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ABOUT COVER

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MINIREVIEWS

COVID-19-induced liver injury in infants, children, and adolescents

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Abstract

Coronavirus disease 2019 (COVID-19) typically presents with fever and respiratory symptoms in children. Most children develop an asymptomatic and mild illness, with a minority requiring specialist medical care. Gastrointestinal manifestations and liver injury can also occur in children following infection. The mechanisms of liver injury may include infection following direct viral hepatic tissue invasion, immune response, or medication effects. Affected children might develop mild liver dysfunction which has a benign course in most children with no pre-existing liver disease. However, the presence of non-alcoholic fatty liver disease or other pre-existing chronic liver disorders is associated with a higher risk of developing severe COVID-19 illness with poor outcomes. On the other hand, the presence of liver manifestations is associated with the severity of COVID-19 disease and is considered an independent prognostic factor. Respiratory, hemodynamic, and nutritional supportive therapies are the mainstay of management. Vaccination of children at increased risk of developing severe COVID-19 disease is indicated. This review describes the liver manifestations in children with COVID-19, detailing its epidemiology, basic mechanisms, clinical expression, management, and prognosis in those with and without pre-existing liver disease and also children who have had earlier liver transplantation.

Key Words: Child; COVID-19; Gastroenterology; Hepatic dysfunction; Infection; Liver diseases; SARS-CoV-2; Liver injury; Liver transplant

Core Tip: Liver injury presenting with elevated levels of alanine aminotransferase and aspartate aminotransferase is common in children infected with the coronavirus disease 2019 (COVID-19) virus. The mechanism of liver injury is not fully understood and is likely secondary to the viral invasion of the liver, hepato-toxic medications, and the patient's own immune-mediated response. Liver injury in children is generally mild and resolves spontaneously but is usually seen in children with more severe illnesses. In addition, children with underlying non-alcoholic fatty liver disease or another chronic liver disease may have a higher risk of severe COVID-19 illness. Management of liver injury after COVID infection is supportive. Proactive vaccination may reduce the transmission of infection and the severity of the disease.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) typically presents with fever, weakness, myalgia, malaise, and pulmonary symptoms[1]. In addition, a significant percentage of those infected with the virus develop gut manifestations such as loss of appetite, colics, and lose stools[2]. Similarly, hepatic involvement has been reported in many studies[3,4]. Previous waves of the Middle East respiratory syndrome (MERS) have shown an association with elevated serum transaminases and bilirubin and concentrations with decreased serum albumin levels[5,6]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) shares up to 80% genomic sequence similarity with MERS and, consequently, hepatic injury is not an unexpected manifestation of COVID-19[7].

This review aims to describe liver injury in children with COVID-19, detailing its epidemiology, underlying mechanisms, clinical manifestations, management, and prognosis. We will also describe liver involvement in high-risk groups, including children with pre-existing liver disease.

EPIDEMIOLOGY

Acute liver injury in adults and children with SARS-CoV-2 infection is defined as an elevation in the serum concentration of aminotransferases (transaminases). The spectrum of liver injury ranges from asymptomatic elevated serum transaminase levels to severe liver injury, with reports of acute-on-chronic liver failure in patients with underlying liver disease. Usually, 14%-53% of adult patients develop mild to moderate elevation of liver enzymes[8,9].

Abnormal transaminase levels have also been linked to the severity of COVID-19[9-13]. Higher morbidity and mortality have been reported in those COVID-positive and altered liver function, with liver injury being an independent prognostic factor of COVID-19[14,15]. A review by Bende *et al*[15] of post-acute COVID-19 syndrome of 97 subjects demonstrated increased liver stiffness, viscosity, and steatosis in around one-third of the patients, worse in subjects with pulmonary injury compared to those without. COVID-19 in children and adolescents may be asymptomatic or cause only mild symptoms. These include fever, cough, upper respiratory tract symptoms, diarrhoea, nausea, and vomiting. In a multinational, multicentre cohort study, 22% of patients had gastrointestinal symptoms, of whom 7% had no respiratory symptoms[16]. In early pediatric reports, the rate of transaminase elevation was 14%-50%[12,17,18]. However, these data may not be representative because transaminase levels and liver function tests were only reported in a small proportion of patients. In a study involving 280 children ≤ 17 years of age with COVID-19, the elevation of serum transaminases was mild, with a prevalence of 29%, and predominantly children < 3 years of age[19]. Those with chronic liver diseases have developed more aggressive diseases with an increased risk of hepatic failure[20].

MECHANISMS OF LIVER INJURY

The causes of elevated liver transaminases in COVID-19 still need to be fully understood[21]. Some possible risk factors, illustrated in Figure 1, include:

Viral invasion of liver tissue

There is evidence that the virus infects the organ cells by exploiting the angiotensin-converting enzyme (ACE) 2 receptor, followed by intracellular replication. ACE2 receptors are found in the respiratory

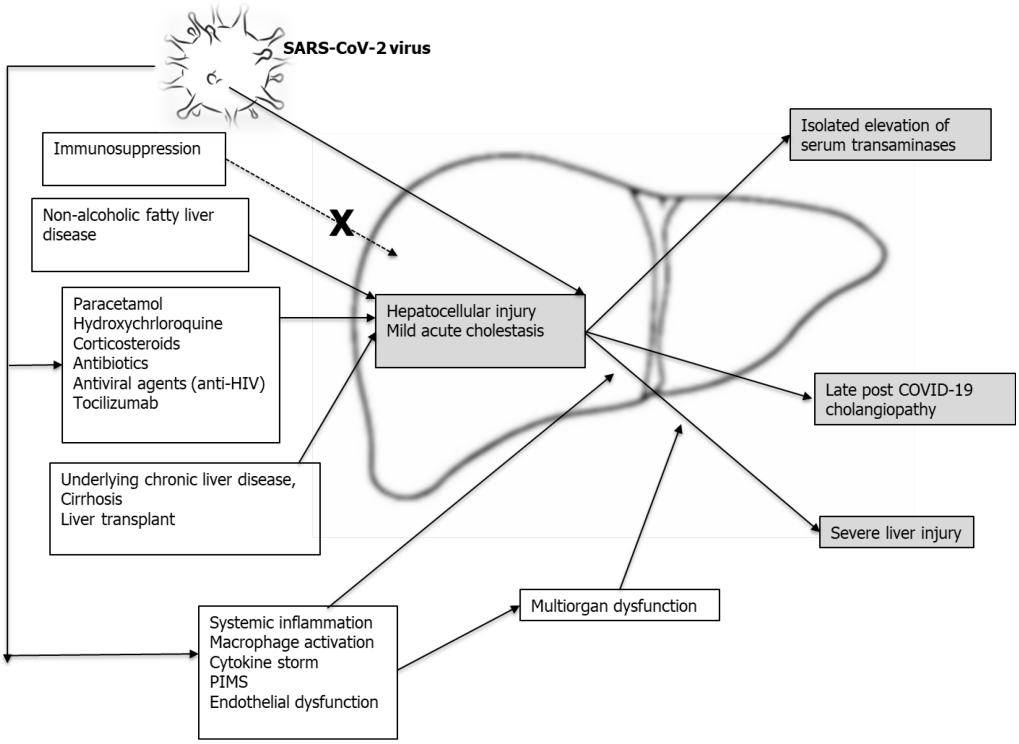

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Figure 1 Mechanisms of liver injury in severe acute respiratory syndrome coronavirus 2 infections. COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; HIV: Human immunodeficiency virus.

tissues, gut, liver, kidney, and heart. However, compared to the viral load in the lungs of acutely infected children, the viral load in the hepatic cells was found to be low. Evidence of hepatic cell injury with a high level of serum transaminases has been found in > 70% of patients with severe COVID-19 disease[22,23]. Moreover, the virus has also been isolated from patients' stools, indicating that the infection spreads to the gastrointestinal tract and not exclusively the pulmonary cells[22,23]. This direct viral invasion of liver tissue and replication inside the hepatocytes can explain the resulting hepatic injury.

Medications

Another mechanism for liver injury associated with SARS-CoV-2 is the polypharmacy commonly used during COVID-19 illness. Antiviral drugs, antibiotics, and steroids used to treat moderate and severe COVID-19 may also cause liver toxicity in their own right[24,25]. Antipyretics, such as paracetamol, do not play a significant role in COVID-19 liver injury. Other drugs include chloroquine, isoniazid, antivirals, particularly anti-human immunodeficiency virus medications (lopinavir/ritonavir), and biological agents such as tocilizumab, which also be considered potential co-factors in the pathophysiology of liver injury in children with COVID-19[9,22,23]. In a study of 147 patients with COVID-19-induced liver injury treated as outpatients, the prevalence of hepatic injury was the same as in those with normal or impaired liver function. However, it was observed to be higher in those patients who received hospital care and with a higher rate of utilization of ritonavir[26].

The immune response

The resulting immune response is immature in infants and children with COVID-19 infection, and while it is mild in most patients, it can be severe. Hepatic injury caused by the SARS-CoV-2 virus in children is associated with systemic and local inflammatory responses of varying severity. During the acute stage of the infection, the immune system attempts to limit the reproduction of the virus through both immediate and delayed immune responses by producing specific antibodies against it. When exaggerated, this immune-mediated response can damage the hepatic tissue in children with more aggressive and prolonged disease[1]. The inflammatory markers such as cytokines, T helper 17 cells, cytotoxic DC8 T cells, interleukins 1, 2, and 6, serum ferritin, tumor necrosis factor, interferon, and other mediators[9], as well as C-reactive protein, are commonly elevated. In some patients, this may result in a "cytokine storm", leading to rapid clinical deterioration with multiple organ failure and endothelial dysfunction, further aggravating liver damage[2,26-32]. Endothelial dysfunction is associated with the stimulation of neutrophil extracellular traps through immunological mechanisms[19], causing the development of microthrombi in the lungs[33]. The liver is similarly affected, and hepatic damage may

be accelerated by a hypercoagulative disease state, which can involve other organs and tissues. Autopsy reports have confirmed the presence of hepatic sinusoidal congestion and micro thrombosis[20,27].

Acute liver injury is also a prominent feature of multi-system inflammatory diseases in children, occurring as a late complication of SARS-CoV-2 infection[34]. The exact mechanism still needs to be fully understood. Some researchers suggest an abnormal immune response to the SARS-CoV-2, similar to Kawasaki disease[35], or immunoglobulin G antibodies enhancement of monocytes and cytotoxic CD8+ T cells[8], with downregulation of neutrophil and lymphocyte functions[6,7]. The pediatric multi-system inflammatory syndrome temporally associated with COVID-19, also known as a multi-system inflammatory syndrome in children (MIS-C), is a persistent acute febrile illness progressing to multi-organ dysfunction, conferring over a 2-fold increased risk of elevated serum transaminases. Although affected children often have an underlying medical condition, such as obesity, immunocompromised state (including malignancy), or chronic liver disease (CLD)[36], it may also occur in previously healthy children and adolescents[37]. A few weeks after contracting SARS-CoV-2, affected children present with either a Kawasaki-like picture, shock, or macrophage activation syndrome, usually warranting admission to the pediatric intensive care unit (PICU). The clinical manifestations includes fever and multi-organ involvement, including gastrointestinal, cardiovascular, mucocutaneous, and neurological symptoms, with laboratory evidence of severe inflammatory activity and coagulopathy[38,39]. Although liver involvement is reported, it occurs as part of intense multi-organ involvement[24,25].

CLINICAL MANIFESTATIONS

Acute Manifestations

Liver injury in children infected with COVID-19 is suspected in the presence of elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) serum levels in 13% to 50% of patients[12,18,24,25,40]. AST levels > 50 UI/L are observed in 20%-50% of cases, and ALT levels > 45 UI/L in up to 35%[12,40]. Abnormal serum bilirubin levels may also occur but to a lesser extent than with transaminase. Raised alkaline phosphatase and gamma-glutamyl transferase levels are rarely observed. Liver injury is generally mild and resolves over time, with severe liver dysfunction being uncommon. Abnormal transaminase levels have also been linked to the severity of COVID-19, with liver injury occurring in 58.8% of patients with moderate and 66.7% of those with severe disease[10,11,41]. Other studies demonstrated elevated liver enzymes in 40%-60% of those with severe illness as compared to asymptomatic or patients with mild disease (18%-25%)[9,12,13]. In a meta-analysis and systematic review, significantly higher levels of aminotransferases and significantly lower albumin levels were more common in severe cases of COVID-19[42].

Severe acute liver injury

Severe acute liver injury, defined as serum ALT values five times above the upper limit of normal[9,36,43], is commonly associated with severe COVID-19 infection, shock, respiratory compromise, higher serum inflammatory markers, and longer overall length of stay in hospital[20]. However, acute liver failure (ALF) is rare and is more common in patients with severe illness and multi-organ dysfunction [20,22]. In one published case report, an early teenager died with acute fulminant hepatic failure secondary to COVID-19 infection. However, a similar child's life was saved with liver transplant (LT) [44,45].

Chronic manifestations

Post-COVID-19 cholangiopathy: This proliferative cholangiopathy is associated with lymphocytic portal and parenchymal infiltration, after excluding other possible causes such as adenovirus infection. It occurs at least several weeks after full recovery from asymptomatic or mild acute infection[40]. Two clinical patterns of presentations have been described: ALF in infants and acute hepatitis and cholestasis in older children. The group with hepatitis and cholestasis showed an excellent response to systemic steroids, while patients with ALF needed LT.

Secondary sclerosing cholangitis: Secondary sclerosing cholangitis (SSC) has been described in adults following COVID-19 as prolonged cholestasis with severe cholangiopathy. Unlike children, it occurs mainly in patients who have been through a complex and critical course of COVID-19 requiring admission to an intensive care unit (ICU), with a mean time of 118 d (range 138-319) between COVID-19 disease and the diagnosis of cholangiopathy. Compared to adults, ultrasound findings include strictures of intrahepatic bile ducts along with intraluminal sludging and casts formation[44,46]. Biliary duct dilatation, periportal and gallbladder wall oedema with thickening are more common in children.

Adult patients with post-COVID-19 cholangiopathy and SSC show progressive disease unresponsive to treatment with ursodiol therapy, with those most severely affected requiring LT. Corticosteroids, immunomodulators, or immunosuppressant therapies have not been studied in those patients.

Special considerations

Obesity and non-alcoholic fatty liver disease: In a meta-analysis of 285004 children infected with the novel virus, 9353 (3.3%) suffered from one or more comorbidities including obesity. Among 507 obese children, 64 had either severe COVID-19 or required ICU admission, with a calculated risk of severity of 2.87 (95%CI, 1.16-7.07)[46]. Obesity is thus the most common comorbidity reported in children with severe SARS-CoV-2 infection[20,47-50]. Although the proportion of patients with non-alcoholic fatty liver disease (NAFLD) in published obese cohorts remains unknown, children with NAFLD, especially those with obesity, should be considered a risk group for severe COVID-19[20].

Immunosuppressive therapy

The link between immune deficiency and severe gastrointestinal and liver involvement has not been proven[47,51,52]. Furthermore, some immunosuppressive medications even mitigate against severe COVID-19. These include calcineurin inhibitors, which potentially inhibit coronavirus replication[53]. European surveillance disproved any link between the use of calcineurin inhibitors and severe SARS-CoV-2 infections[54]. Moreover, drugs with antimetabolic activities such as mycophenolic acid have been reported, in laboratory studies, to interfere with the virus activity[55]. In addition, the regular use of immunosuppressants is not associated with a severe form of the disease[56,57]. In a study involving 180 children with an LT, 30 required non-ICU hospital admission (median 5 d) and three required ICU admission. However, none of them required inotropes or invasive ventilatory support[20]. Children on post-transplant immunosuppressive regimens have been shown to experience mild disease, similar to the general paediatric population[57-59].

MANAGEMENT

While liver involvement is commonly associated with COVID-19 infection in children, most children demonstrate mildly abnormal liver function, which usually normalises without any specific treatment [9].

Supportive therapy

Like most other viral illnesses with inflammatory liver involvement, the management of hepatic involvement with COVID-19 infection is supportive. It includes stabilisation of vital signs, fluid and electrolytes correction, and ensuring adequate liver oxygenation. Avoiding hypo-perfusion and hypoxia (especially in patients with respiratory distress) is essential. Liver recovery will likely be enhanced with the ongoing improvement of the systemic inflammatory status. Some patients might require poly-pharmacotherapy depending on the severity of their lung injury and the other organs involved. Avoidance of hepatotoxic medications is crucial. All specific virus-targeted therapies are still employed exclusively in clinical research trial settings[13].

Nutritional therapy

Nutrition is essential, especially in children with a prolonged critical illness. They are at higher risk of developing malnutrition, associated with increased morbidity and mortality. Hence, early oral or nasogastric tube feeding is recommended. It is preferred to parenteral nutrition, except in patients with severe gastrointestinal dysfunction. During the acute phase, the energy requirements do not need to exceed resting energy expenditure. Based on the tolerance and the patient's general condition, the European Society of Pediatric and Neonatal Intensive Care recommends a gradual increase toward the target caloric need. Enteral nutritional support must be maintained as long as required until adequate oral intake is reliably attained to support physical and nutritional rehabilitation[60,61].

Children with pre-existing CLD and LT recipients

Infected patients with underlying primary liver diseases and other metabolic liver diseases should continue to receive treatment for their underlying condition[9]. Elevated liver enzymes are not a reason to discontinue antiviral treatment as long as liver function is monitored[10]. Post-LT patients are advised to continue their immunosuppressants and modulator medications.

The COVID-19 pandemic has profoundly impacted transplantation worldwide, both donor's and recipients' viral transmission and healthcare resources[58]. There is no indication for delaying or interrupting oncological treatments, withdrawing immune suppression, or postponing any required treatments to those patients with liver-transplant[57].

PROGNOSIS

Mortality is higher in COVID-19 children with deranged hepatic function and the proportion of liver injury is directly related to the poor prognosis[14]. A literature review of 12 studies with a total of 6976

patients, whose laboratory tests were obtained at admission, showed high levels of transaminases and low albumin levels that were significantly more common in severe cases of COVID-19[42]. In a meta-analysis of 12 studies with a total of 5135 COVID-19 subjects with collected data on raised AST and outcomes, increased AST values were associated with three times higher risk of poor effects (pooled odds ratio: OR, 2.98; 95%CI, 2.35-3.77; $P < 0.00001$)[62]. Similarly, ten studies documented reported elevated ALT and outcomes, including 5091 patients, showed a marked increase in poor outcomes (pooled OR: 1.73; 95%CI: 1.32-2.27; $P < 0.0001$). Furthermore, a meta-analysis of four studies with a total sample size of 485 patients demonstrated that those with acute liver injury had higher odds of poor outcomes with a pooled OR of 1.68 (95%CI, 1.04-2.70; $P = 0.03$)[62].

Studies of COVID-19 outcomes among children with CLD are limited. Data from adult patients have reported mixed results and occasionally conflicting conclusions, making it difficult to determine a prognosis[63-65]. An earlier meta-analysis of 17 studies with a sample size of 8800 COVID-19 patients revealed that chronic liver disease did not significantly affect the outcomes (pooled OR, 0.96; 95%CI, 0.71-1.29; $P = 0.78$)[62]. A similar conclusion was also reached in a review where there were no major differences in COVID-19 severity and mortality between patients with liver disease and those without [66]. However, given the limitations of these studies, their results must be cautiously interpreted.

A more recent and comprehensive meta-analysis of 40 studies with 908032 participants concluded that CLD markedly affected clinical outcomes among COVID-19 patients[67]. For disease severity, the pooled OR was 2.44 with 95%CI of 1.89-3.16; for mortality, it was 2.35 (95%CI, 1.84-3.00). Subgroup analysis indicated that NAFLD, metabolic-associated fatty liver disease, and cirrhosis had the highest odd ratios of 5.6, 3.2, and 3.09 for COVID-19 severity. In other studies, cirrhosis was implicated as a significant risk factor for hospitalization, intensive care admission, and mortality. Mortality among cirrhotic patients was 32% compared to 8% among non-cirrhotic patients[68]. Other reports have also confirmed a higher risk of COVID-19 severity and mortality in CLD patients, up to four and two times, respectively, compared with those without CLD[62,69]. In children, a systematic review and meta-analysis inferred that those with COVID-19 have preserved effector and immunosuppressive components, and encountered a milder disease compared to adults[33].

Most children with MIS-C achieve full clinical recovery with a death rate of < 1%. However, in those where the clinical course was severe and required intensive care interventions for ALF, the possibility of death was 11 times higher than in those without these complications[70].

PREVENTION

Preventative measures should be implemented for vulnerable patients at risk of exposure to SARS-CoV-2, as they may develop severe illness.

General public health measures

General measures for distancing, maintaining good hygiene and avoiding contamination with the virus are important for healthy children and the general public as well as for children with an underlying liver condition.

Vaccinations

Children suffering from CLD and/or LT are recommended to be administered the COVID-19 vaccination, which is generally safe in this group[71]. However, CLD among adults with non-cirrhotic compensated cirrhotic or decompensated cirrhotic was associated with lower rates of development of positive SARS-CoV-2 neutralizing antibodies compared with healthy individuals (77 *vs* 90 percent)[72]. Other studies suggested that patients with liver disease who received COVID-19 vaccination have a negligible risk of infection and COVID-19-associated mortality[73]. Likewise, children awaiting a LT also would need to be prioritized for receiving COVID-19 vaccine. The type of vaccine would depend on the active strain of the virus as well as the chance to choose from different vaccines as per the local infectious disease department recommendations and regardless of the time available prior to the transplant to allow the child to receive the 2 doses as in certain protocols[74]. Routine serology tests to check for the COVID-19 virus antibodies are not indicated[71].

CONCLUSION

The spectrum of liver injury in children with COVID-19 ranges from being asymptomatic with elevated serum transaminase levels to severe liver injury, with reports of acute-on-chronic liver failure in patients with underlying liver disease. The mechanism of liver injury is multifactorial. Most children demonstrate a mild self-resolving liver injury; the level of severity of the damage is linked to how severe the infection is with COVID-19 disease and is considered an independent prognostic factor**.** Treatment is supportive and LT is required only in very few patients. Children with underlying NAFLD and other

pre-existing chronic liver diseases carry a higher risk of developing severe COVID-19 illness and poor outcomes.

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Abstract

Hirschsprung's disease (HSCR) is a congenital disorder characterized by failure of the neural crest cells to migrate and populate the distal bowel during gestation affecting different lengths of intestine leading to a distal functional obstruction. Surgical treatment is needed to correct HSCR once the diagnosis is confirmed by demonstrating the absence of ganglion cells or aganglionosis of the affected bowel segment. Hirschsprung's disease associated enterocolitis (HAEC) is an inflammatory complication associated with HSCR that can present either in the pre- or postoperative period and associated with increased morbidity and mortality. The pathogenesis of HAEC remains poorly understood, but intestinal dysmotility, dysbiosis and impaired mucosal defense and intestinal barrier function appear to play a significant role. There is no clear definition for HAEC, but the diagnosis is primarily clinical, and treatment is guided based on severity. Here, we aim to provide a comprehensive review of the clinical presentation, etiology, pathophysiology, and current therapeutic options for HAEC.

Key Words: Hirschsprung's; Enterocolitis; Pathogenesis; Microbiome; Dysbiosis; Dysmotility; Treatment

Core Tip: Hirschsprung's disease associated enterocolitis (HAEC) is an inflammatory complication of Hirschsprung's disease (HSCR) with variable degrees of severity. It is important for pediatric providers to be aware of the signs and symptoms of HAEC as it can affect patients before or after corrective surgery. The pathogenesis of HAEC is multifactorial and previous and ongoing studies continue to improve our knowledge of this potentially fatal complication of HSCR and will ultimately allow clinicians to provide personalized care for these patients. In the meantime, current preventive measures and treatment guidelines have helped decrease the morbidity and mortality associated with HAEC.

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INTRODUCTION

Hirschsprung's Disease (HSCR) is an intestinal motor disorder caused by failure of neural crest cells (precursors of intestinal ganglion cells) to migrate completely during intestinal development. The aganglionic segment of bowel with impaired relaxation leads to a functional obstruction and symptoms [1]. In healthy children, craniocaudal migration of neural crest cells commence at 4 wk gestation and finishes at 7 wk, but the true etiology of this failure of migration in HSCR is unknown. However, theories include premature differentiation of neural crest cells leading to lack of further migration and local ganglion cell destruction[1].

The incidence of HSCR ranges from 1 in 3500 to 5000 live births[2] and has a male predominance with a male to female ratio of 4:1[3]. The extent of aganglionosis varies from short-segment disease comprising the recto-sigmoid (75%-80% of cases), to total colonic aganglionosis (5%-7% of cases). Ten to 15% of cases, referred to as long-segment disease, display aganglionosis proximal to the sigmoid colon [4]. Common presentations of HSCR vary depending on several factors, mainly the length of the affected colonic segment. These include symptoms and signs of neonatal distal intestinal obstruction: Abdominal distension, bilious vomiting, failure to pass meconium and explosive stools[4]. Screening modalities for HSCR include contrast enema (demonstrating a dilated colon, transition zone, or abnormal recto-sigmoid ratio), and anorectal manometry (to asses for the presence of a recto-anal inhibitory reflex) and when abnormal, a suction or full thickness rectal biopsy confirms the diagnosis by demonstrating absence of ganglion cells (aganglionosis)[4]. Treatment for HSCR is primarily limited to surgical resection of affected segment, or pull-through procedure, where innervated bowel is reconnected to the anus while attempting to preserve anal sphincter function[4]. Although most patients have normal quality of life and bowel function after surgery, some will have ongoing obstructive symptoms[5] like abdominal distension, chronic constipation, and intestinal inflammation or Hirschsprung's disease associated enterocolitis (HAEC) which is considered one of the most fatal complications in patients with HSCR. In this review, we will discuss the clinical presentation, etiology, pathophysiology, and current therapeutic options for HAEC (Figure 1) and discuss the future directions for the evaluation and management of this condition that is still encountered in patients with HSCR.

HIRSCHSPRUNG'S DISEASE ASSOCIATED ENTEROCOLITIS

HAEC is a severe and potentially lethal complication of HSCR. HAEC can have a variable clinical presentation but is classically manifested as fever, lethargy, abdominal distention, foul-smelling and explosive diarrhea[6]. This condition can occur both pre- and postoperatively with varying reported incidence. Preoperative incidence is estimated between 6%-60% while the postoperative incidence is estimated between 25-42%[6]. Mortality associated with HAEC ranges between 5%-50%, with higher prevalence in the neonatal period prior to definitive surgical correction[7]. Nevertheless, mortality rates have continued to decline to less than 1% due to advances in surgical technique and medical care[3]. HAEC has also been reported as the presenting symptom of HSCR in up to 25% of infants[8]. HAEC can also present with bowel perforation in the neonatal period documented as occurring in 3%-6% of HSCR patients[9-11]. In a retrospective analysis of complications in patients awaiting definitive surgical correction for HSCR, bowel perforation was noted as the most common complication (7% of total patients analyzed)[12]. Theories for perforation as a presentation in HSCR include increased luminal pressure, transmural inflammation and vascular accidents leading to ischemia and subsequently perforation. Zhu *et al*[13] performed a retrospective review looking at risk factors for perforated HSCR in neonates. They noted that most perforations occurred at the proximal ganglionic bowel (71%) as opposed to the transition zone or aganglionic bowel and that perforation was more common with

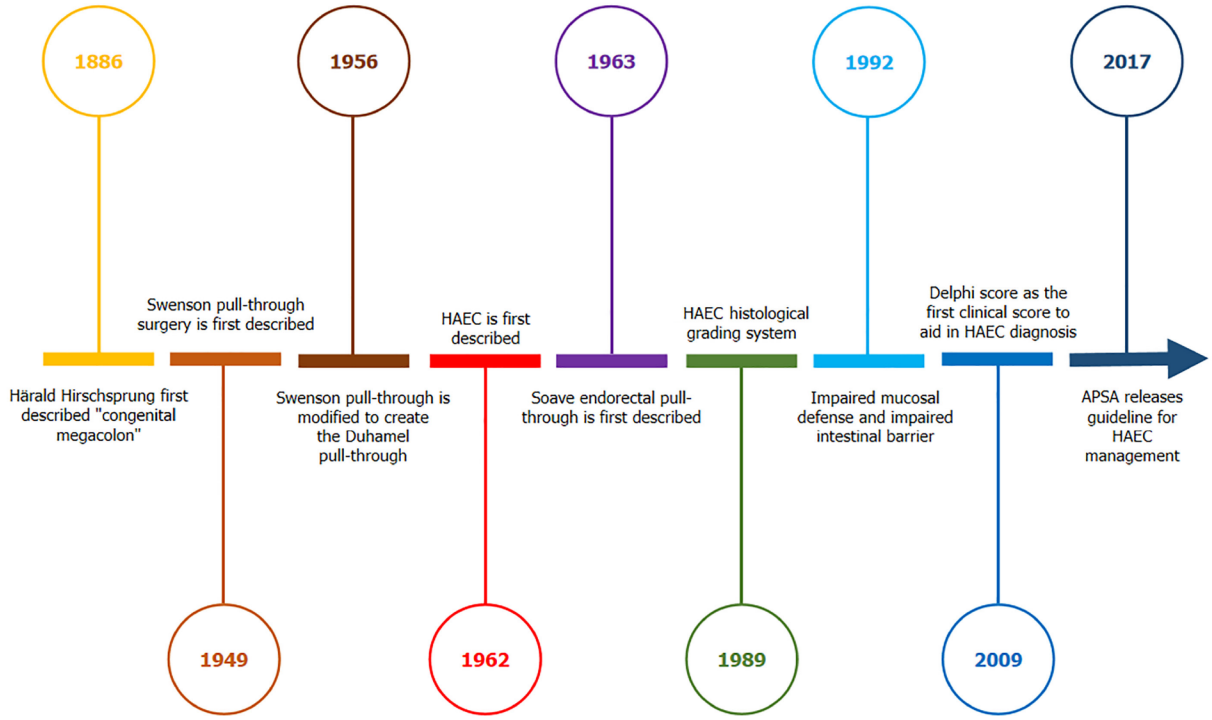

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Figure 1 Timeline graphic illustrating pivotal definitions, surgical treatment, and management guideline for Hirschsprung's disease associated enterocolitis. HAEC: Hirschsprung's disease associated enterocolitis.

higher grade inflammation of the bowel wall. They demonstrated that laboratory studies and bowel histopathologic changes in patients with perforated HSCR were similar to those found in HAEC, thus illustrating a potential association between the two.

The variety of presenting symptomatology of HAEC leads to difficulty in making the diagnosis and there is no standardized definition of HAEC. However, several groups have tried to establish a scoring system to standardize the diagnosis. Notably in 2009, an expert panel used the Delphi method to achieve a consensus of 18 items present in patient history, physical exam, laboratory and imaging findings to aid in the diagnosis of HAEC[14]. A score of 10 or more indicated a diagnosis of HAEC, with equal weight given to all factors other than diarrhea with explosive stool, diarrhea with foul-smelling stool, explosive discharge of stool on rectal exam, and distended abdomen which were weighted more heavily in support of the diagnosis. These criteria, while expansive, had limited validation and have been used more in research studies rather than in clinical practice[15]. In 2018, Frykman *et al*[16] performed a multicenter retrospective review to optimize the sensitivity and specificity of the Delphi score. In this study, they found that lowering the score threshold for diagnosis from 10 to 4 optimized sensitivity and specificity (83.7% and 98.6%, respectively). Most recently, Lewit *et al*[15] performed a multicenter data collection and used multivariate analysis to create a new scoring system limited to fever, bloody diarrhea, leukocytosis, obstipation, distention, and dilated loops of bowel in x-ray. This score seemed to outperform both the Delphi and Frykman scores due to its higher sensitivity. Finally, while not including a scoring system, the American Pediatric Surgery Association (APSA) released its guidelines in 2017 to aid in the diagnosis of this variably presenting complication of HSCR. This system places patient presentations into three categories (possible, definite, and severe) based off patient history, physical exam, and imaging studies. The goal of this system was to create an easily used yet clinically relevant grade to help provide consistency in therapy[17].

Histopathology

In 1989, Teitelbaum *et al*[18] described a grading system based on the histological intestinal mucosal changes found in HAEC. They included factors such as intestinal crypt dilation, cryptitis, mucin retention, crypt abscess, mucosal ulceration, and necrosis and proposed a classification system of 5 grades with increasing severity of disease, with grade 0 being normal mucosa and grade 5 being the most severe. They reported a significant correlation between clinically apparent HAEC and histopathologic scores of grade 3 and above. This grading system has persisted and is still used for both clinical and research purposes.

Predisposing risk factors for HAEC

There are several known risk factors for developing HAEC and can be subdivided into preoperative and postoperative. Commonly reported preoperative risk factors include a family history of HSCR, long-segment disease, trisomy 21, presence of associated congenital anomalies, and delay in diagnosis of HSCR[19]. Engum *et al*[20] reported a series of 20 infants and children with history of HSCR and found that the incidence of HAEC was more than double in patients with family history of HSCR (35% *vs* 16%). The reason for this increased risk is thought to be secondary to heritable factors. Trisomy 21 is one of the best-established clinical risk factors conveying a risk as high as 54% of HAEC[19,21] and hypothesized to be due to an intrinsically decreased humoral and cytotoxic T-cell function present in infants with this syndrome[22]. Long-segment disease has also shown to confer larger risk of HAEC, thought to be secondary to increased stasis of luminal contents[19]. Several reports have demonstrated an increased rate of HAEC, as high as 56%, in patients with long-segment disease[23,24]. Finally, delay in diagnosis in the newborn period also seems to be a significant risk factor for HAEC. Lee *et al*[25] performed a retrospective review of 51 newborns diagnosed with HSCR and found a preoperative incidence of 63% of HAEC in patients diagnosed after 7 days of life compared to 12% in those diagnosed before 7 days. They also noted a significant increase in morbidity after HAEC in the late diagnosis group including increased risk of developing postoperative adhesive bowel obstruction and failure to thrive.

Postoperative risk factors for HAEC can be subdivided into histopathologic and mechanical. Histologically, the presence of a segment of aganglionic bowel after definitive surgery is a risk factor for HAEC. This can be seen if there is residual disease after surgery, if an area of bowel becomes aganglionic due to degenerative changes in the bowel after surgery, if a skip area was present where an unknown proximal portion of bowel was also aganglionic, or if the transition zone between normal and aganglionic bowel is not entirely resected[26]. Mechanical predisposing risk factors include bowel torsion proximal to the anastomosis site and formation of an anastomotic stricture or cuff stenosis on the pulled-through segment of normal bowel. Overall, the common premise uniting these risk factors for postoperative HAEC are mechanisms that affect the motility or produce a functional obstruction of the pulled-through bowel. Other clinical risk factors that have been investigated during the postoperative period include a history of preoperative episodes of HAEC and definitive surgery before age of 6 mo[27,28]. Additionally, socioeconomic risk factors for the development of HAEC have been identified. In a study of 100 children awaiting surgical correction for HSCR, the authors found that patients that used public transportation for clinic visits, had one or more missed appointments, had any reported safety concerns, had parents or guardians who were not married, lived with people other than their immediate family, or had mothers who reported drug use or lack of prenatal care were found to have a higher likelihood of developing HAEC[29].

Pathophysiology

The exact mechanism underlying HAEC remains unknown. However, there has been significant progress in our understanding of the pathogenesis of this disorder and studies underscore the potential role of the following pathways:

Intestinal dysmotility: Impaired intestinal motility affecting the aganglionic segment was one of the earliest described mechanisms causing HAEC. However, ongoing dilation of the proximal ganglionated bowel leading to fecal stasis, bacterial translocation and ischemia was later proposed as a cause for HAEC. Nevertheless, HAEC still develops after surgical correction or in the presence of a diverting ostomy in some patients suggestive of an intrinsic defect at the level of the enteric nervous system leading to dysmotility. Several HSCR mouse model studies have demonstrated a decrease in neuronal cell density at the level of the proximal ganglionated bowel[30] and alteration in the balance of local cholinergic and nitrergic neurons[31], with overrepresentation of the latter which are involved in intestinal relaxation. These findings were later corroborated in a human study and most importantly, demonstrated a possible correlation with clinical outcomes[32]. In contrary, a retrospective study in humans concluded that in HSCR patients with a low mucosal nerve fiber innervation grade in the distal aganglionic bowel have a higher risk of developing HAEC[33]. Similarly, a prospective study also demonstrated that lack of cholinergic innervation in the distal colon of HSCR patients was associated with increased risk of postoperative HAEC[34].

Impaired mucosal defense and intestinal barrier function: One of the initial studies implicating impaired mucosal defense in HSCR evaluated the role of secretory immunoglobulin A (sIgA). The authors found that the transfer of sIgA across the gastrointestinal wall is impaired in patients with HSCR (despite increased sIgA levels in the lamina propria plasma cells) and decreased in those with HAEC[35]. Other studies have suggested that the production and transport of intestinal mucins may be abnormal in HSCR and may have a potential role in the pathogenesis of HAEC[36,37]. Of these, MUC-2 is the predominant mucin expressed in humans and *in vitro* studies have demonstrated that it can prevent bacterial translocation across the intestinal wall[38]. A study that analyzed stool samples in humans found that the protein expression of MUC-2 was significantly decreased in patients with HSCR when compared to controls and absent in those with clinical features of HAEC[39]. Interestingly, studies

in a HSCR mouse model demonstrated an increase in goblet cell proliferation and differentiation in areas of aganglionosis, and subsequent altered surface mucus properties prior to the development of inflammation in the distal colon epithelium in HAEC[40]. Other studies of the caudal type homeobox gene-1 and -2 (CDX-1 and CDX-2) that control proliferation and differentiation of intestinal mucosal cells[41], intracellular adhesion moclecule-1 (ICAM-1) a cell surface adhesion glycoprotein involved in leukocyte recruitment[42], and caveolin-1 involved in inflammation and intestinal epithelial barrier function[43], have shown altered gene expression in the colonic mucosal epithelium of patients with HAEC.

Dysbiosis: Emerging techniques, like next generation sequencing, have provided novel insight of the human intestinal microbiota, both in health and disease. Animal and human studies have demonstrated that the microbiota composition and diversity are different between controls, HSCR and HAEC. However, most are limited to a small number of samples or differences in technique that demonstrate variation in results. Nevertheless, it seems evident that dysbiosis is part of the pathogenesis in HAEC. A study by Frykman *et al*[44] evaluated the intestinal microbiota in fecal samples of HSCR patients with and without HAEC. By using DNA sequencing they demonstrated that not only the bacterial, but also the fungal composition was different in children with HAEC compared to those without HAEC. The authors found modest reductions in Firmicutes and Verrucomicrobia and increases in Bacteroidetes and Proteobacteria. Varieties of fungi were also observed. Specifically, Candida was increased and Malassezia and Saccharomyces were reduced[44]. Li *et al*[45] collected fecal samples from the proximal and distal colon during routine or emergency surgery in patients with HSCR, prior history of HAEC, and active HAEC and found a predominance of Bacteroidetes in the first group and of Proteobacteria the latter groups. Interestingly, these changes persisted in patients with HAEC and the microbiota composition was different between the proximal and distal colon sites in HSCR patients, but not in those with a prior history or active HAEC. More recently, Parker *et al*[46] demonstrated longitudinal changes in the intestinal microbiota from fecal samples of HSCR patients with active enterocolitis and demonstrated composition similarity in patients that achieved remission (also enrichment with Blautia), while patients with recurrent HAEC demonstrated ongoing substantial variability in their microbiota composition. We have demonstrated that the microbiota composition and diversity is different between patients with and without a history of postoperative HAEC by 16S rDNA sequencing of colon tissue samples. Specifically, we reported an increased relative abundance of the phyla Bacteroidetes, Firmicutes and Cyanobacteria in HAEC patients and Fusobacteria, Actinobacteria and Proteobacteria in HSCR patients and an increased relative abundance of the genera Dolosigranulum, Roseouria and Streptococcus in HAEC patients and Propionibacterium and Delftia in HSCR patients[47]. These findings highlight that changes in the intestinal microbiota composition and diversity can be seen both in the intestinal lumen and the bowel wall in HSCR patients with and without HAEC.

Treatment

There are several treatment modalities utilized in the care of patients with HAEC. The HAEC severity grading system described by the APSA provides recommendations for management based on grade of severity (Table 1)[17]. Grade 1, or possible HAEC, can be managed in the outpatient setting with oral antibiotics (metronidazole), oral hydration and potential use of rectal irrigations. Rectal irrigations are meant to wash out retained stool to help relieve any obstruction that is present. They are typically given 2-4 times per day using large bore rubber catheters until the effluent is clear[19]. Grade 2 (definite HAEC) requires inpatient management where the patient is usually kept Nil Per Os (NPO) and treated with intravenous (IV) antibiotics (metronidazole) with consideration of broad-spectrum antibiotic coverage, and rectal irrigations. Patients should have stool tests to rule out potential infections that could be involved and cause a similar presenting symptomatology (Clostridioides difficile, Salmonella, Shigella, Rotavirus)[19]. Grade 3 management is largely similar to grade 2. However, these patients are quite ill, often requiring intensive care unit level care, nasogastric decompression, and may need surgical management such as proximal bowel diversion. Several studies have shown that use of this standardized algorithm or other similar tools to guide management decreases length of stay, use of IV antibiotics, and readmission[48,49].

Another treatment option for HAEC is the use of Botulinum toxin injection (BTI) to the internal anal sphincter (IAS). In patients with HSCR, due to the absence of the recto-anal inhibitory reflex, the IAS does not relax upon rectal distension with stool or gas leading to continued distal bowel obstruction after surgical correction and potentially increasing the risk of HAEC. Botulinum toxin prevents the presynaptic release of acetylcholine producing a state of temporary local denervation with subsequent decrease of the resting anal pressure, potentially relieving the distal functional obstruction. In 2021, Svetanoff *et al*[50] performed a retrospective study looking at BTI in the setting of HAEC and found a statistically significant increase in the time between readmission in patients with recurrent HAEC. BTI has also been shown to decrease the duration of IV antibiotics and length of stay in patients with HAEC [51]. However, most studies assessing the utility of BTI in HAEC are retrospective and underpowered. Roorda *et al*[52] performed a meta-analysis of the evidence for BTI in HSCR and specifically looked at effectiveness in HAEC. They included 3 studies involving 52 patients which showed reduction of

Table 1 Hirschsprung's disease associated enterocolitis severity score and management[17]

APSA category	Symptom	Radiography	Treatment	Additional measures
Grade 1 (Possible HAEC)	Anorexia, diarrhea, mild abdominal distension	Normal, or mild signs of ileus	Oral hydration; Oral metronidazole	Rectal irrigations
Grade 2 (Definite HAEC)	One or more of the following: Explosive diarrhea; Fever, tachycardia, or lethargy; Moderate abdominal distension and/or tenderness; Explosive gas/stool on rectal examination;	May include: Signs of ileus (air fluid levels, dilated bowel loops); Distension of the proximal colon w/rectosigmoid cutoff	Clear liquids or NPO; IV hydration; Metronidazole (PO or IV); Broad spectrum antibiotic coverage; Rectal irrigations	NGT decompression
Grade 3 (Severe HAEC)	Grade II symptoms plus: Obstipation; Poor perfusion; Hypotension; Altered mental status; Marked abdominal distension; Signs of peritonitis	Signs of Grade II PLUS possible: Pneumatosis intestinalis; Pneumoperitoneum (rare)	NPO; Metronidazole (IV) + broad spectrum antibiotics (IV ampicillin + gentamicin, IV piperacillin/tazobactam); Rectal irrigations	NGT decompression; Possible surgical intervention

APSA: American Pediatric Surgery Association; HAEC: Hirschsprung's disease associated enterocolitis; IV: Intravenous; NGT: Nasogastric tube; NPO: Nothing by mouth; PO: Per oral.

enterocolitis in an average of 58% of patients, however the effect was not statistically significant. Further studies are needed to truly evaluate the use of BTI for active HAEC. Additionally, others have evaluated the use of BTI as a preventative measure for postoperative obstructive symptoms and HAEC. After other causes of obstruction are ruled out, BTI into the internal and external sphincter can serve as a therapeutic intervention and may reduce the incidence of obstructive symptoms and HAEC[51]. Other studies have suggested there may be a decrease in hospitalizations for patients with recurrent HAEC. Chumpitazi *et al*[53] performed a retrospective review looking at BTI use in patients with surgically repaired HSCR and IAS achalasia. They demonstrated a potential decrease in hospitalizations per year in their HAEC subgroup; however, the long-term response to the injections varied and children with IAS achalasia seemed to respond better than HAEC patients. They also noted that initial short-term improvement in symptoms after first BTI was useful in predicting favorable long-term outcomes.

Other postoperative preventive measures include the daily use of rectal irrigations, anal dilations, and rectal tube placement. A systematic review and meta-analysis demonstrated that the use of rectal irrigations after pull-through surgery significantly reduced the incidence of postoperative HAEC[54]. However, this same study concluded that the potential role of routine anal dilations in preventing postoperative HAEC remains unclear. A randomized trial demonstrated that the temporary use of a rectal catheter for 5 days after surgery reduced the postoperative incidence of HAEC in the first 30 days [55].

In terms of operative management for HAEC, there does appear to be a role for intestinal diverting ostomy in severe cases. Several features which may warrant consideration of diversion include delayed presentation for HSCR, presence of multiple risk factors for HAEC, or multiple concomitant comorbid conditions including sepsis, trisomy 21, and Bardet- Biedl Syndrome[19]. Prior to corrective pull-through, diversion can be considered in the decompensating neonate with long-segment disease given that they have higher failure rates of rectal washouts[56]. In these rare cases, a leveling colostomy is performed with intraoperative frozen section histology which is essential to ensure the colostomy is created just proximal to the transition zone[57]. While diversion may not entirely resolve HAEC, it does improve the patient's clinical status and quality of life.

CONCLUSION

There are several aspects of HAEC care that still require further study. Notably, improvement in both diagnostic strategies and standardization of care is needed across institutions. Promising areas of research include intestinal microbiota analysis which may help to personalize therapy, stem cell administration to restore the motor function to the remaining portions of bowel, and therapies aimed at altering colonic mucus barrier properties could be explored towards preventing the onset of enterocolitis in HSCR. This along with advances in our understanding of the pathophysiology itself will allow us to better care for HSCR patients suffering from recurrent HAEC.

FOOTNOTES

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MINIREVIEWS

Seronegative autoimmune hepatitis in childhood

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Abstract

Comprehensive guidelines on seropositive autoimmune hepatitis have been published for both adults and children, although these guidelines comprise only limited knowledge about seronegative autoimmune hepatitis. Autoimmune hepatitis presents as an acute or chronic progressive disease and poor outcomes are inevitable if left untreated. The absence of autoantibody positivity, hypergammaglobulinemia and lack of comprehensive algorithms makes seronegative autoimmune hepatitis a mysterious disease. In general, seronegative autoimmune hepatitis often presents with acute hepatitis, and its treatment and prognosis similar to seropositive autoimmune hepatitis. The present review focuses on the known characteristics of seronegative autoimmune hepatitis in childhood, and those of which current knowledge is vague.

Key Words: Seronegative autoimmune hepatitis; Autoantibody negative; Lymphocytopenia; Aplastic anemia

Core Tip: Seronegative autoimmune hepatitis is a diagnostic dilemma. The absence of autoantibodies and hypergammaglobulinemia which is not uncommon in seronegative autoimmune hepatitis complicates the diagnosis. Seronegative autoimmune hepatitis often presents with acute hepatitis, and its treatment and prognosis similar to seropositive autoimmune hepatitis. This review discusses whether seronegativity is only a matter of laboratory issue or if it implies an entity with different pathogenesis, clinical features, treatment algorithms, and prognosis.

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INTRODUCTION

The diagnosis of autoimmune hepatitis is based on the ruling out of other causes of liver damage with the presence of non-organ specific autoantibodies and specific histological findings. The value of autoantibodies cannot be denied in the diagnosis and subtyping of autoimmune hepatitis and in the follow-up of disease activity. Failure to diagnose may increase mortality in children presenting for the first time with acute hepatic failure or cirrhosis will be inevitable in children due to progressive disease course if not treated. Autoimmune hepatitis is a progressive inflammatory disease that responds well to immunosuppressive therapy and is diagnosed with histologically interface hepatitis, serologically presence of non-organ-specific autoantibodies, and biochemically elevated transaminase and immunoglobulin G (IgG) levels[1,2]. The term seronegativity refers to the condition in which no autoantibodies are detected, but other features partially or completely support the diagnosis of autoimmune hepatitis, although the term seronegative autoimmune hepatitis has not been widely accepted. It is not known whether seronegativity is only a matter of laboratory issue or if it implies an entity with different pathogenesis, clinical features, treatment algorithms, and prognosis. We present here a discussion of the aspects of seronegative cases that are already known or those that require further elucidation.

EPIDEMIOLOGY

Autoimmune hepatitis can present in childhood or adulthood. Different incidence and prevalence rates have been reported for autoimmune hepatitis from different countries, with reported incidences in the range of 0.23-0.4 cases/100.000 people and prevalence in the range of 2.4-9 cases/100.000 people. Differences in the incidence and prevalence in the same ethnic origins but in different geographic regions suggest that factors other than genetic predisposition play a role in disease development. Autoimmune hepatitis is more commonly observed in females than in males[3]. There is a lack of detailed information about the prevalence of seronegative autoimmune hepatitis in which conventional autoantibodies are not detected. Seronegative autoimmune hepatitis account for 5%-20% of all autoimmune hepatitis, and on top of the uncertainties regarding which patients should be considered seronegative-it is no secret that some seronegative cases are classified as cryptogenic hepatitis-there is also a possibility of false-negative results in autoantibodies[4]. In our series of 54 patients, 27.7% (15/54) were identified as seronegative autoimmune hepatitis at the time of diagnosis, and a significant proportion (60%) of the cases were female, as is the case with type-1 autoimmune hepatitis. The average age at presentation was 5.69 years in those with seronegative autoimmune hepatitis. The mean age at presentation was 11 years in patients with type-1 autoimmune hepatitis and 5.1 years in those with type-2 autoimmune hepatitis[5].

PATHOGENESIS

The liver cells become damaged in cases of autoimmune hepatitis as a result of the joint effects of cellular and humoral immunity. It is suggested that damage develops in the target organ with the loss of immunity control that is triggered by a virus in individuals with a genetic predisposition**.** The loss of immune tolerance to hepatocyte antigens (these antigens are considered to be asialoglycoprotein receptors, liver cytosolic antigens, and soluble liver antigens) due to the compromised functioning of regulatory T cells (Tregs) results in the activation of the CD4 and CD8 T-cells, which release such proinflammatory cytokines such as interferon-γ and tumor necrosis factor-α[6]. A recent study suggested a decrease in Tregs in the peripheral blood of patients with untreated seropositive autoimmune hepatitis, together with increased Treg/T-cell and Treg/B-cell ratios identified on liver biopsy, and this finding was associated with the migration of these cells to the center of inflammation [7]. Proinflammatory cytokines initiate hepatocyte damage and result in the immune activation and proliferation of macrophages, B and T-cells, and natural killer cells. B-cells subsequently transform into plasma cells, which produce the antibodies that serve as the diagnostic instruments in autoimmune hepatitis[6]. The antibodies and target antigens described in seropositive autoimmune hepatitis are listed in Table 1.

T-cells serve as the trigger in the initiation of autoimmune hepatitis and mediate the activation of humoral immunity[8]. Autoantibodies are currently used in the diagnosis of autoimmune hepatitis, and for the determination of the subtype and the assessment of remission. Anti-nuclear antibody (ANA) and/or anti-smooth muscle antibody (ASMA) are detected in type-1 autoimmune hepatitis, and anti-liver-kidney microsomal antibody (LKM) and/or liver cytosol type-1 antibody (LC-1) in type-2 autoimmune hepatitis. ANA and ASMA are positive in approximately half of the patients with autoimmune hepatitis, while ANA alone is positive in 10%–15% and ASMA alone in 30%–35% of patients. Both anti-LKM and anti-LC-1 are positive in approximately half of the patients with type-2 autoimmune hepatitis. A positive anti-LC-1 alone is reported in 10% of patients with type-2 autoimmune hepatitis. A positive anti-soluble liver antigen/liver–pancreas antigen (anti-SLA) reported

Table 1 The antibodies and target antigens in autoimmune hepatitis

Antibody	Target antigen
ANA	Single-stranded/double-stranded DNA, ribonucleoproteins
ASMA	Filamentous actin, vimentin, desmin
LKM	Cytochrome P450 2D6 (CYP2D6)
anti-SLA	UGA serine transfer RNA associated protein
LC-1	Formiminotransferase cyclo-deaminase
pANCA	Nuclear lamina proteins
ASGP-R	Asialoglycoprotein receptor

ANA: Anti-nuclear antibody; ASMA: Anti-smooth muscle antibody; LKM: liver-kidney microsomal antibody; LC-1: Liver cytosol type-1 antibody; SLA: Anti-soluble liver antigen/liver–pancreas antigen; ASGP-R: Asialoglycoprotein receptor; pANCA: Perinuclear anti-neutrophil cytoplasmic antibody.

in both types of autoimmune hepatitis, being positive in approximately one-fifth of those with type-1 and half of those with type-2 autoimmune hepatitis. A positive anti-SLA alone is reported in less than 10% of all patients[9]. Serum concentrations of anti-LKM, anti-LC-1, and ASMA have been identified as indicators of disease severity. In other words, hepatocyte necrosis can be severe, and the disease may progress rapidly to cirrhosis[2,9]. This raises the question: "Is the pathogenesis of seronegative autoimmune hepatitis different, and does it have a milder disease course?" Under normal circumstances, T cells initiate the immune cascade in seropositive autoimmune hepatitis, while the inflammatory events continue with B cells (Figure 1). Activated B cells, which are switched to plasma cells with the stimulation of T cells, release autoantibodies and cytokines/chemokines, cause autoantibody-mediated activation of complement and macrophage/dendritic cells and continue to contribute to inflammation with antigen presentation to T cells, while on the other hand suppress Treg and B cells' anti-inflammatory effects[10-12]. There is a lack of comprehensive data on the contribution of autoantibodies to cell damage in seronegative autoimmune hepatitis. The presence of plasma cells in the liver biopsies of patients with seronegative autoimmune hepatitis suggests that similar physiopathological mechanisms are involved in the pathogenesis of seronegative autoimmune hepatitis. Perhaps a defect in differentiation and maturation of B cells could impair antibody production, but its effects on T cell regulation were preserved. There is, however, a lack of evidence supporting this theory in seronegative patients.

There may also be a case of pseudo-seronegativity. This may be attributed to several reasons for this. Firstly, the autoantibody tests may not have been performed as recommended. The International Autoimmune Hepatitis Group has determined a threshold of ≥ 1:40 for autoantibodies to be detected by an indirect immunofluorescence method by diluting the serum in adults[13]. The recommended autoantibody threshold levels in children are lower than those determined for adults, with a titer of 1:20 for ANA and ASMA and a titer of 1:10 for anti-LKM being considered significant[14]. In adults, thresholds for all antibodies are ≥ 1:40. False-negative results may be obtained if standard high dilutions are used in the laboratory designated for adult patients. This problem can be overcome by communicating with the laboratory personnel for testing serum in low dilutions or it may be beneficial to test such autoantibodies using an enzyme-linked immunosorbent assay (ELISA), even if its validity has not been fully demonstrated. Secondly, previous studies have suggested that the commonly used immunofluorescence tests may initially produce false-negative results due to an intense antigen-antibody reaction in patients presenting with acute hepatic failure and acute hepatitis[8,15]. This theory is supported by the observation of seroconversion during the disease course in some patients who were initially seronegative. Furthermore, immunosuppressive agents such as corticosteroids and azathioprine may lead to conversion from seronegative to seropositive with the elimination of the effect of unknown factors. It is currently unknown when, and in what titers will the autoantibodies be positive due to limited data. In an earlier study by the present authors, the majority of patients with seronegative autoimmune hepatitis had an acute presentation (13 out of 15 patients), and the autoantibody tests turned positive in half of the patients (7 of the 15 patients) during follow-up, with a median time to seroconversion of 28 d (18–51 d)[5]. Thirdly, antibodies other than ANA, ASMA, and anti-LKM such as anti-SLA and anti-LC-1, tested by ELISA or immunoblotting methods and cannot be studied in many centers, can be checked[16]. The investigation of these autoantibodies and novel antibodies that are yet to be discovered can reduce the number of cases labeled as seronegative autoimmune hepatitis when conventional antibodies are negative.

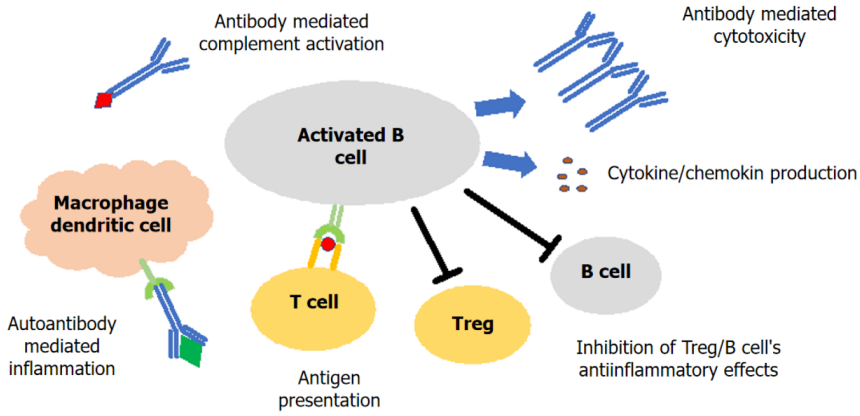

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Figure 1 B cell role in the pathogenesis of autoimmune hepatitis. T cells allow B cells to switch to antibody-producing plasma cells. Autoreactive B cells release autoantibody and cytokine/chemokines. B cells continue to contribute to inflammation by presenting antigen to T cells and cause autoantibody-mediated activation of macrophage/dendritic cells, while suppressing the anti-inflammatory effects of Treg and B cells. Treg: Regulatory T cell.

PATHOLOGY

A liver biopsy is essential for the establishment of a diagnosis of autoimmune hepatitis. The anticipated primary histological finding is lymphoplasmacytic infiltration in portal areas extending to the lobule center, in other words, interface hepatitis. That said, interface hepatitis can also be observed in other liver diseases, such as acute and chronic viral hepatitis, drug-induced liver disease, and Wilson's disease. Other histological findings include portal lymphoplasmacytic infiltration, rosette formation, emperipolesis, central perivenulitis, and portal-to-portal or portal-to-central fibrosis. Centrilobular necrosis and multilobular collapse can be observed in acute presentations. Interface hepatitis may not be obvious in cirrhotic patients and those receiving immunosuppressive therapy. It has been stated that the presence of central perivenulitis and hyaline droplets in Kupffer cells may be an important diagnostic finding in the absence of interface hepatitis[1,6].

Studies of adult patients have suggested that a histopathological finding specific to seronegative autoimmune hepatitis is lacking, although there have been contradictory statements on whether the severity of histopathological findings differs from that observed in seropositive autoimmune hepatitis. Previous studies have reported that advanced histological-stage cirrhosis is more common in seronegative patients than in seropositive patients[17]. Despite the limited data on pediatric patients, we commonly encounter centrilobular necrosis in patients with seronegative autoimmune hepatitis in our practice due to the frequency of acute presentation.

In one study, CD8 T-cell-dominant infiltration was identified in the liver biopsies of a small number of pediatric patients with seronegative autoimmune hepatitis and aplastic anemia[18]. In a study of 33 patients in whom the authors described the underlying disease as "acute hepatic failure with an unknown cause", including eight patients who had hepatitis-associated aplastic anemia (HAAA), CD8 T-cell infiltration was identified in the livers of the majority of cases. The patients diagnosed with "acute hepatic failure with an unknown cause" actually fully meet the definition of seronegative autoimmune hepatitis. The authors state, however, that CD8 T-cell infiltration presented to various degrees in a small number of patients with autoimmune hepatitis, although further research is needed in this regard[19].

CLINICAL FINDINGS

Seropositive autoimmune hepatitis can be discovered incidentally with asymptomatic transaminase elevation but can also be diagnosed after presentation with a severe clinical course. The presentation may vary between different regions but is generally as follows: Approximately one-third of patients present with fatigue, nausea, abdominal pain, and jaundice, as in acute viral hepatitis (acute presentation), while the other third presents with such symptoms of chronic hepatitis as lack of appetite, weight loss, amenorrhea, and intermittent jaundice. Less than one-fifth presents with the symptoms of cirrhosis and its complications, such as ascites, abdominal distention, splenomegaly, and variceal hemorrhage. Type-1 autoimmune hepatitis is often observed in adolescence, while type-2 autoimmune hepatitis is mostly encountered in young children. Patients with type-2 autoimmune hepatitis commonly present with acute hepatitis or acute hepatic failure[1]. The data derived from adult patients suggests that acute presentations are uncommon in seronegative autoimmune hepatitis[20]. There are no detailed clinical findings related seronegative autoimmune hepatitis in children. In a study of 38 pediatric patients with seronegative autoimmune hepatitis, three-quarters presented with acute

symptoms[16]. In our previous study, 13 of 15 patients who were considered to have seronegative autoimmune hepatitis presented with acute hepatitis[5]. There is another terminology called HAAA in the literature[21]. Aplastic anemia develops within a couple of weeks or months after the onset of hepatitis, while it rarely develops after one year. Patients can be recognized at the acute hepatitis stage with symptoms such as vomiting and jaundice but can also be diagnosed after the development of aplastic anemia. HAAA, is thought to develop as a result of autoimmunity, triggered by an unknown factor, although a virus is suspected. Although HAAA can be diagnosed at any age, including adulthood, reports in literature focus mostly on pediatric cases, and most are case reports or small case series[22]. The prevalence of HAAA was found to be 5% in a multicenter European study of 3916 adult patients with aplastic anemia[23]. While previous studies have described the histopathological findings of the liver as lobular inflammations as in viral hepatitis[24], some have described features of autoimmune hepatitis and termed it as seronegative autoimmune hepatitis with the absence of autoantibodies[25]. The confusing situation for the diagnosis of autoimmune hepatitis is the spontaneous normalization of transaminases without any treatment. Our clinical experience suggests that transaminase elevation is no longer observed once aplastic anemia has developed. Autoimmune hepatitis in fact has a chronic disease course that is characterized by fluctuations. In our previous study, aplastic anemia developed in two patients with seronegative autoimmune hepatitis who presented with cholestatic hepatitis, despite dramatic improvement in hypertransaminasemia and direct bilirubinemia after corticosteroid treatment[5]. Furthermore, hepatitis did not recur within two years of the discontinuation of immunosuppressive therapy.

DIAGNOSIS

As is the case with seropositive autoimmune hepatitis, there is no pathognomonic finding of seronegative autoimmune hepatitis, so it is important to rule out other conditions such as viral hepatitis, alpha-1 antitrypsin deficiency, metabolic conditions such as Wilson's disease, and drug-induced liver injury. Hypergammaglobulinemia is one of the vital criteria for a diagnosis of seropositive autoimmune hepatitis[4]. Alongside the absence of autoantibodies, hypergammaglobulinemia which is not uncommon in seronegative autoimmune hepatitis, further complicates diagnosis. While serum IgG levels may be within normal ranges for age in seronegative cases, a decrease from baseline may be observed with treatment[12,25]. Patients diagnosed in the hepatitis stage who subsequently develop aplastic anemia are often found to have lymphocytopenia before the development of aplastic anemia. It has been found that the CD4 T-cell count is decreased in these patients[18]. If a patient is found to have isolated persistent lymphocytopenia without stigmas of a viral infection, the patient will most likely develop aplastic anemia in the future. Finally, it is essential to identify any histopathological liver features specific to autoimmune hepatitis to confirm a diagnosis of seronegative autoimmune hepatitis, although some histopathological findings can be observed also in other liver diseases.

Simplified diagnostic criteria is used for research purposes in autoimmune hepatitis but may also be used in cases that pose diagnostic challenges[4]. This scoring system has been found to have a sensitivity of 77% and a false-negative rate of 17%, and these false-negative cases are indeed seronegative cases[26]. In cases where conventional antibodies negative with an immunofluorescence assay, repeat tests with other techniques such as ELISA or immunoblotting and investigations of other autoantibodies may aid the diagnosis of autoimmune hepatitis. Monitoring treatment response seems to be the best option to avoid the consequences of delayed diagnosis. The algorithm followed in our clinic for the treatment of seronegative patients is presented in Figure 2.

TREATMENT

Delays in treatment can lead to disease progression in patients with autoimmune hepatitis, while timely treatment can prevent such severe complications as cirrhosis. The treatment of seronegative autoimmune hepatitis involves immunosuppressive therapy, as in seropositive autoimmune hepatitis. The goal of treatment in seropositive autoimmune hepatitis is to normalize transaminase and IgG levels, to turn autoantibodies negative and to provide improvement to histological inflammation. Clinical and biochemical improvement is expected immediately after treatment[4]. Even if IgG level by age is within normal range a decrease within the normal range is often expected with treatment and can be regarded as a marker of biochemical response. Repeat autoantibody tests should be carried out to observe if they turn positive during treatment. Patients who develop aplastic anemia often have lymphocytopenia initially, but in those without lymphocytopenia, it should be evaluated whether lymphocytopenia develops during treatment, even if transaminase levels decrease with immunosuppressants[5,16,25]. Aplastic anemia may develop even in the early period during corticosteroid induction therapy. You can begin the treatment with corticosteroid (prednisone or prednisolone) and continue with low-dose corticosteroid or corticosteroid plus azathioprine or azathioprine monotherapy. The main challenge in the treatment of seronegative patients is the timing of the switch to such second-line therapies as

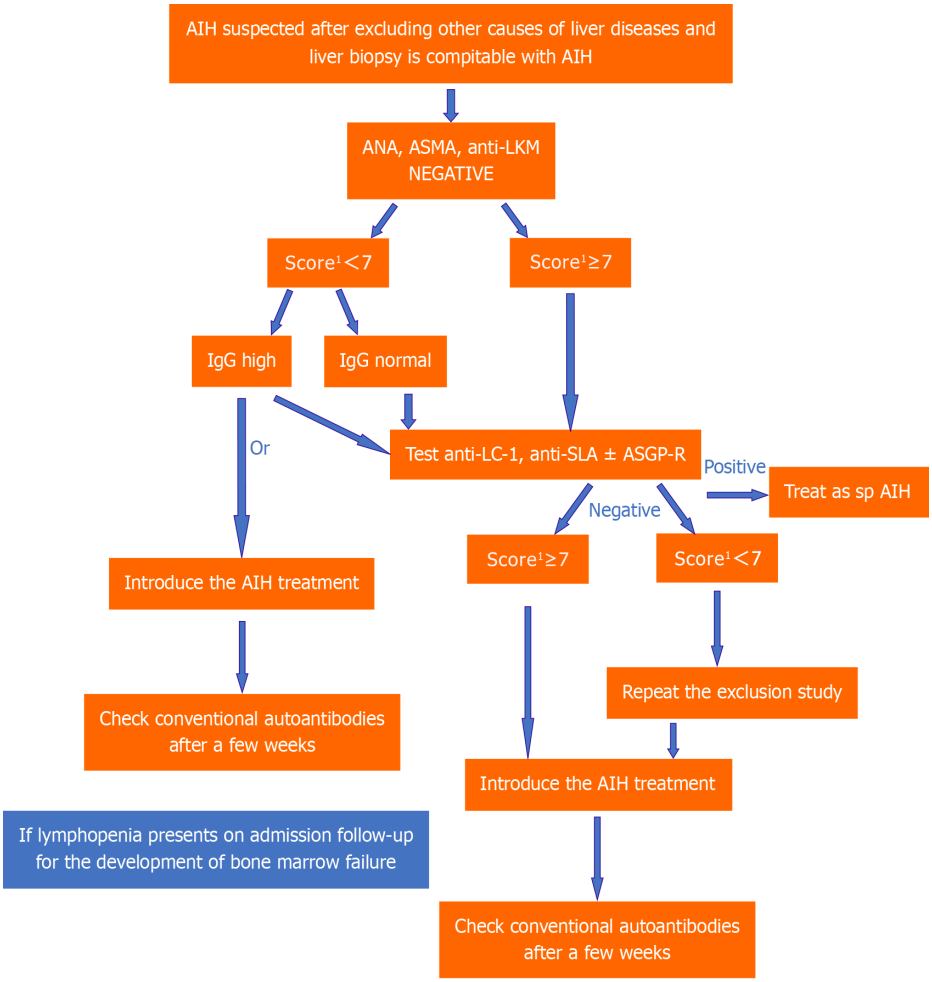

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Figure 2 Algorithm for the diagnosis of seronegative autoimmune hepatitis. [1]Proposed scoring criteria for the diagnosis of juvenile autoimmune liver disease by ESPGHAN 2018 (10). AIH: Autoimmune hepatitis; ANA: Anti-nuclear antibody; ASMA: Anti-smooth muscle antibody; LKM: liver-kidney microsomal antibody; IgG: Immunoglobulin G; LC-1: Liver cytosol type-1 antibody; SLA: Anti-soluble liver antigen/liver–pancreas antigen; ASGP-R: Asialoglycoprotein receptor.

mycophenolate mofetil or calcineurin inhibitors when the patient fails to respond to first-line therapies. In such cases, we recommend re-assessing differential diagnoses, including metabolic disorders, and re-checking autoantibody status before initiating second-line therapies. Current literature on adult patients suggests that the treatment response in seronegative patients is similar to that of seropositive patients [11], although there is a paucity of such data on pediatric cases. Based on our experience and available pediatric data[5,16,18,25], we consider that the response to treatment is not different from seropositive patients. The cessation of therapy may be considered if biochemical and histological remission is observed following two years of therapy in patients with type-1 autoimmune hepatitis, although this is not recommended in patients with type-2 autoimmune hepatitis due to the high relapse rates. It is unclear whether treatment can be discontinued in patients with seronegative autoimmune hepatitis. Although a previous study[25] reported the successful cessation of treatment in pediatric seronegative patients, we made no such attempt at cessation due to the unpredictability of the outcomes, as in our practice, young seronegative children exhibited acute severe clinical presentations similar to that of patients with type-2 autoimmune hepatitis.

The benefits of corticosteroid therapy are arguable, even in patients with seropositive autoimmune hepatitis who present with acute hepatic failure. Survival without transplantation is possible in patients treated with corticosteroid, although an increased risk of sepsis and mortality has been reported[1]. The appropriate approach to patients presenting with acute hepatic failure and unresponsive to corticosteroid therapy-if steroid therapy has been attempted—and in those with decompensated cirrhosis is liver transplantation.

PROGNOSIS

Despite the limited data related to pediatric patients, prognosis is generally good in patients with

Table 2 The differences between seropositive and seronegative autoimmune hepatitis

Seropositive individuals	Seronegative individuals
High IgG	Normal IgG (may be high)
Presents with an acute or chronic course of disease	Generally, presents with acute manifestations
Does not show bone marrow abnormality	Lymphopenia may accompany (generally initially) and bone marrow failure may develop
Autoantibodies are detectabl on admission	Autoantibody positivity may develop after immunosuppressive therapy
Disease onset is usually in the second decade for type 1 AIH and at any age in the first decade for type 2	Disease onset is similar to type 2 AIH (may be at any age)
Treatment response is generally good	Treatment response is generally good
Immunosuppressant withdrawal possible (Recurrence rate is higher in type 2 AIH than type 1)	Immunosuppressant withdrawal possible (Recurrence rate is unknown)

IgG: Immunoglobulin G; AIH: Autoimmune hepatitis.

seronegative autoimmune hepatitis. In a study of 38 seronegative patients, Maggiore *et al*[25] reported that all were still alive after 4-17 years. Among the study participants, one presented with acute hepatic failure underwent liver transplantation, while four patients with aplastic anemia underwent bone marrow transplantations. The median time to the cessation of immunosuppressive therapy in 20 out of the 38 cases was 4 years (1-6 years), and nine in whom the immunosuppressive therapy was stopped had aplastic anemia[25]. One adult study reported a high risk of developing hepatitis in the transplanted livers of patients with seronegative autoimmune hepatitis[20], although there is a lack of long-term data that would allow us to speculate on the situation in children. The differences between seropositive and seronegative autoimmune hepatitis are summarized in Table 2.

CONCLUSION

While seronegative autoimmune hepatitis is not a rare entity, little is known about its diagnosis and treatment. However, based on this limited literature and our experience, we can summarize seronegative autoimmune hepatitis as follows. Since autoantibody positivity at low dilutions in immunofluorescence is sufficient for a diagnosis of autoimmune hepatitis in children, it should be ensured that the laboratory conditions are arranged for opportunity to test autoantibodies in low dilutions, or other non-conventional autoantibodies should be studied. The presence of lymphopenia points to the development of bone marrow failure in the future. Treatment should not be delayed after other causes have been ruled out in patients with liver biopsy features consistent with autoimmune hepatitis to prevent the development of complications. The treatment of seronegative autoimmune hepatitis is similar to seropositive autoimmune hepatitis and the authors believe that the prognosis is good in seronegative autoimmune hepatitis.

FOOTNOTES

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MINIREVIEWS

Various aspects of hearing loss in newborns: A narrative review

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Abstract

Hearing loss is considered the most common birth defect. The estimated prevalence of moderate and severe hearing loss in a normal newborn is 0.1%-0.3%, while the prevalence is 2%-4% in newborns admitted to the newborn intensive care unit. Neonatal hearing loss can be congenital (syndromic or non-syndromic) or acquired such as ototoxicity. In addition, the types of hearing loss can be conductive, sensorineural, or mixed. Hearing is vital for the acquisition of language and learning. Therefore, early detection and prompt treatment are of utmost importance in preventing the unwanted sequel of hearing loss. The hearing screening program is mandatory in many nations, especially for high-risk newborns. An automated auditory brainstem response test is used as a screening tool in newborns admitted to the newborn intensive care unit. Moreover, genetic testing and screening for cytomegalovirus in newborns are essential in identifying the cause of hearing loss, particularly, mild and delayed onset types of hearing loss. We aimed to update the knowledge on the various aspects of hearing loss in newborns with regard to the epidemiology, risk factors, causes, screening program, investigations, and different modalities of treatment.

Key Words: Newborns; Hearing loss; Deafness; Sensorineural hearing loss; Congenital hearing loss; Universal hearing screening program in newborns

Core Tip: Hearing loss in newborns is a common problem worldwide. Hearing is responsible for the acquisition of language, speech, cognition, and learning. Deaf individuals have a great negative impact on public health and the economic state. Early detection and prompt intervention lead to better outcomes. The universal hearing screening program, genetic testing, and cytomegalovirus detection are useful tools for the early detection of hearing loss in newborns. Rehabilitation of deaf infants with hearing aids or cochlear implants, gene therapy, and treatment of cytomegalovirus infection are satisfactory methods of treatment. However, researchers are focused on resolving the ambiguities regarding the diagnosis and treatment of hearing loss.

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INTRODUCTION

Hearing loss is the most common sensory deficit and one of the most common congenital abnormalities [1,2]. It affects 432 million adults and 34 million children across the globe (https://www.who.int/en/news-room/fact-sheets/detail/deafness-and-hearing-loss). It was estimated that the prevalence of bilateral moderate to severe hearing loss ranged from 1-3/1000 normal newborns and 2-4/1000 in high-risk group newborns[3,4].

Hearing loss in newborns can be caused by a genetic factor in 50% of cases, while acquired hearing loss is related to many causes in the prenatal, natal, and postnatal periods[5]. Hearing is essential for the acquisition of speech, language, and learning development[6]. Therefore, hearing loss particularly of bilateral severe to profound severity harms the development of newborns and results in them living with a significant handicap if not detected and treated early[7].

Early detection of hearing loss and prompt intervention are of utmost importance to minimize the negative impact of hearing loss and at the same time to maximize healthy development of the auditory pathway during the critical period of neural growth. Hence, the Joint Committee on Infant Hearing (JCIH) recommends that all newborns must be screened for hearing and the diagnosis should be established by the age of three months of life, and deaf infants treated at the age of six months[8]. Of course, timely fitting of hearing aids or cochlear implants is useful for deaf children[9].

The diagnosis of hearing loss depends on the doctor or family's suspicion and cannot diagnose all cases of significant hearing impairment. Besides, hearing screening of high-risk newborns (such as a family history of congenital hearing loss) can detect approximately 50% of cases with significant hearing loss. Therefore, it is essential to perform universal hearing screening of all newborns[3].

Otoacoustic emissions as well as auditory brainstem response tests are the usual screening tools for hearing screening in newborns. However, Universal Newborn Hearing Screening is not able to detect mild or delayed onset hearing loss in newborns, in addition, the cause of hearing loss cannot be identified using this program[10]. Therefore, nowadays genetic testing of hearing loss is a useful adjunct to the Universal Newborn Hearing Screening in the early identification of a significant number of newborns with hearing loss[10].

Owing to the importance of hearing and early detection and treatment of hearing loss in newborns, we conducted this comprehensive review to update and summarize the various aspects of hearing loss in newborns (a critical period of human life).

ANATOMY OF THE EAR AND AUDITORY PATHWAY

The hearing pathway consists of the peripheral (structural) and the central component (sensorineural). These differ in their function and timeline development. The peripheral part consists of the external, middle, and internal ear. The functions of the external and middle ear are to collect and conduct the sound waves into the Organ of Corti of the inner ear. Then, these mechanical waves are converted into electrical energy which is transmitted through the auditory nerve fibers to the auditory cortex[11]. This cortex is tonotopically arranged in areas 22, 41, and 42 of the temporal lobe[12].

The labyrinth or inner ear starts to form at the 4th gestational week and is completely developed in the 20th gestational week[11-13]. Also, the auditory cortex is fully developed at the 20th gestational week[14].

The cochlea and temporal lobe are the most important sensitive parts of the auditory pathway. There are many deleterious conditions affecting these components including, for example, prenatal and postnatal infection, postnatal antibiotic, and noise exposure in the newborn intensive care unit[15]. This deleterious effect starts from full development of the neurosensory component at the 20th week of

intrauterine life until the 5th month of extra-uterine life[11].

The auditory pathway can transmit sound waves to the developing brain of the fetus during the period from the 25th to the 29th gestational week. The uterus acts as a protective barrier from deleterious factors to fetal development and protects the auditory pathway from high-intensity sounds[12,16]. However, the developing fetus can recognize various sounds (both attenuated and distorted sounds), particularly the mother's speech[17]. Furthermore, intrauterine sound stimulation helps the tonotopic development of the inner ear hair cells and auditory higher center[18]. The cortical auditory center continues to develop due to surrounding sound stimuli in the neonatal period. Therefore, this period is considered the time of the continuous auditory development process to fetal life[11]. This is supported by evidence from a study that compared vision and hearing development. Sight develops only in extra-uterine life, while hearing develops during the last 10th to 12th gestational weeks as well as after birth [11].

NEWBORN LIFE

The neonatal period is defined as the first 28 d of life[19]. The transition from intrauterine life (fetus) to extra-uterine life (newborn) is a complex process. This process is affected by certain factors, including gestational age, the health of the mother and chronic medical problems, placenta state, congenital anomalies, and care level in the delivery room. Despite the majority of infants passing this stage smoothly, around 10% need adequate resuscitation in the newborn intensive care unit to pass this process[20].

Actually, in many nations, there is a lack of contact between the mothers and their newborns and the health services with around 50% of deliveries across the globe occurring in the home without proper postnatal care[21]. This factor might harm the general health of newborns, in general, and hearing development, in particular.

The maturation of the auditory pathway might be affected by many factors including prematurity, admission to the intensive care baby unit, gestational age, and the gender of the newborn[22,23]. Therefore, great care is necessary during this critical period of life to prevent any preventable causes of hearing loss or to reduce the effect of hearing impairment by early detection of hearing loss and prompt intervention.

EPIDEMIOLOGY

Hearing loss is the 4th leading cause of handicap worldwide[24]. Hearing loss of more than 40 dB in the better ear can be considered disabling for adulthood (≥ 15 years), while, in children (0-14 years), a deficit of > 30 dB in the better ear has a disabling effect[25].

There was an increment in the number with disabling hearing loss across the globe from 42 million in 1985 to 360 million in 2010[26]. This included 7.5 million children less than 5 years old. At present, there are 466 million individuals with disabling hearing loss across the globe (https://www.who.int/en/news-room/fact-sheets/detail/deafness-and-hearing-loss). Of note, the actual number is more than the reported number with an expected continuous rising with time. This might be due to increased life span of people[27,28]. It is expected that 630 million individuals will have disabling hearing loss by the year 2030 and approximately 900 million by 2050 if no counter-measures are taken[29].

There is no gender predilection for hearing loss in newborns. However, there is a geographical variation concerning the prevalence of hearing loss. The highest prevalence was seen in Asia Pacific, South Asia, and Sub-Saharan Africa[30].

CAUSES

There are two main reasons for congenital hearing loss in newborns; genetic and environmental. According to recent investigations in developed countries, 80% of the causes are genetic, while the remaining 20% of cases are acquired or due to environmental reasons[31].

There are three reasons for genetic hearing loss; (1) Non-syndromic and syndromic; (2) Autosomal dominant/recessive/X-linked; and (3) Mitochondrial inheritance patterns[32].

The classification of syndromic and non-syndromic hearing loss depends on whether other systemic manifestations are associated with hearing loss. It is very important to diagnose syndromic hearing loss early and this depends on clinical assessment and molecular diagnostic tools. The advantages of early diagnosis include; predicting the progress of hearing impairment, looking for other systemic abnormalities, and guidance of treatment. Otolaryngologists are the first physicians to deal with children with syndromic hearing impairment and cooperate with other specialties for prompt management[33].

The non-syndromic and autosomal recessive cases outnumber the cases of syndromic and autosomal dominant cases. This means that congenital hearing loss can occur with a negative family history of hearing loss or without systemic abnormalities, which might be an unexpected aspect of the family[32]. Several investigations studied adding genetic testing to the current universal newborn hearing screening. However, only 1.4% of newborns who passed the hearing screening had a positive genetic screening test[10,34]. DFNB1 is the most prevalent form of congenital hearing loss in developed countries. DFNB1 results from mutations in the gap junction protein beta 2 (GJB2) gene[35]. GJB2 is expressed between the supporting cells and spiral ligament, stria vascularis, and spiral limbus of the cochlea. It is included in the potassium recycling mechanism, that hair cells utilize to produce an action potential to external sound waves[36]. Hence, GJB2 gene mutations are considered a cause of sensorineural hearing loss (SNHL). The common causes of hereditary hearing loss are shown in Table 1 [37,38].

Although the environmental causes of hearing loss in newborns are relatively low in number, great attention should be paid to prevent the significant sequel of hearing loss in the individual, family, and population. Another issue should be mentioned here, that is infections (such as cytomegalovirus infection) might lead to delayed onset hearing loss[39].

Generally, the causes of hearing loss are divided into three groups; prenatal, natal, and postnatal causes. In the prenatal period, TORCH infections include toxoplasmosis, others (syphilis, hepatitis B), rubella, cytomegalovirus, herpes simplex infections are groups of congenital infections and caused by *Toxoplasma gondii*, *Treponema pallidum*, *Hepatitis B* virus, *Rubella* virus, *cytomegalovirus*, and *herpes virus simplex* (HSV) viruses, respectively. If these infections occur in the first trimester, the severity of the infection is worse[40]. These infections cause different congenital anomalies and SNHL is one of them. In the era of coronavirus disease 2019 (COVID-19), the maternal-fetal transmission of severe acute respiratory syndrome coronavirus 2 could occur and harm the fetal ear[41]. Maternal smoking may have a deleterious effect on the inner ear of the fetus[42]. A pregnant woman with cardiovascular diseases, diabetes mellitus, ototoxic drugs such as aminoglycoside antibiotics, loop diuretics, and immunosuppressive drugs, and other conditions might have teratogenic effects on the well-being of the developing fetus including development of the ear[43].

During parturition, many factors might affect the hearing of newborns such as vertical transmission of infection from the mother to the fetus, birth asphyxia (Apgar score ≤ 6 at 5 min), meconium aspiration, and trauma[44].

In the neonatal period, several causes lead to hearing impairment including, but not limited to, prematurity, low birth weight, severe hyperbilirubinemia, ototoxic drugs like aminoglycosides, bacterial meningitis, respiratory distress, assisted ventilation > 5 d after delivery, long stay in the newborn intensive care unit (more than 5 d), and head trauma or intracranial hemorrhage[44].

TYPES AND SEVERITY OF HEARING LOSS

Hearing loss is a difficulty in hearing. Many classifications of hearing loss depend on the laterality of the hearing loss (unilateral or bilateral), symmetry (symmetrical or asymmetrical), affected frequencies (low, moderate, or high), involved site of the auditory pathway (conductive, sensorineural, or mixed), and the onset of hearing loss (congenital or acquired)[45].

In conductive hearing loss, the lesion involves the conductive hearing pathway, namely the external and middle ear, such as stenosis or atresia of the external ear, otitis media with effusion, or dislocation of ossicles. In SNHL, there is an abnormality in the cochlea, or auditory nerve fibers, or in the auditory cortex, or a combination of them. The majority of congenital cases of hearing loss are due to genetic causes, as seen in the United States and other developed nations (around 80%). Other causes of hearing loss include, but are not limited to, prenatal and postnatal infections, noise exposure, hyperbilirubinemia, and hypoxia[31].

Regarding severity, hearing loss is divided according to the degree of hearing loss into slight (where the hearing loss of 16-25 dB), mild (26–40 dB), moderate (41–55 dB), moderately severe (56–70 dB), severe (71–90 dB), and profound (> 90 dB)[45].

EVALUATION OF HEARING IN NEWBORNS

Currently, three screening programs are useful in detecting the majority of causes of hearing loss in newborns[39].

Newborn hearing screening program

In the past, hearing screening in the infant was performed by distraction or other behavioral tests[46]. These tests are usually performed in high-risk groups of hearing loss in newborns or depend on parental concern for their infants.

Table 1 Common causes of hereditary hearing loss

Type	Mode of inheritance	Gene or syndrome	Type of deafness	Laterality	Severity of deafness	Systemic disorders
Non-syndromic	Autosomal dominant	WFS1	Mostly SNHL	Uni- or bilateral	Variables	No
		TECTA	Mostly SNHL	Uni- or bilateral	Variables	No
		COCH	Mostly SNHL	Uni- or bilateral	Variables	No
		KNCQ4	Mostly SNHL	Uni- or bilateral	Variables	No
	Autosomal recessive	GJB2	Mostly SNHL	Uni- or bilateral	Variables	No
		SLC26A4	Mostly SNHL	Uni- or bilateral	Variables	No
		MYO15A	Mostly SNHL	Uni- or bilateral	Variables	No
		OTOF	Mostly SNHL	Uni- or bilateral	Variables	No
		CDH23	Mostly SNHL	Uni- or bilateral	Variables	No
		TMC1	Mostly SNHL	Uni- or bilateral	Variables	No
Syndromic	Autosomal dominant	Neurofibromatosis 2	High frequency SNHL	Bilateral	Mild to profound	Facial nerve paresis or paralysis; Tinnitus; Vertigo
		Branchio-oto-renal syndrome	Mixed (50%), Conductive (30), SNHL (20%)	Bilateral	Severe and progressive	Otological problems (*e.g.* cochlear dysplasia), Branchial anomalies *e.g.* lateral cervical fistulae, Renal such as agenesis
		Treacher Collins	Conductive; Sensorineural or mixed hearing loss less common	Unilateral or bilateral	Various severities	Craniofacial abnormalities such as hypoplastic facial bones and external auditory canal atresia
		Stickler syndrome	Conductive; SNHL; Mixed	Unilateral or bilateral	Various severities	Ophthalmological such as vitreous anomaly. Joint hypermobility; Craniofacial anomalies such as hypertelorism
		Waardenburg syndrome				Dystopia canthorum, heterochromia iridium, white forelock, synophrys, broad nasal root, hypoplasia of, the alae nasi, patent metopic suture line, and a square jaw
	Autosomal recessive	Pendred syndrome	SNHL			Goiter and a partial defect in iodide organification
		Jervell and Lange–Nielsen syndrome	SNHL		Severe to profound	Marked prolongation of the QT interval, and multiple syncopal attacks induced by exercise or emotion
		Usher syndrome	SNHL	Bilateral	Various severities	Vestibular dysfunction, retinitis pigmentosa
		Refsum disease	SNHL		Severe and progressive	Peripheral polyneuropathy; Cerebellar ataxia; Retinitis pigmentosa; Ichthyosis
	X-linked dominant	Alport syndrome	SNHL	Bilateral	Progressive	Hemorrhagic nephritis; Vision changes
	Mitochondrial	MELAS	SNHL	Bilateral	Progressive	Short stature; Nausea; Migraines; Seizures; Alternating hemiparesis; Hemianopia; Cortical blindness
		MERRF				Myoclonic epilepsy; Ataxia; Dementia; Optic atrophy; Short stature; Neuropathy

SNHL: Sensorineural hearing loss.

In 1982, the Joint Committee on Infant Hearing of the United States recommended that detection of hearing loss should be screened in newborns. This early identification has a crucial role in achieving an optimum outcome of rehabilitation[47]. Despite the benefit of early detection of hearing loss in newborns and early infantile life having been recognized for 80 years, the real efforts on a country level to detect congenital hearing loss were started at the beginning of the last decade of the 20th century[48]. Currently, the national universal newborn hearing screening program was practiced in all developed countries and some developing nations[32,45,49]. Unfortunately, Iraq is one of the developing countries that still have not practiced this vital program[50]. A recent large global survey reported that 38% of the world's neonates and infants had no or minimal hearing screening and 33% screened approximately 85% of newborns[51].

As a rule of thumb, a screening test for hearing should have the following characteristics; cheap, easy to learn and apply by screeners, quick to administer, not invasive, high compliance, and high specificity and sensitivity. There are two screening tests used in the newborn hearing screening program; otoacoustic emission (records responses from the outer hair cells of the cochlea) and automated auditory brainstem response (measures response to sound based on the neural transmission of a signal from the cochlea to the brainstem) or a combination of both screening tests[31]. Owing to the high validity of the tests, they are accepted across the globe. These screening tests give either pass or fail, the latter indicates the possibility of hearing loss in the screened newborn who requires a referral for further audiological evaluation to detect the type, severity, and configuration of hearing loss[31].

If the above-mentioned step is unable to detect the cause of hearing loss, genetic testing, radiological evaluation, laboratory tests, and consultation from other specialists are necessary depending on the case under the evaluation process[52].

Application of the universal hearing screening program in newborns is cost-effective[53].

Genetic testing

Genetic screening is an adjuvant to Universal Newborn Hearing Screening as the latter fails to identify syndromic hearing loss, risk factors for aminoglycoside-related hearing loss, auditory neuropathy, mild hearing loss, and delayed-onset hearing loss[10,45].

There are 124 identified genes implicated in non-syndromic congenital SNHL (https://hereditary-hearingloss.org).

There are three main technologies for genetic testing: Direct sequencing, Microarrays, and Next-generation sequencing. Direct sequencing can identify the exact order of nucleotide bases in an examined gene or the part of interest[54]. Sanger Sequencing is the most widely used technique of direct sequencing. The benefits of this technique are its ability to detect the vast majority of mutations (including novel mutations) present in a sequence, and it is the most accurate method. The drawbacks are as follows; costly, time-consuming, and labor-intensive. Therefore, this technique is used mainly in the identification of novel mutations or to confirm the results of other experimental screening methods [10].

Microarrays or mutation chips can be used for screening multiple mutations at one time. Microarrays are easily adjusted according to a specific population depending on the frequencies of the gene mutations. The benefits of this method over direct sequencing are low cost and speed as multiple genes can be screened at the same time. However, this technique cannot determine novel mutations as the direct sequencing method can. Despite the many mutations that can be screened simultaneously, this technique is limited by increasing the mutations without a significant increment in the time and cost [54]. At present, there are 15-300 mutations in 4-31 common hearing loss-related genes[55].

Next-generation sequencing or high-throughput sequencing techniques or massively parallel sequencing is now available and able to test all hearing loss-related genes in children with congenital hearing loss[37].

Cytomegalovirus testing

Congenital cytomegalovirus infection is considered the main non-hereditary reason for hearing loss at birth, the estimated incidence is approximately 10% of all causes of congenital hearing loss and 15%-20% in all children with hearing loss[56]. Approximately 6% of newborns who fail the hearing screening tested positive for cytomegalovirus[57].

Newborns with cytomegalovirus infection are divided into asymptomatic (90%) and symptomatic (10%). The most common symptomatic conditions are premature delivery, intrauterine growth restriction, and dysfunction of multiple organs. Approximately 50% of symptomatic newborns can develop SNHL[58]. Unilateral hearing loss is mostly seen among asymptomatic newborns with cytomegalovirus infection which is detected during screening. Owing to the high possibility of late occurrence of hearing loss in childhood, therefore, long-term follow-up of those children with cytomegalovirus infection is of utmost importance to detect late-onset hearing loss[59].

It is not necessary to test all neonates for cytomegalovirus because the test is not useful or cost-effective, as the majority of the infected neonates are asymptomatic. The correct timing of testing for congenital cytomegalovirus is either during pregnancy or during the first 21 d of neonatal life[60]. There are two methods for testing cytomegalovirus in the fetus; culture and polymerase chain reaction (PCR) testing of the amniotic fluid through amniocentesis[61]. Amniocentesis is not recommended for routine

screening testing as there is a 0.49% risk of demise in the fetus. The best samples used for the detection of cytomegalovirus by PCR are saliva or urine because they have sensitivities and specificities reaching 100%[58]. In newborns, detection of IgM antibodies against cytomegalovirus is not recommended as only 70% of those with positive cytomegalovirus infection can be detected using this serological test. There is limited value of cytomegalovirus detection using PCR of dried blood spots due to low sensitivity (28.3%)[62].

A recent study adopted a comprehensive hearing screening of newborns which comprised hearing screening, genetic testing, and cytomegalovirus testing[45]. The benefits of this program include; detection of the causes of hearing loss in newborns who were not detected on the routine hearing screening program, providing the etiological pattern of the hearing loss, reducing the number of children that might be lost to follow-up, and reducing the cost by decreasing the cases that need later testing.

Table 2 shows certain studies from various countries using the above-mentioned investigations in the diagnosis of neonatal hearing loss.

TREATMENT

Successful treatment depends on early detection of hearing loss in newborns as well as prompt intervention. The main treatment modalities are discussed below.

Hearing aid and cochlear implant

A multidisciplinary team is necessary for audiological, educational, and medical management. The team consists of an otolaryngologist, audiologist, pediatrician, specialist in genetics, and others[39]. The main factors that affect the development of language in a deaf infant are early detection and intervention[63]. It is critical to start intervention in a deaf infant at the age of 6 mo for better acquisition of language. At this age, the infant gets similar results to normal-hearing infants[64].

There are two options for the rehabilitation of hearing-impaired infants; hearing aids and cochlear implants. The hearing aid is the treatment of choice for mild-to-moderate congenital SNHL, while those with severe-to-profound SNHL can benefit from cochlear implants[65].

Gene therapy

Due to the developments in genetic sequencing technology in the last several years, there have been significant advancements in the molecular and biochemical pathways concerning the treatment of congenital hearing loss[66]. Following the first clinical approval protocol of human gene therapy by the Food and Drug Administration in 1990[67], there has been a significant increase in the acceptance of human gene therapy as a treatment option for different clinical problems including hearing loss.

There are four methods of human gene therapy; gene suppression, cell replacement, gene replacement, and targeted gene editing[68]. The application of these methods in cases of hearing loss faces difficulty in their administration to the inner ear as it is not an easily accessible structure and is covered by a strong bony labyrinth. Besides, most treated cases of hearing loss are severe and associated with irreversible destruction of the hair cells (outer and inner). However, many hearing loss-related genes have been successfully treated with curative gene therapy in an animal model[39].

Novel gene therapy in humans to prevent or restore SNHL is still under investigation[68].

Treatment of cytomegalovirus infection

The recommended treatment for symptomatic cytomegalovirus infection is either parenteral use of ganciclovir or oral valganciclovir. The triphosphate derivative of ganciclovir can inhibit cytomegalovirus DNA replication[69]. A previous clinical trial in 2003 reported that there was preservation of hearing in infants at 6 mo and one year following treatment with ganciclovir for symptomatic cytomegalovirus infection for those infants who received treatment during the neonatal period. The study also reported that 63% of the infants (29/46 treated group) had grade 3 or 4 neutropenia following antiviral treatment with ganciclovir[70].

Recently, three randomized controlled clinical trials studied the efficacy of valganciclovir antiviral therapy on the severity and course of cytomegalovirus-related SNHL[39].

CONCLUSION

Hearing is vital for speech, language, cognition, and learning. Hearing loss is the most common sensory abnormality. Hearing loss harms the person, family, and community. Early identification and intervention of hearing loss in newborns can result in an excellent outcome. Early detection of hearing loss in newborns can be accomplished by the hearing screening program, genetic testing, and cytomegalovirus infection testing. The rule of 1, 3, and 6 should be applied to hearing loss in newborns and

Table 2 Studies from various nations using different tools to diagnose hearing loss in newborns

Authors	Country	Year	Sample size	Study method	Data type	Diagnostic tool	Predictor(s)
Malesci *et al*[7]	Italy	2022	318878	Longitudinal retrospective study	Newborns	UNHS	UNHS is feasible and effective
Chu *et al*[34]	Taiwan	2015	15345	Retrospective study	Newborns	UNHS; Genetic testing	A genetic profile of the connexin genes and SLC26A4 gene among infants with hearing impairment detected by a UNHS program in Taiwan
Durante *et al*[42]	Brazil	2021	105	Comparative study	Newborns	Transient-evoked otoacoustic emissions and distortion product otoacoustic emissions	The impact of smoking exposure could be analyzed through transient-evoked otoacoustic emissions in newborns.
Bielecki *et al*[44]	Poland	2011	5282	Comparative study	Newborns	UNHS	Most common risk factors for hearing loss; Ototoxic drugs; Premature birth; Low birth weight; Intensive care in excess of 7 d
Pitathawatchai *et al*[53]	Thailand	2023	126	A decision analytical model with a 78-year time horizon	Newborns	UNHS; TNHS	Both tools are cost-effective
Rawlinson *et al* [57]	Australia	2018	1669	Cohort study	Newborns, Infants	UNHS; CMV testing	Congenital CMV (5.9%) in infants with permanent hearing loss and who did not pass the UNHS
Boppana *et al* [62]	United States	2010	20448	Comparative study	Newborns	CMV testing	Saliva rapid culture had low sensitivity in comparison with CMV testing with DBS real-time PCR

UNHS: Universal newborn hearing screening; TNHS: Targeted newborn hearing screening; CMV: Cytomegalovirus; PCR: Polymerase chain reaction.

infants. Number 1 means that the assessment of hearing should be started at the first month, number 3, accomplish the diagnosis at three months, and number 6, intervention should be started at 6 mo of life. Rehabilitation of deaf infants with hearing aids or cochlear implantation, gene therapy, and antiviral therapy for cytomegalovirus infection are recommended treatment modalities for hearing loss. Further investigations are necessary to solve the many ambiguities concerning hearing loss in newborns.

FOOTNOTES

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MINIREVIEWS

Emerging role of computed tomography coronary angiography in evaluation of children with Kawasaki disease

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Abstract

Coronary artery abnormalities are the most important complications in children with Kawasaki disease (KD). Two-dimensional transthoracic echocardiography currently is the standard of care for initial evaluation and follow-up of children with KD. However, it has inherent limitations with regard to evaluation of mid and distal coronary arteries and, left circumflex artery and the poor acoustic window in older children often makes evaluation difficult in this age group. Catheter angiography (CA) is invasive, has high radiation exposure and fails to demonstrate abnormalities beyond lumen. The limitations of echocardiography and CA necessitate the use of an imaging modality that overcomes these problems. In recent years advances in computed tomography technology have enabled explicit evaluation of coronary arteries along their entire course including major branches with optimal and acceptable radiation exposure in children. Computed tomography coronary angiography (CTCA) can be performed during acute as well as convalescent phases of KD. It is likely that CTCA may soon be considered the reference standard imaging modality for evaluation of coronary arteries in children with KD.

Key Words: Coronary artery abnormalities; Computed tomography coronary angiography; 2D-echocardiography; Kawasaki disease; Imaging modality; Acquired heart disease

Core Tip: In recent years advances in computed tomography technology have enabled explicit evaluation of coronary arteries along their entire course including major branches with optimal and acceptable radiation exposure in children. Computed tomography coronary angiography (CTCA) can be performed during acute as well as convalescent phases of Kawasaki disease (KD). It is likely that CTCA may soon be considered the gold standard imaging modality for evaluation of coronary arteries in children with KD.

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INTRODUCTION

Kawasaki disease (KD) is the most common vasculitis in children with a special predilection for coronary arteries. Coronary artery abnormalities (CAAs) are usually proportional to the extent of inflammation and without appropriate treatment, up to a quarter of patients with KD can develop CAAs. With early diagnosis and prompt institution of therapy, the incidence of CAAs is less than 5%, however there may be non-responsiveness to standard intravenous immunoglobulin therapy posing risk of developing severe CAAs[1-3]. CAAs can be assessed by several imaging techniques. 2D-echocardiography is the preferred imaging modality for coronary arteries evaluation both during the acute phase as well as during convalescence[4]. However, there has been increasing interest about other evolving modalities that can address the limitations of echocardiography[4,5]. In this context, we have discussed the role of computed tomography coronary angiography (CTCA) for detection of CAAs in KD and compared its performance with other available modalities. Current guidelines on use of CTCA have also been discussed along with the proposed use of CTCA in management of children with KD.

CORONARY ARTERY ABNORMALITIES IN KD AND NEED OF IMAGING

Coronary artery abnormalities (CAA) are the dreaded complications of KD requiring prompt and accurate diagnosis. In the acute phase of illness, typical CAAs include dilatation and aneurysm formation. These may resolve, remodel or persist during convalescence or may be complicated by thrombosis and steno-occlusive lesions mandating long term surveillance[6-10]. Concerns have also been raised that KD may act as a risk factor for premature atherosclerosis[11]. Precise imaging is required for assessment of these complications.

2D-echocardiography is the standard imaging modality for coronary arteries at presentation and during follow-up[12]. However, it has several limitations and these preclude its use in certain circumstances[12,13].

Other imaging techniques that have been used for coronary artery evaluation include catheter angiography (CA), CTCA and magnetic resonance coronary angiography (MRCA).

CA is an invasive procedure with uncontrolled radiation exposure[12], whereas MR angiography is technically difficult and very few centers have requisite expertise[4]. With the availability of modern CT scanners there is increasing interest in CTCA as an imaging modality of KD. It is non-invasive, has optimized sub-millisievert radiation exposure and has the potential to address all the limitations of CA and echocardiography[14-19]. Moreover CTCA has an ability to detect the earliest changes of atherosclerosis[20,21]. In this scenario CTCA seems promising and its incorporation into the management algorithm of KD should be considered. In this review we have discussed the emerging role of CTCA in evaluation of children with KD for detection of CAAs.

CTCA IN KD: NEEDS AND CHALLENGES

Transthoracic echocardiography is the presently standard of care for KD. However, it has several limitations. CA is invasive, has significant radiation exposure and cannot be repeated frequently.

After the advent of 64-Slice CT platforms, CTCA has become feasible. Radiation associated with CTCA is the biggest challenge as such radiation exposure has been linked to malignancies in children [22,23]. The older platforms also had sub-optimal image quality due to inherent high heart rates in children[14,24]. In recent years, however, CT technology has undergone a remarkable progress enabling the radiologist to acquire high resolution coronary artery images with acceptable radiation exposure and at any heart rate. This was possible due to higher slice CT (128, 256 and 320 slice) platforms and

dual source (DS) CT scanners[14-18]. DSCT has superior diagnostic performance as compared to single-source CT in the evaluation of coronary arteries and this gives an advantage of scanning in children who otherwise have inherent high heart rates and obviates the need of large doses of beta-blockers[17, 18].

As a result, CTCA is now being increasingly used for evaluation of children with KD and CAAs. It provides information about coronary arteries and the major branches with exquisite details of luminal caliber and intramural changes. Moreover, it can be repeated on follow-up as it is non-invasive. CTCA is especially useful in older children and adolescents who often have a poor acoustic window for echocardiography.

CTCA: CALCIUM SCORING AND LUMINOGRAPHY

CT calcium scoring is a technique that identifies calcium deposition in coronary arteries without the need of intravenous contrast (Figure 1). Calcium deposition in coronary arteries is a strong predictor of previous coronary artery involvement in patients with KD. Kahn *et al*[21] reported coronary artery calcium scoring using a low radiation dose CT protocol on 70 patients with KD at median of 14.8 years' follow-up and showed that coronary calcification was not present in patients with KD and normal coronaries during acute phase of disease. Ten out of 14 subjects with CAAs in acute phase had coronary calcification. A subsequent study from the same group of investigators affirmed that calcium deposition was not seen in patients with KD who did not develop CAAs during acute phase of disease[25]. The authors have shown that calcium scoring by CT is also a useful tool for identification of unidentified CAAs in patients with remote history of KD. It was also noted that sensitivity and specificity of calcium scoring to identify presence of CAAs is highest when scans were performed after more than 10 years of follow-up. Whether the degree of calcification has prognostic value in patients with KD is still conjectural. Zero calcium score in patients with remote history of KD is reassuring if performed at least 10 years after the initial illness.

Angiography or luminography is acquisition of data after injection of intra-venous contract for evaluation of CAA. Acquisition of data should preferably be done with low radiation protocols and following strategies should be employed to reduce the radiation exposure:

Lower kilovoltage (kVp) for acquisition: kVp below 80 is appropriate - this reduces radiation exposure up to 70%[26-28].

Prospective ECG triggering: In this technique data acquisition is regulated by ECG signal and the X-ray tube current is either switched off or markedly lowered according to phase of R–R interval. This allows reduction of radiation exposure up to 90% as compared to retrospective ECG-gating, where X-ray exposure is given continuously[29-31]. Duan *et al*[17] and Kim *et al*[32] reported mean effective dose of 0.36 ± 0.06 mSv and 0.6 ± 0.5 mSv respectively on DSCT. Even in our experience the radiation had always been below 1 mSv[18].

(ECG)-controlled tube current modulation: With this technology up to 50% reduction in radiation exposure is achievable[32,33].

High pitch: Pitch in CT refers to area coverage with overlap and has inverse relationship with radiation exposure. With DSCT higher pitch (up to 3.4) there is further reduction in radiation exposure [34-36].

Iterative image reconstruction method: This is a newer development that allows to reconstruct data post-acquisition with high resolution images even at low radiation parameters (lower kilovoltage and tube current values)[36,37].

Using the dose saving strategies discussed above, radiation exposure can be brought down significantly below 1 mSv level[18,36].

CTCA: STRENGTH AND ADVANTAGES

CTCA with the current technologies of radiation optimization and fast scanning has capability to image the entire course of all coronary arteries especially left circumflex coronary artery which is difficult to evaluate on 2D-echocardiography (Figure 2). CTCA also allows to detect CAAs in middle and distal segments of coronary arteries[38]. These are usually missed on echocardiography (Figure 3). It also precisely identifies location and morphology of aneurysms (Figure 4) and thrombo-occlusive lesions (Figures 5 and 6). Mural abnormalities (calcifications, plaque, and adherent thrombus to luminal wall) are also well characterized on CTCA (Figures 1, 5 and 6).

LIMITATIONS OF CTCA

CTCA has few limitations as it may not be available at all the centers, need of sedation in infants and

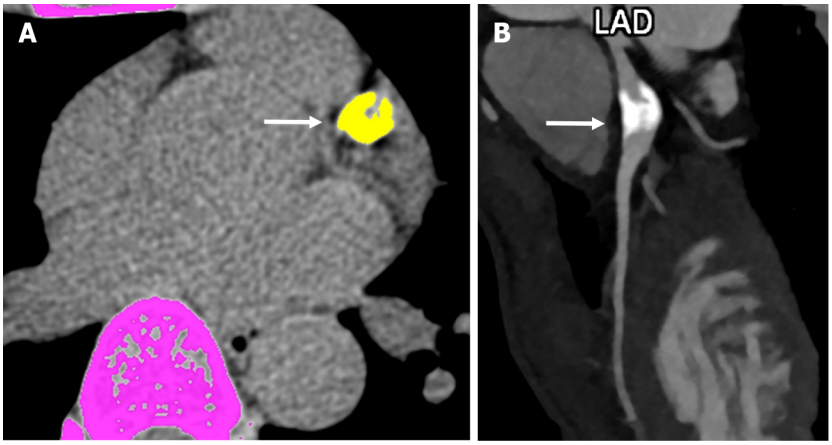

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Figure 1 Computed tomography derived calcium score and role of angiography in convalescent phase of Kawasaki disease. A: Computed tomography (CT) derived calcium scoring in a 19 years male patient on follow-up with history of Kawasaki disease in childhood shows a thickly calcified lesion in the proximal course of left anterior descending coronary artery (color marked as yellow with an arrow (calcium score was 910); B: Subsequent CT coronary angiographic curved reformatted image shows calcified aneurysm (arrow). LAD: Left anterior descending.

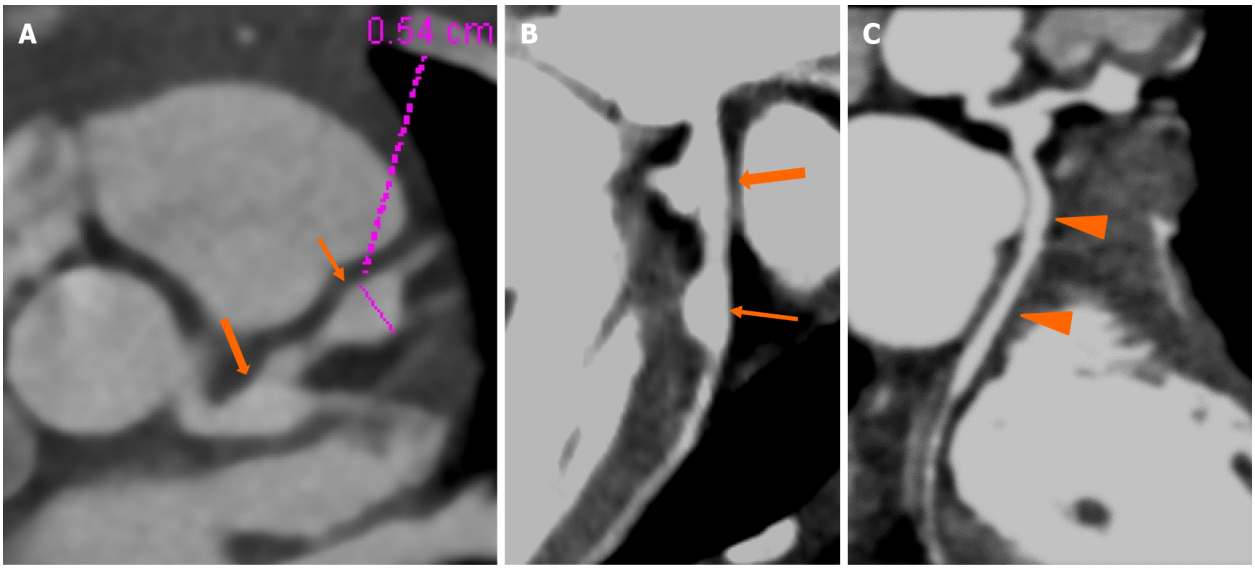

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Figure 2 Computed tomography coronary angiography images showing its strength to evaluate coronary artery abnormalities in left circumflex artery. A: 3 years male child at presentation shows fusiform aneurysm at bifurcation of left main coronary artery [left main coronary artery (LMCA)- thick arrows in A and B] with extension into osteo-proximal segment of left anterior descending (LAD). Note a skip fusiform aneurysm in proximal LAD (thin arrow in b). C: Proximal and mid segments of left circumflex (LCX) are dilated (arrow heads in C). Echo demonstrated LMCA and LAD aneurysms however cannot evaluate LCX due to its orientation and course.

young children, portability and radiation exposure. However, these are minor considering the advantages derived and moreover advanced CT scanners with radiation optimization are now finding space in large centers. Sedation if so, needed in infants and young children is of short duration and general anesthesia is not required in our experience[38-40].

CTCA: COMPARISON WITH OTHER IMAGING MODALITIES

2D-echocardiography

It is known that CAAs in patients with KD can involve all segments of main coronary arteries. 2D-echocardiography remains the imaging modality of choice of evaluation of CAAs in patients with KD because of its inherent advantages – it is easily available, is inexpensive and can be repeated as often as required. However, it has only a limited role in evaluation of middle and distal coronary arteries and

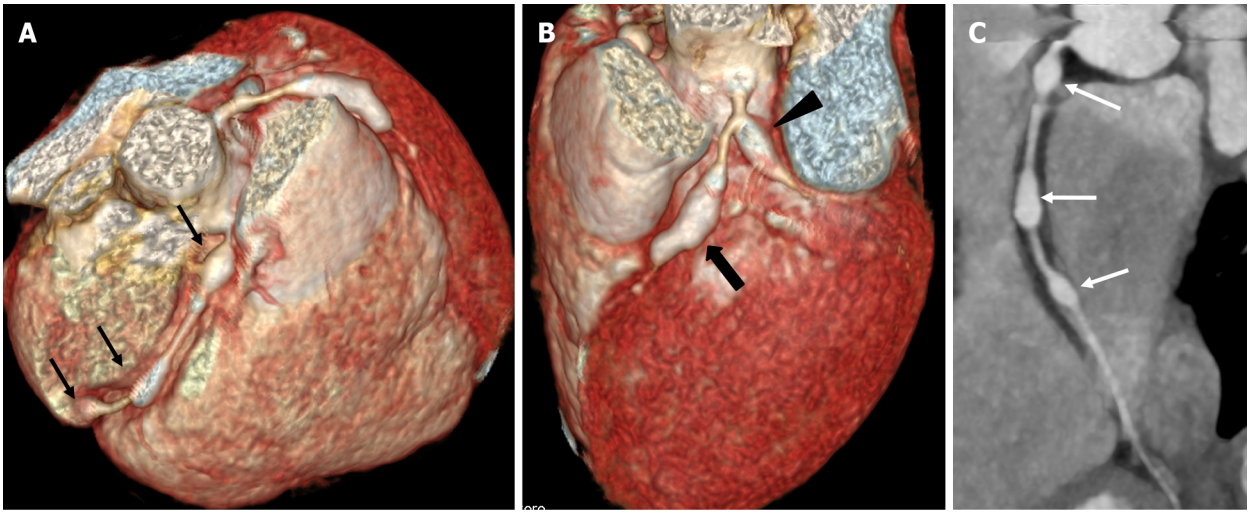

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Figure 3 Computed tomography coronary angiography images showing its ability to evaluate mid and distal segments of coronary arteries. Computed tomography coronary angiography (A and B: Volume rendered images; C: Curved reformatted image of RCA) of 4 years male at presentation demonstrate skip fusiform aneurysms in RCA (Thin arrows in A and C) and fusiform aneurysms in proximal LAD (thick arrow in B) and proximal left circumflex (arrow head in B). Fusiform aneurysm in mid and distal RCA could not be visualized on transthoracic echocardiography.

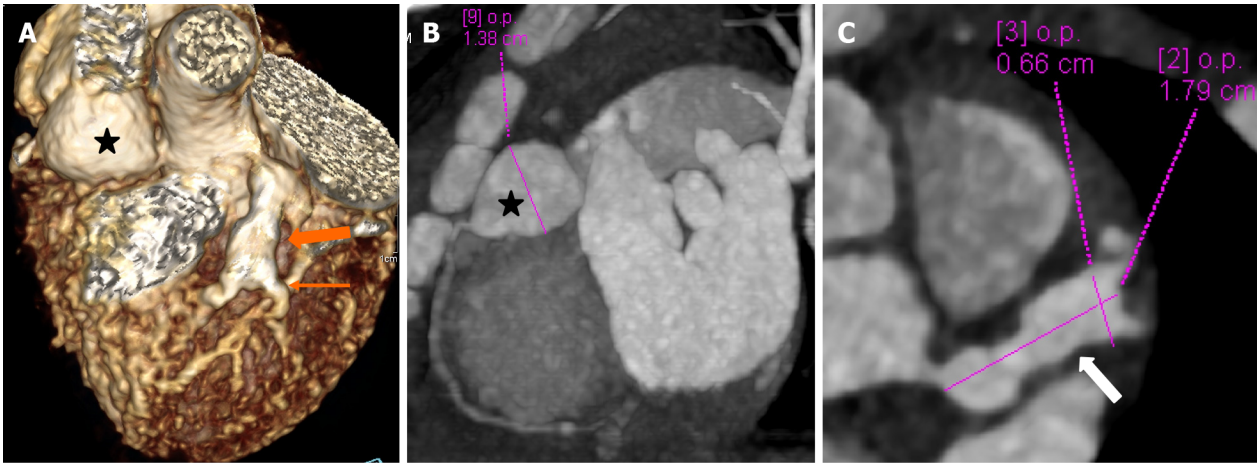

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Figure 4 Panel of computed tomography coronary angiography images showing its ability to precisely identify location and morphology of aneurysms with extension into side branches. Computed tomography coronary angiography (A: Volume rendered image; B: Curved reformatted image and C-axial image) of 4 years female child in acute phase (presentation) demonstrate giant saccular aneurysm in proximal resonance coronary angiography (asterisk in A and B). Fusiform aneurysm is seen in proximal left anterior descending (thick arrow in A) with extension into diagonal-1 branch (thin arrow in A).

the left circumflex coronary artery[41]. CTCA provides an ideal method for evaluation of all segments of coronary arteries[38,42-45]. Several investigators have reported a good correlation between echocardiography and CTCA for the size of the aneurysms.

MRCA

It is still under evaluation for assessment of CAAs in children with KD. MRCA has lower spatial (related to image accuracy that measure fineness of image) and temporal (scanning speed) resolution and poorer image quality compared to CTCA[46,47]. Moreover, MRCA takes long scan time and often requires sedation in young children[32]. Steno-occlusive lesions are better delineated on CTCA compared to MRCA[32]. MRCA, however, is better for evaluation of coronary arteries with heavy intramural calcifications (leading to blooming artefact on CT), assessment of myocardial perfusion and viability, and serial follow-up of thrombotic aneurysms[48].

CA

It is the gold standard for evaluation of coronary artery lumen, but is of limited value for assessment of mural abnormalities (thickening, plaque and calcifications) and intramural thrombi. Moreover, it is an

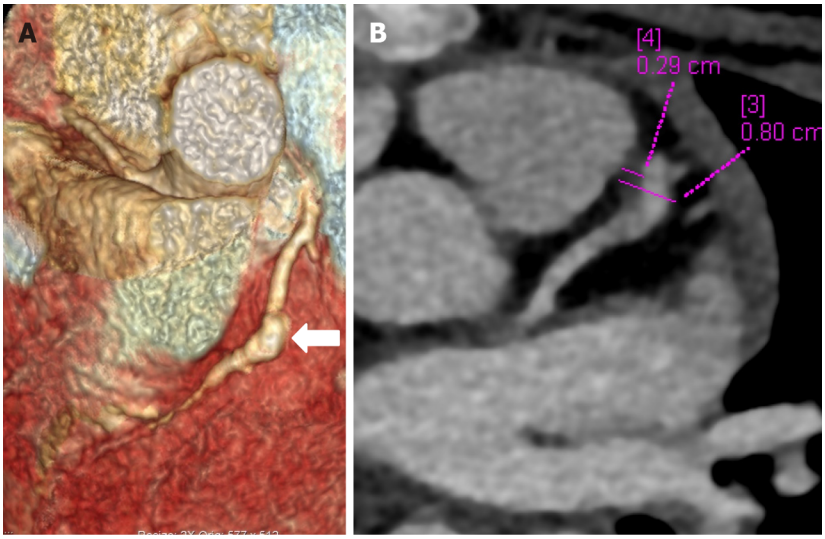

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Figure 5 Computed tomography coronary angiography images depicting complications in coronary artery abnormalities (thrombus). Computed tomography coronary angiography [(A: Volume rendered image; B: Axial image in plane of left anterior descending (LAD)] during follow up at shows a giant fusiform aneurysm in mid segment of LAD (thick arrow in A) with a hypodense plaque like tissue attached to the anterior wall (B) suggestive of thrombus. Child was having chest pain and ECHO at presentation and during the current episode was reported as normal; ECHO fails to elicit coronary artery abnormalities and its complication of thrombus in the aneurysm.

invasive procedure with inordinate radiation exposure. CTCA with CA has been shown to have excellent agreement for measurement of size of aneurysms[49].

CTCA: WHEN TO ADVICE?

Current guidelines and the way forward

The American Heart Association Guidelines 2017 have recommended use of CTCA in following circumstances during follow-up when 2D-echocardiography becomes limiting[50]: (1) Due to poor acoustic window in older children; (2) Poor sensitivity to detect complications like thrombosis, stenosis; (3) Inability to detect distal abnormalities; and (4) For detection of mural abnormalities or calcification; However, based on our clinical experience over 25 years we suggest that CTCA may be considered under the following circumstances: As a baseline additional investigation in acute phase in children having significant CAAs on 2D-echocardiography for confirmation of echocardiography findings, detection of distal CAAs and for follow-up[38]. When the initial 2D-echocardiography examination in acute phase is equivocal or sub-optimal, Apparently normal 2D-echocardiography examination in acute phase with a stormy clinical course, On follow-up assessment of CAAs to document resolution or complications (*e.g.*, thrombosis, stenosis), Long term surveillance for detection of mural abnormalities and dystrophic calcifications. At the present time there is no consensus amongst experts on the timing and frequency of carrying out CTCA during follow up of children with KD.

Recent advances in CTCA in KD

Cardiac single-photon emission computed tomography (SPECT) and CT hybrid imaging has been recently described for accurate demonstration of ischemic regions of the myocardium. Abe *et al*[51] have performed SPECT/CT in 17 patients with KD in chronic phase of disease and showed that this fusion imaging was capable of accurately evaluating myocardial ischemia/infarction as cardiovascular sequelae of KD and delineating the affected coronary arteries.

CONCLUSION

State of the art CT platforms now allow CTCA with high resolution images at sub-millisievert radiation exposure. CTCA has the ability to detect CAAs along the entire course of coronary arteries and delineates mural abnormalities, which otherwise are missed on current standard of care 2D-echocardiography. CTCA can be performed during acute as well as convalescent phases of KD. It is likely that CTCA may soon be considered the imaging modality of choice for evaluation of coronary arteries in children with KD and multi-centric studies focused on use of CTCA is desirable to formulate guidelines.

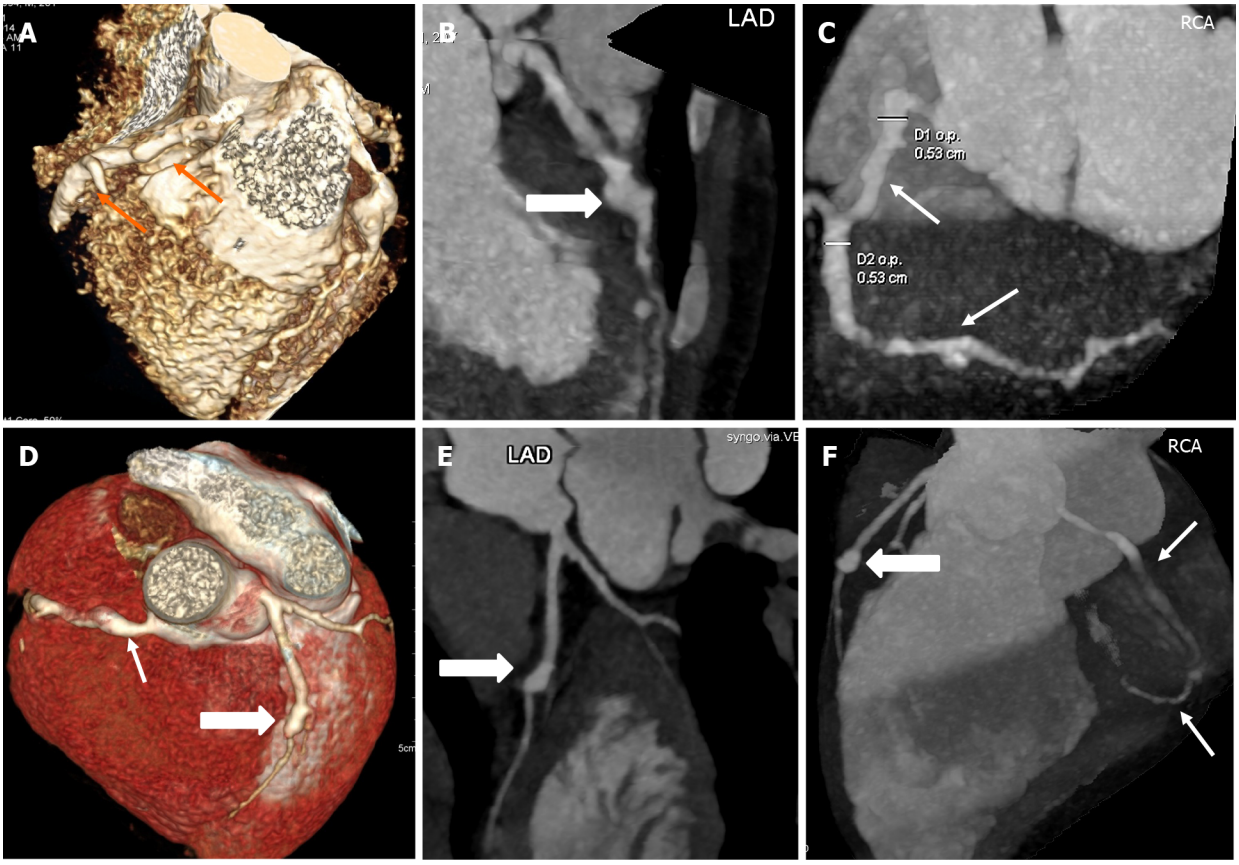

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Figure 6 Computed tomography coronary angiography images showing its role in follow-up imaging and its role in assessment of compications. Computed tomography coronary angiography (CTCA) at presentation in 1 year male (top row A-C) shows a giant complex aneurysm in mid segment of left anterior descending (LAD) (thick arrow in A and B) with multiple segmental aneurysms along the entire course of resonance coronary angiography (RCA). Follow-up CTCA after 3 years of presentation shows remodelling of LAD aneurysm (now becomes fusiform with mural calcification and severe stenosis its distal aspect (thick arrows D-F), also note resolution of aneurysmal dilatations of RCA (lower row D-F).

FOOTNOTES

Author contributions: Singhal M and Pilania RK contributed equally and shared the first authorship. Singhal M and Pilania RK designed the research, written first draft, review of literature, editing of manuscript and critical revision of manuscript at all stages; Gupta P and Johnson N contributed in literature review and editing of the manuscript; Singh S review of literature, editing of manuscript, critical revision of manuscript at all stages. Singhal M and Pilania RK are joint first authors.

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ORIGINAL ARTICLE

Retrospective Cohort Study

IFIH1 and *DDX58* gene variants in pediatric rheumatic diseases

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Abstract

BACKGROUND

The *IFIH1* gene codes the MDA5 protein and the *DDX58* gene codes the RIG-I receptor. Both proteins are parts of the interferon (IFN) I signaling pathway and are responsible for antiviral defense and innate immune response. IFIH1 and DDX58 polymorphisms are associated with a spectrum of autoimmune diseases. Rare gain-of-function IFIH1 mutations have been found in Singleton-Merten and Aicardi-Goutières syndrome, while DDX58 mutation can cause atypical Singleton-Merten syndrome.

AIM

To characterize children with pediatric rheumatic diseases (PRD) carrying *DDX58* or *IFIH1* variants.

METHODS

Clinical exome sequencing was performed on 92 children with different PRD. *IFIH1* and *DDX58* variants have been detected in 14 children. IFN-I score has been analyzed and the clinical characteristics of patients have been studied.

RESULTS

A total of seven patients with systemic lupus erythematosus (SLE) (n = 2), myelodysplastic syndrome with SLE features at the onset of the disease (n = 1), mixed connective tissue disease (MCTD) (n = 1), undifferentiated systemic autoinflammatory disease (uSAID) (n = 3) have 5 different variants of the *DDX58* gene. A common non-pathogenic variant p.D580E has been found in five children. A rare variant of uncertain significance (VUS) p.N354S was found in one patient with uSAID, a rare likely non-pathogenic variant p.E37K in one patient with

uSAID, and a rare likely pathogenic variant p.Cys864fs in a patient with SLE. Elevated IFN-I score was detected in 6 of 7 patients with *DDX58* variants. Seven patients had six different *IFIH1* variants. They were presented with uSAID (n = 2), juvenile dermatomyositis (JDM) (n = 1), SLE-like disease (n = 1), Periodic fever with aphthous stomatitis, pharyngitis, and adenitis syndrome (n = 1), and systemic onset juvenile idiopathic arthritis (n = 1). Three patients have VUS p.E627X, one patient has benign variant p.I923V. Rare VUS p.R595H was detected in the JDM patient. Another rare VUS p.L679Ifs*2 and previously not reported variant p.V599Ffs*5 were detected in the patient with uSAID. One patient with uSAID has rare VUS p.T520A. All patients had elevated IFN-I scores.

CONCLUSION

Rare compound-heterozygous IFIH1 variant (p.L679Ifs*2 and p.V599Ffs*5), heterozygous IFIH1 variant (p.T520A) and heterozygous DDX58 variant (p.Cys864fs) are probably disease causative for uSAID and SLE. The majority of patients with different *DDX58* and *IFI1* variants had hyperactivation of the IFN I signaling pathway.

Key Words: IFIH1; DDX58; Undifferentiated systemic autoinflammatory disease; Systemic lupus erythematosus; Interferon-I score

Core Tip: Interferon (IFN) I signaling pathway is the important part of innate immune system and antiviral defense. It's known that defects in the components of IFN I signaling system can leads to its hyperactivation. This pathogenetic phenomenon is considered as one of the most important in the pathogenesis of immune-mediated diseases, such as systemic lupus erythematosus, dermatomyositis, systemic autoinflammatory diseases. From database containing 92 patients with different rheumatic diseases, whom clinical exome sequencing was performed we selected 14 children (10 girls and 4 boys): 7 patients had *DDX58* and 7 had *IFIH1* gene variants. The majority of patient with different *DDX58* and *IFI1* variants had hyperactivation of IFN I signaling pathway.

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INTRODUCTION

The *DDX58* gene encodes the RIG-I receptor (retinoic acid-induced protein I), which is responsible for the virus's ribonucleic acid (RNA) recognition[1]. RIG-1 interacts with short-stranded RNA (ssRNA) of viruses that lead to mitochondrial antiviral-signaling protein (MAVS) activation, which in turn leads to the expression of interferon (IFN)-regulated genes and the secretion of type I IFNs. The *IFIH1* gene encodes a cytoplasmic receptor that senses double-stranded RNA viral products to activate type I IFN signaling through the MAVS adaptor molecule. This can inhibit virus replication and modulate cellular immune responses. IFIH1 may also help recognize and limit the replication of ssRNA viruses[2].

IFN I signaling pathway is an important part of the innate immune system and antiviral defense[3]. It's known that defects in the components of the IFN I signaling system can lead to its hyperactivation. This pathogenetic phenomenon is considered one of the most important in the pathogenesis of immune-mediated diseases, such as systemic lupus erythematosus (SLE), dermatomyositis (DM), and systemic autoinflammatory diseases (SAID)[4]. The roles of *DDX58* and *IFIH1* gene variants in the pathogenesis of immune-mediated diseases are not fully studied. Our study aimed to describe children with different rheumatic diseases who have variants in *DDX58* or *IFIH1* genes.

MATERIALS AND METHODS

From a database containing 92 patients with different rheumatic diseases, for whom clinical exome sequencing was performed we selected 14 children (10 girls and 4 boys) having the variants of *DDX58* or *IFIH1* genes. They have the following diagnosis: SAID (n = 6), SLE (n = 5), juvenile DM (JDM) (n = 1), systemic onset juvenile idiopathic arthritis (n = 1), mixed connective tissue disease (n = 1).

IFN-I score was measured in the majority of patients. Real-time polymerase chain reaction with previous reverse transcription of RNA was used for IFN-I score assessment. Amplification was carried out using hybridization probes (TaqMan probes); changes in gene expression were evaluated by the ratio of signals "studied gene/referee gene"); the value of the IFN-I score corresponds to the median relative expression of 5 genes studied (*IFI44L*, *IFI44*, *IFIT3*, *LY6E*, *MX1*). The IFN-I score value of ≥ 2.0 was taken as a cut-off, indicating increased transcription of IFN-I-regulated genes *i.e.,* the presence of an IFN signature.

RESULTS

Five different variants of the *DDX58* gene were found in 7/14 patients included in the study, among which the p.D580E variant was found in 4 patients. One patient had 2 different variants of *DDX58*, including p.D580E. The variant p.D580E is a frequent polymorphism [minor allele frequency (MAF): 0.11]. Two patients had likely non-pathogenic variants *DDX58* according to American College of Medical Genetics (ACMG) (p.S144F and p.E37K). A rare variant of uncertain significance (VUS) of the *DDX58* (p.N354S) gene was detected in one patient. Only one patient with SLE had a likely pathogenic variant of the *DDX58* gene - p.Cys864fs. Patients had the following distribution according to the diagnosis: SLE (n = 2), myelodysplastic syndrome with SLE features at the onset of the disease (n = 1), mixed connective tissue disease (n = 1), undifferentiated SAID (uSAID) (n = 3). IFN-I score was evaluated in 6/7 patients with *DDX58* variants. IFN-I score was higher by 4 or more times compared to reference values in 5 patients, whereas in one patient IFN-I score was slightly increased - 2.13 UE/mL (normal value is less than 2.0 UE/mL). Table 1 shows variants of the *DDX58* genes and the values of the IFN-I scores. Brief clinical characteristics of patients with rare *DDX58* variants will be presented below.

Patient's description

Patient 1 (Table 1) is 12-year-old the boy developed fever, abdominal pain, diarrhea, livedo reticularis, and edema of the 4th proximal interphalangeal (PIP) joint of the left hand and 3rd PIP joint of the right hand. *Shigella spp.* was detected and he was treated with antibiotics. Abdominal symptoms and fever resolved, but he had periodic fever episodes and livedo reticularis. Blood tests showed elevated inflammatory markers. We ruled out autoimmune diseases, inflammatory bowel disease. Genetic testing was performed and VUS in the *DDX58* gene (p.N354S) was detected. The patient was treated with short-course corticosteroids. Fever, livedo reticularis, and laboratory inflammation resolved.

Patient 2 (Table 1) is a 7-year-old boy who has had 7 episodes of exudative pericarditis for one year preceding our hospital admission. He required pericardiocentesis twice. Pericardial effusion usually was accompanied by systemic inflammation (leukocytosis, increased C-reactive protein) and has been resolved on treatment with corticosteroids. Infectious, oncologic, and autoimmune diseases have been excluded. Multigene-targeted sequencing revealed a pathogenic mutation in the *JAK1* gene and likely a non-pathogenic variant of the *DDX58* gene (p.E37K). Colchicine and canakinumab were initiated, however, due to four following flares during the year of treatment, he was switched to tocilizumab.

Patient 3 (Table 2) is a 16-year-old girl with SLE. Clinical manifestations in the disease onset included fever, lymphadenopathy, pancytopenia, and minimal proteinuria (0.2 g/d) were noted. The malar rash, stomatitis, and polyserositis (by computed tomography) were developed. She had positive ANA, anti-dsDNA antibodies, and hypocomplementemia. She's been treated with corticosteroids (IV, oral), hydroxychloroquine, and rituximab. Disease remission was achieved and corticosteroids were stopped. IFN-I score was increased 10 times than the normal value (21.0 UE, normal value less than 2.0 UE), and following multigene targeted sequencing revealed two variants in the *DDX58* gene (p.Cys864fs, p.D580E). A rare variant of p.C864Ffs*9 was inherited from a healthy mother. There is no information about the pathogenicity of this variant in the ClinVar database. Variant *DDX58* p.D580E refers to frequent benign variants of the gene.

Different variants in the *IFIH1* gene were found in 7/14 patients (Table 2). All patients had elevated IFN scores. Three patients had the p.E627X variant. This variant has conflicting interpretations of pathogenicity according to ClinVar and uncertain significance according to ACMG. One patient with systemic onset juvenile idiopathic arthritis had a benign p.I923V variant, and one patient with JDM had a rare (MAF 0.0001) likely benign coding sequence variant p.R595H.

Patient 1 (Table 2) had compound-heterozygous variants in the *IFIH1* gene (p.L679Ifs*2 and p.V599Ffs*5) that can contribute to disease development. She is 17-year-old girl with undifferentiated interferonopathy. Her clinical manifestations included fever, systemic inflammation, panniculitis, sialadenitis, nodular rash, hepatitis, migraine headaches, and growth failure. Treatment with corticosteroids, azathioprine, and mycophenolate mofetil was ineffective. The application of tofacitinib partially controlled her disease (no fever flares and rash) and allowed her to taper corticosteroids to 0.15 mg/kg.

Patient 2 (Table 2) is 16-year-old girl with fever, pancytopenia, petechial rash, hepatomegaly, lower extremities edema, inflammation, and hyperferritinemia. She initially was treated with IV corticosteroids and cyclosporine A. Then she developed panniculitis nodules in the back, the abdomen, and the lower extremities, and muscle weakness. Pancytopenia and inflammation had recurred. Biopsy of

Table 1 *DDX58* variants in children with immune-mediated diseases

No.	*DDX58* variant	MAF	ClinVar	ACMG	IFN-I score (n.v.0-1.9 UE/L)	Diagnosis
1	c1061A>G (p.N354S)	0.0001	VUS	VUS	2.13	uSAID
2	c109G>A (p.E37K)	0.000008	Not reported	Likely non-pathogenic	N/A	uSAID
3	c.2587_2590dup (p.Cys864fs)	0.0006	Not reported	Likely pathogenic	21.0	SLE
	c.1740T>A (p.D580E)	0.11	Non-pathogenic	Non-pathogenic		
4	c.431C>T (p.S144F)	0.0277	Non-pathogenic	Likely non-pathogenic	13.31	MCTD
5	c.T1740A (p.D580E)	0.11	Non-pathogenic	Non-pathogenic	8.5	SLE and MDS
6	c.1740T>A (p.D580E)	0.11	Non-pathogenic	Non-pathogenic	24.35	SLE
7	c.1740T>A (p.D580E)	0.11	Non-pathogenic	Non-pathogenic	18.93	uSAID

ACMG: The American College of Medical Genetics; GnomAD: The Genome Aggregation Database; MAF: Minor allele frequency; MCTD: Mixed connective tissue disease; MDS: Myelodysplastic syndrome; n.v.: Normal value; SLE: Systemic lupus erythematosus; uSAID: Undifferentiated systemic autoinflammatory disease; VUS: A variant of uncertain significance; N/A: Not applicable.

Table 2 *IFIH1* variants in children with immune-mediated diseases

No.	*IFIH1* variant	MAF	ClinVar	ACMG	IFN-score (n.v. 0-1.9 UE/L)	Diagnosis
1	c.2035_2036del (p.L679Ifs*2)	0.0001	VUS	VUS	5.4	uSAID
	c.1795delG (p.V599Ffs*5)		Not reported	Not reported		
2	c.1558A>G (p.T520A)	0.0002	CIP	VUS	5.52	uSAID
3	c.1784G>A (p.R595H)	0.0001	Likely benign	VUS	29.0	JDM
4	c.1879G>T (p.E627X)	0.003	CIP	VUS	20.2	SLE-like disease
5	c.1879G>T (p.E627X)	0.003	CIP	VUS	11.3	SLE
6	c.1879G>T (p.E627X)	0.003	CIP	VUS	2.95	PFAPA
7	c.A2767G (p.I923V)	0.0126	Benign/likely benign	Benign	10.0	soJIA

ACMG: The American College of Medical Genetics; CIP: Conflicting interpretations of pathogenicity; GnomAD: The Genome Aggregation Database; JDM: Juvenile dermatomyositis; MAF: Minor allele frequency; n.v.: Normal value; PFAPA: Periodic fever with aphthous stomatitis, pharyngitis, and adenitis; SLE: Systemic lupus erythematosus; soJIA: Systemic onset juvenile idiopathic arthritis; uSAID: Undifferentiated systemic autoinflammatory disease; VUS: A variant of uncertain significance.

nodules revealed adipocytes and xanthoma cells infiltrating by lymphocytes. Electromyography detected axonal-demyelinating polyneuropathy of motor and sensory nerve fibers of the upper and lower extremities. Further treatment with different medications, including cyclosporine A, etanercept, tocilizumab, tofacitinib, and anakinra showed partial efficacy. It's unknown does her heterozygous variant p.T520A lead to disease manifestations or not. Functional tests are necessary to prove its pathogenicity.

DISCUSSION

Studies of the *DDX58* gene in patients with rheumatic diseases are mostly limited to the evaluation of DDX58 polymorphisms as one of the factors of susceptibility to viral diseases. It is known that some *DDX58* gene variants can lead to atypical Singleton-Merton syndrome, which was first described in 2015 in family members who had glaucoma, aortic calcification, and skeletal abnormalities[5]. Subsequently, the *DDX58* gene variants were studied in 100 patients with congenital glaucoma, and in one family with congenital glaucoma, dental abnormalities, and skeletal dysplasia, variant c.803G>T (p.Cys268Phe) was found. The functional tests confirmed the pathogenicity of this gene variant. Hyperactivation of the type

I IFN signaling system was observed in all the above-mentioned patients[5]. Two families with the Signleton-Merten syndrome having glaucoma, psoriasis-like rashes, calcifications of the joints, and aorta had *DDX58* gene variants[6].

In the study of 15 patients with IIM 5/5 patients with DM had an increased expression of DDX58, which was associated with excessive secretion of IFN-beta[7]. All patients with *DDX58* variants had high levels of IFN-I scores in our study. The association between DDX58 p.D580E polymorphism and SLE has not been confirmed in the study of 344 patients with SLE and 641 healthy persons[8]. Three of our patients with SLE had the same DDX58 polymorphic variant which is unlikely to have any causal role.

A novel DDX58 pathogenic variant R109C has been recently identified in five unrelated families with lupus nephritis. Transcriptome analysis revealed an increased IFN signature in patient monocytes. One patient was effectively treated with baricitinib[9]. Gain-of-function *IFIH1* gene variants lead to an inadequate perception of both own and viral nucleic acids and contribute to the hyperactivation of the IFN-I type[10]. Currently, less than 100 IFIH1 mutations are known.

It was recently shown that some IFIH1 polymorphisms are associated with a spectrum of autoimmune diseases[11]. Rare *IFIH1* variants have been found in Aicardi- Goutières syndrome-7, Singleton-Merten syndrome, and MDA-5 immunodeficiency. All these diseases are characterized by IFN signaling upregulation[12]. In our group of patients with the IFIH1 variant, hyperactivation of the IFNI signaling pathway was also observed, but it is unclear whether it was caused by IFIH1 defects.

In our opinion, two patients with uSAID have probably causative *IFIH1* variants (compound-heterozygous p.L679Ifs*2, p.V599Ffs*5, and heterozygous p.T520A). Functional tests are pending. Almlöf *et al* [13] detected two heterozygous missense *IFIH1* variants (p.Arg77Trp and p.Arg374Cys) with high potential to contribute to SLE. *IFIH1* gene variant p.E627X found in our patients showed a significant association with decreased risk of type 1 diabetes[14].

Combined exome sequencing, transcriptomic analysis, and *in vitro* functional tests have been analyzed to identify genetic variants causing predisposition to severe courses of common respiratory viral infections. Pathogen-restricted immunodeficiency due to loss-of-function variants in *IFIH1* (p.Glu627Ter, p.Leu509_Glu547del, and p.Ile872Ter) have been detected. They result in defective innate recognition of RNA viruses, preventing the activation of an efficient antiviral IFN response[15].

Homozygous nonsense mutation, c.2665A>T (p.Lys889*) in the *IFIH1* gene was identified in a patient with microcephaly, severe psychomotor retardation, seizures, cataracts, and recurrent episodes of prolonged and severe chest infections. The results of the western blot analysis of protein from cultured fibroblasts of the patient indicated the absence of wild-type MDA5/IFIH1, compatible with nonsense-mediated decay[16].

It is not fully understood whether influence detected variants *IFIH1* and *DDX58* on the severity and activity of rheumatic diseases. The patients with rare pathogenic or likely pathogenic variants have had clinical features of interferonopathy (fever, livedo, nodular rash, panniculitis). It seems that patients with *IFIH1* and *DDX58* variants may be considered candidates for agents blocking the IFN-I signaling pathway (IFN-I receptor antibodies, JAK inhibitors) especially when standard treatment is ineffective.

We believe that the results of our study allow us to consider some patients with rheumatic diseases with unusual manifestations or resistance to standard treatment as patients with monogenic disorders, in which other pathogenic signaling pathways are involved and another type of treatment can be assumed. This information added to the discussion.

Genetic testing is becoming an increasingly accessible and widely used method in clinical practice. Careful assessment of clinical signs and family history, selection of patients with unusual clinical manifestations, and paying more attention to patients who do not respond to standard treatment protocols should alert the doctor about possible genetic disorders. Evaluation of the activity of the IFN type I signaling pathway may be an additional criterion when selecting patients for genetic testing. However, the results of the IFN-I score analysis remain contradictory in several studies, a high concentration can be observed both in classical autoimmune (SLE, DM) and in rare forms of auto-inflammatory diseases[17]. Sönmez *et al*[18] proposed preliminary classification criteria for type I interferonopathy, which were developed based on the analysis of a small group of patients. Assessing the sensitivity of these criteria is difficult due to the rare occurrence of these conditions. The development of international registries of both patients with interferonopathies and with genetic variants is promising for the development of diagnostic tools.

Future perspectives are associated with the wider use of genetic testing in patients with seemingly classic rheumatic diseases. The creation of new drugs or clinical trials of existing drugs, but to new indications (*e.g.*, JAK inhibitors in DM and SLE, IFN-I receptor antibodies for DM), seem promising. The limitations of our study are related to a very small number of patients, and the heterogeneity of the selected group of patients. The results are preliminary. Without functional studies, it is very difficult to judge the actual pathogenicity of these variants.

CONCLUSION

The majority of patients with *DDX58* and *IFI1* variants had hyperactivation of the IFN I signaling pathway. Thus, the use of RNA-based IFN-I score seems to help select candidates for further genetic analysis. This study extends the existing data on the spectrum of DDX58 and IFIH1-associated phenotypes. Further studies and collection of patients with *IFIH1* and *DDX58* variants are needed.

ARTICLE HIGHLIGHTS

Research background

The *IFIH1* gene and the *DDX58* gene both are involved in the interferon (IFN) type I signaling pathway. Monogenic diseases with the features of systemic rheumatic diseases were described in patients with these genetic variants. Rheumatic disease patients with IFN type I hyperactivation may have these variants.

Research motivation

Patients with rheumatic diseases with unusual manifestations (clinical features of interferonopathy) or resistant to standard treatment may have molecular variants in genes, regulating IFN I type pathway.

Research objectives

To describe children with different rheumatic diseases who have variants in *DDX58* or *IFIH1* genes.

Research methods

Clinical exome sequencing was performed 92 patients with different rheumatic diseases, and 14 children (10 girls and 4 boys) with *DDX58* or *IFIH1* genes were selected. They have the following diagnosis: Systemic autoinflammatory disease (n = 6), systemic lupus erythematosus (n = 5), juvenile dermatomyositis (n = 1), systemic onset juvenile idiopathic arthritis (n = 1), mixed connective tissue disease (n = 1). Real-time polymerase chain reaction with previous reverse transcription of RNA was used for IFN-I score assessment.

Research results

All patients had elevated IFN-I scores. Variants in both genes were described in the studied population.

Research conclusions

Patients with *DDX58* and *IFI1* variants had hyperactivation of the IFN I signaling pathway. The RNA-based IFN-I score is a good tool to select candidates for further genetic analysis.

Research perspectives

Research perspectives are more on molecular tests in rheumatic diseases, more functional studies confirming the role of genetic variants, and an assessment of the efficacy and safety of drugs on new indications.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Clinical characteristics of community-acquired pneumonia in children caused by mycoplasma pneumoniae with or without myocardial damage: A single-center retrospective study

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Abstract

BACKGROUND

Mycoplasma pneumoniae (MP) is a prevalent pathogen that causes respiratory infections in children and adolescents.

AIM

To assess the differences in the clinical features of MP-associated community-acquired pneumonia (CAP) in children who presented with mild or severe mycoplasma pneumoniae pneumonia (MPP); to identify the incidence of myocardial damage between the two groups.

METHODS

This work is a retrospective study. We identified children between 2 mo and 16 years of age with clinical and radiological findings consistent with CAP. We admitted patients to the inpatient department of the Second Hospital of Jilin University, Changchun, China, from January 2019 to December 2019.

RESULTS

A total of 409 hospitalized patients were diagnosed with MPP. Among them were 214 (52.3%) males and 195 (47.7%) females. The duration of fever and cough was the longest in severe MPP cases. Similarly, plasma levels of highly sensitive C-reactive protein (t = -2.834, P < 0.05), alanine transaminase (t = -2.511, P < 0.05), aspartate aminotransferase (t = -2.939, P < 0.05), and lactate dehydrogenase (LDH) (t = -2.939, P < 0.05) were all elevated in severe MPP cases compared with mild MPP cases, and these elevations were statistically significant (P < 0.05). Conversely, the neutrophil percentage was significantly lower in severe MPP cases than in mild MPP cases. The incidence of myocardial damage was significantly higher in severe MPP cases than in mild MPP cases (χ^2 = 157.078, P < 0.05).

CONCLUSION
Mycoplasma pneumoniae is the main cause of CAP. The incidence of myocardial damage was higher and statistically significant in severe MPP cases than in mild MPP cases.

Key Words: Community-acquired pneumonia; Mycoplasma pneumoniae; Mild mycoplasma pneumoniae pneumonia; Severe mycoplasma pneumoniae pneumonia; Myocardial damage

Core Tip: Our study highlighted which clinical parameters should be focused on to differentiate between mild and severe mycoplasma pneumoniae pneumonia (MPP), which is crucial for pediatricians as it would enable us to make a quick diagnosis and consequently prompt treatment in case of severe MPP. We found that the duration of fever and cough was longer in the severe MPP group than in the mild MPP group. Similarly, the high sensitivity C-reactive protein levels, procalcitonin, alanine transaminase, aspartate aminotransferase, and lactate dehydrogenase were significantly higher in the severe MPP cohort than in the mild MPP group. Paradoxically, the neutrophil count was significantly higher in the mild MPP group than in the severe MPP group. More importantly, the incidence of myocardial damage was significantly higher in the severe MPP group than in mild MPP cases. However, it is unknown whether there is a causal link between severe MPP and myocardial damage; therefore, to ascertain this hypothesis, future research is recommended.

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INTRODUCTION

Community-acquired pneumonia (CAP) is a pulmonary infection (parenchyma or pleura) acquired outside the hospital[1]. CAP is a significant cause of inpatient hospitalization and mortality in children. The annual incidence of CAP requiring hospitalization is over 20 million[2]. In 2015, data from Asia showed that 15% of all fatalities in children under five years of age were caused by pneumonia, with an estimated 922000 children in this age group dying[3]. Similarly, global mortality is estimated at 14%, ranging from 2% of those treated as outpatients to 37% of those admitted to intensive care units (ICUs)[4].

In China, the incidence density of pneumonia in children under five years of age is 0.06 to 0.27% per year. According to a systematic review of data from the China Mortality Surveillance System from 2001 to 2015, the mortality rate for children under the age of five was 153.2 per 100000 live births[5]. Multiple microorganisms drive the pathophysiology of CAP. Classical typical pneumonia is caused by bacteria, while atypical pneumonia is caused by atypical pathogens, such as Mycoplasma pneumoniae (MP), Legionella pneumoniae, and Chlamydia pneumoniae. These three pathogens combined are responsible for 21% to 28% of adult CAP worldwide[6]. MP is one of the most common pathogens causing respiratory illness in adolescents and children, accounting for up to 40% of CAP in children above five years of age[7].

Mycoplasma is a small cell wall-deficient prokaryote. Microbes are cell-free and malleable organisms that can grow and proliferate in a cell-free environment[8].

According to the mycoplasma pneumoniae pneumonia (MPP) diagnostic criteria of CAP in children, MP patients are classified as mild mycoplasma pneumoniae pneumonia (MMPP) and severe mycoplasma pneumoniae pneumonia (SMPP) (revised in 2013). Typical clinical symptoms, such as cough and fever, radiological findings, elevated inflammatory markers, and the detection of serum specificity MP-IgM antibody are the diagnostic criteria of MMPP.

SMPP is defined as MPP with protracted fevers, worsening clinical symptoms, and persistent radiological features following a week-long routine of macrolide antibiotic therapy[9]. Similarly, SMPP is defined as a fever (> 38.5°C), persistent cough for more than two weeks, CRP > 40 mg/L, radiological features showing consolidation in two or more pulmonary lobes, and extrapulmonary complications were the criteria to diagnose SMPP as per the algorithm of community-acquired pneumonia in children [10,11].

Consensus on the definition of SMPP is lacking because it can affect any part of the body, including the musculoskeletal system, neurological system, hematological system, and skin[12]. However, MP infection most severely affects the respiratory system; hence, respiratory and metabolic acid-base disturbances may indirectly indicate severe disease. Therefore, prompt and effective treatment is recommended[13]. Moreover, immune evasion by specific pathogens *via* the transmission of host-derived lipid membranes can lead to uninhibited proliferation, resulting in overt clinical symptoms and a worsening disease course[14].

MP is contagious and can be transmitted through aerosols from coughing and sneezing, causing acute upper and lower respiratory tract inflammation[15]. These respiratory pathogens are ubiquitous on environmental surfaces, and mucous membrane contact with these contaminated surfaces aids in disease transmission. The propensity for children to play with toys and have poor hand hygiene make children a high-risk and susceptible group in daycare and school settings[16]. MP infection also causes nonrespiratory symptoms, including myocarditis, arthritis, and thrombosis, in newborns. If left untreated, multiple organ failures may ensue[17]. Acute myocardial injury in people hospitalized with community-acquired pneumonia (CAP) is caused by many different factors. These factors include type-2 myocardial infarction with or without prior coronary artery disease (CAD) due to an imbalance between demand and supply and non-CAD myocardial damage caused by toxins, direct myocardial infection, inflammatory mediators, and stress-induced cardiomyopathy[18]. MP-induced myocarditis is usually confirmed *via* an electrocardiogram (ECG), which shows conduction arrhythmias and myocardial atrioventricular block. Chest pain can be a sign of myocarditis or pericarditis and has been linked to anti-cardiolipin antibodies[19].

Although uncommon, the prevalence of myocarditis in children with MP ranges from 1% to 8%, and the prevalence rate is slightly higher in adults than in children[20]. Mycoplasma-associated carditis (myo- or pericarditis) is a rare condition that has affected 1%-5% of patients since Pönkä's study in 1979. However, individuals with mycoplasma carditis seem to be older on average. This study supports Pönkä's conclusion that the mean age was 32. This recurring finding is not fully understood. However, it may be related to the increased rates of mycoplasma infection in older persons appearing as pneumonia, which is more common in patients with carditis[21].

This study aims to assess the differences in the clinical characteristics of children diagnosed with CAP caused by MP and to further identify the cohort of patients who developed MP-induced myocardial damage and those without heart failure.

MATERIALS AND METHODS

Study population

This study was a single-center retrospective study. We identified children between 2 mo and 16 years of age with clinical and radiological findings consistent with CAP admitted to the inpatient department of the Second Hospital of Jilin University, Changchun, China, from January 2019 to December 2019. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of The Second Hospital of Jilin University (In 2022, research review No. 073).

Inclusion criteria were as follows

(1) Age between 2 mo and 16 years old; (2) Children admitted to the inpatient pediatric department of the Second Hospital of Jilin University in 2019 with diagnosed MPP; (3) Radiological findings, such as interstitial infiltration, linear opacities, patchy infiltration, segmental or lobar consolidation, reticulonodular infiltrate, or pleural effusion; and (4) Diagnosed with MP by serology with an immunoglobulin M (IgM) titer of > 1.1 considered positive. MP-IgM was identified by enzyme-linked immunosorbent assay (ELISA) as serum MP antibodies.

The exclusion criteria were as follows

(1) Children aged less than two months and greater than 16 years old; (2) Children with chronic respiratory tract infection or other pulmonary illness; (3) Community-acquired pneumonia caused by other species, such as chlamydia pneumonia; and (4) Concomitant other pathogenic infections

Data collection

Clinical data were collected uniformly from the Second Hospital of Jilin University pediatrics inpatient department database. Based on the following symptoms, all patients were diagnosed with CAP: Cough, tachypnea, chest retractions, fever, wheezing, crackles or reduced breath sounds, and radiological abnormalities with pulmonary fever, wheezing, or infiltrates. IgM titer (> 1.1), age, gender, white blood cell (WBC) count, lymphocyte percentage, neutrophil percentage, C-reactive protein (CRP), high-sensitivity C-reactive protein, procalcitonin, alanine transaminase (ALT), aspartate aminotransferase (AST), creatine phosphokinase and lactate dehydrogenase (LDH) were obtained from the patient chart. Fever (> 38.5°C), persistent cough for more than two weeks, CRP > 40 mg/L, and intra- and extrapul-

monary complications were the criteria to diagnose SMPP per the algorithm of community-acquired pneumonia in children. White blood cell (WBC) count > 15000 cells/mL or < 5500 cells/mL for children < 5 years old and WBC count > 11000 cells/mL or < 3000 cells/mL for children ≥ 5 years old were considered abnormal. Fever (> 38.5°C), persistent cough for more than two weeks, CRP > 40 mg/L, and intra- and extrapulmonary complications were the criteria to diagnose SMPP per the algorithm of community-acquired pneumonia in children. According to myocardial damage, an ECG was performed to check for different heart conditions. We also performed blood tests to check for proteins associated with heart damage, such as troponin.

Data analysis

The data were populated in Microsoft Excel 2016. Categorical data and comparisons among these two groups between mild and severe MPP were analyzed using the chi-squared or Fisher's exact tests. An independent t test was used to compare the differences between continuous variables. Statistical analyses were performed using IBM SPSS statistics 26, and statistical significance was set at a P value of < 0.05. The results are presented as the mean ± SD for numerical variables.

RESULTS

Sociodemographics

In our study, 409 children with CAP were included, among whom 214 (52.3%) were males and 195 (47.7%) were females. MP infection was more prevalent in males than females (Table 1). Among the mild MPP cases, 232 patients were < 5 years old, accounting for 77.6% of patients: 67 patients were ≥ 5 years old, accounting for 22.4% of patients. In severe cases, 85 patients were < 5 years old, accounting for 77.3% old, while 25 patients were ≥ 5 years, accounting for 22.7% of patients, as shown (Table 2 and Figure 1).

The seasonal distribution of MP infection: The seasonal distribution of hospitalized children with mild MPP (102/299, 34.10%) and severe MPP indicated that 41/110 children (37.30%) were diagnosed during winter. In comparison, mild MPP (80/299, 26.80%) and severe MPP (28/110, 25.50%) patients were diagnosed during the spring. Moreover, 28/299 (9.40%) patients with mild MPP and 28/110 (10.00%) patients with severe MPP were diagnosed during summer, whereas 89/299 (29.80%) patients with mild MPP and 30/110 (27.3%) patients with severe MPP were diagnosed during autumn. These results indicated that the prevalence rate of M pneumonia in hospitalized children was highest in winter (Table 3).

According to Pearson's chi-square test, a significant difference was not detected between seasons according to severe MPP cases and mild MPP cases ($\chi^2 = 0.487$, $P > 0.05$).

Clinical characteristics

Clinical symptoms of children in both groups were compared head-to-head. In our study, the incidences of mild and severe MPP cases did not differ by sex or age ($t = 0.54$, $P > 0.05$, $t = 0.69$, $P > 0.05$, respectively) (Table 4). Common clinical symptoms included phlegm (31/409, 7.6%), hoarseness (22/409, 5.3%), rhinorrhea (12/409, 3%), diarrhea (9/409, 2.2%), vomiting (7/409, 1.7%), and rash (7/409, 1.7%). These symptoms, signs, or physical findings did not significantly differ between mild and severe MPP.

However, auscultated respiratory sounds significantly differed between severe and mild MPP cases in our study ($\chi^2 = 11.915$, $P < 0.05$) (Table 5).

Similarly, myocardial damage significantly differed between mild and severe MPP cases ($\chi^2 = 157.078$, $P < 0.05$). Specifically, the incidence of myocardial damage was higher in severe MPP cases than in mild MPP cases (Table 5).

Independent t test samples showed that the duration of fever was significantly different between severe and mild MPP ($t = -2.72$, $P < 0.05$). The duration of cough was also significantly longer in severe MPP cases than in mild MPP cases ($t = -5.103$, $P < 0.05$). Conversely, the neutrophil percentage was significantly higher in mild MPP cases than in severe MPP cases ($t = 2.113$, $P < 0.05$) (Table 4).

High sensitivity C-reactive protein was significantly higher in severe MPP cases than in mild MPP cases ($t = -2.834$, $P < 0.05$). Both ALT and AST were significantly higher in severe MPP cases than in mild MPP cases ($t = -2.511$, $P < 0.05$ and $t = -2.939$, $P < 0.05$, respectively). Lactate dehydrogenase (LDH) was also significantly higher in severe MPP cases than in mild MPP cases ($t = -2.939$, $P < 0.05$). The remaining variables did not significantly differ ($P > 0.05$) between severe and mild MPP (Table 4).

DISCUSSION

This work is the first study to discuss the relationship between Mycoplasma pneumoniae pneumonia and myocardial damage in children. We investigated the clinical and laboratory characteristics of

Table 1 Gender distribution

Gender	Frequency	Percentage
Female	195	47.68
Male	214	52.32
Total	409	100.00

Table 2 Age distribution of community-acquired pneumonia in hospitalized children with mycoplasma pneumoniae pneumonia categorized as mild and severe, *n* (%)

Age group	Total	Mild MPP	Severe MPP
< 5 yr	317	232 (77.6)	85 (77.3)
≥ 5 yr	92	67 (22.4)	25 (22.7)
Total	409	299	110

MPP: Mycoplasma pneumoniae pneumonia.

Table 3 Seasonality of mycoplasma pneumoniae pneumonia, *n* (%)

Season	Mild MPP	Severe MPP
Winter	102 (34.10)	41 (37.30)
Spring	80 (26.80)	28 (25.50)
Summer	28 (9.40)	11 (10.00)
Autumn	89 (29.80)	30 (27.30)

MPP: Mycoplasma pneumoniae pneumonia.

children with CAP caused by MP and compared them with those with mild MPP and severe MPP. Our study showed that MP was the leading cause of CAP in hospitalized children in Changchun, China, in 2019.

CAP is a nonhospital-acquired illness of the lower respiratory tract[22]. MP is one of the most common infections in children with CAP. MPP is usually self-limiting and is adequately treated with macrolides. Conversely, severe MPP is common and may result in problems such as pleural effusion, atelectasis, and lung consolidation[23]. In recent years, an upsurge in the number of refractory, severe, and even deadly MPP cases has been reported[24]. The pathogen MP, discovered in the 1940s, causes a wide range of clinical symptoms with a unique seasonal pattern; it is most active in the fall/early winter, with favorable peak rates of 3% to 4% between September and January[25]. MP is a benign, self-limiting disease; however, missed early detection opportunities, clinical misdiagnosis, and drug resistance often lead to poor outcomes[26].

Following the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, comprehensive testing and positivity rates of MP plummeted compared to previous years[27]. A national multicenter prospective survey of all-age patients (52.2% were aged 18 years) with acute respiratory tract infections in China between 2009 and 2019 revealed a peak in the positivity rate of MP in 2011 and a gradual upward trend in the positivity rate of MP from 2015 to 2019 (the majority being pediatric patients)[28]. MP is contagious and can be transmitted through aerosols from coughing and sneezing, causing acute upper and lower respiratory tract inflammation. The positivity rate for MP was low during 2020, which coincided with the COVID-19 era, suggesting that the implementation of nationwide countermeasures, such as strict face mask-wearing and population quarantine measures, may have also effectively prevented the concurrent spread of MP[29]. Our data showed that the rate of MP in hospitalized children was higher in winter than in autumn, which corroborated previously published data[30]. Conversely, a study from Serbia reported that the highest number of MP infections was recorded in the fall (33.3%), and this rate was higher than that in winter (29.2%)[31]. Similar studies on the seasonality of MP infection from Shanghai, China, showed a peak in spring that declined precipitously until the following summer[29]. However, some studies from Italy and Tunisia found no seasonal correlation in MP infection[31]. In our research, we found that children < 5 years of age were likely to have more severe MPP than mild MPP, accounting for 77.3% of cases. This finding was similar to data from a study

Table 4 Clinical characteristics and laboratory investigations of hospitalized children with community-acquired pneumonia caused by mycoplasma pneumonia were compared between the severe and mild case groups

Parameters	Mild MPP (*n* = 299)	Severe MPP (*n* = 110)	*Z*	*P* value
Gender	1.48 ± 0.501	1.45 ± 0.500	0.54	0.58
Age (yr)	3.59 ± 2.63	3.40 ± 2.16	0.69	0.49
Fever (℃)	38.73 ± 0.86	38.71 ± 0.83	0.163	0.87
Duration of fever	4.27 ± 3.37	5.76 ± 5.39	-2.72	0.007
Duration of cough	5.98 ± 6.9	11.4 ± 10.33	-5.103	< 0.001
WBC (10^9/L)	8.98 ± 4.77	9.34 ± 4.23	-0.691	0.49
Lymphocyte (%)	35.87 ± 14.04	38.93 ± 18.29	-1.59	0.114
Neutrophil (%)	54.48 ± 15.46	49.98 ± 20.28	2.113	0.036
Neutrophil to lymphocyte ratio	2.06 ± 1.702	2.046 ± 2.20	0.078	0.938
CRP (mg/L)	12.59 ± 19.24	10.48 ± 17.82	1	0.318
hsCRP (mg/L)	6.1 ± 5.84	8.35 ± 7.5	-2.834	0.005
PCT (ng/mL)	0.42 ± 0.93	0.76 ± 3.15	-1.097	0.27
Alanine transaminase (U/L)	15.95 ± 8.42	24.97 ± 37.32	-2.511	0.013
Aspartate aminotransferase (U/L)	32.25 ± 20.31	41.37 ± 30.11	-2.939	0.004
Creatine kinase (U/L)	97.3 ± 110.38	101.4 ± 83	-0.354	0.724
Lactate dehydrogenase (U/L)	286.55 ± 69.12	317.55 ± 93.77	-3.633	< 0.001

CRP: C-reactive protein; hsCRP: C-reactive protein; PCT: Procalcitonin; WBC: White blood cell.

Table 5 Auscultatory and myocardial damage findings among the mild and severe mycoplasma pneumoniae pneumonia cases, *n* (%)

Parameters		Mild MPP	Severe MPP	χ^2	*P* value
1 Auscultation	Crackles	37 (12.40)	23 (20.90)	11.915	0.008
	Normal	141 (47.20)	35 (31.80)		
	Wet rales	7 (2.30)	7 (6.40)		
	Wheezing	114 (38.10)	45 (40.90)		
2 Myocardial damage	Yes	0 (0.0)	52 (47.30)	157.078	< 0.001
	No	299 (100)	58 (52.70)		

MPP: Mycoplasma pneumoniae pneumonia.

conducted in Luzhou, China, which reported an MP positivity rate of 75% in children between the ages of 5 and 1 year[32]. However, some studies also report a higher risk of MP infection in children above > 5 years of age compared to those < 5 years of age[31]. Severe Mycoplasma infections are prevalent not only in children older than five years but also in those aged 2 to 4 years, and 10% of MP-infected patients admitted to the ICU were less than two years old. In addition, prior research identified MP as a significant cause of CAP in babies younger than one year[33]. Our findings are not easily compared to those of other studies because of the wide range of epidemiological conditions, varying populations, and different diagnostic modalities.

We also compared mild and severe MPP and found that the duration of fever and cough was longer in the severe MPP group than in the mild MPP group. Similarly, the high-sensitivity C-reactive protein, alanine transaminase, aspartate aminotransferase, and lactate dehydrogenase levels were significantly higher in the severe MPP cohort than in the mild MPP group. Paradoxically, the neutrophil count was significantly higher in the mild MPP group than in the severe MPP group, and we found that the neutrophil-to-lymphocyte ratio (NLR) did not significantly between mild MPP and severe MPP cases in children ($P > 0.05$). In another study of adults, the NLR was shown to have good prognostic value for short- and long-term mortality, ICU admission, and rehospitalization. This ratio is distinguished by

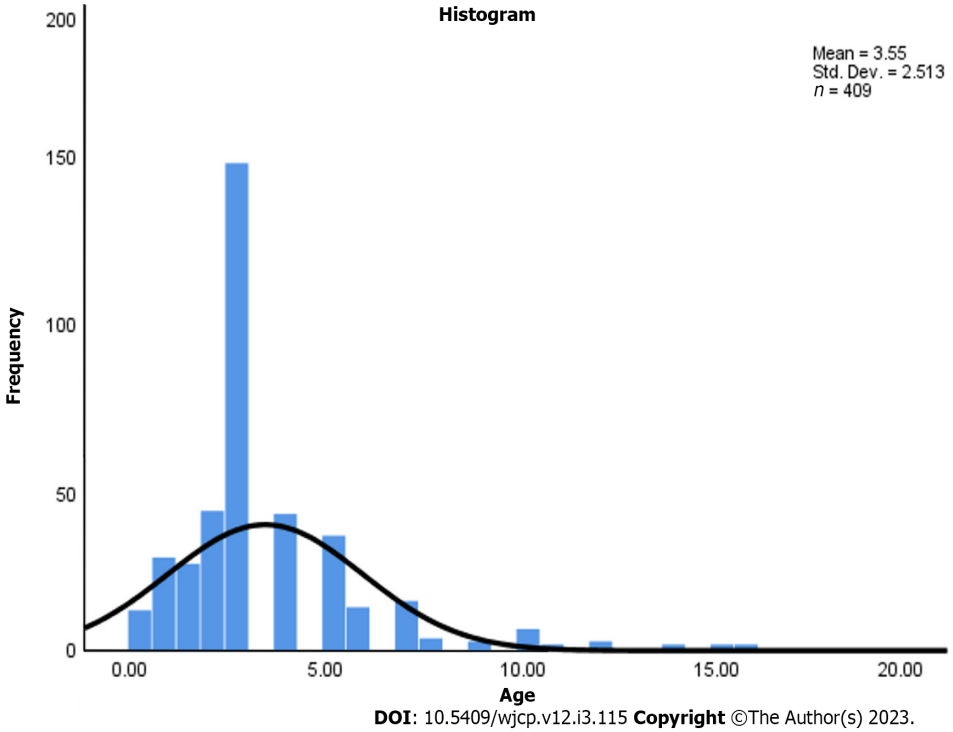

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Figure 1 Age distribution of 409 children with Mycoplasma Pneumoniae-associated community-acquired pneumonia.

high death and morbidity rates, particularly among older individuals. As a result, the NLR was linked with post-CAP mortality better than standard pneumonia ratings (Patient-specific instrumentation; and Confusion, Urea, Respiratory rate, and Blood pressure, aged 65 and older, CURB-65)[34].

As a result, novel, simple, specific, and low-cost biomarkers to diagnose and monitor CAP are still needed. Neutrophilia and lymphocytopenia are innate immune system physiological responses to systemic inflammation. Lymphocytopenia is characterized by rapid apoptosis and the margination of lymphocytes in the reticuloendothelial system, liver, and splanchnic lymphatic system as well as lymphocyte redistribution throughout the lymphatic system. Neutrophilia is the opposite phenomenon and occurs during systemic inflammation due to neutrophil emargination and growth factor stimulation of stem cells (granulocyte-colony stimulating factor)[34]. In previously published research, WBC count and CRP were also demonstrated to be possible markers of pneumonia; however, they did not play a significant role in determining the causative pathogen of pneumonia, similar to our findings[35]. More importantly, the incidence of myocardial damage was significantly higher in the severe MPP group than in the mild MPP group. The remaining parameters, did not significantly differ between the two cohorts ($P > 0.05$).

Cardiac complications caused by MP are infrequent, with a prevalence rate of 1.0-8.5% and a slightly higher prevalence rate in adults than in children. Almost half of MP patients showed symptoms or evidence of cardiac abnormalities at a mean of 16 mo following infection. Constrictive pericarditis caused by MP infection has also been documented[20].

In some instances, MP-related extrapulmonary illnesses may be this infection's most obvious clinical issue, particularly in young people and children. MP infection has also been connected to several extrarespiratory symptoms. Numerous disorders affecting the skin, musculoskeletal, neurological, hematological, digestive, and renal systems have been described in pediatric populations[36]. CD4- T cells, B cells, and plasma cells invade the lungs, causing additional immunological amplification, including lymphocyte proliferation, immunoglobulin synthesis, and the release of proinflammatory cytokines. Total immunoglobulin, immunoglobulin A (IgA), IgM, and IgG levels in serum have previously been shown to rise throughout the convalescent phase of the illness; furthermore, IgE specific to MP is produced during infection[37]. The concentrations of serum cytokines, such as Interleukins (IL) IL-1, IL-4, and IL-6, also increase. The intensity of inflammation is determined by its degree. The production of acute-phase proteins, such as C-reactive protein, the amount of leukocytosis, the level of fibrinogen, and the rate of erythrocyte sedimentation are all pathogenetically relevant in pneumonia, determining the severity of the illness and increased mortality[38].

Our study highlighted the clinical parameters that should be focused on to differentiate mild and severe MPP cases. These paratmeters are crucial for pediatricians because they allow for rapid diagnosis and prompt treatment in cases of severe MPP.

This study's limitations include its retrospective nature and small sample size. Some data were omitted because they were missing and could not be extrapolated to represent hospitalized children with CAP throughout the year. Moreover, only cases were analyzed and this study lacked a control group.

CONCLUSION

Mycoplasma pneumoniae is the leading cause of community-acquired pneumonia. We found a significantly higher incidence of myocardial damage in children with severe MPP than in those with mild MPP. However, a causal link between severe MPP and myocardial damage has not yet been identified; therefore, future research is recommended to confirm this hypothesis.

ARTICLE HIGHLIGHTS

Research background

Community-acquired pneumonia (CAP) is a significant cause of inpatient hospitalization and mortality in children.

Research motivation

This is crucial for pediatricians as it would enable us to make a quick diagnosis and consequently prompt treatment in case of severe mycoplasma pneumoniae pneumonia (MPP).

Research objectives

Our study highlighted which clinical parameters should be focused on to differentiate between mild and severe MPP.

Research methods

We identified children between 2 mo and 16 years of age with clinical and radiological findings consistent with CAP.

Research results

We found that the duration of fever and cough was longer in the severe MPP group than in the mild MPP group. Similarly, the high sensitivity C-reactive protein levels, procalcitonin, alanine transaminase, aspartate aminotransferase, and lactate dehydrogenase were significantly higher in the severe MPP cohort than in the mild MPP group. Paradoxically, the neutrophil count was significantly higher in the mild MPP group than in the severe MPP group.

Research conclusions

The incidence of myocardial damage was significantly higher in the severe MPP group than in mild MPP cases.

Research perspectives

It is unknown whether there is a causal link between severe MPP and myocardial damage; therefore, to ascertain this hypothesis, future research is recommended.

FOOTNOTES

Author contributions: Yusuf SO conducted data collection, analysis, and manuscript drafting; Chen P conceived the study and supervised the entire study process; All authors read and approved the final manuscript.

Institutional review board statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of The Second Hospital of Jilin University (In 2022, research review No. 073). Parents of all eligible children gave their informed consent for inclusion before they were admitted to the hospital. The confidentiality of the patients was ensured throughout the study.

Informed consent statement: This study consists of two parts: (1) We collected children's medical history, diagnosis and supplementary examination in the inpatients department through the hospital computer; and (2) the results of this study may provide information for future clinical activities. At the same time, we will keep the children's information and privacy strictly confidential. We promise to use it only for this study. Without permission, we will

not disclose this information to third parties. We make every effort to protect the privacy of the personal medical data. We will not use any patients name or patients ID.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Data sharing statement: No additional data is available.

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ORIGINAL ARTICLE

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Psychiatric disorders and caregiver burden in children with transfusion dependent β-thalassaemia and their caregivers

Samiksha Sahu, Amit Agrawal, Jyotsna Shrivastava, Sudhir Tonk

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Abstract

BACKGROUND

Children with thalassemia need care from the first years of life owing to the physical and psychological effects of their disorder. Thalassemia is a concern not only for the children's physical health but also the mental health of themselves and their caregivers.

AIM

To screen the psychosocial problems and assessment of psychiatric morbidities among thalassaemic children and their caretakers, along with an assessment of caregiver burden in them.

METHODS

In this observational cross-sectional study, children with transfusion-dependent thalassemia, were included and were assessed for psychiatric morbidity and global functioning. Their parents were assessed for psychiatric morbidity and the caregiver burden they faced. All the parents completed two different questionnaires to assess their knowledge about the psycho-social functioning [using Pediatric Symptom Checklist-35 (PSC-35)] of their children and the level of the burden faced by them by Caregiver Burden Scale (CBS).

RESULTS

A total of 46 children (28 boys and 18 girls) with transfusion-dependent thalassemia with a mean age of 8.83 ± 2.70 years and 46 parents (12 fathers and 34 mothers) were included in this study. More than 32 children had some psychosocial problems on screening by PSC-35. On assessment by CBS moderate caregiver burden was perceived in domains of general strain, isolation, disappointment, emotional involvement, and environment. A total of 65.3% of

children and 62.7% of parents were diagnosed with psychiatric problems.

CONCLUSION
Thalassemia affects not only the persons with the disorder but also their caregivers in several aspects, including their psychosocial well-being. This study emphasizes the role of a supportive group in the psychological well-being of caregivers, which could be used to prevent the pathological effects of caregiver burden and enhance their psychological well-being through counselling.

Key Words: Thalassemia; Children; Caregiver burden scale; Psychiatric morbidity

Core Tip: Thalassemia is a major public health problem because of its high prevalence ranging from 2%-5%. Like other chronic illnesses, patients with thalassemia are vulnerable to emotional and behavioral problems making them susceptible to a myriad of psychiatric disorders. The emotional and psychological problems faced by thalassaemic children and their caregivers are often overlooked resulting in increased suffering and poor outcome. In this observational, cross-sectional study we analyze 46 children with transfusion-dependent Thalassemia for the presence of psychiatric disorders along with the caregiver burden experienced by the caregivers of these children.

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INTRODUCTION

Thalassemia is a major public health problem because of its high prevalence ranging from 2%-5%, it extends from parts of Africa, the Mediterranean throughout the Middle East, Southeast Asia, and the Indian subcontinent[1-3]. Each year 50000-100000 children die of Thalassemia major in low- and middle-income countries[4]. The carrier rate for the beta thalassaemia gene varies from 1%-2% in Southern India to 3%-15% in Northern India. Children with thalassemia major present with pallor, failure to thrive, intercurrent infections, and hepatosplenomegaly, and they are generally diagnosed between 6 mo and 2 years of life. If undiagnosed and untreated, more than 90% do not survive beyond 3 to 4 years of age[5]. Similar to other chronic illnesses, patients with thalassemia are vulnerable to emotional and behavioral problems[6]. These children are susceptible to anxiety and depression due to fear of separation from family, restricted social activity, physical and facial deformities, fear of death, and limitations in school and outdoor activities. It has been observed that up to 80% of children with thalassaemia are likely to have psychological problems like anxiety disorder, depression, and oppositional defiant disorder[2]. Psychosocial burden is perceived even more in adolescents when they are confronted with various difficulties like identity formation and developing intimate relationships dealing with work. Their physical appearance and absence of sexual development is the major obstacle to social and personal life. Thalassemia also affects the caregivers' mental health, and family life as it causes lots of financial strain leads to ignorance of other children, and hampers occupational duties due to its long-term complications, and burdensome medical protocols[7-9]. There are many studies about psychiatric problems and the quality of life of patients with thalassemia[10]. Understanding of the psychiatric aspect of this disease is still in its infancy. Therefore, we planned this study to assess the occurrence of psychiatric disorders amongst children and their caregivers as well as to assess the caregiver burden in children of transfusion-dependent β thalassaemia major.

MATERIALS AND METHODS

This observational, cross-sectional study was conducted in the department of Pediatrics of a tertiary care teaching institution in central India over a period of one year. Prior approval from the institutional ethics and research committee was obtained. Children with an established diagnosis of transfusion-dependant β thalassemia major in the age range of 5 to 16 years and their caregivers regularly attending the department for blood transfusion were chosen for the study. A sample size of 46 patients was

calculated to complete the objective of the study using the formula (n = 4pq/L2) where prevalence (p) was 3%, q = (100-p), and allowable error (L) was 5%. Written consent was taken from the parents/caregiver and assent was taken from children above seven years of age. Children, with other chronic disorders like epilepsy and comorbid neurological conditions like pre-existing mental retardation, developmental delay, and cerebral palsy and thalassaemic children less than five years and more than 16 years of age, were excluded. Relevant information including socio-demographic profile, age at diagnosis, details of chelation therapy, and blood transfusion was collected in a predesigned proforma. Socio-economic status was assessed using Modified Prasad's classification[11].

After recruitment, the complete physical and systemic examination was done by the paediatrician. The parents of the recruited children were given two questionnaires: Pediatric Symptom Checklist-35 (PSC-35) and Caregiver Burden Scale (CBS)[12]. PSC-35 is a parent-reported questionnaire designed to assess the psychosocial functioning of children in the domains of attention, externalizing, and internalizing symptoms. It has a sensitivity of 80% to 95% and specificity of 68% to 100% The PSC consists of 35 items that are rated as "never", "sometimes", or "often present" (scored 0, 1, and 2, respectively). The scores for all 35 items are summed up to calculate the total score. For children aged 6 through 16 years, the cut-off score is 28 or higher while the cut-off is 24 or higher for 4- and 5-year-old children. Children who scored above the cut-off were referred for Psychiatric assessment.

CBS had 22 questions about different aspects of caregivers' burden and it has factor analysis to yield results about 5 indices - general strain (8 questions), disappointment (5 questions), emotional involvement (3 questions), isolation (3 questions), and environment (3 questions)[13]. Scoring was done on a scale of 1-4 (not at all, seldom, sometimes, and often). The total burden index was the mean of all 22 items and the higher scores indicated a greater burden. The total burden of each domain was divided into three groups: Low burden (1.00-1.99), moderate burden (2.00-2.99), and high burden (3.00-4.00)[14]. All the children who met the cut-off score on PSC-35 were clinically interviewed by the Professor in psychiatry and were diagnosed using DSM-IV TR. All the parents, who perceived a higher burden of illness, were also interviewed by a psychiatrist and were diagnosed and managed accordingly. Quantitative variables were analyzed in terms of mean and SD. Qualitative data was depicted in numbers and percentages.

RESULTS

A total of 46 children and their parents were included in this study, out of which 28 were males and 18 were females. Among parents 12 were fathers and 34 were mothers. The mean age of children was 8.83 ± 2.70 years. Most of them were staying in Urban settings (63%). 58.69% of the population were belonging to nuclear families. Patients came from all the socio-economic strata of society but the lower class was dominant. Demographic details of the study population have been given in Table 1. The mean medical expense per month was 11.89% ± 6.27% of the total family income. In terms of caregiver burden, the caregivers have faced a moderate amount of burden in terms of general strain, isolation, disappointment, emotional involvement, and environment (Table 2). A total of 35 out of the 46 children scored above the cut-off score in assessment on PSC-35 and out of them, 30 children were diagnosed with various psychiatric disorders like major depressive disorder (15.2%), anxiety disorder (19.6%), attention deficit hyperactivity disorder (ADHD) (8.7%), elimination disorder (19.6%), panic disorder (2.2%) as shown in Table 3. Whereas in caregivers, 28.2% of caregivers suffer from depression, 4.3% from bipolar disorder, substance use disorder (10.9%), somatisation disorder (13.04 %), and 6.6% suffered from anxiety disorder (Table 3).

DISCUSSION

Thalassemia is among the most common hemoglobinopathy in India. It has become a major health problem for patients and their families in many countries due to the cost of treatment which involves regular transfusions, iron chelation, medical follow-ups, and hospitalisations[15,16]. In recent years, attention is drawn to the evaluation of psychiatric disorders, and caregiver burden among patients and their caregivers[17,18]. Our study highlights the sociodemographic variables, caregiver burden, and psychiatric morbidities in children suffering from transfusion-dependent Thalassemia Major and their parents. In our study, the mean age of the children was 8.83 ± 2.70 years with a male preponderance which is commonly seen in Indian settings[19]. However, studies done in the Middle East, Mediterranean, and west have shown the equal incidence of diseases in both sexes[20,21-24]. This male preponderance has been attributed to a gender bias, rather than an actual dominance of disease in the boys. Various studies across India have seen that a boy child is taken to a health facility more often than a girl child[25]. We further found that the majority of the caregiver (73.91 %) were females, this finding may be attributed to the Asian culture of parenting where mothers tend to stay at home and take care of their children. We have found, similarly, a significant impairment in the mental health of the caregivers of β-thalassaemic children, while their children undergo years of treatment, they often face isolation, strain,

Table 1 Demographic details of the study population

Variable	Male (28)	Female (18)	Total, *n* (%)
Age (children)			
4-8 years	10	9	19 (41.30)
9-12 years	12	5	17 (36.95)
13-16 years	6	4	10 (21.73)
Age (parents)			
< 20 years	2	5	7 (15.2)
21-30	6	18	24 (52.17)
31-40	3	9	12 (26)
> 40	1	2	3 (6.5)
Residence			
Rural	15	2	17 (37)
Urban	13	16	29 (63)
Family type			
Nuclear	17	10	27 (58.69)
Joint	11	8	19 (41.30)
Socioeconomic status (prasad's scale)			
Upper middle class	3	4	7 (15.21)
Middle class	7	3	10 (21.7)
Lower middle class	6	5	11 (23.91)
Lower class	12	6	18 (39.13)

Table 2 Caregiver burden in the parents of thalassaemic children

Items	Mean
General strain	2.77
Isolation	2.93
Disappointment	2.77
Emotional involvement	2.78
Environment	2.75

and disappointment. Most of them suffer from moderate caregiver burden. As mothers are emotionally more vulnerable and they undertake the caregiver role in our society we found a higher ratio of burden in females caregiver, our finding is by a study done by Sinno *et al*[26] and a study done in Iranian mothers of thalassaemic children where they also observed high caregiver burden and strain[27].

Children and families suffering from any chronic illness have a significant impact on their mental health. Parents 'anxiety about their child's illness may lead to restrictions on many normal activities of childhood and can prevent the overall development of the child. These things in the long run can make a child prone to many psychiatric disorders. Along with children even parents of these children faces isolation, and emotional and financial burden in their life, over time the parents' attitude may result in over-protective behaviour or open rejection. The child's feelings and reaction to his illness may affect his relationships with his siblings, peers, and his parents[28]. Studies done in the past 25 years have shown that the prevalence of Psychiatric disorders in thalassaemic children ranged from 23 to 80%, and these problems affect treatment compliance[29]. In the present study, 65.3% of the thalassaemic children had a psychiatric problem and Among caregivers, 62.67% had psychiatric problems which is in accordance with the results of the previous studies[4,5,13]. Depression which is associated with medical illness is one of the important subgroups of mood disorders. The increased prevalence of depression has been associated with chronic medical diseases, and the prevalence of depression increases with co-occurring medical conditions[13]. We found that 15.2% of children suffered from Major Depressive disorder

Table 3 Psychiatric diagnosis among thalassaemic children and caregiver, *n* (%)

Psychiatric Disorder	Children	Caregiver
Major depressive disorder	7 (15.2)	13 (28.2)
Bipolar I disorder	0 (0.0)	2(4.3)
Generalized anxiety disorder	9 (19.6)	2 (4.3)
ADHD	4 (8.7)	0 (0.0)
Elimination disorder	9 (19.6)	0 (0.0)
Panic attack	1 (2.2)	1 (2.2)
Substance use disorder	0 (0.0)	5 (10.9)
Somatization disorder	0 (0.0)	6 (13.04)
Total	30 (65.3)	29 (62.67)

ADHD: Attention deficit hyperactivity disorder.

earlier studies have noted a similar trend. In our study, we found that 28.2% of parents of children with Beta Thalassemia Major suffered from a major depressive disorder. In a previous study, UL Haq *et al*[30] found that most of the caregivers suffered from mild depression which is similar to our finding. In a study done for the evaluation of depression in mothers of patients with thalassemia or hematological malignancies, Shargi *et al*[31] reported the frequency of depression as 51%.

In the present study, 19% of patients were found to have nocturnal enuresis. In an earlier study, Beratis found that 12 % of their sample of pre-adolescent children with Thalassemia had nocturnal enuresis. Aydin *et al*[7] reported the prevalence of nocturnal enuresis to be 8% of children with TM. As we have not investigated the renal function in our study, it will not be possible to comment on the etiological factor of nephropathy. The impact of nocturnal enuresis extends to the caregiver as well adding up their miseries, as they have to wake up every night or change and wash their beddings. Generalized anxiety disorder, was seen in more than 19% of children followed by ADHD and panic attacks. Not many studies have assessed the long-term effect of chronic anaemia on the attention and hyperactivity of children, but some studies should be encouraged to study these aspects of long-term illness[31]. A significant number of parents suffered from somatization disorder (13.04%), generalized anxiety disorder, and bipolar disorder. This high percentage of somatisation disorder indicates the caregivers' fragile mental state as they are using neurotic defenses to deal with the struggle of life. We found that substance use disorder was seen in 10.9% of parents, it can be assumed that keeping aside the genetic susceptibility we may attribute substance use to cope with problems and hardships which accompany the lives of these parents. Studies done in Bangalore reported a high prevalence of psychiatric problems in caregivers of thalassaemic children which includes substance use disorder and depression[29]. Our study was limited by the small sample size. Also, it was a hospital-based study so the results cannot be generalized.

CONCLUSION

Our study showed that the parents of children with transfusion-dependent thalassemia major suffer from high caregiver burden and many of them also suffered from dysthymic disorder, somatoform disorder, and substance addictions. These children also suffered from various psychiatric problems like generalized anxiety disorder, elimination disorder, dysthymic disorder, and other psychiatric ailments. Due to their chronic condition and associated psychiatric morbidity, they have slight impairment in global functioning. Our study highlights the importance of comprehensive care and appropriate psychiatric intervention for thalassaemic children and their caregivers.

ARTICLE HIGHLIGHTS

Research background

Thalassemia is highly prevalent in Indian Subcontinent with prevalence rates varying from 2%–5%. These children and their caregivers experience multiple emotional and psychological problems stemming from the poor physical health of the child and resultant recurrent hospitalisations.

Research motivation

Psychiatric co-morbidities in these children and their caregivers have remained unexplored resulting in high emotional and psychological suffering. Assessing the same would result in the recognition of high psychiatric co-morbidities faced by this subset leading to the holistic care of these patients.

Research objectives

Current study aimed to screen the psychosocial problems and assessment of psychiatric morbidities among thalassaemic children and their caretakers, along with an assessment of caregiver burden in them. The objectives of the study were all met implicating the high prevalence of psychiatric co-morbidities faced by these patients.

Research methods

In this observational cross-sectional study, children with transfusion-dependent thalassemia were included and were assessed for psychiatric morbidity and global functioning. Their parents were assessed for the psychiatric morbidity and caregiver burden faced by them. All the parents completed two different questionnaires to assess their knowledge about the psycho-social functioning [using Pediatric Symptom Checklist-35 (PSC-35)] of their children and the level of the burden faced by them by Caregiver Burden Scale (CBS).

Research results

A total of 46 children (28 boys and 18 girls) with transfusion-dependent thalassemia with a mean age of 8.83 ± 2.70 years and 46 parents (12 fathers and 34 mothers) were included in this study. More than 32 children had some psychosocial problems on screening by PSC-35. On assessment by CBS moderate caregiver burden was perceived in domains of general strain, isolation, disappointment, emotional involvement, and environment. A total of 65.3% of children and 62.7% of parents were diagnosed with psychiatric problems.

Research conclusions

The study implicated a high burden of psychiatric disorders like generalized anxiety disorder, elimination disorder, and dysthymic disorder among children. The caregivers were also revealed to be suffering from an entire spectrum of psychiatric disorders ranging from dysthymic disorders to substance addictions.

Research perspectives

More such research should be conducted with a larger sample size to better gauge the extent of psychiatric co-morbidities among these patients. There is a need to bring about a paradigm shift in the healthcare protocols to ensure holistic care of these patients and their caregivers.

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FOOTNOTES

Author contributions: Sahu S participated in the data collection, and interpretation of data and executed the study; Tonk S participated in the data collection, and interpretation of data; Agrawal A participated in the data analysis and manuscript writing; Srivastava J participated in drafting and editing the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Evaluation of children and adults with post-COVID-19 persistent smell, taste and trigeminal chemosensory disorders: A hospital based study

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Abstract

BACKGROUND

Smell disorders are the most frequent persistent coronavirus disease 2019 (COVID-19) complications.

AIM

To describe the patterns and characteristics of persistent smell and taste disorders in Egyptian patients.

METHODS

Assessment was done to 185 patients (adults = 150, age: 31.41 ± 8.63 years; children = 35; age: 15.66 ± 1.63 years). Otolaryngology and neuropsychiatric evaluations were done. Measurements included: A clinical questionnaire (for smell and taste); sniffin' odor, taste and flavor identification tests and the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS).

RESULTS

Duration of disorders was 11.53 ± 3.97 ms (6-24 ms). Parosmia (n = 119; 64.32%) was developed months after anosmia (3.05 ± 1.87 ms). Objective testing showed anosmia in all, ageusia and flavor loss in 20% (n = 37) and loss of nasal and oral trigeminal sensations in 18% (n = 33) and 20% (n = 37), respectively. Patients had low scoring of sQOD-NS (11.41 ± 3.66). There were no specific differences in other demographics and clinical variables which could distinguish post-COVID-19

smell and taste disorders in children from adults.

CONCLUSION

The course of small and taste disorders are supportive of the nasal and oral neuronal compromises. Post-COVID-19 taste and trigeminal disorders were less frequent compared to smell disorders. Post-COVID-19 flavor disorders were solely dependent on taste and not smell disorders. There were no demographics, clinical variables at onset or specific profile of these disorders in children compared to adults.

Key Words: Post-COVID-19 complications; Anosmia; Ageusia; Trigeminal sensory loss; Parosmia; Quality of life

Core Tip: Smell loss is the most frequent acute manifestation of coronavirus disease 2019 (COVID-19) infection with an estimated prevalence of 40%-86% in adults and 16%-20% in children. Smell disorders (loss or distortion) are also the most frequent long-lasting complications of COVID-19 infection with an estimated prevalence of 20%-40% in adults. Compared to smell, taste disorders are less frequent acute manifestation of viral infection (occurring in 10%-42% of adults) and long-lasting complications of COVID-19 infection. Reports about the prevalence and prognosis of these disorders in children are few or even lacking compared to adults. Also the mechanisms and treatment of these persistent disorders are still challenges. Evidence from experimental studies suggested that injury and degeneration of the neuronal olfactory and gustatory sensory epithelia by severe peripheral viral infection and its immunopathology and the delay or lack of neuronal regeneration might contribute to these disorders. Here, we tried to determine the predictors for persistent disorders and distinguish their differences in children compared to adults.

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INTRODUCTION

Several months after the initial description of the severe acute coronavirus disease 2019 (COVID-19) infection, many data emerged about the prevalence of its mild manifestations including smell and taste disorders. The majority of reports about post-COVID-19 smell and taste disorders were devoted for adult population. Meta-analyses studies reported an estimated prevalence of 40%-86% for smell loss and 10.2%-42% for taste loss in adults infected with COVID-19[1]. Smell loss has been found to be the hallmark or the isolated symptom of COVID-19 infection in 25%-44% of adults[2]. Reports about these disorders in children and adolescents as a manifestation of COVID-19 infection are few and their results are highly variable[3-5]. In the meta-analysis study done by Yan *et al*[4], the authors estimated that the pooled prevalence of post-COVID-19 anosmia, ageusia, anosmia or ageusia and both anosmia and ageusia in children were 16% (95%CI: 8.2-23.8), 9.2% (95%CI: 4.3-14.2), 15.5% (95%CI: 10.3–20.7) and 20.2% (95%CI: 14.1–26.3), respectively. Smell disorders were found to be the most frequent long-lasting or persistent (months to years) COVID-19 complications in approximately 20%-40% of adults[6-8], however, the systematic estimation of the prevalence of these disorder in children is lacking.

Studies reported two main patterns for smell loss (with or without taste loss) as acute manifestations of COVID-19 infection: (1) Sudden smell loss in association with general, systemic or other ear, nose and throat (ENT) viral manifestations. This was the most frequent pattern. It might occur either at the same time with other viral manifestations (22.8%-88.0%)[9,10], after the recovery of other viral manifestations (26.6%-65.4%)[11], or before the onset of other manifestations (11.8%)[9]; and (2) Isolated smell loss without any other viral manifestations (approximately 16%-19.4%)[10].

Studies also reported two prognoses for these disorders. They are: (1) Transient deficits which resolved within days to weeks after onset (mean: Approximately 20 d). This was the most frequent prognosis occurring in 60%-80% of patients[12-14]; and (2) Long-lasting/persistent disorders (deficits and distortions) lasting for months to years. The long-lasting/persistent disorders have been reported to occur in 20%-40% of patients[14].

Studied found that the nose and mouth are the main sites for entry of β-coronaviruses (CoVs) into the body including severe acute respiratory syndrome coronavirus 1[15], Middle east respiratory syndrome coronavirus (MERS-CoV)[16] and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[17,18]. The olfactory epithelial cells, the susentacular, Bowman's gland, micovillar cells (but not neuronal cells or receptors) are overloaded by the angiotensin-converting enzyme type 2 (ACE2) receptors, which are the targets for viral entry into the body[19]. In golden Syrian hamsters, the researchers observed infection of large proportion of sustentacular cells by SARS-CoV-2 within few days after its instillation, followed by desquamation and infiltration of immune cells into the olfactory epithelium and lamina propria, disorganization of the epithelial structure and loss of cilia necessary for olfactory transduction. The authors also observed partial restoration of the epithelium within approximately 2 wk[17,18]. Authors suggested that the relatively fast recovery (approximately 15 d) observed in the majority of patients (60%-80%) after COVID-19 infection is compatible with the rapid regeneration of the non-neuronal olfactory epithelial cells in hamsters and the partial recovery of the olfactory epithelium within 1-2 wk. However, the mechanisms that cause long-lasting/persistent smell loss and distortion are due to the dysfunction or destruction of the olfactory neurons due to viral infection and the disorganization of the olfactory receptors within the epithelium[20,21].

Post-COVID-19 taste disorders are less frequent compared to smell disorders and their pathogenesis is understudied. In animal models, researchers found that ACE2 and sialic acid receptors are the tongue cells by which SARS-CoV-2 enters the body. Sialic acid is a salivary mucin component. Mucin conveys the molecules of tastants into taste pores to prevent their enzymatic degradation[22]. It has been suggested that SARS-CoV-2 infection could interfere with the transport of tastants and accelerate their degradation.

This work aimed to determine the patterns of post-COVID-19 smell and taste disorders at onset in a cohort of adults and children and quantify the extent of these disorders using validated objective measures. The intra- (within the same group) and inter- (adults *vs* children) individual variability in demographics, clinical characteristics and quality of life variables, were determined. The inter-individual variability of clinical characteristics within the same family members infected with COVID-19 was also explored. This is the first study in our country which systematically evaluated adults as well as children with post-COVID-19 persistent smell and taste disorders.

MATERIALS AND METHODS

Study design, period and region

This was a cross-sectional observational study carried throughout a period of a year (August 2020 to September 2021). The initial sample size was 320 patients with post-COVID-19 persistent smell and taste disorders. The diagnosis of COVID-19 infection was relied on the high clinical suspicion (*i.e.* having sudden onset of smell and taste deficits during the locally active COVID-19 pandemic in absence of obvious alternative explanation), and according to the World Health Organization (WHO) interim guidance[23]. Patients were recruited from the out-patient clinic (for care of post-COVID-19 ENT disorders in children and adults) of the Otolaryngology department of Assiut University Hospital (a tertiary referral hospital), Assiut, Egypt. Inclusion criteria: (1) Adults and children with sudden onset of smell loss during the active COVID-19 pandemic in absence of alternative causes; and (2) Persistence of smell disorders (with or without taste disorders) for ≥ 6 mo. Smell disorder was defined as subjective complete or partial smell loss or distortion. Taste disorder was defined as subjective loss or distortion of all (total) or any (partial) of the 5 basic tastes (sweet, salt, sour, bitter and umami). Flavor disorder was defined as subjective loss of aroma of foods and drinks. Exclusion Criteria: (1) Progressive smell and taste loss; (2) An existing cause which could explain the patient's disorders as otolaryngological conditions (*i.e.*, rhinitis, rhinosinusitis or any nasal disorders), head or nasal surgery or trauma, unusual exposure to toxins, chemicals or metals or regular intake of drugs; and (3) Medical, neurologic or psychiatric diseases which are known causes of smell or taste disorders, *e.g.* brain tumors (*e.g.* olfactory groove meningioma, pituitary adenoma with suprasellar extension, *etc.*), temporal lobe epilepsy, Parkinson's disease, Alzheimer's disease, *etc.*), or vitamin deficiencies (*e.g.* zinc or thiamine deficiencies).

After application of inclusion and exclusion criteria, 185 patients (adults = 150; Children = 35; males = 89, females = 96) were included for the final statistical analysis. Excluded were 135 adult patients due to presence of diabetes Mellitus (n = 52), rhinosinusitis (n = 50), psychosis (n = 13), allergic rhinitis (n = 15) and Parkinson's disease (n = 5). The statistical analyses were done to the included 185 patients.

Methods

Data collection: Detailed ENT evaluation was done by the consultant otolaryngologist (Ahmed MAA). Evaluation included routine clinical examination. It also included rhinoscopy and nasal endoscopy. Detailed medical and neuropsychiatric histories and examinations (Hamed SA and Kamal-Eldeen EB) were done. Clinical data were gathered during face to face interviewing. The data included: (1) Demographics: Age, gender, residence, smoking habit, and socioeconomic status. The socioeconomic status was classified according to the Socio-Economic Scale[24] into high, middle, low or very low; (2)

COVID-19 infection inquiries included: Manifestations and their severity, investigations, course, recurrence, comorbidities, consequences and previous treatments' for smell and taste disorders. The severity of viral infection manifestations at the onset were classified as: Mild: Slight symptoms, no viral pneumonia or hypoxia and normal chest imaging; moderate: Fever, dry cough, dyspnea and tachypnea and abnormal chest radiology (*i.e.* manifestation of pneumonia); severe: Either dyspnea, respiratory rate > 30/min, or a PaO2/FiO2 < 300 mmHg or SpO2 < 90% on room air (*i.e.* manifestations of severe pneumonia and severe respiratory distress); and critical: Which included acute respiratory distress syndrome, respiratory failure, multiorgan failure or sepsis or septic shock [*i.e.* requirements for admission to the intensive care unit (ICU)][23]; and (3) The patterns and prognoses of COVID-19 infection in contacts (*i.e.* incubation carriers) were also determined.

A clinically designed questionnaire

It was a questionnaire for clinical data collection and included the questionnaire component (for smell and taste) of the National Health and Nutrition Examination Survey[25]. The answers to questions characterized the individual differences' in perception and intensity of appetizing aroma and scents; sweetness, saltiness, sourness and bitterness of foods and drinks (which helps to differentiate taste as a gustatory, as opposed to flavor which is a function of retronasal olfaction) and pungent odorants and tastants (*i.e.* with strong trigeminal compounds; nippy, blazing, hot or irritant as black pepper, mustard, vinegar, ginger, cinnamon, chiles, mint gum and spices). Data were also gathered about the demographics and clinical characteristics of close contacts infected with COVID-19.

The occurrence of anosmia, hyposmia, dysosmia, parosmia, cacosmia, phantosmia, ageusia, dysguesia or distortion of aroma, had been differentiated in the questionnaire. Anosmia is the term used to define the absence or loss of the sense of smell. Hyposmia is the decreased sense of smell. A distortion of the sense of smell is defined as dysosmia. Dysosmia has two types, parosmia and phantosmia. Parosmia refers to a perception of different odor of an odorant than it was in the past. Cacosmia is a type of parosmia in which the odor, which was previously enjoyable, is smelled as repulsive or offensive. Phantosmia is the perception of an odor in absence of actual staff to be smelled. Ageusia refers to the loss of sense of taste. Hypogeusia is a diminished sense of taste. Dysgeusia refers to the distortion of the sense of taste. In this study, we used the term dysgeusia to refer to distortion of taste as well as flavor (or aroma).

Sniffin' odor identification test

Sniffin' odor identification test (SOIT) was used for quantitative assessment of smell (orthonasal olfaction) loss. We used 16 odorants familiar to Egyptians[26]. They were tea, vanilla, coconut, cacao, coriander, cardamom, thyme, fennel, clove, green cumin, garlic, mixed oregano, old Rumi cheese chips, cinnamon, black pepper and ginger. Odorants were kept in opaque containers and arranged in order so that cinnamon, black pepper and ginger were the last to be tested (*i.e.* three hot smells with strong nasal trigeminal sensory stimulation). The examiner covered the patient's eyes with a blindfold before exposure to the odorants; then asked the patient to smell each substance as often as liked or even to choose from four named odorants options. Each nostril was examined separately and the correct answer received one point. The total score of SOIT equals 16. Normosmia was considered if total SOIT's scoring ranged from 12 to 16, hyposmia if it ranged from 9 to 11, and anosmia if ≤ 8.

Taste identification test

This test was used for quantitative assessment of smell loss. We used sugar (sweet), salt (salty), lemon (sour), old Rumi cheese chips (umami) and coffee (bitter), the five basic tastants. They were kept in opaque containers. Coffee was the last to be tasted as it may alter subsequent taste perceptions if tasted first. The patient's eyes were covered with a blindfold and nostrils were plugged with cotton to block concurrent smell. The examiner put half a teaspoon of a tastant on the patient's hand and allowed him/her to taste as often as liked, then rinsed the mouth with tap water after each tastant's exposure.

Flavor identification test

The same 16 substances of SOIT were used to test flavor (retronasal olfaction) which were tea, vanilla, coconut, cacao, coriander, cardamom, thyme, fennel, clove, green cumin, garlic, mixed oregano, old Rumi cheese chips, cinnamon, black pepper and ginger. Tastants were kept in opaque containers and arranged in order so that cinnamon, black pepper and ginger were the last to be tasted (*i.e.* tastants with strong oral trigeminal sensory stimulation). The patient's eyes were covered with a blindfold and nostrils were plugged with cotton to block concurrent smell (orthonasal olfaction). The examiner put half tea spoonful from each tastant on the patient's hand and asked the patient to taste as much substance as often as liked to recognize it. The total score of the test equals 16. Normal flavor was considered if total score ranged from 12 to 16, impaired (partial loss) if it ranged from 9 to 11, and complete loss if ≤ 8.

Psychiatric interviewing

It was done for determination of comorbid psychiatric condition (s) in response to the presence of the

chemosensory disorders and for the differentiation between psychiatric symptoms and disorders. The impact of olfactory dysfunction on the quality of life (QoL) of patients has been evaluated by the Arabic translated and validated short version of the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS). sQOD-NS is a seven-item questionnaire about the impact of smell disorder on social activities, eating behavior, annoyance and anxiety. The rating scale for each item is ranged from 0 to 3. A total score of 21 indicated no impact on QoL and zero scoring indicated severe impact[27].

Imaging studies

It included computed tomography (CT) on nasal cavities, anterior cranial fossa and sinuses as a part of ENT evaluation and CT of the brain as a part of neurologic evaluation.

Statistical analyses

Data were analyzed with SPSS (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Descriptive statistics were reported as numbers (%) and mean (SD). Comparative statistics (intra- and inter- individuals) between variables for adults and children were performed using independent sample *t*-test, Chi square test and Mann-Whitney U test. Correlation analyses was done between total scores of sQOD-NS and different demographic and clinical variables (age, gender, duration of disorders, presence or absence of parosmia, presence or absence of taste/flavor loss) using Spearman's correlation coefficient. The level of statistical significance was set at $P < 0.05$.

RESULTS

Demographics and patterns of viral infection at onset

This work included 185 patients. The majority were rural residents (64.86%) and of low socioeconomic status (51.9%) (Figure 1). The duration of persistent disorders at the period of the study ranged from 6 to 24 mo (mean = 11.53 ± 3.97 mo), among were 51.35% (n = 95) had duration of ≥ 12 mo. Patients had normal rhinoscopy, nasal endoscopy and CT on nasal cavities, anterior cranial fossa, and sinuses. None had previous hospital admission due to COVID-19 infection and none received vaccination by the time of the study. Patterns of viral infection at onset were isolated sudden smell (with or without taste loss) (n = 63, 34.5%) or sudden smell loss in concurrent association with systemic and/or ENT manifestations (n = 122, 65.95%). Systemic manifestations were reported in 54.05% (n = 100, or 100/185) and ENT (other than smell or taste disorders) manifestations were reported in 37.84% (n = 70 or 70/185). Fever (> 38 °C) was the most common systemic manifestation (100%). Sore throat was the most common ENT manifestation (n = 36, 51.34% or 36/70) (Figure 2). The duration of recovery of systemic and ENT manifestations varied from 3 to 21 d after onset (mean = 8.11 ± 3.69). The most frequently done investigations after onset for diagnosis of COVID-19 infection were complete blood count (CBC) (n = 130, 70.27%), serology (n = 130, 70.27%) and CT of the chest (particularly for patients with moderate manifestations of viral infection) (n = 32, 17.3%) (Figure 1). Only 43 (23.24%) did reverse transcription polymerase chain reaction (RT-PCR). The majority of patients (78.92%; n = 146) did frequent otolaryngology consultations (at onset and afterward) and received different treatment modalities for months, but none was effective (Figure 1). They included nasal irrigations, particularly patients with cacosmia, (duration: Range: 3–15 d, mean = 8.34 ± 3.86), local steroids (duration: Range: 6–60 d, mean = 18.28 ± 9.94), systemic steroids (duration: Range: 3–30 d, mean = 11.89 ± 6.41), and vitamins and supplements as omega-3 capsule, vitamin B complex (vitamins B1, B2, B6, B9, B12), vitamin C, vitamin E, zinc, selenium, L-carnitine and pentoxifylline tablets (duration: Range: 6–90 d, mean = 41.65 ± 24.04). The most frequently prescribed vitamins and supplements were zinc, omega 3 and vitamin B complex. Some patients (22.70%, n = 42) turned to facebook groups to share tips and vent to subjects with same symptoms. This group practiced sniffing strong odors (as essential oils or scents) or pungent herbs (duration: Range: 30–120 d, mean = 65.50 ± 32.84). However, none provided a beneficial effect. Few (n = 39, 21.08) neither did previous otolaryngology consultation nor received any treatment modalities (Figure 1).

Characteristics of contacts (incubation carriers)

The majority of patients (n = 108, 58.38%) were the only affected family member, the remaining (n = 77, 41.62%) had ≥ 1 household contact (range: 1–5) who developed systemic and/or ENT manifestations of COVID-19 infection at the same time as the patients or within the previous 2-4 wk before patients' onset. They developed complete recovery of systemic or ENT manifestations within 3 to 30 d (mean = 12.95 ± 5.97) and of smell and taste loss (n = 40, 21.62%) deficits within 2 to 30 d (mean = 5.03 ± 1.10) with the exception of 4 (2 mothers and 2 daughters, included in the study) who developed persistent smell and taste disorders. None of the completely recovered contacts developed distortion of chemosensations. Inter-individual manifestations were present in the same infected family members (mild, moderate or severe infection; systemic or ENT manifestations or both; fever, cough, diarrhea, fatigue, insomnia, uveitis, *etc.*). A prominent example was a family case cluster of 5 patients who demonstrated highly variable presentations, durations, severities, and progression of COVID-19 infection manifestations. The

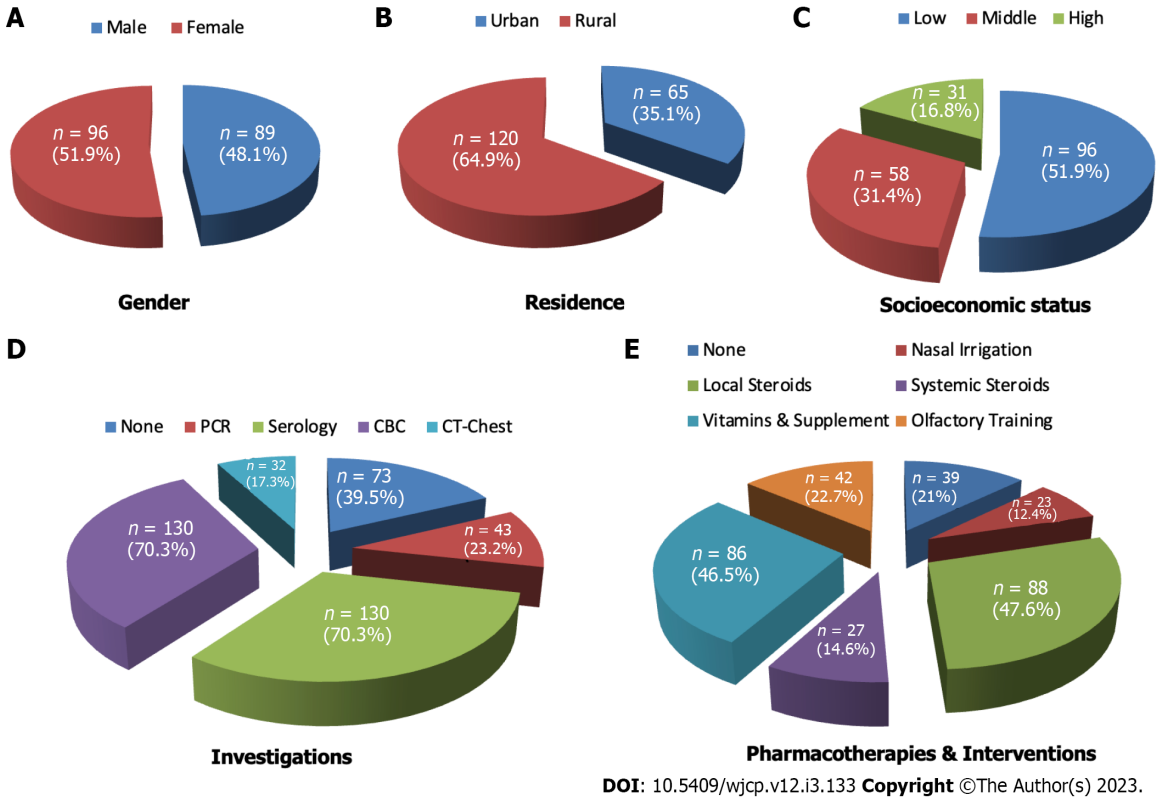

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Figure 1 Demographics, laboratory and treatment characteristics of the studied patients. A: This study included 96 (51.9%) females and 89 (48.1%) males; B: The majority were rural residents (64.9%, *n* = 120), while 35.1% (*n* = 65) were urban residents; C: The majority were of low socioeconomic status (51.9%, *n* = 96), while 31.4% (*n* = 58) and 16.8% (*n* = 31) were of middle and high socioeconomic states, respectively; D: Investigations done by patients included serology and complete blood count (70.3%, *n* = 130, polymerase chain reaction (23.2%) and computed tomography-chest (17.3%, *n* = 32). While 39.5% (*n* = 73) did not do any investigations. E: The received pharmacotherapies and interventions to treat chemosensory disorders included local steroids (47.6%, *n* = 88), vitamins and supplements (46.5%, *n* = 86), olfactory training (22.7%, *n* = 42) and systemic steroids (12.4%, *n* = 23), while 22.7% of the patients (*n* = 42) did not receive any therapy. PCR: Polymerase chain reaction; CBC: Complete blood count; CT: Computed tomography.

presented patient (included in the study) was a 20-year old-female with persistent anosmia and ageusia for 14 mo duration and developed parosmia within approximately 3 mo after smell loss. She did not have other viral manifestations at onset. Her infected household contacts were: (1) A 58-year-old father with severe manifestations of viral infection (fever, cough, shortness of breath, myalgia and sore throat) and confirmed diagnosis of severe viral pneumonia due to COVID-19 infection. He was also admitted to ICU for weeks and markedly improved within approximately 30 d; (2) A 52-year old mother with fever, abdominal pain, severe diarrhea and myalgia for 15 d. She did home-isolation and recovered completely within approximately 21 d; (3) A 16-year old brother with moderate infection (fever, cough, sore throat and rhinorrhea or flu-like symptoms). He did self-isolation and completely recovered within about 7-14 d; and (4) A 23-year old brother with mild manifestations of low grade fever, minimal cough, sore throat and reversible smell and taste loss. He recovered completely within 7-10 d.

Manifestations of smell and taste disorders

Subjective manifestations: At presentation, all complained of severe smell loss. They firstly noticed the sudden inability to recognize cooking scents or odors. However, taste and flavor (aroma) losses and loss of nasal and mouth irritation by pungent odorants (odors with strong trigeminal stimulation) and tastants were the complaint of 79.46% (*n* = 147) (Figure 3). Examples of complaints: "I can no longer smell the familiar scent of my favorites from perfumes, food dishes, and drinks"; "I have forgotten what normal tastes and smells are like", "I changed my eating habits by adding too much sugar or salt to food to try to make it taste better"; "the pungent tastes don't affect me'. One hundred and nineteen (64.32%) also complained of parosmia. The onset of development of parosmia was ≥ 2 mo after smell loss (range: 2–6 mo; mean = 3.05 ± 1.87 mo). Cacosmia was the complaint of 40.34% of patients with parosmia (*n* = 48 or 48/119). The smells experienced by patients with parosmia included burnt (like burnt hair or burnt leather), rotten (as spoiled or fermented food), gasoline, fecal, smoke or metallic (like copper), or chemical (like sulphur). However, the majority (*n* = 65, 54.62%) complained of unpleasant unknown odor which was difficult to describe (*i.e.* new). Examples of complaints: "I can't stand the scent of my own body sweat'; "smell of food was disgusting, repulsive and intolerable resulting in gastric upset'; 'even tap water smells putrid'. None had phantosmia. Two experienced pleasant odors (1.68%) which

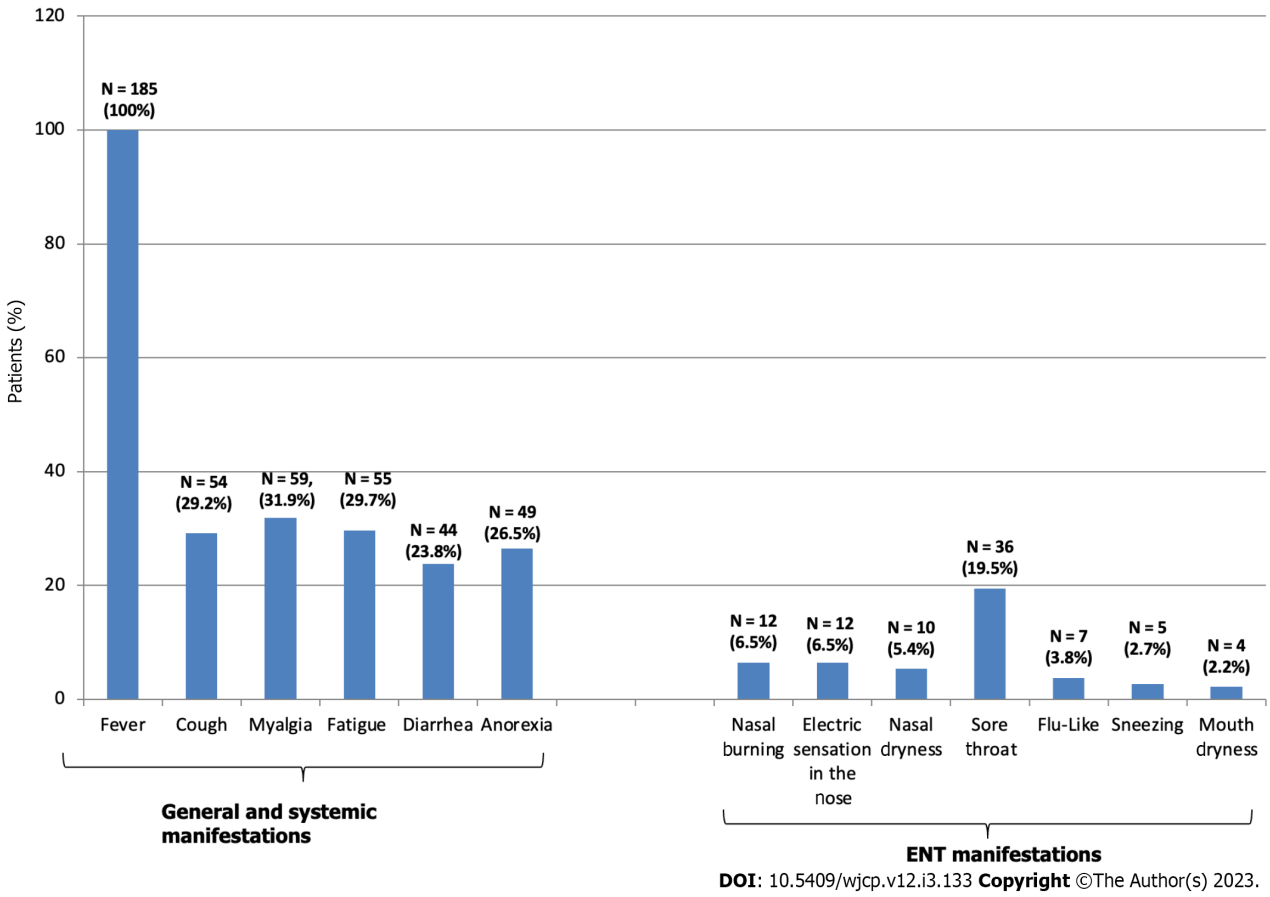

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Figure 2 General, systemic and ear, nose and throat manifestations of viral infection of the studied patients. ENT: Ear, nose and throat.

were difficult to describe (*i.e.* unknown) (Figure 4). The majority of patients with parosmia complained of an aberrant taste with different foods and drinks similar to that being smelled. Few described aberrant tastes for only selective food types (*e.g.* proteins as meat, cheese, *etc.* or fruits as cucumber, Guava, *etc.*). But these distortions of taste/aroma were fluctuant in severity (*i.e.* not constant), however, five adults developed dysgeusia/distortion of flavor (approximately 1 mo) after improvement of parosmia, among were 3 described a taste/aroma of "metallic" and 2 had "soap' as dominant or the overriding sensation in the mouth for a whole range of foods and drinks including water.

Objective manifestations

Objective testing revealed that participants had anosmia (SOIT scoring ≤ 8). True ageusia was found in only 20% (n = 37) (Figure 4) Patients with ageusia also had flavor (retronasal olfaction) loss (n = 37, 20%). Loss of all type of taste sensation (*i.e.* complete or total ageusia) was the most frequent (n = 21, 56.76% or 21/37), however, few (n = 16, 43.24% or 16/37) had selective (or partial) ageusia (salt and sweet = 3, 18.75% or 3/16); bitter and sour = 6, 37.5% or 6/16; umami = 7, 43.75% or 7/16). Losses of nasal and oral trigeminal sensations were found in 18% (n = 33) and 20% (n = 37) of patients, respectively (Figure 4).

Consequences of smell and taste disorders

Consequences of smell and taste disorders on patients were anorexia (n = 36; 19.46%) (particularly with cacosmia), anxiety symptoms (n = 21; 11.35%), insomnia (n = 12; 6.49%) and headache (n = 10; 5.41%). None had psychiatric disorders. The results of sQOD-NS are shown in Table 1. Patients had low total score (11.41 ± 3.66) of quality of life due to these disorders. All were afraid of permanent loss of smell and taste. None did self-isolation after onset and the problems did not restrict the patient's social activities. Loss of appetite and even anorexia were reported by some patients particularly those with cacosmia but none developed significant weight loss.

Comparative results between adults vs children

For each group (adults or children), no significant differences had been identified in relation to gender. No significant differences have been identified between adults and children in other demographics (with the exception that the majority of adults were rural residents), patterns of COVID-19 infection at onset and manifestations of disorders apart of the significantly lower frequency of children with loss of

Table 1 Results of the questionnaire of olfactory disorders-negative statements

	sQOD-NS items	Patients	Adults	Children	*P* value
1	Changes in my sense of smell isolate me socially	0.0–3.0 (2.84 ± 0.57)	3	0.0–3.0 (2.17 ± 1.10)	0.0001
2	The problems with my sense of smell have a negative impact on my daily social activities	0.0–3.0 (2.84 ± 0.57)	3	0.0–3.0 (2.17 ± 1.10)	0.0001
3	The problems with my sense of smell make me more irritable	0.0–3.0 (1.19 ± 1.03)	0.0–3.0 (1.67 ± 0.99)	0.0–3.0 (1.31 ± 1.180)	0.497
4	Because of the problems with my sense of smell, I eat out less	0.0–3.0 (1.34 ± 1.06)	0.0–3.0 (1.18 ± 1.01)	1.0–3.0 (2.09 ± 0.85)	0.0001
5	Because of the problems with my sense of smell, I eat less than before (loss of appetite)	0.0–3.0 (1.66 ± 1.28)	0.0–3.0 (2.00 ± 1.03)	0.0–3.0 (2.00 ± 1.03)	0.0001
6	Because of the problems with my sense of smell, I have to make more effort to relax	0.0–3.0 (1.49 ± 1.11)	0.0–3.0 (1.35 ± 1.12)	0.0–3.0 (1.31 ± 1.180)	0.065
7	I'm afraid I'll never be able to get used to the problems with my sense of smell	0	0	0	-
	Total score of sQOD-NS	2.0–18.0 (11.41 ± 3.66)	6.0–18.8 (11.49 ± 3.37)	2.0–18.0 (11.06 ± 4.74)	0.515

sQOD-NS: Questionnaire of olfactory disorders-negative statements.

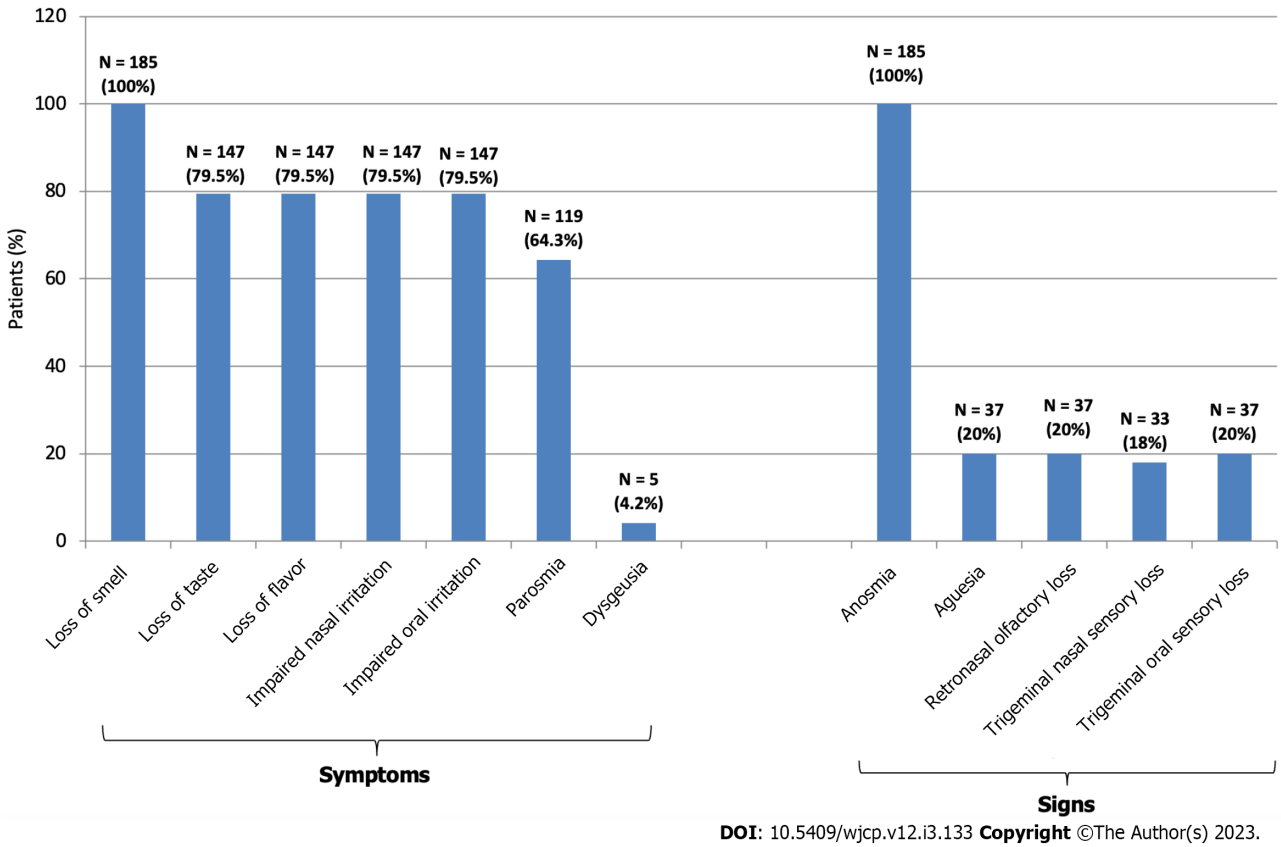

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Figure 3 Manifestations of smell, taste, flavor and trigeminal sensory disorders of the studied patients.

nasal trigeminal sensation compared to adults (P = 0.025) (Table 2). At presentation and compared to adults, the disorders had a moderate impact on many children daily routines and they caused restriction of food intake, lack of appetite or even anorexia, however, there was no significant difference in the total score of sQOD-NS for children compared to adults (Table 1).

Table 2 Comparative results of adults versus children with smell and taste disorders, *n* (%)

Characteristics	Adults (*n* = 150)	Child (*n* = 35)	*P* value
Age	20–50 (31.41 ± 8.63)	12–19 (15.66 ± 1.63)	-
Gender			0.952
Male	72 (48)	17 (48.6)	
Female	78 (52)	18 (51.4)	
Residence			0.009
Urban	46 (30.7)	19 (54.3)	
Rural	104 (69.3)	16 (45.7)	
Socio-economic status			0.589
Low	79 (52.7)	17 (48.6)	
Middle	47 (31.3)	11 (31.4)	
High	24 (16)	7 (20)	
Classification of patients			0.077
Mild COVID-19 infection	123 (82)	30 (85.7)	
- Minimal systemic manifestations	72 (58.54)	18 (51.43)	
- Isolated smell and taste loss	51 (41.46)	12 (34.29)	
Moderate COVID-19 infection	27 (18)	5 (14.3)	
Patterns of smell loss at onset (with or without taste loss)			0.593
Concurrent association with systemic and/or ENT viral manifestations at onset	99 (66)	23 (65.7)	
Isolated loss	51 (34)	12 (34.3)	
Systemic manifestations	82 (54.67)	18 (51.43)	0.897
Fever	82 (100)	18 (100)	
Cough	42 (51.22)	12 (66.67)	
Myalgia	49 (59.76)	10 (55.56)	
Fatigue	45 (54.88)	10 (55.56)	
Diarrhea	34 (41.46)	10 (55.56)	
Anorexia	31 (37.80)	18 (100)	
ENT manifestations	56 (53.33)	14 (40)	0.989
Nasal burning	9 (16.07)	3 (21.43)	
Electric like sensation in the nose	9 (16.07)	3 (21.43)	
Nasal dryness	8 (14.29)	2 (14.29)	
Sore throat	29 (51.79)	7 (50)	
Flu-like	5 (8.93)	2 (14.29)	
Sneezing	5 (8.93)	0	
Mouth dryness	4 (7.14)	0	
Duration of recovery of general, respiratory, gastrointestinal and other ENT manifestations; days	4–30 (12.55 ± 6.04)	5–15 (7.13 ± 2.69)	0.082
Previous treatment trials for smell and taste disorders			0.335
None	29 (19.3)	10 (28.57)	
Nasal irrigation	19 (12.67)	4 (11.43)	
Local steroids	65 (43.33)	23 (65.71)	
Systemic steroids	14 (9.33)	13 (37.14)	

Vitamins and supplements	69 (43.33)	17 (48.57)	
Olfactory training	25 (16.67)	17 (48.57)	
Consequences of sensory disorders			0.516
Headache	6 (4)	4 (11.43)	
Insomnia	10 (6.67)	2 (5.71)	
Anxiety	16 (10.67)	5 (14.29)	
Anorexia	31 (20.67)	5 (14.29)	
Recurrence of COVID-19 infection with smell loss	3 (2)	-	
Duration of disorders at presentation	6–24 (11.43 ± 3.87)	6–24 (11.96 ± 4.41)	0.515
< 12 mo	77 (51.33)	13 (52.38)	0.131
≥ 12 mo	73 (48.67)	22 (62.86)	
Onset of parosmia after smell loss	2–6 (3.60 ± 1.52)	1–5 (2.81 ± 1.47)	0.442
Parosmia	98 (65.33)	21 (60)	0.284
Types of parosmia	42 (42.86)	6 (28.57)	0.709
Unknown (unpleasant)	52 (53.06)	13 (52.38)	
Rotten	17 (17.35)	4 (19.05)	
Burnt	15 (15.31)	3 (14.29)	
Smoke	3 (3.06)	1 (4.76)	
Fecal	5 (5.10)	-	
Gasoline	2 (2.04)	-	
Metallic	2 (2.04)	-	
Unknown (pleasant)	2 (2.04)	-	
Dysgeusia	5 (3.33)	-	
Types of dysgeusia			
Metallic	3 (60)	-	
Soap	2 (40)	-	
Objective manifestations			
Anosmia (orthonasal olfactory loss)	150 (100)	35 (100)	-
Ageusia	30 (20)	7 (20)	0.918
Flavor loss (retronasal olfactory loss)	30 (20)	7 (20)	0.596
Nasal trigeminal sensory loss	30 (20)	3 (8.57)	0.025
Oral trigeminal sensory loss	30 (20)	7 (20)	0.918

Data are presented as number (%) and range (mean ± SD).
Analysis (adults versus children) was done using nonparametric tests: Independent Samples Mann-Whitney U test. Criteria: Alpha = 0.05, CI level = 95.
COVID-19: Coronavirus disease 2019; ENT: Ear, nose and throat.

DISCUSSION

Studies which provided information about the prevalence, patterns and prognoses of post-COVID-19 smell and taste disorders are mainly from Europe and Asia. The majority were based on subjective self-evaluation or questionnaire completion of adult patients. The majority evaluated patients after short periods of follow-ups. Also little is known about the prevalence of these disorders in children. There are few reports which estimated the true frequency of these disorders after direct medical examination and comprehensive objective testing of patients over long periods (≥ 1 year) of follow-ups[7,8,28,29]. We provided the first detailed characterization of a cohort of Egyptian adults and children who developed persistent smell, taste and aroma disorders after COVID-19 infection.

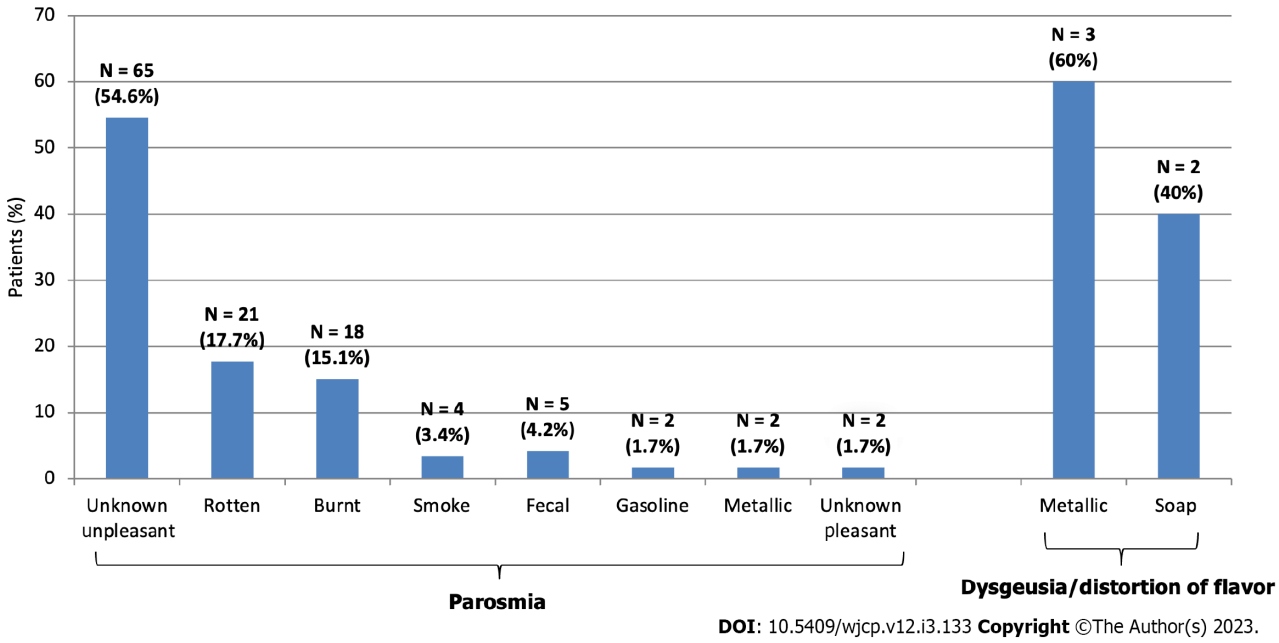

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Figure 4 Types of parosmia and dysgeusia/distortion of flavor in the studied patients.

Despite the increasing number of publications of post-COVID-19 complications, there is no consensus definition for "persistent post-COVID-19 smell disorders", because of the wide variability of the periods of follow-up of patients since the onset of acute viral manifestations. In adults, some used these terms if the duration of disorders exceeded a month while many suggested longer durations equal or more than 3 or 6 mo. They also suggested other terms for these complications as "Long-lasting COVID-19 disorders" and "Chronic COVID-19 disorders"[6,9,12,14]. In this study, we included participants with duration of disorders of at least 6 mo since onset of acute manifestations, among were 52.43% of the patients (n = 97) had duration of disorders for ≥ 12 mo and 6 patients had the disorders for 24 mo. Fortunato *et al*[28] reported persistent smell dysfunction in 70% of patients at one year after the onset of COVID-19 infection. Boscolo-Rizzo *et al*[7] reported persistent smell dysfunction in 46% of patients by objective testing after a median of 401 d after the onset of COVID-19 infection. Lechien *et al*[8] followed 171 patients with post-COVID-19 smell disorders for 24 mo and reported a prevalence of olfactory dysfunction to range from 2.9% to 29.8%. For children, the definition of persistent post-COVID-19 smell disorders has been suggested in March 2022 by the Delphi process (which involved both researchers and family advocates) as manifestations that are lasting in a child for ≥ 3mo after the acute viral manifestations and cannot be explained by other known etiologies of smell disorders[29]. To our knowledge, there are only two reports for evaluation of smell and taste disorders in children[5,30]. In the study of Elvan-Tuz *et al*[30], the authors reported that in 8.4% of children, anosmia did not regress after a month since the onset of COVID-19 infection. In the study of Buonsenso *et al*[5], the authors found that 1.7% (13/784) of children had persistent smell disorders at a mean of 3mo after the onset of COVID-19 infection.

In this study, it is obvious that the number of adults with persistent disorders was 2.9 higher than children. We could not provide a prevalence of the disorders in patients with previous COVID-19 infection in spite of the fact that the patients were recruited from the Otolaryngology out-patient clinic of the university hospital (a tertiary referral hospital). This is because the healthcare service in our country is patchy and distributed between private clinics and governmental and university hospitals' clinics. Patients were mainly referred from specialist otolaryngologists to the university hospital for the purpose of comprehensive evaluation. We did not find gender difference in the development of smell disorders after COVID-19 infection which is consistent with most of the previous reports. Few found potential gender difference with higher susceptibility for females to develop smell and taste disorders compared to males[31].

The most frequently done investigations (in approximately 70%) by the patients at onset were CBC, quick serology testing (IgM/IgG), CT of the chest (17%) and RT-PCR, particularly in patients with moderate manifestations. However, 17.3% did not do any investigations particularly those with isolated disorders. It has been indicated that the sudden onset of chemosensory dysfunctions in absence of a cause to explain these conditions in the presence of active local pandemic are often the main warning manifestations and the strongest predictors of COVID-19 infection[10,11]. Studies reported that people with loss of smell and taste had six-fold higher odds of being infected with COVID-19 positive and loss of smell and taste were associated with 10-fold higher odds of COVID-19 diagnosis[31-33]. The followings are the possible reasons for paucity of investigations at onset: (1) The presence of household

members and intimately contacted friends at work places who experienced similar manifestations and diagnosed as having COVID-19 infection; (2) The information from the social media that smell and taste loss after COVID-19 infection are transient conditions in the majority of patients, *i.e.* disappear within weeks or few months (1-3 mo)[1,2,6,12]; (3) The reluctance to do investigations because of the minimal systemic manifestations or isolated disorders; (4) Polymerase chain reaction (PCR), serology and chest CT impose significant constraints on medical healthcare services in many parts of the world especially with limited infrastructure and resources and poor socioeconomic status of patients; and (5) Many healthcare providers are also reluctant to ask for investigations particularly if there was a delay for several weeks or months between the onset of chemosensory manifestations and the patient's realization of the olfactory evaluations. It has been indicated that the viral load is significantly reduced after 14 d from onset and the estimated false-negative PCR rates for SARS-CoV-2 are high[33].

In this study, participants who had infected household family members distinguished the heterogeneity in phenotypes and prognoses of smell and taste losses encountered in their contacts[34]. It has also been previously reported that COVID-19 exhibits wide variation in duration, severity, and progression of symptoms, even within same family (*i.e.* a familial cluster of COVID-19 infection)[10,11]. It is interesting to mention that none of the participants, who were the only affected family members (~60%) did self-isolation or limited their social activities or transmitted the viral infection to other close contacts at the acute stage. Therefore, the questions are: Whether minimal/mild manifestations or isolated deficits at onset are highly contagious or not?, and, whether self-quarantine is a requirement as previously announced by the WHO and the ENT UK or not? More data are required to prove these issues. The announced recommendations by the WHO and the ENT UK for self-isolation for those with de novo loss or smell or taste during the active pandemic of COVID-19 was not clear compared to the recommendation for persons in intimate contact with patients having active COVID-19 infection (which is self-isolation for ≥ 2 wk). Some suggested self-isolation for ≥ 7d for those with de novo loss or smell or taste[10,11].

In this study, most of the participants (82%) had mild systemic or ENT manifestations at onset, among were 41.5% had isolated deficits in absence of any other viral manifestations. Many studies indicated that mild viral manifestations at onset could predict the prognosis of persistent smell disorders[9]. It has been suggested that the site and dosage of the initial viral burden, along with the effectiveness of the host's innate immune response to SARS-CoV-2 infection are important variables which potentially determine the spread of the virus within an individual and therefore the clinical course of infection, *i.e.* the high viral load in the upper airway could be correlated with reduction of the overwhelming host's immune response resulting in a less severe general and systemic viral infection [35]. However, persistent smell disorders have also been reported in patients with severe viral infection diagnosis at onset[1,2,6,12].

At presentation, all patients complained of severe deficits in smell and the majority (approximately 80%) complained of associated taste loss, loss of aroma perception when eating foods and drinking beverages and loss of smell and taste of pungent substances. While objective testing showed that all had anosmia (orthonasal olfactory loss), 20% had true ageusia, flavor loss (retronasal olfactory loss) and oral trigeminal chemosensory loss and 18% had nasal trigeminal chemosensory loss. This mismatch between subjective and objective findings is not surprising. This also can explain the wide variability in the estimated prevalence of these disorders (*i.e.* over estimation bias) as the majority of reports relied on subjective or self-reported manifestations. In general, it is often difficult to distinguish between taste and smell and the belief that taste loss is a secondary result of smell loss is true to a great extent. This usually reflects loss of flavor perception as a function of smell and not true loss of taste. Also there is an intimate functional correlation between the flavor and taste systems and the intimate central connections between the olfactory and trigeminal systems and the overlapping activations in the piriform cortex, the ventral insula, and the frontal cortex[36]. The majority of patients with ageusia (56.8%) had total loss of sensation for the 5 basic types (salt, sweet, bitter, sour and umami) (*i.e.* complete ageusia), while, 43.24% had specific losses (or partial ageusia) particularly for umami[6]. Previous studies reported true complete or partial ageusia due to COVID-19 infection in 10.2%-42%. Some authors also found selective loss for sweet and bitter tastes[1,9,37]. Schwab *et al*[37] followed more than 400 patients infected with COVID-19 for 4 mo and reported little or no recovery from aguesia in patients who did not regained normal taste after approximately 2 mo. The prevalence of true nasal sensory (trigeminal) loss has been estimated to be 18%-20% with COVID-19 infection and the true oral trigeminal sensory loss was reported in 20%-33%[38].

We observed that none of the patients reported aguesia or flavor loss or trigeminal sensory loss in absence of anosmia. Flavor and loss of oral trigeminal sensation were dependent on aguesia and not anosmia. Discoveries found that orally sourced odors share processing circuitry with taste internal odors to produce flavor preferences[39,40]. Furthermore, the oral trigeminal sensation is considered a part of flavor perception[41]. The occurrence of taste, flavor and trigeminal sensory losses at lower frequencies and the differential taste loss in some patients, support that viral infection could involve taste and trigeminal tissues independent to smell[40,42].

In this study, rhinorrhea was a less frequent nasal (15% or 7/46) and ENT manifestation (10% or 7/70) at onset of viral infection. This is consistent with previous reports which found that the prevalence of rhinorrhea and nasal congestion was 4%-25% in patients infected with COVID-19 prior to experiencing

anosmia[9,43]. We also observed that patients clearly distinguished their current conditions from the previously encountered fluctuation in the severity of smell and taste losses associated with runny nose, post-nasal discharge and congested and blocked nose associated with heavy cold or influenza. They mentioned that "previous nasal manifestations due to flu or influenza always resolve within days, and never affected taste of non-odorant tastants as sugar and salt".

In this study, parosmia was also the complaint of 64.3% (n = 119) of patients. They developed parosmia after anomia by several months[9,44]. Recently, Ferreli *et al*[43] reported that reported persistent smell dysfunction in 15.1% and 13.1% at 12 and 18 mo after the onset of COVID-19 infection based on a self-reported smell score. They also observed that 23.1% of patients developed parosmia at 18 mo after the onset of COVID-19 infection. We observed that many patients believed that parosmia was a manifestation of smell recovery. Parosmia and particularly cacosmia were also the dominant cause for repeated otolaryngology consultations and the use of nasal douches as a trial to reduce the intensity of the repulsive odors. In this study, the majority of patients with parosmia reported fluctuation in the experience of the same aberrant odor in the oral cavity with different foods and drinks (dysgeusia/distortion of aroma). However, five patients reported dominance of metallic (n = 3) or soap (n = 2) perception as baseline for every food or drink including tap water. They also mentioned that the abnormal sensation in the oral cavity became more apparent, intense and repulsive after reduction of the intensity of parosmia. Dysgeusia, the distortion of taste after COVID-19 infection, has been reported previously[45]. Vaira *et al*[44] reported anosmia and aguesia in 77% (67/87), anosmia only in 2.3% (2/87) and dysgeusia in 20% (18/87) of patients after COVID-19 infection. Distortion of aroma was reported in approximately 12% of patients after COVID-19 infection[41].

In this study, we did not identified apparent difference in other different demographic and clinical variables between adults and children with persistent disorders. In the literature, studies which addressed president smell and taste disorders in children are scare or poorly addressed[3-5]. This might be due to difficulty to apply objective testing or lack of standardized objective testing for smell and taste for children. In this study, symptoms of anxiety, insomnia, anorexia and headache were prominent among children compared to adults. They were often distressed by the impairments which hinder the enjoyment of food and hygiene problems related to body odor. It has been reported that the loss of the feeling of the depth and complexity of foods may result in anorexia, depression and anxiety. Deficits of olfaction disrupt the joy of eating and drinking and associated with the dangers of inability to know about the surrounding (*e.g.* environmental toxins as leaking gas or spoiled food). Parosmia as the constant repulsive odor is more distressing than loss of smell in many patients.

In this study, psychiatric evaluation at presentation and determination of quality of life in relation to smell disorders using sQOD-NS revealed lower performances and poor enjoyment of life particularly being afraid of development of permanent disorders. Smell and taste are essential for everyday life and psychological wellbeing. Many studies from Europe and Asia reported the adverse impact of long-lasting smell disorders on quality of life, personal-social functioning and mental health[45,46]. In a crosssectional study by Bagheri *et al*[46] on 10069 participants responded to an online checklist which evaluated the sense of smell and taste. The results indicated a significant correlation between anosmia and SARSCoV2 infection, decreased taste sensation, and decreased quality of life. In the cross-sectional survey of Abdelhafiz *et al*[47], the researchers enrolled 502 participants from Egyptians infected with COVID-19; the authors reported high prevalence of mental health symptoms among healthcare workers. Overall, 77.3%, 69.5%, 79.3%, and 83.1% of all participants reported symptoms of, anxiety, insomnia, depression, and stress, respectively. There was no particular assessment of quality of life due to chemosensory disorders in the same patients.

The detailed mechanisms for the persistent smell and taste disorders after COVID-19 infection are still understudied. There are evidences which support that injury of the neuroepithelium is the cause of persistent olfactory disorders after COVID-19 infection[48-50], they include: (1) Previous studies found that the olfactory neuronal epithelium requires 1-3 mo or longer to regenerate, restore the odorant receptor mapping, restore the olfactory receptor connections and rewire the axons within the olfactory system after injury compared to non-neuronal olfactory epithelium (which have susentacular, Bowman's and microvillar cells) which requires 1-3 wk for recovery after degeneration[21]. Zazhytska *et al*[50] found that in infected golden hamsters, SARS-CoV-2 caused severe, persistent and widespread disruption of mature olfactory receptors' nuclear genomic architecture. It also caused down regulation of olfactory receptors and olfactory sensory neuronal signaling genes for odor perception. The authors observed delayed olfactory neuronal transcription than susentacular cells and persistent disruption of olfactory receptor's layer even after their restoration; (2) Studies indicated that parosmia is a step towards regeneration after olfactory receptors' or neuronal degeneration (*i.e.* step toward recovery) and the unpleasant smell will disappear with full recovery[20,21]; and (3) Studies suggested that the disturbance of the spatially organized pattern of the olfactory receptors within the epithelium following viral infection, scars and gliosis are the causes of lost odor (*i.e.* anosmia) and distortion of smell sensation (*i.e.* parosmia)[20,21,51]. Earlier in pandemic, some authors suggested that nasal dryness which is attributed to the injury of the mucin producing cells (*i.e.* Bowman's gland) by viral pathology, is the cause of aberrant nasal smell (or parosmia) because they reported high frequency of nasal dryness among their patients. Lechien *et al*[52] reported nasal dryness in ≥ 60% of patients. They suggested that, this could be attributed to the damage of the mucous secreting olfactory cells (Bowman's glands) which

provide constant flow of mucous to the surface of the nasal epithelium to trap and dissolve odorous substances for the neurons. The findings of this and other studies do not support this suggestion because: Firstly, nasal dryness is an acute manifestation in some patients which recovered shortly within days to weeks like other ENT or systemic manifestations. In this study, only 5.4% (n = 10) had nasal dryness. Secondly, parosmia developed after recovery of acute manifestations by months. Thirdly, none of the contacts with transient smell loss developed parosmia.

The cause of nasal trigeminal sensory loss could be due to viral infection and damage to brush cells (or their feeding blood vessels). Brush cells are the microvilli columnar cells in the basal surface and in contact with afferent nerve endings of the trigeminal nerve responsible for transduction of nasal general sensation[53].

The mechanisms of taste disorders after COVID-19 infection are less studied compared to smell disorders. In animal models, researchers found that the family of CoVs, including MERS-CoV and SARS-COV-2, potentially use multiple entry oral receptors, making taste bud cells being highly susceptible for SARS-CoV-2 infections. These sites include ACE2, sialic acid and toll like receptors (TLRs)[54,55]. The tongue taste buds express ACE2 and sialic acid[55,56]. Sialic acid is a salivary mucin component. Mucin conveys the molecules of tastants into taste pores to prevent their premature enzymatic degradation[22]. Therefore, infection with SARS-CoV-2 could interfere with glycoproteins mediated transport of tastants and accelerated the degradation of the gustatory particles which contribute to loss of taste. The main function of the TLRs is to recognize the common structural components of microorganisms and activate the endogenous inflammatory immune system. In-situ models of direct binding of coronavirus spike protein of SARS-CoV-2 with TLR 1, 4 and 6, have support the specific roles of these TLRs in severe inflammation of the tongue tissue[57].

We believe that this study have strengths: (1) Up to our knowledge, this is the first study done in Egypt to explore the patterns at onset and characteristics of children as well as adults with post-COVID-19 persistent smell and taste disorders. In general, the evaluations of these disorders in children are limited or even lacking; and (2) The measures used for objective evaluation of smell, taste and flavor sensations are validated and reliable and can be generalized for evaluation of functional recovery overtime of smell and taste disorders in Egyptians. However, this study has limitations: (1) It may appear that patients with persistent disorders have severe deficits (*i.e.* anosmia or ageusia). This might be due to the recruitment of patients from a tertiary referral hospital (a University Hospital). It is possible that patients with persistent less severe disorders (*i.e.* hyposmia or hypogeusia) were reluctant to seek medical advice or might visited other available healthcare services (*e.g.* private clinics); and (2) The number of included children is lower than adults. This could be due to lower frequency of these disorders in children compared to adults. Future studies are required to determine the prevalence of these disorders in pediatric population.

CONCLUSION

This study indicates that children can develop persistent smell and taste disorders due to COVID-19 infection similar to adults. The reported course of small and taste disorders are supportive of the peripheral neuronal compromise. True taste and trigeminal chemosensory disorders could be a complication of COVID-19 infection but with lower frequency compared to smell disorders and also might occur independent to smell disorders. Post-COVID-19 retronasal olfactory (flavor) disorders were solely dependent on taste and not on smell disorders. Smell and taste disorders significantly impair quality of life of patients particularly being afraid of permanent disorders. There were no clinical variables which characterize smell and taste disorders in children from adult patients.

ARTICLE HIGHLIGHTS

Research background

Smell loss with or without taste loss is the most frequent acute manifestation of coronavirus disease 2019 (COVID-19) infection with an estimated prevalence of 16%-20% in children and 40%-86% in adults. Smell disorders are also the most frequent complications of COVID-19 infection with an estimated prevalence of approximately 20%-40% of adults. This indicates that COVID-19 has high affinity to olfactory sensory epithelium (and to less extent gustatory sensory epithelium) compared to other parts of the body. Data from patients and their contacts showed that it is impossible to predict the prognosis of smell loss (*i.e.* none of the demographics, acute manifestations and severity at onset were predictors for the development of persistent disorders). It has been indicated that the mechanisms of transient smell and taste deficits due to COVID-19 infection are different from that of long-lasting/persistent disorders. It has been suggested that injury of the non-neuronal olfactory epithelial cells by viral infection and their rapid regeneration (within days to weeks) are the causes of transient smell deficits because these cells are important for the health of the neuronal cells. However, lasting smell disorders

are due to injury of the neuronal olfactory epithelial cells and disorganization of the receptors within the epithelium, because these cells require months to regenerate after injury and restore olfactory epithelium function. The mechanisms of taste disorders after COVID-19 infection are less understood compared to smell disorders but suggested to be due to injury of the gustatory sensory epithelium by viral infection and disturbed salivary milieu which is necessary for the function of the gustatory neurons.

Research motivation

The research hotspots include determination of (1) The patterns of smell and taste disorders at onset; (2) The course of these disorders till presentation; and (3) Whether or not there is/are distinguished features for children with these disorders which differentiate them from adult patients with the same disorders.

Research objectives

This study aimed to systematically evaluate patients with post-COVID-19 infection persistent smell and taste disorders because related studies from many areas of the world including our country are lacking. The descriptive characteristics of patients at onset and presentation and predictors for the development of these disorders were determined in children and adult populations.

Research methods

Data collection which included a clinical questionnaire (for smell and taste); objective testing which included the sniffin' odor, taste and flavor identification tests and the Questionnaire of Olfactory Disorders-Negative Statements for determination of quality of life in response to these disorders.

Research results

This study included 185 patients (adults = 150, age: 31.41 ± 8.63 years; children = 35; age: 15.66 ± 1.63 years) from both gender and had post-COVID-19 infection smell and taste disorders. The duration of the disorders till the time of presentation ranged from 6 to 24 mo (mean: 11.53 ± 3.97 mo) with nearly half of the patients had duration of at least a year. Parosmia was a frequent manifestation (64.32%) in patients with persistent anosmia and was developed after months from onset (3.05 ± 1.87 ms). Total or partial true ageusi, retronasal olfactory loss (or flavor) and trigeminal chemosensory loss were present in 18%-20% of patients. There were no significant differences in patterns at onset and clinical variables at onset and at presentation between children and adults with persistent disorders. These disorders significantly lower quality of life of patients.

Research conclusions

Persistent smell, taste and trigeminal chemosensory disorders are frequent post-COVID-19 complications in children similar to adults. There were no demographics, clinical variables at onset or specific profile of these disorders which distinguish children from adults' patients.

Research perspectives

Future studies are needed to: (1) Determine the prevalence of these disorders in children and in adults from understudied populations (*e.g.* Africans); (2) Determine the relationship between smell and taste disorders due to different COVID-19 variants (alpha, delta or omicron). In the literature, there were no relevant studies which stratified recovery according to COVID-19 variants. Here, the period of patients' recruitment in this study indicated a high possibility of being infected with the wild types of the virus; and (3) Understand the detailed cellular and molecular pathogenic aspects underlying long-lasting/persistent chemosensory disorders after COVID-19 infection.

FOOTNOTES

Author contributions: Hamed SA, Kamal-Eldeen EB and Ahmed MAA designed the conception, did data collection and physical examinations. Ahmed MAA did ear, nose and throat evaluation; Kamal-Eldeen EB and Ahmed MAA referred the patients to the neurologist (Hamed SA) and critically reviewed the manuscript; Hamed SA applied the objective measurements for smell and taste and the final statistical analyses, wrote the manuscript and had the final responsibility to submit the manuscript for publication; All authors had full access to raw data and verified the underlying data and interpretation of the results and final approval of the manuscript.

Institutional review board statement: The protocol of the study was in accordance to the revised Helsinki Declaration (2013) and approved by the medical research ethics committees of the Faculty of Medicine, Assiut University, Assiut, Egypt, No. AUH_SARS-CoV2_SAH/2019.

Informed consent statement: All study participants, or their guardian, provided informed written consent prior to study enrollment.

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ORIGINAL ARTICLE

Prospective Study

Prevalence of gastroesophageal reflux disease in children with extraesophageal manifestations using combined-video, multichannel intraluminal impedance-pH study

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Abstract

BACKGROUND

Gastroesophageal reflux disease (GERD) might be either a cause or comorbidity in children with extraesophageal problems especially as refractory respiratory symptoms, without any best methods or criterion for diagnosing it in children.

AIM

To evaluate the prevalence of extraesophageal GERD using conventional and combined-video, multichannel intraluminal impedance-pH (MII-pH), and to propose novel diagnostic parameters.

METHODS

The study was conducted among children suspected of extraesophageal GERD at King Chulalongkorn Memorial Hospital between 2019 and 2022. The children underwent conventional and/or combined-video MII-pH. The potential parameters were assessed and receiver operating characteristic was used for the significant parameters.

RESULTS

Of 51 patients (52.9% males), aged 2.24 years were recruited. The common problems were cough, recurrent pneumonia, and hypersecretion. Using MII-pH, 35.3% of the children were diagnosed with GERD by reflux index (31.4%), total reflux events (3.9%), and symptom indices (9.8%) with higher symptom recorded in the GERD group (94 *vs* 171, $P = 0.033$). In the video monitoring group ($n = 17$), there were more symptoms recorded (120 *vs* 220, $P = 0.062$) and more GERD (11.8% *vs* 29.4%, $P = 0.398$) by symptom indices. Longest reflux time and mean nocturnal baseline impedance were significant parameters for diagnosis with receiver operating characteristic areas of 0.907 ($P = 0.001$) and 0.726 ($P = 0.014$).

CONCLUSION

The prevalence of extraesophageal GERD in children was not high as expected. The diagnostic yield of symptom indices increased using video monitoring. Long reflux time and mean nocturnal baseline impedance are novel parameters that should be integrated into the GERD diagnostic criteria in children.

Key Words: Extraesophageal reflux; pH-impedance; Children; Gastroesophageal reflux; Mean nocturnal baseline impedance

Core Tip: This was a retrospective and cross-sectional study with 51 children suspected extraesophageal gastrointestinal esophageal reflux disease (GERD). This study found the prevalence of GERD in these pediatric patients was 35.3% by using combined-video, multichannel intraluminal impedance-pH study. Moreover, longest reflux time and mean nocturnal baseline impedance were depicted as the significant parameters for GERD diagnosis with satisfied diagnostic value in children.

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INTRODUCTION

Gastroesophageal reflux (GER) is a physiologic process that commonly occurs in infants. Gastroesophageal reflux disease (GERD) occurs when the refluxates cause troublesome symptoms. The incidence of GERD has increased in children (0.84 per 1000 persons-year)[1]. Its manifestation varies. Hence, a high index of suspicion is necessary, especially for extraesophageal manifestations[2]. In clinical practice, respiratory problems that are refractory to the standard treatment might be from the disease itself or are extraesophageal manifestations of GERD. Moreover, GERD can be a serious comorbidity that worsens those respiratory conditions. Consequently, the development of a standard tool to diagnose extraesophageal GERD and its prompt management are crucial.

There are many diagnostic tools for extraesophageal GERD, including pH monitoring, combined multichannel intraluminal impedance and pH (MII-pH) study, esophagogastroduodenoscopy (EGD) with biopsies, and laryngoscopy[3]. According to clinical practice guidelines for GERD diagnosis and management in children (North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition), the MII-pH study is the best diagnostic method for esophageal manifestations of GERD[4]. Recent studies in adults also propose that additional parameters from the MII-pH study, mean nocturnal baseline impedance (MNBI), and post-reflux swallow-induced peristaltic wave (PSPW), increase the diagnostic value of this tool[5]. However, there is scarce evidence to support the best method for diagnosing extraesophageal GERD in children. Further evaluation is necessary. The main purpose of this study is to determine the prevalence of GERD in children with extraesophageal symptoms using conventional and combined-video MII-pH studies. The secondary aim is to assess the diagnostic usefulness of combined-video MII-pH studies for GERD and other diagnostic parameters.

MATERIALS AND METHODS

Patient selection

The present study is a retrospective and cross-sectional study in children and adolescents with respiratory symptoms and other extraesophageal manifestations suggestive of GERD. Participants were treated at King Chulalongkorn Memorial Hospital (KCMH) from February 2019 to December 2021. Patients who had extraesophageal symptoms (cough, apnea or brief resolved unexplained event, uncontrolled asthma, recurrent pneumonia, stridor, hoarseness, chronic sinusitis with unknown causes, allergic rhinitis with difficulty to treatment), and who were between 1 mo and 18 years old were included in the study. The exclusion criteria were patients who were on proton pump inhibitors or prokinetics during MII-pH monitoring, unwillingness to participate in the study, and patients who were already known the other causes that could explain those extraesophageal symptoms.

The Chulalongkorn University Institutional Review Board approved this study (IRB 029/64). Informed consents and assents were obtained from the patient's guardians and patients, respectively, before recruitment to the study.

MII-pH study and/or video monitoring

According to the protocol, patients had to fast for one to two hours before a nasal impedance catheter with a pH probe (Pediatric ZandorpH catheter with one antimony and six impedance sensors with 1.5 cm interval, Laborie, The Netherlands) was distributed throughout the esophagus. The Strobel formula [6] was used to calculate the proper position of the catheter. Chest X-ray was then used to confirm that the pH probe was located at 2–3 vertebral distance from the diaphragm. During the MII-pH monitoring, all patients had their regular meals. Video monitoring was conducted simultaneously with MII-pH monitoring in 17 patients. The total time of monitoring after excluding meal periods was at least 18 h. The number of reflux events, the reflux index (RI), the symptom index (SI)/symptom sensitivity index (SSI)/symptom association probability (SAP), longest reflux time (LRT), the MNBI, and PSPW were recorded.

Pathological reflux is defined according to the position statement by the British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) Motility Working Group[6] as RI > 7% in children aged ≥ 1 year, and > 10% in children aged < 1 year, or if reflux episodes occur ≥ 70 times in children aged ≥ 1 year, and ≥ 100 times in children aged < 1 year or positive SI/SSI/SAP. Regarding symptom recoding, SI is calculated as (reflux-related symptom occurrences/total symptom events) × 100. SI is considered positive if the value is ≥ 50%. SSI is calculated as (number of symptom-associated reflux/total number of reflux episodes) × 100. If the percentage of SSI is ≥ 10%, it is considered positive. SAP is calculated by dividing the total measuring time into 2-min intervals, and creating a four-field contingency table: The number of intervals with and without GER symptoms, number of intervals with and without GER symptoms, number of intervals without GER and with the symptoms, and number of intervals without GER and symptoms. Fisher's exact test was performed for statistical examination of correlation. A percentage greater than 95% was considered positive.

Regarding the new parameters, MNBI was measured from the most distal impedance channel during sleep, with three 10-min time intervals that did not interfere with swallowing. The mean of these three values was then calculated. PSPW was defined as an antegrade 50% drop in impedance originating in the proximal esophagus within 30 s after the end of a reflux event and reaching the distal lumen. The PSPW index was calculated by the number of PSPW divided by the total number of refluxes[5,7].

Esophageal gross and histopathology finding

Within three months of the MII-pH study esophagogastroduodenoscopy with biopsy was performed on selected patients from recruitment according to decisions by the doctors in charge. The Los Angeles (LA) Classification[8] was routinely used to record endoscopic findings. The esophageal histopathology finding was reported by a pathologist using the modified Esohisto criteria as described in our previous study[8]. In short, a calculated severity score of 0–0.25 was considered normal and a score of ≥ 0.5 was regarded as esophagitis.

Statistical analysis

Data of categorical variables were expressed as percentages or proportions, and continuous variables as median [interquartile range (IQR)]. These variables were compared using Fisher's exact test and Wilcoxon signed ranks test as appropriate. Univariable and multivariable analyses were used to assess the independent factors of extraesophageal GERD from demographic variables and parameters from MII-pH analysis. Statistical significance was defined as P value < 0.05. Receiver operating characteristic analysis with calculation of the area under the curve was used to assess the diagnostic yield of the potential parameters of extraesophageal GERD. Statistical analysis was performed using SPSS software version 24.0.0 (SPSS Inc., Chicago, IL, United States) and Stata version 15.1 (Stata Corp, LLC, College Station, TX, United States).

RESULTS

Baseline characteristics of children with suspected extraesophageal GERD

There were 83 children with suspected extraesophageal GERD at KCMH from February 2019 to July 2022. Thirty-two participants were excluded from the present study because they received proton pump inhibitors/prokinetics during the MII-pH study (n = 21), had unwilling guardians (n = 3), and because they had known causes of respiratory symptoms (n = 8). Consequently, a total of 51 children were recruited and 17 of them underwent both the MII-pH study and video monitoring. Twenty-five children underwent upper endoscopy, while 22 underwent esophageal biopsy for histopathology. The median age of these 51 participants was 2.24 (1.11, 7.67) years and 27 (52.9%) participants were males. Their underlying diseases were multiple anomalies (47%), respiratory disorders (35.3%), and neurological disorders (17.7%). The most common extraesophageal symptoms indicated in the MII-pH study were cough (41.2%), recurrent pneumonia (25.5%), and hypersecretion (11.8%). However, 16 (31.4%) participants also had concurrent gastrointestinal symptoms. The median duration of MII-pH recording was 22.09 (20.20, 23.41) h. Only 265 symptoms were recorded by guardians, including cough (n = 109, 41.1%), irritability (n = 54, 20.4%), apparent secretion (n = 24, 9.1%), vomiting (n = 34, 12.8%), and heartburn (n = 44, 16.6%). In total, 18 (35.3%) participants were diagnosed with GERD using the MII-pH study. In the subgroup of children who underwent upper endoscopy (n = 25) and 22 of them had received esophageal tissue biopsy, 18 (72%) and 16 (72.7%), respectively, were diagnosed with GERD using the LA classification and modified Esohisto, respectively (Figure 1).

MII-pH study

According to the diagnostic criteria by the BSPGHAN Motility Working Group[6], 18 participants had parameters that were compatible with GERD. A comparison between the GERD and non-GERD groups did not reveal any statistical difference in the baseline characteristics. Besides the parameters from the MII-pH study that were used for diagnosing GERD (total reflux event, reflux index, and symptom index), total symptom record (94 *vs* 171 times, P = 0.033), LRT (1.3 (0, 4.3) *vs* 17.2 (9.43, 38.55), P < 0.001), and MNBI (1897.69 (806.89) *vs* 1300.48 (600.31) ohms, P = 0.008), were significantly different between the non-GERD and GERD groups, respectively. Meanwhile, PSPW, another novel metric, did not show a significant difference between the groups [53.57 (27.59) *vs* 56.11 (15.7), P = 0.721]. In the multivariable analysis, LRT and MNBI were the independent parameters that were significantly differences in participants diagnosed with GERD (P < 0.05) (Table 1).

Combined MII-pH study with video monitoring

The MII-pH study with video monitoring was performed in 17 participants. By the novel combined video-MII-pH study is different from the conventional MII-pH study. The video-MII-pH study had conducted simultaneously with MII-pH monitoring and given the clinical symptoms recorded by the investigator that can make more accurate of symptoms in children who cannot even report their symptoms. Then we compared the symptoms that were recorded by the participants' guardians (conventional study) to the symptoms that were recorded by the video monitoring which is the same participants.

The total number of symptoms recorded from video by an investigator who simultaneously viewed throughout the recording, was detected higher than from participants' guardians even though there's no statistical significance (220 *vs* 120, P = 0.062. This led to an increase in the number of participants who were diagnosed with GERD by using symptom association indices (SI/SSI/SAP) (n = 2, 11.8% *vs* n = 5, 29.4%, P = 0.398) (Table 2).

Diagnostic value of the novel parameters from MII-pH study

When using the significant parameters from multivariable analysis to identify GERD, longest reflux duration and MNBI yielded an area under the curve (AUC) of 0.907 (95%CI: 0.802–1) and 0.726 (95%CI: 0.581–0.870), correspondingly. Combining these two parameters yielded an AUC of 0.914 (95%CI: 0.819–1) (Figure 2). A cutoff value of eight minutes for longest reflux duration had a sensitivity of 83.33% and a specificity of 90.91%. A cutoff value of 1466 ohm for MNBI had a sensitivity of 50.0% and a specificity of 33.33%.

DISCUSSION

The prevalence of extraesophageal GERD was 35.3% by using the MII-pH study in this study. Interestingly, 31.4% of children who had extraesophageal manifestations of GERD also had gastrointestinal symptoms. Total symptom record, LRT, and MNBI were the parameters that were significantly different between the GERD and non-GERD groups. LRT and MNBI were the independent parameters from multivariable analysis. Using video monitoring during MII-pH study to depict more symptom record increases the diagnostic yield of extraesophageal GERD.

Table 1 Demographic characteristics and parameters from Multichannel intraluminal impedance-pH study in children diagnosed with extraesophageal gastroesophageal reflux disease and no extraesophageal gastroesophageal reflux disease, *n*, (%)

Characteristics	No extraesophageal GERD (*n* = 33)	Diagnosed extraesophageal GERD by MII-pH study (*n* = 18)	*P* value	
			Univariable analysis	Multivariable analysis
Age (yr) (median, IQR)	1.67 (0.91, 3.38)	4.58 (1.70, 13.15)	0.174	
Age < 1 yr	10 (30.3)	2 (11.1)		
Age ≥ 1 yr	23 (69.7)	16 (88.9)		
Sex, male	17 (51.5)	10 (55.6)	1	
Underlying diseases			0.441	
Respiratory disorder				
Bronchiectasis	1 (3.03)	0		
Chronic lung disease	7 (21.21)	2 (11.11)		
Congenital hypoventilation syndrome	0	2 (11.11)		
Subglottic stenosis	0	1 (5.56)		
Tracheobronchomalacia	1 (3.03)	0		
Laryngomalacia	1 (3.03)	0		
BRUE	1 (3.03)	0		
Chronic cough	1 (3.03)	0		
Neurological disorder				
Swallowing dysfunction	2 (6.06)	1 (5.56)		
Spastic cerebral palsy	2 (6.06)	3 (16.67)		
Infantile spasm	1 (3.03)	0		
Multiple anomalies				
Syndromic disorder	6 (18.18)	2 (11.11)		
Non-syndromic disorder	9 (27.27)	7 (38.89)		
Indication for evaluation				
Extraesophageal symptoms			0.679	
Recurrent pneumonia	9 (27.3)	4 (22.2)		
Hypersecretion	4 (12.1)	2 (11.1)		
Cough	11 (33.3)	10 (55.6)		
Glossoptosis	1 (3.0)	0		
Tracheobronchomalacia	1 (3.0)	0		
Stridor	1 (3.0)	0		
Choking	4 (12.1)	1 (5.6)		
Chronic rhinosinusitis	0	1 (5.6)		
BRUEs	1 (3.0)	0		
Apnea	1 (3.0)	0		
Esophageal symptoms			0.293	
Vomiting	8 (24.2)	6 (38.9)		
Heartburn	1 (3.0)	1 (5.6)		
None	24 (72.7)	11 (61.1)		
Total recorded symptoms	94	171	0.033	0.064

(times, %)				
Cough	43 (45.75)	66 (38.60)	0.404	
Irritability	32 (34.04)	22 (12.86)	0.754	
Apparent secretion	7 (7.44)	17 (9.94)	0.346	
GI symptoms (vomiting or heartburn)	12 (12.77)	66 (38.60)	0.081	
Impedance parameters (median, IQR)				
Total time (hours)	22.12 (20.34, 24.04)	21.34 (19.97, 22.62)	0.391	
Reflux index[1]	0.40 (0, 1.45)	8.4 (4.43, 14.20)	0.001	
Longest reflux time (min)	1.3 (0, 4.30)	17.2 (9.43, 38.55)	0.001	
Total reflux events[1]	12 (5.00, 37.50)	28 (18.50, 45.50)	0.032	0.012
Weakly acid reflux events				
Acid reflux events	9 (2.50, 27.00)	10 (3.75, 21.75)	0.79	
Nonacid reflux events	1 (0, 4.50)	15.5 (8.75, 25.25)	0.001	
Symptom indices	0 (0, 4.00)	0 (0,1.00)	0.381	0.212
Symptom index[1]	0 (0, 0.00)	0 (0, 12.73)	0.208	
Symptom sensitivity index[1]	0 (0, 0.00)	0 (0, 1.40)	0.32	
Symptom associated index[1]	0 (0, 0.00)	0 (0, 85.63)	0.168	
MNBI (ohms) (mean, SD)	1897.69 (806.89)	1300.48 (600.31)	0.008	
PSPW (%) (mean, SD)	53.57 (27.59)	56.11 (15.70)	0.721	
Diagnosis GERD				
Gross finding (n = 25)	8/12 (66.7)	10/13 (76.9)	0.673	
Histopathology (n = 22)	6/11 (54.5)	10/11 (90.9)	0.149	

[1]Significant factors in univariable analysis were not included in the multivariable analysis because of collinearity with criteria diagnosis gastroesophageal reflux disease using the MII-pH study.

BRUE: Brief resolved unexplained event; MNBI: Mean nocturnal baseline impedance; PSPW: Post-reflux swallow-induced peristaltic wave index; GERD: Gastroesophageal reflux disease; MII-pH: Multichannel intraluminal impedance-pH; IQR: Interquartile range.

Table 2 Comparing symptoms recorded by conventional and combined visual data object -monitoring in children who underwent multichannel intraluminal impedance-pH study (n = 17), n, (%)

Characteristics	Conventional MII-pH study	Combined video-MII-pH study	*P* value
Total recorded symptoms	120	220	0.062
Cough	31 (25.83)	46 (20.90)	0.259
Irritability	38 (31.67)	101 (45.90)	0.114
Apparent secretion	3 (2.50)	43 (19.55)	0.02
GI symptoms (vomiting or heartburn)	48 (40.00)	33 (15.00)	0.339
Symptom indices (median, IQR)			
Symptom index	0 (0–5.00)	0 (0–11.65)	0.306
Symptom sensitivity index	0 (0–2.65)	0 (0–5.80)	0.306
Symptom associated index	0 (0–37.60)	0 (0–93.15)	0.306
Diagnosis GERD using symptom indices	2 (11.76)	5 (29.41)	0.398

GI: Gastrointestinal; GERD: Gastroesophageal reflux disease; MII-pH: Multichannel intraluminal impedance-pH; IQR Interquartile range.

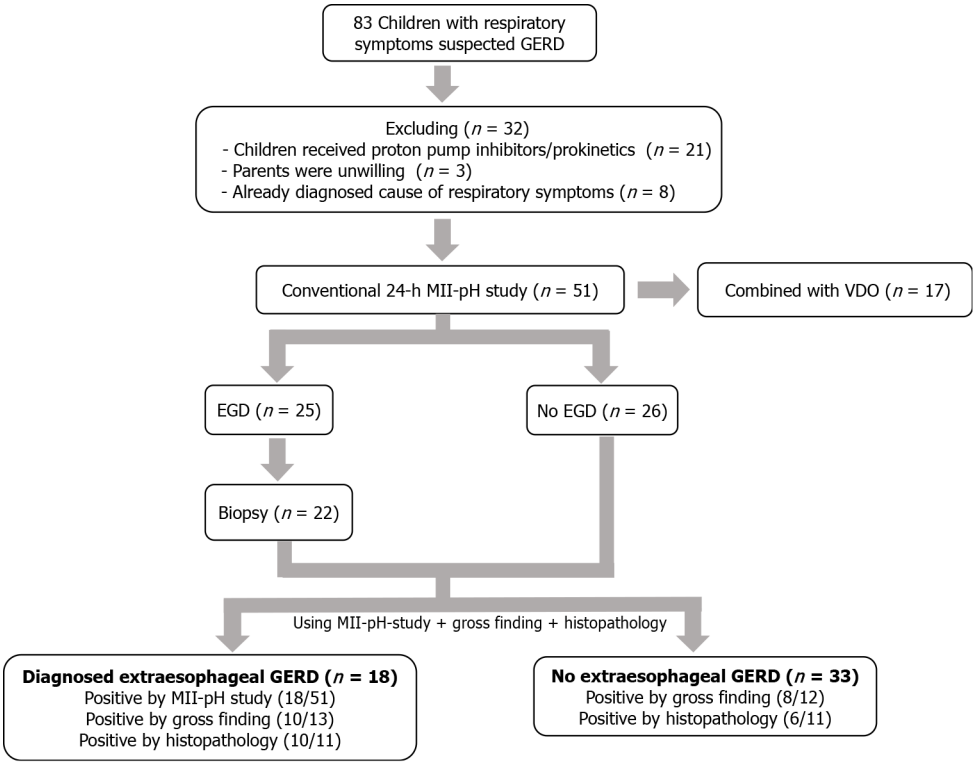

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Figure 1 Recruitment of children with respiratory symptoms suggestive of gastroesophageal reflux disease. EGD: Esophagogastroduodenoscopy; GERD: Gastroesophageal reflux disease; MII-Ph: multichannel intraluminal impedance and pH.

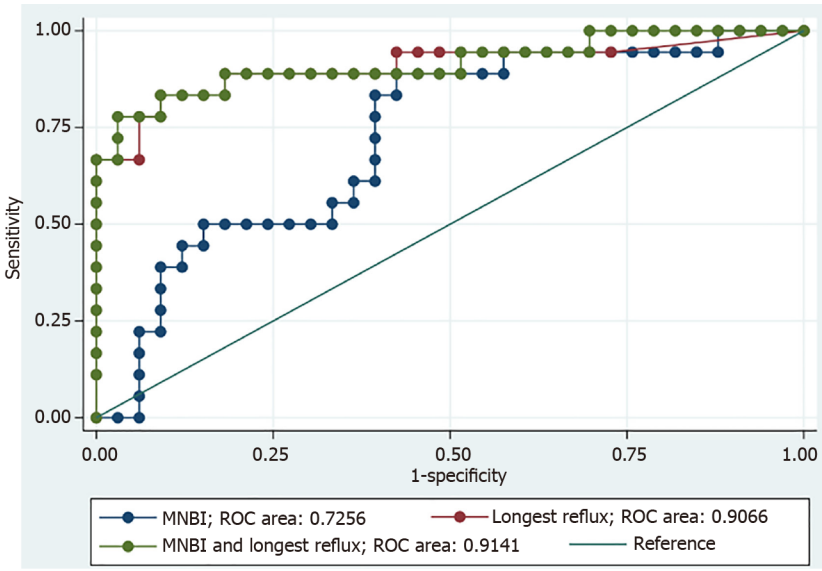

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Figure 2 Area under the receiver operating characteristic curve of the novel parameters to diagnose extraesophageal gastroesophageal reflux disease. MNBI: Mean nocturnal baseline impedance; ROC: Receiver operating characteristic curve; GERD: Gastroesophageal reflux disease.

There are several debates over clinical symptoms of extraesophageal reflux disease in children because of heterogeneity, non-specificity, and unreliability. Moreover, the prevalence of extraesophageal GERD reflects the real burden and depends on the modalities for diagnosis. Hence, finding the best diagnostic tool for extraesophageal GERD is crucial. Many proposed diagnostic tools, such as oropharyngeal pH monitoring/salivary pepsin, have been studied with unsatisfactory results[9-11]. As a result, the present study was designed using MII-pH study and histopathology—which are the gold standard for diagnosing esophageal GERD—to be the gold standard diagnosis for extraesophageal GERD. Moreover, combined-video monitoring was performed in 17 participants. The present study

found that video monitoring increased the value of symptom-reflux association in extraesophageal GERD. This is congruent with our previous study which depicted a trend of symptom-reflux association with particular symptoms of GERD in children diagnosed with esophageal atresia[12]. The real-time video captured in MII-pH monitoring with physician symptom recordings had higher symptom indices. There were more symptoms recorded including cough, hypersecretion, irritability, and vomiting. There were also more GERD diagnoses secondary to the symptoms that were more trustworthy than conventional methods. These studies highlight that symptom recording by video monitoring in children increases the value of symptom association for GERD diagnosis.

Although identifying extraesophageal manifestation of GERD is challenging and needs evaluation regarding whether it represents true GERD or a mimicker, the present study found concomitant gastrointestinal symptoms or signs in a majority of these children. Moreover, esophagitis was also detected in a majority of children with extraesophageal symptoms in the present study. This might explain the gastrointestinal symptoms they experienced. The reflex theory is a possible explanation regarding why children with extraesophageal GERD also had gastrointestinal involvement. The theory suggests that reflux stimulates the vagus nerve in the esophagus leading to cough, bronchoconstriction, or other extraesophageal symptoms *via* vagally mediated reflexes[13,14]. However, previous studies demonstrated a lower prevalence of esophagitis in patients with extraesophageal GERD. A positive reflux-laryngitis varies from 5% up to 31%[15-18]. Routine upper endoscopy in all children with solely extraesophageal symptoms might be avoided. This invasive procedure should be preserved for patients who have both extraesophageal and esophageal manifestations of GERD. To increase the reliability of symptom assessment, we encourage the physician to have the dedicated history taking or possible video recording of symptoms during MII-pH study simultaneously with the routine symptom recorded by patients or their guardians. Upper endoscopy with biopsy is necessary and could increase the yield of GERD diagnosis in these selected children.

Besides using symptom association to diagnose extraesophageal GERD, we found that acid reflux was mainly present in the present study in accordance with Borrelli *et al*'s work. Borrelli *et al*[19] found that 66% of cough bursts were related to acid reflux episodes. However, different results were demonstrated by Zenzeri *et al*[20] who found predominantly weak acid and nonacid reflux in children with respiratory problems. Because of the lack of standardized protocol and children's conditions in previous studies, a large multicenter study regarding children with different manifestations is necessary to extend the knowledge and narrow the specific treatment for them. In the present study, a majority of children had complicated underlying diseases (multiple anomalies, respiratory disease, or neurological deficit) that increased the risk of esophageal motility disorder and reflux. This could explain the high predominance of acid reflux.

The pathogenesis of GERD is complex and multifactorial. Though abnormal transient esophageal relaxation is the main pathogenesis, other factors such as-esophageal mucosal disease, esophageal dysmotility, gastroparesis, and anatomical defect (hiatal hernia, short segment of abdominal esophagus)-must be considered as aggravated risk factors of GERD[21]. Children with multiple comorbidities, especially neurological deficit, usually have sedentary lifestyles or are bedridden, and this affects gastrointestinal motility. We found that the LRT had statistically significant discriminate GERD and non-GERD children, reflexes the impairment of esophageal volume clearance as one of the pathogenesis of GERD[22,23]. However, there was no impairment of chemical clearance as shown by the insignificant difference in PSPW in both groups. MNBI is another parameter that can discriminate GERD from non-GERD children. MNBI represents esophageal integrity[5] and has a reasonably low value in GERD. To the best of our knowledge, PSPW and MNBI are the new impedance-pH parameters which are integral in the Lyon Consensus criteria for diagnosing GERD in adults[24]. The impact of PSPW and MNBI on increasing the yield of GERD diagnosis in children is rare. There is only one study concerning the impact of MNBI in children with GERD by Rosado-Arias *et al*[25]. That study found that a low MNBI is associated with a pathological AET. Our study is compatible with the study by Rosado-Arias *et al*[25] and confirmed the role of a low MNBI in helping the diagnostic yield of GERD. To the best of our knowledge, the present study is the first study to evaluate the PSPW parameter between GERD and non-GERD children. A previous study by Park *et al*[26] showed impairment of PSPW in adults with laryngopharyngeal reflux and esophageal GERD, but our study is incongruent with same. It is possible that the chemical clearance is important for the pathogenesis of extraesophageal GERD in adults *vs* in children. Further studies from multicenter or with the higher number of participants about PSPW and MNBI parameters, are crucial in aiding the diagnosis of GERD in children.

The certain strength of our study is that we integrated video monitoring into MII-pH study for diagnosing extraesophageal GERD in children. Moreover, the novel parameters (PSPW and MNBI) were evaluated to increase the yield of GERD diagnosis. However, there are some limitations. Firstly, it was a small number of children in a single center study. Therefore, the results are specific to the particular comorbidities that were present and cannot be extrapolated to children with previously healthy or less comorbidities. Secondly, because of the coronavirus disease 2019 pandemic, upper endoscopy was not performed in all children. Given this, there is the potential for selective bias and a high prevalence of children with extraesophageal GERD having esophagitis.

CONCLUSION

In conclusion, the prevalence of GERD was not as high as expected. Employing video monitoring into conventional MII-pH study increases the diagnostic yield of symptom indices. LRT and MNBI are novel parameters that should be integrated into the diagnostic criteria for GERD.

ARTICLE HIGHLIGHTS

Research background

Gastroesophageal reflux disease (GERD) might be either a cause or comorbidity in children with extraesophageal problems especially as refractory respiratory symptoms, without any best methods or criterion for diagnosing it in children.

Research motivation

Recent studies in adults also propose that additional parameters from the multichannel intraluminal impedance (MII)-pH study, mean nocturnal baseline impedance (MNBI), and post-reflux swallow-induced peristaltic wave, increase the diagnostic value of this tool. However, there has been scarce evidence to support the best method for diagnosing extraesophageal GERD in children.

Research objectives

To study the prevalence of extraesophageal GERD, especially in children who presented with refractory respiratory problems by using combined video-MII-pH study. Furthermore, to identify other parameters from MII-pH study that can help the diagnosis of extraesophageal GERD.

Research methods

Children with respiratory symptoms and other extraesophageal manifestations suggestive of GERD were enrolled to participate in the present study. MII-pH study and/or video monitoring and/or upper endoscopy with esophageal histopathology were performed. The prevalence of extraesophageal GERD and the novel diagnostic parameters to diagnose extraesophageal GERD were analyzed.

Research results

The prevalence of extraesophageal GERD was 35.3% by using the MII-pH study and 31.4% of children who had extraesophageal manifestations of GERD also had gastrointestinal symptoms. Total symptom record, longest reflux time (LRT), and MNBI were the parameters that were significantly different between the GERD and non-GERD groups. LRT and MNBI were the independent parameters from multivariable analysis. Using video monitoring during MII-pH study to depict more symptom record increases the diagnostic yield of extraesophageal GERD.

Research conclusions

In conclusion, the prevalence of GERD was not as high as expected. Employing video monitoring into conventional MII-pH study increases the diagnostic yield of symptom indices. LRT and MNBI are novel parameters that should be integrated into the diagnostic criteria for GERD.

Research perspectives

The diagnostic test for extraesophageal GERD in children is limited and there have been a few data support the favorable treatment outcome in these children. Hence, the extensive investigations in these difficult cases are needed and other mimic causes should be ruled out. Further study in aspect of esophageal manometry combined with video-MII-pH study and histopathology in various presentations of GERD should be initiated to extend the knowledge about the pathogenesis of GERD and hopefully, could tailor therapy for these patients.

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FOOTNOTES

Author contributions: Eiamkulbutr S, Dumrisilp T and Sintusek P performed the upper endoscopy and MII-pH study; Eiamkulbutr S, Dumrisilp T collected all the data; Sanpavat A analyzed and interpreted the histopathological data; Eiamkulbutr S recorded all symptoms from video recording; Eiamkulbutr S and Sintusek P analyzed and interpreted the MII-pH study and wrote the manuscript; Sintusek P was responsible for designing, editing, and revising the manuscript; Sintusek P edited the intellectual content in the manuscript; all approved for the final version of the manuscript.

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