with standard deviations. The responses were anonymized and statistically analysed using SPSS.

RESULTS

Of the 180 ophthalmologists who responded, 94 (52.2%) were female and 86 (47.8 %) were male. Most of the participants, 98 (54.4%), were in the age group of 30-40 years. Of these, 24 (13.3%) had ophthalmologists with practicing experience of less than 5 years, 73 (40.6%) were practicing ophthalmology for 5-10 years, 53 (29.4%) had 10-20 years, and 30 (16.7%) had more than 20 years of practical experience. Notably, 106 (58.9%) practiced in urban areas, while only 8 (4.4%) practiced in rural areas, 35 (19.4) in Semi-urban and 31 (17.2) in Metropolitan areas. Majority of ophthalmologists 69 (38.3%) were private practitioners, followed by ophthalmologists who practiced in institutes 43 (23.9%), trust hospitals with large volume of surgeries 35 (19.4%), and 33 (18.3%) worked in medical colleges. There were 109 comprehensive ophthalmologists (60.6%) and 71 fellowship-trained specialists (39.4%). Of these, 78(43.8%) expressed their view that they didn't treat oculoplasty disorders and refer them to a specialist, 52 (29.2%) had an interest in oculoplasty and treat simple conditions, 19 (10.7%) treated all common Oculoplastic conditions but more interested in their own sub-specialty and 29 (16.3%) practiced their sub-specialty exclusively.

Practice pattern in treating concomitant lacrimal conditions

Respondents were asked to give opinions regarding preoperative lacrimal syringing, done routinely in their practice. Majority of them 89 (49.7%) thought ROPLAS testing was sufficient to confirm nasolacrimal duct (NLD) patency before subspecialty surgery. However, 79 (44.1%) were doing lacrimal passage irrigation in all cases, while only 11 (6.2%) were of the opinion that nasolacrimal duct patency testing was not required before performing their subspecialty surgeries. When asked about their preferred surgical approach for nasolacrimal duct obstruction, 63.3% (114 individuals) favored dacryocystorhinostomy, while 10% (18 individuals) chose dacryocystectomy. Of the remaining participants, 13.3% (24 individuals) opted for punctal cautery in cases where there was partial regurgitation of clear fluid. Another 13.3% (24 individuals) continued with their subspecialty surgery in cases of asymptomatic nasolacrimal duct obstruction (NLDO). Meanwhile, 2.2% (4 individuals) were uncertain about the best approach to the situation. Managing patients with partial nasolacrimal duct obstruction is also a dilemma among ophthalmologists regarding whether to treat or not. While 90 (50.8%) preferred to proceed with ocular surgery in asymptomatic partial NLDO, 48 (27.1%) of them preferred punctal cautery, and the rest of them opted for definitive lacrimal surgeries. Most ophthalmologists preferred a minimum gap of 4 weeks before allowing a sub-specialty surgery after lacrimal surgeries.

Practice pattern while treating concomitant eyelid malposition

Eyelid malposition such as entropion, ectropion, and ptosis can be problematic, acting as potential triggers for infection in the pre-operative phase. When participants were questioned about treating these conditions, 43% (77 individuals) favored surgical treatment before the subspecialty surgery. In contrast, 36.9% (66 individuals) chose surgical treatment only in specific cases. The remaining participants did not opt for surgical treatment, either due to concerns about delaying their scheduled surgery or because they did not perceive any increased risk of infection.

Practice patterns while treating concomitant thyroid eye disease

We also tried to evaluate the practice pattern in managing thyroid eye disease before ocular surgery, which is crucial for ensuring the best surgical outcomes. Eighty-five (47.5%) of them wanted to treat thyroid eye disease in selective cases, and 53 (29.6%) of them wanted to treat thyroid disease first before proceeding with subspecialty surgery. Twenty-seven (15.1) of them did not want to get treated as they didn't pose any intra-operative problem or because the treatment would delay their planned surgery. Regarding the type of anesthesia they would prefer in the presence of thyroid eye disease, the majority of ophthalmologists 67 (38.3%) prefer topical anesthesia followed by the peribulbar route in 52 (29.7%), few of them, 42 (24%) preferred Sub-tenon route while 11 (6.3%) of them were not sure about the route of anesthesia during ocular surgery.

Practice patterns while treating concomitant periocular infections

Adnexal infections, such as stye, chalazion, and canaliculitis, can increase the risk of endophthalmitis after intraocular surgery. As a result, it is essential to address these infections in the preoperative phase. Of the participants, 84.7% (150 individuals) chose to treat any coexisting infectious conditions in all instances. In contrast, 13.6% (24 individuals) opted to treat only in specific cases. A small group, 1.7% (3 individuals), did not see the need for treatment, either because they didn't believe these conditions increased the risk of infection or because treatment might postpone their scheduled surgery. Table 1 shows the number of ophthalmologists grouped according to their experience and opinion regarding managing concomitant periocular infections.

The demographic characteristics of the participants and the responses to the survey questions have been summarized in Table 1.

Table 1 The demographic characteristics of the participants and responses to the survey questions, *n* (%)

Parameters	*n* = 180
Age of the ophthalmologist (in years)	
< 30	4 (2.2)
30-40	98 (54.4)
40-50	49 (27.2)
> 50	29 (16.1)
Gender	
Male	86 (47.8)
Female	94 (52.2)
Years of practice	
< 5	24 (13.3)
5-10	73 (40.6)
10-20	53 (29.4)
> 20	30 (16.7)
Area of practice	
Rural	8 (4.4)
Urban	106 (58.9)
Semi-urban	35 (19.4)
Metropolitan	31 (17.2)
Type of hospital	
Govt. hospital	33 (18.3)
Private practice	69 (38.3)
Single institution practice with teaching	43 (23.9)
Trust hospital with large volume of surgeries	35 (19.4)
Which part of the India do you practice in clinically	
North zone	30 (16.7)
East zone	75 (41.7)
South zone	60 (33.3)
West zone	15 (8.3)
Comprehensive ophthalmologist	
Yes	109 (60.6)
No	71 (39.4)
Exposure into common oculoplastic disorders	
I don't treat and refer them to a specialist	78 (43.8)
I have an interest in oculoplasty and treat simple conditions	52 (29.2)
I treat all common oculoplastic but more interested in sub-specialty	19 (10.7)
My practice is exclusively sub-specialty based	29 (16.3)
NLD patency testing prior to sub-specialty surgery	
Yes, irrigation in all cases	79 (44.1)
Yes, checking for ROPLAS is sufficient	89 (49.7)
No, NLD patency testing is not required	11 (6.2)
NLD obstruction detected during preoperative evaluation	

Dacryocystectomy	18 (10)
Dacryocystorhinostomy	114 (63.3)
Punctal cautery in cases of partial regurgitation of clear fluid	24 (13.3)
Planned ocular surgery in asymptomatic NLDO	24 (13.3)
Not sure	4 (2.2)
Partial NLD detected during pre-op evaluation	
Dacryocystectomy	6 (3.4)
Dacryocystorhinostomy	18 (10.2)
Punctal cautery in cases of partial regurgitation of clear fluid	48 (27.1)
Planned ocular surgery in asymptomatic NLDO	90 (50.8)
Not sure	15 (8.5)
Minimum gap that you prefer prior to allowing a sub-specialty surgery after dacryocystorhinostomy	
< 1 week	1 (0.6)
2 weeks	49 (27.5)
4 weeks	85 (47.7)
6 weeks	40 (22.5)
Not sure	3 (1.7)
Minimum gap that you prefer prior to allowing a sub-specialty surgery after dacryocystectomy	
< 1 week	10 (5.6)
2 weeks	69 (38.8)
4 weeks	70 (39.3)
6 weeks	19 (10.7)
Not sure	10 (5.6)
Treat any stye/chalazion/canaliculitis before performing your subspecialty ophthalmic procedure	
Yes, in all cases	150 (84.7)
Yes, in selective cases	24 (13.6)
No, because they do not pose any risk of infection	1 (0.6)
No, because procedure may delay planed surgery	2 (1.1)
Waiting time after treating stye/chalazion/canaliculitis before performing	
< 1 week	47 (26.3)
2 weeks	81 (45.3)
4 weeks	13 (7.3)
6 weeks	33 (18.4)
Not sure	5 (2.8)
Treat co-existing entropion and ectropion before procedure	
Yes, in all cases	77 (43)
Yes, in selective cases	66 (36.9)
No, because they do not pose any risk of infection	14 (7.8)
No, because procedure may delay planed surgery	17 (9.5)
Not sure	5 (2.8)
Waiting time after ocular surgery	
< 1 week	7 (3.9)
2 weeks	56 (31.3)

4 weeks	69 (38.6)
6 weeks	20 (11.2)
Not sure	27 (15.1)
Treat coexisting thyroid eye disease before performing your ocular surgeries	
Yes, in all cases	53 (29.6)
Yes, in selective cases	85 (47.5)
No, because they don't pose any intra-operative problem	27 (15.1)
No, because procedure may delay planed surgery	7 (3.9)
Not sure	7 (3.9)
Treat coexisting ptosis before performing your ocular surgeries	
Yes, in all cases	16 (8.9)
Yes, in selective cases	105 (58.7)
No, because they don't pose any intra-operative problem	41 (22.9)
No, because procedure may delay planned surgery	12 (6.7)
Not sure	5 (2.3)
Waiting time after ptosis repair	
< 1 week	3 (1.7)
2 weeks	34 (19.2)
4 weeks	75 (42.4)
6 weeks	34 (19.2)
Not sure	31 (17.5)
Anesthesia preferred prior to any surgery in thyroid eye disease patients	
Topical	67 (38.3)
Peri-bulbar	52 (29.7)
Sub-tenon	42 (24)
Don't know	11 (6.3)
Topical + sub-tenon	1 (0.6)
Retro-bulbar	2 (1.1)

NLD: Nasolacrimal duct; NLDO: Nasolacrimal duct obstruction.

DISCUSSION

Managing oculoplastic conditions during the preoperative period presents unique challenges and opportunities for ophthalmic surgeons. Therefore, this survey was conducted with the intent to understand the prevailing practices in managing concomitant oculoplastic conditions during the preoperative period among Indian ophthalmologists. In the present study, 102/180 participants were comprehensive ophthalmologists. This could explain the varied responses, as the primary focus of the questions pertained to coexisting oculoplastic conditions. The data reveals 107/180 participants referred cases to an oculoplasty specialist. This indicates that comprehensive and non-oculoplastic subspecialty surgeons do not have considerable knowledge acquired during their training regarding managing basic oculoplastic conditions. Given this, the present study becomes even more pertinent, aiming to establish a consensus on managing co-existing oculoplastic conditions alongside other subspecialty eye conditions. This definitely needs a revision in the subspecialty curriculum in India, where ophthalmologists opting for fellowships must be trained in comprehensive ophthalmology before pursuing their subspecialty. However, there are few institutes that provide comprehensive ophthalmic knowledge before entering into their subspecialty practice.

In the present study, the majority favor ROPLAS over syringing as a screening test before any subspecialty surgery. The results are similar to a study by Thomas *et al*[7], who assessed the effectiveness of the ROPLAS test as a screening tool for coexisting dacryocystitis and compared it to syringing. In their study, out of 621 outpatients examined, the sensitivity and specificity of ROPLAS were 93.2% and 99.3%, respectively, and this high specificity suggested that if ROPLAS was negative, preoperative syringing may be redundant unless suspicion for the condition is high. In the present study, 10%

of those surveyed reported performing dacryocystectomy, while 13.3% cited using punctal cautery. These figures suggest that, besides the more extensive dacryocystectomy for nasolacrimal duct obstruction, less invasive procedures also play a role in managing the condition, especially when patients undergo surgery for other ophthalmic issues. The specific circumstances where these less invasive options may be chosen include advanced age and ambiguous cases of nasolacrimal duct obstruction, where there is regurgitation of clear fluid without the presence of obvious pus, which might lead to dacryocystectomy. Punctal cauterization is commonly used to treat a range of ocular surface conditions linked to a deficiency in tear production, such as primary dry eye syndrome, Sjögren syndrome, ocular graft-versus-host disease, mucous membrane pemphigoid, and Stevens-Johnson syndrome[8-11]. Although there are no documented instances in the literature of using punctal cautery for the temporary occlusion of the lacrimal passage before cataract surgery, our study indicates that the practice persists. This area warrants further investigation.

In a study by Zucoloto *et al*[12], 78% of surgeons performed lacrimal surgery before the intraocular surgery, waiting 4 to 6 weeks to proceed with the cataract surgery. The procedure of choice for treating nasolacrimal duct obstruction before cataract surgery was dacryocystorhinostomy (88.4%). Similarly, in the present study, the consensus among respondents was to wait four weeks between lacrimal surgery and subsequent major eye procedures such as cataract, corneal, glaucoma, or vitreoretinal surgery. However, a few suggested a shorter interval of approximately one week. This shortened timeframe is particularly relevant in camp settings, where there is a risk that patients, once released after duct surgery, may not return for their subsequent cataract operation. Therefore, surgeons prefer to retain patients in the camp hospital for a week, performing cataract surgery within that period before discharge to ensure the promised treatment is fulfilled. Discharging patients before their cataract surgery could necessitate uncomfortable explanations, as patients are often unsatisfied if the promised treatment is not delivered. Additionally, there is the matter of increased costs for the patient's extended stay and meals at the hospital, which is also a consideration.

There is still debate regarding the time sequence of surgical correction of eyelid malposition in relation to cataract surgery. Previously there was a consensus as to treat eyelid malposition before cataract surgery since it could lead to postoperative ocular irritation and endophthalmitis, but a remarkable study published by Yarmak *et al*[13] in 2022 supports the fact that out of 129 instances across 90 patients, which included 86 cases of involutional entropion and 43 of involutional ectropion, not a single case of endophthalmitis was reported. In the present study, the consensus among ophthalmologists varied for ptosis and ectropion, as well as entropion. While 67% opted to treat ptosis before subspecialty procedures, 80% wanted to treat ectropion and entropion at first, most likely due to the reason that it could lead to irritation and pose a risk for endophthalmitis. However, there is another school of thought that supports the idea that patients undergoing phacoemulsification have an increased chance of getting lower eyelid laxity, probably due to intraoperative eyelid stretch by speculum[14].

In the present study, 77% of participants opted to treat thyroid eye diseases before subspecialty surgeries, with most of them indicating that they would address these conditions under 'special circumstances.' This indicates that, nowadays, ophthalmologists are aware of the nuances involved while performing surgeries in patients with coexisting thyroid eye disease. According to a study by Strong Caldwell *et al*., patients with thyroid eye disease are at increased risk for refractive prediction error following cataract surgery, which needs discussion with patients regarding their risk and possible need for glasses following surgery[15]. There are reports of flare-ups of activity in orbit after receiving retrobulbar anesthesia for cataract surgeries, which is probably the reason why few participants in the present study prefer subtenon and topical anesthesia[16-18].

Apart from nasolacrimal duct obstruction, certain conditions like blepharitis, conjunctivitis, canaliculitis, the use of contact lenses, presence of an artificial prosthesis elevate the risk for acquiring endophthalmitis[19]. Therefore, it is imperative to treat coexisting stye, chalazion and canaliculitis prior to any intraocular procedure more so in large outreach camps where patients have doubtful lid hygiene. In a study by Gangwe *et al*[20], they diagnosed 98 patients with concomitant oculoplasty diseases such as NLDO, stye, chalazion, and ectropion, which needed surgical correction in 73 patients prior to cataract surgery and therefore emphasized the need for comprehensive ophthalmic evaluation in camps. In the present study, 97% participants opted for treating periocular infections probably because more than half of them were involved in private practices or single institution practice or trust hospitals with large volume surgeries.

There are certain limitations of this study. One is that it solely included Indian ophthalmologists as participants. Incorporating international ophthalmologists would have provided a more comprehensive understanding of global practice patterns. Another limitation of this study is the small sample size, which may reduce the generalizability of the findings to a broader population. The questionnaire was not framed about the activity of thyroid eye disease and the degree of entropion and ectropion; therefore, some answers might have ambiguity. There are still some areas like keratorefractive surgeries which were not covered in the questionnaire.

CONCLUSION

There is a need to provide comprehensive ophthalmic knowledge, specifically in the management of common oculoplastic conditions, to the Ophthalmic residents and to the young Ophthalmologists opting for various subspecialties. Future collaborative efforts between different subspecialties of ophthalmology could focus on creating comprehensive guidelines that balance individualized patient care with standardized best practices.

FOOTNOTES

Author contributions: Panda BB and Mishra C conceived and designed the study; Panda BB, Mishra C, and Roy AK collected the data; Nayak B and Mishra P contributed data; Panda BB wrote the paper; Balakrishnan L performed the statistical analysis; Mishra C, Nayak B, and Roy AK critically analyzed the paper.

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ORIGINAL ARTICLE

Observational Study

Assessing healthcare workers' knowledge and confidence in the diagnosis, management and prevention of Monkeypox

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Abstract

BACKGROUND

Monkeypox (Mpox), is a disease of global public health concern, as it does not affect only countries in western and central Africa.

AIM

To assess Burundi healthcare workers (HCWs)s' level of knowledge and confidence in the diagnosis and management of Mpox.

METHODS

We conducted a cross-sectional study *via* an online survey designed mainly from the World Health Organization course distributed among Burundi HCWs from June-July 2023. The questionnaire comprises 8 socioprofessional-related questions,

22 questions about Mpox disease knowledge, and 3 questions to assess confidence in Mpox diagnosis and management. The data were analyzed *via* SPSS software version 25.0. A *P* value < 0.05 was considered to indicate statistical significance.

RESULTS

The study sample comprised 471 HCWs who were mainly medical doctors (63.9%) and nurses (30.1%). None of the 22 questions concerning Mpox knowledge had at least 50% correct responses. A very low number of HCWs (17.4%) knew that Mpox has a vaccine. The confidence level to diagnose (21.20%), treat (18.00%) or prevent (23.30%) Mpox was low among HCWs. The confidence level in the diagnosis of Mpox was associated with the HCWs' age (*P* value = 0.009), sex (*P* value < 0.001), work experience (*P* value = 0.002), and residence (*P* value < 0.001). The confidence level to treat Mpox was significantly associated with the HCWs' age (*P* value = 0.050), sex (*P* value < 0.001), education (*P* value = 0.033) and occupation (*P* value = 0.005). The confidence level to prevent Mpox was associated with the HCWs' education (*P* value < 0.001), work experience (*P* value = 0.002), residence (*P* value < 0.001) and type of work institution (*P* value = 0.003).

CONCLUSION

This study revealed that HCWs have the lowest level of knowledge regarding Mpox and a lack of confidence in the ability to diagnose, treat or prevent it. There is an urgent need to organize continuing medical education programs on Mpox epidemiology and preparedness for Burundi HCWs. We encourage future researchers to assess potential hesitancy toward Mpox vaccination and its associated factors.

Key Words: Monkeypox; Public health emergency of international concern; Healthcare workers; Epidemic; Preparedness; Knowledge; Confidence

Core Tip: On August 14, 2024, the World Health Organization director-general declared that the upsurge of Monkeypox (Mpox) cases in the Democratic Republic of Congo (DRC) and in Africa constitute a public health emergency of international concern. Burundi, which borders the DRC to the east, declared a Mpox outbreak on July 25, 2024 and had just over 500 confirmed cases of Mpox, classifying Burundi as the second most affected country in Africa after the DRC. This study revealed that Burundi healthcare workers have the lowest level of knowledge regarding Mpox and a lack of confidence in the ability to diagnose, treat or prevent Mpox.

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INTRODUCTION

Monkeypox (Mpox) is a viral zoonosis with symptoms similar to those seen in the past in smallpox patients[1]. Mpox primarily occurs in central and western Africa, often in proximity to tropical rainforests, and has increasingly appeared in urban areas. Mpox was discovered in 1958 when two outbreaks of a pox-like disease occurred in group of monkeys in a lab. Despite being named "monkeypox," the source of the disease remains unknown. The first human case of Mpox was recorded in 1970, and the first Mpox outbreak outside Africa occurred in 2003[2]. Cases were also documented in the United States of America and was linked to contact with infected pet prairie dogs[3].

Mpox was also reported in travelers from Nigeria to Israel in September 2018, to the United Kingdom in September 2018, December 2019, May 2021 and May 2022, to Singapore in May 2019, and to the United States of America in July and November 2021[4]. In China, an Mpox epidemic was declared on September 16, 2022, when an imported case was found in Chongqing Municipality[5]. In May 2022, multiple cases of Mpox were identified in several nonendemic countries. Since January 2023, the Democratic Republic of Congo (DRC) has reported more than 22000 suspected cases of Mpox and 1200 deaths[6]. On August 14, 2024, the World Health Organization (WHO) director-general declared that the increase in Mpox in the DRC and the increasing number of countries in Africa constitute a public health emergency of international concern under the International Health Regulations[7]. Burundi, which borders the DRC to the East, declared an Mpox outbreak on July 25, 2024. By September 13, 2024, Burundi had 516 Mpox confirmed cases, classifying it as the second most affected country in Africa after the DRC[8]. Mpox is a disease of global public health importance, as it affects not only countries in western and central Africa but also the rest of the world.

Burundi is located in the East African Community (EAC), a region with a tropical climate where some epidemics begin. It shares borders with DRC, Tanzania and Rwanda, which have faced many viral epidemics of Ebola, Marburg fever,

coronavirus disease 2019 (COVID-19) and Mpox[9,10]. Burundi has a fragile health system and is facing an enormous burden of infectious diseases such as malaria, HIV/AIDS, tuberculosis, hepatitis B and C and the most recent strain of COVID-19. Currently, it is facing an outbreak of cholera, and poliomyelitis outbreaks were announced more than 30 years ago[11,12]. Considering the important role played by healthcare workers (HCWs) in mitigating and preventing emerging diseases and outbreaks, we aimed to evaluate the level of knowledge and confidence that physicians and nurses have in diagnosing, treating, and managing Mpox.

MATERIALS AND METHODS

Study design

We conducted a cross-sectional study in which an online questionnaire was distributed to assess Mpox knowledge and confidence levels in the management of Mpox among HCWs in Burundi. An online survey with questions designed mainly from the WHO course "Mpox: Epidemiology, preparedness and response for African outbreak contexts" was conducted among Burundian HCWs from June-July 2023. The occupational categories that fit our definition of HCWs include medical doctor (MD), allied professions (laboratory, radiology technicians, physiotherapists, anesthesiologists, and pharmacists), nurses and midwives.

Population and sample size calculation

We used diverse authors' professional backgrounds to guarantee a representative sample that covers different healthcare groups. The sample size (n) was calculated according to the formula[13].

$n = [z2 \times p \times (1 - p)/e^2]/[1 + (z2 \times p \times (1 - p)/(e2 \times N))]$ where $Z = 1.96$ for a confidence level (α) of 95%, p = proportion (expressed as a decimal), N = population size, e = margin of error. Overall, we collected data from a total sample of 471 HWCs, including 301 MDs, 128 HWCs from allied professions, and 142 nurses and midwives.

Data collection and analysis

A questionnaire translated into French, the official language in Burundi, was distributed online *via* the Kobo toolbox. The questionnaire comprises 8 socioprofessional-related items, 22 questions about Mpox disease knowledge, and 3 questions to assess confidence in Mpox management (Supplementary material). Participants were required to answer all questions to avoid item nonresponse bias. We used a random sampling method based on chain referrals that targeted mainly HCW groups online. To maximize the chance of questionnaire distribution and avoid selection bias, we started with the authors' contacts and other online platforms, such as Facebook, Twitter, Instagram and direct messaging on WhatsApp, Gmail and Messenger. The last method helped to include a large number of older HCWs who may be not comfortable with online surveys. We analyzed the data *via* IBM SPSS, version 25.0. Chi-square tests and logistic regression analyses were used as appropriate. The statistical significance level was set at a P value < 0.05.

RESULTS

The study participants were mainly male (83.7%) and relatively young, with 72.6% being under 40 years old. They are mainly MDs (63.9%) and nurses (30.1%) working in the capital (60.9%). Many of them work in public health facilities (63.3%) (Table 1).

None of the 22 questions concerning Mpox knowledge had at least 50% correct responses. Some questions related to whether Mpox and smallpox have similar signs and symptoms received a high percentage of incorrect responses (71.8%). Many participants in this study were not aware of Mpox vaccination (74.3%) or of how Mpox specimens are transported after sampling (58.6%), as shown in Figure 1.

The confidence level to diagnose (21.20%), treat (18.00%) or prevent (23.30%) Mpox was low among Burundi HCWs (Figure 2).

Overall, confidence in diagnosing, treating or preventing Mpox was greater in young (< 40 years old) HCWs than in HCWs who were more than 40 years old (17.3% *vs* 3.6% for diagnosis, 14.6% *vs* 3.4% for treatment and 17.6% *vs* 4.7% for prevention).

As shown in Table 2, the confidence level in diagnosing Mpox was associated with the HCWs' age ($\chi^2 = 6.889$, P value = 0.009), sex ($\chi^2 = 12.603$; P value < 0.001), work experience ($\chi^2 = 9.381$; P value = 0.002), and residence ($\chi^2 = 13.766$; P value < 0.001). The confidence level in managing Mpox was significantly associated with the HCWs' age ($\chi^2 = 3.826$; $P = 0.050$), sex ($\chi^2 = 18.025$; P value < 0.001), education ($\chi^2 = 6.833$; P value = 0.033) and occupation ($\chi^2 = 10.723$; P value = 0.005). The confidence level in preventing Mpox was significantly associated with the HCWs' education ($\chi^2 = 18.396$; P value < 0.001), work experience ($\chi^2 = 9.406$; P value = 0.002), residence ($\chi^2 = 14.913$; P value < 0.001) and type of work institution ($\chi^2 = 11.889$; P value = 0.003).

All factors that were correlated with confidence in diagnosing, treating or preventing Mpox (P value < 0.05) were included in the binary logistic regression analysis model as explanatory variables, with their corresponding P values, odds ratios and 95% confidence intervals. The confidence in diagnosing Mpox in males was significantly greater than that in females ($P = 0.001$, OR = 0.350), almost two times greater in AS than in MD (P value = 0.040, OR = 2.827) and two times greater in HCWs from the capital than in those from out of the capital (P value = 0.003, OR = 2.337). The confidence level in treating Mpox was significantly greater in male HCWs than in female HCWs (P value = 0.001, OR = 0.328) and almost

Table 1 Socio-professional characteristics of Burundi healthcare workers

Variable		Frequency	Percentage (%)
Gender	Female	77	16.3
	Male	394	83.7
Age (years)	< 40	342	72.6
	≥ 40	129	27.4
Experience in (years)	≤ 5	165	35.03
	> 5	306	64.97
Residence	Capital	287	60.9
	Out of capital	184	39.1
Profession	Nurses and midwives	142	30.1
	Allied professions	28	5.9
	Medical doctor	301	63.9
Affiliation	Clinical facility	298	63.3
	Administrative facility	173	36.7
Health facility type	Public	352	74.7
	Private	66	14.0
	NGO	53	11.3
Education level	Secondary	60	12.7
	Graduate	310	65.8
	Postgraduate	101	21.4

NGO: Non-government organization.

three times greater in MD HCWs than in other HCWs (P value = 0.028, OR = 3.118). Additionally, confidence in preventing Mpox was significantly greater in HCWs with postgraduate education levels than in those with other education levels (P value = 0.032, OR = 3.556), in HCWs working in the capital than in those working outside the capital (P value = 0.001, OR = 2.611), in HCWs with more than 5 years of work experience than in those with no more than 5 years of experience (P value = 0.012, OR = 0.514), and in HCWs working in public health institutions than in those working in private or nongovernment health institutions (P value = 0.017, OR = 0.300) (Table 3).

A deep cause analysis of factors that independently influence confidence levels in diagnosing, treating, and preventing Mpox among Burundi HCWs revealed that sex was a significant factor for confidence in both diagnosing and treating Mpox, with males having higher confidence level. Residence in the capital was a strong predictor of confidence in both diagnosing and preventing Mpox. Education level plays a critical role in HCWs' confidence in preventing Mpox, particularly for those with postgraduate education. Experience and type of institution were important for having confidence in preventing Mpox, with more experienced HCWs and those in public health institutions showing higher confidence levels.

DISCUSSION

Since 2005, thousands of suspected cases of Mpox have been reported in the DRC every year. Before the 2022 outbreak, Mpox was reported in people in several central and western African countries. Previously, almost all Mpox cases in people outside Africa were linked to international travel to countries where the disease commonly occurs or through imported animals. These cases occurred on multiple continents[14]. From January 1, 2022 through November 30, 2023, a cumulative total of 92783 Laboratory-confirmed cases of Mpox, including 171 deaths, were reported to the WHO from 116 countries/territories/areas in all six WHO regions. The DRC is a country in East Africa Community that shares borders with Burundi. A high level of transmission occurs in the country, as reflected by the high number of suspected (clinically compatible) cases reported[15].

Considering the crucial role played by HCWs in the prevention and management of emerging infectious diseases, this study aimed to assess Burundi HCWs' knowledge of and confidence in diagnosing, treating, and preventing Mpox. It also aimed to understand conspiracy beliefs about emerging viral diseases among Burundi HCWs. The sample included 471 HCWs who were mainly male (83.7%) and relatively young, 72.6% of whom were under 40 years old. Many of them were MDs (63.9%) and nurses (30.1%) working in the capital (60.9%) or public health facilities (63.3%).

Table 2 Correlation analysis of factors associated to confidence level to diagnose, treat or prevent mpox among Burundi healthcare workers

Variables		Confidence to diagnose		Confidence to treat		Confidence to prevent	
		No *n* (%)	Yes *n* (%)	No *n* (%)	Yes *n* (%)	No *n* (%)	Yes *n* (%)
Age	< 40	259 (55.0)	83 (17.3)	273 (58.0)	69 (14.6)	259 (55.0)	83 (17.6)
	≥ 40	112 (23.8)	17 (3.6)	113 (24.0)	16 (3.4)	107 (22.7)	22 (4.7)
		χ^2 = 6.889; [a]*P* = 0.009		χ^2 = 3.826; [a]*P* = 0.050		χ^2 = 2.815; *P* = 0.093	
Education	Secondary	50 (10.5)	10 (2.1)	42 (8.9)	18 (3.8)	52 (11.0)	8 (1.7)
	Graduate	239 (50.7)	71 (15.1)	258 (54.8)	52 (11)	251 (53.3)	59 (12.5)
	Postgraduate	82 (17.4)	19 (4.0)	86 (22.3)	15 (17.6)	63 (17.2)	38 (21.4)
		χ^2 = 1.619; *P* = 0.445		χ^2 = 6.833; [a]*P* = 0.033		χ^2 = 18.396; [a]*P* < 0.001	
Occupation	Nurse	114 (24.2)	28 (5.9)	110 (23.4)	32 (6.8)	115 (24.4)	27 (5.7)
	AS	17 (3.6)	11 (23.0)	18 (3.8)	10 (2.1)	18 (3.8)	10 (2.1)
	MD	240 (51.0)	61 (13.0)	258 (54.8)	43 (9.1)	233 (49.5)	68 (14.4)
		χ^2 = 5.820; *P* = 0.054		χ^2 = 10.723; [a]*P* = 0.005		χ^2 = 3.108; *P* = 0.149	
Experience	≤ 5 years	117 (24.8)	48 (10.2)	135 (28.7)	30 (6.4)	115 (24.4)	50 (10.6)
	> 5 years	254 (53.9)	52 (11.0)	251 (53.3)	55 (11.7)	251 (53.3)	55 (11.7)
		χ^2 = 9.381; [a]*P* = 0.002		χ^2 = 0.003; *P* = 0.955		χ^2 = 9.406; [a]*P* = 0.002	
Gender	Female	49 (10.4)	28 (5.9)	50 (10.6)	27 (5.7)	61 (13.0)	16 (3.4)
	Male	322 (68.4)	72 (15.3)	336 (71.3)	58 (12.3)	305 (64.8)	89 (18.9)
		χ^2 = 12.603; [a]*P* < 0.001		χ^2 = 18.025; [a]*P* < 0.001		χ^2 = 0.122; *P* = 0.727	
Residence	Capital	210 (44.6)	77 (16.3)	230 (48.8)	57 (12.1)	206 (43.7)	81 (17.2)
	Out capital	161 (34.2)	23 (4.9)	156 (33.1)	28 (5.9)	160 (34.0)	24 (5.1)
		χ^2 = 13.766; [a]*P* < 0.001		χ^2 = 1.634; *P* = 0.201		χ^2 = 14.913; [a]*P* < 0.001	
Affiliation	Clinical facility	237 (50.3)	61 (13.0)	240 (51.0)	58 (12.3)	233 (49.5)	65 (13.8)
	Administrative	134 (28.5)	39 (8.3)	146 (31.0)	27 (5.7)	133 (28.2)	40 (8.5)
		χ^2 = 0.281; *P* = 0.596		χ^2 = 1.100; *P* = 0.294		χ^2 = 0.108; *P* = 0.742	
Institution	Public	283 (60.1)	69 (14.6)	286 (60.7)	66 (14.0)	260 (55.2)	92 (19.5)
	Private	48 (10.2)	18 (3.8)	54 (11.5)	12 (2.5)	59 (12.5)	7 (1.5)
	ONGs	40 (8.5)	13 (2.8)	46 (9.8)	7 (1.5)	47 (10.0)	6 (1.3)
		χ^2 = 2.343; *P* = 0.310		χ^2 = 0.958; *P* = 0.619		χ^2 = 11.889; [a]*P* = 0.003	
Total		371	100	386	85	366	105

[a]*P* < 0.05.

To assess the level of knowledge about Mpox, we chose 22 knowledge questions about Mpox epidemiology, diagnosis, treatment and prevention from the WHO course on Mpox[16]. None of the 22 questions concerning Mpox knowledge had at least 50% correct responses. Some questions related to whether Mpox and smallpox have similar signs and symptoms received a high percentage of incorrect responses (71.8%). Many participants (74.3%) in this study were not aware of Mpox vaccination or of how Mpox specimens are transported after sampling (58.6%). A similar result was reported by Riccò *et al*[17] in Italy and Sahin *et al*[18] in Turkey, stating that knowledge status was quite unsatisfactory, with substantial knowledge gaps in all aspects of Mpox. Our results are revealed even more substantial knowledge gaps compared to the results reported in the Middle East, where four out of 11 Mpox knowledge questions had more than 70% correct responses and 33.3% of the study respondents knew that vaccination is available to prevent Mpox, and those of Dong *et al*[19] in China, where 53.9% of participants were categorized as having greater knowledge of Mpox. However, the knowledge level in our study was greater than that in the study conducted by Harapan *et al*[20] in Indonesia, where only 10% of the study respondents had good knowledge of Mpox use. This difference in knowledge level may be because our study was conducted during the Mpox outbreak, which is not the case for the above-cited study. In addition, a very low number of HCWs (17.3%) knew that Mpox had a vaccine. For the prevention of smallpox and Mpox disease in adults

Table 3 Logistic regression analysis model of factors associated to the confidence level to diagnose, treat and prevent mpox

Independent Variables	Dependent variables								
	Confidence to diagnose			Confidence to treat			Confidence to prevent		
	P	OR	CI	*P*	OR	CI	*P*	OR	CI
Age	0.149	0.637	0.345-0.176	0.275	0.703	0.374-1.323	0.425	0.787	0.436-1.419
Gender	[a]0.001	0.350	0.186-0.660	[a]0.001	0.328	0.173-0.621	0.935	0.971	0.480-1.963
Education	0.743	1.179	0.440-3.158	0.789	0.855	0.271-2.701	[a]0.032	3.556	1.118-11.313
Occupation	[a]0.040	2.827	1.046-7.39	[a]0.028	3.118	0.128-8.615	0.165	0.632	0.331-1.208
Residence	[a]0.003	2.337	1.335-4.090	0.102	1.624	0.909-2.904	[a]0.001	2.611	1.481-4.605
Experience	0.117	0.660	0.393-1.109	0.768	1.090	0.614-1.937	[a]0.012	0.514	0.305-0.864
Affiliation	0.979	1.008	0.557-1.826	0.672	0.871	0.459-1.652	0.799	1.075	0.617-1.873
Institution	0.525	1.298	0.582-2.896	0.608	0.778	0.299-2.026	[a]0.017	0.300	0.112-0.805

[a]$P < 0.05$.

18 years of age and older, who are at high risk for smallpox or Mpox infection, JYNNEOS is an Food and Drug Administration-approved vaccine[21,22]. These findings suggest that the JYNNECOS vaccine is effective in preventing Mpox disease and that two doses provide better protection[23].

The confidence level to diagnose, treat or prevent Mpox was generally low among our study participants (21.20%, 18.00%, and 23.30%, respectively). In contrast, it is more common in young HCWs (17.3% *vs* 3.6% for diagnosis, 14.6% *vs* 3.4% for treatment and 17.6% *vs* 4.7% for prevention), although they were born and have lived in the postsmallpox eradication era, with a declining focus on poxviruses in education and training[17,20,24,25]. A low confidence level was also observed in Indonesia by Harapan *et al*[20]. Only a small percentage (10.1%) of general practitioners had good confidence in the ability to diagnose and treat Mpox in a clinical setting[20]. Confidence level in diagnosing Mpox was associated with the HCWs' age ($\chi^2 = 6.889$, *P* value = 0.009), sex ($\chi^2 = 12.603$; *P* value < 0.001), work experience ($\chi^2 = 9.381$; *P* value = 0.002), and residence ($\chi^2 = 13.766$; $P < 0.001$). The confidence level in managing Mpox was significantly associated with the HCWs' age ($\chi^2 = 3.826$; *P* value = 0.050), sex ($\chi^2 = 18.025$; *P* value < 0.001), education ($\chi^2 = 6.833$; *P* value = 0.033) and occupation ($\chi^2 = 10.723$; *P* value = 0.005). The confidence level in preventing Mpox was significantly associated with the HCWs' education ($\chi^2 = 18.396$; *P* value < 0.001), work experience ($\chi^2 = 9.406$; *P* value = 0.002), residence ($\chi^2 = 14.913$; *P* value < 0.001) and type of work institution ($\chi^2 = 11.889$; *P* value = 0.003). In the studies performed by Sallam *et al*[26] in Jordan and Harapan *et al*[20] in Indonesia, low confidence levels in the diagnosis and management of Mpox were attributed to the relatively young age of HCWs, with subsequent lower confidence in medical practice.

We further conducted a logistic regression analysis model of factors associated with confidence level to diagnose, treat and prevent Mpox. Our results revealed that confidence in the ability to diagnose and treat Mpox was significantly greater in males than in females. The confidence level in diagnosing and preventing Mpox was significantly greater in HCWs working in capital than in those working out in capital. This may be due not only to differences in access to medical information but also to the fact that the capital, Bujumbura, directly shares borders with RDCs where Mpox began and faced many Mpox outbreaks[17,27,28]. The confidence in diagnosing Mpox is almost two times greater in medical allied sciences professionals than in MD professionals and nurses (*P* value = 0.040, OR = 2.827). This is because HCW workers are included in this category and most of them are laboratory technologists who may possess more information on disease laboratory diagnosis, including Mpox. The confidence level for treating Mpox was almost three times greater in the MD than in the other HCWs (*P* value = 0.028, OR = 3.118). This is related to their occupation, as in the Burundi health system, decisions to treat and treatment protocols are made by the MD. Additionally, the confidence level for preventing Mpox was significantly greater in HCWs with a postgraduate education level than in those with other education levels (*P* value = 0.032, OR = 3.556), in HCWs working in the capital than in those working outside capital (*P* value = 0.001, OR = 2.611), in HCWs with more than 5 years of work experience than in those with no more than 5 years of experience (*P* value = 0.012, OR = 0.514), and in HCWs working in public health institutions than in private or nongovernment health institutions (*P* value = 0.017, OR = 0.300). This is due to more opportunities to participate in seminars or continuing medical education (CME) that involve HCWs in public health facilities. These seminars are funded by the government itself *via* the Ministry of Health or its partners, such as the WHO and Family Health International (FHI 360) [27,28]. A previous study has shown that attending conferences and receiving data during CME helps with better confidence acquisition[20,29].

Limitations

Most positive Mpox cases during the 2022/2023 outbreak were identified among gay, bisexual, and other men who have sex with men (GBMSM)[30]. Our study did not analyze conspiracy beliefs among HCWs about GBMSM. This phenomenon should be evaluated further, especially in the EAC region, where it has been shown that stigma for the GBMSM community can have a negative impact on the management of other emerging viral diseases, such as HIV/AIDS

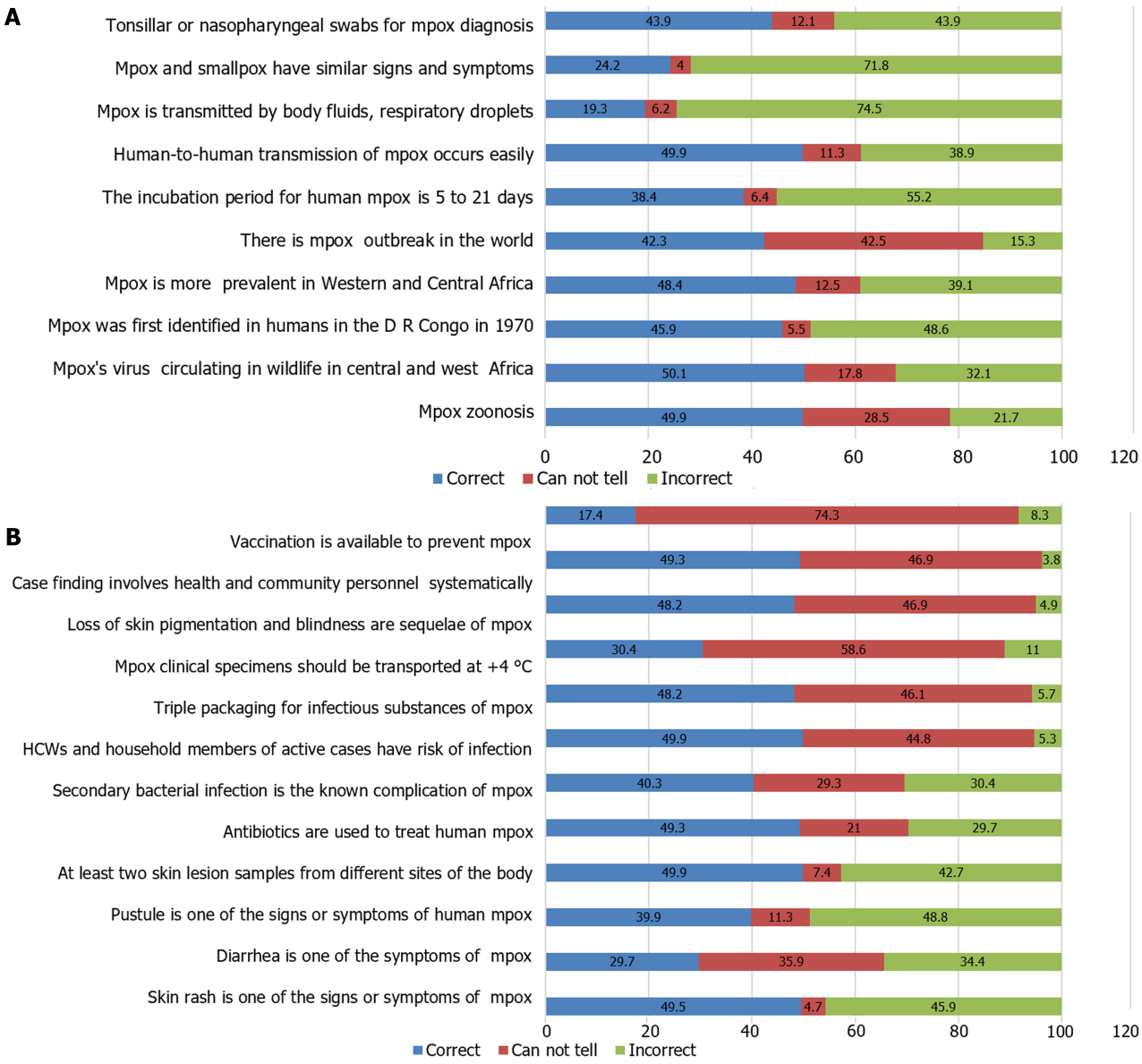

Figure 1 Knowledge level of Burundi healthcare workers about mpox per item. A: Knowledge on mpox history and transmission; B: Knowledge on mpox diagnosis, treatment and vaccination.

and COVID-19[31-33]. Hesitancy toward the COVID-19 vaccine was observed in Burundi, as in other African countries, whereas the Chinese population has demonstrated a willingness to receive the Mpox vaccine[34]. This study evaluated Burundi HCWs' level of knowledge and confidence in the diagnosis and management of Mpox, which are considerations of subjective perception. We encourage further studies to assess potential hesitancy toward Mpox vaccination and its associated factors as well as objective analysis of the diagnostic and management capacity of Mpox, such as institutional setup, staffing, medical conditions, emergency response, or the fragility of the health system.

CONCLUSION

To the best of our knowledge, this study was conducted in a region that has faced many deadly epidemics of viral diseases, such as Ebola, Marburg, HIV, and COVID-19. The results revealed a low level of knowledge and confidence in the ability to diagnose, treat and prevent Mpox. It will then constitute a first scientific database for researchers, health system partners, and policymakers to prepare EAC and the international community to mitigate an eventual Mpox epidemic. Finally, we encourage future studies to assess potential causes of stigma to populations at high risk of emerging infectious diseases and hesitancy toward Mpox vaccination and its associated factors.

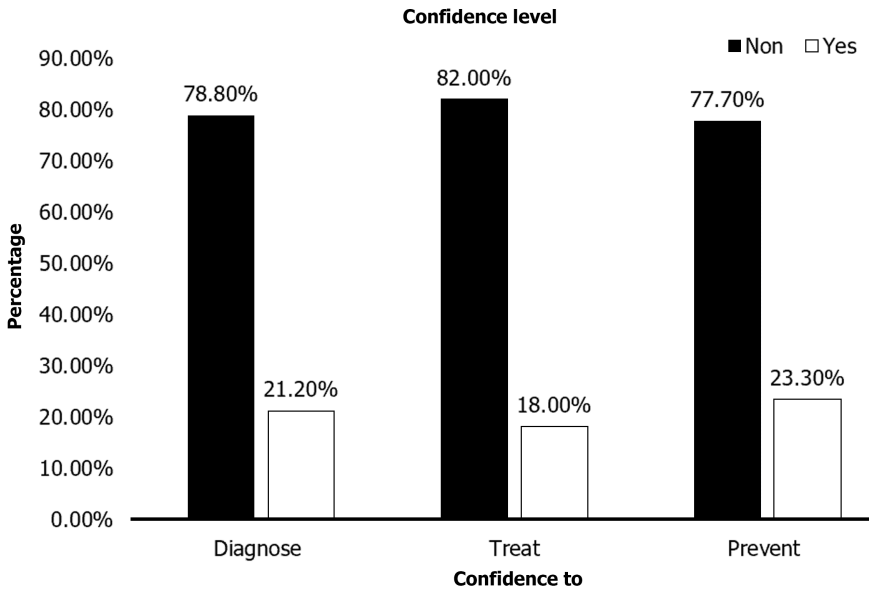

Figure 2 Confidence level to diagnose, treat or prevent mpox among Burundi healthcare workers.

FOOTNOTES

Author contributions: Ntawuyamara E and Ingabire T performed conceptualization and manuscript writing; Yandemye I analyzed data; Ndayiza P and Bhandari B wrote methodology; Liang YH supervised all research activities. All authors have read and approved the final manuscript.

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CASE REPORT

Lipomatous ependymoma with ZFTA: RELA fusion-positive: A case report

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Abstract

BACKGROUND

Ependymoma with lipomatous differentiation is a rare type of ependymoma. The ZFTA fusion-positive supratentorial ependymoma is a novel tumor type in the 2021 World Health Organization classification of central nervous system tumors. ZFTA fusion-positive lipomatous ependymoma has not been reported to date.

CASE SUMMARY

We reported a case of a 15-year-old Chinese male who had a sudden convulsion lasting approximately six minutes. Magnetic resonance imaging showed a round cystic shadow of approximately 1.9 cm × 1.5 cm × 1.9 cm under the right parieto-occipital cortex. Microscopic examination showed characteristic perivascular pseudorosettes and adipose differentiation in the cytoplasm. Immunohistochemical staining showed that the tumor cells were negative for cytokeratin, NeuN, Syn and p53, but positive for GFAP, vimentin and S-100 protein. Significant punctate intracytoplasmic EMA immunoreactivity was observed. The level of Ki-67 was about 5%. Genetic analysis revealed ZFTA: RELA fusion. A craniotomy with total excision of the tumor was performed. The follow-up time was 36 months, no evidence of disease recurrence was found in magnetic resonance imaging.

CONCLUSION

Based on these findings, the patient was diagnosed as a ependymoma with ZFTA fusion and lipomatous differentiation. This case report provides information on the microscopic morphological features of ependymoma with ZFTA fusion and lipomatous differentiation, which can help pathologists to make a definitive diagnosis of this tumor.

Key Words: Ependymoma; Lipomatous; Molecular classification; Supratentorial; ZFTA: RELA fusion; Case report

Core Tip: Ependymoma with lipomatous differentiation is a rare type of ependymoma. The ZFTA fusion-positive supratentorial ependymoma is a novel tumor type in the 2021 World Health Organization classification of central nervous system tumors. ZFTA fusion-positive lipomatous ependymoma has not been reported to date. This case report provides information on the microscopic morphological features of ependymoma with ZFTA fusion and lipomatous differentiation, and highlights the possibility that ZFTA fusion and lipomatous differentiation may co-occur, adding a new layer to the molecular classification of ependymomas.

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INTRODUCTION

Ependymoma with lipomatous differentiation is a rare type of ependymoma, characterized by well-defined lipomatous differentiation, whose biological behavior is generally considered to be World Health Organization (WHO) grade 2[1-5]. ZFTA (formerly known as C11orf95) fusion-positive supratentorial ependymoma is a new tumor type listed in the 2021 WHO classification of central nervous system (CNS) tumors[6-8]. To the best of our knowledge, there are no reports of lipomatous ependymoma with ZFTA fusion-positive. After obtaining informed consent from the patient and the legal guardian, we discussed one such rare case and reviewed the existing literature to provide further insights into the clinicopathological nature of this rare tumor.

CASE PRESENTATION

Chief complaints

The patient is a 15-year-old Chinese male who presented with a sudden convulsion lasting approximately six minutes without an apparent cause.

History of present illness

A 15-year-old boy was admitted to the Department of Neurosurgery at our hospital who presented with a sudden convulsion lasting approximately six minutes without an apparent cause. Magnetic resonance imaging (MRI) showed a round cystic shadow of approximately 1.9 cm × 1.5 cm × 1.9 cm under the right parieto-occipital cortex, with a regular envelope, clear and smooth margins, and slightly compressed surrounding brain tissue.

History of past illness

The patient had been previously healthy.

Personal and family history

No obvious abnormalities were found in the personal and family history.

Physical examination

The patient's physical examination reveals no abnormalities.

Laboratory examinations

The resected specimens were fixed with 10% neutral-buffered formalin and embedded in paraffin blocks. Then tissue blocks were cut into 4 μm sections, deparaffinized in xylene, rehydrated with graded alcohols, and immunostained with the following antibodies: Cytokeratin, GFAP, S-100 protein, vimentin, synaptophysin (Syn), oligodendrocyte transcription factor 2 (Olig-2), neuronal nuclear antigen (NeuN), epithelial membrane antigen (EMA), D2-40, tumor protein 53 (p53), alpha-thalassemia/mental retardation syndrome X and Ki-67 (MaiXin, China). The samples were counterstained with hematoxylin, dehydrated and then mounted. The negative controls were incubated with phosphate-buffered saline (PBS), pH 7.4 instead of the primary antibody, as described above.

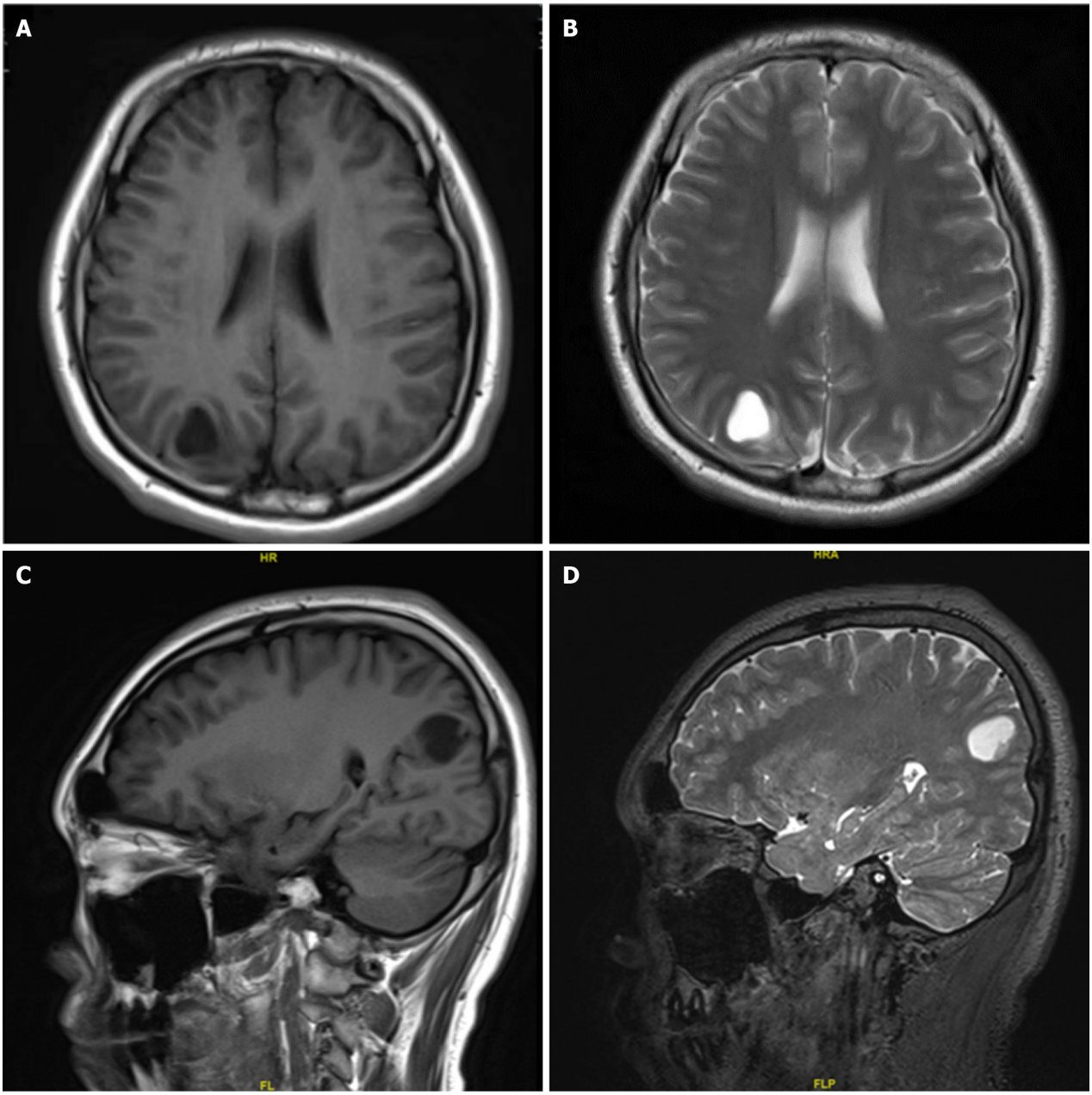

Figure 1 Magnetic resonance imaging showed a cystic mass of about 1.9 cm × 1.5 cm × 1.9 cm under the cortex of the right parietal occipital lobe, with a uniform long T1 and long T2 signal. The cystic mass was regular, the edges were clear and smooth, and the surrounding brain tissue was slightly compressed. The remaining brain parenchyma showed no abnormal signal shadows. A: Axial T1; B: Axial T2; C: Sagittal T1; D: Sagittal T2.

Imaging examinations

MRI showed a round cystic shadow of approximately 1.9 cm × 1.5 cm × 1.9 cm under the right parieto-occipital cortex, with a regular envelope, clear and smooth margins, and slightly compressed surrounding brain tissue (Figure 1).

MULTIDISCIPLINARY EXPERT CONSULTATION

Pathological findings

Microscopic examination showed that the tissue boundary in the cystic wall-like structure was clear, and density of tumor cells in the cyst cavity was moderate, with no obvious necrosis. Calcifications were seen on the cyst wall, and large vacuoles were seen in the cytoplasm of tumor cells on the cyst wall. Characteristic perivascular pseudorosettes were seen. We also observed localized vascular endothelial cell proliferation, resembling a glomerular structure. The tumors were irregularly arranged and primarily sheet-like, and the cytoplasm of most tumor cells contained large vacuoles of different sizes, pushing the crescentic nucleus along the cell membrane to the periphery, similar to signet ring cells. The mitosis was rare (Figure 2). Immunohistochemical staining showed that the tumor cells were negative for cytokeratin, NeuN, Syn and p53, but positive for GFAP, vimentin and S-100 protein. The tumor cells were negative and individual cells were

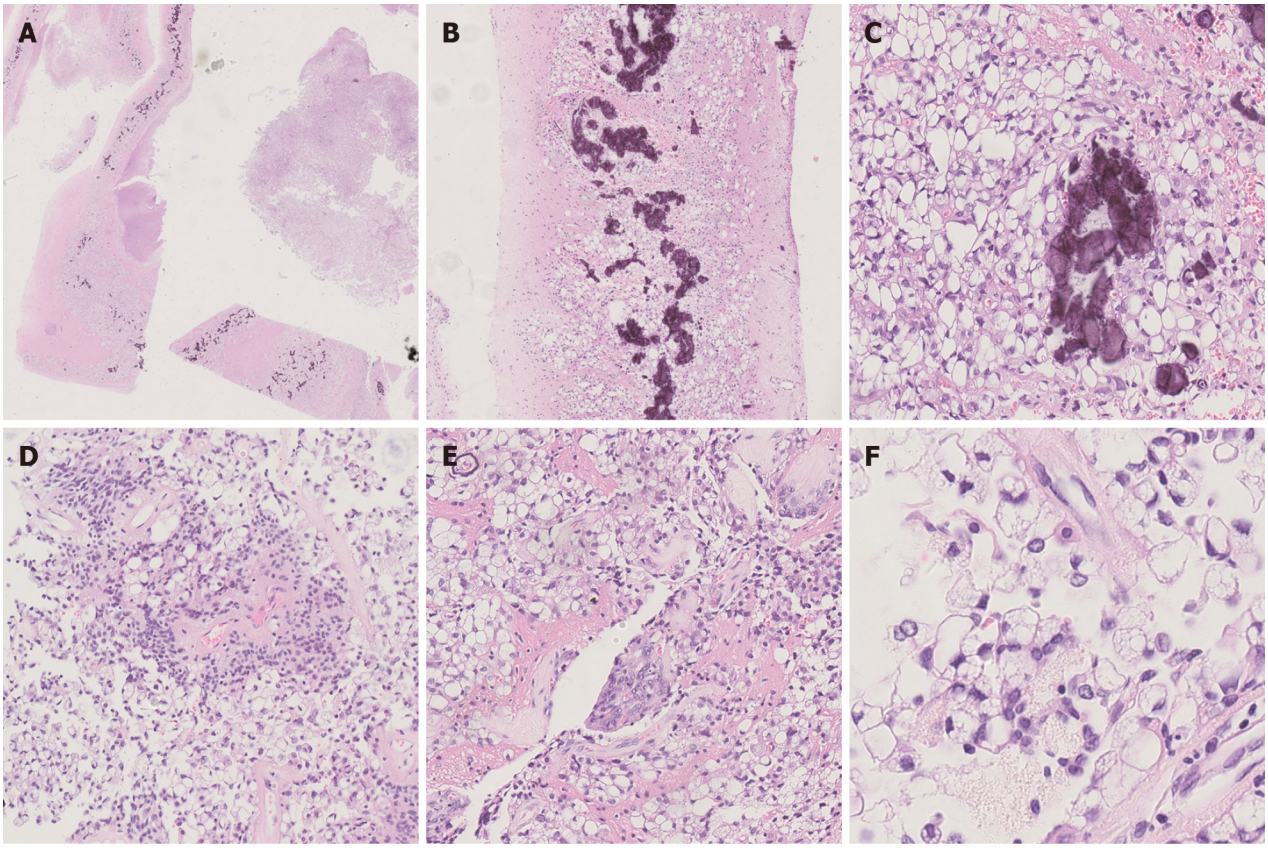

Figure 2 Histopathological findings. A: The tissue boundary in the cystic wall-like structure was clear [hematoxylin and eosin (HE) × 40]; B: Calcifications were seen on the cyst wall (HE × 100); C: Large vacuoles were seen in the cytoplasm of tumor cells on the cyst wall (HE × 400); D: Characteristic perivascular pseudorosettes (HE × 200); E: Vascular endothelial cell proliferation was seen, resembling a glomerular structure (HE × 200); F: Vacuoles in the cytoplasm pushed the crescentic nucleus, similar to signet ring cells (HE × 1000).

positive for Olig-2. Moreover, significant punctate intracytoplasmic EMA immunoreactivity was observed. The level of Ki-67 immunoreactivity was about 5% (Figure 3).

Genetic findings

Total DNA was extracted from formalin-fixed, paraffin-embedded sections. The targets of examined genes or chromosomes were IDH1 (R132), IDH2 (R172), TERT, BRAF, H3F3A/HIST1H3B/HIST1H3C, ATRX, TP53, EGFR, CDKN2A/B, RELA, YAP1, MYB, 1p/19q, chromosome 7 and chromosome 10.

Genetic analysis revealed ZFTA: RELA fusion (Figure 4), while no homozygous deletion of CDKN2A and/or CDKN2B, mutations in IDH1 or IDH2, TERT promoter mutations, KIAA1549-BRAF fusion or deletion of 1p/19q were found.

FINAL DIAGNOSIS

Based on these findings, the patient was diagnosed as WHO grade 2 ependymoma with ZFTA fusion and lipomatous differentiation.

TREATMENT

A craniotomy with total excision of the tumor was performed.

OUTCOME AND FOLLOW-UP

The follow-up time was 36 months, no evidence of disease recurrence was found in MRI.

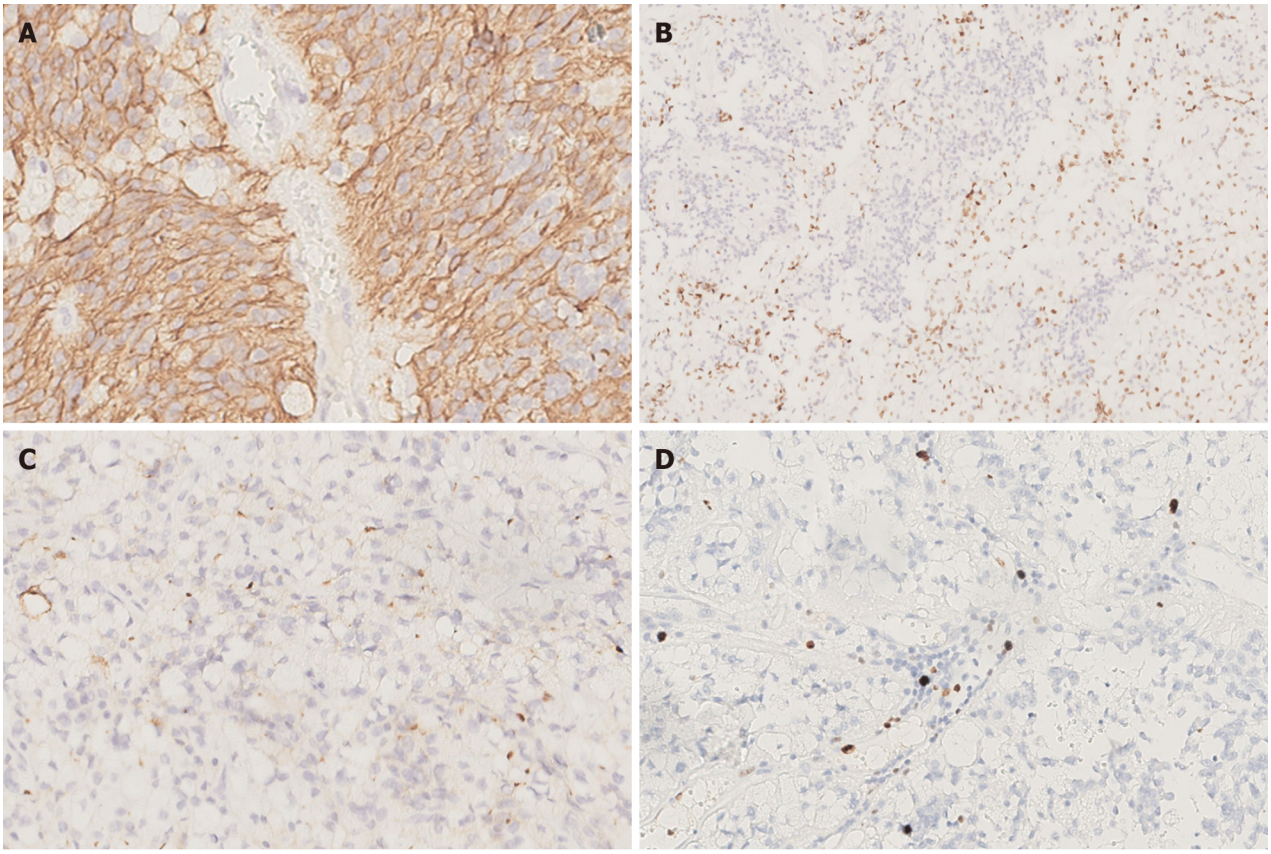

Figure 3 Immunohistochemistry findings. A: The tumor cells were positive for GFAP [Immunohistochemistry (IHC) × 400]; B: Individual cells were positive for Olig-2 (IHC × 200); C: Significant punctate intracytoplasmic EMA immunoreactivity was observed (IHC × 400); D: The Ki-67 proliferation index was about 5% (IHC × 400).

DISCUSSION

Ependymoma is a relatively rare CNS tumor that originates in the spina ventricles or central canal as a glioma composed of tumorigenic ventricular meningeal cells that can occur at any age, but is more common in children. Ependymomas account for 2% of all CNS tumors and 3%-5% of gliomas in adults[9]. Among them, ependymoma with lipomatous differentiation is a more rare histological type seen in young patients, mainly in the supratentorial (ST) location. Ruchoux *et al* [5] in 1998 first described three cases of classical ependymoma with lipomatous differentiation. Histologically, scattered single or patchy mature adipose-like cells were seen. The vacuoles within the tumor cells varied in size but were all single. The nucleus was pushed to the periphery by a large single cytoplasmic vesicle, which formed a ring-like pattern.

The accompanying lipomatous changes may be due to differentiation or disturbance of cellular metabolism rather than as a result of metaplasia[2]. The vacuoles in ependymoma were thought to be microrosettes and degenerated and swollen cytoplasmic processes of tumor cells[3]. The diagnosis of ependymoma with lipomatous differentiation requires differentiation from other intracranial tumors with lipomatous differentiation. In primary CNS tumors, tumor cell adipocyte differentiation morphology is mainly seen in meningiomas, medulloblastomas and neurocytomas[10-12]. Lipomatous meningioma microscopic presentation typically shows a meningioma-like region and adipocyte-like cell mixture. It can be identified by immunomarkers such as GFAP and somatostatin receptor 2 (SSTR2). The latter two types of tumors generally have neuronal differentiation and are therefore easier to distinguish by histopathological observation and immunomarkers.

According to research statistics, half of the lipomatous ependymomas reported to date have recurred, the follow-up duration is 8 months to 4 years, and most cases were histological grade 3[1]. The current case showed no necrosis and the Ki-67 index was about 3%, so this case was classified as WHO grade 2. To date, only 30 cases of lipomatous ependymomas have been reported worldwide[4], so the relationship between the presence or absence of adipose differentiation and the prognosis of ependymoma remains unclear[1,2]. Since both lipomatous ependymoma and ependymoma with ZFTA fusion-positive are rare, and this report is the first case of lipomatous ependymoma with ZFTA fusion-positive, so the relationship between the presence or absence of adipose differentiation and ependymoma with ZFTA fusion-positive remains unclear.

Before 2015, the classification of ependymal tumor was mainly based on histopathological features, which was classified as WHO grade 1-3. However, the correlation between this grade and prognosis is unclear, and it cannot effectively judge and predict the malignancy of tumors and the survival of patients[13]. Moreover, ependymal tumors show significant heterogeneity in their histopathological and molecular characteristics, so it is difficult to obtain a definitive diagnosis primarily based on morphology. Histopathological variants described separately in the 2016 WHO

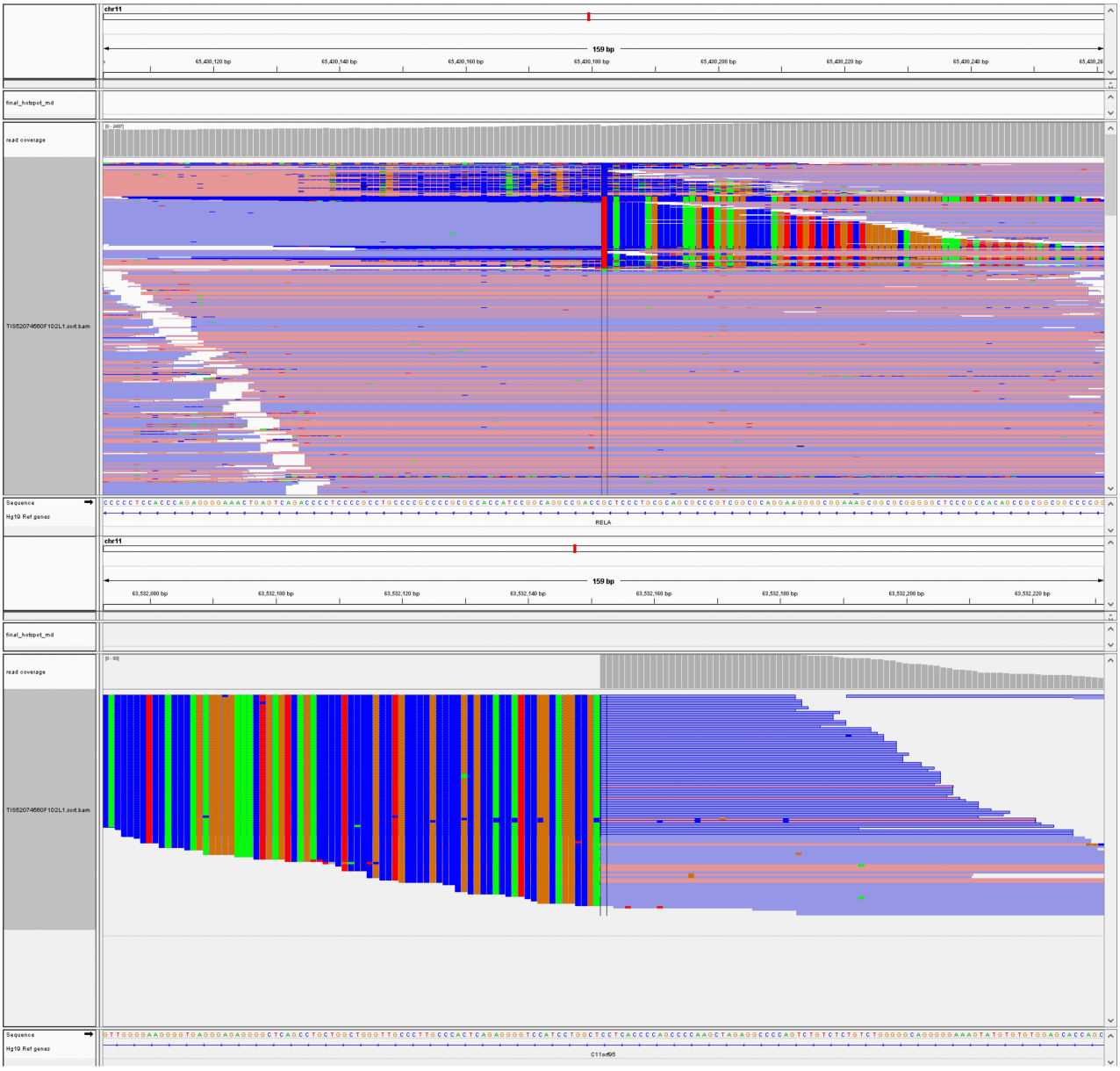

Figure 4 Genetic analysis revealed ZFTA: RELA fusion.

classification of CNS tumors are no longer classified as subtypes of ependymoma because it has been recognized that tanycytic, papillary, or clear cell morphology has no clinical value by itself[14].

Recent large-scale genome sequencing studies of ependymal tumor identified nine molecular subsets associated with different genomic alterations, clinical behavior, age distribution, and anatomical locations[15]. The 2021 WHO classification of the CNS is a new classification system for ependymal tumors based on the anatomical location and molecular characteristics of CNS tumors[6-8]. Based on the results obtained by genetic and epigenetic profiling studies, there are at least nine molecular groups of ependymal tumors in three CNS locations[16]. ST ependymoma has two high-frequency fusion genes, ZFTA: RELA fusion and YAP1: MAMLD1 fusion. Parker *et al*[17] found that ZFTA: RELA fusion of the 11q chromosome was the most recurrent genetic alteration in ependymoma, affecting more than 70% of ST tumors and predominantly occurring in older patients, which may be caused by chromothripsis. ZFTA: RELA fusion is capable of cellular transformation and tumor initiation when expressed in the developing mouse brain or when neural stem cells are expressed after transplantation[17]. RELA is a well-known major transcription factor in the NF-κB pathway, which is intimately associated with various pathophysiological processes such as inflammation and cancer[18]. While the normal molecular function of the ZFTA protein is currently unknown, studies have shown that the zinc finger domain of this gene plays an important role in the pathogenesis of tumors that may lead to new DNA binding and transcriptional regulation[17]. These findings suggest that the ZFTA: RELA fusion protein and its direct target gene may be candidates for therapy and may provide clues for future treatments.

Studies have found that ST ependymoma with ZFTA: RELA fusion-positive has a poor prognosis, and the survival rate of patients is remarkably lower than that of ST ependymoma with YAP1 fusion-positive[8,15]. Recent retrospective studies suggested that progression-free survival in ependymal tumor with non-RELA: ZFTA fusion-positive might be worse than in ependymal tumor with ZFTA: RELA fusion-positive[19]. Additionally, homozygous deletion of CDKN2A

on 9p21.3 is a powerful independent indicator of unfavorable prognosis[20]. In our patient, no homozygous deletion of CDKN2A was detected and no recurrence or metastasis was found for 36 months after surgery. The prognosis of ependymoma with ZFTA: RELA fusion-positive remains unknown.

CONCLUSION

In this paper, we reported the first case of lipomatous ependymoma with ZFTA fusion-positive. Since both lipomatous ependymoma and ependymoma with ZFTA fusion-positive are rare, more case reports and long-term follow-up studies are needed on the prognostic impact of adipose differentiation and ZFTA fusion-positive and whether they are linked.

FOOTNOTES

Author contributions: Zhao XY conception and design of study, drafting of manuscript and critical revision; Yu JH conception and design of study, approval of final version of manuscript; All authors have read and approved the final manuscript.

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CASE REPORT

Stage IV malignant transformation of mature cystic teratoma palliatively treated with concurrent chemoradiotherapy: A case report

Saori Kondo, Takashi Suzuki, Kanato Yoshiike, Sakura Yamanaka, Kenta Sonehara, Hiroshi Nabeshima, Osamu Oguchi

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Abstract

BACKGROUND

Malignant transformation (MT) of mature cystic teratoma (MCT) has a poor prognosis, especially in advanced cases. Concurrent chemoradiotherapy (CCRT) has an inhibitory effect on MT.

CASE SUMMARY

Herein, we present a case in which CCRT had a reduction effect preoperatively. A 73-year-old woman with pyelonephritis was referred to our hospital. Computed tomography revealed right hydronephrosis and a 6-cm pelvic mass. Endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB) revealed squamous cell carcinoma. The patient was diagnosed with MT of MCT. Due to her poor general condition and renal malfunction, we selected CCRT, expecting fewer adverse effects. After CCRT, her performance status improved, and the tumor size was reduced; surgery was performed. Five months postoperatively, the patient developed dissemination and lymph node metastases. Palliative chemotherapy was ineffective. She died 18 months after treatment initiation.

CONCLUSION

EUS-FNB was useful in the diagnosis of MT of MCT; CCRT suppressed the disease and improved quality of life.

Key Words: Mature cystic teratoma; Malignant transformation; Squamous cell carcinoma; Concurrent chemoradiotherapy; Endoscopic ultrasound-guided fine-needle biopsy; Case report

Core Tip: Malignant transformation (MT) of mature cystic teratoma (MCT) is uncommon and has a poor prognosis, especially in advanced cases. Surgery and chemotherapy are selected in accordance with ovarian cancer, but the prognosis is typically poor due to the high degree of malignancy, making treatment often challenging. We present a case of stage IV MT of MCT in which concurrent chemoradiotherapy (CCRT) had a reduction effect preoperatively. Endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB) was used for diagnosis due to the patient's poor general condition. EUS-FNB was useful in diagnosing MT of MCT; CCRT suppressed the disease and improved the patient's quality of life.

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INTRODUCTION

Malignant transformation (MT) of mature cystic teratoma (MCT) is uncommon, occurring in 0.17%-2% of MCTs[1]. There is no established treatment method; debulking surgery and multidrug chemotherapy are performed in accordance with epithelial ovarian cancer. However, the prognosis of advanced cancer is poor: the 2-year survival rate is approximately 30% for stage III and 0% for stage IV[2]. In some cases, due to systemic conditions or complications, adequate treatment is not available. We present a case of stage IV MT of MCT that was diagnosed using endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB) and palliatively treated with concurrent chemoradiotherapy (CCRT).

CASE PRESENTATION

Chief complaints

A 73-year-old multiparous woman was referred to the emergency department of our hospital with fever and right lower back pain.

History of present illness

Symptoms started 2 weeks before presentation.

History of past illness

She had a medical history of cerebral infarction, hypertension, hyperlipidemia, and benign left ovarian tumor.

Personal and family history

She denied any family history of malignancy.

Physical examination

On physical examination, the vital signs were as follows: Body temperature, 38.5 °C; blood pressure, 120/68 mmHg; heart rate, 82 beats per minute; respiratory rate, 20 breaths per minute. Internal examination revealed that the tumor was adhered to the pelvic wall and had poor mobility.

Laboratory examinations

The serum squamous cell carcinoma antigen level was 5.7 ng/mL, carcinoembryonic antigen level was 0.9 ng/mL, CA19-9 level was 26 U/mL, and CA125 level was 10.8 U/mL. The white blood cell count was 18200/μL, C-reactive protein level was 9.62 mg/dL, serum creatine level was 1.17 mg/dL, and the estimated glomerular filtration rate was 35 mL/min.

Imaging examinations

Ultrasonography revealed an irregular solid pattern and a small amount of ascitic fluid. Computed tomography (CT) revealed right hydronephrosis and a 68 cm × 64 cm × 45 mm solid cystic mass with fat and calcification densities in the right pelvic cavity. Chest CT showed multiple grain-sized nodules in both lungs. Magnetic resonance imaging (MRI) showed that the tumor was adhered to both the uterus and rectum, with a 1.5 cm peritoneal dissemination at the right pelvic wall near the ureter (Figure 1).

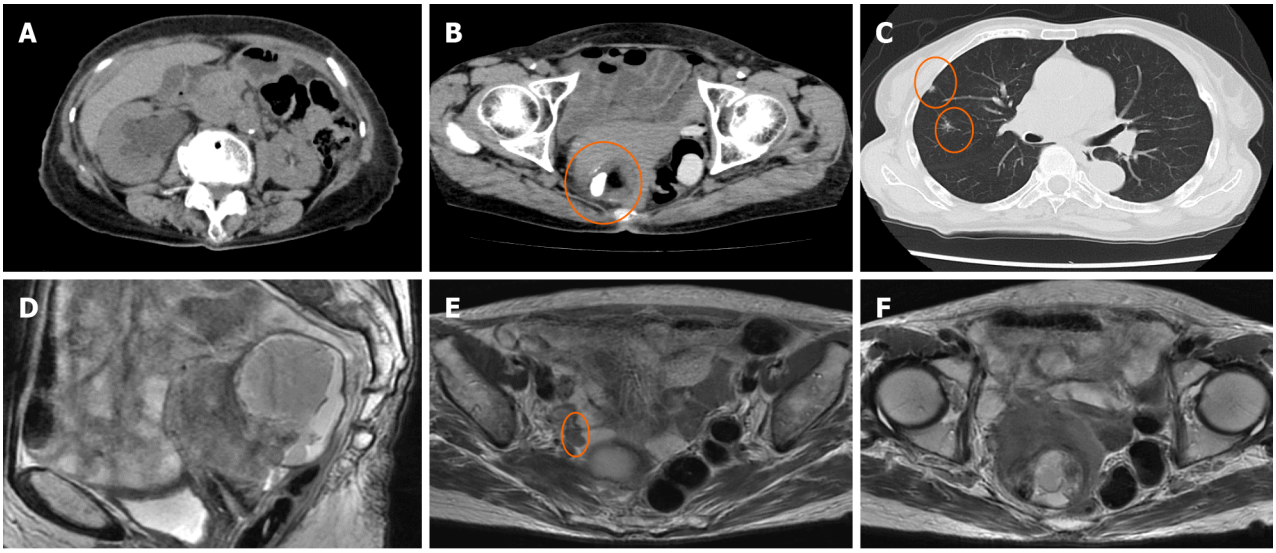

Figure 1 Computed tomography and magnetic resonance imaging findings. A-C: Computed tomography revealed right hydronephrosis, a 6-cm solid cystic mass with fat and calcification densities, and multiple nodules in the lungs (orange circles); D-F: Magnetic resonance imaging showed that the tumor was adhering to the uterus and rectum. There was suspected dissemination near the right ureter (orange circle).

MULTIDISCIPLINARY EXPERT CONSULTATION

Cervical cytology was negative for intraepithelial lesions or malignancy, and there were no findings suggestive of human papillomavirus infection. We suspected MT of the MCT from CT and MRI findings. Paracentesis or laparoscopic biopsy are usually considered for diagnosis; however, as there was some ascites, and the tumor was located deep in the pelvis and invaded surrounding organs, we concluded that both were difficult. Therefore, we performed EUS-FNB based on the location of the tumor and its adhesion to the rectum. Pathological examination revealed squamous cell carcinoma (Figure 2).

FINAL DIAGNOSIS

The patient was diagnosed with stage IV MT of the MCT.

TREATMENT

We were hesitant to perform debulking surgery because her Eastern Cooperative Oncology Group performance status (PS) score was 2. In addition, multidrug chemotherapy has side effects that could exacerbate renal dysfunction. Since CCRT is performed in hospital, it is possible even if the PS is 2 or higher, and we considered that side effects can be observed and dealt with in detail. In addition, the amount of cisplatin used in combination can be reduced according to renal function, and the treatment results are better than those with radiation alone. Therefore, we selected CCRT. The patient received 50 Gy of radiotherapy in 25 fractions to the lower pelvis with 30 mg/m^2 cisplatin for 4 weeks. The side effects included loss of appetite and weight, fever, and diarrhea, all grade 1 according to the Common Terminology Criteria for Adverse Events v5.0. Medication was given for fever and diarrhea, and the patient quickly recovered. After CCRT, the tumor size was reduced by 7.3%, mobility improved, and the PS score improved from 2 to 1. Total abdominal hysterectomy, right salpingo-oophorectomy, and removal of the dissemination were performed. The ascites cytology was positive. No tumors remained in the abdomen postoperatively. The patient was asymptomatic but requested follow-up.

Five months postoperatively, edema was observed in the right lower leg. Positron emission tomography showed peritoneal dissemination in the right pelvic wall, multiple lymph node metastases, and increased lung metastases. The patient requested palliative chemotherapy to reduce the edema. We administered doxorubicin hydrochloride liposome 40 mg/m^2 on day 1 but had to stop treatment due to a decrease in blood pressure and generalized rashes that could indicate an allergic reaction. We then administered three courses of gemcitabine 1000 mg/day, on days 1, 8, and 15, but discontinued due to disease progression.

OUTCOME AND FOLLOW-UP

The patient died 18 months after treatment initiation due to multiple organ failure. Information from this case report

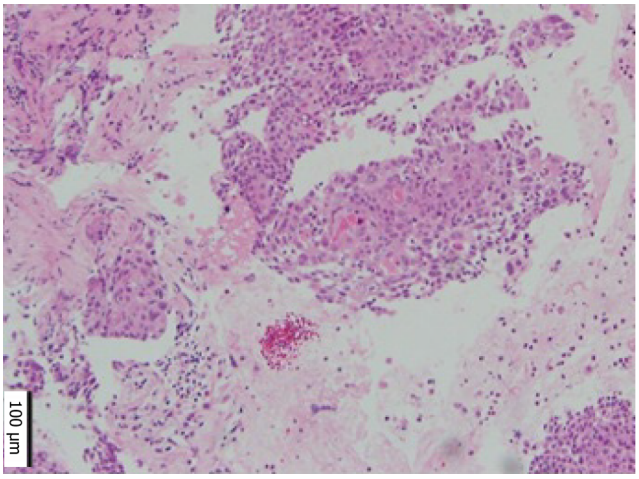

Figure 2 Pathological diagnosis using endoscopic ultrasound-guided fine-needle biopsy was squamous cell carcinoma.

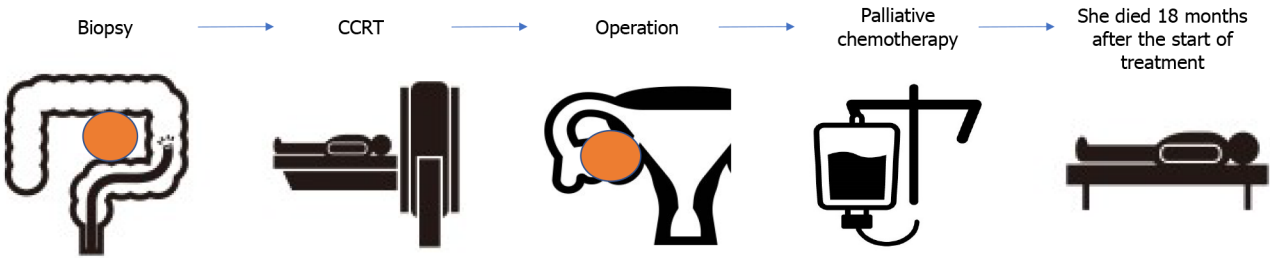

Figure 3 Timeline of this case. CCRT: Concurrent chemoradiotherapy.

organized into timeline (Figure 3).

The patient and her family were satisfied with the treatment and its progress.

DISCUSSION

This case demonstrates the following two points: CCRT had a preoperative reduction effect in MT of MCT, and EUS-FNB is useful for diagnosing MT of MCT.

CCRT reduced the MT of MCT. Table 1 shows previous cases in which CCRT was administered for MT of MCT[3-8]. The advanced cases survived with no evidence of disease. However, all of these cases had CCRTs administered postoperatively. To our knowledge, this is the first case report of preoperative CCRT. Similar to the postoperative cases, CCRT showed a reduction in the MT of MCT, and the side effects were tolerable. According to the literature, cases of long-term survival even in advanced stages have been completely removed by surgery. However, in cases such as this case, where the general condition is poor or the patient is elderly or has complications, treatment that prolongs the prognosis without causing complications is necessary, and CCRT can be said to be a treatment that satisfies such needs. Of course, CCRT also has side effects such as intestinal perforation, radiation enteritis, and cystitis, which may be necessary to treat, but these can be avoided to some extent by narrowing the irradiation field with intensity-modulated radiation therapy. Another long-term disadvantage is that it is difficult to use angiogenesis inhibitors such as bevacizumab because of the increased possibility of intestinal perforation. Although preoperative CCRT for ovarian cancer is currently uncommon, preoperative radiotherapy is often used for colorectal cancer. Recent reports have shown that patients with recurrent MT of MCT have been treated with a combination of surgery, chemotherapy, and CCRT to achieve long-term survival[9,10]. More definitive conclusions can be drawn as more cases accumulate in the future.

EUS-FNB is useful for diagnosis. Paracentesis or endoscopic biopsy are the usual methods for ovarian cancer biopsy; however, in the present case, there were minimal ascites, the tumor was adhered to the rectum and pelvic wall and had poor mobility, and dissemination was deep in the pelvis. EUS-FNB is a minimally invasive rapid diagnostic technique. At our hospital, EUS-FNB is used for lymph node biopsies and histological examination of intestinal submucosal tumors. Other cases of MT of MCT that were incidentally diagnosed on colonic biopsy have been reported[11]. Advanced MT of MCT may directly invade adjacent organs; however, investigation of further cases is required.

The effects of immune checkpoint inhibitors for recurrence or chemo-resistant cases have been reported in recent years [12-14]. We hope to collect data from additional cases and develop effective treatments.

Table 1 Summary of patients with malignant transformation of mature cystic teratomas who received concurrent chemoradiotherapy

Ref.	Age	Stage	Surgery	Adjuvant therapy	Follow-up (months)	Outcome
Rose *et al*[3], 1993	42	III C	RSO, retroperitoneal dissection, PAN	CCRT (cisplatin)	11	DOD
Do *et al*[4], 2001	44	II B	LSO	CCRT (5-FU, leucovorin)	36	NED
Park *et al*[5], 2008	43	III C	PLN, PAN, total omentectomy, Appe	CCRT, TP	13	NED
Yoshida *et al*[6], 2016	37	II B	TAH, BSO	CCRT (cisplatin, 5-FU)	27	NED
Tokunaga *et al*[7], 2016	49	III A	TAH, BSO, pOM, PLN, PAN	CCRT	?	NED
Tokunaga *et al*[7], 2016	40	III C	TAH, BSO, pOM, PLN, PAN	CCRT	?	NED
Bacalbasa *et al*[8], 2020	47	I A	TAH, LSO	CCRT (cisplatin)	24	NED

Appe: Appendectomy; BSO: Bilateral salpingo-oophorectomy; DOD: Died of disease; LSO: Left salpingo-oophorectomy; NED: No evidence of disease; Pom: Partial omentectomy; PLN: Pelvic lymphadenectomy; PAN: Para-aortic lymphadenectomy; TAH: Total abdominal hysterectomy; TP: Paclitaxel, cisplatin; CCRT: Concurrent chemoradiotherapy.

CONCLUSION

EUS-FNB is a useful method of diagnosing MT of MCT. Although advanced-stage patients have poor prognosis, CCRT has the potential to suppress the disease temporarily and improve the patient's quality of life with few adverse effects.

FOOTNOTES

Author contributions: Kondo S and Suzuki T contribute equally to this study as co-corresponding authors. Kondo S and Suzuki T contributed to manuscript writing, editing, and data collection; Yamanaka S and Yoshiike K contributed to data analysis; Sonehara K, Nabeshima H, and Oguchi O contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

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LETTER TO THE EDITOR

Intricacies during pregnancy with gestational diabetes mellitus

Richa Rattan, Rimesh Pal, Parul Chawla Gupta, Arvind Kumar Morya, Ripunjay Prasad

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Abstract

The study by Cao *et al* aimed to identify early second-trimester biomarkers that could predict gestational diabetes mellitus (GDM) development using advanced proteomic techniques, such as Isobaric tags for relative and absolute quantitation isobaric tags for relative and absolute quantitation and liquid chromatography-mass spectrometry liquid chromatography-mass spectrometry. Their analysis revealed 47 differentially expressed proteins in the GDM group, with retinol-binding protein 4 and angiopoietin-like 8 showing significantly elevated serum levels compared to controls. Although these findings are promising, the study is limited by its small sample size (n = 4 per group) and lacks essential details on the reproducibility and reliability of the protein quantification methods used. Furthermore, the absence of experimental validation weakens the interpretation of the protein-protein interaction network identified through bioinformatics analysis. The study's focus on second-trimester biomarkers raises concerns about whether this is a sufficiently early period to implement preventive interventions for GDM. Predicting GDM risk during the first trimester or pre-conceptional period may offer more clinical relevance. Despite its limitations, the study presents valuable insights into potential GDM biomarkers, but larger, well-validated studies are needed to establish their predictive utility and generalizability.

Key Words: Gestational diabetes mellitus; Biomarkers; Differentially expressed proteins; Retinol-binding protein 4; Angiopoietin-like 8; Proteomics; Lifestyle interventions; Early prediction

Core Tip: The letter highlights certain limitations of the study by Cao *et al*, which explored early second-trimester biomarkers, retinol-binding protein 4 and angiopoietin-like 8, for predicting gestational diabetes mellitus (GDM). While valuable, identifying GDM in the early second trimester may not provide sufficient time for pregnant mothers to adopt major lifestyle interventions. Early first-trimester prediction or pre-conceptional identification would be more clinically significant. While the study uses advanced proteomic techniques, including isobaric tags for relative and absolute quantitation and liquid chromatography-mass spectrometry, to identify differentially expressed proteins, it is constrained by a small sample size and methodological gaps. Specifically, the reliability of protein quantification and high-abundance protein removal is unclear, and the lack of experimental validation limits the functional interpretation of identified protein interactions.

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TO THE EDITOR

Gestational diabetes mellitus (GDM) is a significant global health concern, affecting 7%-10% of pregnancies, and posing risks for both maternal and fetal complications. Its pathophysiology is quite intricate and requires newer diagnostic, screening, and management techniques to keep mother and child health a priority.

GDM

GDM is a major public health problem. It is estimated that GDM affects around 7%–10% of all pregnancies globally. The diagnosis of GDM is primarily based on an oral glucose tolerance test performed usually between 24-28 weeks of gestation. Identification and prompt management are essential, as uncontrolled hyperglycemia in pregnant mothers with GDM often leads to adverse maternal and fetal outcomes[1]. GDM can ultimately lead to significant development of diabetic retinopathy (DR) during pregnancy or aggravation of an already active DR resulting in impairment of vision[2]. Besides, nearly 50% of women with GDM later go on to acquire type 2 diabetes mellitus.

Considering the plethora of short-term and long-term repercussions, lifestyle interventions introduced before pregnancy or even early in pregnancy have the potential to prevent GDM development[3]. Hence, identifying women at a high risk of developing GDM is of paramount importance.

Cao *et al*[4] have attempted to identify potential biomarkers in pregnant women in their early second trimester (12-16 weeks) that can help predict the subsequent development of GDM. While their findings contribute to our understanding of GDM, it is unclear if identifying GDM in the early second trimester would provide sufficient time for pregnant mothers to adopt major lifestyle interventions that can avert the subsequent development of GDM. On the contrary, it would be clinically more relevant if the subsequent development of GDM could be predicted in the early first trimester or even in the pre-conceptional period, which could allow for timely preventive measures.

The study[4] involves the utilization of advanced proteomic techniques that allow comprehensive analysis of protein expression alterations associated with GDM. Isobaric tags for relative and absolute quantitation and liquid chromatography-mass spectrometry facilitate high-throughput identification and quantification of differentially expressed proteins (DEPs), providing valuable insights into the molecular mechanisms triggering GDM pathophysiology. Furthermore, the inclusion of bioinformatics analysis augments the understanding of the proteomic data by elucidating the functional importance of the recognized proteins. Gene Ontology (GO) analysis, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis, and protein-protein interaction network construction contribute to a deeper understanding of the biological processes and pathways involved in GDM[5]. Although 47 DEPs were identified in the GDM group, serum levels of only retinol-binding protein 4 (RBP4) and angiopoietin-like 8 (ANGPTL8) were found to be significantly higher in the GDM as compared to the non-GDM control group. The authors thus conclude that RBP4 and ANGPTL8 may be early predictors of GDM.

Although praiseworthy, the study[4] is markedly limited by its small sample size (only four mothers each with and without GDM). Besides, specific methodological issues deserve mention. First, while the methodology mentions the use of the Bradford method for protein quantification and sodium dodecyl sulfate-polyacrylamide gel electrophoresis for quality assessment, it lacks detailed information about the reproducibility and reliability of these methods. Second, the methodology mentions the removal of high-abundance proteins. Still, it does not specify which proteins were removed that might account for potential bias introduced by incomplete removal or unintended protein loss. Third, although the protein interaction network provides insights into possible interactions among DEPs, the interpretation of these interactions is limited by the lack of experimental validation. Without empirical evidence confirming the interactions, the functional significance of these networks remains uncertain. The bioinformatics analysis, including GO functional

annotation, KEGG pathway analysis, and protein-protein interaction network construction, relies on computational algorithms and databases. It is essential to acknowledge the likely drawbacks and biases linked with these tools and provide validation strategies to confirm the biological relevance of the findings. Lastly, while enzyme-linked immunosorbent assay validation confirms the upregulation of RBP4 and ANGPTL8 in GDM patients, the small sample size and demographic restrictions raise concerns about the generalizability of these findings.

CONCLUSION

In conclusion, while the study by Cao *et al*[4] provides valuable insights into potential biomarkers for GDM, its limitations, particularly the small sample size, insufficient methodological details, and lack of experimental validation, should be addressed in future studies. Additionally, earlier prediction of GDM, potentially in the first trimester or preconception, would offer more time for lifestyle interventions and could enhance the clinical relevance of such findings.

FOOTNOTES

Author contributions: Morya AK, Rattan R, and Pal R designed the study; Rattan R, Pal R, Gupta PC, and Morya AK wrote the manuscript; Prasad R edited the manuscript; all of the authors read and approved the final version of the manuscript to be published.

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