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CASE REPORT

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ABOUT COVER

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CASE REPORT

Hereditary hemorrhagic telangiectasia presenting as a recurrent epistaxis in an adolescent: A case report

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Abstract

BACKGROUND

Epistaxis can be an isolated finding or a manifestation of a systemic disease. Some of the potential etiologies are usage of anticoagulants, bleeding disorders, vascular aneurysms, nasal neoplasm, hypertension and nasal steroids. Hereditary hemorrhagic telangiectasia (HHT) as a cause of recurrent epistaxis is uncommon.

CASE SUMMARY

In this report, we describe an 18-year-old adolescent with recurrent epistaxis, mucocutaneous telangiectasia and family history of HHT, consistent with HHT.

CONCLUSION

Timely diagnosis is needed not only to treat the epistaxis but also to be vigilant for other serious manifestations of this condition.

Key Words: Epistaxis; Telangiectasia; Hemorrhagic; Hereditary; Pediatrics; Case report

Core Tip: In patients with recurrent spontaneous epistaxis, a thorough history, family history, physical examination and investigation is necessary to exclude hereditary hemorrhagic telangiectasia which can present with multi-system involvement along with epistaxis.

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INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant vascular disorder. Epistaxis, gastrointestinal (GI) bleeding, iron deficiency anemia, and mucocutaneous telangiectasia are the most common manifestations of the disease[1]. Epistaxis is secondary to telangiectasia of the nasal mucosa. Arteriovenous malformations (AVM) in the visceral organs such as lungs, liver and brain can occur for which symptomatic patients should be screened, as they can be fatal. Intestinal polyps have been described in association with HHT (juvenile polyposis-HHT overlap syndrome), which is seen in 1 percent of HHT cases and is due to mutations in *SMAD4*. Pulmonary and cerebral AVMs are more common in HHT1 patients, while hepatic AVMs and pulmonary hypertension are more common in those with HHT2[2].

CASE PRESENTATION

Chief complaints

An 18-year-old male patient with a past medical history of renal calculi, asthma, environmental allergies, irritable bowel syndrome, and frequent nosebleeds presented to the pediatric clinic for evaluation of nosebleeds.

History of present illness

Patient has had recurrent nosebleeds throughout his life, which seemed to have worsened as a teenager. The bleeding would usually last for 15 min and resolve with nasal compression. There was no history of nose picking or trauma to the nose.

History of past illness

The patient denied bleeding while brushing his teeth, long duration of wound healing or swelling of joints. He denied bruising or petechiae but reported to have small red spots on his chest. Patient was known to have episodes of syncope during the episodes of nosebleeds. There was no history of black, tarry or grossly bloody stool, vomiting or blood in urine. There was no history of chest pain, shortness of breath, hemoptysis, hematemesis or seizures.

Personal and family history

He had a history of mild intermittent asthma and dust mite allergy for which he was taking albuterol and montelukast. The family history was positive for primary biliary cholangitis, Hashimoto's thyroiditis, psoriasis, asthma, arthritis along with pulmonary and liver AVMs and telangiectasias of the finger in the mother. Father had atrial fibrillation, hypertension and hyperlipidemia. Further family history revealed extensive bleeding history in the maternal side, including intestinal telangiectasias in maternal aunt and cousin and frequent nosebleeds in the maternal uncle. Maternal grandmother has had "bleeding problems in intestine and brain".

Physical examination

Physical examination revealed stable vital signs with blood pressure of 120/78 mmHg. Skin examination showed telangiectasias on gum line and inner lips along with cherry hemangiomas on the chest and back (Figures 1 and 2). There were no other skin rashes or lesions suggestive of autoimmune disease. Nasal examination showed erythematous mucus membranes with excoriation in bilateral nares, dilated blood vessels in anterior nares with no active bleeding, and no mass or polyps (Figure 3). Conjunctiva was injected. Rest of the physical examination was normal.

Laboratory examinations

Investigations showed evidence of iron deficiency anemia (hemoglobin 9.5 gm/dL), which was thought to be secondary to long standing history of spontaneous recurrent epistaxis. Stool occult blood was normal. Liver function test was normal. Coagulation and bleeding profile were normal. Upper and/or lower GI endoscopies were not performed as there was no history suggestive of GI bleeding. Renal function panel showed serum creatinine of 0.7 mg/dL and stable electrolytes. Urinalysis was negative for proteinuria or hematuria. Thyroid function test was normal.

Imaging examinations

Chest X-ray was normal. Although he did not have clinical evidence of pulmonary or

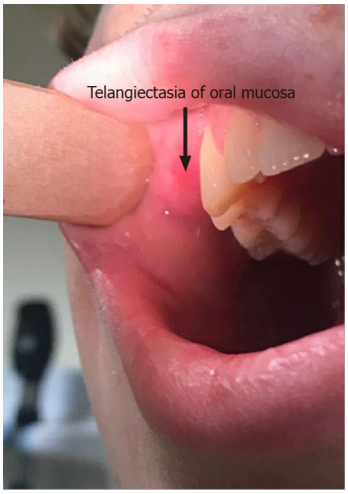

Figure 1 Telangiectasia of oral mucosa.

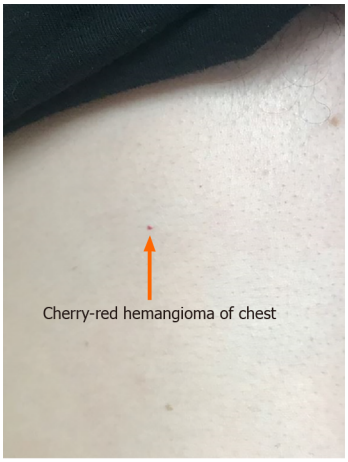

Figure 2 Cherry-red hemangioma of chest.

hepatic AVMs, screening for the latter with computed tomography (CT) of chest and abdomen showed no evidence of pulmonary or hepatic AVMs. Given absence of headache, seizures, and altered sensorium, a CT scan of the head and neck initially was not performed. The prior history of syncopal attacks during episodes of epistaxis was attributed to hypotension from significant blood loss. He was also referred to Genetics for genetic testing and was found to have mutation of *ENG* in chromosome 9, typical of HHT type 1. After genetic confirmation, a further screening with CT angiogram of head and neck did not reveal presence of AVMs.

MULTIDISCIPLINARY EXPERT CONSULTATION

Experts of Ear, Nose and Throat, Hematology, and Genetics.

FINAL DIAGNOSIS

Patient's family history and current symptoms were consistent with HHT (Osler-Weber-Rendu syndrome). Patient's mother and maternal cousin had also been diagnosed with this condition in the past. Since he met three out of four criteria for HHT (spontaneous and recurrent epistaxis, mucocutaneous telangiectasias, and first degree relative with HHT), a definite diagnosis of HHT was made.

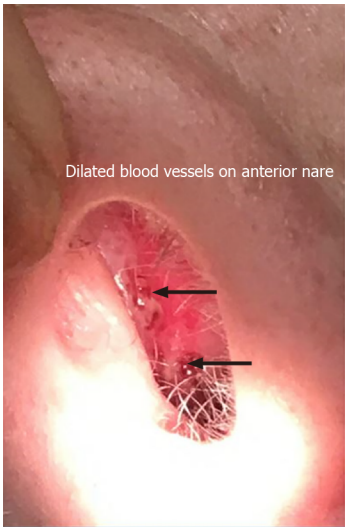

Figure 3 Dilated blood vessels on anterior nare.

TREATMENT

Iron therapy was started for iron deficiency anemia. An ENT evaluation was also recommended who recommended supportive treatment given absence of bleeding at the time of evaluation.

OUTCOME AND FOLLOW-UP

Patient continues to have recurrent epistaxis with mild anemia, for which he continues to take oral iron therapy. Given absence of visceral involvement at this time, he is being followed up closely every few months in the outpatient clinic.

DISCUSSION

The presence of HHT may be suspected in patients with spontaneous and recurrent epistaxis, mucocutaneous telangiectasia in the fingertips, lips, oral mucosa or tongue, visceral involvement (such as GI, pulmonary, cerebral, spinal or hepatic AVM), and/or a first-degree relative with HHT[2]. Three or more criteria indicate definite disease (Curacao criteria). The disease is suspected in patients meeting only two criteria. It is inherited as an autosomal dominant trait. Multiple variants of the three main genes can cause HHT. HHT1 is caused by mutations in the gene *ENG* which transcribes protein product, endoglin. HHT2 is due to sequence variants in *ACVRL1*, a gene than encodes protein product activin receptor-like kinase-1, or ALK-1. HTJP (HHT in association with juvenile polyposis) is due to mutation in *SMAD4*, which encodes the protein Smad4. Since genetic testing does not detect all mutations, the diagnosis of HHT does not rely on genetic testing. However, if genetic testing is done, identification of a pathogenic sequence variant in *ENG*, *ACVRL1*, or *SMAD4* is typically seen[3]. Our patient had HHT1 sary to mutation of ENG in chromosome 9 (Invitae Hereditary Hemorrhagic Telangiectasia Panel, San Francisco, CA, United States).

The telangiectasias are generally not present at birth but develop with increasing age. Epistaxis is usually the earliest sign of disease, often occurring in childhood. Mucocutaneous and gastrointestinal telangiectasia develop with age and pulmonary AVM (PAVM) generally become apparent after puberty. Cerebral vascular malformations are also thought to develop during childhood and are clinically silent. Giordano *et al*[4] studied 44 children (mean age, 10.3 years; range, 1-18) with HHT1 and HHT2 and found that cerebrovascular AVMs were present in 7 of 44 cases, pulmonary AVMs in 20 of 44 cases, and liver AVMs in 23 of 44 cases. Large visceral AVMs were found in 27% children and were significantly more frequent in patients with HHT1. Only large AVMs were associated with symptoms and complications.

Over the age of 40, recurrent GI bleeding occurs in up to one-third patients with

HHT, mostly occurring in the stomach or duodenum rather than the colon. In patients with severe anemia and/or overt GI bleeding, endoscopy is recommended to evaluate and visualize telangiectasias, which appear similar to their mucocutaneous counterparts and are surrounded by an anemic halo[5]. GI bleeding can present with iron deficiency anemia. Mucocutaneous telangiectasias are not used for diagnostic purposes but are frequently seen in lips, tongue, buccal mucosa and fingertips and present later in life[2].

PAVMs are abnormal thin-walled vessels that replace normal capillaries between the pulmonary arteries and veins. They often result in sac-like structures and provide a direct capillary-free communication creating a shunt. Arterial blood passing through these right-to-left shunts cannot be oxygenated, leading to hypoxemia resulting in polycythemia. PAVMs are mostly asymptomatic; however, one-third of affected patients may exhibit cyanosis, clubbing, and polycythemia. Patients are at risk for neurologic sequelae due to paradoxical embolism passing through the shunts. Cerebral events such as abscess or stroke along with transient ischemic attacks can occur in patients with asymptomatic PAVMs[6].

Patients with HHT may have cerebral or spinal cord involvement which can be clinically silent. Symptomatic patients with AVMs, or high-flow AV fistulae may present with seizures, ischemia of the surrounding tissue due to a steal effect, or hemorrhage. Thus, patients with symptoms suggestive of cerebral AVMs warrant further assessment with imaging. Medical management may be sufficient; however, some may need interventions such as neurosurgery, embolization, or stereotactic radiotherapy, alone or in combination[7].

Hepatic involvement may occurs in up to two-thirds of patients with HHT. Common manifestations are portal hypertension, biliary disease and heart failure. Hepatic AVMs places patients at risk for angina and heart failure secondary to shunts created between the hepatic artery and vein. Hepatic AVMs are suspected in patients with abnormal liver function test, hepatomegaly or liver bruit. Liver biopsy is not recommended due to risk of bleeding, but diagnosis can be confirmed with CT, magnetic resonance imaging, or sonogram[2].

Patients with HHT are at increased risk for venous thromboembolism for which treatment or prophylactic anticoagulation may be required[8]. Low serum iron level is associated with elevated factor VIII level which can lead to thromboembolic phenomenon. Hence, it is important, to identifying and treat iron deficiency anemia in these patients[2].

The second international HHT guidelines state that all children with recurrent bleeding and/or symptoms of anemia should be tested for iron deficiency anemia and started on oral or intravenous iron therapy, and blood transfusions for severe anemia[8]. Although, the genetic testing is not required for diagnosis of HHT, the testing is recommended for asymptomatic children of a parent with HHT. Also, screening for brain and pulmonary AVMs in asymptomatic children with HHT or at risk for HHT at the time of presentation/diagnosis is recommended. Brain AVMs with high risk features, large pulmonary AVMs and AVMs associated with reduced oxygen saturation should be treated in children, with a repeat screening for such at every five-year intervals[8].

The management of HHT is focused on reducing the symptoms arising from each organ system involvement. Recently, new therapeutic interventions targeting at vascular endothelial growth factor (VEGF) and the angiogenic pathway with anti-VEGF antibody (such as bevacizumab) and VEGF receptor 2 tyrosine kinase inhibitor (such as pazopanib) are being studied[9]. Tacrolimus and sirolimus have also shown promising results in some studies[9].

CONCLUSION

Patients with HHT are at risk for non-traumatic recurrent epistaxis and hemorrhages in the brain, liver, lungs, or other organs. A high index of suspicion for HHT is necessary in patients who present with recurrent epistaxis for timely evaluation and management.

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CASE REPORT

Neonatal cholestasis can be the first symptom of McCune–Albright syndrome: A case report

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Abstract

BACKGROUND

McCune–Albright syndrome (MAS) is caused by postzygotic somatic mutations of the *GNAS* gene. It is characterized by the clinical triad of fibrous dysplasia, café-au-lait skin spots, and endocrinological dysfunction. Myriad complications in MAS, including hepatobiliary manifestations, are also reported.

CASE SUMMARY

This is a case of a 4-year-old boy who presented with MAS with neonatal cholestasis. He was suspected to have Alagille syndrome due to neonatal cholestasis with intrahepatic bile duct paucity in liver biopsy, peripheral pulmonary artery stenosis, and renal tubular dysfunction. By the age of 2 years, his cholestatic liver injury gradually improved, but he had repeated left femoral fractures. He did not exhibit endocrinological abnormality or café-au-lait skin spots. However, MAS was suspected due to fibrous dysplasia at the age of 4 years. No mutation was identified in the *GNAS* gene in the DNA isolated from the peripheral blood, but an activating point mutation (c.601C>T, p.Arg201Cys) was observed in the DNA extracted from the affected bone tissue and that extracted from the formalin-fixed paraffin-embedded liver tissue, which was obtained at the age of 1 mo.

CONCLUSION

MAS should be considered as a differential diagnosis for transient cholestasis in infancy.

Key Words: McCune–Albright syndrome; *GNAS*; Neonatal cholestasis; Alagille syndrome; Bile duct paucity; Case report

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Core Tip: McCune–Albright syndrome (MAS) is caused by postzygotic somatic mutations of the *GNAS* gene. It is characterized by the clinical triad of fibrous dysplasia, café-au-lait skin spots, and endocrinological dysfunction. MAS complications other than the triad are also reported. This is the case of a boy with MAS diagnosed with Alagille syndrome in his infancy based on intrahepatic bile duct paucity in liver biopsy, neonatal cholestasis, cardiac manifestation, and renal tubular dysfunction. MAS should be considered as a differential diagnosis for transient cholestasis in infancy.

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INTRODUCTION

McCune–Albright syndrome (MAS) is a rare sporadic disease characterized by the clinical triad of fibrous dysplasia, café-au-lait skin spots, and endocrinological dysfunction[1,2]. Its estimated prevalence ranges from 1/100000 to 1/1000000[3]. MAS is caused by postzygotic somatic mutations of the *GNAS* gene, which encodes the G protein stimulatory α subunit[4]. MAS complications other than the clinical triad, including hepatobiliary dysfunction, are reported[4-6].

Alagille syndrome (ALGS) is an autosomal dominant disorder with a wide spectrum of clinical variability. The main clinical features and malformations are chronic cholestasis due to intrahepatic bile duct paucity (decreased bile duct-to-portal tract ratio: < 0.4), cardiac disease (particularly peripheral pulmonary artery stenosis), skeletal deformity (particularly butterfly vertebrae), ocular abnormalities (particularly posterior embryotoxon), and characteristic facial features. Additional features include intracranial bleeding, dysplastic kidneys, and bone fractures[7,8]. The majority of cases are caused by *JAG1* gene haploinsufficiency, encoding a ligand jagged1 in the Notch signaling pathway[9,10]. Mutations in *NOTCH2*, a receptor in the same signaling pathway, are identified in some ALGS patients who do not have mutations in *JAG1*[11].

This is a case of a boy who was diagnosed with ALGS in his infancy based on intrahepatic bile duct paucity in liver biopsy, peripheral pulmonary artery stenosis, and renal tubular dysfunction and later with MAS based on radiographic findings of fibrous dysplasia.

CASE PRESENTATION

Chief complaints

A 4-year-old boy complained of repeated left femoral fractures.

History of present illness

The patient had repeated left femoral fractures for four times (at 1 year and 3 mo, 1 year and 11 mo, 2 years and 10 mo, and 4 years and 3 mo old), and the difference in the length of his lower limbs gradually became apparent by the age of 2 years. While repeated femoral fractures were initially considered as bone metabolic disorders associated with ALGS, the serum phosphate levels had remained at the lower limit of the standard for age, and the level of fibroblast growth factor 23 (FGF23) was high as 117 pg/mL (reference range: 15-49 pg/mL[12]). At the age of 4 years and 8 mo, radiographic findings revealed a "ground-glass" appearance in his left femur and tibia and "shepherd's crook deformity" in his left thigh bone, which were characteristic features of fibrous dysplasia (Figure 1).

History of past illness

The patient was born at 40 wk and 6 d' gestation; with a birth weight of 2726 g. Failure to thrive was noted at 18 d following birth. Further evaluation of this concern revealed

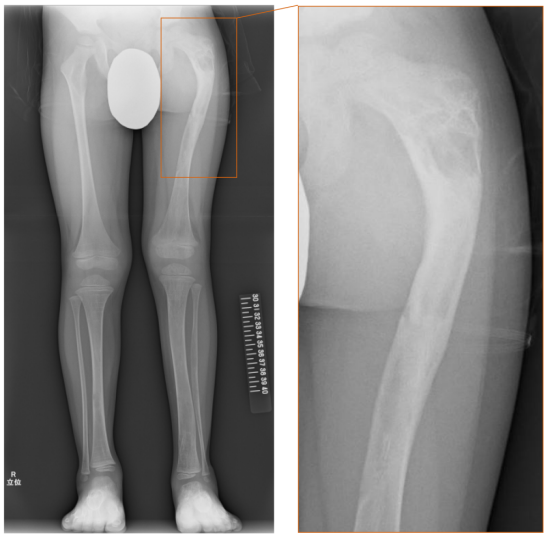

Figure 1 Radiograph at the age of 4 years and 8 mo. The radiograph demonstrated a "ground-glass" appearance in his left femur and left tibia and "shepherd's crook deformity" which is characterized by the presence of proximal femoral varus deformity and retroversion deformity, in his left thigh bone.

hepatomegaly, elevated liver transaminase level [aspartate aminotransferase (AST) 193 U/L, alanine aminotransferase (ALT) 424 U/L], and hyperbilirubinemia (T-Bil 8.0 mg/dL, D-Bil 6.6 mg/dL). Liver biopsy was performed at the age of 1 mo, which revealed bile duct paucity (the ratio of the bile duct to the portal tract was 0.1) (Figure 2). Other than cholestasis, peripheral pulmonary artery stenosis, hypokalemia, and metabolic acidosis due to renal tubular dysfunction were observed. No butterfly vertebrae or ocular abnormalities were found. Although any large deletion and duplication were not observed in the *JAG1* gene by the fluorescence *in situ* hybridization analysis, the patient was clinically suspected to have ALGS and was listed for liver transplantation. Cholestatic liver injury was gradually normalized by the age of 2 years under oral ursodeoxycholic acid and glycyrrhizic acid treatment and did not deteriorate even after both medications were tapered. His DNA was further subjected to a targeted next-generation sequencing that covers 14 genes responsible for cholestatic liver diseases[13], and no pathogenic variants were found in his genes including *JAG1* and *NOTCH2*.

Personal and family history

The patient was born to non-consanguineous Japanese parents. The pregnancy had been uncomplicated, and his family history was unremarkable.

Physical examination

At the age of 4 years and 9 mo, his height was 101.7cm (-0.81 SD); body weight, 15.2kg (-0.82 SD); and arm span, 104 cm. The difference in the length of the lower limbs was 1 cm (right, 53 cm; left, 52 cm). He did not exhibit jaundice or hepatosplenomegaly. He was noted to have a grade 2/6 systolic heart murmur. He did not have café-au-lait skin spots. His testicular capacity was 2 mL, pubic hair had not yet grown, and no precocious puberty was observed.

Laboratory examinations

Laboratory examination at the age of 4 years revealed elevated levels of serum alkaline phosphatase (2506 U/L, reference range: 430-1200 U/L), bone alkaline phosphatase (216 U/L, reference range: 59-107 U/L[14]), FGF23 (86 pg/mL), and serum type I collagen cross-linked N-telopeptide (171 nmolBCE/L, reference range: 14-57 nmolBCE/L[15]). No endocrinological abnormalities were found. The transaminase and bilirubin levels were within the reference ranges (AST 28 U/L, ALT 25 U/L, T-Bil 0.6 mg/dL, and D-Bil 0.2 mg/dL).

Imaging examinations

Bone scintigraphy with 99 mTc-hydroxymethylene diphosphonate, which was employed to detect lesions with enhanced bone metabolism, revealed multiple lesions with increased uptake in the left skull and upper left limb in addition to the left femur

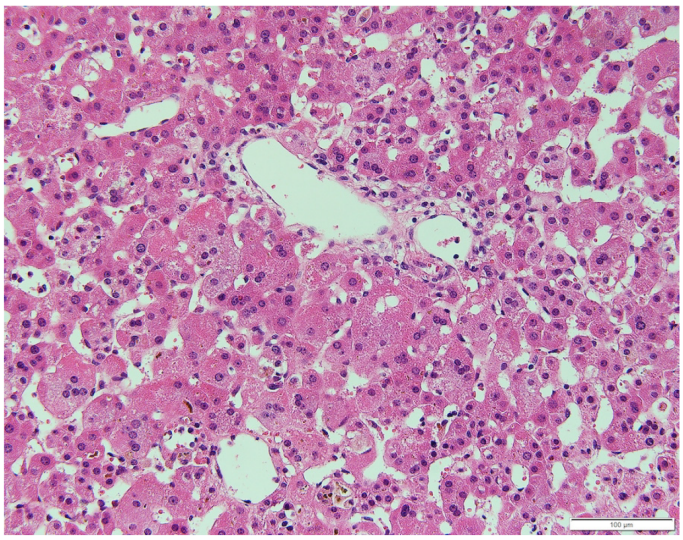

Figure 2 Liver specimen at the age of 1 mo. Microscopic examination revealed a lack of bile ducts in the portal area and giant cell transformation of hepatocytes (hematoxylin and eosin staining).

and left tibia (Figure 3).

Further diagnostic work-up

For the mutational analysis of the *GNAS* gene, genomic DNA from the peripheral blood was extracted using magLEAD Consumable Kit® (Precision System Science Co., Ltd., Chiba, Japan). In addition, it was polymerase chain reaction (PCR)-amplified for exons 7 to 10 and their splice sites of the *GNAS* gene, where mutation hotspots for MAS were reported. PCRs were conducted using the 5′-TCACTTCCG TTGAGCCTGAC-3′ and 5′-CTTGCACGGGGTTCTTCTCT-3′ primer set designed for detecting the mutation; however, sequencing after PCR did not reveal any mutations (Figure 4A).

Therefore, mutation analysis of the *GNAS* gene was also conducted from bone tissue samples, which were obtained from fibrous dysplastic lesions during a fracture surgery at the age of 5 years and 6 mo. The dissected bone sample was immediately snap-frozen using liquid nitrogen and crushed using 6700 Freezer/Mill (SPEX SamplePrep, NJ, United States). Genomic DNA from the bone tissue was extracted using DNeasy Blood & Tissue Kit (QIAGEN, Hilden, Germany) and was PCR-amplified and sequenced similar to that of the peripheral blood. As a result, an activation point mutation (c.601C>T, p.Arg201Cys)[4] was detected in genomic DNA, and the patient was diagnosed with MAS (Figure 4B).

Furthermore, when he was 6 years old, DNA was extracted from a formalin-fixed paraffin-embedded (FFPE) liver tissue that was collected during the biopsy performed at the age of 1 mo. To isolate genomic DNA from the FFPE liver tissue, Agencourt FormaPure XL Total kit (Agencourt Bioscience Corporation, Beverly, MA, United States) was used. Genomic DNA from the liver tissue was PCR-amplified and sequenced for the corresponding site to the peripheral blood and bone tissue. PCRs and sequencing were conducted using the 5′-TTCGGTTGGCTTTGGTGAGA-3′ and 5′-CACGTCAAACATGCTGGTGG-3′ primer set designed for detecting the mutation. The same mutation from the bone tissue samples was observed (Figure 4C).

FINAL DIAGNOSIS

The final diagnosis of the presented case is MAS.

TREATMENT

When he was 7 years old, an osteotomy was performed to correct the curvature of the left femur.

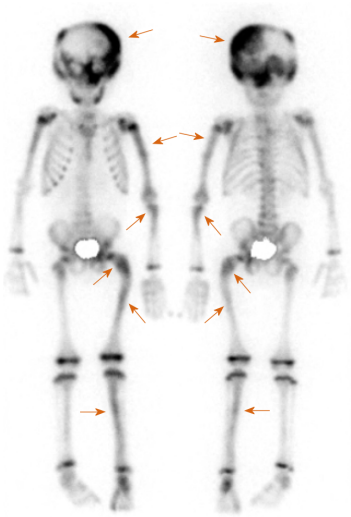

Figure 3 Bone scintigraphy with Tc-99 m-hydroxymethylene diphosphonate. There are multiple hotspots with uptake at the left dominant skull and upper left limb in addition to the left femur and the left tibia.

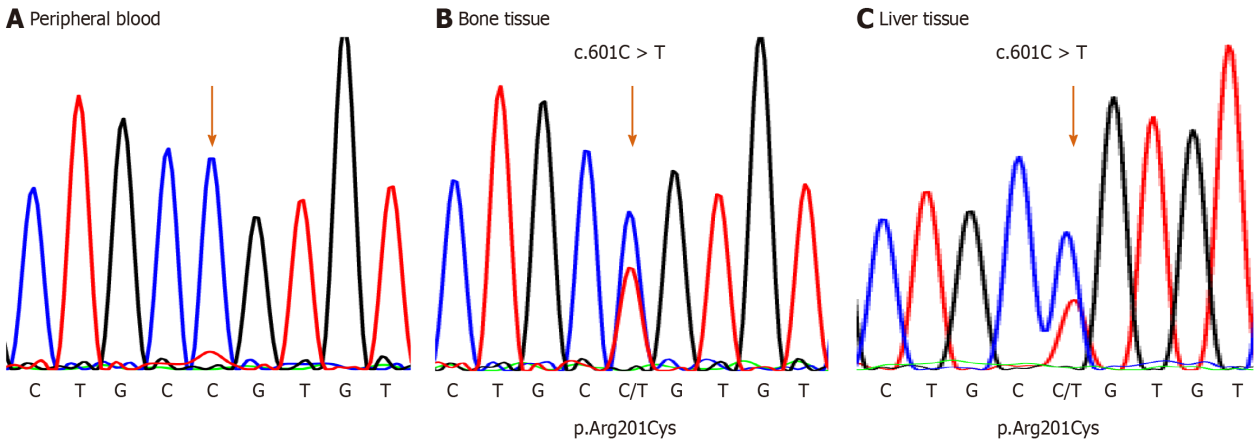

Figure 4 DNA sequencing of the *GNAS* gene. A: Normal sequencing is shown in the peripheral blood; B and C: Arg201Cys mutation was detected in the bone tissue samples and the liver tissue.

OUTCOME AND FOLLOW-UP

The patient was followed up for endocrine abnormalities, such as premature puberty and compression optic neuropathy, since bone scintigraphy revealed increased uptake in his skull. Furthermore, although his liver dysfunction did not persist, follow-up was continued with semiannual to annual abdominal ultrasonography for neoplasm in the liver.

DISCUSSION

MAS is caused by activating somatic mutations within the *GNAS* gene. These mutations occur in the early postzygotic period. The patient's somatic cells are mosaic for the mutation; hence, the clinical features are determined by the distribution of the affected cells[4,16,17].

In MAS, hepatobiliary dysfunction is relatively rare, with a frequency of 5%-10%[18,19], and usually develops in the early stage of life as neonatal cholestasis[5,6,16,20,21]. Although cholestasis can be the first symptom of MAS and is sometimes followed by persistent elevation of the levels of serum liver enzymes, natural history has been reported as benign in most patients[5,6], and only a few cases required liver

transplantation[20].

The histological findings of the patient in this report revealed intrahepatic bile duct paucity, which suggested ALGS along with characteristic features, such as neonatal cholestasis, peripheral pulmonary artery stenosis, renal tubular dysfunction, and recurrent bone fractures. Giant cell transformation has been the most common finding in the liver histology of MAS[5,22,23]. However, intrahepatic bile duct paucity was also reported in cases with MAS. In such cases, distinguishing MAS from ALGS based on clinical symptoms and pathological features is difficult as in our case, in which the difference in the length of the patient's legs prompted us to suspect enhanced bone metabolism[6]. MAS should be considered among the differential diagnoses of ALGS when the liver tissue demonstrates intrahepatic bile duct paucity. A recent manuscript reported that combined sequencing of *JAG1* and *NOTCH2* along with copy number variant analysis of *JAG1* did not identify pathogenic variants in 3.2% of patients who met the diagnostic criteria for ALGS[24]. Regarding renal tubular dysfunction and peripheral pulmonary artery stenosis in our case, we did not extract and sequence genomic DNA from renal tubular epithelial cells and pulmonary artery to detect the mutation in the tissues. Although our patient did not meet the classical diagnostic criteria of AGLS which is based on the presence of intrahepatic bile duct paucity on liver biopsy in association with at least three of the major clinical features: chronic cholestasis, cardiac disease, skeletal abnormalities, ocular abnormalities, and characteristic facial features, it is still possible that some other genes than *GNAS* or mutations in *JAG1/NOTCH2* genes that cannot be detected with current methods are involved in AGLS-like renal and pulmonary features in our case.

Due to the somatic mosaic nature of the disease, a negative result of mutation analysis from the peripheral blood does not exclude the possibility of MAS[3,19], and DNA should be isolated from the affected tissues. In this case, *GNAS* gene mutation was detected from the surgical bone specimen and FFPE liver biopsy tissue, which was collected 6 years ago. As in this report, *GNAS* mutations have been detected in the liver tissue obtained from patients with neonatal cholestasis in previous reports[5,16,19,20]. The occurrence and severity of the hepatic phenotype depend on the number and location of the cells with the mutation[5,16]. Whether the patients still keep hepatic cells with the mutation in the *GNAS* gene following amelioration of their hepatic symptoms is unknown.

In most cases, neonatal cholestasis in patients with MAS resolves spontaneously. However, liver dysfunction may persist, and subsequent hepatic lesions may develop and exhibit malignant potential, such as hepatoblastoma and hepatocellular adenomas[6,21]. In this case, liver dysfunction did not persist, and liver lesions were not identified, but we continued to follow-up the patient for serum tumor markers with semiannual to annual abdominal ultrasonography.

We presented a case of a patient with MAS who was suspected of ALGS due to neonatal cholestasis and histological findings that revealed intrahepatic bile duct paucity. No pathogenic variants were noted in the *JAG1* and *NOTCH2* genes, and MAS was suspected from repeated fractures and radiographic findings. The mutation in the *GNAS* gene was detected in the bone and liver tissues, and the patient was diagnosed with MAS. MAS should be considered as a differential diagnosis for cholestasis in infancy.

CONCLUSION

Hepatobiliary dysfunction is relatively rare in MAS, but MAS should be considered as a part of the differential diagnosis of neonatal cholestasis with unknown causes, and genetic diagnosis using liver tissue is possible.

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EDITORIAL

Autism medical comorbidities

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Abstract

Medical comorbidities are more common in children with autism spectrum disorders (ASD) than in the general population. Some genetic disorders are more common in children with ASD such as Fragile X syndrome, Down syndrome, Duchenne muscular dystrophy, neurofibromatosis type I, and tuberous sclerosis complex. Children with autism are also more prone to a variety of neurological disorders, including epilepsy, macrocephaly, hydrocephalus, cerebral palsy, migraine/headaches, and congenital abnormalities of the nervous system. Besides, sleep disorders are a significant problem in individuals with autism, occurring in about 80% of them. Gastrointestinal (GI) disorders are significantly more common in children with ASD; they occur in 46% to 84% of them. The most common GI problems observed in children with ASD are chronic constipation, chronic diarrhoea, gastroesophageal reflux and/or disease, nausea and/or vomiting, flatulence, chronic bloating, abdominal discomfort, ulcers, colitis, inflammatory bowel disease, food intolerance, and/or failure to thrive. Several categories of inborn-errors of metabolism have been observed in some patients with autism including mitochondrial disorders, disorders of creatine metabolism, selected amino acid disorders, disorders of folate or B12 metabolism, and selected lysosomal storage disorders. A significant proportion of children with ASD have evidence of persistent neuroinflammation, altered inflammatory responses, and immune abnormalities. Anti-brain antibodies may play an important pathoplastic mechanism in autism. Allergic disorders are significantly more common in individuals with ASD from all age groups. They influence the development and severity of symptoms. They could cause problematic behaviours in at least a significant subset of affected children. Therefore, it is important to consider the child with autism as a whole and not overlook possible symptoms as part of autism. The physician should rule out the presence of a medical condition before moving on to other interventions or therapies. Children who enjoy good health have a better chance of learning. This can apply to all children including those with autism.

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Core Tip: Medical comorbidities are common in children with autism. Some genetic disorders are more common in children with autism spectrum disorders. Medical comorbidities have a significant impact on the child's behaviour and development. Early identification and treatment of these comorbidities will help to improve the child's ability to learn and improve his or her circumstances and those of his or her family.

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INTRODUCTION

Comorbidity is the presence of one or more additional diseases or disorders that coincide with a primary disease or disorder. A comorbid condition is a 2nd order diagnosis that has core symptoms that are distinct from the primary disorder. Comorbidity is much more common in people with autism spectrum disorders (ASD) than in the general population. For example, patients with autism are 1.6 times more likely to have eczema or skin allergies, 1.8 times more likely to have asthma and food allergy, 2.1 times more likely to have frequent ear infections. 2.2 times more likely to have severe headaches, 3.5 times more likely to have diarrhoea or colitis, and 7 times more likely to report gastrointestinal (GI) problems[1].

A child with autism may have symptoms of other comorbidities in addition to the core symptoms of autism (*e.g.*, social deficits, language impairment, repetitive behaviours, *etc.*). Recognising these medical conditions is important because many of the medical conditions could stimulate or exacerbate the abnormal behaviour that occurs in children with autism. Once these medical conditions are treated, the behaviours stop. Because unwell people do not perform adequately, some children with autism may lose skills and/or fail to retain skills because of their medical conditions. Effective learning requires a healthy state. Comorbid conditions may be markers of the underlying pathophysiology and require a more sophisticated therapeutic approach. In the meantime, it is more likely that the increased mortality risk associated with ASD is related to the presence of comorbid medical conditions and intellectual disabilities than to ASD itself. Since most of them are treatable, the treatment of comorbid medical conditions can lead to a substantial improvement in the quality of life of the child and the family[2,3]. However, it is not always easy to identify comorbid conditions in children with ASD due to several factors, such as communication disorders, the ambiguity of symptoms, their deviation from those in the general population, or their change over time. These factors are also compounded by the widespread belief that deviant behaviours and symptoms are 'just part of autism'. The lack of diagnostic tools available to screen for these disorders is another important limitation[4]. Many symptoms and behaviours commonly attributed to autism, may reflect the presence of other organic disorders. For example, headbanging could be due to the presence of headaches, or pain when frustrated and the inability to communicate these symptoms. If the child fidgets frequently, he or she could have complaints related to constipation. Aggression and self-injurious behaviour could also be related to the presence of the pain and the child's inability to communicate about his/her condition. Pica could also be a sign of nutrient deficiencies, particularly iron, which is relatively common in children with autism. Food refusal may be related to the high food selectivity observed in children with autism but could also reflect the presence of food allergy or intolerance or be due to a more local cause such as the presence of dental problems[5]. Table 1 showed the different comorbidities that could present in children with autism.

Table 1 Autism comorbidities

Related disorders
Anxiety disorder
Obsessive-compulsive disorders
Attention deficit hyperactivity disorders
Mood disorders
Sleep disorders: Difficulty falling asleep, inability to sleep in a flat position, nighttime reawakenings, sleepwalking
Epilepsy
Systemic medical disorders
Accidents
Injuries, drowning, suffocation, *etc.*
Genetic disorders
Fragile X syndrome, Down syndrome, Duchenne muscular dystrophy, neurofibromatosis type I, and tuberous sclerosis complex
Metabolic disorders
Mitochondrial disorders, disorders of creatine metabolism, selected amino acid disorders, disorders of folate or vitamin B12 metabolism, and selected lysosomal storage disorders
Endocrine disorders
e.g., hypothyroidism
Neurological disorders
Congenital abnormalities of the nervous system, epilepsy, macrocephaly, hydrocephalus, cerebral palsy, migraine/headaches, paralytic muscular disorders like Duchenne muscular dystrophy, increase in sympathetic and a decrease in parasympathetic activity, and dysautonomia
Immune dysfunction
Neuroinflammation, immune deficiency and dysfunction
GI disorders
Chronic constipation, chronic diarrhea, eosinophilic esophagitis, gastroesophageal reflux and/or disease, nausea and/or vomiting, chronic flatulence, abdominal discomfort, ulcers, colitis, inflammatory bowel disease, food intolerance, and/or failure to thrive
Feeding disorders
Selective eating, difficulty swallowing, abnormal behaviors during meals such as ritualistic behaviour, throwing tantrums or gagging and vomiting
Allergic disorders
Asthma, nasal allergies, atopic diseases (immunoglobulin E-mediated), food allergies and intolerances
Toileting problems
Difficulties in learning how to use the toilet during the day and at night, knowing when they need to use the toilet, communicating the need to use the toilet, being able to get to the toilet independently or in time, learning to use different toilets with which they are unfamiliar, wiping themselves, sensory differences (dislike of the noise made by toilets, the sensation of passing urine/faeces, a cold toilet seat, or a preoccupation with water in the toilet), smearing faeces, a range of continence-specific difficulties, including bowel or bladder difficulties such as bedwetting and constipation

GENETIC DISORDERS

Certain known genetic disorders are associated with an increased risk of autism, including but not limited to Fragile X syndrome (FXS), Down syndrome (DS), Duchenne muscular dystrophy, neurofibromatosis type I (NF1), and tuberous sclerosis complex (TSC). It may be useful to view ASD as a cloud, representing the interaction of several different genetic and other etiologies that end with abnormal brain wiring. FXS is the most common cause of inherited intellectual disability; characterized by the presence of abnormal patterns of neural "wiring" or connectivity that leads to ASD symptoms, including impaired communications. FXS is the most common-known single-gene disorder in all ASD cases. It has been observed that about 2%-3% of all children with ASD cases have FXS, and about 25%-33% of FXS patients have ASD. Children with both FXS and ASD have higher rates of social anxiety, intellectual disability, hyperarousal, repetitive behaviors, and other FXS-related differences than those with ASD of unknown cause[6].

Only a small number of children with ASD may also have DS as DS is uncommon and occurs in only 1/800 births. On the other hand, ASD is relatively common in children who have DS; up to 40% of children with DS also have ASD[7]. Children with DS-ASD were more likely to have a history of developmental regression, including loss of language and social skills, poor communication skills (many children did not have meaningful speech or singing), self-injurious and disruptive behaviors (such as skin pulling, biting, and head hitting or banging), repetitive motor behaviors (such as teeth grinding, hand flapping, and rocking), unusual vocalizations (such as grunting, humming, and guttural sounds), unusual sensory responses (such as spinning, staring at lights, or sensitivity to certain sounds), feeding problems, (such as food refusal or strong preference for certain textures), increased anxiety, irritability, difficulty with transitions, hyperactivity, attention problems, and significant sleep disturbances[8,9]. Children with DS and ASD are more prone to other comorbidities such as congenital heart defects, anatomical abnormalities of the GI tract, neurological findings (*i.e.*, seizures, dysphagia, severe hypotonia, and motor delays), ophthalmological problems, and respiratory problems (*i.e.*, pneumonia and sleep apnea)[10].

There is a high prevalence of ASD in patients with dystrophinopathies. Duchenne muscular dystrophy is not only a muscle disease but also a disease that affects the brain. Any child with autism who has toe-walking should have creatine phosphokinase (CPK) levels determined to rule out Duchenne muscular dystrophy[11,12]. Some studies have shown that symptoms of autism are increased in patients with NF1, as well as a significant co-occurrence with symptoms of attention-deficit/hyperactivity disorder (ADHD)[13,14]. However, a recent study by Morotti *et al*[15] showed that only ADHD, not ASD, was more common in children with NF1 than in the general child population. They related the notion of increased ASDs in NF1 to increased use of autism questionnaire scores due to co-occurring ADHD symptoms. They found that adaptive behavior in patients with NF1 showed normal socialization but lower communication skills. TSC is a rare genetic multisystem disorder characterized by hamartoma formation in multiple organs and systems. It is one of the main syndromes associated with ASD; with a prevalence of ASD ranging from 26% to 45%. Therefore, children with TSC have an increased risk of developing ASD, which depends on the presence of several factors, including brain lesion burden, prominent lesion type, the tuber size and location, cyst-like tubers, presence of a *TSC2* mutation, early-onset and refractory seizures, and the presence and severity of cognitive impairment. Consequently, early termination of seizures may improve the neuropsychiatric outcome, at least in some cases[16,17]. Because of the increased incidence of genetic disorders in children with autism, any child diagnosed with ASD should have a consultation with a geneticist. Currently, there are therapeutic interventions for many of the genetic disorders that can help guide the treatment pathway and make a significant difference in helping children reach their full potential.

NEUROLOGICAL DISORDERS

Children with autism are more likely than the general population to have several neurological disorders, including epilepsy, macrocephaly, hydrocephalus, cerebral palsy, migraine/headaches, and congenital abnormalities of the nervous system. The behaviours of autism overlap with a variety of different neurological disorders, suggesting common molecular mechanisms[18]. Epilepsy is a brain disorder characterised by episodic, unpredictable changes in mental status with recurrent seizures or convulsions. Epilepsy, like autism, is increasingly described as a spectrum disorder. Up to 60% of children with autism have abnormal electroencephalogram (EEG), compared with 6%-7% in normal children and 10% to 30% of children with autism have epilepsy. At the same time, up to 8% of epileptic children have ASD. Therefore, autism is considered as a comorbidity to epilepsy, and epilepsy is considered as a comorbidity to autism. Both may occur together[19]. Severity of seizure activity varies from grand mal to subtle activities such as rapid eye blinking, zoning out, inattention for prolonged periods; with/without disturbed consciousness or even epileptic encephalopathies. At the same time, there is an increased incidence of epilepsy, autism, and intellectual disability simultaneously in some neurological disorders[20]. Infantile spasms have a high rate of intellectual disability and deficits in social communication are lower than expected for the child's intelligence or developmental quotient. Approximately 10%-15% of children with infantile spasms develop autism. A history of spasms is found in 6% of all children with ASD[21]. Children with TSC have very high rates of both epilepsy and ASD (40%). ASD is higher in children with

intellectual disability and the risk for ASD increases especially in children with epilepsy and with temporal lobe brain lesion[22]. Other neurological syndromes associated with high rates of both ASD and epilepsy include FXS, *CDKL5* gene (responsible to making a protein needed for normal brain development), Rett syndrome, and Angelman' syndrome.

The co-occurrence of epilepsy and autism is due to the presence of common pathogenic mechanisms. Synucleinopathy (abnormal accumulation of aggregates of alpha-synuclein protein in neurons, nerve fibers, or glial cells), synaptopathies (dysfunction of synapses in the brain, spinal cord, or peripheral nervous system), excitopathies (tetrad from epilepsy, ataxia, **s**ensorineural deafness, and a renal salt-wasting **t**ubulopathy), channelopathies, inflammation, and abnormal glial cell interaction are common underlying pathogenic mechanisms for autism and epilepsy[23]. Early-childhood seizures may also induce "autism-like" behaviour in rodents. Increased excitability in the developed brain causes impaired plasticity which in turn induces both cognitive deficits, autism, and epileptogenesis. Seizures, impaired neuroplasticity, and autism-like behaviours appear to cluster during early brain development, which may indicate a link between them[24]. Understanding and harnessing these relationships may help in autism treatment and biomarker discovery. The risk of developing epilepsy in children with ASD increases with the presence of intellectual disability, and with female gender. The risk of epilepsy in children with intellectual disability without autism is about 21.4%, which increases to 50% when both autism and intellectual disability are present. The risk of epilepsy also increases in the presence of temporal lobe pathology secondary to conditions such as TSC[25]. Distinguishing between seizures and seizure-free activities is challenging in children with autism, especially in the presence of learning disabilities and communication difficulties. Odd behaviours, stereotypy, aggressive behaviour, neurological deficits, self-injurious behaviour, and decreased responsiveness may be present in children with autism, whether they have epilepsy or not. Seizures can often manifest in various subtle ways, features, or behaviours that confound distinction between seizure-related from non-seizure related behaviours[26]. Therefore, any child with autism should be evaluated for the presence of seizures with an EEG for 24 h or longer by a paediatric neurologist. A video EEG is strongly recommended when autism is present with high intellectual disability (50% will have epilepsy) and when autism is associated with secondary conditions such as Angelman syndrome, DS, or tuberous sclerosis. Parents, friends, therapists, family members, and caregivers should know the signs, what a seizure looks like, and possible precursors to a seizure. It is also important to know that seizures can be fatal. If the child has recordable seizure activity, it is medically necessary to treat the seizure disorder[27].

Autonomic nervous system dysfunction is common in children with ASDs. An increase in sympathetic and a decrease in parasympathetic activity are commonly present in children and adults with ASDs, with/without the presence of obvious symptoms and/or signs of autonomic abnormalities. This autonomic imbalance may be evident in changes in heart rate and its variability, mean arterial and diastolic blood pressure, atypical pupillary light reflex, atypical autonomic response to anxiety, elevated plasma levels of nor-epinephrine suggestive of a chronic state of sympathetic nervous system hyperactivity, and lower baseline respiratory sinus arrhythmia suggestive of reduced vagal modulation[28]. Toe-walking is one of the common stereotypic motor movements observed in children with autism, aiming to reduce sensory overstimulation in the feet caused by walking on the whole foot. However, it could be related to the presence of motor coordination difficulties, a tight Achilles tendon, or a sensory processing difference. Toe-walking is also seen in other neurological or developmental disorders, such as cerebral palsy, and paralytic muscular disorders like Duchenne muscular dystrophy. Any child with autism who has toe-walking should have a CPK level to rule out Duchenne muscular dystrophy[29].

Toileting is an important skill necessary for independent living. Therefore, incontinence is a significant barrier to good quality of life for people with autism. Lower cognition and verbal levels correlate significantly with the age at which bowel and urine training is completed in children with autism[30]. Approximately 30% of children with autism have anxiety related to toileting, with verbally impaired individuals having the most. Children with autism have potty training problems due to sensory hypersensitivity, communication problems, self-confidence problems, and short-attention-span. The most common problems with toileting were urinating in places other than the toilet, constipation, clogging the toilets, constant flushing, and smearing. Unfortunately, children with toilet training problems are at more risk of public embarrassment, punishment, and loss of self-esteem. In addition, children who do not use the toilet by age 5 tend to lose control of their bladder. Children with lower

adaptive functioning were associated with greater toileting problems[31,32].

SLEEP DISORDERS

Sleep disorders are significant problems in individuals with autism, present in about 80% of them. Sleep disturbances are one of the most common concerns reported by parents of children with autism; because sleep affects not only the children, but their families as well. Sleep problems can cause difficulty falling asleep, inability to sleep in a flat position, nighttime reawakenings, sleepwalking, learning problems, hyperactivity, inattention, anxiety, aggression, and various health problems. It could be due to hormonal imbalances, GI disorders, seizure activity, poor sleep environment, sleep apnea, or as a side effect of some medications commonly used to treat autistic symptoms. Polysomnographic studies of children with ASD showed that most of their abnormalities are related to rapid eye movement sleep (REM), which includes decreased quantity, increased undifferentiated sleep, immature organization of eye movements into discrete bursts, decreased time in bed, total sleep time, REM sleep latency, and increased proportion of stage 1 sleep[33]. The sleep community has identified autism as a priority population for targeted interventions for sleep disorders. Poor sleep affects the health of the individual and daily functioning, as well as the integrity of the family. Sleep disorders are highly treatable. Therefore, evidence-based standards of care for monitoring, assessing, and treating sleep disorders in children with ASDs are of great importance[34]. Sleep disorders have been found to be associated with GI dysfunction in children with ASDs. About 24.5% of a sample of children with ASDs had both chronic GI symptoms and sleep problems. Chronic GI symptoms were independently associated with increased sleep disturbance. Sleep problems were most common in children with GI symptoms (50%) than in children without (37%)[35,36]. Poor sleep causes a higher percentage of behavioural problems (such as stereotypy and self-injurious behaviour) than observed with good sleep. Medication use, sleep problems, and anxiety explained 42% of the variance in challenging behaviour, with sleep problems being the strongest predictor. Stereotypic behaviour may be predicted in the presence of fewer hours of sleep per night and crying at night[37]. The implementation of non-pharmacotherapeutic interventions such as bedtime routines and sleep-appropriate approaches is the mainstay of behavioural management. Treatment strategies along with limited regulated pharmacotherapy can help improve the quality of life of children with ASD and have a positive effect on the family[33].

GI DISORDERS

GI Problems are significantly more common in patients with ASD, occurring in 46% to 84% of autistic children. The most common GI problems observed in children with ASD are chronic constipation, chronic diarrhoea, gastroesophageal reflux and/or disease, nausea and/or vomiting, chronic flatulence, abdominal discomfort, ulcers, colitis, inflammatory bowel disease, food intolerance, and/or failure to thrive. Food allergies are more common in children with ASDs, reaching up to 20%-25% compared to 5%-8% in the general paediatric population[38]. Common mechanisms for GI disorders in children with ASDs include immune dysfunction, gut inflammation, microbiota dysregulation and dysbiosis, dietary metabolites, and/or dysautonomia. Insistence on sameness can lead sufferers to demand stereotypical diets, that can lead to inadequate intake of fiber, fluids and other foods, which can cause GI symptoms. Some medications can affect bowel function; for example; stimulants can cause abdominal pain, and βeta-blockers can cause diarrhoea, constipation and stomach irritation[39].

These GI disorders can cause pain and discomfort to and interfere with learning in individuals with ASD. Unrecognized GI disorders; specifically reflux esophagitis and disaccharide malabsorption may contribute to behavioural problems in children with nonverbal autism. These behavioural problems may present as posturing, self-injury, or outbursts with no apparent causes. Unfortunately, these manifestations can be overlooked as a behavioural problem rather than a medical condition, especially since many children with autism are unable to effectively communicate their symptoms or express discomfort to their doctors. Lactase deficiency not associated with intestinal inflammation or injury is common in children with autism and may contribute to abdominal discomfort, pain, and observed behavioural problems[40]. At the same

time, GI symptoms are difficult to diagnose in ASD because there are no clinical practice guidelines that provide for routine consideration of possible GI symptoms or other medical conditions in patients with ADS. These guidelines are especially needed because many individuals with ASD are nonverbal and cannot express pain or discomfort through language, and they cannot communicate symptoms as clearly as their typically developing peers. Even those who can communicate verbally may have difficulty describing subjective experiences or symptoms. Healthcare professionals should consider the possibility of the presence of GI dysfunction in patients with ASD, especially those who present with odd postures or movements, sleep disturbances, food intolerances, and aggressive or self-injurious behaviours. For this reason, clinicians should obtain a proper GI/nutritional history that includes eating patterns, presence of allergies and food intolerances, and stool patterns[41]. Sleep history is very important as many underlying GI disorders can manifest in sleep pattern[36]. Clinicians should review the child's growth across the lifespan, medication, and sleep history. They should also be able to identify vocal or motor behaviours that may reflect the presence of pain or GI disorders. Common vocal behaviours that may be associated with the presence of GI disorders (such as gastroesophageal reflux disease, eosinophilic esophagitis, or allergic esophagitis), including but not limited to throat-clearing behaviours, guttural vocalizations, spitting up in infants, ear rubbing, habitual coughing, and/or difficulty swallowing. Motor behaviours associated with the presence of GI disorders include seeking belly pressure, some pointing behaviours, neck or body posture, certain repetitive behaviours, aggressive or self-injurious behaviours. There is a strong correlation between aggressive behaviours and underlying GI disorders[42].

The strong correlation of GI symptoms with the autism severity suggests that children who have more severe autistic features are more likely to have severe GI symptoms. Symptoms of GI disorder are more likely to be associated with sleep disturbances and food intolerances. Therefore, it is important to consider this association when assessing and treating these comorbidities. Clinicians should screen for constipation, diarrhoea, or soiling of underwear in children with ASD who have prominent rigid–compulsive symptoms[43]. Paediatricians should refer children with autism for GI evaluation in the presence of eczema, vocal or motor signs, aggressive or self-injurious behaviours, chronic constipation or diarrhoea, and chronic spitting or vomiting. Increased intestinal permeability is a common finding in children with ASD; especially those who present with GI symptoms. Although it is a real challenge, measurement of intestinal permeability can be done by measuring plasma zonulin level, which is a valuable blood marker to evaluate abnormal intestinal permeability[44]. Endoscopy may reveal signs of allergic esophagitis, acid reflux damage, allergic changes, or evidence of inflammatory bowel disease in patients with ASD and abdominal manifestations[45]. If the GI disorder is recognized and medical treatment is effective, the behavioural problem may improve. If abdominal pain or discomfort is a framing event, psychotropic medications are unlikely to be effective and may even exacerbate the problem if they have adverse GI effects. The emerging concept of a microbiota-gut-brain axis suggests that modulation of the gut microbiota may be a tractable strategy for developing new therapeutics for complex CNS disorders[46].

Despite studies finding no higher prevalence of celiac disease (CD) in ASD, one child per 68 children with CD will develop autism, and one child per 130 children with autism will develop CD. There is a strong association between CD—even in the absence of GI symptoms—and epilepsy, and cerebral calcifications, as well as positive responses to dietary changes in these patients. Investigation and treatment of CD, non-celiac gluten sensitivity (NCGS), and epilepsy—even in the absence of typical GI symptoms or overt seizures—could potentially yield good outcomes for patients with ASD[47]. Since children with ASD are more likely to have atopy and allergies, possible NCGS or wheat sensitivity must be considered in these children, especially if irritable bowel symptoms are present[48]. In children with unclear neurological manifestations with probable autoimmune etiology, transglutaminase-2 autoantibody titer should be determined considering the possibility of gluten sensitivity. The gluten-free diet remains the only effective treatment reported to date. Therefore, it should be recommended to all patients with gluten sensitivity, regardless of the type of manifestations. Medical professionals should be aware of the possibility of the presence of NCGS in some patients with ASD; especially those presenting with atopic disease, migraine, mood and anxiety disorders. Many children with autism do very well on a gluten-free, soy-free, and dairy-free diet. However, this diet should not be attempted until a celiac test has been performed[49].

METABOLIC DISORDERS

Metabolic disorders are inborn errors of metabolism (*i.e.*, a single-gene metabolic disorder) that can affect the synthesis or functions of proteins (*e.g.*, enzyme), fats, or carbohydrates, resulting in accumulation or deficiency of certain metabolites and consequently the appearance of certain symptoms and signs, depending on the metabolic pathway affected. Several categories of inborn errors of metabolism have been observed in some patients with autism including mitochondrial disorders, disorders of creatine metabolism, selected amino acid disorders, disorders of folate or vitamin B12 metabolism, and selected lysosomal storage disorders[50]. Mitochondrial dysfunction is one of the relatively common metabolic disorders in patients with autism. Recent studies have increasingly associated mitochondrial dysfunction with ASD, with a prevalence rate of 5% in patients with autism. Since the mitochondria are the "powerhouse of the cell" and produce most of the cellular energy, they play an integral role in various cellular functions, especially for the brain as it has very high energy demands. Consequently, mitochondria are prone to many insults, which explains how a variety of factors may contribute to a consistent behavioural phenotype in ASD[51].

Many clues could help to identify the presence of metabolic disorders in patients with ASD. Patients with metabolic disorders may have unexplained fatigue and usually become very ill (unusually lethargic) with prolonged recovery time from illnesses that do not usually cause significant illness. They may also have developmental regression during/after the illness. Metabolic disorders are usually multisystem disorders that affect many organs and present with various problems such as seizures, sensorineural hearing loss, renal tubular problems, or unexplained cardiac myopathy. It is important to look for signs of multisystem involvement such as growth abnormalities, abnormalities of head circumference and its change over time, possible cardiac involvement (*e.g.*, heart murmur), possible organomegaly or other abdominal pathology, hypermobile or stiff joints, and signs of possible autonomic dysfunction. Neurologic manifestations are very common in inborn errors of metabolism. Common neurological manifestations include developmental or neurologic regression, encephalopathy, seizures, abnormal ocular findings including extraocular movement, abnormalities of muscle tone (hypotonia, hypertonia, and dystonia), abnormalities of deep tendon reflexes, and movement disorders (*e.g.*, ataxia, myoclonus)[52,53].

Some laboratory findings may help predict the presence of comorbid metabolic disorders in children with autism. Abnormal blood count such as anaemia, abnormal mean corpuscular volume (high in vitamin B12 or folate deficiency or disorders), neutropenia and/or thrombocytopenia could be a clue[54]. Abnormal blood chemistry is another important clue. It may include the presence of hypoglycaemia, hyperglycaemia, ketosis, hyperammonemia, lactic acidaemia, abnormal serum bicarbonate, abnormal anion gap, abnormal plasma amino acid levels, and abnormal lactate or pyruvate. Urine analysis may elaborate enormous information including the urine pH, urinary glucose, abnormal urinary organic acids such as lactic aciduria, elevated levels of Krebs cycle intermediates, 3-methyl glutaric acid, metabolites that suggest impaired mitochondrial fatty acid oxidation, or unexplained ketonuria. Almost one-third of children with autism have elevated plasma lactate and/or the lactate-to-pyruvate ratio, and elevated levels of many other mitochondrial biomarkers (pyruvate, carnitine, and ubiquinone) with significant differences between ASD and controls[55].

IMMUNE, AUTOIMMUNE, AND ALLERGIC DISORDERS

A significant proportion of children with ASD have evidence of persistent neuroinflammation, altered inflammatory responses, and immune abnormalities. Approximately 25% of children with ASD have immune deficiency and dysfunction. Most children with autism do not have symptoms of immune dysregulation, so it is important to perform laboratory testing to rule this out[56]. Children who have GI disorders are more likely to have immunodeficiency. Testing for immunodeficiency and dysfunction is very simple and inexpensive. Laboratory tests can include immunoglobulin G (IgG) subclasses, total IgG, and quantitative immunoglobulin[57]. To treat immunodeficiency, intravenous immunoglobulin could be given every 3-4 wk. With this treatment, some children with autism experience cognitive progress and improvement in language and social skills[58]. Some studies also showed that anti-brain antibodies may play an important pathoplastic mechanism in autism. Prenatal

and/or postnatal exposure to these antibodies may increase the severity of autism by impairing cognitive processes and adaptive functions, increasing motor stereotypies, altering the sleep-wake cycle, and delaying or halting neurodevelopment, especially as it relates to verbal and nonverbal language. Therefore, anti-brain antibodies can be used as biomarkers that predict the severity of autism and the clinical features of ASD; and potentially provide new avenues for preventive and therapeutic strategies[59]. At the same time, children with autism who have high titers of seropositive systemic antibodies should be clinically followed up at regular intervals to detect the possible development of symptoms and signs of systemic autoimmune diseases. In the meantime, treatment of CNS or peripheral infections, such as those in the GI system or sinuses, calming of autoimmune responses, or discontinuation of therapy with inflammation-inducing agents often leads to reversal and normalization of behaviours, and restoration of normal brain function[60].

Allergic disorders are significantly more common in people with ASD from all age groups. They influence the development or severity of symptoms and induce problematic behaviours in at least a subset of the affected individuals. Various allergic manifestations such as asthma, nasal allergies, atopic diseases (IgE-mediated), food allergies and intolerances may occur in children with ASD[61]. There is a positive association between the frequency and severity of allergic manifestations and the severity of autism. Discomfort and pain associated with allergic conditions exacerbate behavioural symptoms. Allergic neuroimmune activation may, in some cases, underlie core autism symptoms and behavioural problems. Therefore, treatment of allergies can lead to improvement in negative and challenging behaviours and improve overall functioning[38]. Allergic irritability syndrome is a brief, measurable approach to define the decreased ability to concentrate, bouts of irritability, and temper tantrums that occasionally occur as a complication of allergic rhinitis. We should consider the possibility of the presence of allergic and non-IgE hypersensitive conditions in any child or adult with autism who presents with irritability or increased aggressiveness, anxiety, inability to fall asleep or stay asleep, inability to concentrate, hyperactivity, and daytime fatigue[62]. It should be noted that commonly used allergy tests do not always detect allergy; therfore a comprehensive clinical history and physical examination are also important to assess the possibility of allergies or food intolerances[62]. Treatment of allergies can improve negative and challenging behaviours and lead to better overall functioning.

EMERGENCY ROOM AND OUTPATIENT GUIDELINES

Children with ASDs have a 30% higher risk of medical emergencies than their unaffected peers. This risk increases to 70% in teens between the ages of 15 and 18 years. The emergency department setting is in itself a real challenge for any clinician[63]. These settings become even more difficult when dealing with children with autism due to many barriers including communication and behavioural problems and anxiety. These children are also more vulnerable to inappropriate treatment[64,65]. Taken together these challenges can make the experience in the emergency room (ER) overwhelming and potentially traumatic for a child with autism and his or her family. Therefore, parents of children with autism should prepare a list of guidelines/concerns in advance with the support of the medical team[66]. At the same time, additional education and training of the emergency team and other hospital staff in dealing with children with ASD is needed. Table 2 showed the criteria of autism friendly Emergency Department. Improving staff knowledge, skills, approach, and confidence is the most important factor in minimizing the risk for inappropriate emergency management of children with ASD. Implementing patient- and family-centred care emerges as a priority for optimising ER care[67]. Environmental adaptations can have a direct impact on how comfortable children with ASD feel when they come to ER. These changes can be as small as ensuring the availability of calming objects, such as toys, books, activities, allowed snacks, and electronics such as iPads. Improvements could also include separate, quieter waiting areas with dim lighting for children with ASD where they can receive the attention they need while feeling safe and less anxious[68,69]. The outpatient setting should meet the necessary requirements for care coordination for children with autism with multiple waiting areas so that children can seclude themselves when they are anxious or fearful. It should be quiet with as little noise, dim lights, toys, and activities as possible to avoid agitating the children. Children should be explained and shown beforehand what the doctor will be doing. If a procedure is planned, such as a dental procedure, parents should

Table 2 Criteria of "Autism Friendly Emergency Department"

Staff
Available staff with additional training in autism management, and stakeholder engagement
Staff education includes awareness about sensory sensitivity, communication, and pain threshold, as well as how to interact with patients
Parenting with the experts
Minimizing the number of personnel to only the essential
Able to gain as much information as possible from both the patient and the caregiver
Facilities
Calming environment with offering calming objects like toys and iPads, or sending patients to separate, quieter waiting rooms and using dimmer lighting and noise control system
Special waiting room with calming toys and suitable TV shows
Short waiting time when possible
Available quiet examination room
Available admission questionnaire or checklist to help the physician discovered disorders that are difficult to be detected in children with autism
Well design exam room and treatment area to help motivate the children to stay in the room
Available sensory equipment to use such as ear defenders, sensory boxes filled with various sensory items, Picture Exchange Communication System cards, sensory toys (*e.g.*, squeezy balls), social stories, and communication aids
Available items to provide support, comfort, and security, including compression vests, blankets. and noise reduction earmuffs
Avoiding using sensory stimuli such as clutter, loud equipment, bright or fluorescent lighting
Parents
The use of one-page autism alert card or patient passport to provide emergency physicians with the needed information
Adequate partnership with parents
Family-centered care
The caregiver should be the guide to success
Medications and instruments
When choosing a medication, sensory issues such as taste or smell, textures, and temperature of treatment materials should be considered
The child should be exposed to and to touch all materials prior to using them if possible
The intervention can be modelled on the caregiver
Splints or bandages can be covered with non-threatening images

attend the appointment in advance[70].

CONCLUSION

Comorbidities are more common in children with ASDs than in the general population. Some genetic disorders are more common in children with ASD, such as FXS, DS, Duchenne muscular dystrophy, NF- type I, and TSC. Children with autism are more likely than the general population to have several neurological disorders. Sleep disorders are significant problems in individuals with autism, present in about 80% of them. GI problems are significantly more common in children with ASD, occurring in 46% to 84% of autistic children. Several categories of inborn errors of metabolism have been observed in some patients with autism including mitochondrial disorders, as well as other disorders. Some children with ASD have evidence of persistent neuroinflammation, altered inflammatory responses, and immune abnormalities. Anti-brain antibodies may play an important pathoplastic mechanism in autism. Allergic disorders are significantly more common in ASD and run through all age groups. The physician should rule out any medical concerns before moving on to other interventions or therapies. Children who enjoy good health have a better chance of learning. This can apply to all children, including those with autism.

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ORIGINAL ARTICLE

Retrospective Study

Repetitiveness of the oral glucose tolerance test in children and adolescents

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Abstract

BACKGROUND

Data regarding the most suitable diagnostic method for the diagnosis of glucose impairment in asymptomatic children and adolescents are inconclusive. Furthermore, limited data are available on the reproducibility of the oral glucose tolerance test (OGTT) in children and adolescents who are obese (OB).

AIM

To investigate the usefulness of the OGTT as a screening method for glucose dysregulation in children and adolescents.

METHODS

Eighty-one children and adolescents, 41 females, either overweight (OW), OB or normal weight (NW) but with a strong positive family history of type 2 diabetes mellitus (T2DM), were enrolled in the present observational study from the Outpatient Clinic of Paediatric Endocrinology of the University Hospital of Patras in Greece. One or two 3-h OGTTs were performed and glucose, insulin and C-peptide concentrations were measured at several time points (t = 0 min, t = 15 min, t = 30 min, t = 60 min, t = 90 min, t = 120 min, t = 180 min).

RESULTS

Good repetitiveness was observed in the OGTT response with regard to T2DM, while low repetitiveness was noted in the OGTT response with regard to impaired glucose tolerance (IGT) and no repetitiveness with regard to impaired

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fasting glucose (IFG). In addition, no concordance was observed between IFG and IGT. During the 1st and 2nd OGTTs, no significant difference was found in the glucose concentrations between NW, OW and OB patients, whereas insulin and C-peptide concentrations were higher in OW and OB compared to NW patients at several time points during the OGTTs. Also, OW and OB patients showed a worsening insulin and C-peptide response during the 2nd OGTT as compared to the 1st OGTT.

CONCLUSION
In mild or moderate disorders of glucose metabolism, such as IFG and IGT, a diagnosis may not be reached using only one OGTT, and a second test or additional investigations may be needed. When glucose metabolism is profoundly impaired, as in T2DM, one OGTT is probably more reliable and adequate for establishing the diagnosis. Excessive weight and/or a positive family history of T2DM possibly affect the insulin and C-peptide response in the OGTT from a young age.

Key Words: Oral glucose tolerance test; Obesity; Impaired fasting glucose; Impaired glucose tolerance; Children; Adolescents

Core Tip: In mild or moderate disorders of glucose metabolism, such as impaired fasting glucose and impaired glucose tolerance, a diagnosis may not be reached using only one oral glucose tolerance test (OGTT), and a second test or additional investigations may be needed, whereas when glucose metabolism is profoundly impaired, as in type 2 diabetes mellitus, one OGTT is probably more reliable and adequate for establishing the diagnosis. Also, overweight and obese patients showed a worsening insulin and C-peptide response during the 2nd OGTT as compared to the 1st OGTT.

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INTRODUCTION

The prevalence of obesity during childhood and adolescence shows an alarmingly increasing trend worldwide. Obesity is highly correlated with a constellation of disorders, including impaired glucose metabolism manifesting as impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM)[1].

With regard to the diagnosis of T2DM, recommendations of the American Diabetes Association (ADA) involve measurement of fasting plasma glucose as a screening method because of its availability and ease of performance[2]. Rocchini[3] has suggested that the oral glucose tolerance test (OGTT) may be a useful screening tool for diagnosing impaired glucose in children and for identifying those at high risk for diabetes, due to the low variation between people. However, the International Diabetes Federation Consensus Workshop on Type 2 Diabetes in the Young recommends further investigations in order to determine the role of the OGTT in screening asymptomatic young people[4].

In adults, the OGTT is considered to be superior to fasting glucose (FG) for the identification of subjects at increased risk for cardiovascular disease; however, the ADA recommends a second OGTT to confirm the diagnosis of T2DM, due to its low reproducibility[5]. Limited data are available on the reproducibility of the OGTT in obese (OB) children.

The objective of the present study was to investigate the possible repetitiveness of the response to repeat OGTTs and assess its diagnostic and prognostic value in children and adolescents with excess weight or a strong family history of T2DM.

MATERIALS AND METHODS

A total of 81 children and adolescents, 41 females, who were determined to be overweight (OW), OB or with a strong positive family history of T2DM (defined as more than 3 individuals within three generations), were enrolled in the study from the Outpatient Clinic of Paediatric Endocrinology and Diabetes of the University Hospital of Patras in Greece, during a period of 5 years. Fifty-five out of the 81 patients (67.9%) were OB, 17 (21%) were OW and 9 (11.1%) had a normal weight (NW) but a positive family history of T2DM. The participants were randomly selected. The research was approved by the Research Ethics Committee of the University Hospital of Patras (IRB number: 348/9.5.2017) and informed consent was obtained from the parents of the children involved in the study. OW was defined as a body mass index (BMI) of 85%-95% and OB as a BMI of > 95%. The mean age of the studied subjects was 12.27 + 2.96 years (min: 4.91 years, max: 21.25 years).

A 3-h OGTT was performed in all patients. After the administration of oral glucose at a dose of 1.75 g/kg (max: 75 g), blood samples were obtained at t = 0 min, t = 15 min, t = 30 min, t = 60 min, t = 90 min, t = 120 min and t = 180 min, and glucose, insulin and C-peptide concentrations were measured. C-peptide concentrations were measured for 28 subjects, due to cost restrictions, 23 of the participants underwent 2 OGTTs (6 with NW, 4 OW and 13 OB). Three-hour OGTTs were performed in the studied population as it has been our experience that the 3-h OGTT can identify the children who have a delayed insulin response and are able to normalize their glucose levels at the 3-h time-point if they have an abnormal glucose response at the 2-h point. Other groups have also found that 3 h is a better duration for an OGTT to capture the full spectrum of glucose and insulin excursions in youth[6,7].

The OGTT was repeated in order to assess the glucose, insulin and C-peptide response in OB and OW patients, who did not manage to achieve a significant weight loss and agreed to undergo a second OGTT during the study period.

IFG was defined as plasma glucose between 100 mg/dL and 125 mg/dL at time 0 min (t = 0 min) and IGT as plasma glucose between 140 mg/dL and 199 mg/dL at 120 min (t = 120 min). T2DM was defined as plasma glucose at time 0 min > 125 mg/dL and plasma glucose at 120 min ≥ 200 mg/dL[8].

Weight, height and pubertal development were assessed in all the participants. Tanner stages in the boys were correlated with testicular volume as follows: (1) Tanner I: < 4 cm^3; (2) Tanner II: 4-8 cm^3; (3) Tanner III: 10-12 cm^3; (4) Tanner IV: 15-20 cm^3; and (5) Tanner V: 20-25 cm^3.

Fasting plasma glucose was assessed by the hexokinase method with the use of a biochemical analyzer (Olympus AU600). Insulin concentrations were measured with the Electro-Chemiluminescence immunoassay method and the E170 Immunology Analyzer by Roche was used for the process. C-peptide was determined by radio-immunoassay (Merck KGaA, Darmstadt, Germany).

Statistical analysis

Data are presented as mean ± SD for normally distributed continuous variables. Comparisons of the glucose, insulin and C-peptide concentrations between the OGTTs were made using the Mann Wilcoxon test for unpaired data and the Wilcoxon Signed Rank test for paired data. Correlations between glucose, insulin or C-peptide concentrations and BMI or age were assessed with Spearman's rho correlation coefficient. The threshold for statistical significance was defined as $P \leq 0.05$. All analyses were performed with the SPSS Statistical Software Package (IBM SPSS Statistics, version 24, Chicago, IL, United States).

RESULTS

Of the 23 patients who underwent 2 OGTTs, the mean age during the 1st OGTT was 12.46 years and during the 2nd OGTT it was 14.55 years.

Patients with pathological glucose response during the OGTTs

Of the entire population, during the 1st OGTT there were 2 patients (2.4%) who had IFG (1 NW and 1 OW), 5 patients (6.1%) who had IGT (2 NW and 3 OB) and 2 patients (2.5%) who had T2DM (1 OB patient who had T2DM based on glucose concentrations of > 125 mg/dL at t = 0 min, and 1 NW patient who had T2DM based on glucose concentrations of > 125 mg/dL at t = 0 min and > 200 mg/dL at t = 120 min) (Table 1).

The 2 patients who had IFG during the 1st OGTT underwent 2 OGTTs in total and had normal FG during the 2nd OGTT. Of the 5 patients with IGT during the 1st OGTT, only 1 OB patient also had IGT during the 2nd OGTT (repetitiveness: 20%). The OB patient who had a glucose concentration of > 125 mg/dL during the 1st OGTT also had a glucose concentration of > 125 mg/dL during the 2nd OGTT. The NW patient who had a glucose concentration of > 125 mg/dL at t = 0 min and > 200 mg/dL at t = 120 min during the 1st OGTT, had IFG and glucose concentrations of > 200 mg/dL at t = 120 min during the 2nd OGTT (Table 1).

Only one of the 2 patients who fulfilled the criteria for T2DM based on the t = 0 min criterion, also fulfilled the criteria for T2DM based on the t = 120 min criterion. No concordance was observed between IFG and IGT, as of the 5 patients with IGT, none had IFG.

As previously mentioned, 4 of the 5 subjects who had IGT during the 1st OGTT, had normal glucose concentrations at t = 120 min during the 2nd OGTT.

In the 2 patients with IFG, IFG was not present in both OGTTs. In contrast, FG remained abnormal in the patients with T2DM.

The number of patients with IFG, IGT or T2DM during the 1st or 2nd OGTT in whom the glucose disorder was confirmed in both OGTTs is shown in Table 2.

Pathological glucose response during the OGTTs, by weight status

NW patients: These patients increased their BMI-SDS (no statistically significant difference, P > 0.05) by 0.37, but retained a normal weight.

During the 1st OGTT, one patient had IFG (106 mg/dL), two patients had IGT (142 mg/dL and 146 mg/dL, respectively), and one patient fulfilled the criteria for T2DM based on both FG [Glu (t = 0 min): 128 mg/dL] and glucose at t = 120 min (Glu: 211 mg/dL). The patient with IFG did not have IGT or T2DM.

During the 2nd OGTT, one patient had IFG (Glu: 122 mg/dL), the same one who had T2DM during the 1st OGTT. The patient who had IFG during the 1st OGTT did not have IFG or T2DM during the 2nd OGTT. Also, one patient had T2DM (t = 120 min, Glu: 244 mg/dL). This is the same patient who had T2DM during the 1st OGTT. No patients had IGT.

OW patients: The OW patients increased their BMI-SDS by 0.23, but remained overweight.

During the 1st OGTT, one patient had IFG, with a borderline glucose concentration at t = 0 min of 100 mg/dL. None of the patients had IGT or T2DM. During the 2nd OGTT, one patient had IGT. This patient did not have IFG, IGT or T2DM during the 1st OGTT. None of the OW patients had IFG or IGT.

OB patients: The OB patients showed no statistically significant changes in the BMI-SDS between the 1st and 2nd OGTT (P > 0.05).

During the 1st OGTT, one patient had T2DM based on glucose at t = 0 min (Glu: 142 mg/dL) and 3 patients had IGT (Glu: 185 mg/dL, Glu: 157 mg/dL, Glu: 168 mg/dL). During the 2nd OGTT (n = 19), two patients had IGT, one of whom also had IGT during the 1st OGTT, and no patients had IFG and 1 patient had T2DM (the same one with T2DM during the 1st OGTT).

Of the 2 patients with T2DM, one was of normal weight, but with a positive family history of T2DM (Tanner III, 14 years old), and the second was OB (Tanner II and 7.75 years old).

Results of glucose, insulin and C-peptide concentrations, by weight status

During the first OGTT, no statistically significant difference was found in the glucose concentrations between the NW, OW and OB patients (Figure 1A). Insulin concentrations were significantly higher in the OW compared to the NW patients at t = 15 min, t = 60 min, as well as in OB compared to NW patients at t = 15 min, t = 60 min, t = 90 min, t = 120 min and in OB compared to OW patients at t = 15 min, t = 30 min, t = 60 min, t = 90 min, t = 120 min (Figure 1B). C-peptide concentrations were signi-ficantly higher in OW compared to NW patients at t = 15 min, t = 30 min, t = 60 min, t = 90 min, t = 120 min and in OB compared to NW patients at t = 0 min, t = 15 min, t = 30 min, t = 60 min. C-peptide concentrations were also lower in OB compared to OW

Table 1 Repetitiveness of the oral glucose tolerance test among the patients who had impaired fasting glucose, impaired glucose tolerance or type 2 diabetes mellitus during the 1st oral glucose tolerance test

Number of patients	IFG	IGT	T2DM
1st OGTT	2	5	2
2nd OGTT	0	1	2
Repetitiveness (%)	0/2 (0)	1/5 (20)	2/2 (100)

IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; T2DM: Type 2 diabetes mellitus; OGTT: Oral glucose tolerance test.

Table 2 Repetitiveness of the oral glucose tolerance test among the patients who had impaired fasting glucose, impaired glucose tolerance or type 2 diabetes mellitus during the 1st or 2nd oral glucose tolerance test

Number of patients	IFG	IGT	T2DM
1st or 2nd OGTT	3	8	2
Confirmation of results in both OGTTs	0	2	2
Repetitiveness (%)	0/3 (0)	2/8 (25)	2/2 (100)

IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; T2DM: Type 2 diabetes mellitus; OGTT: Oral glucose tolerance test.

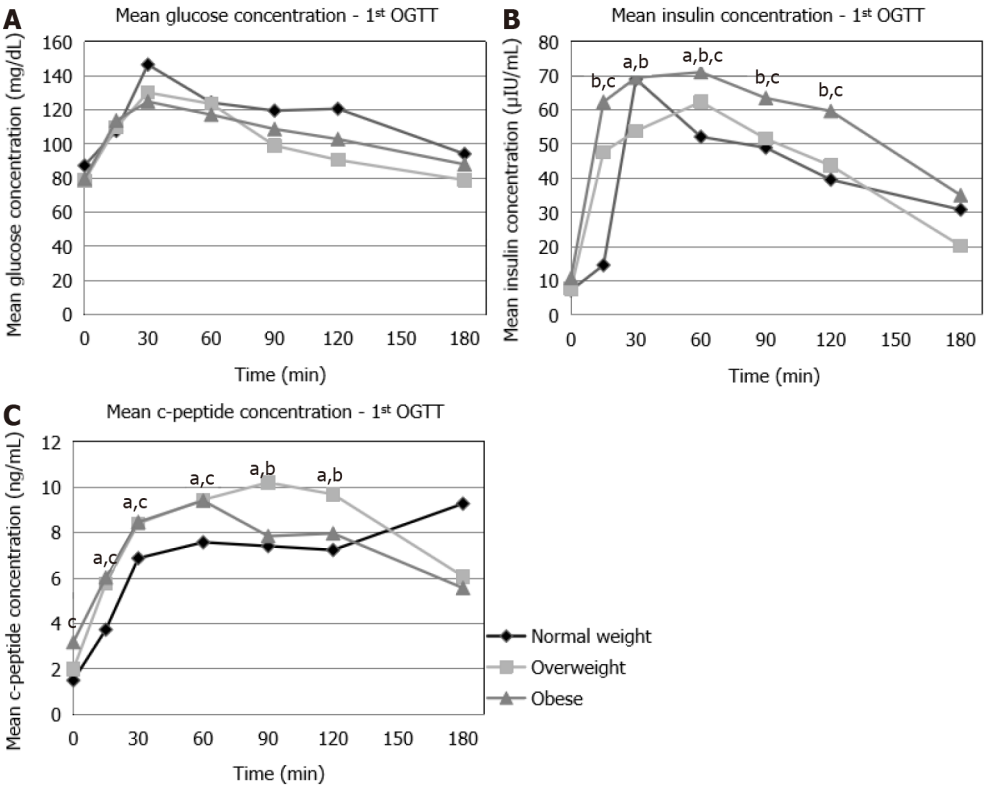

Figure 1 Parameters measured during the 1st oral glucose tolerance test in normal weight patients, overweight patients and obese patients. A: Mean glucose concentrations; B: Mean insulin concentrations; C: Mean C-peptide concentrations. [a]*P* < 0.05, overweight *vs* normal weight; [b]*P* < 0.01, obese *vs* overweight; [c]*P* < 0.001, obese *vs* normal weight. OGTT: Oral glucose tolerance test.

patients at *t* = 90 min and *t* = 120 min (Figure 1C).

During the 2nd OGTT, no statistically significant differences were observed in the glucose concentrations between the NW, OW and OB patients (Figure 2A). Insulin concentrations were significantly higher in OW (*t* = 15 min, *t* = 30 min, *t* = 60 min, *t* = 90 min, *t* = 120 min) and in OB (*t* = 15 min, *t* = 30 min, *t* = 60 min, *t* = 90 min, *t* = 120 min) compared to NW patients (Figure 2B). C-peptide concentrations were also

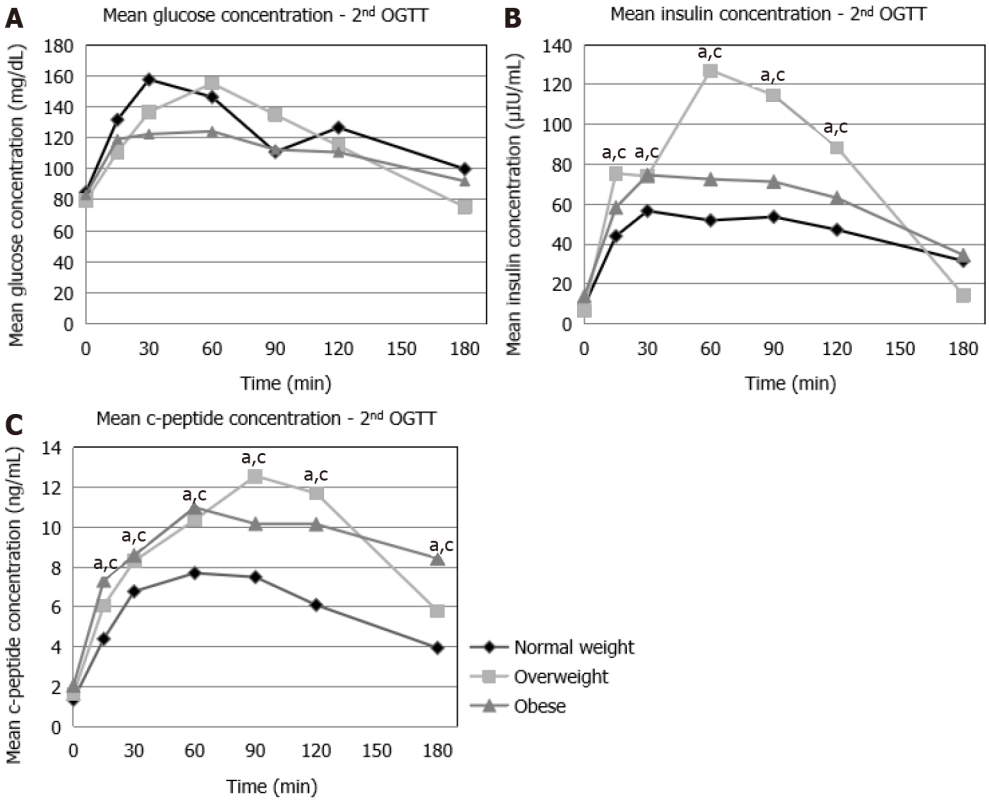

Figure 2 Parameters measured during the 2nd oral glucose tolerance test in normal weight patients, overweight patients and obese patients. A: Mean glucose concentrations; B: Mean insulin concentrations; C: Mean C-peptide concentrations. [a]*P* < 0.05, overweight *vs* normal weight; [c]*P* < 0.001, obese *vs* normal weight. OGTT: Oral glucose tolerance test.

significantly higher in OW and in OB (t = 15 min, t = 30 min, t = 60 min, t = 90 min, t = 120 min, t = 180 min) compared to NW patients (Figure 2C).

When glucose, insulin and C-peptide concentrations were compared for each BMI category between the different OGTTs, the results were as follows:

NW: No statistically significant differences were observed in the glucose concentrations between the 1st and 2nd OGTT (Figure 3A). No statistically significant differences were observed in the insulin concentrations between the 1st and 2nd OGTT, with the exception of t = 15 min, which was higher in the 2nd OGTT (Figure 3B). No statistically significant differences were observed in the C-peptide concentrations between the 1st and 2nd OGTT, with the exception of t = 180 min, which was lower in the 2nd OGTT (Figure 3C).

OW: A significant increase was seen in the glucose (t = 60 min, t = 90 min and t = 120 min), insulin (t = 60 min, t = 90 min and t = 120 min) and C-peptide (t = 90 min, t = 120 min) concentrations in the 2nd OGTT compared to the 1st OGTT (Figure 4).

OB: No statistically significant differences were observed in the glucose concentrations between the 1st and 2nd OGTTs at all time points (Figure 5A). Insulin concentrations showed no statistically significant difference between the 1st and 2nd OGTTs (Figure 5B). C-peptide concentrations were significantly higher during the 2nd OGTT compared to the 1st OGTT at t = 15 min, t = 60 min, t = 90 min, t = 120 min, t = 180 min) (Figure 5C).

DISCUSSION

Our study suggests that a reliable diagnosis of disorders of glucose metabolism, such as IFG and IGT, may not be possible using only one OGTT; hence, a second test or additional investigations may be needed to confirm the diagnosis. It may be that in the case of patients with profoundly impaired glucose metabolism, as in the case of T2DM, one OGTT is probably more reliable and adequate for establishing the diagnosis, whereas in mild or moderate disorders of glucose metabolism, a second OGTT is

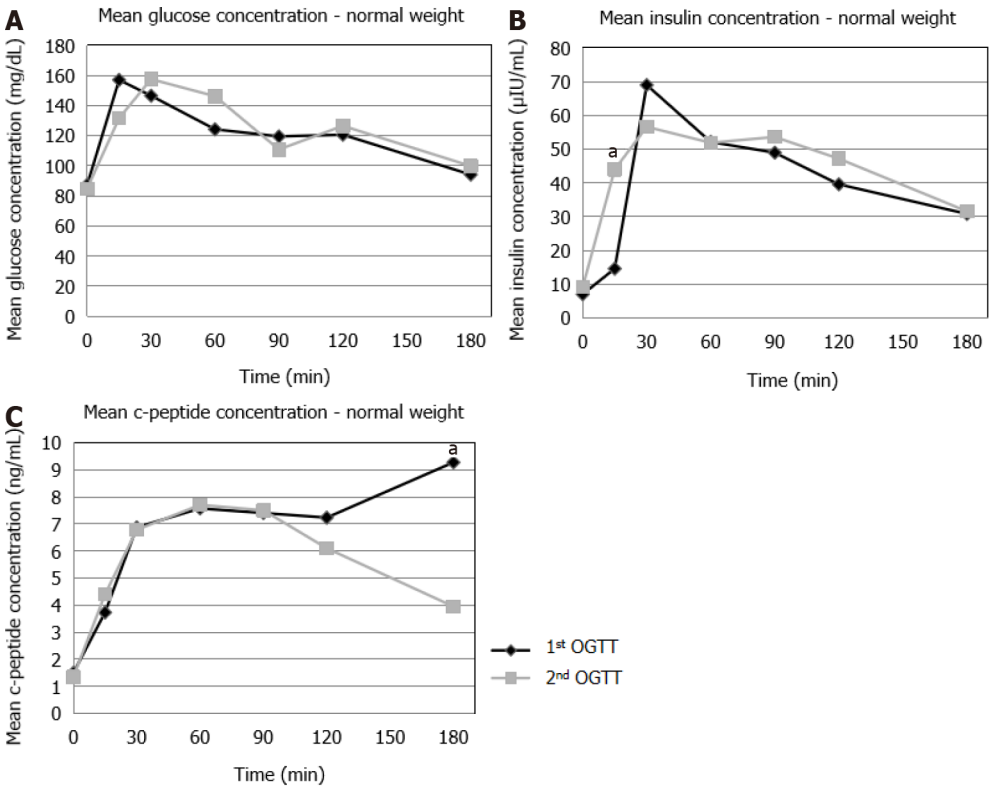

Figure 3 Comparison between parameters measured during the 1st and 2nd oral glucose tolerance test in normal weight patients. A: Mean glucose concentrations; B: Mean insulin concentrations; C: Mean C-peptide concentrations. $^{a}P < 0.05$, 2nd *vs* 1st. OGTT: Oral glucose tolerance test.

possibly needed for confirmation. This is in agreement with the ADA recommendation for performing a second OGTT in order to confirm the diagnosis of diabetes in adults[5]. Importantly, it should be taken into consideration that, despite the controlled research conditions, reproducibility of the OGTT is not always ideal, particularly in the case of mild or moderate disorders of glucose metabolism, due to procedural variability and intra-individual variation.

In addition, no repetitiveness in the OGTT response was observed with regard to IFG in the total population. Low repetitiveness was noted in IGT, as among the 6 patients who underwent 2 OGTTs and had IGT during the 1st or the 2nd OGTT, only 1 (16.7%) had IGT in both OGTTs. Of note, of the 4 patients who had IGT during the 1st OGTT, none had IFG. All these patients would not have been identified as being at increased risk for T2DM if only a FG had been performed.

In contrast, the normal weight patient who met the criteria for T2DM during the 1st OGTT at t = 0 min and t = 120 min, also exhibited repetitiveness in the glucose response at t = 0 min and t = 120 min during the 2nd OGTT. Similarly, the OB patient who met the criteria for T2DM during the 1st OGTT at t = 0 min, also exhibited repetitiveness in the glucose response at t = 0 min during the 2nd OGTT. These data may suggest that repetitiveness between different OGTTs is better in the context of more severe abnormalities in glucose regulation. The fact that FG remained abnormal in the second patient may also suggest that IFG is a reliable marker of abnormal glucose regulation when the dysregulation is significant. Of course, the sample was very small (only 1 patient had T2DM).

The poor correlation we observed between IFG and IGT has also been reported in the literature[8,9]. The percentage of IGT during the 1st OGTT in our study was 13.7%, whereas the percentage of IFG was 3.4%. In the 2nd OGTT, the percentage of IGT was 10.3%, whereas that of IFG was 3.4%. This is in agreement with reports in adult populations, which show that patients with IGT are not identified by a FG test[9]. This observation is also in agreement with reports in the literature stating that the reproducibility of glucose at t = 120 min is worse than that of FG[10]. Furthermore, Sinha *et al*[11] reported that the prevalence of IGT in children and adolescents is 25% and 21%, respectively, whereas in another study, 4.2% had IGT and 0.4% had IFG[12].

One interesting finding of the present study is that of the studied population, only a small percentage exhibited disorders of glucose metabolism such as IFG, IGT or T2DM. Obesity in children is a predisposing factor for glucose dysregulation;

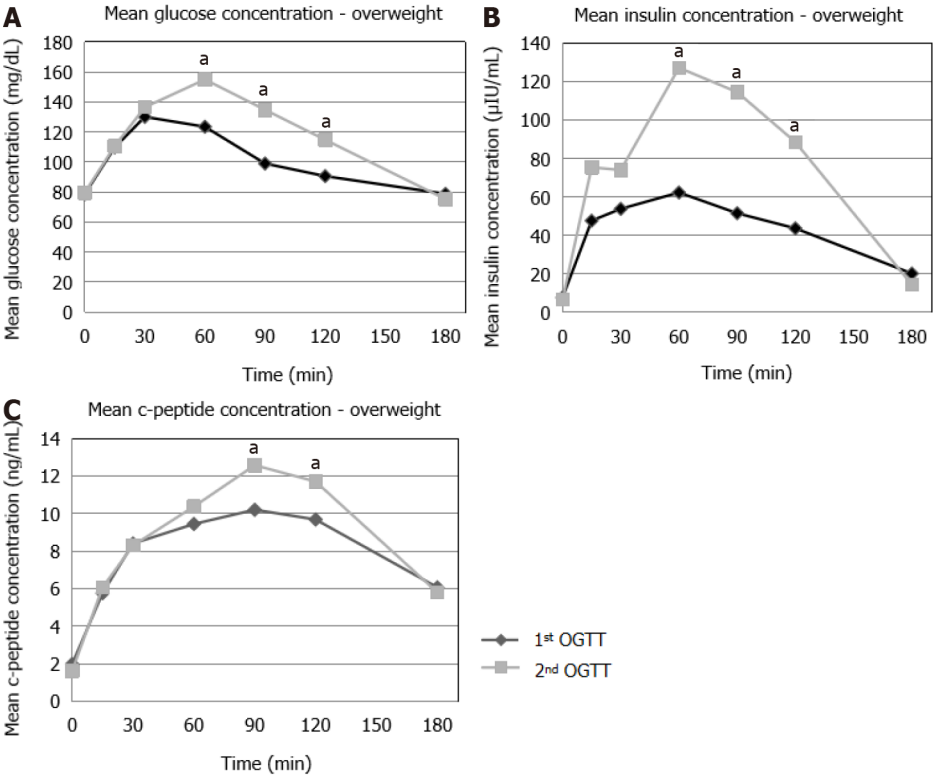

Figure 4 Comparison between parameters measured during the 1st and 2nd oral glucose tolerance test in overweight patients. A: Mean glucose concentrations; B: Mean insulin concentrations; C: Mean C-peptide concentrations. $^{a}P < 0.05$, 2nd *vs* 1st. OGTT: Oral glucose tolerance test.

however, a prolonged period is possibly needed before the effects of excessive weight become manifest, possibly due to the existence of reserves or protective mechanisms in children and adolescents. Our study also supports the notion that there seems to be a predisposition for impaired glucose metabolism in subjects with a strong family history of T2DM, independent of their weight status.

Furthermore, during the 1st OGTT and the 2nd OGTT, a positive correlation was observed between BMI and insulin, as well as between BMI and C-peptide concentrations (Figure 1B, 1C, 2B and 2C). Also, OW and OB patients showed a worsening insulin and C-peptide response during the 2nd OGTT (Figure 4B, 4C, 5B and 5C). Since the weight status did not worsen between the two OGTTs, this may be explained by progressed puberty since it is well known that there is a "physiologic insulin resistance" seen normally in pubertal children[13]. Also, it may suggest that children with excessive weight gain are prone to metabolic disturbances with the progression of age compared to their normal-weight peers.

The present study has some strengths and limitations. The strong points include the fact that the study population consisted of a quite large and wide age-range sample of children and adolescents. Also, the present study is, to our knowledge, the first to assess the beneficial role of the OGTT in identifying disorders of glucose metabolism in children and adolescents, as compared to single measurements, such as FG. In addition, although studies comparing two OGTTs have been performed in children and adolescents with an interval of 1 d to 25 d in order to assess the reproducibility of the OGTT, no studies of longer intervals have been performed, thus far, in order to investigate the repetitiveness of the OGTT in the paediatric population. On the other hand, the small sample of patients with impaired glucose metabolism and the small sample of patients who repeated the OGTT, represent limitations of the study. Also, C-peptide concentrations were measured in only 28 patients and the number of patients with NW and a positive family history of T2DM was limited. Therefore, further studies on larger populations are needed to verify these findings.

CONCLUSION

Our study of the glucose response during repeated OGTTs, adds to the existing knowledge pertaining to glucose regulation in children and adolescents with excess

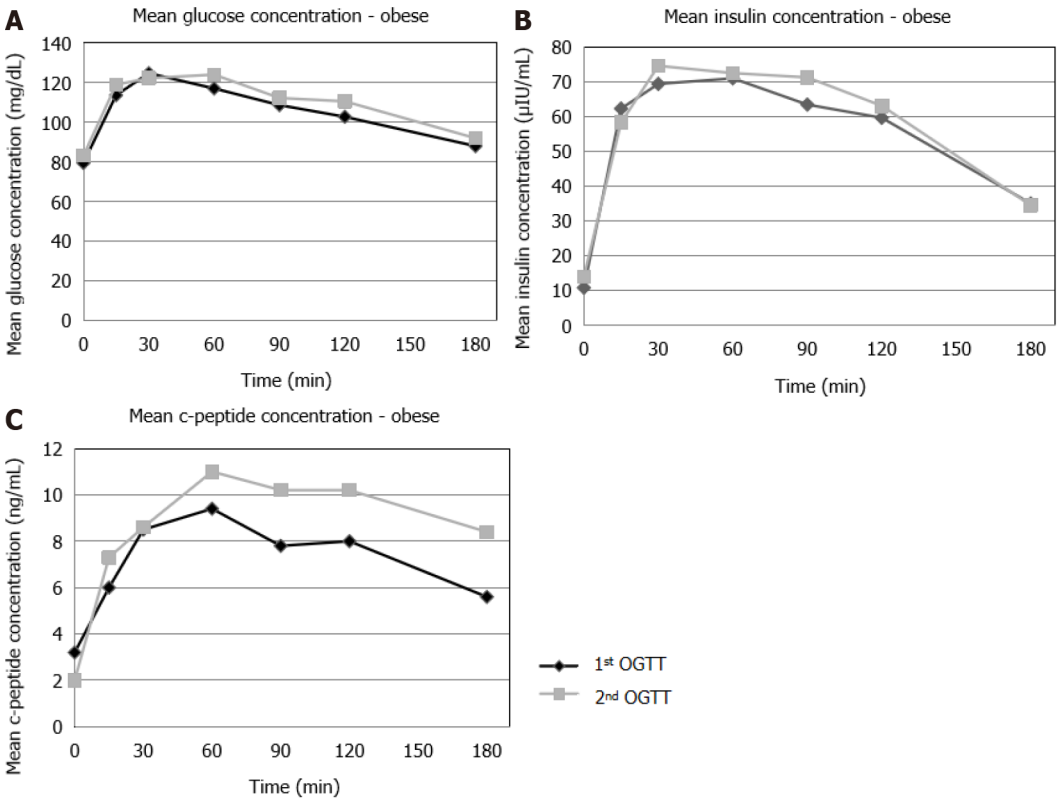

Figure 5 Comparison between parameters measured during the 1st and 2nd oral glucose tolerance test in obese patients. A: Mean glucose concentrations; B: Mean insulin concentrations; C: Mean C-peptide concentrations in obese patients during the 1st and 2nd oral glucose tolerance test. OGTT: Oral glucose tolerance test.

weight. It also highlights that a family history of abnormal glucose metabolism may place children and adolescents at a higher risk for glucose dysregulation. More importantly, the findings of this study infer that the OGTT is superior to single measurements, such as FG, in diagnosing disorders of glucose metabolism, particularly in patients with mild glucose dysregulation, *i.e.*, IFG and IGT. Hence, our results suggest that routine clinical practice could involve performing an OGTT in all OW or OB children or in NW children with a strong positive family history of T2DM, instead of a single FG measurement, in order to avoid missing the diagnosis of disorders of glucose metabolism. Also, a second OGTT may be necessary in children and adolescents with excessive weight who exhibit IFG or IGT in an initial OGTT in order to confirm the diagnosis.

ARTICLE HIGHLIGHTS

Research background

Fasting plasma glucose is used as a screening tool for the diagnosis of disorders of glucose metabolism due to its ease of performance. The oral glucose tolerance test (OGTT) has been proposed as a possibly useful screening method for the diagnosis of impaired glucose metabolism and increased risk for diabetes in children. Data regarding the most appropriate screening method to diagnose disordered glucose metabolism are inconclusive.

Research motivation

Additional information is needed in order to determine the usefulness of the OGTT in diagnosing impaired glucose metabolism.

Research objectives

To investigate the pattern of glucose, insulin and C-peptide responses in repeated OGTTs and to determine the diagnostic and prognostic value of the OGTT regarding the development of disorders of glucose metabolism.

Research methods

A 3-h OGTT was performed in 81 children and adolescents with excess weight or a strong positive family history of type 2 diabetes mellitus (T2DM), and the glucose, insulin and C-peptide responses were evaluated at multiple time points. The OGTT was repeated in a proportion of the patients and comparisons were made between the responses of glucose, insulin and C-peptide. The glucose, insulin and C-peptide concentrations between the two OGTTs were compared using the Mann Wilcoxon Test for unpaired data and the Wilcoxon Signed Rank test for paired data. Correlations between the body mass index or the age and the glucose, insulin or C-peptide concentrations during the OGTTs were assessed using Spearman's rho correlation coefficient.

Research results

None of the patients with impaired fasting glucose exhibited repetitiveness of the finding in both OGTTs. Eighty percent of the subjects with impaired glucose tolerance during the 1st OGTT, had normal glucose concentrations at t = 120 min during the 2nd OGTT. Repetitiveness was observed for the diagnosis of T2DM in both OGTTs.

Research conclusions

In patients with profoundly impaired glucose metabolism, as in the case of T2DM, one OGTT is probably adequate for diagnosing the disorder. In patients with milder disorders of glucose metabolism, a second OGTT is possibly needed for confirmation. The OGTT seems to be superior to single measurements, such as fasting glucose, in diagnosing disorders of glucose metabolism, particularly mild glucose dysregulation, *i.e.*, impaired fasting glucose and impaired glucose tolerance. Disorders of glucose metabolism are uncommon in overweight or obese children and adolescents.

Research perspectives

Further studies are needed in order to determine the possible repetitiveness of the OGTT in children and adolescents with risk factors for T2DM, such as increased weight or a positive family history. Further studies are needed in order to confirm the diagnostic and prognostic superiority of the OGTT with regard to glucose dysregulation, compared to single glucose measurements.

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CASE REPORT

Chilaiditi syndrome in pediatric patients - Symptomatic hepatodiaphragmatic interposition of colon: A case report and review of literature

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Author contributions: Caicedo L, Rivera A, and Lopez MS collected data and drafted initial manuscript; Wasuwanich P collected data, carried out the formal analysis, and revised the manuscript. Karnsakul W conceptualized and designed the study, supervised the study, and revised the manuscript; all authors have reviewed the manuscript and approved the final manuscript as submitted and agree to be accountable for all aspects of the work; Caicedo L and Wasuwanich P are contributed equally to this study.

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Abstract

BACKGROUND

Chilaiditi syndrome is a rare disorder characterized by the hepatodiaphragmatic interposition of the intestine.

CASE SUMMARY

Here we report a case of a 12-year-old male who was admitted to the pediatric intensive care unit secondary to abdominal pain and severe respiratory distress. He was treated conservatively but the symptoms persisted requiring a surgical approach. While there have been several cases of Chilaiditi syndrome reported in adults, there is a scarcity of cases reported in the pediatric population. Our review of the literature found only 30 pediatric cases, including our reported case, with Chilaiditi syndrome, 19 (63%) of which were male. The median age of diagnosis was 4.5 years old with an interquartile range of 2.0-10.0 years. In our review, we found that the most common predisposing factors in children are aerophagia (12/30 cases) and constipation (13/30 cases). Ninety percent of the cases

presented with complete intestinal interposition, in 100% of which, the colon was involved. Three of the 30 cases were associated with volvulus.

CONCLUSION
In the pediatric population, conservative (21/30 cases) and surgical (8/30 cases) treatment approaches have produced satisfactory outcomes for all the patients, regardless of approach.

Key Words: Abdominal pain; Dyspnea; Constipation; Rare diseases; Respiratory insufficiency; Colon; Case report

Core Tip: We describe a pediatric case of Chilaiditi syndrome with successful treatment, as well as a literature review of all pediatric case reports of Chilaiditi syndrome. In the pediatric patients, both conservative and surgical approaches in treating Chilaiditi syndrome with treatment of predisposing factors have resulted in satisfactory outcomes.

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INTRODUCTION

Chilaiditi syndrome, first described by Viennese radiologist Dr. Chilaiditi[1] in 1910, is noted to be an extremely rare disorder associated with various symptoms including nausea, vomiting, abdominal pain, constipation, and respiratory distress. The condition is recognized radiologically by the presence of the hepatodiaphragmatic interposition of the intestine, called Chilaiditi sign. Chilaiditi sign can be confused radiologically with other conditions such as pneumoperitoneum and subdiaphragmatic abscess. The cause of Chilaiditi syndrome is currently unknown, but may include intestinal, diaphragmatic, or hepatic factors. While most cases can be managed conservatively, a few cases require surgical intervention[2]. We report a pediatric case of Chilaiditi syndrome and a literature review of a pediatric case series of Chilaiditi syndrome.

CASE PRESENTATION

Chief complaints

A 12-year-old male was admitted to the pediatric intensive care unit due to severe respiratory distress.

History of present illness

With this present admission, the patient presented with respiratory distress and right upper quadrant abdominal pain. He was placed on oxygen supplementation *via* nasal cannula to maintain normal oxygen saturations.

History of past illness

Prior to this admission, he experienced persistent cough, dyspnea, nausea, and chest pain for over two months. He was prescribed antibiotics, nebulizations, and pain medication; however, there were no improvements in his respiratory symptoms. The patient has a history of asthma, gastroesophageal reflux disease, constipation, and a prior diagnosis of Chilaiditi syndrome. The diagnosis of Chilaiditi syndrome was made two years prior to this admission when the patient presented with a one-week

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history of right upper quadrant pain, nausea, and vomiting. There was no history of recent weight loss. An abdominal computerized tomography (CT) showed constipation and colonic interposition between the liver and the diaphragm with displacement of the liver (Figure 1). Constipation was initially managed with a routine bowel cleansing protocol and a daily stool softener; however, intermittent episodes of abdominal pain persisted.

Personal and family history

No relevant family history.

Physical examination

No relevant physical examination.

Laboratory examinations

Laboratory results from complete blood count, comprehensive metabolic panel, and C-reactive protein were within normal limits.

Imaging examinations

A chest X-ray revealed that the transverse colon was above the liver. On the first hospital admission day, a kidney, ureter, and bladder X-ray (KUB) showed significant amount of fecal material and air-filled colonic loops which were slightly dilated and reaching the right hemidiaphragm (Figure 1).

FINAL DIAGNOSIS

A final diagnosis of Chilaiditi syndrome was given.

TREATMENT

He subsequently received a bowel-cleaning regimen with GoLytely®. A follow-up KUB on the second hospital admission day showed the resolution of fecal retention or constipation. However, the patient continued to complain of tachypnea and right upper quadrant pain. Because of his persistent respiratory and abdominal symptoms, and due to the lack of significant improvement, surgery was consulted. The patient underwent laparoscopic colopexy and peritoneal abrasion of the diaphragm and liver. Significant intraoperative findings included a redundant transverse colon, no evidence of volvulus or adhesions in the upper abdomen, a relatively small right liver lobe (noncirrhotic), and a large gap between the liver and the anterior chest wall and diaphragm.

OUTCOME AND FOLLOW-UP

His respiratory distress and abdominal pain resolved completely post-operatively and the patient was discharged with a maintenance stool softener regimen, colonic stimulant, and adequate dietary fiber. At the one-month follow-up after surgery, the patient reported regular bowel movements and no recurrence of his respiratory distress. He reported some mild intermittent episodes of right upper quadrant abdominal pain but never required emergency care or any interventions since the surgery.

DISCUSSION

The essential hallmark of Chilaiditi sign in Chilaiditi syndrome is that the air-filled loops of intestine remain unchanged in position of the patients due to its immobilization in a relatively limited space between the liver and the anterior chest wall[3]. Chilaiditi sign may be described as an incidental finding on plain radiological studies in asymptomatic patients. It is thought to occur in 0.025% to 0.28% of the general population. It is markedly more prevalent in the elderly and in men. This increased prevalence in the elderly suggests that it is an acquired rather than a congenital

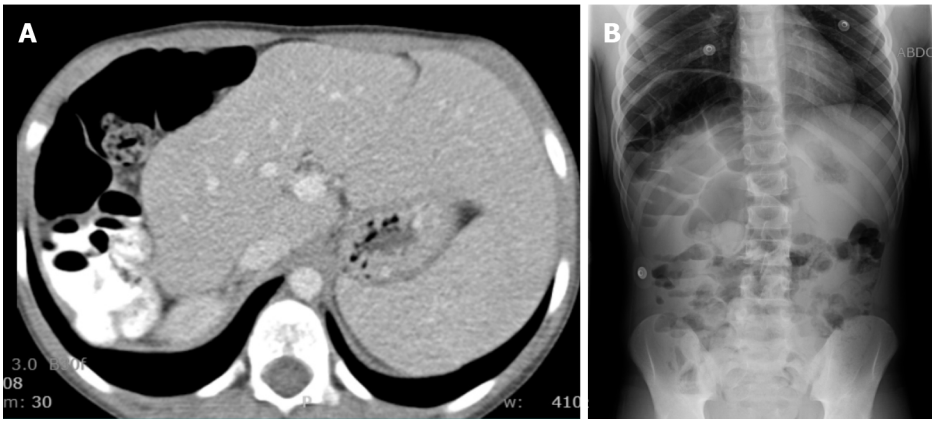

Figure 1 Imaging of abdomen and pelvis of a 12-year-old male with Chilaiditi syndrome and constipation. A: Computerize tomography. Marked air and fecal retention of the entire colon with colonic interposition above the liver with displacement of the liver leftwardly. This phenomenon indicates segmental agenesis of the right lobe of the liver and relaxation of the hepatic suspensory ligament; B: Plain X-ray. Markedly greater than average amount of fecal material particularly in the rectosigmoid colon. Few air fluid levels in the distal small bowel and air filled colonic loops that reach the right hemidiaphragm.

condition. Torgersen reported the prevalence of Chilaiditi syndrome to be 0.2% in men older than 65 years and 0.02% in men 15-65 years, with a male to female ratio of 4:1[4]. Murphy *et al*[5] associated Chilaiditi syndrome with being overweight or obese. Five of his ten patients found to have Chilaiditi syndrome on abdominal CT were obese (850 patients in the study, 10 of whom had Chilaiditi syndrome)[5]. In obese patients, a significant amount of fat accumulates between liver and diaphragm, with secondary widening of potential space, which is subject to substantial swings in pressure during the respiratory cycle. Following the same concept, the increased proportion of intraabdominal fat among men compared with women might explain the increased prevalence of Chilaiditi syndrome in men[6]. While there have been severe cases of Chilaiditi syndrome reported in adults, there is a scarcity of cases reported in the pediatric population. Our review of the literature found only 30 pediatric cases with Chilaiditi syndrome, 19 (63%) of which were male (Table 1). The median age of diagnosis was 4.5 years old with an interquartile range of 2.0-10.0 years[7-28].

The etiology of Chilaiditi syndrome has been categorized into (1) Intestinal: megacolon, abnormal colonic motility or redundancy, constipation, and congenital malrotation; (2) Hepatic: cirrhosis, segmental agenesis of the right lobe of the liver, and relaxation of the hepatic suspensory ligament; and (3) Diaphragmatic: phrenic nerve injury and diaphragmatic eventration[15,17]. Several risk and predisposing factors have been associated with this entity including, aerophagia, adhesions, obesity, constipation, mental retardation, pregnancy, muscular dystrophy, and significant weight loss[17,22]. Very rarely, episodes of volvulus have been associated to this syndrome, especially in the elderly population and could be complicated with cecal perforation[4,7,22,29,30]. Chilaiditi syndrome can further be divided in two types, depending on the degree of intestinal interposition and liver displacement: (1) In the complete form, the colon typically lies above the liver, there being contact between the liver and diaphragm, with the liver displaced inferiorly, anteriorly, and medially; and (2) In the incomplete (partial) form, the colon does not typically rise above the liver, but lays lateral or posterior to it[23]. In theory, patients after orthotic liver transplantation will have some degrees of intestinal interposition with the transplanted liver being displaced inferiorly, anteriorly, and medially.

In our review of the pediatric literature, we found the most common predisposing factors in children to be aerophagia (12/30 cases) and constipation (13/30 cases). Ninety percent of the cases presented with complete intestinal interposition, in 100% of which the colon was involved. Three of the 30 cases were associated with volvulus. In the case we described here, the predisposing factor was believed to be a combination of constipation, redundant colon, and intestinal dysmotility, associated with a relatively small right lobe of the liver, in turn, allowing a big space between the liver and the anterior chest wall and diaphragm.

The most common clinical presentation of Chilaiditi syndrome is constipation, abdominal pain, nausea, vomiting, abdominal distention, and respiratory distress. On physical examination, it is possible to encounter loss of hepatic dullness on percussion (Joubert sign)[7,8,23,25]. The diagnosis of hepatodiaphragmatic interposition can be demonstrated with radiologic tests such as a plain KUB, a right upper quadrant

Table 1 Case series of Chilaiditi syndrome in the pediatric population

Ref.	Sex	Age	Predisposition	Bowel segment	Symptoms	Type of interposition	Dx procedure	Treatment	Type of surgery	Outcome
[24]	M	16 mo	Aerophagia	Colon	Abdominal distention and pain, vomiting	Complete	KUB	Conservative	---	Resolution
[24]	F	3 yr	Aerophagia	Colon	Abdominal distention and pain, passed flatus	Complete	KUB	Conservative	---	Resolution
[24]	F	5 yr	Aerophagia, constipation	Colon	Abdominal pain, constipation	Partial	KUB	Conservative	---	Resolution
[24]	F	4 yr	Aerophagia	Colon	Anorexia, recurrent abdominal pain, vomiting	Complete	KUB	Conservative	---	Resolution
[27]	F	2 yr	---	Colon	Marasmus, vomiting, lethargy, inability to walk	Complete	KUB	Surgery (Volvulus)	Laparoscopic colopexy and transverse colectomy	Resolution
[26]	M	6 mo	---	Colon	Abdominal pain, vomiting	Partial	KUB	Conservative	---	Resolution
[19]	M	8 yr	Aerophagia	Colon	Abdominal pain, distention	Complete	KUB	Conservative	---	Resolution
[7]	M	12 yr	---	Colon	Respiratory distress, pleuritic pain, fever	Complete	CXR, BE	Surgical (Volvulus)	Laparoscopic detorsion	Resolution
[22]	M	17 yr	Mental retardation, constipation, congenital adhesions	Colon	Abdominal distention, vomiting, constipation	Complete	CXR, KUB	Surgical (Volvulus)	Laparoscopic transverse colectomy	Resolution
[28]	F	9 yr	Constipation	Colon	Abdominal pain, nausea, constipation	Complete	CXR, KUB	Conservative	---	Resolution
[9]	F	11 yr	Constipation	Colon	Abdominal pain, vomiting	Complete	KUB, CT	Surgery	Laparoscopic transverse colectomy	Resolution
[23]	F	9 yr	DE, constipation	Colon	Epigastric pain, constipation, nausea	Complete	CXR, KUB, CT	Conservative	---	Resolution
[23]	M	1 yr	DE	Colon	Recurrent respiratory distress	Complete	CXR, KUB, CT	Surgery	Correction of diaphragmatic, eventration and elevation of right hemidiaphragm	Resolution
[23]	F	16 mo	DE	Colon	Recurrent respiratory distress	Complete	CXR, KUB, CT	Surgery	Correction of diaphragmatic, eventration and elevation of right hemidiaphragm	Resolution
[25]	M	5 mo	---	Colon	Recurrent respiratory distress	Complete	CXR, CT	Conservative	---	Resolution
Present study	M	12 yr	Constipation	Colon	Recurrent respiratory distress, abdominal pain, constipation	Complete	CXR, KUB	Surgical	Laparoscopic colopexy	Resolution
[33]	F	2 yr	Constipation	Colon	Recurrent respiratory distress, abdominal pain,	Complete	CXR	Conservative	---	Resolution

					constipation					
[10]	M	8 yr	Constipation	Colon	Abdominal pain, constipation	Complete	KUB, CT	Conservative	---	Resolution
[11]	M	10 d	Constipation	Colon	Abdominal distension, respiratory distress, constipation	Complete	KUB	Conservative	---	Resolution
[12]	F	3 yr	Constipation	Colon	Recurrent respiratory distress, constipation	Complete	CXR	Conservative	---	---
[13]	M	4 yr	Aerophagia	Colon	Respiratory distress	Complete	CXR	Conservative	---	Resolution
[14]	M	6 yr	---	Colon	Abdominal pain, emesis, FTT	Complete	CXR	Surgical	Laparoscopic colopexy	Resolution
[15]	M	10 yr	Aerophagia	Colon	Recurrent respiratory distress	Complete	CXR, MRI	Conservative	---	Resolution
[15]	M	7 yr	Aerophagia	Colon	Recurrent respiratory distress, abdominal distention	Complete	CXR, MRI	Conservative	---	Resolution
[8]	M	4 yr	Aerophagia, constipation	Colon	Recurrent respiratory distress, abdominal pain, constipation	Complete	CXR, CT	Conservative	---	Resolution
[16]	M	3 yr	Aerophagia	Colon	Recurrent respiratory distress, abdominal distention	Complete	CXR	Conservative	---	Resolution
[17]	M	20 yr	Duchenne muscular	Colon	Recurrent respiratory distress	Complete	CT	Conservative	---	Resolution
[18]	M	19 yr	Dystrophy, aerophagia, constipation	Colon	Chest pain, respiratory distress, abdominal pain	Complete	CXR	Conservative	---	Resolution
[20]	F	1 yr	Aerophagia	Colon	Respiratory distress	Partial	CXR	Conservative	---	Resolution
[21]	M	10 yr	Constipation, mental retardation	Colon	Respiratory distress, constipation, failure to thrive, abdominal distention	Complete	CXR	---	---	---

BE: Barium Enema; CT: Computerized tomography; CXR: Chest X-Ray; DE: Diaphragmatic eventration; KUB: Kidney, Ureter, and Bladder X-Ray; MRI: Magnetic resonance imaging.

ultrasound or an abdominal CT scan. Identifying haustra or plicae circularis between the liver and the diaphragm can distinguish pneumoperitoenum from Chilaiditi syndrome.

The majority of the cases with Chilaiditi syndrome require a conservative therapy which includes bed rest in a supine position, daily maintenance bowel regimen with laxatives and normal fiber diet, frequent bowel cleansing, fluid supplementation, and nasogastric decompression[23,25]. In some specific cases emergency surgery may be re-quired: associated volvulus, internal hernia, or acute intestinal obstruction[7,9,22,30,31]. Cases who have lacked the aforementioned surgical condi-tions and continue to have intractable abdominal pain and respiratory distress may benefit from undergoing a colopexy[6,9,23]. Colopexy is a surgical procedure which involves repositioning of the colon to adhere to the abdominal wall. In our literature review, 21

of the 30 reported cases were managed with a conservative approach and 8 required a surgical intervention (3 had associated volvulus, 4 presented with persistent respiratory distress, and 2 with recurrent vomiting). And of those 8 cases that required surgery, 2 were transverse colectomies, 2 were colopexies, 1 was a colopexy with transverse colectomy, 1 was detorsion, and 2 involved correction of diaphragmatic eventration and elevation of the right hemidiaphragm (Table 1). Of the 30 cases with reported outcomes, the final outcome was satisfactory for all those cases regardless of the treatment approach[6,7,9,22,23].

The teaching point of this uncommon but intriguing syndrome is to have a high index of suspicion of this condition in patients who have predisposing factors. In addition, it is essential to exclude pathologic conditions such as pneumoperitoneum, subphrenic abscess, posterior hepatic lesions, and Morgagni hernia, which can mimic Chilaiditi sign on a radiologic film. A subphrenic abscess usually features a comparatively smaller air fluid level in the right upper quadrant often associated with pleural effusions and basilar atelectasis (this last two conditions not commonly seen with Chilaiditi sign), if the diagnosis is unclear, an abdominal CT scan is recommended for further evaluation[3,23]. In patient with cirrhosis (in the absence of ascites), the prevalence of Chilaiditi sign has been reported be between 5% and 20%, higher than the general population[31,32]. It is essential to recognize Chilaiditi syndrome particularly in medical procedures requiring percutaneous transhepatic approach such as percutaneous liver biopsy, percutaneous transhepatic cholangiography, or biliary drainage. Real-time ultrasound guide during these procedures can prevent the intestinal injury before the percutaneous access to the liver[33].

CONCLUSION

Chilaiditi syndrome is a rare condition especially among the pediatric population. It should be suspected when patients present with constipation, abdominal pain (particularly located in the right upper quadrant), nausea, vomiting, abdominal distention, and respiratory distress of unknown cause. In the cases previously reported, there were no data about recurrence or timeline from first symptomatology to diagnosis; given the lack of information, long-term follow-up in these cases is necessary. In the pediatric population, both conservative and surgical approaches in treating Chilaiditi syndrome, with treatment of the predisposing factors, have resulted in satisfactory outcomes.

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EVIDENCE REVIEW

Can omalizumab be used effectively to treat severe conjunctivitis in children with asthma? A case example and review of the literature

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Abstract

A 14-year-old girl with poorly controlled asthma attended the difficult-to-treat asthma clinic for review. Although she has eosinophilia and significantly raised immunoglobulin E levels, she is not currently a candidate for omalizumab (Xolair). She also suffers from chronic urticaria, eosinophilic eosophagitis and severe conjunctivitis. You wonder if omalizumab would be effective in treating her multiple atopic conditions, in particular her troublesome conjunctivitis. PubMed was searched using the following search terms: (Omalizumab) or (Xolair) and (conjunctivitis). Searches were conducted in November 2020. Abstracts were selected for full text review if the study population identified asthma as a comorbidity. Non-paediatric studies and those that were not written in English were excluded. The use of omalizumab has the potential to be effective in the treatment of conjunctivitis associated with asthma and other atopic conditions. However, research is needed to address the question, in the form of multicenter, double-blind randomized control trials.

Key Words: Omalizumab; Conjunctivitis; Allergy; Asthma; Pediatrics; Atopy

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Core Tip: Asthma is often associated with multiple atopic conditions which can be more debilitating than the asthma itself. The use of omalizumab has the potential to be effective in the treatment of conjunctivitis associated with asthma and other atopic conditions. However, research is needed to address the question, in the form of multicenter, double-blind randomized control trials.

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INTRODUCTION

Scenario

A 14-year-old girl with poorly controlled asthma attended the difficult-to-treat asthma clinic for review. Although she has eosinophilia and significantly raised immunoglobulin E (IgE) levels, she is not currently a candidate for omalizumab (Xolair) due to poor adherence. She attends immunology clinic for spontaneous urticaria which has not improved despite high dose antihistamine. Gastroenterology are treating her for eosinophilic oesophagitis with proton pump inhibitors. During the consultation, you note that she also has severe vernal keratoconjunctivitis (VKC). She reported itching, burning and tearing of her eyes and it was evident at the review that she had marked conjunctival hyperaemia and blepharitis. Although adherence has been an issue in relation to her asthma treatment, she is reportedly compliant with both enteral and topical antihistamine therapy for her conjunctivitis.

You wonder if omalizumab would be effective in treating her multiple atopic conditions, in particular her troublesome conjunctivitis.

STRUCTURED CLINICAL QUESTION

Does treatment with omalizumab (intervention) in children with allergic conjunctivitis as a comorbidity of asthma (population) improve their conjunctivitis symptoms (outcome) compared to current treatment (control)?

SEARCH

PubMed was searched using the following search terms: (Omalizumab) or (Xolair) and (conjunctivitis). Searches were conducted in November 2020.

RESULTS

The literature search returned a total of 31 studies. Abstracts were selected for full text review if the study population identified asthma as a comorbidity. Non-paediatric studies and those that were not written in English were excluded. Following abstract review, 5 papers were deemed relevant for full text analysis and all were felt to address the question. Included studies are summarized in Table 1 and graded according to the Oxford Centre for Evidence-based medicine Levels of Evidence[1].

Table 1 Studies assessing the use of omalizumab in conjunctivitis as a comorbidity

Ref.	Study group	Study type (level of evidence)	Intervention	Outcome	Results
Doan *et al* [13], 2017	4 patients with severe VKC, asthma, rhinitis and AD	Non-controlled, open-label, retrospective case series (Level 4)	2 weekly treatment with Omalizumab for range of 16-42 mo	Ocular VAS scale. Bonini grading. ACT score	3/4 had improvement in VAS score and Bonini grading. 3/4 had total control
Sánchez and Cardona [18], 2012	1 patient. 16 years old with severe refractory VKC, asthma, AD and rhinitis	Case report (Level 4)	2 weekly treatment with Omalizumab for 18 mo	Ocular VAS scale. Objective physician evaluation including cessation of immunosuppressive therapies	Ocular VAS improvement. Reduction of red eyes, photophobia and papillae. Cessation of ciclosporin and corticosteroids
de Klerk *et al*[19], 2013	1 patient. 12 years old with severe refractory VKC, asthma and rhinitis	Case report (Level 4)	Monthly treatment with Omalizumab for 18 mo	Juniper's rhinoconjunctivitis QOL score. Reduction in immunosuppressive ocular therapy	Improvement in Juniper's rhinoconjunctivitis score. Cessation of ciclosporin and olapatadine
Occasi *et al* [20], 2015	1 patient. 15 years old boy with asthma, severe VKC and AD	Case report (Level 4)	2 weekly treatment with Omalizumab for 3 mo	Achieving asthma control. Resolution of AD and VKC symptoms	Asthma control achieved at 3 mo. Resolution of VKC symptoms at 3 mo
Rossberg *et al*[11], 2020	2 patients with severe VKC, asthma and AD	Case report (Level 4)	2 weekly treatment with Omalizumab for 11 mo and 6 mo	Bonini grading	Improvement in Bonini grading

QOL: Quality of life; VKC: Vernal keratoconjunctivitis; VAS: Visual analogue scale; ACT: Advanced communication training.

DISCUSSION

Hypersensitization of IgE plays an important role in many allergic diseases. This means that patients often have multiple atopic conditions (multimorbidities). Patients with allergic asthma frequently present with other atopic conditions including: Rhinoconjunctivitis/allergic rhinitis, atopic dermatitis, food allergies, chronic spontaneous urticaria, eosinophilic oesophagitis and allergic bronchopulmonary aspergillosis [2]. Having these multimorbidities adversely impacts on asthma control and can contribute significantly to the overall burden of the disease[2].

IgE secreted by plasma cells in response to an exposure to allergens play an integral role in the allergic inflammatory cascade. Allergen-specific IgE binds to the surface of mast cells, causing degranulation of certain mediators (including histamine, chymase and tryptase) which are responsible for the classic symptoms of itching, redness and oedema. Omalizumab is a recombinant monoclonal antibody that sequesters free IgE and accelerates the dissociation of the IgE-Fcε receptor I complex[3]. This disrupts the IgE-mediated inflammatory cascade. Based on an extensive body of evidence, NICE now recommends use of omalizumab for patients with asthma and chronic spontaneous urticaria (CSU) who meet specific criteria[4,5] (Table 2). Guidance for its use in chronic rhinosinusitis with nasal polyps is expected[6]. These conditions are considered in isolation and current guidelines do not account for patients with multiple severe atopic conditions.

Dosing of omalizumab in Asthma is based on age, baseline, pre-treatment serum IgE levels and body weight[7]. As a result, a mg/kg dosing value is not usually given. Usual doses range from between 75-600 mg and depending on weight and serum IgE levels, dosing intervals may be fortnightly or monthly. At the upper extremes of weight and serum IgE levels, the theoretical dose *via* extrapolation is not licensed and therefore not recommended[7]. Currently, there is no guidance for this situation, however other biologics targeting different pathways may be trialed. Dosing in CSU is not dependent on serum IgE levels or body weights[7]. Recommendations are to administer 150 mg or 300 mg by subcutaneous injection every 4 wk. Dosing tables for asthma and chronic idiopathic urticaria are included in the appendix.

VKC is a chronic, relapsing condition mainly affecting children. Its pathophysiology involves both IgE and non-IgE mediated reactions[8]. The binding of specific allergens to specific IgE's causes degranulation of mediators leading to symptoms of redness and itching. Later, mediators cause infiltration of eosinophils, neutrophils and macrophages into the tissue. Eosinophils in particular play a major role in inflammation and tissue lesions such as epitheliopathy in VKC[9]. The mainstay of treatment is topical immunosuppressive medications and topical steroids. However, these are

Table 2 Current Indications for prescribing omalizumab

Ref.	Age	Previous treatment
NICE[4]	> 6 yr	Optimised standard treatment with documented compliance
		Continuous or 4 or more courses of oral steroids in the previous year
NICE[5]	> 12 yr	Poor response to standard treatment with H1-antihistamines and leukotriene receptor antagonists
		Objective severity score (weekly urticaria activity score) > 28

associated with significant side effects including ocular hypertension, glaucoma and cataract formation. Additionally, a large prospective study by Bonini *et al*[10] showed that 31% of patients with VKC requiring treatment with topical steroids had no improvement[10].

Four case reports and one case series followed a total of 9 patients with severe conjunctivitis as a comorbidity of asthma. Prior to omalizumab, all patients had worsening ocular symptoms despite topical and oral medications including immunosuppressants and corticosteroids. Omalizumab was associated with clinical improvement in 8 out of the 9 children including a reduction in the use of topical steroids and immunosuppressive therapies. Associated allergic multimorbidities also improved in 6 patients. Asthma control was achieved and lid eczema and atopic dermatitis completely resolved.

In the case report by Rossberg *et al*[11], effect on asthma symptoms was not reported. One patient required commencement of Dupilumab (an alternative monoclonal antibody that inhibits Interluekin-4 and Interleukin-13 signalling[12] mainly due to worsening AD, and reached complete control[11].

One patient in the case series by Doan *et al*[13] did not respond to omalizumab for either their conjunctivitis or their associated atopic conditions[13]. Notably, this patient did not have detectable sensitization to any allergen. This shows the complex and multifactorial pathogenesis of VKC, of which IgE plays a role[8,9].

A study by Heffler *et al*[14] in 2016 discusses treatment with omalizumab in 2 patients with severe VKC[14]. They did not meet our inclusion criteria as neither patient had concomitant asthma, however one patient was a child, in her first decade of life. Omalizumab was administered at 300 mg *per* month for 6 mo. Ocular visual analogue scale (VAS) scores, ophthalmologic examination and conjunctival scrape smears for cytologic examination were the outcomes measured. This is the first case report where cytologic examination has been used as an outcome. After 6 mo, the patient experienced improvement in all outcomes. Ocular VAS scores improved from 8 to 0, eye redness and cobblestone papillae were abolished, and eosinophil levels decreased from 69% to 3% on cytologic examination.

None of the five studies in this literature review report any adverse effects to treatment with omalizumab in children for conjunctivitis. The most common previously reported adverse effects to omalizumab include upper respiratory infections, headaches, arthralgia, pain, fatigue and abdominal discomfort[15]. The risk of anaphylaxis is 0.14% in patients receiving omalizumab, similar to other biologic drugs [16]. The British National Formulary reports further, rarer side effects, including eosinophilic granulomatosis with polyangiitis (usually associated with reduction of oral corticosteroids) and hypersensitivity reactions[17].

These findings are limited as the studies available were heterogeneous and of low quality. Sample size was small, with only case reports or small case series conducted. The dose, duration and frequency of omalizumab varied between the studies. Some studies used omalizumab as a single therapy and others as combination therapy. An array of different outcome measures were used and different grading systems were applied. Compliance to medication prior to commencing omalizumab was a concern in one case report, making conclusions of symptom improvement due to omalizumab more difficult.

CONCLUSION

The use of omalizumab has the potential to be effective in the treatment of conjunctivitis associated with asthma and other atopic conditions. However, research is needed to address the question, in the form of multicenter, double-blind randomized control trials.

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REVIEW

Celiac disease in children: A review of the literature

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Abstract

Celiac disease is an immune-mediated systemic disease triggered by intake of gluten in genetically susceptible individuals. The prevalence of celiac disease in the general population is estimated to be 1% in the world. Its prevalence differs depending on geographical and ethnic variations. The prevalence of celiac disease has increased significantly in the last 30 years due to the increased knowledge and awareness of physicians and the widespread use of highly sensitive and specific diagnostic tests for celiac disease. Despite increased awareness and knowledge about celiac disease, up to 95% of celiac patients still remain undiagnosed. The presentations of celiac disease have significantly changed in the last few decades. Classical symptoms of celiac disease occur in a minority of celiac patients, while older children have either minimal or atypical symptoms. Serologic tests for celiac disease should be done in patients with unexplained chronic or intermittent diarrhea, failure to thrive, weight loss, delayed puberty, short stature, amenorrhea, iron deficiency anemia, nausea, vomiting, chronic abdominal pain, abdominal distension, chronic constipation, recurrent aphthous stomatitis, and abnormal liver enzyme elevation, and in children who belong to specific groups at risk. Early diagnosis of celiac disease is very important to prevent long-term complications. Currently, the only effective treatment is a lifelong gluten-free diet. In this review, we will discuss the epidemiology, clinical findings, diagnostic tests, and treatment of celiac disease in the light of the latest literature.

Key Words: Celiac disease; Children; Intestinal biopsy

Core Tip: Celiac disease is a systemic lifelong disease. The prevalence of celiac disease has increased significantly in the last three decades due to the increased awareness of physicians and widespread use of highly sensitive and specific diagnostic tests for celiac disease. Despite increased awareness and widespread use of diagnostic tests, up

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to 95% of celiac patients still remain undiagnosed. Early diagnosis is very important to prevent long-term complications. The only effective treatment is still a lifelong gluten-free diet. In this review, we will discuss the epidemiology, clinical findings, diagnostic tests, and treatment of celiac disease in the light of the latest literature.

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INTRODUCTION

Celiac disease is an immune-mediated systemic disease triggered by intake of gluten and related prolamines in genetically susceptible individuals, characterized by presence of various combinations of small intestinal damages, celiac specific antibodies, human leukocyte antigen (HLA)-DQ2 or HLA-DQ8, and gluten-dependent clinical manifestations[1]. Gluten is found in wheat, barley, rye, and oats[2].

PATHOGENESIS

The key elements of the celiac disease, an autoimmune disease, are genetics HLA-DQ2 and HLA-DQ8 genotypes, environmental factors (gluten intake), and autoantigen to tissue transglutaminase (tTG), which are known to play an important role in the pathogenesis[3]. In addition to genetic susceptibility and gluten exposure, loss of intestinal barrier function, gluten-induced proinflammatory innate immune response, inappropriate adaptive immune response, and unbalanced gut microbiome all seem to be components of the celiac disease autoimmunity[3]. More than 99% of celiac patients have HLA-DQ2 or HLA-DQ8 compared to 40% in the general population[4].

It has been suggested that breast milk, mode of delivery, and the age of gluten intake in infants are a risk for developing celiac disease and may affect the incidence of celiac disease. However, there is a limited information in retrospective studies that those factors affect the risk of developing celiac disease[5-7].

Furthermore, it has been suggested that gastrointestinal system (GIS) infections such as rotavirus may increase the risk of developing celiac disease, and therefore rotavirus vaccine may significantly reduce the risk of celiac disease especially in infants with gluten intake before 6 mo[8].

EPIDEMIOLOGY

The prevalence of celiac disease in the general population is estimated to be 1% in the world[9]. The seroprevalence of celiac disease and a biopsy-proven prevalence of celiac disease in the world is 1.4% and 0.7%, respectively[10]. Its prevalence varies depending on geographical and ethnic variations. The highest prevalence is in Europe (0.8%) and Ocenia (0.8%), and the lowest prevalence is in South America (0.4%). The biopsy-proven prevalence of celiac disease was found to be 1.5 times higher in women than men, and approximately two times higher in children than adults. The reason for this difference may be genetic factors [human leukocyte antigen (HLA) and non-HLA genes], environmental factors such as wheat consumption, age at gluten intake, gastrointestinal infections, proton pump inhibitor and antibiotic use, and the rate of cesarean section[10-12].

Celiac disease can occur at any age from early childhood to old age. It has two peaks; the first peak occurs after gluten intake within the first 2 years of life, the second is seen in the second or third decade of life. The diagnosis of celiac disease is difficult because symptoms vary from patient to patient[13].

The prevalence of celiac disease has increased significantly in the last 30 years, the reason for this is not only the increased knowledge and awareness of physicians about celiac disease but also due to the widespread use of highly sensitive and specific

diagnostic tests for celiac disease[14,15]. For example, the incidence of pediatric celiac disease in Canada has increased 3-fold after the use of the endomysial antibody (EMA) test[16]. Despite increased awareness and knowledge about celiac disease, up to 95% of celiac patients still remain undiagnosed[17-19]. The delay in celiac disease diagnosis is reported to be 4-10 years in some studies[20,21]. There are many undiagnosed cases even in developed countries. Very few patients have clinically significant signs of celiac disease. The majority of cases have atypical signs or vague symptoms, so the diagnosis could not be made or diagnosis is delayed[22,23]. The reason for delayed or overlooked diagnosis may be the limited accessibility to serological diagnostic tests in developing countries and the lack of experienced specialists in this field[24].

The risk of developing celiac disease is higher in first- and second-degree relatives of celiac patients, Down syndrome, type 1 diabetes mellitus (DM), selective immunoglobulin (Ig)A deficiency, autoimmune thyroiditis, Turner syndrome, and Williams syndrome (Table 1)[25-28]. Screening tests for celiac disease at risk groups such as type 1 DM, autoimmune thyroid diseases, and first degree relatives of celiac patients also contributed to the increase in prevalence of celiac disease[27,29,30].

The prevalence of celiac disease in first degree relatives of celiac patients is as high as 10%-20%[1,31]. In a recent study of Sahin *et al*[32] the prevalence of celiac disease (CD) in siblings of pediatric celiac patients is reported to be 3.9%. The prevalence of CD in monozygotic twins has been found as high as 75%-80%[33,34].

In recent years, there has been a marked increase in the number of people having gluten-free diet. Furthermore, it has been observed that first-degree relatives of celiac patients start on a gluten-free diet before serologic tests for celiac disease were performed[35]. Therefore, before performing a serological test for celiac disease, it should be paid attention to whether they are on a gluten-free diet. Otherwise, the result of serological tests may be negative, and it would be difficult to diagnose celiac disease. Patients should take gluten-containing foods for 2-8 wk before serological tests[36].

CLINICAL MANIFESTATIONS

Symptoms usually occur in children after ingestion of gluten containing grains between 4 and 24 mo. There may be a delay or latent period between gluten intake and the onset of symptoms[37].

GIS and extra-intestinal manifestations are common in celiac disease[38]. The main GIS manifestations of celiac disease are chronic diarrhea, recurrent abdominal pain, nausea, vomiting, and abdominal distension. Common extra-intestinal manifestations are failure to thrive, short stature, chronic anemia, osteopenia, osteoporosis, delayed puberty, dental enamel defect, irritability, chronic fatigue, neuropathy, arthritis, arthralgia, amenorrhea, and increased liver enzymes[1,38].

Symptoms are usually different in infants than older children. Diarrhea, anorexia, abdominal distension, and abdominal pain are usually seen in younger children. If the diagnosis is delayed, failure to thrive, irritability, and severe malnutrition can be seen. GIS symptoms such as diarrhea, nausea, vomiting, abdominal pain, abdominal distension, weight loss, and constipation may occur in older children depending on the amount of gluten intake[28,37]. GIS signs of celiac disease such as diarrhea are seen in approximately 50% of patients[39-41].

The presentations of CD have significantly changed in the last few decades[41-48]. Classical symptoms of celiac disease occur in a minority of celiac patients, while older children have either minimal or atypical symptoms. GIS symptoms are mild or nonspecific[48,49].

It has been shown that pediatric patients diagnosed with celiac disease who are younger age at the diagnosis have less severe symptoms in the last 20 years. Also, it has been reported that the rate of asymptomatic patients, closer follow up, and strict adherence to gluten-free diet is higher in the last 10 years and that normalization of serological tests is faster than in the last decade[42].

Recently, the clinical symptoms of children with celiac disease are observed to change from GIS symptoms to extra-intestinal symptoms[39,50]. The exact reason for this is unclear, but it has been suggested that there may be increased awareness and widespread use of highly sensitive and specific serologic tests. It has been reported that isolated short stature is seen in up to 47.5% of celiac patients[41,51].

Table 1 Groups with higher risk of developing celiac disease

Groups with higher risk of developing celiacdisease
First-degree relatives of celiac patients
Second-degree relatives of celiac patients
Type 1 diabetes mellitus
Autoimmune thyroid disease
Autoimmune liver disease
Down syndrome
Turner syndrome
Williams syndrome
Selective IgA deficiency
Systemic lupus eryhtematosus
Juvenile chronic arthritis

EXTRA-INTESTINAL MANIFESTATIONS

Extra-intestinal findings are seen in up to 60% of pediatric celiac patients (Table 2)[52]. Short stature is the most common finding in children[52-54]. It has been reported that 10%-47.5% of pediatric celiac patients have short stature at the time of diagnosis[41,54-57]. Nineteen percent to 59% of the non-endocrinologic causes of short stature are reported to be celiac disease[55,56,58-60]. Starting a gluten-free diet in the early period causes rapid growth and weight catch up, especially in the first 6 mo. The target height is usually reached within 3 years after diagnosis. If the target height is not reached despite a strict gluten-free diet, endocrinological evaluation should be done to rule out growth hormone deficiency[55,61-63].

Hypogonadism in girls and delayed puberty in boys due to androgen resistance is a common finding in undiagnosed or untreated pediatric celiac patients[55,64,65]. Delayed puberty is seen in 10%-20% of celiac patients[52,66]. Generally, the development of puberty occurs within 6-8 mo after starting a gluten-free diet. If delayed puberty persists, the patient should be referred to pediatric endocrinology for further evaluation of other disorders of the reproductive system[55,67].

Iron deficiency anemia is seen in up to 40% of pediatric celiac patients[52,53,68,69]. Since iron is absorbed from the first part of the duodenum, which is mainly affected by celiac disease, iron deficiency anemia is common in celiac patients. It has been reported that 84% of pediatric celiac patients have the complete recovery of iron deficiency anemia with a strict gluten-free diet and iron supplementation therapy within 12-24 mo[52].

Hypertransaminasemia is seen in 9%-14% of celiac patients[70]. Mostly, liver damage is reversible, and liver failure rarely occurs[71]. It has been suggested that as a result of exposure to more hepatotoxins through the portal circulation due to the altered intestinal permeability, inflammation and liver damage may occur[54,72]. The response to a strict gluten-free diet is excellent. The increased liver enzymes return to normal by the rate of 75%-90% within 12-24 mo with a strict gluten-free diet[73].

Osteopenia and osteoporosis are usually seen in patients with celiac disease. Approximately 75% of celiac patients have osteopenia and 10%-30% have osteoporosis [74]. Secondary hyperparathyroidism occurs due to the insufficient absorption of vitamin D and calcium from the damaged duodenal mucosa. It is commonly seen in 12%-54% of celiac patients[75]. Normal blood levels of vitamin D and calcium is observed within the first year after a strict gluten-free diet[76,77].

The most common joint and muscle disorders seen in celiac disease are myopathy, arthralgia, and non-erosive arthritis[55,78]. Since arthralgia is mostly seen after the age of 12, the most common finding in pediatric celiac patients is subclinical synovitis. It is most commonly seen in the knee joint. Its incidence is 5%-10%[54]. Since symptoms are mild, ultrasonography is important in the diagnosis of joint disorders.

The most common finding of neurological manifestations is headache, which is seen in up to 20% of celiac patients. More rarely, ataxia and neuropathy (0.1%-7.4%) are seen[79,80]. The prevalence of epilepsy is reported to be 1.43 times higher in children with celiac disease compared to the general population[81]. The relationship between

Table 2 Extra-intestinal manifestations of celiac disease

Extra-intestinal manifestations of celiac disease
Short stature
Anemia
Osteopenia/osteoporosis
Delayed puberty
Dental enamel defects
Dermatitis herpetiformis
Recurrent aphtous stomatitis
Neurological manifestations; peripheral neuropathy, epilepsy, ataxia, headache
Arthritis, arthralgia
Infertility
Amenorrhea
Elevated liver enzymes
Alopecia
Anxiety, depression

epilepsy and CD is still unclear.

The exact prevalence of enamel defects in celiac disease is unknown. In recent studies, it has been reported that enamel defects are seen in 55%-64% of celiac patients [82,83].

Aphthous stomatitis is seen in up to 46% of celiac patients[84]. Although its mechanism is not known exactly, it is usually completely cured with a strict gluten-free diet[52].

Dermatitis herpetiformis is thought to be an extra-intestinal manifestation of celiac disease, but it is relatively rare in pediatric celiac patients in Finland[85]. Unlike celiac disease, its annual incidence is decreasing. The reason for this is unknown exactly[85]. In contrast to that study, it has been reported that it is more common in childhood[86].

ASSOCIATED DISEASES WITH CELIAC DISEASE

The risk of another autoimmune disease is three to 10 times higher in patients with celiac disease compared to the general population[87,88].

The most common accompanying disease is type 1 DM since it has common genetic factors and pathogenic mechanisms with celiac disease[89]. HLA-DQ2 is present in approximately 90%-95% of celiac patients and 50% of type 1 DM patients, but HLA-DQ8 is detected in approximately 10% of celiac patients and approximately 70% of type 1 DM patients[90]. In a systematic review, the prevalence of celiac disease in patients with type 1 DM was reported to be approximately six times higher than in the general population[91]. The prevalence of celiac disease was reported to be 2.4%-16.4% in children with type 1 DM[92-95]. There is consensus about initial screening for celiac disease in newly diagnosed DM patients, but it is not clear when and how often to screen for celiac disease and initiate a gluten-free diet in asymptomatic patients[93]. It has been recommended that screening test for CD should be done at the time of type 1 DM diagnosis and then every 2 years[96]. In another study, it was recommended that children diagnosed with type 1 DM should be screened for celiac disease once a year for the first 5 years[92]. In other studies, it has been recommended that serological screening tests for celiac disease should be done within the first 2 years when the diagnosis is made, then 5 years after the diagnosis and if there is any symptom suggestive of CD[93,97]. Since 58%-85% of type 1 DM patients diagnosed with CD are asymptomatic, early diagnosis of CD is very important to prevent long-term complications such as failure to thrive, osteopenia, infertility, and malignancy[29,77,92,93,98,99].

There is good evidence that autoimmune thyroid diseases are associated with celiac disease[1,100]. The prevalence of celiac disease in patients with autoimmune thyroid

disease is found to be 3.0%-4.8%[30,101,102].

Also, the prevalence of celiac disease in patients with selective IgA deficiency is reported to be 10-20 times higher than in the general population[103].

There is a close relationship between Down syndrome and celiac disease. The prevalence of celiac disease in patients diagnosed with Down syndrome is reported to be 5%-12%[104-108]. The North American Society for Paediatric Gastroenterology, Hepatology and Nutrition and The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommend screening tests for celiac disease in children with Down syndrome due to the increased risk of developing celiac disease [28]. In a study conducted in 2020, involving 1317 pediatric patients with Down syndrome aged 3 and over, the prevalence of celiac disease was found to be 9.8% in children with Down syndrome[109]. If screening test for celiac disease is not done, the diagnosis of celiac disease is either overlooked or delayed in 82% of the patients with Down syndrome, thus causing increased morbidity[109].

The increased prevalence of celiac disease is also seen in autoimmune liver disease, Turner syndrome, and Williams syndrome[1,110-116].

THE DEFINITONS RELATED TO CELIAC DISEASE

Silent celiac disease

Silent celiac disease is defined by the presence of celiac antibodies and HLA-DQ2 or HLA-DQ8 and small intestinal biopsy findings compatible with celiac disease especially in patients with autoimmune disease or a genetic disorder or relatives of celiac disease but without any symptoms suggestive of CD[1].

Potential celiac disease

Potential celiac disease is defined by the presence of celiac antibodies, HLA-DQ2 or HLA-DQ8, but intestinal biopsy is not compatible with celiac disease. Marsh classification score 0 or 1 is detected in intestinal biopsy, and the risk of developing celiac disease is increased[117].

Clinical symptoms and signs of the celiac disease are not always seen. Even if there are clinical findings, they are usually mild. The diagnosis of potential CD has increased significantly in recent years due to increased use of serological screening for celiac disease in the general population. A lower prevalence of HLA-DQ2 and a higher prevalence of HLA-DQ8 are detected in potential celiac patients compared to active celiac patients[118].

It should be considered that the cause of negative intestinal biopsy may be the patchy involvement of the small intestinal mucosa, low gluten intake, and inappropriate biopsy orientation[119].

Its treatment is still uncertain and controversial. There is no consensus about how often celiac serological tests should be performed in potential celiac patients on a gluten-containing diet, and how often they should be evaluated clinically[120]. It has been reported that villous atrophy is observed in 33% of symptomatic potential celiac patients after 3 years[121]. Therefore, it has been suggested that symptomatic patients should be given a gluten free diet.

Refractory celiac disease

Refractory celiac disease is characterized by the persistence of symptoms and intestinal villous atrophy despite a strict gluten-free diet for at least 12 mo. Generally, celiac antibodies are negative in most patients at the time of diagnosis, but the presence of high-titer antibodies does not rule out the refractory celiac disease. In all cases, dietary adherence should be carefully questioned. It can cause complications such as ulcerative jejunoileitis, collagenous sprue, and intestinal lymphoma[117].

Seronegative celiac disease

It is characterized by the presence of clinical signs of severe malabsorption and intestinal villous atrophy and negative celiac antibodies[122]. It constitutes approximately 2%-3% of celiac patients. Seronegative celiac disease can be confirmed with improvement in both symptoms and histology 1 year after starting a gluten-free diet [122]. Compared with classical celiac disease, seronegative celiac patients are associated with a higher rate of autoimmune disease, and these patients have a higher risk of developing refractory celiac disease[122].

In this form of celiac disease, genetic analysis is the key step for the diagnosis, because if it is found as negative, celiac disease is ruled out. Other diseases causing villous atrophy are parasitic infections (*e.g.*, *Giardia lamblia*), autoimmune enteropathy, small intestinal bacterial overgrowth, common variable immunodeficiency, eosinophilic gastroenteritis, drug induced enteropathy (*e.g.*, olmesartan, mycophenolate), intestinal lymphoma, Crohn's disease, tropical sprue, human immunodeficiency virus enteropathy, and Whipple disease should be considered in the differential diagnosis (Table 3)[122-124].

Non-responsive celiac disease

Non-responsive celiac disease is defined by the persistence of GI symptoms more than 12 mo despite a strict gluten-free diet. The most common causes of non-responsive celiac disease are persistent gluten ingestion and incorrect diagnosis[125,126]. It needs to be differentiated from active celiac disease and other conditions associated with celiac disease.

DIAGNOSIS

The clinical symptoms of celiac disease are very diverse. Celiac patients may present with symptoms of GIS or extra-intestinal symptoms or no symptoms at all. Therefore, serologic tests for celiac disease should be done in patients with unexplained chronic or intermittent diarrhea, failure to thrive, weight loss, delayed puberty, short stature, amenorrhea, iron deficiency anemia, nausea, vomiting, chronic abdominal pain, abdominal distension, chronic constipation, recurrent aphthous stomatitis, and abnormal liver enzyme elevation[1].

Furthermore, celiac disease should be investigated in patients with high risk of developing celiac disease, such as type 1 DM, Down syndrome, autoimmune thyroid disease, Turner syndrome, selective IgA deficiency, autoimmune liver disease, and first-degree relatives of celiac patients, even if they are asymptomatic[1].

Celiac disease is diagnosed by a variable combination of symptoms, positive celiac antibodies, presence of HLA-DQ2/DQ8, and duodenal histology[1].

ESPGHAN guidelines from 2012 recommend tissue tTG-IgA test, which is highly sensitive and specific and less costly compared to EMA IgA antibody test, as an initial screening test for suspected celiac disease, and the total IgA test to rule out selective IgA deficiency. The analysis of deamidated gliadin peptide (DGP) IgA test is recommended for children under 2 years of age. If there is IgA deficiency, the tTG-IgG test or the EMA-IgG test or the DGP-IgG test should be performed[1].

If serological tests are negative for tTG-IgA and total IgA level is normal, celiac disease is unlikely. In this condition, the reasons leading to the false negative tTG result should be considered. Those are low gluten intake, protein-losing enteropathy, use of immunosuppressive drugs, and patients under 2 years of age. If the tTG is found as positive [lower than 10 times upper limit of normal (ULN)], gastroduodenoscopy and multiple biopsies of the small intestine should be performed to confirm the diagnosis[1].

If the tTG is higher than 10 times ULN in a symptomatic patient, it should be discussed with the parents in order to make a diagnosis of celiac disease without biopsy. If the parents agree, EMA test and HLA-DQ2/DQ8 analysis are performed. To rule out false positivity of the tTG test, an EMA test is performed from a second blood sample. If EMA and HLA-DQ2 or HLA-DQ8 are positive, celiac disease is diagnosed without biopsy[1]. In practice, it has been reported that this reduces the need for endoscopy by 30%-50%[127].

Since celiac disease causes patchy involvement in the small intestine, at least four biopsies from the duodenum and at least one biopsy from the bulbus should be performed by gastroduodenoscopy. Biopsies are evaluated according to modified Marsh-Oberhuber classification (Table 4)[128]. Since the lesion of celiac disease can only be seen in the bulb, at least one biopsy should be taken from the bulb[129].

While interpreting the serological test results of celiac disease, serum total IgA levels, the amount of gluten consumption, use of immunosuppressive drugs, and age of the patient should be considered[1]. IgG class celiac antibody tests should be performed in patients with low serum IgA levels (total serum IgA < 0.2 g/L)[1].

If the patient has the gluten-free diet for a long time or gluten-free diet for a short time before testing, false negative results may occur[130]. Therefore, patients should take definitely gluten-containing foods before the test. Gluten challenge test should be performed for patients with a gluten-free diet before serological tests, 3-7.5 g/d gluten-

Table 3 Other diseases causing villous atrophy

Other diseases causing villous atrophy
Parasitic infections (*Giardia lamblia*)
Autoimmune enteropathy
Small intestinal bacterial overgrowth
Common variable immunodeficiency
Cow's milk or soya protein hypersensitivity
Intractable diarrhea of infancy
Eosinophilic gastroenteritis
Drug induced enteropathy (*e.g.*, olmesartan, mycophenolate)
Intestinal lymphoma
Crohn's disease
Human immunodeficiency virus enteropathy
Tropical disease

Table 4 The modified Marsh classification

	IEL	Crypts	Villi
Type 0	< 40	Normal	Normal
Type 1	> 40	Normal	Normal
Type 2	> 40	Hypertrophic	Normal
Type 3a	> 40	Hypertrophic	Mild atrophy
Type 3b	> 40	Hypertrophic	Marked atrophy
Type 3c	> 40	Hypertrophic	Absent

IEL: Intraepithelial lymphocyte count/100 epithelial cells.

containing diet (approximately two slices of bread) is recommended for 2 wk[131].

If the patient is strongly suspected of celiac disease, multiple intestinal biopsy and HLA-DQ2/DQ8 analysis are recommended, even if the serological tests for celiac disease are negative. If the histology is compatible with celiac disease but HLA-DQ2/8 negative, celiac disease is unlikely and other causes of enteropathy should be investigated (Table 3)[1]. Celiac disease is diagnosed if the celiac serological tests are positive and the biopsy is compatible with celiac disease.

ESPGHAN guidelines from 2020 report that the tTG-IgA test and total IgA test combination give more accurate results than other test combinations as the initial test for suspected celiac disease regardless of age. If total IgA level is found to be low, tTG-IgG test or EMA-IgG test or DGP-IgG test should be performed (Figure 1)[119].

If the tTG test is found as positive (> 10 times ULN), HLA-DQ2/8 analysis is not recommended in the ESPGHAN 2020 guidelines even if the patient is asymptomatic. It has been suggested that the EMA test should be checked in a second blood sample and if the EMA test is detected positive and the family agrees, celiac disease can be diagnosed without biopsy. In other words, the presence of HLA-DQ2/8 analysis and clinical symptoms are not mandatory for celiac diagnosis in last guideline in 2020 (Figure 1)[119].

If HLA-DQ2/DQ8 test is negative, the probability of celiac disease is low, but a positive HLA-DQ2/DQ8 test does not confirm the diagnosis of celiac disease[132]. If the tTG test is detected positive (< 10 times ULN), multiple intestinal biopsy is recommended to rule out false positivity. It is not recommended to diagnose without biopsy in patients with selective IgA deficiency even if IgG-based antibody positivity is detected[119].

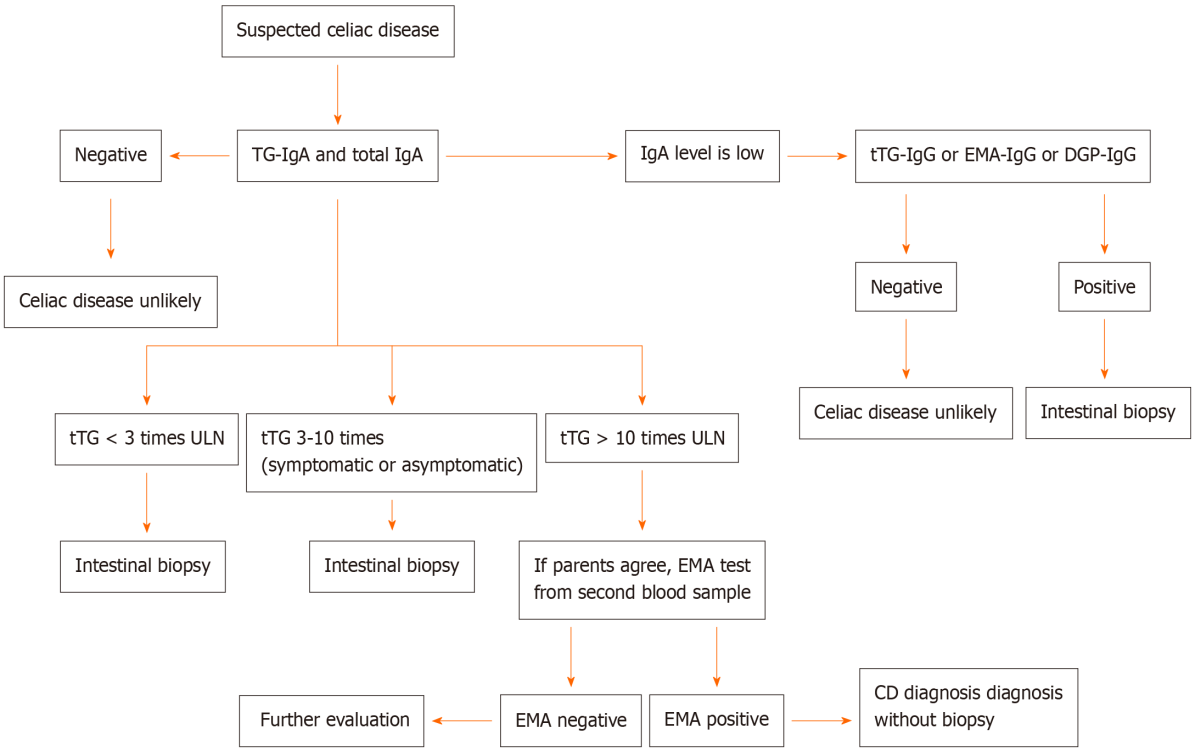

Figure 1 Algorithm for diagnosis of celiac disease. CD: Celiac disease; DGP: Deamidated gliadin peptide; EMA: Endomysial antibody; tTG: Tissue transglutaminase antibody; ULN: Upper limit of normal.

It has been considered that villous atrophy may be seen in other GIS diseases such as parasitic infections, autoimmune diseases, bacterial overgrowth in the small intestine, and Crohn's disease (Table 3)[133].

It has been reported that the pooled sensitivity and specificity of tTG or DGP or tTG + antigliadin antibodies for diagnosing celiac disease is 94.0% and 94.4%, respectively, in a systematic review[134]. It has been suggested that those tests can be used in places where access to laboratory tests is limited.

MANAGEMENT

Currently, the only effective treatment is a lifelong gluten-free diet. Significant improvements in symptoms, normalization of biochemical tests, and improvement in quality of life with a strict gluten-free diet are seen[135].

Rapid improvement in clinical symptoms is observed within 2-4 wk in children. Serological and histological responses are slower compared to clinical symptoms[136]. Although histological response in children is observed within 2 years by a rate of 95%, this rate is 60% in adults[137].

The amount of tolerable gluten varies from patient to patient. As little as 50 mg of gluten, present in a few amounts of bread crumbs or a small piece of cake or traces of contamination, may cause symptoms and/or enteropathy in asymptomatic patients [135,138]. It is unlikely that a gluten intake of less than 10 mg/d will cause significant histological abnormality[139].

Adherence to the gluten-free diet is better in children diagnosed with CD at an early age and those who continue to follow up regularly. It is less in adolescents compared to adults[135].

It has been reported that there is a direct relationship between the duration of exposure to the gluten-free diet and increased autoimmune disorders[140].

In a multicenter prospective study involving 6605 children with the HLA genotype associated with celiac disease, it was shown that the amount of gluten exposure in the first 5 years of life is associated with the development of celiac disease and celiac autoimmunity[141]. Since celiac disease is a multisytemic disease that affects multiple organs, a lifelong gluten-free diet may reduce malignant and non-malignant complications[142].

FOLLOW-UP

Currently, there are no standard evidence-based recommendations for the follow-up of pediatric celiac disease[143].

Patients with celiac disease should be followed up 6 mo after diagnosis and every 6 mo in terms of improvement in symptoms, compliance with the gluten-free diet, quality of life, and progressive normalization of celiac-associated antibodies. Screening tests should be done in terms of autoimmune thyroid disease. A control duodenal biopsy is not required after a gluten-free diet. However, if there is a partial or no response to the gluten-free diet, careful examination should be done for involuntary gluten contamination or poor compliance with the gluten-free diet. If the response to a strict gluten-free diet is poor, duodenal biopsy can be performed[135,143,144].

Earlier diagnosis of celiac disease in asymptomatic patients is associated with better quality of life as well as better compliance with the gluten-free diet[42,145,146].

It has been shown that pediatric patients who are lost to follow up are less adherent to the gluten-free diet and have positive celiac serological antibodies[147]. It has been shown that the regular control is very important.

Routine testing for vitamin and mineral deficiency is reported to be unnecessary in the vast majority of children who follow up to regular controls and have normal growth and development and have no symptoms[148].

The essential marker of the success of the gluten-free diet is still satisfactory height and weight gain in children and adolescents[135].

The best marker of proper follow-up and management is the decline in the antibody levels and the return of antibody levels to normal in follow-up. The presence of persistent positive antibodies usually indicates ongoing intestinal damage and gluten exposure. Serological follow-up should be done within 6 mo and 12 mo after diagnosis and then once a year[149].

tTG-IgA test is reported to be best test in follow up[150]. It has been shown that the average time to return to normal levels of the tTG test in patients with strictly adherent to the gluten-free diet is 1 year[151].

It has been detected that there is no correlation between symptoms and mucosal healing[152]. Gluten challenge test can be performed in cases when there is a doubt about the initial diagnosis of celiac disease. However, HLA typing should be done before evaluation of mucosal damage. Gluten challenge is not recommended under 5 years of age and during pubertal development[1].

In recent studies, it has been reported that gluten consumption can be shown in symptomatic and asymptomatic patients who are unaware of gluten intake by gluten immunogenic peptide tests in stool and urine[153,154]. Gluten intake of more than 50 mg/d for stool test and more than 25 mg/d for urine test seems to be necessary for the sensitivity of the test[153]. Dietary adherence to the gluten-free diet can be evaluated with this test. It can replace serological tests in follow-up, but its use in routine practice is still uncertain and further studies are needed.

DIETS AND NEW TREATMENTS

Currently, the only effective treatment is still to avoid gluten completely for life. The adherence to the gluten-free diet has some disadvantages; negative impact on quality of life, psychological problems, involuntary gluten contamination, possible vitamin and mineral deficiencies, metabolic syndrome, increased cardiovascular risk, and severe constipation[153,155-157].

Approximately 40% of celiac patients are not satisfied with the gluten-free diet due to the negative effect on their quality of life and seek alternative treatments[158,159].

Clinical studies are still ongoing in the treatment of celiac disease. Larazotide acetate is a zonulin antagonist that blocks the tight junction, thus restricting the passage of gluten through the permeable intestinal mucosa[160]. This drug is shown to be effective in controlling gluten-related symptoms[160]. There is also limited information that larazotide may allow patients to tolerate minimal amounts of gluten (involuntary gluten contamination or short-term feeding with a small amount of gluten).

ALV003 (latiglutenase) reduces gluten into small pieces in the stomach before it passes into the duodenum[161]. In a study involving 494 celiac patients, latiglutenase was compared with placebo. It has been shown that latiglutenase did not improve histological findings or symptoms[162]. Further studies are needed.

Vaccination (Nexvax2) is another therapeutic option intended to be used for desensitization in celiac patients against gliadin peptides. Although its major side effects are abdominal pain and vomiting, it passed phase 1. Given the effectiveness of vaccines, it can be a definitive cure for celiac disease[163].

COMPLICATIONS

Complication are usually manifested in late-diagnosed celiac patients (after the age of 50) and in patients not adhering to a strict gluten-free diet. These patients have a higher mortality than the general population[164], but complications are rare (< 1%)[165].

Complications of celiac disease include hyposplenism, refractory celiac disease, intestinal lymphoma, small bowel adenocarcinoma, and ulcerative jejunoileitis[166].

Despite adhering to a gluten-free diet and having complaints that cannot be explained by any other reason, complications should be considered in every patient whose symptoms persist.

CONCLUSION

Celiac disease is a lifelong multi-systemic disease triggered by intake of gluten in genetically susceptible individuals.

Serologic tests for CD should be done in patients with unexplained chronic or intermittent diarrhea, failure to thrive, weight loss, delayed puberty, short stature, amenorrhea, iron deficiency anemia, nausea, vomiting, chronic abdominal pain, abdominal distension, chronic constipation, recurrent aphthous stomatitis, and abnormal liver enzyme elevation.

Since tTG-IgA test and total IgA test combination give more accurate results than other test combinations, ESPGHAN 2020 guideline recommends this combination as the initial test for suspected celiac disease regardless of age. While interpreting the serological test results of celiac disease, serum total IgA levels, the amount of gluten consumption, use of immunosuppressive drugs, and age of the patient should be considered.

Early diagnosis of CD is very important to prevent long-term complications such as failure to thrive, osteopenia, infertility, and malignancy.

Currently, the only effective treatment is a lifelong gluten-free diet.

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ORIGINAL ARTICLE

Retrospective Study

Indirect determination of serum creatinine reference intervals in a Pakistani pediatric population using big data analytics

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Author contributions: Ahmed S designed and conceived the idea, performed the literature review/comparison, interpreted the data and performed the majority of the write up in the first draft; Zierk J performed the statistical analysis, assisted in the write up of the first draft and critically reviewed the manuscript; Siddiqui I critically analyzed the results and reviewed the manuscript; Khan AH assisted with data acquisition and critically reviewed the manuscript; all the authors have accepted responsibility for the entire content of the submitted manuscript and approved submission.

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Abstract

BACKGROUND

The indirect methods of reference intervals (RI) establishment based on data mining are utilized to overcome the ethical, practical challenges and the cost associated with the conventional direct approach.

AIM

To generate RIs for serum creatinine in children and adolescents using an indirect statistical tool.

METHODS

Data mining of the laboratory information system was performed for serum creatinine analyzed from birth to 17 years for both genders. The timeline was set at six years from January 2013 to December 2018. Microsoft Excel 2010 and an indirect algorithm developed by the German Society of Clinical Chemistry and Laboratory Medicine's Working Group on Guide Limits were used for the data analysis.

RESULTS

Data were extracted from 96104 samples and after excluding multiple samples for the same individual, we calculated RIs for 21920 males and 14846 females, with stratification into six discrete age groups.

CONCLUSION

Serum creatinine dynamics varied significantly across gender and age groups.

Key Words: Creatinine; Pediatric; Reference intervals; Indirect; Data mining; Pakistan

identification anonymized.

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Core Tip: Good laboratory practices advocate the necessity for generation of population specific reference intervals (RIs). The indirect methods of RIs establishment based on data mining are utilized to overcome the ethical, practical challenges and the cost associated with the conventional direct approach. The population specific RIs generated for pediatric serum creatinine levels in this study will assist in more accurate comprehension of the variations in creatinine and facilitate patient care.

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INTRODUCTION

Reliable, accurate and population specific reference intervals (RIs) for laboratory analyses are pivotal for laboratory results interpretation and appropriate clinical decision-making. RIs for an analyte are based on the 2.5th and 97.5th centiles values from a set of pre-defined healthy individuals[1,2]. Furthermore, to improve the diagnostic efficiency of biomarkers, various partitioning criteria for RIs have been deployed, particularly aimed to evaluate the influence of increasing age and gender dependence[3,4]. In the pediatric population, this portioning becomes more essential as physiological developments after birth and during adolescence result in fluctuations in the levels of many biomarkers, especially serum creatinine (CREA)[5].

The most commonly utilized and recommended 'direct approach' for RIs generation follows a more robust strategy, with a pre-selected population, that undergoes sample collection, processing and analysis in a controlled environment[6]. However, to utilize this approach in pediatrics is a challenging task, owing to ethical, financial and practical issues. Whereas, the indirect approach can be more effectively and conveniently utilized as an alternative route[6,7]. Analyte specific results from laboratory health records that comprise results obtained from healthy individuals as well as pathologic test results from clinical care areas are extracted in the indirect method and no additional blood samples are drawn, which is of utmost concern in children. This approach is swift and cost-effective especially for low middle-income countries (LMIC). Moreover, use of a minimum of 400 reference subjects for each partition aimed at obtaining statistically reliable RI calculations is further recom-mended, which can be conveniently accomplished with this approach[8].

In most clinical settings, evaluation of kidney function is carried out by requisition of biochemical analysis of serum CREA and 24 h CREA clearance as an indirect measure for the estimation of glomerular filtration rate (GFR)[9]. However, the growth mediated changes in CREA, especially in infancy and during puberty, due notably to its renal tubular secretion and the influence of muscle mass and dietary intake, makes the interpretation even more challenging[10].

The majority of laboratories in LMIC, are unable to establish their population specific RIs and seldom rely on published literature or adopt the ones cited by the manufacturers in kit information sheets[11]. Whereas, some laboratories also imple-ment RIs calculated based on different analytical platforms and reagents than the ones in actual use. The inappropriate RIs adopted can lead to errors in report interpretation, ultimately leading to compromised patient safety, unnecessary further testing and costs, especially for LMIC. Our primary objective was to establish gender- and age-specific RIs for CREA specific to Pakistani children and adolescents using a validated indirect statistical approach[5,7,12].

MATERIALS AND METHODS

Study design and subjects

A team of investigators performed data mining of the laboratory information system at the Section of Clinical Chemistry, Aga Khan University. Ethical approval for the study was obtained from the Ethical review committee (ERC, #5348-Pat-ERC-18) of the university. All serum CREA measurements for both genders, including both in-house as well as ambulatory cases from birth to 17 years, were retrieved, regardless of the indication for test requisition. The timeline was set at six years from January 2013 to December 2018.

Biochemical analysis

The biochemical analysis was carried out on a Siemens ADVIA 1800 platform. The precision of the assay was 3.8% at 1.8 mg/dL (159 μmol/L) and 3.7% at 8.4 mg/dL (743 μmol/L), and the method was linear from 0-25 mg/dL (0-2210 μmol/L). As most of the laboratories in Pakistan are well versed with the conventional system of units, the levels of CREA are expressed in mg/dL. The laboratory is accredited by the College of American Pathologist and internal quality assurance is practiced in light of the Clinical & Laboratory Standards Institute standards.

Statistical analysis

The statistical analysis was performed using Microsoft Excel 2010 and the indirect algorithm proposed and pre-validated the German Society of Clinical Chemistry and Laboratory Medicine's Working Group freely available online as a software pack-age [5,7,12]. The method is based on utilizing an input dataset of laboratory values containing both non-pathologic and pathologic samples, but only one sample per patient. A Power Normal distribution, defined as Gaussian distribution following Box-Cox transformation was performed to model the distribution of non-pathologic samples in the dataset. As per the default settings, the abnormal values are expected outside the distribution of normal CREA results, with an adjustment of the algorithm for the generation of the upper limits of the RI, by setting the Pathological value to "high", compared to the physiological test results.

To calculate the respective 2.5th and 97.5th percentiles, the data were split into six age groups, for each gender, ranging from birth *i.e.*, 0 d- < 2 years, 2- < 5 years, 5- < 9 years, 9- < 12 years, 12- < 15 years and 15- < 17 years, respectively, as defined previously by Tahmasebi *et al*[11] in the CALIPER cohort of healthy children and adolescents[11].

For the evaluation of calculated RIs, we performed a comparison of our results with Tahmasebi *et al*[11] that has established pediatric RIs for CREA on the Siemens ADVIA 1800[11]. Additionally, we also compared our findings with a local study by Molla *et al* [13] that has established direct RIs for CREA in an apparently healthy Pakistani population, for the combined 0-14 and 15 years onwards age groups, respectively, without partitioning into fine grained age clusters[13]. Lastly, the RIs currently in use by our laboratory for children and adolescents adopted from the Tietz textbook of clinical chemistry and molecular diagnostics were also evaluated[14].

RESULTS

From a total of 96104 samples analyzed for CREA over the study timeline, patients with multiple samples were further scrutinized and only the first sample analyzed was included in the final analysis. The lower and upper RIs were calculated based on 36766 CREA results obtained, including 21920 males and 14846 females as depicted in Tables 1 and 2. The complex age-related dynamics were more pronounced in the pre-pubertal group as represented by a significant proportion of samples in this age range.

Figures 1 and 2 illustrate the comparison of our results with RIs established using the direct method as reported by Tahmasebi *et al*[11], Molla *et al*[13] and the current RIs being used for reporting by our laboratory adopted from the Tietz textbook of clinical chemistry and molecular diagnostics.

DISCUSSION

Due to the lack of standardized data formats and experience in dealing with big data analytics, the majority of laboratories in LMIC as well as a few developed countries,

Table 1 Distribution of lower and upper reference intervals of creatinine in Pakistani male children

Age (yr)	*n*	Our study, LRI	Our study, URI	Tahmasebi *et al*[11], LRI	Tahmasebi *et al*[11], URI
< 2	9658	0.15 mg/dL (13 μmol/L)	0.39 mg/dL (34 μmol/L)	0.17 mg/dL (15 μmol/L)	0.52 mg/dL (46 μmol/L)
2- < 5	2964	0.15 mg/dL (13 μmol/L)	0.80 mg/dL (71 μmol/L)	0.18 mg/dL (16 μmol/L)	0.49 mg/dL (43 μmol/L)
5- < 9	2833	0.16 mg/dL (14 μmol/L)	0.69 mg/dL (61 μmol/L)	0.31 mg/dL (27 μmol/L)	0.61 mg/dL (54 μmol/L)
9- < 12	1796	0.27 mg/dL (24 μmol/L)	0.92 mg/dL (81 μmol/L)	0.41 mg/dL (36 μmol/L)	0.68 mg/dL (60 μmol/L)
12- < 15	2291	0.29 mg/dL (26 μmol/L)	1.06 mg/dL (94 μmol/L)	0.43 mg/dL (38 μmol/L)	0.85 mg/dL (75 μmol/L)
15- < 17	2378	0.40 mg/dL (35 μmol/L)	1.26 mg/dL (111 μmol/L)	0.61 mg/dL (54 μmol/L)	1.02 mg/dL (90 μmol/L)

LRI: Lower reference limit, URI: Upper reference limit.

Table 2 Distribution of lower and upper reference intervals of creatinine in Pakistani female children

Age (yr)	*n*	Our study, LRI	Our study, URI	Tahmasebi *et al*[11], LRI	Tahmasebi *et al*[11], URI
< 2	6323	0.12 mg/dL (11 μmol/L)	0.73 mg/dL (65 μmol/L)	0.17 mg/dL (15 μmol/L)	0.52 mg/dL (46 μmol/L)
2- < 5	2012	0.15 mg/dL (13 μmol/L)	0.74 mg/dL (65 μmol/L)	0.18 mg/dL (16 μmol/L)	0.49 mg/dL (43 μmol/L)
5- < 9	1997	0.16 mg/dL (14 μmol/L)	0.68 mg/dL (60 μmol/L)	0.31 mg/dL (27 μmol/L)	0.61 mg/dL (54 μmol/L)
9- < 12	1204	0.26 mg/dL (23 μmol/L)	0.78 mg/dL (69 μmol/L)	0.36 mg/dL (32 μmol/L)	0.63 mg/dL (56 μmol/L)
12- < 15	1573	0.24 mg/dL (21 μmol/L)	0.84 mg/dL (74 μmol/L)	0.40 mg/dL (35 μmol/L)	0.72 mg/dL (64 μmol/L)
15- < 17	1737	0.34 mg/dL (35 μmol/L)	0.93 mg/dL (82 μmol/L)	0.50 mg/dL (44 μmol/L)	0.77 mg/dL (68 μmol/L)

LRI: Lower reference limit; URI: Upper reference limit.

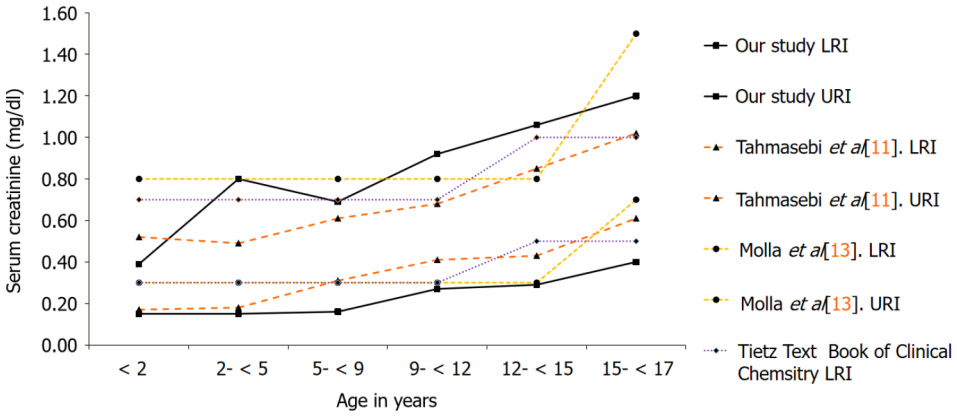

Figure 1 Comparison of serum creatinine reference intervals in males. LRI: Lower reference limit; URI: Upper reference limit.

considerably lag behind in evaluating the transformative potential of the big data they have in store. The methodology employed was based on big data analytics and extraction of data from the laboratory information system of a tertiary care hospital's laboratory that receives specimens from the entire country in order to ensure participation from all the ethnic groups existing in Pakistan.

Compared to the study by Molla *et al*[13] and RIs reported in the Tietz textbook of clinical chemistry and molecular diagnostics, a notable strength of this study is that it demonstrates a strong influence of age on CREA activity with the age-wise partitioning of RIs[12,13]. The differences noted, adds strength to the fact that it is imperative in clinical care to use age- and gender-specific RIs, for adequate comprehension of the dynamics of this widely used renal biomarker[5].

A literature review revealed that most of the reported RIs for CREA, have been established using healthy population-based approaches *i.e.* direct methods. While this approach is undoubtedly considered the gold standard, it has certain limitations

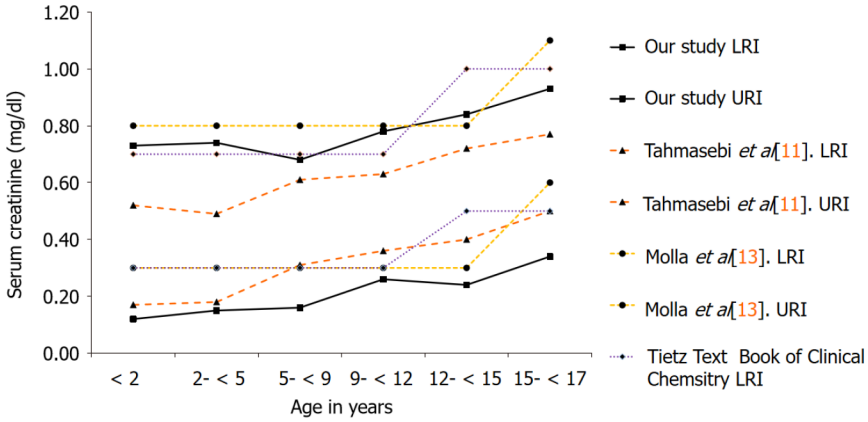

Figure 2 Comparison of serum creatinine reference intervals in females. LRI: Lower reference limit; URI: Upper reference limit.

including those specifically pertaining to expenses for conducting these large-scale prospective studies especially for a LMIC. Additionally, attainment of a minimally acceptable sample size for the different age groups in pediatrics is also a concern. The indirect method not only made it possible to statistically analyze big data (n = 36766), acquired as part of routine care, which further minimized the ethical and practical concerns. However, this approach, requires significant refinement of the specimen selection alongside validated and robust statistical analysis. In this context, we utilized an established algorithm that had already been extensively evaluated and validated by large scale multicenter studies[4,15]. Notably, a literature review revealed that RIs in children established using direct methods do not correctly account for the extensive changes with age as most of them lack age-based partitioning. Moreover, in instances of non-normal distribution, the direct method often generates unacceptably broad confidence intervals (CIs) limiting their widespread adoption[16].

Next to, the RIs reported in the CALIPER cohort, our proposed RIs for CREA seem to differ. In particular, our lower reference limits (LRIs) are considerably lower than the CALIPER cohort, indicating that Pakistanis tend to have a different genetic structure with significantly lower lean tissue mass and a lower GFR compared to the CALIPER cohort. The LRIs and upper reference limits from the CALIPER cohort and the study by Molla *et al*[13] remain continuous up to five years of age, on the contrary, this study demonstrates pronounced age-related fluctuations in this age group for both genders. The maximum values were attained at 12 years in all the studies evaluated, trailed by an incline, having a probable association with the increase in muscle mass with age and attainment of puberty. On gender stratification, our study demonstrated that the peak levels of CREA attained in males *i.e.*, 1.26 mg/dL (111 μmol/L) significantly differed from females *i.e.* 0.93 mg/dL (82 μmol/L). The need for fine grained age- and gender-based RIs for CREA is also supported by another study by Pottel *et al*[17] that has established age- and gender-specific CREA RIs from hospital laboratory data based on different statistical methods, and has shown pronounced age-based fluctuation in CREA for both genders[17]. This phenomenon is in accordance with the dependency of CREA on physical structure, muscle mass, physical activity and protein uptake which differs significantly between the two gen-ders[18,19]. Furthermore, as the utilized method does not allow creation of CIs, equivalence limits were derived according to previously established and validated equations and significant differences between our study RIs and Tahmasebi *et al*[11] were noted as depicted in Tables 1 and 2. It is evident the direct and indirect methods can more often generate overlapping but not identical values[20].

Considering the scarcity of literature on fine grained age group-based pediatric RIs for CREA in Pakistan, one of the highly densely populated countries reportedly with a high burden of kidney disease, the data mining approach can serve as the missing link [21,22]. Furthermore, the deployment of indirect approaches using "big data" solutions are barely utilized in LMIC and this study highlights the utility of this approach at no additional cost. Several LMIC lack a medical insurance system with universal coverage; thus, in most instances, the expenditure has to be self-born by the subjects [23]. Adequate interpretation based on population specific RIs can prevent unnecessary further investigations and medical interventions[24]. This study is in line with good laboratory practices that advocate the need for RIs establishment alongside the attainment of the quality improvement of the post analytical phase, aimed at appro-

priate report interpretation.

In addition to the merits of this real-world big-data approach in laboratory medicine, there is a notable limitation of this indirect algorithm, that any potential differences cannot be analyzed between the groups formulated; hence, individual results have to been complemented with clinical judgement and correlation. Moreover, the CIs with the established RIs were not calculated, as the used algorithm does not contain a provision for CI generation.

CONCLUSION

Good laboratory practices advocate the necessity for generation of population specific RIs, which is widely lacking, particularly in LMIC owing to the various challenges of the conventional direct method. This study has highlighted and further substantiated the utility of an alternative validated indirect algorithm by data mining in a clinical laboratory in Pakistan. This approach can be easily adopted by laboratories in resource constrained regions and the RIs generated will provide more accurate comprehension of laboratory reports in order to facilitate clinical care.

ARTICLE HIGHLIGHTS

Research background

Population specific reference intervals (RIs) are pivotal for laboratory results interpretation.

Research motivation

The indirect methods of RIs establishment based on big data analytics overcome the challenges and the cost associated with the conventional direct approach.

Research objectives

To establish RIs for serum creatinine (CREA) levels in Pakistani children using an indirect data mining approach.

Research methods

RIs were calculated using a previously validated indirect algorithm developed by the German Society of Clinical Chemistry and Laboratory Medicine's Working Group on Guide Limits.

Research results

The lower and upper RIs were calculated based on 36766 CREA results obtained from 21920 males and 14846 females.

Research conclusions

These RIs generated for serum CREA demonstrate the complex age- and gender-related dynamics occurring with physiological development.

Research perspectives

This indirect approach can be easily adopted by laboratories in resource constrained regions and the RIs generated will provide more accurate comprehension of laboratory reports in order to facilitate clinical care.

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CASE REPORT

Glans ischemia after circumcision in children: Two case reports

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Author contributions: Codrich D, Boscarelli A and Cerrina A collected the data, conceptualized the report and drafted the initial manuscript; Scarpa MG, Iaquinto M and Olenik D contributed to the collection of iconographic material and revised the manuscript; Guida E and Schleef J contributed to critically review the manuscript for important intellectual content and language editing.

Informed consent statement: Consent to publish the case report not obtained. The report does not contain any personal information that could lead to identification of the patient.

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Abstract

BACKGROUND

Circumcision refers to the removal of the skin covering the tip of the penis and is one of the most common surgical procedures performed in childhood. Even though circumcision is a well-standardized operation, several minor and major complications may be experienced by paediatric surgeons. Glans ischemia (GI) has been widely reported in the paediatric literature as a complication following circumcision. Nonetheless, etiopathogenesis of GI is not well defined and management guidelines are lacking.

CASE SUMMARY

We describe our experience with this rare and scary complication using subcutaneous enoxaparin alone or in association with a topical vasodilator.

CONCLUSION

Hypothetical causes and different management strategies are discussed.

Key Words: Circumcision; Children; Complications; Glans penis; Ischemia; Case report

Core Tip: Glans ischemia (GI) after circumcision is a rare complication, which has been widely described by paediatric surgeons in the modern literature. To date, etiopathogenesis of GI is not well defined and management guidelines are lacking. In order to achieve a prompt diagnosis and to start appropriate treatment, an accurate postoperative medical assessment and parental education are crucial before hospital discharge for children undergoing circumcision.

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INTRODUCTION

Circumcision refers to the surgical removal of the foreskin covering the glans and is one of the most common paediatric procedures. The complication rate after circumcision in childhood varies between 0% and 16%[1]. Minor complications include penile shaft swelling, bleeding, meatal stenosis, recurrent preputial stenosis and unsatisfactory cosmetic appearance. Major complications reported in the literature are glans or penile amputation, septicaemia, and urethrocutaneous fistulas[1,2]. Glans ischemia (GI) after circumcision is an extremely rare but scary complication in children[3]. We describe our experience with two cases of GI after circumcision in males aged 8 and 10 years old. Hypothetical causes and different treatment strategies are debated.

CASE PRESENTATION

Chief complaints

Case 1: An 8-year-old boy underwent circumcision at our paediatric surgery department for a true phimosis. The child's medical history was uneventful. Surgery was performed under general anaesthesia with a dorsal nerve penile block using mepivacaine. During surgery, a monopolar electrocautery was used to excise the excessive foreskin and to execute the frenulotomy. The coronal suture was performed with 5-0 interrupted absorbable sutures. No excessive bleeding was noted neither during intervention nor in the immediate post-operative course. No compressive bandaging was used.

Case 2: A 10-year-old boy presented to our paediatric outpatient clinic for a true phimosis. Personal history was unremarkable, except for childhood vitiligo. Circumcision was performed under general sedation with spinal anaesthesia. Bipolar electrocautery was used and coronal suture was performed with 5-0 interrupted absorbable stitches. No compressive bandaging was applied. No excessive bleeding was noted neither during intervention nor in the immediate postoperative course. Minimum glans swelling was reported two hours after surgery.

History of present illness

Phimosis.

History of past illness

Case 1: Uneventful.

Case 2: Unremarkable, except for childhood vitiligo.

Personal and family history

Unremarkable.

FINAL DIAGNOSIS

Case 1

At the clinical examination 6 h after surgery, an ischemic appearance of the glans was documented, without pain or difficulty to urinate. A colour doppler imaging (CDI) showed normal flow in the dorsal penile artery.

Case 2

Four hours after surgery, an ischemic appearance of the glans was documented (Figure 1A). Whole blood count and blood clotting were checked and found to be within normal ranges.

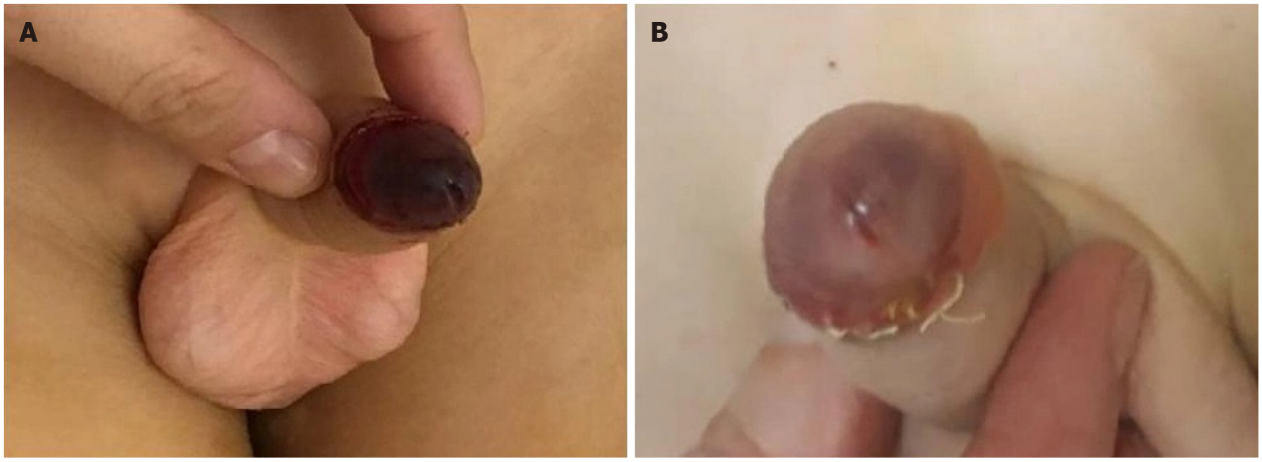

Figure 1 Close up view of circumcision procedure. A: Close up view of a glans ischemia four hours after the circumcision procedure; B: Glans appearance few days after starting therapy with subcutaneous enoxaparin injections.

Case 1

Subcutaneous enoxaparin 2000 UI injection was started and continued once a day for 5 d. Moreover, a galenic preparation of nitric oxide ointment was applied on the glans once a day for a week.

Case 2

Anticoagulant therapy was started with subcutaneous enoxaparin 3000 UI once a day for 5 d.

OUTCOME AND FOLLOW-UP

Case 1

The child was discharged home on postoperative day 6 when an improvement of the GI was noted. Complete restitution integrum was achieved one month after surgery.

Case 2

The colour of the glans rapidly improved to reddish (Figure 1B), and the patient was discharged home on postoperative day 4. At one-month follow-up, the penis and glans were found to be in a normal status.

DISCUSSION

Circumcision is a common paediatric surgical procedure; approximately 0.5% of patients require a repeat surgery. The most frequent complication reported in patients undergoing circumcision is haemorrhage (0.8%), with more than 60% of cases requiring surgical revision[2].

GI after circumcision has been widely reported in the paediatric literature. However, the etiopathogenesis of GI is not well known. The most commonly reported cause for GI is dorsal nerve block using local anaesthetics with or without vasoconstrictor agents[3]. Compression dressing, tight sutures, and excessive use of monopolar electrocautery are other potential reasons for GI after circumcision[3,4]. In our first case, anaesthesia was achieved by a dorsal penile nerve block; during surgery, a monopolar electrocautery device was used. In the second case, a spinal block and bipolar electrocautery were used. After surgery, we routinely use a combination of antibiotic and corticosteroid ointment on the coronal suture and the penis is gently covered with gauze but without any tight circumferential bandage. Notably, in a similar case, Efe *et al*[5] reported an elevated D-dimer level, with restoration to normal level after five days of enoxaparin treatment, suggesting a penile vascular thrombosis even though CDI showed normal penile and glandular blood flow. Conversely, both Karaguzel *et al*[4] and Gnatzy *et al*[6] reported their experiences, describing two cases of acute GI after circumcision with a normal level of D-dimer and good penile blood

flow at CDI. Regarding our cases, the first one showed normal blood flow at CDI but D-dimer value was not checked. In the second case, the D-dimer level was normal but CDI was not performed. Many authors have reported normal penile blood flow at CDI [5-8], and only one case in the paediatric literature described reduced penile blood flow[9]. Therefore, it is questionable whether a thrombosis may be responsible for GI after circumcision, as suggested by Efe *et al*[5], or whether a transient vasospasm of the dorsal artery may be to blame. Moreover, doubt persists regarding whether the use of monopolar electrocautery in our first case could have played a role in the development of GI.

To date, several treatment options for GI are reported in the literature, but a defined protocol or guidelines are still lacking. Some authors reported a successful outcome with endovenous or oral administration of pentoxifylline (PTX), alone or in association with other therapeutic stratagems. PTX is a hemorheological agent which improves the viscosity of blood and is used in peripheral vascular and cerebrovascular insufficiency [4,9,10]. Comparatively, caudal block reduces sympathetic tone, improves arterial supply and venous drainage, and has been proposed as the sole therapeutic strategy [7], or in association with intracavernous injection of glycerol trinitrate, to improve postarteriolar smooth muscle relaxation[11]. Furthermore, Aminsharifi *et al*[11] reported the use of topical testosterone, which has been shown to improve the vascular density of foreskin *in vitro*, in two cases of delayed GI after circumcision, which resulted in complete healing after one month. Selective angiography with intra-arterial injection of a vasodilator agent has been reported by Gnatzy *et al*[6] in association with oral sildenafil and infusion of L-arginine hydrochloride and unfractionated heparin. Lastly, as previously reported, anticoagulant therapy using enoxaparin has been effective in case of GI after circumcision[5]. In both our cases, we administered subcutaneous enoxaparin injection once a day for 5 d with complete resolution of GI. Notably, in the first case, a topical vasodilator was added and the complete resolution required additional days compared with the second case.

CONCLUSION

In conclusion, although a unique causative factor for GI after circumcision cannot be identified, a favourable outcome has been reported in nearly all cases. The unfavourable outcomes reported in literature are due to delayed discovery of the ischemic condition or late presentation of the patients back to the hospital. Consequently, we strongly recommend that discharge home should be preceded by an accurate medical assessment and should not be scheduled until at least 6 h postoperatively. Additionally, parents and patients should be well instructed in evaluating any possible signs of complication in the postoperative course. Lastly, we recommend rigorously following-up patients experiencing GI after circumcision for at least the first month after surgery.

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MINIREVIEWS

Prospects for clinical applications of butyrate-producing bacteria

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Abstract

As the major source of energy for colonic mucosal cells and as an important regulator of gene expression, inflammation, differentiation, and apoptosis in host cells, microbiota-derived butyrate can enhance the intestinal mucosal immune barrier, modulate systemic immune response, and prevent infections. Maintaining a certain level of butyrate production in the gut can help balance intestinal microbiota, regulate host immune response, and promote the development and maintenance of the intestinal mucosal barrier. Butyrate-producing bacteria act as probiotics and play important roles in a variety of normal biological functions. Bacteriotherapeutic supplementation by using fecal microbiota transplantation to restore butyrate-producing commensal bacteria in the gut has been very successful in the treatment of recurrent and refractory *Clostridium difficile* (*C. difficile*) infection or *C. difficile*-negative nosocomial diarrhea. Administration of probiotics that include butyrate-producing bacteria may have a role in the treatment of inflammatory bowel diseases and in the prevention of necrotizing enterocolitis and late-onset sepsis in premature infants. Furthermore, modulating gut microbiota with dietary approaches may improve intestinal dysbiosis commonly seen in patients with obesity-associated metabolic disorders. Supplementation with a butyrate-producing bacterial stain might be used to increase energy expenditure, improve insulin sensitivity, and to help control obesity and metabolic syndrome.

Key Words: Butyrate; Butyrate-producing bacteria; Gut microbiota; Intestinal mucosal barrier; Metabolic syndrome; Probiotics

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Core Tip: This minireview summarizes the potential clinical applications of butyrate-producing bacteria in disorders related to pediatrics and possible underlying mechanisms. Acting as probiotics, butyrate-producing bacteria play important roles in a variety of normal biological functions that include balancing gut microbiota, maintaining the mucosal barrier, modulating the host immune response, preventing infections, and regulating energy expenditure. Therefore, butyrate-producing bacteria may have a potential therapeutic value in a wide range of clinical conditions associated with intestinal dysbiosis such as inflammatory bowel disease, necrotizing enterocolitis, late-onset sepsis in the premature infant, nosocomial diarrhea, and obesity-associated metabolic disorders.

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INTRODUCTION

Short chain fatty acids (SCFAs), in particular butyric acid, play important roles in human intestinal health. They are the major source of energy for the colonic mucosal cells[1]. Maintaining a certain level of butyric acid production in the lumen can help to balance gut microbiota, regulate host immune response, and enhance intestinal mucosal barrier function. When butyrate is taken orally in food or as a medicine, it is digested and absorbed by the body before it reaches the colon, making it difficult for butyrate to perform its functions in the hindgut. Butyrate-producing bacteria are capable of fermenting undigested carbohydrates in the intestinal lumen, producing acidifying SCFAs such as butyric acid. Therefore, butyrate-producing bacteria may be used as probiotics with the goal of promoting gut health, and thus having a wide range of potential clinical applications[2]. This minireview focuses on recent research on butyrate-producing bacteria and their potential clinical applications, especially in disorders related to pediatrics.

BUTYRATE-PRODUCING BACTERIA AND THEIR MAIN PHYSIOLOGICAL FUNCTIONS

Butyrate-producing bacteria are not a coherent phylogenetic group but rather a group of commensal intestinal flora that can ferment carbohydrates and produce butyric acid [2,3]. Both lactic acid and acetic acid can be used as substrates in the biochemical synthesis of butyric acid[3]. The majority of *Firmicutes* are butyrate-producing bacteria. At the genus level, *Ruminococcus*, *Clostridium*, *Eubacterium*, and *Coprococcus* are common butyrate-producing bacteria. *Clostridium butyricum* (*C. butyricum*) is relatively common in the *Clostridium* genus[4]. Others include *Faecalibacterium, Butyrivibrio, etc.*, [5]. In the genus *Eubacterium, Eubacterium Hallii* (*E. Hallii*) and *Eubacterium Rectale* are among the most abundant butyrate-producing bacterial strains in human feces[6]. *Actinomycetes, Bacteroidetes, Proteobacteria, Spirochetes* also have been identified as potential butyrate-producing bacteria[2].

The butyrate-producing commensal bacteria are mainly anaerobes. The acidic environment generated by butyrate-producing bacteria during metabolism keeps a balanced microbiota and maintains a normal microecological environment in the intestinal tract. Therefore, butyrate-producing bacteria act as probiotics and play important roles in a variety of normal biological functions, such as maintaining the mucosal barrier, improving immunity, and facilitating nutrient digestion and absorption in animals[7]. Like other probiotics, butyrate-producing bacteria can ferment carbohydrates to produce SCFAs and synthesize folic acid, pyridoxol, vitamin B1 and other vitamins[8,9]. By using an *in vitro* model of the colonic mucosa barrier, Lewis *et al*[10] have shown that butyrate can ameliorate increased translocation of bacteria across metabolically stressed intestinal epithelia. With a similar model, we have shown previously that butyrate can enhance the intestinal barrier function by facilitating the

assembly of tight junctions through the activation of AMP-activated protein kinase (AMPK) and have demonstrated that butyrate is important in the maintenance and regulation of the barrier function of the colonic epithelium[11]. Also, Wang *et al*[12] recently demonstrated that butyrate dynamically regulates intestinal homeostasis through regulation of synaptopodin, an actin-binding protein that is critical for barrier integrity and cell motility. Therefore, it is evident that production of butyrate in the intestinal lumen is vital for the maintenance of the intestinal mucosal barrier.

Butyrate is a potent histone deacetylase inhibitor, which can promote the proliferation and activation of regulatory T-cells (Treg cells) and thereby play an important role in the immune regulation[13,14]. Microbiota-derived butyrate can reduce the release of pro-inflammatory cytokines by regulating the activity of G protein-coupled receptors, NF-κB, JAK/STAT and other inflammation-related pathways, thereby inhibiting intestinal inflammation and maintaining intestinal immune balance[15]. In addition to the direct effects on the mucosal barrier, microbiota-derived butyrate can be absorbed and directly transmitted to mesenteric lymph nodes, into the lymphatic system, and then into the systemic circulation, affecting other organ systems. NF-kB pathway is involved in the expression of tumor necrosis factor (TNF), interleukin (IL)-1, IL-6 and other inflammation-related genes in the immune and inflammatory responses. The role of butyrate is to inhibit NF-κB from entering the nucleus. Without active NF-κB, the mRNA of pro-inflammatory factors cannot be transcribed and pro-inflammatory factors will not be expressed, resulting in inflammatory response inhibition[15]. Studies have shown that butyrate regulates the function of T cells in the induction of colitis by differentially regulating Th1 and Th17 cell differentiation, thus modulating the production of inflammatory cytokines[16,17]. Moreover, butyrate can inhibit the release of IL-12, TNF-α, IL-1β and nitric oxide in monocytes, up-regulate the expression of IL-10, and reduce the activity of NF-κB, thereby playing an anti-inflammatory role in other organ systems, such as the respiratory system[18]. In short, as the major source of energy for the colonic mucosa and as an important regulator of gene expression, inflammation, differentiation and apoptosis in host cells, microbiota-derived butyrate enhances the role of the intestinal mucosal immune barrier, modulates the systemic immune response, and thus prevents bacteria and their metabolites from entering the bloodstream and causing inflammation[19,20].

POTENTIAL CLINICAL APPLICATIONS OF BUTYRATE-PRODUCING BACTERIA

Maintenance of the intestinal mucosal barrier

A monolayer of intestinal epithelial cells separates the body tissues from the dense communities of bacteria in the intestinal lumen. Therefore, maintenance of the mucosal epithelial barrier that prevents the invasion of host tissues by resident bacteria is vital for normal intestinal function. It is well known that the main energy source for the colonic epithelium is derived directly from the lumen rather than from blood. More than 90% of SCFAs produced in the intestinal lumen by bacterial fermentation are normally absorbed by intestinal epithelial cells. Lack of luminal SCFAs or the inability to oxidize butyrate leads to a nutritional deficiency of the colonic epithelium, causing mucosal atrophy in the short term and 'nutritional colitis' in the long term[1]. In patients with ulcerative colitis, the ability of the colonic epithelial cells to oxidize butyrate is weakened, so the energy obtained through oxidation is reduced; and thus the ability of butyrate to repair colonic mucosa is decreased[21]. The depletion of gut commensal flora by a prolonged course of broad spectrum of antibiotics can lead to more severe intestinal mucosal injury in a dextran sulfate sodium (DSS)-induced mouse colitis model[22]. Furthermore, reduced abundance of butyrate-producing commensal bacteria species has been found in the fecal microbial community in patients with inflammatory bowel disease (IBD)[23,24].

Probiotics have been advocated in clinical practice for prevention or treatment of intestinal mucosal injury associated with IBD or neonatal necrotizing enterocolitis (NEC)[25,26]. In children with IBD, a specific probiotic preparation (VSL#3) combined with *Lactobacillus* was shown to have a significant effect in achieving a clinical response[27]. A study in an animal model of DSS-induced colitis has shown that administration of *C. butyricum*, one of the butyrate-producing bacterial strains, can increase the luminal production of butyrate in the cecum and alleviate DSS-induced injury to colonic mucosa[28]. *C. butyricum* may induce intestinal macrophages to secrete IL-10, thereby inhibiting the occurrence of experimental colitis[29]. Geirnaer *et al*[30] used an *in vitro* system to examine the response of microbiota from patients with

Crohn's disease to the treatment with different combinations of butyrate-producing bacterial stains. They assessed the effects of butyrate-producing bacteria supplementation on short-chain fatty acid production, bacterial colonization of the mucus environment and intestinal epithelial barrier function. They demonstrated that treatments with butyrate-producing bacteria improved epithelial barrier integrity *in vitro*. More recently, Steppe *et al*[31] isolated and characterized the butyrate-producing strain *Butyricicoccus pullicaecorum* 25-3(T) and identified it as a potential probiotic for patients with IBD.

Regulation of intestinal immune response

The human intestine normally harbors billions of commensal bacteria. Intestinal epithelia cells actively sense those commensal bacteria and play an essential role in maintaining host-microbial homeostasis at the mucosal interface[19]. Commensal bacteria such as butyrate-producing bacteria can ferment undigested carbohydrates to produce small molecular metabolites such as lactic acid and SCFAs in the intestine, promote the proliferation of beneficial intestinal bacteria such as *bifidobacterium*, lactobacillus and fecal bacillus, and inhibit the growth of pathogenic bacteria such as *Staphylococcus, Escherichia coli, Salmonella typhus* and *Clostridium difficile* (*C. difficile*)[32, 33]. Thus, butyrate-producing bacteria promote intestinal microecological balance and participate in the regulation of the production of amines, indole, hydrogen sulfide and other potential harmful substances. Therefore, they not only can improve intestinal digestive and absorptive capacity, but also play important roles in improving the body's immunity and preventing infections[8].

SCFAs promote intestinal peristalsis and reduce the duration of the presence of toxin in the intestinal tract. Among the SCFAs, butyrate is a potent mediator involved in the effects of gut microbiota on intestinal mucosal immune functions[34]. Butyrate can act as a ligand to activate specific G-protein-coupled receptors, activate intestinal mucosal immune activity, and enhance immunity[34]. Enhanced butyrate production by colonic butyrate-producing bacteria after diet manipulation is associated with increased levels of the anti-inflammatory cytokine IL-10 in mice[35]. Using intestinal mucosa biopsy tissues obtained from the patients with Crohn's disease, Segain *et al*[15] have shown that butyrate can ameliorate the inflammatory response of isolated lamina propria cells and that of cultured peripheral blood mononuclear cells. NF-κB pathway is involved in the inhibition of immune cell activation[15].

Butyrate regulation of Toll-like receptor (TLR) expression in human colonic epithelial cells may be one of the key mechanisms mediating the cross talk and interplay between normal gut microbiota and a host's innate and adaptive immune systems[36]. TLRs in intestinal epithelial cells and mucosal immune cells are pattern-recognition-receptors that are critical components of the symbiosis between the host and commensal microflora[37]. Therefore, bacterial production of butyrate plays a key role in maintaining intestinal homeostasis. Other factors such as antimicrobial peptides produced by commensal bacteria or the host may also be involved in the process[38-40]. More recently, a clinical study found that higher fecal SCFA concentrations were associated with the efficacy of immunotherapy in solid tumor cancer patients, indicating that gut microbiota might have wide-ranging impacts on host immune response[41].

Dysbiosis of intestinal microbiota and infection

Dysbiosis of intestinal microbiota may lead to so-called leaky gut and therefore microbial translocation, contributing to the development of infection. It is well accepted that an impaired interaction between intestinal microbiota and the host immune response can lead to an increased risk of infection caused by gram-negative bacteria or other pathogens[37,42]. It has been shown that reductions in mucosal butyrate from diminished colonic butyrate-producing bacteria contribute to HIV-associated mucosal pathogenesis[43]. SCFA uptake coupled with sodium absorption is one of the major mechanisms for salt and water uptake in the colon. The association between the depletion of intestinal microbiota and nosocomial diarrhea is well recognized. Normally abundant gut commensal organisms, including the butyrate-producing C2 to C4 anaerobic fermenters, are significantly depleted in the patients with *C. difficile* infection or *C. difficile*-negative nosocomial diarrhea[44]. Furthermore, dysfunction of the intestinal mucosal barrier and impaired mucosal immunity can lead to pathological translocation of intestinal bacteria or endotoxins, causing sepsis and multiple organ dysfunction syndrome in patients who experienced severe trauma, serious burn, major surgery or hemorrhagic shock[45]. Loss of the intestinal microbiota diversity and a subsequent loss of health-promoting SCFAs, such as butyrate, contribute to the dysregulated immune response and organ failure associated with sepsis

[46].

Bacteriotherapeutic supplementation may restore normal gut microbiota. For example, using fecal microbiota transplantation (FMT) to restore butyrate-producing bacteria in the gut and therefore the normal host immune response has been tested in clinical practice for the treatment of diseases related to dysbiosis of the intestinal microbiota[47]. FMT has been very successful in the treatment of recurrent and refractory *C. difficile* infection[48]. FMT has also been trialed for aiding in the recovery of septic patients[49]. However, concerns for lethal complications associated with FMT prevent its use other than for quite restricted clinical indications. Oral administration of health-promoting next-generation probiotics to ameliorate dysbiotic microbiota may be a safe alternative[9]. As summarized by a recent systematic review and meta-analysis, administration of probiotic mixtures, not single-strain products, has a beneficial effect of reducing the incidence of late-onset sepsis in human milk-fed very low birth weight preterm infants[50].

Role in obesity-associated metabolic disorders

Diet can modulate and support the symbiotic microbial communities that colonize the digestive tract. Modulating gut microbiota with dietary approaches may improve health, and prevent or treat diseases related to intestinal dysbiosis[51]. Dietary prebiotics are a group of nutrients that are degraded by gut microbiota. It is defined as a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improving host health[52]. Most complex carbohydrates and plant polysaccharides ingested are metabolized by fermentation of commensal bacteria in the colon, which generate butyrate and other SCFAs (Figure 1). Consumption of a diet rich in fiber or prebiotic supplementation can boost the growth and metabolism of beneficial commensals in the colon, specifically targeting butyrate production[35,51].

Numerous studies have demonstrated the beneficial effects of a diet rich in fiber on obesity-associated metabolic syndrome. A fiber rich diet is beneficial in the prevention of obesity, improving insulin resistance, and control of abnormal blood lipid profile commonly seen in metabolic syndrome[53]. We previously have proposed that increased production of SCFAs as a result of colonic bacterial fermentation of dietary fiber might, in part, account for some of the beneficial effects of dietary fiber on the metabolic syndrome[53]. Indeed, while on a high-fat diet, supplementation of butyrate prevented development of insulin resistance and obesity in mice. Fasting blood glucose, fasting insulin, and insulin tolerance were all preserved in the treated mice. In the obese mice, supplementation of butyrate led to an increase in insulin sensitivity and a reduction in adiposity[54]. Oral administration of *E. Hallii*, a butyrate-producing bacterial stain, can improve insulin sensitivity and increase energy expenditure in diabetic *db/db* mice[55]. As a potential therapeutic strategy for obesity and metabolic syndrome, FMT has also been trialed in a few randomized controlled human studies with some mixed beneficial results[56]. Promotion of energy expenditure, induction of mitochondrial function by activation of AMPK, and serving as an agonist of free fatty acid receptors, may be some of the mechanisms underlying the beneficial effects of butyrate on the abnormalities characterizing the metabolic syndrome[54,57-59].

CONCLUSION

This minireview summarizes the potential clinical applications and possible underlying mechanisms of butyrate-producing bacteria in disorders related to pediatrics. As the major source of energy of the colonic mucosa and as an important regulator of gene expression, inflammation, differentiation and apoptosis in host cells, microbiota-derived butyrate enhances the role of the intestinal mucosal immune barrier, modulates the systemic immune response, and thus prevents bacteria and their metabolites from entering the bloodstream and causing inflammation. Butyrate regulation of energy metabolism may play a role in the beneficial effects of a high fiber diet on metabolic syndrome. Therefore, acting as probiotics, butyrate-producing bacteria play important roles in a variety of normal biological functions that include balancing gut microbiota, maintaining the mucosal barrier, modulating the host immune response, preventing infections, and regulating energy expenditure. Thus, butyrate-producing bacteria may have a potential therapeutic value in a wide range of clinical conditions associated with intestinal dysbiosis such as IBD, NEC, late-onset sepsis in premature infant, nosocomial diarrhea, and obesity-associated metabolic disorders.

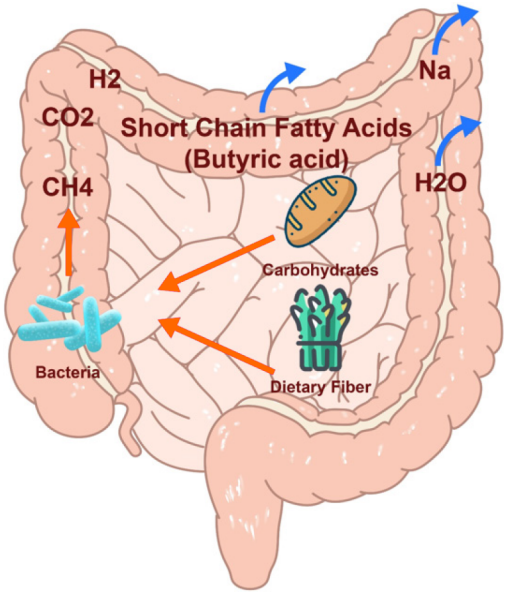

Figure 1 Butyric acid production by bacterial fermentation.

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ORIGINAL ARTICLE

Observational Study

Influence of education and residence on the parental search for pediatric surgical information on the internet

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Abstract

BACKGROUND

The internet is a valuable tool for access to health-related information. There is limited literature regarding its use by parents of children with surgical conditions.

AIM

To investigate internet usage by parents seeking information about the surgical conditions of their offspring in relation to epidemiological factors such as family residential area and parental educational level and to subsequently review the literature regarding this topic.

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METHODS

An anonymous questionnaire about internet usage was completed by eligible parents of children who were admitted to our clinic for minor surgical procedures during a six-month period.

RESULTS

Our results demonstrated that the internet has been mostly used by mothers for children's health information. Google was the most commonly used search engine, while pediatricians were the first parental choice for 'live' information. Only one-quarter of the parents informed their doctor about the information found online. Nine of ten parents had a positive opinion of an official website managed by the doctors of our clinic. Our results mostly agreed with the international literature.

CONCLUSION

In conclusion, the establishment of official websites (designed and managed by specialists) that parents can access to receive appropriate health information is mandatory in the internet era.

Key Words: Internet; Child; Health; Mothers; Fathers

Core Tip: The internet is a valuable tool for accessing health-related information. Parents of children with forthcoming surgery often seek online information about the specific conditions and symptoms of their children. Herein, we describe the influence of education and residence on the parental search for pediatric surgical information on the internet in a multicultural region of northern Greece, and we compare our results with the recent literature.

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INTRODUCTION

Fifty years have passed since the onset of the internet, and the increase in numbers of people who access it worldwide is remarkable. According to the hellenic statistical authority, the last decade (2009–2018) saw a 100.8% increase in internet access at home. In Greece, more than 76.5% of homes accommodate internet access. The vast majority of adults (96.6%) use the internet more than once a week, and the internet is a popular source of health-related information[1]. Recent studies have demonstrated that up to 91% of adults access online sources of health information[2-4]. In Greece, the proportion of internet health users increased from 23% in 2007 to 65.2% in 2018[1,5]. Parents of children with chronic medical conditions are motivated by a desire to increase their knowledge and relieve their anxiety[6-13]. Nevertheless, there is limited literature regarding the use of the internet for pediatric surgical conditions[4,14-17]. Previous studies in Europe have shown that the use of the internet for health information varies significantly in different parts of the continent[5,18]. No similar studies have been recorded in South Europe, a region with diverse cultural and socioeconomic environments. Previous studies on parental internet exploration have mostly focused on three parameters: (1) Identification of the websites used; (2) Evaluation of the information found in relation to its readability and accuracy; and (3) The influence of the information on the parents' decisions to visit the emergency department when their child is sick[6-9]. The objectives of this study were first to evaluate the epidemiological characteristics of parents in relation to the magnitude of

internet usage for health-seeking information and second to review the literature regarding this topic.

MATERIALS AND METHODS

Participants

The survey was conducted from January 2018 to June 2018 in the Department of Pediatric Surgery, Alexandroupolis University Hospital, Greece. Eligible participants were parents of children (ages: 0–14 years) who were admitted to our clinic for minor elective surgical treatment (herniotomy, orchidopexy, hypospadias repair, circumcision) or emergency surgery (appendectomy, gonadal torsion, traffic accident, or fall-related injuries) and lived in the regions of Eastern Macedonia and Thrace. We excluded illiterate parents and parents who had already been included in the study group. Additionally, we excluded parents of children with chronic health problems and those of children who were admitted for major surgical procedures due to their increased anxiety. If both parents were present, only one of them could complete the questionnaire. In this cohort study, parents were divided into two categories according to their residency (urban or rural).

Questionnaire

The questionnaire was designed by MA and KK (authors) and was anonymous and voluntary. The questionnaire was designed and adjusted according to the characteristics and needs of people of our region regarding the difficulties they confront in communicating with a hospital doctor to accomplish sufficient and satisfactory medical information. In this region, with many scattered and isolated villages, the inhabitants form a multicultural society with different habits. The questionnaires were designed to be simple, unintimidating and easy to complete. There was no need for stratification, and the questionnaire consisted of a paper that required approximately 4 to 6 min to complete. It included 17 questions addressing three areas: (1) The use of the internet and its accessibility at home/work/elsewhere. Personal computers (PCs) at home, frequency of internet use, engagement in social media, parental engagement in social media and parental groups; (2) The use of the internet for access to medical information by family members, the use of the internet on a regular basis and 24 h prior to admission and which search engines were used; and (3) The use of the internet by parents addressing information for a specialist pediatric surgeon, other sources of information and the need for an official website with online, up-to-date medical information. In addition, there were questions about demographic data [gender, age and parental educational level, family income, residence, child insurance, type of admission (elective or emergency)]. The questionnaire was in Greek. Nevertheless, the option for a questionnaire written in Turkish was offered for some parents who were more fluent in that language. To reduce bias from the influence of medical staff of our clinic on the participants, a team consisting of two doctors and two medical students from the university was responsible for distributing these questionnaires (in paper) to the parents. The parents, if they agreed to participate, were asked to complete and return the questionnaires up to the day after their child's admission.

Sample size derivation and statistical analysis

With 600 admissions for minor surgical treatment in the University Pediatric Surgery Clinic annually, 234 completed questionnaires were required to achieve a 5% margin of error with a 95% confidence interval[19]. The main emphasis was on parents who searched the internet for children's health-related information in the past (202/235, 86%). Two parameters were analyzed: (1) The residence of the family; and (2) The educational level of the parent who searched the internet for child-related medical information. Descriptive statistics such as frequency, proportions, chi-squared test for categorical variables, and Mann–Whitney U test [nominal scale, when the point of interest was the residence (urban or rural)] or Kruskal–Wallis H (nominal scale, when the point of interest was the education level of the parent; categorized into three groups: (1) Completed high school or less; (2) Completed college or some college; or (3) Advanced degree or beyond) were employed to analyze data. We used R software (version 3.4.1), and a P value < 0.05 was considered statistically significant. The study was completed with a review of the existing literature on this topic.

Review of literature

Study design and inclusion criteria: The inclusion and exclusion criteria were defined before the initiation of the research. Only research studies were included. Commentaries, conference abstracts, any type of review, editorials, letters to the editor, case series, and case reports were not considered. The selection criteria were defined by applying the problem/population, intervention, comparison, and outcome framework. Participants included parents or guardians of children who required pediatric surgeon management. Intervention consisted of telephone interviews, live interviews, questionnaires or surveys. Any comparison between different populations was acceptable. Desired outcomes were socioeconomic status; residence (urban or rural area); internet usage; internet search platforms; internet sites and any other result reported in the questionnaire, survey or interview.

Literature search strategy and study selection: A literature search was performed based on the PubMed and Cochrane libraries using the following search terms: Internet health service; internet health information; internet; network; net; search; E-health; e-mail; mail; parents; guardians; family; questionnaire; survey; interview; pediatric; pediatric; and pediatric surgery. Articles published in English were retrieved from inception to October 2020. The records found were checked for duplicates. Then, the remaining articles were screened. Any article that met our criteria was included.

RESULTS

Demographics

All parents completed the questionnaire (235 of 235, 100%). Two hundred two (86%) parents searched the internet for children's health-related information. Descriptive data for all participants are presented in Table 1.

Family residence and parental internet usage

Internet usage and accessibility. There was a statistically significant difference between parents living in urban and rural areas regarding several parameters (Table 2): (1) Internet access according to the location of the participants. Most of the parents in urban and rural districts (95.2% and 86.6%, respectively) had internet access at home. Nevertheless, only 1.9% of urban residents used the internet elsewhere as well (library, internet cafes, friend's home), and 9.3% of rural residents used the internet elsewhere ($P = 0.022$); (2) Ownership of PC at home. Only 7.6% of the city homes did not possess a PC in comparison to 27.8% of rural homes ($P = 0.0001$); (3) Frequency of internet usage. The usage of the internet was more than once a week among 94.3% and 85.6% of parents in urban and rural areas, respectively. However, the relevant percentages for internet usage less than three times per month were 5.7% and 14.4%. ($P = 0.038$); and (4) Participation in parents' groups on social media. Participation in parental social media groups varied significantly in the two groups: 66.7% in urban areas and 34% in rural areas ($P < 0.0001$).

Internet usage to access medical information. Almost half of the parents (42.1%) searched for medical information 24 h prior to admission, but 49.5% had doubts about this information. There was a statistically significant difference between parents living in urban or rural areas with respect to several parameters, as shown in Table 3: (1) Regular internet search activity for basic medical information in the past. Almost nine of ten parents (86.7%) from urban areas searched the internet for medical conditions on a regular basis, in contrast to 67% of parents from rural areas ($P = 0.0009$); and (2) Search engines. Multiple answers were possible. Google was the most frequently used search engine by both groups. Parents from urban districts used Wikipedia more often (23.8%) than those from rural areas (12.4%). Rural area participants (12.4%) searched through other unspecified engines, while only 2.9% of the urban area participants used other unspecified engines ($P = 0.0078$).

Internet usage and examination by a pediatric surgeon. Comparing online sources of information with the information provided by a pediatric surgeon, 67.8% of the parents found both sources to be consistent. There were statistically significant differences between parents living in rural and urban areas with respect to several parameters, as shown in Table 4: (1) Searching the internet for a specialist before an appointment. Half the parents from rural areas (50.5%) searched for a specialist before their decision for an appointment, while only 32.4% of those from urban areas did so ($P = 0.008$); (2) Informing the doctor about the internet search. A great percent of parents from urban sites (29.5%) communicated with the specialists regarding their

Table 1 Demographic data of all participants (*n* = 235), *n* (%)

Demographic characteristics	All parents (*n* = 235)
Accompanying parent	
Mother	145 (61.7)
Father	90 (38.3)
Age of father, median (range)	40 (27-57)
Age of mother, median (range)	36 (21-52)
Family condition	
Married	222 (94.5)
Divorsed/Single	13 (5.6)
Educational level of father	
Completed high school or less	148 (63)
Completed college or some college	53 (22.6)
Advanced degree or beyond	34 (14.5)
Educational level of mother	
Completed high school or less	118 (50.2)
Completed college or some college	73 (31.1)
Advanced degree or beyond	44 (18.7)
Gross household income in Euro	
Less than 10000 €	98 (41.7)
10000 €-25000 €	101 (43)
25000 €-40000 €	31 (13.2)
Greater than 40000 €	5 (2.1)
Residence	
Rural	111 (47.2)
Urban	124 (52.8)
Insurance of child	
Public (government)	214 (91.1)
Private/no insurance	21 (8.9)
Type of admission	
Emergency	114 (48.5)
Elective	121 (51.5)

results from their internet search, in contrast to only 17.5% of parents from rural areas (P = 0.045); and (3) The need for an official website. Parents (97.1%) from urban sites believed that an official website managed by doctors from the clinic would be helpful, while 85.6% of parents from rural areas agreed with this opinion (P = 0.003).

Educational level of parents who performed research for medical information

Internet usage and accessibility. Regardless of education level, 90.1% of all parents used the internet more than once a week. There were statistically significant differences when comparing the results between parents from rural and urban areas with respect to several parameters, as shown in Table 5: (1) Ownership of a PC at home. All participants (100%) with an advanced degree owned a PC, in contrast to 92.1% of the parents with a college degree and 70.9% of the parents with a high school diploma (P < 0.0001); and (2) Participation in parental groups on social media. Participation in parental groups on social media was higher among parents with college degrees (71.4%) than among those with high school degrees (37.9%) and university

Table 2 Internet usage and accessibility regarding the residence (*n* = 202), *n* (%)

	Rural residence, *n* = 97	Urban residence, *n* = 105	Total	*P* value
Internet access				
At home	84 (86.6)	100 (95.2)	184 (91.1)	0.022
At work	23 (23.7)	39 (37.1)	62 (30.7)	
Elsewhere	9 (9.3)	2 (1.9)	11 (5.4)	
Personal computer at home				
Yes	70 (72.2)	97 (92.4)	167 (82.7)	0.0001
No	27 (27.8)	8 (7.6)	35 (17.3)	
Frequency of Internet usage				
Daily/1-3 times per week	83 (85.6)	99 (94.3)	182 (90.1)	0.038
1-3 times per month/rare	14 (14.4)	6 (5.7)	20 (9.9)	
Engaging in social media (Facebook, Twitter, Instagram)				
Yes	79 (81.4)	86 (81.9)	165 (81.7)	0.93
No	18 (18.6)	19 (18.1)	37 (18.3)	
Are you member of parents groups in social media?				
Yes	33 (34)	70 (66.7)	103 (51)	< 0.0001
No	64 (66)	35 (33.3)	99 (49)	

degrees (52.8%) (P = 0.0001).

Internet usage to access medical information. Google was the most commonly used search engine by the three groups (85.6%), followed by Wikipedia (18.3%). There was a statistically significant difference between parents living in urban and rural areas with respect to several parameters, as shown in Table 6: (1) Regular internet search activity for basic medical information in the past. One of three parents (35.9%) from the lower education level never previously searched the internet for medical information, in contrast to parents with a college (6.3%) or an advanced degree (13.9%) (P < 0.0001); (2) Internet usage the day before admission. Parents with a higher education level were less likely to search the internet prior to admission (19.4%) than parents with medium (54%) and lower (42.7%) education levels (P = 0.004); and (3) Website validity. Most parents from the higher education levels (77.8%) negatively evaluated the websites in terms of validity. The evaluation from the two other groups was not decisive (P = 0.0009).

Internet usage and examination by a pediatric surgeon. Regardless of the education level of parents, 41.1% of all participants searched for a specialist on the internet. There was a statistically significant difference in parents living in urban and rural areas with respect to several parameters (Table 7): (1) Informing the doctor about the internet search. We noticed that parents from higher education levels (advanced degree or higher) were less likely to inform doctors about the medical information they found online (8.3%), in contrast to parents who had college degrees (23.8%) and high school diplomas (29.1%) (P = 0.041); (2) Agreement between information provided by the doctor and that from the internet. A total of 55.3% of the parents from the lower, 85.7% from the medium and 72.2% from the higher educational level thought information found on the internet and that provided by the doctor were compatible (P = 0.0002); and (3) The need for an official website. All parents from all educational groups consisting of an advanced degree or higher and who completed college or some college (100%) agreed that an official website is necessary for reliable information, while 83.5% of parents from the lower education level agreed with this opinion (P = 0.0001).

Other interesting results

Regardless of the education levels and the residence of the parents, several factors were generally applicable: (1) Most parents (81.7%) were actively engaged in social media (Facebook, Twitter, Instagram); (2) The family member most likely to search the internet for children's health information was the mother (73.8% when the comparison

Table 3 Internet usage to access medical information regarding the residence of the family (*n* = 202), *n* (%)

	Rural residence, *n* = 97	Urban residence, *n* = 105	Total	*P* value
Previous medical information searching on Internet				
Yes	65 (67)	91 (86.7)	156 (77.2)	0.0009
No	32 (33)	14 (13.3)	46 (22.8)	
Internet usage in 24 h prior to admission				
Yes	40 (41.2)	45 (42.9)	85 (42.1)	0.81
No	57 (58.8)	60 (57.1)	117 (57.9)	
Which family member searched on Internet mostly?				
Mother	68 (70.4)	81 (76.7)	149 (73.8)	0.25
Father	29 (29.6)	24 (23.3)	53 (26.2)	
Search engines used				
Google	80 (82.5)	93 (88.6)	173 (85.6)	0.0078
Wikipedia	12 (12.4)	25 (23.8)	37 (18.3)	
Other	12 (12.4)	3 (2.9)	15 (7.4)	
Do you trust the websites in terms of validity?				
Yes	53 (54.6)	49 (46.7)	102 (50.5)	0.26
No	44 (45.4)	56 (53.3)	100 (49.5)	
Were the health information comprehensive?				
Yes	75 (77.3)	71 (67.6)	146 (72.3)	0.12
No	22 (22.7)	34 (32.4)	56 (27.7)	
Level of satisfaction with the medical information				
High	21 (21.6)	25 (23.8)	46 (22.8)	0.12
Medium	70 (72.2)	56 (53.3)	126 (62.4)	
Low	6 (6.2)	24 (22.9)	30 (14.9)	

was according to residence and 68.3% when the comparison was according to the educational level of the parent who searched the internet); (3) Evaluation of the websites in terms of comprehension. Most parents (72.3%) stated that they understood completely, or they thought they understood, the information provided; (4) Level of satisfaction with medical information. Only two of ten parents (22.8%) were satisfied/very satisfied with the medical information they found; and (5) Other resources for health information. Multiple answers were possible. Most parents (97.5%) approached a pediatrician or a general practitioner (GP) for health information about their child's condition. The next most popular source of information consisted of friends and family (37.6%).

Review of the literature

The combined search identified 12 articles that matched our criteria[4,6-8,10-13,16,17,20,21]. In the recent literature, it is stated that highly educated parents are more likely to search online for child-related information on a regular basis (52.2%–97.7%) and less likely to search 24 h prior to admission of their child (11.8%–21%). Although parents from lower education levels were less likely to search the internet on a regular basis (64.1%), they were more likely to use the internet for health-related information 24 h prior to the child's admission (47.2%). In contrast, the proportion of parents from the higher education levels was 86.1% and 19,4% regarding searching on a regular basis and searching 24 h prior to child admission, respectively. It was also reported that lower rates of internet accessibility and PC ownership in rural districts made parents from these areas less likely to search the internet on a regular basis (67%) than parents from urban sites (86.7%)[7,8,10,11,16]. Russo *et al*[20] reported that parents who lived more than 44 km from the hospital were twice as likely to search online for information about their child's surgery than those who lived closer to the hospital[20].

Table 4 Internet usage and examination by a pediatric surgeon regarding the residence of the family (*n* = 202), *n* (%)

	Rural residence, *n* = 97	Urban residence, *n* = 105	Total	*P* value
Other medical information resources				
Pediatrician/GP[1]	95 (97.9)	102 (97.1)	197 (97.5)	0.13
Friends and family	27 (27.8)	49 (46.7)	76 (37.6)	
Parents groups	9 (9.3)	8 (7.6)	17 (8.4)	
Search for a specialist				
Yes	49 (50.5)	34 (32.4)	83 (41.1)	0.008
No	48 (49.5)	71 (67.6)	119 (58.9)	
Did you inform the specialist about the Internet search?				
Yes	17 (17.5)	31 (29.5)	48 (23.8)	0.045
No	80 (82.5)	74 (70.5)	154 (76.2)	
Was the information found on the Internet the same as the one given by the doctor?				
Yes	63 (64.9)	74 (70.5)	137 (67.8)	0.4
No	34 (35.1)	31 (29.5)	65 (32.2)	
Need for an official website, *n*				
Yes	83 (85.6)	102 (97.1)	185 (91.6)	0.003
No	14 (14.4)	3 (2.9)	17 (8.4)	

[1]GP: General practitioner.

Regarding search engines, parents mostly used Google and Wikipedia to locate medical websites[4,8,11,12,16,21]. The evaluation of the websites in terms of validity and general level of satisfaction of the information provided was low, especially when the education level of the parents was higher. Several authors have also reported that the quality of medical information found on the internet was poor, which may cause misinformation[6,11-13]. In contrast, Semere *et al*[16] reported that 98% of parents agreed or somewhat agreed that the information was comprehensible[16]. Regarding other sources of medical information, it was reported that pediatricians and GPs were mainly consulted according to several authors who studied the health information seeking behavior of parents[8,11,12,17]. Some studies conclude that there is a predominance of friends and family instead of pediatricians[4,10,13]. Wong *et al*[4] reported a similar conclusion that only 35.5% of the parents informed the doctor about online medical information because the doctor had already included it in his consultation[4]. Another reason why they were hesitant to discuss the information they found with their doctor might have been the warnings from doctors about the validity of the health-related webpages[21]. A consistency rate of 95.2% was reported when the information found on the internet and the information provided by the doctor were compared[4]. Furthermore, several authors pointed out the overwhelming interest of parents on websites provided by doctors or hospitals[8,10-12,16].

DISCUSSION

The results of this study confirm that the internet is a rapidly growing source of medical information, and parents are using it for child-related health information to make significant decisions regarding their child's health[4,11,12,16]. Parental internet access at home ranged from 84.5% to 100% and 86.6% to 95.2% in relation to education level and location of residence, respectively. The vast majority (82.7%) owned a PC at home. They used the internet more than once a week in 90.1% of the sample, while 81.7% participated in social media. Half the study group (51%), mostly parents in urban sites with college and university degrees, were members of health-related support and parental support groups. Our study was in contrast to a study concluding that parents of children living a long distance (≥ 44 km) from a hospital were twice as likely to search online for information about their child's forthcoming surgery than

Table 5 Internet usage and accessibility regarding the educational level of the parent (*n* = 202), *n* (%)

	Completed high school or less, *n* = 103	Completed college or some college, *n* = 63	Advanced degree or beyond, *n* = 36	Total	*P* value
Internet access					
At home	87 (84.5)	61 (96.8)	36 (100)	184 (91.1)	0.27
At work	27 (26.2)	20 (31.7)	18 (50)	65 (32.2)	
Elsewhere	7 (6.8)	4 (6.3)	0	11 (5.4)	
Personal computer at home					
Yes	73 (70.9)	58 (92.1)	36 (100)	167 (82.7)	< 0.0001
No	30 (29.1)	5 (7.9)	0	35 (17.3)	
Frequency of Internet usage					
Daily/1-3 times per week	88 (85.4)	61 (96.8)	33 (91.7)	182 (90.1)	0.055
1-3 times per month/rare	15 (14.6)	2 (3.2)	3 (8.3)	20 (9.9)	
Engaging in social media (Facebook, Twitter, Instagram)					
Yes	84 (81.6)	53 (84.1)	28 (77.8)	165 (81.7)	0.73
No	19 (18.4)	10 (15.9)	8 (22.2)	37 (18.3)	
Are you member of parents groups in social media?					
Yes	39 (37.9)	45 (71.4)	19 (52.8)	103 (51)	0.0001
No	64 (62.1)	18 (28.6)	17 (47.2)	99 (49)	

those who lived closer to a hospital[20]. In our study, this result probably occurred because families that live far from a hospital are those from rural areas where the parents are simpler and trust without doubt the hospital doctors, and additionally, the internet in their areas is not easily accessible. In our study, most mothers searched the internet regardless of their education level (68.3%) or residence (73.8%). Nevertheless, this result is in line with findings from previous studies[4,5,8,10]. Our questionnaire-based study found that the most commonly used search engines by parents were Google (85.6%) and Wikipedia (18.3%), who are less familiar with child-specific websites managed by specialists and hospitals or because they are not aware of what constitutes good health information. These results coincide with previous studies[4,8,11,12,16,21]. On the one hand, the evaluation of websites in terms of comprehension in our study was high since 72.3% of the parents understood or thought that they understood the online medical information. This finding agrees with the results from a study by Semere *et al*[16] in which 98% of parents agreed or somewhat agreed that the information was comprehensible[16]. In contrast, several studies have shown that the quality of medical information found on the internet is poor and that the results are misleading[6,11-13]. In addition to the internet, other resources for medical information according to our study were mainly pediatricians and GPs (97.5%) regardless of the education level or residence of the parents, while friends and family members were the next most frequently used resources, mostly from urban residents (46.7%), with lower EL (43.7%). The same conclusions were reported by several authors who studied the health information-seeking behavior of parents[5,8,11,12,17], in contrast to other studies in which there was a predominance of friends and family instead of pediatricians[4,10,13]. One study reported that nearly one-third of the parents discussed the information that they found online with their doctors[4]. Our study showed that the higher the education level of the parents, the less likely they were to inform the doctor about their internet searches. Additionally, urban residents discussed the child's health-related information more often (29.5%) than parents from rural sites (17.5%). When comparing the information found on the internet and that provided by the doctor, only half the parents from the lower education level (55.3%), 85.7% with college degrees, and 72.2% with advanced degrees found both sources to be consistent. Wong *et al*[4] reported a consistency rate of 95.2%[4]. Several authors have noted the

Table 6 Internet usage to access medical information regarding the educational level of the parent (*n* = 202), *n* (%)

	Completed high school or less, *n* = 103	Completed college or some college, *n* = 63	Advanced degree or beyond, *n* = 36	Total	*P* value
Previous medical information searching on Internet					
Yes	66 (64.1)	59 (93.7)	31 (86.1)	156 (77.2)	< 0.0001
No	37 (35.9)	4 (6.3)	5 (13.9)	46 (22.8)	
Internet usage in 24 h prior to admission					
Yes	44 (42.7)	34 (54)	7 (19.4)	85 (42.1)	0.004
No	59 (57.3)	29 (46)	29 (80.6)	117 (57.9)	
Which family member searched on Internet mostly?					
Mother	67 (65)	48 (76.8)	23 (63)	138 (68.3)	0.27
Father	36 (35)	15 (23.2)	13 (37)	64 (31.7)	
Search engines used					
Google	86 (83.5)	53 (84.1)	34 (94.4)	173 (85.6)	0.74
Wikipedia	15 (14.6)	15 (23.8)	7 (19.4)	37 (18.3)	
Other	12 (11.7)	7 (19.4)	3 (8.3)	22 (10.9)	
Do you trust the websites in terms of validity?					
Yes	58 (56.3)	36 (57.1)	8 (22.2)	102 (50.5)	0.0009
No	45 (43.7)	27 (42.9)	28 (77.8)	100 (49.5)	
Were the health information comprehensive?					
Yes	76 (73.8)	48 (76.2)	22 (61.1)	146 (72.3)	0.24
No	27 (26.2)	15 (23.8)	14 (38.9)	56 (27.7)	
Level of satisfaction with the medical information					
High	22 (21.4)	18 (28.6)	6 (16.7)	46 (22.8)	0.051
Medium	69 (67)	38 (60.3)	19 (52.8)	126 (62.4)	
Low	12 (11.7)	7 (11.1)	11 (30.6)	30 (14.9)	

overwhelming interest of parents on websites provided by doctors or hospitals[8,10-12,16]. Our study demonstrated that the vast majority of parents (91.6%) supported the idea of an official website designed and managed by the doctors of our clinic in which they would be able to find reliable and accurate child-related infor-mation.

Limitation

Our study included parents of children who were admitted to our clinic but excluded those who were not. It would be interesting to determine parent behaviors when they are not stressed out by their child's hospitalization.

CONCLUSION

Our study is in line with the international literature with some minor deviations. This demonstrates that most parents use the internet to query child-related surgical problems. Internet access is difficult in rural areas of northeastern Greece, probably because many of these regions are isolated mountainous areas where the majority of the population is engaged in agricultural work and has different cultural habits. After

Table 7 Internet usage and examination by a pediatric surgeon regarding the educational level of the parent who searched on the Internet (*n* = 202), *n* (%)

	Completed high school or less, *n* = 103	Completed college or some college, *n* = 63	Advanced degree or beyond, *n* = 36	Total	*P* value
Other medical information resources					
Pediatrician/GP	98 (95.1)	63 (100)	36 (100)	197 (97.5)	0.11
Friends and family	45 (43.7)	20 (31.7)	11 (30.6)	76 (37.6)	
Parents groups	8 (7.8)	9 (14.3)	0	17 (8.4)	
Search for a specialist					
Yes	42 (40.8)	31 (49.2)	10 (27.8)	83 (41.1)	0.11
No	61 (59.2)	32 (50.8)	26 (72.2)	119 (58.9)	
Did you inform the specialist about the Internet search?					
Yes	30 (29.1)	15 (23.8)	3 (8.3)	48 (23.8)	0.041
No	73 (70.9)	48 (76.2)	33 (91.7)	154 (76.2)	
Was the information found on the Internet the same as the one given by the doctor?					
Yes	57 (55.3)	54 (85.7)	26 (72.2)	137 (67.8)	0.0002
No	46 (44.7)	9 (14.3)	10 (27.8)	65 (32.2)	
Need for an official website					
Yes	86 (83.5)	63 (100)	36 (100)	185 (91.6)	0.0001
No	17 (16.5)	0	0	17 (8.4)	

GP: General practitioner.

this survey and this review, the next developmental step that the medical community must support is clear. This is the creation of an easy-to-use (even by people with a low educational level) official website from which the parents could access appropriate health information to give substantial answers to their questions and by which they could contact online medical staff and address their questions. Parents will be reassured about their decisions regarding the right time to visit the hospital and consult the doctor they choose for their child's conditions.

ARTICLE HIGHLIGHTS

Research background

The internet is a valuable tool for access to health-related information. There is limited literature regarding its use by parents of children with surgical conditions.

Research motivation

Our study describes the influence of education and residence on the parental search for pediatric surgical information on the internet in a multicultural region of northern Greece, and we compare our results with the recent literature.

Research objectives

The objectives of this study were first to evaluate the epidemiological characteristics of parents in relation to the magnitude of internet usage for health-seeking information and second to review the literature regarding this topic.

Research methods

In this study, an anonymous questionnaire about internet usage was completed by eligible parents of children who were admitted to our clinic for minor surgical procedures during a six-month period. And the literature was reviewed.

Research results

The results of this study demonstrated that the internet has been mostly used by mothers for children's health information. Google was the most commonly used search engine, while pediatricians were the first parental choice for 'live' information.

Research conclusions

The establishment of official websites that parents can access to receive appropriate health information is mandatory in the internet era.

Research perspectives

It would be interesting to determine parent behaviors when they are not stressed out by their child's hospitalization in the future.

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CASE REPORT

Pediatric case with vaccine-related poliovirus infection: A case report

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Abstract

BACKGROUND

As long as oral poliovirus vaccine (OPV) is used, the potential risk for the emergence of vaccine-related polioviruses remains.

CASE SUMMARY

We report a case of Sabin-like type 1 poliovirus infection in an immunocompetent 17-mo-old child after receiving four scheduled doses of OPV. Somehow, the four doses did not confer full protection, possibly because of interference created by other enteroviruses.

CONCLUSION

The surveillance of vaccine-related polioviruses has important implications for improving health policies and vaccination strategies. Missed cases of vaccine-related poliovirus infection might pose a potential risk to global poliovirus eradication. Therefore, the global withdrawal of OPV and a shift to the inclusion of only inactivated poliovirus vaccine in the vaccination schedule is the main objective of the polio eradication program.

Key Words: Poliovirus; Oral poliovirus vaccine; Vaccine-associated paralytic poliomyelitis; Case report

Core Tip: In this study, we report an unusual case of Sabin-like type 1 poliovirus infection in an immunocompetent 17-mo-old child after receiving four scheduled doses of oral poliovirus vaccine (OPV). Somehow, the four doses did not confer full protection, which may have been caused by interference created by the other enteroviruses. The surveillance of vaccine-related polioviruses (VRPVs) has important implic-

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ations for improving health policies and vaccination strategies. Missed cases of VRPV infection might pose a potential risk to global poliovirus eradication. Therefore, the global withdrawal of OPV and a shift to including only inactivated poliovirus vaccine in the vaccination schedule is the main objective of the polio eradication program.

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INTRODUCTION

The extensive use of trivalent oral poliovirus vaccine (tOPV) in routine and supplementary immunization schedules has led to the control and eradication of wild poliomyelitis in almost all parts of the world[1]. Despite inducing durable mucosal and humoral immunity, conferring immunity to unvaccinated individuals as well as low cost and easy oral administration, oral poliovirus vaccine (OPV) strains are genetically unstable[2]. On rare occasions, OPV might revert toward virulent strains by recombination with other enteroviruses in the human gut or reversion mutations under tropical conditions and with poor sanitation, hygiene and water quality, or under conditions of low vaccination coverage and poor population immunity[1,3]. Vaccine-related polioviruses (VRPVs) can cause vaccine-associated paralytic poliomyelitis (VAPP) in normal and immunodeficient vaccine recipients or their close contacts. However, the risk is much higher in immunodeficient individuals[4,5].

The emergence and spread of VRPVs are the biggest threats to the global poliovirus eradication program. A switch from live-attenuated OPV to inactivated poliovirus vaccine (IPV) seems to be the best option to eliminate the risk of VAPP emergence. However, in reality, OPV cessation is not feasible as long as global polio eradication is not achieved[5-7]. In polio-endemic regions or neighboring countries at risk of wild poliovirus importation and spread, OPV remains the vaccine of choice to block wild polio infection and transmission caused by induction of prolonged intestinal immunity even beyond its recipients[5,8]. Currently, we are on the horns of a dilemma. In these circumstances, timely detection and response to VRPVs need to be emphasized in countries using OPV to prevent paralysis development and community spread[6,9]. Here, we report a pediatric case of Sabin-like type 1 poliovirus infection at 17 mo of age after receiving four doses of tOPV.

CASE PRESENTATION

Chief complaints

A 17-mo-old girl from Bushehr city was admitted to Shohadaie Khalij-Fars Hospital with symptoms of fever (38.5°C-40°C), drowsiness, irritability, cough, rhinorrhea, vomiting, and generalized weakness.

History of present illness

On history, the child was immunocompetent and had no known illness. The immunization history revealed that the child was vaccinated with four scheduled doses of tOPV, one dose at birth and three doses at 2, 4, and 6 mo of age. Approximately, 11 mo after receiving the fourth dose of tOPV at her local public health center, febrile enteritis along with anorexia and vomiting developed, and she was hospitalized a few days later.

History of past illness

The child had no history of prior illness.

Personal and family history

The child was immunocompetent and had no known illness.

Physical examination

A lumbar puncture (LP) was performed and antibiotic therapy with empiric antibiotics including vancomycin and ceftriaxone was initiated immediately. On the fourth day of hospitalization, her condition deteriorated, and the pediatrician referred her to the Pediatric Clinic of Namazi Hospital in Shiraz for further evaluation. On examination, reduced strength in all limbs, most notably in her lower extremities, and regression in her ability to sit and walk were noted. High-grade fever and conjunctivitis were the other clinical symptoms. An LP was repeated and cerebrospinal fluid (CSF) pleocytosis was reported.

Laboratory examinations

CSF analysis showed a clear appearance, lymphocytic pleocytosis, normal glucose, and a mild increase of protein levels. CSF bacterial culture was negative; viral culture and molecular assays were not performed. The diagnosis was aseptic meningitis.

Imaging examinations

There were no imaging examinations.

Further diagnostic workup

About 2 years after this event, a regional survey supported by Bushehr University of Medical Sciences (grant number 4359), was performed on leftover CSF samples of patients with a diagnosis of primary aseptic meningitis. The study was approved by the Ethical Committee of Bushehr University of Medical Sciences (reference number bpums.rec.1394.29). Sabin-like type 1 poliovirus was isolated from the CSF specimen of this patient by enterovirus reverse transcriptase-polymerase chain reaction assay (RT-PCR), targeting the 5′ untranslated region (5′ UTR) of the genome, followed by sequencing (Figure 1). The nucleotide sequence isolated from the CSF sample of this case was submitted to the GenBank sequence database (accession number: KX 011400.10).

The nucleotide sequence of this case (KX011400.1) and the nucleotide sequences of wild-type poliovirus (human poliovirus 1 Mahoney), vaccine-derived poliovirus, and vaccine-strain poliovirus (Sabin type 1) were aligned by the ClustalW program in MEGA software version 4.0 (Biodesign Institute, Tempe, AZ, United States). A change of an A to a G was shown at position 480 of the 5′ UTR of the isolated sequence (Figure 2). The CSF sample was negative for nonpolio enteroviruses, mumps, herpes simplex virus types 1 and 2, cytomegalovirus, and varicella-zoster virus.

FINAL DIAGNOSIS

We present a case of Sabin-like type 1 poliovirus infection that was initially consistent with the diagnosis of aseptic meningitis. On further evaluation, a diagnosis of Kawasaki disease was presumed. However, that diagnosis is unlikely, given that the high-grade fever persisted despite intravenous immune globulin (IVIG) therapy. This was a probable case of VRPV infection, and is supported by isolation of Sabin-like type 1 poliovirus from CSF specimen. The nucleotide sequence isolated from the CSF sample of this case had G at nucleotide position 480 of the 5′ UTR, which differentiates it from the wild-type poliovirus with A-480[10,11]. The probability of nonpolio enteroviral infections was ruled out by the negative RT-PCR enterovirus assay results on the CSF specimen.

TREATMENT

As Kawasaki disease was suspected, a single high-dose (2 g/kg) intravenous administration of immunoglobulin (IVIG) was given. However, the high-grade fever was not responsive to IVIG and persisted for approximately 8 d. Subsequently, the clinical symptoms were gradually improved. It is unclear whether immunoglobulin therapy facilitated the improvement of the clinical symptoms, or they improved spontaneously.

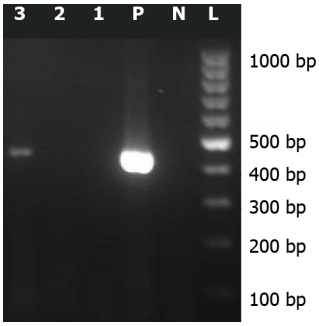

Figure 1 Reverse transcriptase-polymerase chain reaction assay amplification of Sabin-like type 1 poliovirus RNA isolated from cerebrospinal fluid samples of this case. 3: Amplified product (approximately 438 bp) on 2% agarose gel electrophoresis; L: 100 bp DNA ladder; N: Negative control; P: Positive control.

OUTCOME AND FOLLOW-UP

Following clinical improvement, the child was discharged from the hospital, but she had a mild fever, muscular weakness, and difficulty using her lower limbs for approximately 2 mo. At a 1-year follow-up, cardiac complications were not reported, and the strength of all her limbs was completely restored.

DISCUSSION

This is an unusual case of VRPV, as the child was immunocompetent and had received four doses of tOPV. Somehow, the four doses had not conferred full protection, possibly because of interference created by other enteroviruses. Of note, the child lives in a tropical area, where diarrheal diseases frequently occur. Neurovirulent reversion of OPV in the child's gut is a possibility. However, the long interval between administration of the fourth dose of tOPV and onset of clinical symptoms, as well as the child's immunocompetency make that unlikely. Other possibilities include the presence of a prolonged poliovirus excreter or the existence of circulating VRPVs in the environment. However, that is unlikely possibility given that no secondary cases were reported southern Iran before or after this event. She was a close contact of other OPV-vaccinated children in a crowded nursery, and therefore exposure of this patient to VRPVs originating from the other children is another possibility. Overall, the evidence is insufficient to trace the source of this strain. This case was detected through a regional survey to reveal the molecular epidemiology of viral causes of aseptic meningitis. This case was missed by routine surveillance of acute flaccid paralysis because the patient was not paralyzed at the time of admission and was evaluated following a misdiagnosis.

The VRPV surveillance has important implications for improving health policies and vaccination strategies. However, most cases of VRPV infection are captured through the acute flaccid paralysis surveillance system. Recognition of VRPVs remains an important challenge. Missed cases of VRPV infection pose a potential risk to global poliovirus eradication. As long as OPV is used, the potential risk of emergence of VRPVs remains[6]. VRPVs are clinically indistinguishable from wild polioviruses and are capable of causing paralytic poliomyelitis and circulating in society whenever the immunity coverage is reduced[2,6]. The emergence of VAPP is a health dilemma as devastating as wild polio. Therefore, the global withdrawal of OPV and shift toward the all-IPV schedule is the main objective of the polio eradication program[3].

CONCLUSION

In this study, we report an unusual case of Sabin-like type 1 poliovirus infection in an immunocompetent 17-mo-old child after receiving four scheduled doses of OPV. Somehow, the four doses did not confer full protection, possibly because of interference created by other enteroviruses. The surveillance and notification of VRPVs has important implications for improving health policies and vaccination strategies.

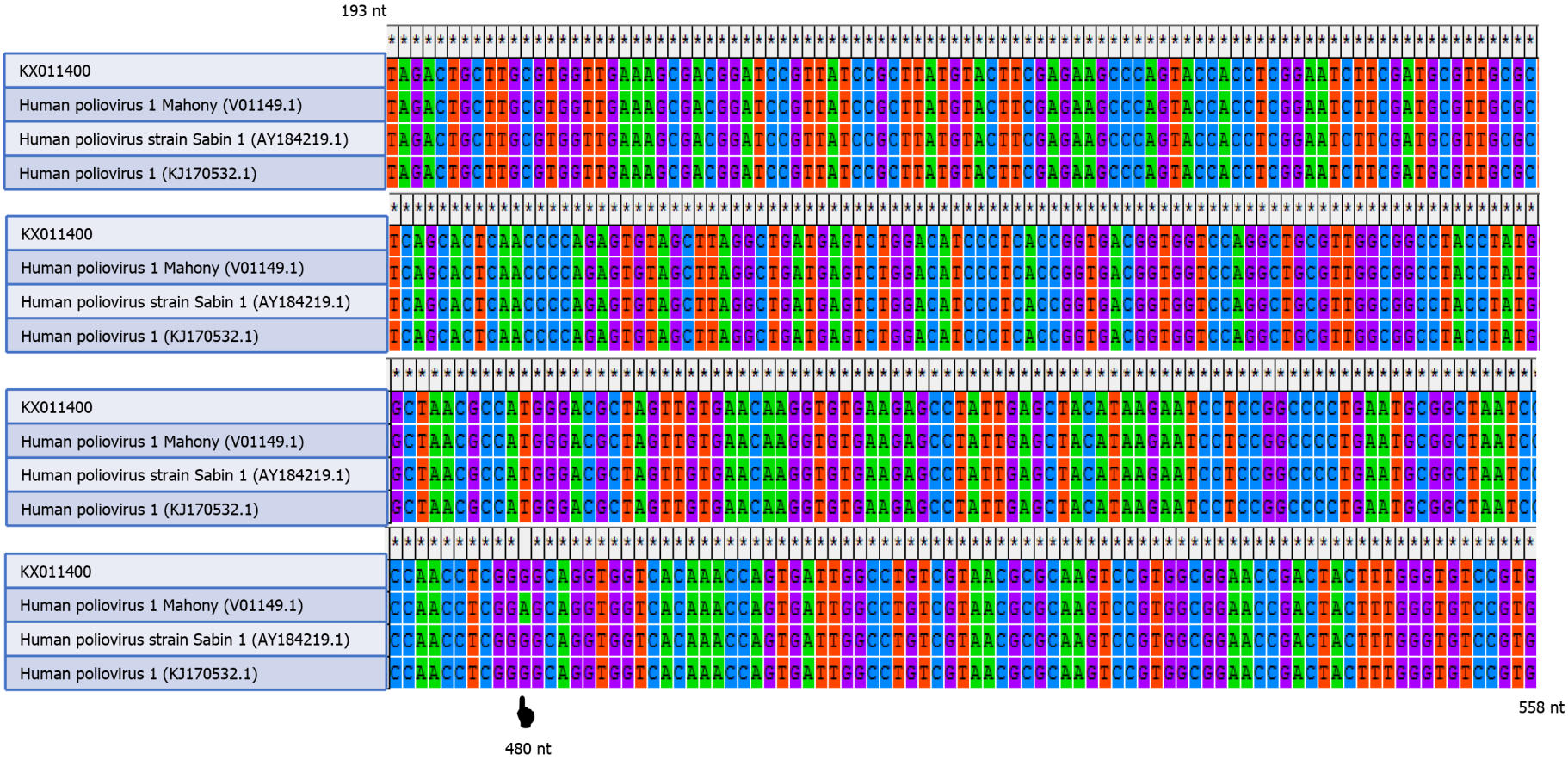

Figure 2 Alignment of the partial nucleotide sequences (193 nt to 558 nt) of this case (KX011400). Wild-type poliovirus (V01149.1), vaccine-strain poliovirus (AY184219.1), and vaccine-derived poliovirus (KJ170532.1) by MEGA software version 4.0 (Biodesign Institute, Tempe, AZ, United States) and appearance of a nucleotide difference at position 480 of the 5' untranslated region. A denotes wild-type poliovirus and G denotes vaccine-strain poliovirus.

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REVIEW

Pediatrician-friendly perspectives on cognitive behavioral therapy for anxious youth: Current status and clinical implications for the next normal

Robert D Friedberg

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Abstract

Pediatric anxiety disorders are common and often debilitating conditions. Cognitive is a psychosocial intervention that represents a potentially powerful antidote to these disorders. This article reviews data from treatment outcome studies, meta-analyses, and systematic reviews as well as from moderation/mediational investigations. The literature supports the efficacy, effectiveness, and durability of positive treatment outcomes for pediatric anxiety disorders. Recommendations for clinical applications are suggested.

Key Words: Pediatric anxiety; Cognitive behavioral therapy; Coping cat; Exposure

Core Tip: There are several core tips in this therapeutic advances article. First, while the state-of-the-science supporting cognitive behavioral therapy (CBT) for pediatric anxiety is very strong, proper delivery of genuine CBT by trained providers is fundamental to its success. Clinicians should provide CBT in a manner that balances flexibility within fidelity. Most importantly, exposure is an essential component to any CBT approach to pediatric anxiety disorders.

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INTRODUCTION

Anxiety disorders are highly prevalent conditions in child and adolescent populations [1-5]. Approximately 6.5% of youth worldwide suffer from anxiety disorders[4]. Anxiety disorders are also gateway disorders[3,6]. Thus, pediatricians frequently care for anxious youth in their practices and these young patients are frequently impaired. Effective psychosocial treatments are needed.

Fortunately, cognitive behavioral therapy (CBT) is widely regarded as the premier psychosocial treatment for pediatric anxiety disorders[7,8]. The approach has been empirically supported by meta-analyses, mediational and moderation studies, systematic reviews, randomized clinical trials (RCTs), controlled investigations, and case reports. Based on the aggregated results, both the American Academy of Child and Adolescent Psychiatry (AACAP) and the American Psychological Association (APA) see CBT as the gold-standard treatment. More specifically, AACAP[9] referred to CBT as the "front-line" psychosocial intervention for pediatric anxiety disorders. The APA defined CBT for anxiety disorders as a "well-established" treatment[10]. Reaching the "Well-Established" threshold means that CBT was evaluated by at least 2 RCTs indicating efficacy where the treatment outperformed pill placebo, psychological placebo, or another treatment comparison group. Further, the specific intervention must have been manualized and examined by two different research teams. Finally, the protocol is required to have demonstrated equivalence to another Well-Established treatment or two approaches studied in investigations with at least $n = 30$. In sum, the well-established threshold is a stringent criterion. While anxiety disorders are highly prevalent and impairing, CBT is a widely deployed and effective intervention.

In this pediatrician-friendly perspective, CBT basics are briefly summarized and the empirical literature supporting the approach is discussed. Results from treatment outcome evaluations examining the seminal Coping Cat program, data from the Child/Adolescent Anxiety Multi-Modal Studies (CAMS) along with findings from reviews and meta-analyses are delineated. Further, the impact of mediators as well as moderators are presented. Finally, the article concludes with clinical recommendations for the peri- and post pandemic period.

BASIC DESCRIPTION OF CBT FOR PEDIATRIC ANXIETY: THERE'S NOTHING LIKE THE REAL THING

CBT is a multi-component treatment paradigm is that is widely adopted[11-14]. Contemporary CBT with youth is increasingly adopting a modular approach to treatment (mCBT)[15-19]. In general, modular approaches identify the best procedures commonly found in many treatment packages/protocols and organize them into conceptual clusters. The techniques are grouped into particular units that share a purpose or function [*e.g.* orienting patients to treatment, cognitive restructuring (CR), *etc.*]. mCBT offers several compelling advantages including parsimony, reduced training burden, personalized/individualized care, and attractiveness to providers [15]. Typical modules include psychoeducation (PE), basic behavioral procedures (BBPs), CR, and exposure/experiments.

PE paves the way for the various intervention strategies. PE teaches patients as well as their families about anxiety disorders and treatment alternatives[20,21]. Moreover, PE enables genuine informed consent as well as increased help-seeking, collaboration, demystification, universality, empowerment, and hopefulness[18,22-25]. It may be delivered verbally or through books, pamphlets, video/audio recordings, internet sites, and mobile applications[17,18].

BBPs are based on "systematic application of conditioning principles to clinical disorders[26]." Typically, these procedures focus on acquiring and applying specific skills to particular problems[14]. BBPs include a stable of familiar approaches including relaxation, contingency contracting, and social skills training.

CR and rational analysis (RA) focus on re-engineering thought content and processes respectively[17,18,27]. Problem-solving, self-instructional, and self-talk techniques are classic CR procedures. A voluminous literature base exists that supports the use of CR methods[27-34]. RA procedures are more advanced methods and enjoy a long history in CBT[35-40]. "Analysis of meaning and attitudes exposes the unreasonableness and self-defeating nature of the attitudes[38]." Tests of evidence, reattribution, decastrophizing, and universal definitions are common techniques used in RA [38-40].

Exposure is seen as essential when treating anxiety disorders in youth[8,17,41-49]. Successful completion of exposure tasks involves young patients' undivided attention, use of coping skills, and persistence amid negative emotional arousal[50]. The exposure component in CBT treatment uniquely differentiates CBT from supportive treatment[45]. Approximately 88% of the strongest studies evaluating treatment outcome for anxiety disorders in youth incorporated exposure in their intervention protocol[46]. When exposure elements were absent from CBT treatment approaches for anxiety, the effects were significantly attenuated[42,49,51]. In a meta-analysis focusing on dismantling the effective components of CBT for anxiety disorders in youth that included 75 studies, in-session exposure resulted in larger effect sizes when comparing CBT to wait-list control groups[41]. Increasing the emphasis on in-session exposure over anxiety management strategies such as those procedures described in the basic behavioral tasks as well as the CR modules may improve CBT's efficacy[41].

Proper delivery and dosing of genuine CBT is crucial. There is data that clinicians self-identify as CBT practitioners, yet their in-session behavior does not resemble the true treatment approach[52]. Practicing flexibly with faithful adherence to CBT tenets is the current clinical watchword[11,53-55]. Competent CBT providers are seen as expert multi-taskers[56]. Consequently, they are able to balance faithful adherence to the model while making immediate adaptations in response to young patients' unique presentations[11]. Flexible applications of CBT enable real-time adaptations, matching treatment to individuals' psychological characteristics, and incorporating cultural vicissitudes into the intervention[53-55]. In this way relevance matching[57] is better achieved which facilitates building a more personalized treatment package.

TREATMENT OUTCOME STUDIES: COPING CAT

Coping Cat is a CBT protocol that is typically delivered in 12-16 sessions divided into two phases[12,58-60]. The classic FEAR plan punctuates the first 9 sessions. The feeling frightened component helps young patients monitor their physiological signs of anxiety. Identifying their catastrophic predictions defines the expecting bad things to happen part. Developing coping counter-thoughts and adaptive problem-solving strategies is the focus of attitudes and actions that can help. The fourth segment, results and rewards, teaches children to reward their productive coping efforts. Exposures and behavioral experiments make up sessions 10-16. During this stage, patients apply the skills acquired *via* the FEAR plan in various anxiety producing situations. Homework assignments called show that I can exercises are completed over the course of the Coping Cat protocol to facilitate treatment generalization and a sense of self-efficacy. The treatment package has been widely implemented in the United States and internationally[59,61].

Early RCTs evaluating the Coping Cat yielded very encouraging findings[62,63]. Coping Cat outperformed a wait-list control group in a RCT on several measures with young patients resulting in less symptoms, greater coping ability, and increased social skills[62]. Moreover, the gains showed durability with improvements holding up at 1 year[62] as well as 3.5 years later[64]. A subsequent RCT[63] also found similar positive results with 50% of patients being symptom-free at the end of treatment. These gains were sustained at 1 year[63] and 7.5 years after treatment[65].

Coping Cat was compared to an active treatment contrast condition (Humanistic Therapy) in a recent study including 133, 9-14 year old youth[45]. Although both treatments yielded similar acute response data, the CBT group was more likely to fully recover and no longer meet diagnostic thresholds at the end of treatment than counterparts receiving the Humanistic approach. Further, the patients in the CBT condition evidenced higher recovery rates at the 1 year follow-up point. The study authors'[45] concluded that CBT resulted in greater breadth and generalizability of treatment gains as well as more durability over time.

In an effectiveness study examining Coping Cat delivered by practitioners in a community setting rather than in a more controlled academic setting, participants in the treatment package outperformed wait-listed control group cohorts and the gains were maintained at 2 year follow up points[66].

Intolerance of uncertainty (IU) was targeted in a study examining Coping Cat's clinical promise[67]. IU is seen as an important mechanism of action in anxiety disorders. This study found that decreased IU from pre-post treatment was associated with lowered functional impairment, increased coping, and decreased anxiety severity. These results imply that focusing specifically on uncertainty in CBT for anxiety may improve outcomes.

Treatment outcome studies: The CAMS

The CAMS was the most wide-ranging RCT evaluating the use of CBT (Coping Cat) and Serotonin Selective Reuptake Inhibitors (SSRI, Sertraline) for the treatment of anxiety in youth[68,69]. The project involved 488 participants (7-17 years of age) across multiple sites and assessed outcomes at 12, 24, and 36 wk. The data indicated that after 12 wk, the CBT, SSRI, and CBT + SSRI conditions all outperformed the placebo group [68]. More specifically, 80.7% of youth in the combination, 59.7% in the CBT alone, and 54.9% in the singular sertraline treatment arm improved on the Clinical Global Impression Scale. A dismantling study of 279 participants enrolled in the CAMS project showed that anxious youth who received more sessions devoted to exposure demonstrated greater symptom reduction and functional improvement[8].

In a project examining response and remission rates, all three arms of CAMS (CBT, SSRI, COMBO) sustained their rates of improvement, however the superiority of the combination treatment did not persist at the 36 wk mark[69]. Extended long term gains were evaluated in a study of 319 youths[70]. Based on linear and quadratic growth models, CBT was associated with faster improvement, academic achievement, and greater life-satisfaction. These gains appear to endure for approximately 6.5 years.

The question of which treatment arm is best-suited for which patients was researched in another secondary data analysis[71]. The single treatments (CBT, SSRI) worked equally well for patients with lower levels of anxiety whereas the combined CBT + SSRI package was essential for symptom remission in patients with more severe anxiety. Additionally, low SES predicted poorer treatment response. Thus, it appears that the combination treatment is indicated for more distressed individuals who may be more financially challenged.

REVIEWS AND META-ANALYSES

An early review article concluded RCTs evaluating CBT spectrum approaches yielded positive treatment outcomes earning medium effect sizes[72]. In a later review of 24 RCT's with children and adolescents diagnosed with a variety of anxiety disorders, large pre-post differences were reported[73]. Additionally, rates of clinical improvement ranging from 60%-80% were found. Further, when a conservative benchmark of remission was applied, 50%-70% of patients claimed they were symptom free[73]. A recent comprehensive review evaluated multiple treatment paradigms for anxiety according to various levels[46]. The review concluded that CBT earned a large effect size and demonstrated durability of outcomes with diverse populations. Moreover, when applying another more stringent criteria such as functional improvement in patients, CBT was the only approach that met the Well-Established threshold. Children who received CBT were 3 to 7 times more likely to show improvement than cohorts in the passive control condition[74].

A variety of meta-analyses examining CBT's potential to reduce anxiety disorders have been conducted[75-78]. In a meta- analysis exploring the efficacy of CBT for anxiety disorders in youth, 11 meta-analyses incorporating 350 comparisons were evaluated[75]. The results yielded medium to large effect sizes for CBT compared to non-active controls [mean weighted effect size (d) = 0.76]. Further, the effect sizes were somewhat smaller when testing CBT *vs* active comparison groups (d = 0.40). Finally, when pre-post differences in anxiety for CBT were studied, large effect sizes were found (d = 0.88). When examining compete symptom recovery, another meta-analysis concluded 61 percent of youth show symptom remittance after a course of CBT[78].

A systematic review and meta-analysis including 115 studies covering 7719 patients with a mean age of 9.2 years showed that when CBT was compared to wait list comparison groups, CBT led to greater symptom reductions and remissions[77]. Moreover, the same meta-analysis found that attrition rates were lower in the CBT condition than the in pill/placebo contrast groups. Moreover there were less adverse events in patients receiving CBT than in counterparts who were in the medication groups (SSRI). These results appear to suggest that CBT is more well-tolerated by young patients than medication[79]. Finally, the combination of CBT with SSRIs was a stronger treatment than either mono-therapy alone[77].

CBT also demonstrates considerable promise when applied to anxious adolescents. Large pre-post differences, medium to large effects sizes, and encouraging remission rates were found. In particular, post-treatment remission rates ranged from 27%-35% and from 52 to 60 percent in various studies[73].

MODERATORS AND MEDIATORS

Examining moderator and mediator variables adds another dimension to treatment outcome studies. Moderation analyses can determine what treatment, for what type of patient, under which circumstances works best[80]. A moderator variable is defined as either a qualitative or quantitative construct that "affects the direction and/or strength of the relationship between an independent or predictor variable and a dependent or criterion variable[81]". Moderator variables represent pre-randomized characteristics that do not explain treatment effects but rather interact with them[82]. In general, moderator analysis examines performance of subgroups in certain conditions[80].

Conversely, mediators specify the mechanisms of change in dependent variables and speak to how or why effects occur[81]. Behavior change, especially decreased avoidance, is a powerful mediator of treatment outcome for anxiety disorders[83]. Negative cognitions especially future-oriented, catastrophic thoughts were also seen as significant mediating variables and homework assignments earned small to medium effect sizes[83]. Results for parental behavior and treatment alliance were deemed inconclusive as far as their contribution to outcomes[83].

Several studies based on the CAMS investigations identified some additional potential mediators. In a follow-up investigation including 488 youths, coping efficacy mediated clinical outcomes[84]. Perception of social threats mediated treatment response in a naturalistic follow-up evaluation of 319 young patients enrolled in CAMS[85]. Somatic symptoms mediated treatment outcome for the sertraline arm of the CAMS study[86]. The most consistent predictors of treatment response found across studies included type of primary anxiety disorder, severity of anxiety, co-morbidities, and parental psychopathology[82].

In an analysis of the CAMS data based on 488 young participants, no demographic variables moderated the clinical outcomes[87]. A recent comprehensive review evaluated research on moderator variables such as co-morbidity, presence of social anxiety, gender, age, race/ethnicity, parental involvement, parental psychopathology, family factors, therapist variables, and dose of therapy[83]. These investigators noted that treatment outcomes did not vary as a function of the severity of illness and regardless of pre-treatment severity, anxious youth demonstrated a similarly favorable treatment response. On the other hand, co-morbid conditions such as autism spectrum disorders, depression, and attention deficit disorder did moderate the outcome. They concluded gender and ethnicity did not significantly influence treatment outcome, indicating that male and female, as well as diverse youth, benefit similarly from CBT. Moreover, parental involvement in treatment and family factors were not seen as significant moderators. Parental psychopathology had some modest influence on treatment depending on the age of the child, with a stronger impact on outcomes for younger youth. Overall, the data on age of the patient was considered inconclusive. Finally, therapist variables such as flexibility and collaboration demonstrated moderating effect on treatment outcomes.

A number of reviews agree that demographic variables (*e.g.* biological sex, race/ethnicity, SES, *etc.*)[43,73,82] do not significantly moderate treatment outcome for anxiety disorders in youth. Nonetheless, there is some evidence that gender and ethnicity are correlated with differential attrition rates[60]. It could be argued that many of these studies are under-powered to detect significance, but this criticism is somewhat recently debunked[72]. The CBT procedures appear to be applicable to a wide range patients[83,87].

RECOMMENDATIONS

The literature reviewed tells a compelling story with multiple implications for clinical practice. The data supports CBT's effectiveness and efficacy as well as its wide applicability to diverse groups of young patients[8,45,62,63,67,83,87]. Additionally, CBT enjoys durable positive effects[64,65,69,70]. CBT is equally as effective as SSRIs but is associated with less adverse side effects[68,77,79]. Psychological distress characterized by anxiogenic cognitions and behavioral avoidance are apparently the most productive targets for intervention[2]. Perhaps most pivotally, the exposure component to treatment is essential to distinguish between more and less effective CBT as well as differentiate CBT from other systems of psychotherapy[8,17,41-51]. Simply, CBT for anxiety without exposure is a diluted approach[88].

The extant literature aids pediatricians in treatment planning. The findings of equivalence between SSRIs and CBT in treating anxious youth gives patients and

providers multiple choices. Either mono-therapy is suitable for these individuals, but CBT is associated with less adverse side effects. Pediatricians might consider starting less severely distressed patients on a course of CBT since it is associated with fewer side effects, track progress, and if indicated, augment the CBT with medication. For more severe presentations especially those with strong somatic complaints, the combination treatment seems best.

The world is currently in the midst of a devastating public health crisis caused by the coronavirus disease 2019 (COVID-19) pandemic. In general, pandemics are characterized by increased anxieties and worries[89-92]. Various authors believe the COVID-19 pandemic is a powerful trigger for health anxiety[93,94]. Hospital records in the United States document a startling increase by 24% and 31% in emergency room visits die to anxious symptoms for children and adolescents respectively[95]. Regrettably, the psychological sequelae do not appear to self-limiting[90]. They are here to stay.

Accordingly, ensuring the proper delivery of CBT to young patients is pivotal to meet the rising tide of cases, provide effective and efficient treatment as well as minimize clinical errors. However, there are relatively few clinicians practicing in treatment-as-usual settings who are trained to deliver a proper dose of evidence-based psychotherapies[96]. Unfortunately, many clinicians incorrectly self-label themselves as CBT clinicians[52,97-99]. In fact, when actual clinical practices were studied, few providers who self-labelled themselves as CBT oriented practitioners genuinely delivered a proper dose of CBT[52]. This finding is consistent with the phenomenon of "posing" as a CBT therapist rather than practicing as one[99]. Thus, attention needs to be regularly directed to the proper application of CBT with youth.

Clinicians are also well-advised to practice CBT in a faithful and flexible manner[53-55]. Patients typically arrive to clinics experiencing different family circumstances and living in diverse cultural contexts. Additionally, pediatric patients' predisposing characteristics and learning styles likely make them more or less receptive to varying therapeutic styles. For instance, some young patients may present to treatment with limited literacy. In these cases, clinicians are well-advised to rely on more concrete behavioral procedures such as exposure techniques. Additionally, scaffolding the cognitive demands to make the methods more accessible is recommended. Fortunately, there are many child-friendly iterations of traditional cognitive interventions available that are suitable for patients with limited literacy[11,16-18,47,58,60,61]. Perhaps, the attention alert CBT-oriented clinicians pay to working faithfully and flexibly partially explains the wide applicability of the approach.

Employing exposure based treatments for youth is a crucial task for clinicians. Exposure is underutilized in general[100-105] especially with younger children and children prescribed medication[8]. For instance, it was found that only 13% CBT oriented therapists used exposure based techniques[100]. In another study, a mere 40% of practitioners employed exposure procedures and these interventions accounted for only 1/5th of all clinical strategies utilized[103]. Further, exposure techniques were applied 19% of the time compared to CR (57%) and breathing exercises (53%)[105]. Finally, 48% percent of clinicians reported not implementing exposure due to lack of training[104]. In sum, continued and close attention to training clinicians in exposure-based treatments is necessary to fully equip practitioners with essential skills.

Multiple guidelines exist to guide clinicians' work with youth during exposure procedures[11,17,18,44]. Collaboration between clinicians and patients is essential during exposure. It is important to remember that exposure is done with rather than to patients. Children spearhead the exposure journey and the key for practitioners is to nurture young patients' willingness to encounter instead of avoid anxiety producing situations.

Exposure starts with PE and providing a rationale. Metaphors and analogies such as germ theory where immunity is often bolstered by exposure are helpful. Additionally, the use of videos or books where coping models (*e.g.* Bruce Wayne aka Batman surrounding himself with feared bats) approach their heretofore dreaded circumstances are other options. Graduated exposure is the preferred delivery mode. Accordingly, exposure hierarchies which include different successive steps (*e.g.* challenges) operationalized through collaboratively constructed Subjective Units of Distress (SUDS) (*e.g.*, 1-10, 1-100) are commonly employed. Patience by providers is recommended and a useful axiom for using a hierarchy is "start in the low-mid SUDS range and proceed slowly."

Exposures should be comprehensive and done repeatedly. In-session exposures should be completed several times and then at-home exposures are attempted regularly between appointments. Moderate to high levels of emotional arousal in response to in-session exposures are favored[106]. Further, the procedure should encompass cognitive, behavioral, physiological, emotional, contextual and inter-

personal elements of the anxiety response.

Developmental sensitivity and clinical creativity is pivotal when crafting exposures [11,16,17,44,53-55,58,60,61]. Rewards for successful efforts are strongly suggested for younger individuals. Game and playful exposures are especially engaging for pediatric patients. It is important to remember that the goal in exposure treatment is for new approach learning to occur[107]. Improved self-efficacy and greater self –control should result. Therefore, any exposure-based procedure should not be terminated before new learning emerges through either reductions in subjective distress, increased emotional tolerance, and/or greater approach behavior.

Finally, after the exposure is completed, clinicians and patients debrief the experience. Patients compare their predictions about what might happen to what actually occurred. They then craft their new conclusions and inferences based on the outcomes of the exposure.

The use of telehealth services has dramatically increased during the COVID-19 pandemic[108,109]. Virtual delivery of clinical services offers intriguing advantages and opportunities[110-112]. CBT provided *via* telehealth platforms is convenient and allows for interventions in young patients' home environment[110,112]. In particular, exposure done *via* telehealth allows for the clinician to process this experience with young patients while they engage in the procedure in their familiar context potentially adding to generalizability.

Finally, integrated pediatric behavior health care settings are well-suited to meet the cascading rate of new cases expected in the post-pandemic period. Ninety percent of children visit a pediatrician[113]. For many families, pediatric offices are the first stop for treating behavioral health complaints[114-116] Additionally, these care settings enable early identification and intervention[112,117-120]. Delivering CBT to anxious youth in pediatric settings increases access in familiar settings and enables better collaboration between pediatrician and behavioral health specialists.

CONCLUSION

CBT with anxious children and adolescents is a clear success story. Reaching the Well-Established threshold as well as equivalence with SSRI's is a major achievement. Extending CBT's reach into pediatric integrated behavioral health settings is an important next step. Broadening access to services from properly training clinicians will enhance the care of young people and sustain CBT practices.

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MINIREVIEWS

Corrosive upper gastrointestinal strictures in children: Difficulties and dilemmas

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Abstract

Children constitute 80% of all corrosive ingestion cases. The majority of this burden is contributed by developing countries. Accidental ingestion is common in younger children (< 5 years) while suicidal ingestion is more common in adolescents. The severity of injury depends on nature of corrosive (alkali or acid), pH, amount of ingestion and site of exposure. There are multiple doubts and dilemmas which exist in management of both acute ingestion and chronic complications. Acute ingestion leads to skin, respiratory tract or upper gastrointestinal damage which may range from trivial to life threatening complications. Esophagogastroduodenoscopy is an important early investigation to decide for further course of management. The use of steroids for prevention of stricture is a debatable issue. Upper gastrointestinal stricture is a common long-term sequelae of severe corrosive injury which usually develops after three weeks of ingestion. The cornerstone of management of esophageal strictures is endoscopic bougie or balloon dilatations. In case of resistant strictures, newer adjunctive therapies like intralesional steroids, mitomycin and stents can be utilized along with endoscopic dilatation. Surgery is the final resort for strictures resistant to endoscopic dilatations and adjunctive therapies. There is no consensus on best esophageal replacement conduit. Pyloric strictures require balloon dilatation , failure of which requires surgery. Patients with post-corrosive strictures should be kept in long term follow-up due to significantly increased risk of carcinoma. Despite all the endoscopic and surgical options available, management of corrosive stricture in children is a daunting task due to high chances of recurrence, perforation and complications related to poor nutrition and surgery.

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Grade B (Very good): 0
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Core Tip: Corrosive ingestion is a life-threatening problem in children. The sequelae are grave and tenacious. There are multiple dilemmas in the acute management of corrosive ingestion. Endoscopic dilatations have challenges and are the cornerstone in management of upper gastrointestinal strictures. Adjunctive therapies may play a pivotal role. Surgery is required in refractory cases.

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INTRODUCTION

Burden of disease

Corrosive ingestion is one of the commonest causes of upper gastrointestinal strictures in children[1]. Worldwide, children represent 80% of all corrosive substance ingestion cases. The introduction of corrosives as household cleaning purposes has led to a rapid rise in accidental and suicidal ingestion in children. Majority are accidental[2,3] especially in children younger than 5 years who constitute 60%-80% of all pediatric corrosive ingestion cases[4,5]. Corrosives include both acidic and alkali substances. When these caustics come in contact with the skin or mucosa, they lead to variable extents of damage. In developed countries, corrosive injuries have decreased significantly due to strong efforts like childproof containers and biohazard labeling of caustics[6]. In developing countries, these substances are inexpensive, sold across the counter, unlicensed and often unlabeled for biosafety hazards[7]. The issue is worsened by poor literacy and unawareness. When it reaches the consumer, the caustics are stored in empty soft drink bottles and not kept out of reach of the children. Moreover, acid substances are transparent, resembling water. Younger children often fall prey to accidental ingestion out of temptation, curiosity or thirst[4]. As toddlers are verbally non-expressive, accidental ingestions may be unwitnessed and unreported till major symptoms arise. Suicidal and intentional ingestion is usually seen in dysfunctional adolescents with psychosocial trauma or in those with pre-existing psychiatric problems. In suicidal cases, caustic consumption is of large volume and symptoms are masked. Hence the cases present delayed with higher severity. Once acute complications are managed, strictures may develop at any site starting from the oropharynx, laryngeal inlet, esophagus or stomach, depending upon site of maximum contact. Strictures can be single or multiple, short or long and may involve multiple sites (*e.g.*, combined esophageal and pyloric strictures). The overall rate of esophageal stricture formation after caustic ingestion is reported between 2%-63%[4,8,9]. Rate of stricture formation varies with the severity of esophageal injury. Developing countries have mean death rate of 4.1% (0%-11.9%) due to corrosive ingestion[10]. Endoscopic dilatation and surgery are the mainstay for the management of strictures. From the emergency room at the time of first presentation to the management of stricture, there are many dilemmas regarding acute management, optimal timing of endoscopy, choice of dilatation (bougie *vs* balloon), use of adjuvant therapies, need of the surgery and long term prognosis of corrosive strictures. There is a paucity of literature on the management of corrosives in children. Practice varies from center to center with lack of uniformity. Therapeutic protocols or formulating guidelines are not available so far.

CLINICO-PATHOLOGICAL ISSUES

Commonly ingested corrosives are given in Table 1. Clinical manifestations are

Table 1 Commonly ingested corrosives in children

Acid	
Sulfuric acid	Batteries, industrial cleaning agents, metal plating, toilet cleaner
Hydrochloric acid	Solvents, metal cleaners, lime solvents, toilet and drain cleaners, muriatic acid, antirust compounds
Acetic acid	Pickling vinegar, vinegar spirit, wart solution
Phosphoric acid	Toilet cleaners
Oxalic acid	Paint thinners, metal cleaners, toilet cleaner
Alkali	
Sodium hydroxide	Grease/oil cleaners, drain cleaners, sink openers, oven cleaners, oil removers
Potassium hydroxide	Oven cleaners, washing powders, paint remover
Sodium carbonate	Soap manufacturing, fruit drying on farms
Sodium hypochlorite	Household bleaches
Ammonium hydroxide	General cleaner and grease remover
Miscellaneous	
Hydrogen peroxide	Surface and food cleaner
Potassium permanganate	Disinfectants, hair dyes

elaborated in Table 2. Alkaline substances have a higher viscosity, and hence remain in contact with esophageal mucosa for longer periods after ingestion. Alkali causes liquifactive necrosis and penetrate deeper into the tissue. Acids that have lower viscosity reach stomach faster, running along lesser curvature to reach the pylorus where there will be physiological stasis. Acid causes coagulative necrosis and deeper penetration is limited due to the same. Other factors that determine site and severity are chemical properties, contact time, contact surface area and urgency of referral. Many of the times, the nature and volume of corrosives are unclear from the history in children. Acids are available as pungent liquids; hence their intake is limited as soon as it is consumed accidentally. Alkalis are available both as liquids or solids (*e.g.*, soap and detergents). Since alkalis are tasteless, their consumption is higher before the patient realises the mistake. Retained solid alkali causes maximum injury to the oral mucosa, oropharynx and laryngeal inlet and lesser to lower esophagus and stomach. In the stomach, some of the ingested alkali may get partially neutralised by the gastric acid lowering the damage further. Ingestion of caustic after food cause a lesser degree of injury in the stomach due to lesser contact surface. Erroneous emergency interventions such as administering emetics and stomach wash cause repeated exposures of the caustic to the esophagus. Both alkali and acids are known to cause severe esophageal burns[11,12]. Initial corrosive injury causes an inflammatory response followed by thrombosis in arterioles and venules leading to ischemic necrosis [2]. Mucosal sloughing and bacterial invasion develop over four to seven days after ingestion warranting antimicrobial therapy. Granulation tissue and fibrin coat cover the ulcers. Ulcers extending beyond the muscle layer may cause perforation. The esophagus is physiologically devoid of serosa and allows the caustic damage to be exposed to the mediastinum. On day four, fibroblasts are recruited and repair of the damaged mucosa starts at day ten. Stricture usually develops by the third week and completes over the next few months[13]. As collagen deposition usually starts after two weeks, the strength of the injured tissue is poor in the first three weeks, contraindicating any intubation or endoscopic procedures. Spontaneous perforation of esophagus or stomach is usually encountered within the first 2 weeks of corrosive ingestion. From the third week onwards till the next few months, scar retraction leads to stricture formation and shortening of gastrointestinal tract. At this time, the pressure of the lower esophageal sphincter decreases and allows gastroesophageal reflux. Repeated acid exposure accelerates stricture formation[14]. In deeper burns (grade 2b and 3), fibrosis is usually complete by 3-6 mo, finally culminating into a stricture[15]. Strictures are hardly seen in grade 1 esophageal injury. Esophageal stricture rates in grades 2a, 2b and 3 are < 5%, 15%-68% and 75%-90% respectively[16, 17]. Diverticulae and deeper damage in the esophagus may result in tracheo-esophageal fistulae. Contraction of the body of the stomach causes hour glass appearance, decreased capacity and rarely fistulous opening into small or large bowel.

Table 2 Clinical features of corrosive ingestion

Symptoms of acute corrosive ingestion	
Organ system	
Skin	Burning sensation and pain on face, mostly perioral
Respiratory tract	Cough, difficulty in breathing, aphonia or dysphonia, chest pain, cynosis. Aspiration of large volume of corrosive may lead to endobronchial inflammation, necrosis and mediastinitis
Gastrointestinal tract	Oral burn, hypersalivation, nausea, vomiting (with or without blood), retrosternal and upper abdomen pain, dysphagia. Rarely perforation of gastrointestinal tract may happen and present with abdominal distension, tenderness and rigidity
Symptoms after gastrointestinal stricture formation	
Esophageal	Vomiting, dysphagia, hematemesis, acute obstruction due to food impaction at stricture site, growth failure
Pyloric	Non-bilious stale food vomiting, upper abdominal distension, growth failure

Antropyloric strictures cause gastric outlet obstruction. Proximal duodenal strictures are very rare. Compromise in nutrition leads to cachexia, dyselectrolytemia, apathy and poor quality of life. The above issues lead to a number of complications (Figure 1). Clinical, endoscopic and radiologic pictures of post-corrosive ingestion are shown in Figure 2.

DILEMMAS IN ACUTE CORROSIVE INGESTION MANAGEMENT

The flow chart for management of corrosive ingestion is shown in Figure 3. The first step is always to prioritize airway, breathing and circulation. Patients presenting with respiratory difficulty, dysphonia or aphonia need urgent airway management like endotracheal intubation and ventilation[18]. Urgent steroids are indicated in life-threatening laryngeal edema. However, there are many dilemmas and doubts which arise during acute management as well as while dealing with strictures.

What are the contraindicated practices?

Gastric lavage and induction of vomiting are common practices after accidental ingestion of corrosive[4,5]. In a survey performed recently in India, it was found that 57% of referred cases had history of induced emesis by the primary physicians[5]. Any effort of induced vomiting will lead to re-exposure of esophageal mucosa to the corrosive and increased risk of aspiration. Cold milk ingestion is not useful and may lead to aspiration and obscures an endoscopist's view. Blind insertion of a nasogastric tube for lavage or feeding may lead to mucosal injury and perforation. Another practice that is not recommended is the trial of neutralization with weak acid or base to decrease the effect of corrosive. The reaction of acid and alkali leads to an exothermic reaction which may cause added thermal burn to an already damaged tissue[18].

Is there any role of adjunctive pharmacotherapy?

Patients with grade 1 and 2a injury do not need any specific treatment, can be initiated on oral feeds and monitored closely. Children with grade 2b and 3 injuries need further treatment depending on clinical, endoscopic and radiological severity[7]. Antacids, H2 receptor blockers and proton pump inhibitors (PPIs) are prescribed in acute ingestion but their efficacies are not proven[2,19]. PPI is used in the majority of cases and may help by decreasing acid exposure to damaged tissue and prevention of stress ulcer formation[5]. Sucralfate which needs an acidic medium to activate provides a protective coating over the ulcers and may aid in delaying stricture formation[20]. However, the role of sucralfate in esophageal ulcers, alkali ingestion and in combination with PPI is debatable. There is no consensus as to how long acid suppression should be administered. In a questionnaire survey, it was found that most physicians arbitrarily prefer 4 week of acid suppression[5]. Antibiotics are not routinely prescribed in corrosive ingestion with grade 1 and 2a injuries. Since oral microbiota is a potential source of infection, injuries higher than grade 2b may merit antibiotic therapy. A combination of gram positive (for oral microbiota) and gram negative cover (gastrointestinal microbiota) is optimal. Optimal duration of antibiotic is not defined but it is preferable to use for 1-2 weeks for an uncomplicated injury. Syrups and suspensions are preferred over tablets and capsules. In a suspected or

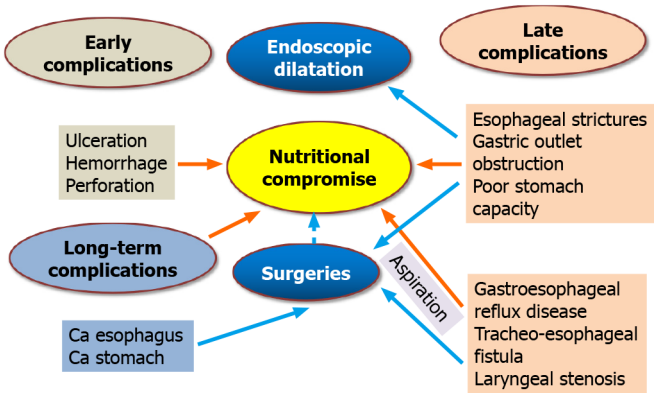

Figure 1 Complications in gastrointestinal system due to corrosive injury.

proven perforation, it would be prudent to add an anaerobic cover. Additional situations meriting antibiotic therapy are aspiration pneumonia, high grade fever and suspected bacteremia[21]. Theoretically, steroids have been potentially considered for use in early post-corrosive ingestion to decrease inflammation and lowering stricture formation. However steroids have not shown consistent improvement in the outcome [22]. In adults, steroids have been associated with higher mortality. In children, an exceptional situation to use steroids is grade 2b injury. Usta *et al*[23] showed in a randomized controlled trial that early use of high dose steroids (1 g/1.73 m^2 per day for 3 d) in grade 2b injuries lead to decreased stricture formation in follow-up. There is no evidence of improvement in other grades of injuries[7,23].

What is the indication and timing for early endoscopy?

In acute caustic ingestion, esophagogastroduodenoscopy (EGD) is the investigation of choice to ascertain the grade of mucosal injury. Esophageal injury is graded as per Zargar classification[24] as shown in Table 3. Endoscopy is best performed within the first 48-72 h of corrosive ingestion after initial stabilization. After 72 h, the injured areas become soft, edematous and friable. There is an increased risk of perforation during the EGD. EGD should be performed gently preferably with a thin (5.5 mm) endoscope, minimal air insufflation and under proper sedation. Blind advances and biopsies are not recommended. Negotiation beyond a charred esophagus to assess the stomach may be a daunting task. Oral or skin injuries are unreliable indicators of esophageal or stomach injury. In a large retrospective study by Doğan *et al*[25], 61% of children with esophageal injury on EGD had no oral burn. Betalli *et al*[26] in a multicentre study found that severe esophageal burns correlate well with symptoms. Risk of esophageal damage increased only with increasing severity of symptoms and signs. Hence the authors concluded that endoscopy can be avoided in asymptomatic patients with accidental ingestion[26]. European Society of Gastrointestinal Endoscopy and the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) 2017 guidelines agree, EGD can be withheld if the child is asymptomatic without any oral symptoms (drooling, hypersalivation or oral ulcers). However, in such cases, close vigilance is required for the development of delayed symptoms[7]. EGD is mandatory in adolescents with suicidal intent who may mask symptoms. The real dilemma of endoscopy arises in delayed presentation or referral (after 72 h). Since the tissue is most friable between days 3 to 21, diagnostic endoscopy is best avoided during this period where expertise and resources are limited. In the author's opinion, an endoscopic assessment may be daunting in this period, best reserved for tertiary care centers where appropriate endoscopes and expert endoscopists are available. Questionnaire surveys reveal that 90% prefer endoscopy between days 1-5, 70% agree that it should be deferred between days 6-21 and 50% agree that endoscopists should not venture beyond a charred area[5]. After 3-4 wk, fibrosis fully sets in making it conducive once again for endoscopic assessment of the stricture.

What is the role of radiology in acute management?

Chest X ray is usually performed in an acute setting[5] and may show mediastinal air in case of esophageal perforation. Computed tomography (CT) scan is a non-invasive test and can be used to ascertain the severity of injury and the need for surgery in complicated cases. Lurie *et al*[27] in a study on adult subjects concluded that CT tends to underestimate the severity of corrosive ingestion compared with endoscopy. CT

Table 3 Zargar classification for corrosive esophageal injury

Zargar classification	
Grade 0	Normal examination
Grade 1	Edema and hyperemia of the mucosa
Grade 2	
2a	Friability, hemorrhages, erosions, blisters, whitish membranes, exudates and superficial ulcerations
2b	Grade 2a plus deep discrete or circumferential ulceration
Grade 3	
3a	Multiple ulcerations and areas of necrosis (areas of brown-black or grayish discoloration were taken as evidence of necrosis)
3b	Small scattered areas of necrosis; extensive necrosis

scan had higher specificity but lesser sensitivity in ascertaining severity of injury in acute corrosive ingestion. The sensitivities of endoscopy in grades 2b and 3 injuries to predict mortality and emergency laparotomy were 1 and 0.8 while it was 0.4 and 0.28 for CT scan. The specificities were 0.38 and 0.37 for endoscopy while for CT scan the specificities were 0.94 and 0.93, respectively. CT scan can additionally show pulmonary infiltrates, features of mediastinitis and perforation[27]. A contrast study is carefully considered and performed only if indicated. Barium is ionic, may lead to chemical pneumonitis due to aspiration or tracheoesophageal fistula. Ingestion of barium also limits endoscopy if retained in luminal stasis. Hence a non-ionic contrast is preferred though the quality of study may be poor.

Should a nasogastric tube be preemptively placed for stricture prevention?

The pre-emptive placement of a nasoenteric tube is controversial. Though it may maintain patency of the esophageal lumen, the tube itself could worsen or contribute to complications. The tube may facilitate greater acidic reflux, delay mucosal healing and cause long strictures. Blind insertion could cause esophageal perforation. Should a tight stricture develop, positioning a tube has the advantage of providing a lumen for dilatation. Experimental studies were performed on rabbits with caustic esophageal burns. One group was treated with a silicone tube was placed immediately after causing the burns, while an untreated group was observed for the natural course of the burn. On day 22, an esophagectomy was performed on all animals. Histopathologic Damage Score and wall thickness were similar in both groups. Stenosis Index and lumen diameter were significantly lower in the treated group than the untreated group. It was concluded that an early placement of an intraesophageal tube with a solid dilator prevents stenosis formation and does not produce greater tissue damage [28]. To limit acid reflux it would be prudent to add an acid suppressant in the presence of a nasogastric tube.

What are the difficulties in sustaining nutrition?

Maintaining nutrition is a challenge in the first 3-4 wk. Nutritional compromise is anticipated due to odynophagia, multiple hospital admissions and overcautious management to prevent perforation. Adequate calories should be provided due to a high catabolic state. In rabbits models, it was found that weight gain is significantly higher after 22 d of caustic ingestion in those animals with nasogastric tubes[28]. Nasoenteric tubes must be placed under endoscopic or fluoroscopic vision. A nasojejunal tube is preferred in those with gastric injuries but may be challenging to place endoscopically especially through an inflamed pylorus. A safer alternative is to consider a gastrostomy tube in an isolated esophageal injury and a jejunostomy tube in gastric injury. Energy dense liquid and semisolid feeds are ensured in tube feeding. Parenteral nutrition is rarely required except for the patients with perforation and shock.

DIFFICULTIES IN MANAGEMENT OF CORROSIVE STRICTURES IN CHILDREN

Once the patient develops a symptomatic stricture, serial endoscopic dilatation is the

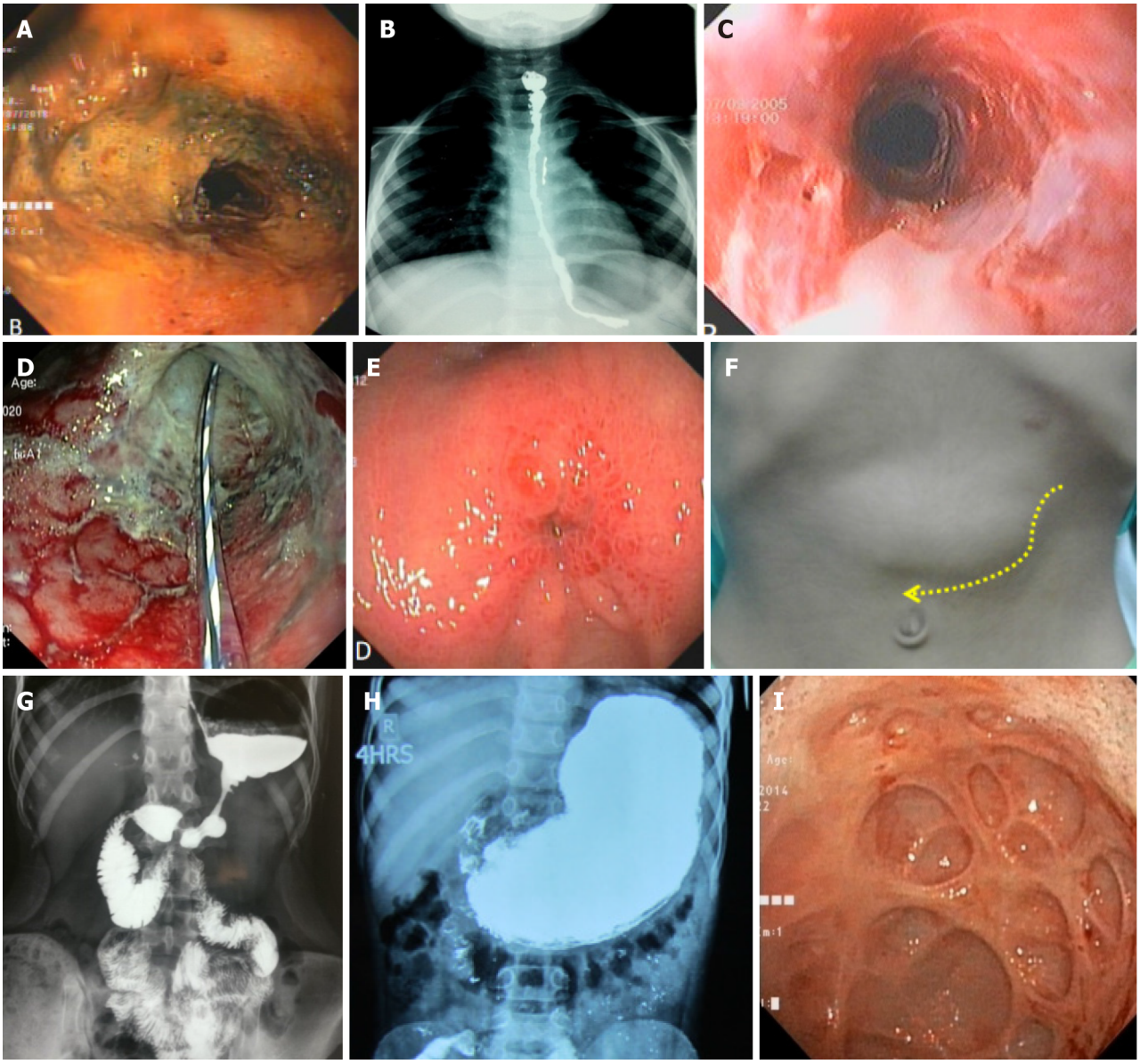

Figure 2 Clinical, endoscopic and radiological images of corrosive injury in children. A: Endoscopic view of corrosive injury of esophagus (areas of necrosis); B: Barium swallow study showing long esophageal stricture; C: Endoscopic view of esophagus after initial healing; D: Endoscopic view of post-acid ingestion antropyloric injury with transpyloric tube *in situ*; E: Endoscopic view of pyloric stricture; F: Dilated stomach in a patient with pyloric stricture; G: Barium meal follow-through study showing corrosive stricture involving body and prepyloric region (Hour-glass appearnce); H: Barium meal follow through study showing post-corrosive pyloric stricture; I: Endoscopic view of diverticulae in stomach in pyloric stricture.

mainstay of therapy to restore the previous anatomy and preserve the normal physiology. A barium study is indicated as a road map prior to endoscopy. The techniques of endoscopic dilatation are taken on a case-to-case basis depending on length, site, diameter, tortuosity and complexity of the stricture. A combination of thin and regular endoscopes may be required for assessment and procedures. Intubation may be a major issue in those with laryngeal stenosis. Unintubated patients are at significant risk of respiratory compromise during the procedure. Surgical therapy may be required for feeding purposes along with dilatation, to manage complications of endoscopic dilatation like perforation and for strictures resistant to endoscopic dilatation.

Should we use a bougie or balloon for endoscopic dilatation?

Strictures can develop as early as 3 weeks. Endoscopic dilatation is done every 2-3 weekly intervals and numbers of dilatation vary widely depending on the anatomy of the strictures. Endoscopic dilatation should be performed by a trained gastroenterologist under general anesthesia and with surgical backup. The first dilemma faced is, the choice of method for dilatation *i.e.*, bougie *vs* controlled radial expansion (CRE)

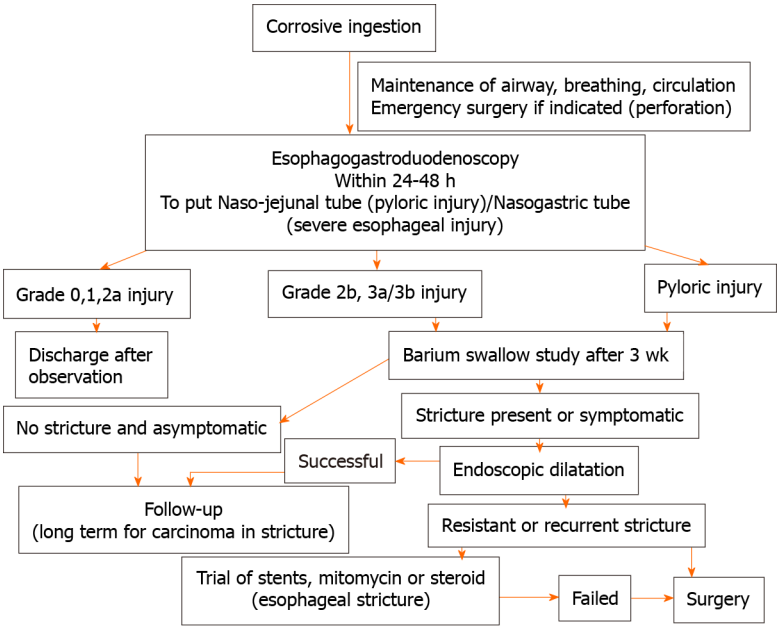

Figure 3 Flowchart for management of corrosive ingestion and upper gastrointestinal strictures.

balloon in an esophageal stricture. Bougie dilates the stricture with a tangential pressure while the CRE balloon asserts a radial pressure over the stricture. Bougie is a better option for multiple or long tortuous strictures while the balloon is preferred for single short strictures[29]. But practically, there are other factors also which influence the final decision like the experience of the endoscopist with both methods, availability of endoscopic accessories and financial constraints[5]. Bougie can be reused multiple times, lowering the overall cost of treatment. There are no head-to-head comparative studies between balloon and bougie. Balloon dilatation is found safe with variable success of 14%-100%[17,30]. Successful dilatation with bougie is 50%-96%[29,31]. It should also be kept in mind that thinner endoscopes have a limited channel length for balloon accessories. Softer guidewires than metallic ones are preferred to negotiate inflammed strictures. In tortuous strictures, optimal positioning of the patient and repeated gentle attempts are required for negotiation. Navigation is often aided by hydrophilic Terumo guidewire. Over the guidewire balloons are preferred if the anatomy of the lumen is uncertain.

Are corrosive esophageal strictures more resistant to dilate?

Of all benign esophageal strictures in children, corrosives are the most challenging to dilate due to the intense fibrosis and complexity. Corrosive strictures require a higher number of sessions of dilatation, have a higher risk of dilatation-related complications and may need surgical therapy more often as compared to other etiologies like post-trachea-esophageal fistula repair and peptic strictures[29,31]. The main complication of dilatation is perforation which is reported from around 2.5% to as high as 50%[31-33]. Other reported complications of dilatation are mediastinitis, lung abscess, empyema, pericardial effusion, sepsis and death.

When should we begin stricture dilatation?

Another dilemma is timing to start dilatation *i.e.* early *vs* late dilatation. Gün *et al*[32] compared patients who underwent early dilatation starting from 3rd week after corrosive ingestion *vs* patients who underwent late dilatation after 6-12 wk of corrosive ingestion. Children with late dilatation of stricture had a poorer response (25% *vs* 65%) along with higher rates of perforation (50% *vs* 21%). None of the patients with late dilatation recovered within 1 year period while 60% with early dilatation improved within the same time period[32]. Patients who are referred late often have a resistant stricture due to extensive fibrosis over time[2]. In a study by Contini *et al*[33], patients who were started on dilatation late (> 6 wk) had recurrence of strictures in 73% *vs* 30% in timely dilatation group ($P < 0.01$).

How to manage refractory esophageal strictures?

ESPGHAN guidelines for endoscopy have defined refractory and recurrent strictures as an anatomic restriction because of cicatricial luminal compromise or fibrosis that results in dysphagia in the absence of endoscopic evidence of inflammation. This may be defined in two clinical settings. Firstly there may be an inability to successfully remediate the anatomic problem to obtain age-appropriate feeding after a maximum of 5 dilation sessions (refractory) with maximal 4-week intervals. Secondly, there may be an inability to maintain a satisfactory luminal diameter for 4 week once the age-appropriate feeding diameter has been achieved (recurrent)[7]. In this subgroup of patients, the following options can be utilized before surgery.

Intralesional steroids: Intralesional steroid injection increases the effect of dilatation by inhibiting inflammatory response to injury, decreases collagen synthesis and cross-linking at the stricture site. Bhan *et al*[34] published data of 32 children with resistant strictures where Triamcinolone acetonide was injected in four quadrants prior to dilatation. 92% of patients with short strictures improved completely. None of the patients with long stricture (> 3 cm) had a resolution of dysphagia and all required esophageal replacement. A meta-analysis of 6 randomized control trials including 176 adult patients with benign esophageal stricture found that intralesional steroid therapy decreased stricture formation rate along with the requirement of endoscopic dilatations without an increase in complications[35].

Mitomycin: Mitomycin is an antineoplastic drug that inhibits cell division and fibroblast proliferation. A mucosal tear during dilatation heals with fibrosis. Hence mitomycin is used to limit this process and augment the effect of dilatation. Mitomycin soaked gauze (0.4 mg/mL) is applied over the stricture after dilatation for 3-4 min[36, 37]. Sweed *et al*[37] compared 18 children who underwent mitomycin injection with dilatation *vs* 12 children with routine dilatation. Results suggested that between the two groups, there were no major differences in the number of dilatations. However, there was a significant improvement in dysphagia in the mitomycin group. In another double-blind, randomized, placebo-controlled trial, the mitomycin group had complete resolution of stricture in 80% of patients as compared to 35% in the non-mitomycin group[38]. Méndez-Nieto *et al*[36] compared patients treated with mitomycin (n = 16) with a retrospective cohort of steroid-treated patients (n = 34). Mitomycin group required significantly less number of dilatation sessions [4.5 (3-8) *vs* 11 (4-24), $P < 0.01$].

Stents: The use of esophageal stents in children is still evolving and experience is limited. Resistant caustic strictures are the most common indication of stent placement in children[39]. Zhang *et al*[40] used nitinol-alloy self-expanding esophageal stent in eight children (2-12 years). Stents were deployed for 1-4 weeks. Stent migration occurred in one patient while two patients required further dilatation. None of the patients had any severe side effects. The use of stents in children is limited due availability of age-appropriate sizes and significant chances of migration. It is not possible to place stents in patients where stricture starts from the upper esophagus or from the pharyngeal inlet.

ESPGHAN guidelines suggest the use of temporary stent placement or application of topical mitomycin following dilation for refractory esophageal stenosis rather than routine use of intralesional steroids for refractory esophageal stenosis in children. There is a theoretical possibility of induction of dysplasia after mitomycin application although there is no proven evidence yet[7].

When is surgery indicated in esophageal strictures?

Surgery is the last resort for recurrent or refractory corrosive esophageal strictures. The optimal time for reconstruction is 6-12 mo post corrosive ingestion. The waiting period is beneficial for the final arrest of the progression of stricture (length, level and tenacity) and optimization of nutritional status. The major controversy in the surgical management of corrosive esophageal stricture is resection *vs* bypass. Currently majority of the surgeons prefer bypass since there is a lesser incidence of malignancy in the residual esophagus and lesser morbidity and mortality as compared to resection. Choices of esophageal replacement are gastric advancement/pull-up, colonic interposition and jejunal interposition. There is no consensus on the ideal replacement for the esophagus. The jejunum is not a preferred conduit because of its limited length. Free jejunal grafts may be used to bridge short defects after excision of localized esophageal stricture. Colonic interposition is a complex surgery requiring multiple anastomoses and affected by issues such as colonic redundancy. However,

colon is a favourable option because of the abundant vascularity and space of the lumen. Two options in colonic interposition are a right colon or a left colon conduit. The choice between these two is still debated. Gastric pull-up is comparatively a simpler surgery but it is dependent on the availability of a healthy stomach which may be partially involved or difficult to assess in corrosive ingestion. Routes available for conduit placement are posterior mediastinum, retrosternal and subcutaneous. The subcutaneous route is less preferred because of poor cosmesis. The retrosternal route is most commonly used in corrosive esophageal stricture as the native esophagus is left in situ. Colonic and gastric replacements both have shown good outcomes [21,41,42]. Studies have shown that there are no significant differences in terms of early complications (cervical anastomotic leaks, vocal cord palsy, and pulmonary complications) in colonic interposition or gastric pull-up[43]. Long term outcomes of these two procedures are also comparable. Overall complications of surgery include anastomotic leak, wound infection, graft redundancy, conduit failure and anastomotic strictures. Endoscopic dilatation may be required for anastomotic strictures[41,44].

What are the challenges in pyloric stricture management?

Acute caustic ingestion causes pylorospasm which increases the duration of contact in antrum and pylorus leading to antropyloric strictures. Adequate gastric decompression is recommended prior to endoscopy to reduce the volume of retained gastric juices. Antral strictures may appear as a pseudopylorus. In the authors' experience, an abnormally dilated stomach alters the usual endoscopic technique of negotiation along the lesser curvature to reach the pylorus. In a contracted stomach, pyloric strictures are often superiorly and eccentrically located than the usual position of pylorus surrounded by a "bird feet appearance" around the narrowing. These strictures are best identified on retroflexion with right-ward deflection of the endoscope. Multiple diverticulae are often misleading in identifying the real pyloric stricture, especially if the lumen is pin-hole in caliber. Blind negotiation of the guidewire may be catastrophic. In the first endoscopy, considerable attempts may be required to negotiate the guidewire. Increased friability of mucosa may lead to considerable bleeding and further edema of the opening. Balloon dilatation is the primary endoscopic procedure of choice. In very narrow strictures, a graded dilatation with biliary balloons is followed by CRE balloons. Unlike esophageal strictures, the bougie is not an option for pyloric strictures and there is limited experience with other adjunctive therapies like steroid and mitomycin in children. In earlier days, surgery was the primary mode of treatment for pyloric strictures. Various surgical options are gastro-jejunostomy with or without vagotomy, pyloroplasty, or antrectomy with Bilroth I anastomosis[45]. One important consideration is that retrocolic gastrojejunostomy should be avoided as it increases the technical difficulty or sometimes it precludes future colonic bypass by interfering with the middle colic vascular arcade. Patients may require repeat surgery due to anastomotic stricture although the incidence is low and patients do well in long term follow up[46,47].

With increasing endoscopic experience, surgery can be avoided especially if successive endoscopic dilatation attempts are successful[48]. This ensures restoration of normal anatomy and sustenance of the physiological outflow.

LONG TERM GASTROINTESTINAL COMPLICATIONS

There are a few other sequelae of corrosive ingestion which increase morbidity in addition to stricture formation.

Gastro-esophageal reflux disease

Cicatrization due to fibrosis in the esophagus leads to gastroesophageal reflux disease. Repeated acid exposure may lead to additional peptic stricture. These subgroups of patients require long term acid suppression for successful endoscopic dilatation[49].

Dysmotility

Corrosive injury and resulting fibrosis may damage the enteric plexus in the esophagus and stomach leading to esophageal dysmotility and gastroparesis respectively. Cicatrized stomach leads to issues of gastric accommodation and antral milling effect of chyme. These complications add to the existing symptoms of dysphagia, gastric outlet obstruction and may lead to persistence of symptoms even after adequate dilatation[50].

Risk of neoplasia

The incidence of esophageal carcinoma can be significantly higher in patients with corrosive ingestion as compared to the general population[51]. Carcinoma develops mostly at the site of stricture. Endoscopic dilatation or surgery does not prevent the development of carcinoma. Development of carcinoma may range anywhere from 1 to 7 decades after corrosive ingestion[52]. Change or onset of new symptoms in a patient with the past history of corrosive ingestion may be an indicator of carcinoma esophagus.

CONCLUSION

Corrosive ingestion is a common and preventable cause of esophageal and gastric injury in children. Development of stricture in the upper gastrointestinal tract is associated with prolonged morbidity, the need for long-term therapy and procedure-related complications affecting the quality of life in children. Despite many daunts and dilemmas in management, the clinical outcome is generally rewarding with endoscopic dilatations. Newer adjunctive therapies may decrease the need for surgery although for resistant and recurrent strictures. Even after the resolution of symptoms these patients should be kept on long-term follow-up. There is a need for further large volume studies regarding the efficacy and safety of newer adjunctive therapies. Long-term follow-up studies are required to evaluate stricture and management-related complications in children.

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MINIREVIEWS

Beyond kidney stones: Why pediatricians should worry about hypercalciuria

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Abstract

The incidence of urolithiasis (UL) is increasing, and it has become more common in children and adolescents over the past few decades. Hypercalciuria is the leading metabolic risk factor of pediatric UL, and it has high morbidity, with or without lithiasis as hematuria and impairment of bone mass. The reduction in bone mineral density has already been described in pediatric idiopathic hypercalciuria (IH), and the precise mechanisms of bone loss or failure to achieve adequate bone mass gain remain unknown. A current understanding is that hypercalciuria throughout life can be considered a risk of change in bone structure and low bone mass throughout life. However, it is still not entirely known whether hypercalciuria throughout life can compromise the quality of the mass. The peak bone mass is achieved by late adolescence, peaking at the end of the second decade of life. This accumulation should occur without interference in order to achieve the peak of optimal bone mass. The bone mass acquired during childhood and adolescence is a major determinant of adult bone health, and its accumulation should occur without interference. This raises the critical question of whether adult osteoporosis and the risk of fractures are initiated during childhood. Pediatricians should be aware of this pediatric problem and investigate their patients. They should have the knowledge and ability to diagnose and initially manage patients with IH, with or without UL.

Key Words: Children; Adolescents; Hypercalciuria; Bone mineral density; Kidney stone

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Core Tip: The incidence of pediatric urolithiasis is increasing, and hypercalciuria is its leading metabolic risk factor. The reduction in bone mass has already been described in hypercalciuric children, and the precise mechanisms of bone loss or failure to achieve adequate bone mass remain unknown. The peak bone mass is achieved by late adolescence, peaking at the end of the second decade of life. This accumulation should occur without interference. The bone mass acquired during childhood and adolescence is the major determinant of adult bone health. Pediatricians should have the knowledge and ability to diagnose and manage pediatric patients with idiopathic hypercalciuria.

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INTRODUCTION

Urolithiasis: A public health concern

Renal, ureteral and bladder stones are present in pediatric clinics and are the end product of a multifactorial process. No age or ethnic group is protected from this clinical problem that commonly afflicts humanity[1].Urolithiasis (UL) is an uncommon cause of death or end-stage renal disease; however, it represents a significant public health problem because its recurrence is a marked characteristic and confers high morbidity. No stone removal technique can decrease this recurrence or change its morbidity, which in pediatric patients is directly related to surgical interventions, to morphofunctional alterations resulting from possible obstructions of the urinary tract, and also to its clinical manifestations. In addition, they have a high potential for complications, as the symptoms are often nonspecific[2].

Incidence and prevalence

The risk of forming a new stone increases with age in patients who have already had it. Thus, the estimated risk of forming a new stone in one year is 15%, 35-40 % in five years and 80 % in ten years[3]. Its prevalence varies according to varied factors such as ethnicity, geographical location, water consumption of that population and age group. Despite being more common in whites and men, new studies have shown that UL is becoming more common in female and black patients[4].

Data on the prevalence and incidence of urinary tract stones in childhood are still scarce in the literature. The true incidence of this disease remains unknown due to the multiplicity of etiopathogenic factors and the non-specificity of the clinical onset. Variations in this incidence are found from 1:1714 to 1:9500 cases in different regions of the United States. However, it is believed that the prevalence is 5% in white North American children[5].

Urinary stones can occur anywhere in the renal collecting system. In industrialized countries, 97% of urinary stones are found in the parenchyma, pelvis, papillae and calyxes, while only 3% in the bladder and urethra. Bladder stones are more frequent in developing countries. The formation of stones in the kidneys and urinary tract is dependent on crystals and matrix, and its constituents are, in most cases, different organic and inorganic substances with a crystalline or amorphous structure. Only one-third of urinary stones have only one mineral in its composition, with calcium oxalate being the most common and found in at least 65% of all stones[2,6].

Risk factors

Several factors are involved in urinary stones formation, such as: infectious, anatomical, epidemiological, climatic, socioeconomic, dietary, genetic and metabolic. These factors, combined with physicochemical and physiological changes in the urine, alter the elements that promote and inhibit the aggregation and growth of crystals, culminating in the formation of stones[6]. However, the etiopathogenesis of UL remains unclear, and multiple aspects still have no explanation.

Crystallization begins when the urine is supersaturated for a particular solute. If the solution is unsaturated, crystals do not form. Supersaturation depends on ionic

strength, abnormalities in urinary pH, reduced urinary volume, deficiency of crystallization inhibitors (citrate, magnesium, pyrophosphate, nephrocalcin, glycosaminoglycans) and the hyperexcretion of calcium, uric acid, phosphorus and more rarely of oxalate and cystine. However, it is not clear how the crystals formed in the tubules become calculi since they are continuously washed away by the urine flow. It is believed that these aggregated crystals reach a certain dimension that allows an anchoring process, usually at the end of the collecting ducts and, slowly, they increase in size over time. This anchoring process is likely to be induced by the crystals themselves and occurs in damaged sites of the tubular epithelial cell. Currently, new studies on the etiopathogenesis of UL and molecular biology have contributed to these new discoveries. The identification of other molecules in the urine with inhibitory capacity for crystallization, as well as the new principles of adhesion of the crystals in the renal tubular epithelium and the endocytosis suffered by the calcium oxalate crystals in the renal tubular cells, are the main examples[7,8].

Some factors are considered main risks for UL, such as excessive salt and animal protein intake, low water intake, use of lithogenic drugs, genetic inheritance and dietary calcium restriction[6]. Unlike what happens in adult patients, overweight and obesity still do not show consistent scientific evidence for pediatric patients with UL [6]. The high sodium intake in healthy people induces an increase in urinary calcium excretion. Experimental studies show that the increase in fractional excretion of sodium in the proximal tubule produces an increase in fractional excretion of calcium in this same tubule, with consequent hypercalciuria, determining a positive correlation between natriuria and calciuria. A high amount of salt in the diet also determines a reduction in citrate excretion by mechanisms not yet known[9,10].

Penido *et al*[11] demonstrated that healthy children and adolescents ingested a higher amount of sodium and proteins and lower amounts of calcium than recommended by the RDA, in all age groups, in a Brazilian pediatric cohort. The authors also found a positive correlation between urinary sodium and calcium excretion ($r = 0.74$; $P < 0.01$)[11]. The high animal protein intake increases the production of fixed acids, causing transient metabolic acidosis. Consequently, there is an increase in urinary calcium excretion, accompanied by urinary pH reduction, hyperexcretion of uric acid, oxalate, and hypoexcretion of citrate, predisposing to UL[6,11].

Oliguria is also a significant risk factor for stone formation. Maintaining adequate urine volume is essential to ensure the solubility of substances excreted in the urine. The reduced urine output is a consequence of decreased water intake, which increases the saturation of solutes and predisposes to the formation of urinary calculi. Studies have shown that calcium oxalate supersaturation increased significantly once urine output decreased to less than 1.0 mL/kg per hour[6,12].

Drugs that promote crystalluria such as sulfadiazine, triamterene, indinavir and ceftriaxone favor the formation of calculi. Inappropriate use of antibiotics is also related to the formation of urinary stones[13]. Oxalate is degraded by Oxalobacter formigenes, Bifidobacterium, Lactobacillus, Escherichia coli, and others that reduce its intestinal absorption and protect against the formation of stones. Antibiotics alter the intestinal microbiome and consequently the oxalate metabolism. Exposure to any of the five main classes of antibiotics in the 3-12 mo prior to calculi formation was associated with an increased risk of stones (sulfas, cephalosporins, fluoroquinolones, nitrofurantoin and penicillin). The magnitude of this association was higher for exposure at younger ages and 3-6 mo before the diagnosis of UL[13].

Mode of Inheritance

Individuals with a positive family history of UL have a relative risk of developing urinary stones 2.57 times greater after an eight-year period when compared to those without. Cystinuria and primary hyperoxaluria are monogenic diseases whose mutations were already described. However, it is in IH that this genetic involvement has been widely studied, and 40% of patients with this disease have a family history of UL. Experimental models have suggested a possible dominant inheritance for IH. Polymorphism of vitamin D receptor genes has also been linked to urinary calcium excretion. It seems to represent one of the genetic factors that affect bone mineral density, although it only partially contributes to the genetic effect on bone mass, and this is not observed in all evaluated populations[14,15].

Metabolic disturbances

Important calcium restriction in the diet determines an increase in urinary oxalate excretion and, consequently, an increased risk for the aggregation of calcium oxalate crystals. In addition, they can facilitate the occurrence of reduced bone mineral density (BMD)[22]. Metabolic alterations are responsible for 80% to 90% of stone formation in

adults as well as in childhood. The most common alterations in pediatric patients are hypercalciuria, hypocitraturia, and low urine output[2,6,16]. As aforementioned, the IH is the leading metabolic risk factor for UL, and it has become more common in children over the past few decades. It has high morbidity with or without UL, and reduced BMD was already described in pediatric patients[16].

HYPERCALCIURIA

In 1953 Albright *et al*[17] used the term "idiopathic hypercalciuria" for the first time. In 1962, Valverde published his firsts Spanish pediatric cases[18]. In the same year, two pediatric groups reported six cases of children with hypercalciuria, osteopenia or rickets, nanism and renal impairment. The authors proposed that those cases would be IH; however, the patients were probably carriers of other tubulopathies[19]. After this publication, others emerged discussing the definition of criteria regarding "primary/idiopathic hypercalciuria" (see below).

IH is a metabolic disorder that affects all ages, genders and race groups[2,20,21]. It has a high prevalence and is the major risk factor to UL in children[2,20] and adults [22]. The "true" IH is a clinical condition characterized by increased urinary calcium excretion in the absence of hypercalcemia or other clinical conditions that can cause hypercalciuria and when dietetic disturbances have been excluded[23-25]. Its incidence in the pediatric group range between 2.2%-6.2%[25] and the prevalence between 0.6% and 12.5%. In Spain, prevalence rates vary between 3.8% and 7.8%[23].

Hypercalciuria is defined as urinary calcium excretion higher than or equal to 4 mg/kg/d for any gender or age[11,26]. Another clinical definition is the random or spot urinary calcium/creatinine ratio. It could be especially useful for children who do not have urinary sphincter control (Table 1)[11,26]. It is important to highlight that young children and infants have higher urinary calcium excretion and lower urinary creatinine levels. Then, the calcium/creatinine ratios differ by age (Table 1)[11,26]. Normal values for the lithogenic substances are described in Table 1.

IH can be related to two conditions: UL and bone resorption. Studies have demonstrated that hypercalciuric calcium stone formers have decreased BMD when compared to matched controls which are neither stone formers nor hypercalciuric[27,28]. Among adults patients with UL, those with hypercalciuria will have BMD measurements 5% to 15% lower than their normocalciuric matched controls[27]. Several studies have also demonstrated reductions in BMD in hypercalciuric pediatric patients with or without hematuria or UL[16,29-34]. This review discusses the association between UL, IH and reduced BMD in pediatric patients and the importance of this association for the clinical practice of pediatricians.

PATHOGENESIS OF HYPERCALCIURIA

The pathogenesis of IH is complex and not yet completely understood. We would say that the excretion of calcium in urine is the end result of an interplay between three organs: the kidneys, bones and gastrointestinal tract. These organs are orchestrated by hormones, such as parathyroid hormone (PTH), calcitonin, 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2$D3), fibroblast growth factor (FGF23), and probably others unknown, acting together as a unique system. It seems that IH is a systemic abnormality with alterations in calcium cellular transport in kidneys, bones and intestines (Figure 1)[22,35,36].

In 1965, Edwards & Hodgkinson started the first studies on the pathogenesis of IH and concluded that its origin should be exclusively renal[37]. Chronic loss of calcium by the kidneys would lead to a reduction in serum calcium, and consequently, an increase in serum PTH. Considering this, Pak *et al*[38] in 1974 observed normal levels of PTH in their hypercalciuric patients and ruled out the possibility that IH was exclusively of renal origin. The same authors proposed a test (acute oral calcium overload test) to distinguish two types of IH, according to the underlying pathophysiological mechanism: absorptive or renal. They classified IH into three distinct pathogenetic pathways: (1) Absorptive hypercalciuria type I (primary intestinal hyperabsorption of calcium); (2) Absorptive hypercalciuria type III (primary renal leak of phosphate); and (3) Renal hypercalciuria (primary renal leak of calcium)[39]. These authors also identified the so-called resorptive hypercalciuria when hypercalciuria is induced by an excessive calcium output from bones. However, the clinical value of the classification was limited, and it is often impossible to classify the patient into a

Table 1 Normal values for random urine and 24 h urine factors for children and adolescents

	24 h urine	Random urine corrected by creatinine		Random urine factored for GFR
Volume	≥ 1.0 mL/kg per h			
Creatinina	2 to 3 yr: 6 to 22 mg/kg; > 3 yr: 12 to 30 mg/kg			
Calcium	< 4.0 mg/kg (0.10 mmol/kg)	Age	mg/mg; mmol/mmol	< 0.10
		0-6 mo	< 0.80; < 2.24	
		6-10 mo	< 0.60; < 1.68	
		1-2 yr	< 0.40; < 1.12	
		2-18 yr	< 0.21; < 0.56	
Citrate	≥ 400 mg/g creatinine	≥ 0.28 (mmol/L/mmol/L)		> 0.18 (mg/L/mg/L)
Calcium/Citrate	< 0.33	< 0.33		
Na/K	< 3.5	< 3.5		
Uric acid	< 815 mg/1.73m^2 BS	< 0.65		< 0.56 mg; < 0.03 mmol
Cystine	< 60 mg/1.73 m^2 BS	< 0.02 (mg/mg); < 0.01 (mmol/mmol)		
Magnesium	> 88 mg/1.73 m^2 BS			
Phosphate	TP/GFR[1]: > 2.8 and < 4.4 mg/dL			
Oxalate	< 50 mg/1.73m^2 BS; < 0.49 mmol/1.73m^2 BS	Age	(mg/mg)	
		0-6 mo	< 0.30	
		7 mo - 4 yr	< 0.15	
		> 4 yr	< 0.10	

[1]TP/GFR = Pp – (Pu × Crp)/Cru.

GFR: Glomerular filtration rate; TP: Tubular phosphate reabsorption; Pp: Plasma phosphate; Pu: Urinary phosphate; Crp: Plasma creatinine; Cru: Urinary creatinine. Adapted from: Penido MGMG, Tavares MS. Pediatric primary urolithiasis: Symptoms, medical management and prevention strategies. *World J Nephrol* 2015; **4**: 444-454. Copyright ©The Author(s) 2015. Published by Baishideng Publishing Group Inc[2].

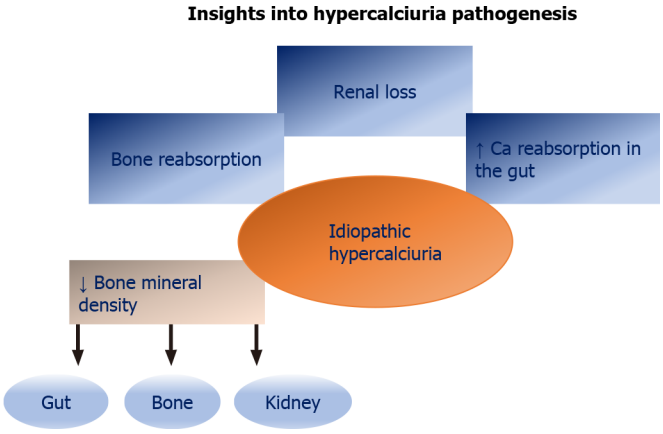

Figure 1 Insights into hypercalciuria pathogenesis (Source: Nephrology Center of Santa Casa de Belo Horizonte - Pediatric Nephrology Unit - by Penido MGMG).

specific type, as described by Aladjem *et al*[40] (1996) in children. Thus, this test and this classification fell out of use.

Alhava *et al*[41] demonstrated that their patients with UL had significantly lower BMD values when compared to controls. In the 1980s, with the assessment of 1,25OH vit. D, it was proven that some of these patients with urinary stones had high levels of this vitamin[42]. The hypothesis of intestinal IH was again highlighted. Buck *et al*[43]

treated 43 patients with HI and hyperproduction of prostaglandin E2 (PGE2) with indomethacin. The authors confirmed the normalization of the calciuria and suggested that PGE2 could be implicated in the origin of IH[43]. Henriquez-La Roche *et al*[44] have also shown an increase in PGE2 in patients with IH.

Urinary phosphate loss was related to IH, and when hyperphosphaturia is important, it favors hypophosphatemia. The reduction in serum phosphate levels favors calcitriol synthesis, increasing intestinal calcium absorption and, consequently, hypercalciuria. A study by Prié and co-workers showed that 20% of hypercalciuric stone-formers with normal PTH have a decreased TmP/GFR (tubular phosphate reabsorption / glomerular filtration rate) value and phosphaturia[45].

Pacifici *et al*[46] demonstrated that blood monocytes from patients with IH produced an increased amount of cytokines: interleukin-1 (IL-1), granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor (TNF-alpha). The increased activity of these cytokines had the ability to reduce BMD in patients with IH, and other studies confirmed these findings[47,48].

Weisinger[49] proposed a new theory on the pathophysiology of HI that combined the findings already published: IL-1 and the other cytokines would stimulate bone resorption[46-48] and the production of PGE2 [44]that induced the synthesis of calcitriol[50]. It is known that an excessive amount of calcitriol stimulates bone resorption[50]. Thus, hypercalciuria would be caused by an increase in bone resorption and an increase in intestinal calcium absorption due to the effect of calcitriol.

Inflammatory mediators such as IL-1 and TNF reduce the epithelial sodium transport due to increased PGE2 synthesis[51] and reduced expression of the epithelial sodium channel (ENaC) and/or Na + -K + -ATPase in the basolateral membrane[52]. A slight distal saline loss has been described in some adult patients, and this loss of sodium would increase urinary calcium[53]. These patients could have a triple origin for IH: bones, intestines and kidneys.

Rats with spontaneous hypercalciuria (genetic hypercalciuric stone-forming - GHS) were identified, and an increase in calciuria was observed in each successive generation of them[54]. Bushinsky and Favus observed that these rats had excessive calciuria due to an increase in the intestinal absorption of this ion, although calcitriol levels were normal[54]. When the rats were submitted to a calcium-restricted diet, the calciuria decreased, suggesting that the mechanism of hypercalciuria observed in these animals was the increase in intestinal calcium absorption[55]. A higher number of vitamin D receptors (VDR) in the intestine of these rats was demonstrated, favoring the functional capacity of calcitriol-VDR complexes[55]. Yao *et al*[56] found that these animals had an increased response to VDR with minimal calcitriol levels, thus causing hypercalciuria. However, this loss of calcium was greater than dietary intake, suggesting another pathogenic mechanism. In sequence, Krieger *et al*[57] demonstrated that this increase in sensitivity to calcitriol was expressed in the bones of these animals, inducing bone resorption, leading to a possible role of bones. Later, Tsuruoka *et al*[58] demonstrated that hypercalciuric rats have a tubular calcium reabsorption defect. This is due to an activation of the sensitive calcium receptor (CaR) that would suppress the activity of the calcium-sensitive potassium channel (ROMK) in ascending portion of the loop of Henle[59]. There is a reduction in the electrical gradient in the tubular lumen with a consequent reduction in the absorption of calcium by the paracellular pathway. Consequently, more calcium is delivered to the distal tubule. In humans, Worcester *et al*[60] showed that hypercalciuric stone-forming patients, eating fixed and identical high-calcium and regular diets, reduce distal and proximal tubule reabsorption more than controls. Favus *et al*[61] demonstrated that peripheral monocytes of humans with IH have an increased VDR number, as previously described in hypercalciuric rats[55]. Based on suggestions by Worcester and Coe[22] that variations in the klotho-FGF23 axis could mediate alterations in calcium and phosphate handling by the kidney and play a role in IH, Penido *et al*[62] decided to explore a potential role for FGF23 in pediatric IH. They concluded there was no difference in plasma FGF23 Levels between hypercalciuric and control children[62]. Pharmacologically treated patients had significantly lower urine calcium excretion rate and plasma FGF23 Levels; elevated TP/GFR and serum phosphate without changes in serum PTH values. It thus seems that the reversal of hypercalciuria may directly or indirectly affect phosphate metabolism[62]. Finally, what has been demonstrated in hypercalciuric rats has also been found in humans with IH: increased intestinal calcium absorption, defect in tubular calcium reabsorption, increased bone resorption, and normal serum calcium and calcitriol levels[61].

The excess sodium intake is accompanied by increased urinary calcium excretion and increased dietary protein intake[63,64]. Breslau *et al*[65] suggested that hypercalciuria induced by excess dietary sodium was accompanied by an increase in calcitriol

synthesis. Excessive protein intake produces acid overload that inhibits renal tubular calcium reabsorption. The increase in net acid production is buffered by bones and other body buffers[63,65]. It could explain the reduction in BMD in IH. Bataille *et al*[66] observed a direct correlation between calciuria and urinary hydroxyproline in their patients, a marker of bone resorption.

The genetic background is also involved in the pathogenesis of IH. It has been described that patients with UL due to hypercalciuria can be carriers of genetic polymorphisms that encode certain proteins involved in the tubular reabsorption of calcium and phosphate (VDR, SLC34A1, SLC34A4, CLDN14, CaSR, TRPV6), or in the prevention of it precipitation of calcium salts (CaSR, MGP, OPN, PLAU, UMOD)[67-69]. Garcia Nieto *et al*[23] published a summary with all the pathophysiological mechanisms involved in IH described to date (Figure 1). According to the authors, it remains to be determined whether the cytokine-producing monocyte hyperreactivity described in IH is related to the increase in VDR in these cells (Figure 2).

Another point to discuss is the role of vitamin D supplementation. This supplementation has been related to hypercalciuria. Milart *et al*[69] analyzed the impact of vitamin D supplementation on 36 children with IH and UL prospectively. Blood and urine samples were collected every three months up to 24 mo of vitamin D intake at a dose of 400 or 800 IU/d. Bone densitometry was performed at time 0, at 12, and 24 mo of vitamin D supplementation. The authors concluded that supplementation with vitamin D caused an increase in 25(OH) vit. D in serum[69]. However, no changes in serum calcium, urine calcium and bone density were observed. There was no significant increase in the risk of development of kidney stones[69].

CLINICAL PRESENTATION OF HYPERCALCIURIA IN PEDIATRICS

Pediatricians are professionals who assist children and adolescents with UL and IH. It is imperative that these professionals have knowledge about these clinical entities and how they present in pediatric patients. IH in children can present as gross or microscopic hematuria, voiding symptoms (urinary urgency, pollakiuria, dysuria, incontinence, enuresis and suprapubic pain), recurrent abdominal pain and flank pain in the absence of calculi, lumbar colic, urinary tract infections or enuresis and other voiding disorders[21,70,71]. Macro or microscopic hematuria and/or abdominal pain are the most common clinical presentations among hypercalciuric pediatric patients [21,25]. Unlike adults, lumbar colic is not common in children, and Penido *et al*[21] found only 14% of lumbar colic as first presentation. These different signs and symptoms can be confusing at the time of clinical presentation. Pediatricians should be aware of this diagnosis in children and adolescents who present clinically with urinary urgency and incontinence, suprapubic pain, nocturnal enuresis, pain in the urethra and recurrent chronic abdominal pain. In this sense, IH must be identified and monitored because it can have consequences other than hematuria, abdominal pain and kidney stones.

BONE CHANGES IN HYPERCALCIURIA

Reduced BMD has been described in adult patients with IH since the 1970s[41,47,48,66], and since then, it has been recognized that hypercalciuric patients with UL could exhibit a decrease in BMD. Different factors may be involved in bone loss in IH, such as negative calcium balance due to reduced tubular reabsorption, increased production of prostaglandin E2[44], increased cytokine reabsorption activity[46] and/or calcitriol[72]. An increased resorptive action of calcitriol would be related to an increased number of VDR[57].

Bone biopsies performed in a patient with IH showed an increase in osteoclastic activity[73], and in some series, a reduction in osteoblastic activity was observed[74]. Gomes *et al*[74] demonstrated a high expression of the receptor activator of nuclear factor kappaB ligand (RANKL) in patients with IH, suggesting an increase in bone resorption mediated by this peptide. The authors found that expression of IL-1 and basic fibroblast growth factor (bFGF) was similar to that of controls and consider that the high expression of cytokines, already described in hypercalciuric patients, could have no causal relationship with the reduction in bone mass. Therefore, Gomes *et al* [74] considered that the primary event would be the increase in VDRs, which favors the increase of the functional capacity of calcitriol-VDR complexes, increasing intestinal calcium absorption, and stimulating the bone expression of RANKL.

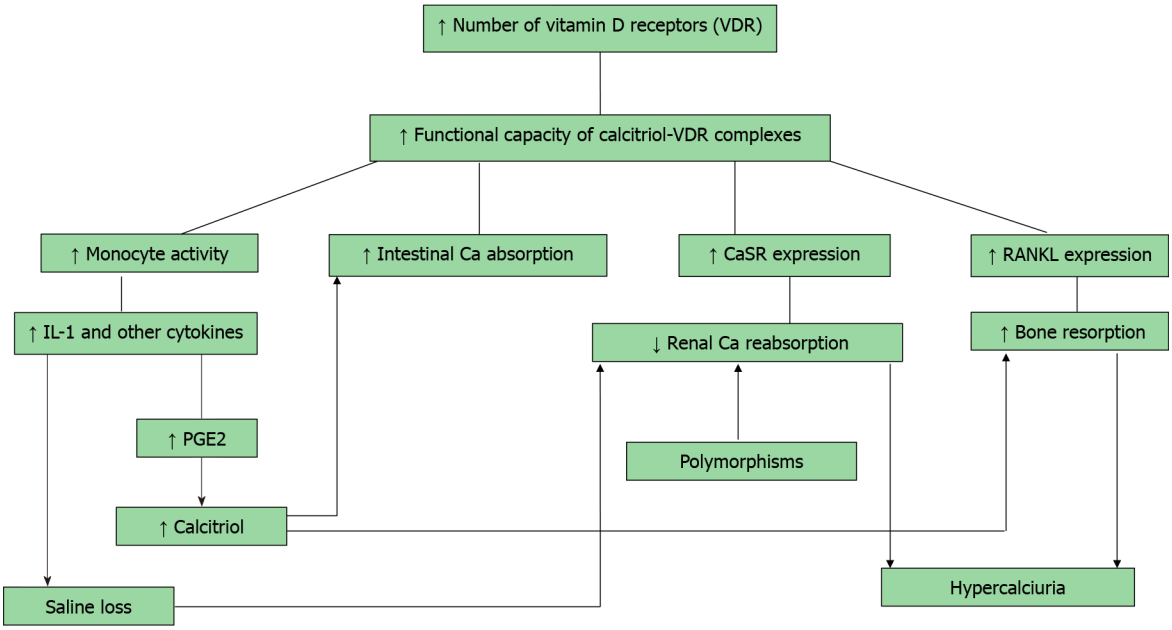

Figure 2 Cytokine-producing monocyte hyperreactivity described in IH is related to the increase in VDR in these cells. Adapted from: García-Nieto VM, Luis-Yanes MI, Tejera-Carreño P, Pérez-Suarez G, Moraleda-Mesa T. The idiopathic hypercalciuria reviewed: Metabolic abnormality or disease? *Nefrologia* 2019; 39: 592-602. Copyright ©The Author(s) 2019. Published by Elsevier España, S.L.U[23].

In 2020, Taguchi *et al*[75] performed a single-center retrospective cohort study to analyze patients with UL who underwent both BMD examination and 24 h urine collection. A total of 370 patients were included, and there was a positive correlation between BMD T-scores and urinary phosphate and citrate excretion. A lower BMD T-score was associated with increased odds ratios for stone symptoms during follow-up. The authors suggested that examining BMD could be a useful tool for effective follow-up of UL and may prevent future risks factors to urinary stones[75].

BONE CHANGES IN PEDIATRIC HYPERCALCIURIA

It is known that life-long hypercalciuria could be an important contributor to diminished bone mass or failure of adequate bone mass gain. In pediatric patients, the studies on IH began with Stapleton *et al*[20,76,77]. The authors used the acute oral calcium overload and found similar linear skeleton growth in both groups (renal and absorptive hypercalciuria)[77]. The same authors studied the BMD of their patients with IH and compared it with a control group. They found no significant differences in BMD between patients and controls or between patients with renal and absorptive hypercalciuria. Also, there was no correlation between BMD, PTH and osteocalcin[77]. Later, studies showed bone changes in pediatric patients with IH. Perrone *et al*[78] showed an improvement in lumbar spine BMD (compared to those untreated) in a prospective study with pediatric IH patients with absorptive type treated with dietary calcium restriction and/or rice bran The BMD of the lumbar spine (L2-L4) and bone markers of bone formation and resorption were assessed in children with IH[78]. The patients had elevated osteocalcin and calcitriol blood levels, as well as magnesium and prostaglandin E2 urinary levels. On the other hand, they had decreased urinary ammonium excretion, tubular reabsorption of phosphate and BMD when compared to controls[78]. BMD reduction was present in 30% of the patients and was negatively correlated with age. The authors hypothesized the increased cytokine activity could explain the reduced BMD in these patients[79]. Freundlich *et al*[31] studied the BMD (lumbar spine and femur) and bone resorption markers (pyridinoline, deoxypyridinoline and telopeptide) of children with IH and of their premenopausal mothers. The authors found BMD reduction in 38% of children and 33% of their mothers. The bone resorption markers were increased in 57% of the mothers with BMD reduction [31]. Garcia Nieto *et al*[29] described the BMD *Z* score as < -1 in 30.1% of their pediatric patients with evaluated IH. Bone markers were analyzed to confirm the resorptive mechanism in pediatric patients with HI. In children with normal BMD, a direct correlation was observed with the levels of osteocalcin (bone formation marker) and

tartrate-resistant acid phosphatase, a bone resorption marker; however, this relationship disappeared in those with reduced BMD[29]. Subsequently, the authors verified a value of < -1 for BMD *Z* score in the lumbar spine in 42.5% of a group of girls and in 47.5% of their mothers (lumbar spine and/or femoral neck). Mothers and daughters had hypercalciuria[32]. More sensitive resorption markers such as deoxypyridinoline (DPir) and the C-terminal telopeptide collagen fraction in the urine (CTx) were evaluated. Hypercalciuric children with or without BMD reduction showed significantly higher values of DPir/Creatinine and CTx/Creatinine ratios than controls. In contrast, osteocalcin levels were significantly higher only in patients with normal BMD[32]. These data would confirm that there is an increase in osteoclastic activity in children with IH, and those with normal BMD would have an adequate compensatory osteoblastic response[23].

Penido *et al*[16] evaluated a group of 88 children with IH at the time of diagnosis and 29 controls. BMD *Z*-score was significantly reduced at the lumbar spine in 31 (35%) patients. The biochemical markers of bone turnover were also evaluated. There was an increased urinary N-telopeptide excretion in the hypercalciuric subjects, as well as increased serum osteocalcin. The authors suggested that the low bone mass in children with IH might have been due to increased bone turnover[16].

Skalova *et al*[33] evaluated 15 pediatric hypercalciuric patients, and 40% of them had BMD Z-scores between -1 and -2 standard deviations (SD), and 20% had BMD Z scores below -2 SDs. The values for 24 h urinary calcium and N-acetyl-β-D-glucosaminidase (NAG - marker of renal tubule impairment) were significantly higher, and lumbar BMD was significantly lower than reference values from a healthy European pediatric population. The authors also demonstrated an inverse correlation between BMD and 24h calciuria[33].

Later, Penido *et al*[80] evaluating 88 pediatric patients with IH, and half of them had associated hypocitraturia (HC). Those with HC had a higher reduction in BMD in the absence of metabolic acidosis. A significant reduction in blood pH and bicarbonate in the group with HC was observed, although venous blood gases were normal in all patients. The authors suggested that lower blood pH and bicarbonate in hypercalciuric patients with associated HC could indicate that there is an intracellular acidification defect more severe in those patients with HC. This acidic environment would stimulate bone buffering, hypercalciuria and reduced BMD. Although age did not differ between patients with and without HC, those with HC had significantly lower height, weight, bone age and body mass index (BMI), suggesting an effect of HC on growth[80].

In 2009, Garcia Nieto *et al*[23] evaluated the BMD of 104 children with IH on two occasions. The first bone densitometry was performed at 10.7 ± 2.6 years and the second at 14.4 ± 2.7 years[34]. There were no differences in the calciuria or citraturia values or age at the time of the two bone densitometries. The authors concluded that there is a tendency to improve BMD in children with IH spontaneously, which is associated with increased body mass[34].

Penido *et al*[30] studied the BMD at the lumbar spine of 80 pediatric patients with IH. BMD Z-scores were evaluated before and after treatment. The patients were followed for a median time of 6.0 years, and they were treated with potassium citrate or potassium citrate and thiazides. BMD Z-score changed significantly from -0.763 ± 0.954 to -0.537 ± 0.898 ($P < 0.0001$). The authors suggested a beneficial effect of treatment in these patients, with significant improvement in bone mass[30].

Pavlou *et al*[81] in 2018 investigated 50 children with IH and matched 50 controls in a prospective study. They evaluated biochemical markers of bone formation and resorption and the osteoprotegerin (OPG) and soluble receptor activator of the nuclear factor-kB ligand (sRANKL) system. Following the diagnosis, the patients were requested to follow a 3 mo dietary recommendation. At diagnosis and at 3 mo of follow-up, patients and in controls were studied for bone-related hormones and serum/urine biochemical parameters. The authors concluded that children with IH had biochemical markers compatible with normal bone formation but increased bone resorption. After a 3 mo dietary intervention, the decrease in the serum β-Crosslaps may have reflected a beneficial response[81].

Kusumi *et al*[82] in 2020 conducted a prospective paired case-control study to assess BMD in adolescents with UL and to evaluate a possible correlation between BMD and urine concentration of lithogenic minerals and/or inflammation markers. It was observed that the BMD Z-score of lumbar spine and total body were not different between groups; however, when patients were separated by gender, there was a significant difference between males *vs* controls for the BMD Z-score of total body. There was no correlation of the lumbar spine and total body BMD Z-score regarding urinary calcium, oxalate, citrate or magnesium. Higher urine IL-13 significantly

correlated with higher total body BMD Z-score (r = 0.677; P = 0.018). The authors concluded that despite the small number of patients, it is a hypothesis-generating study. They demonstrated novel evidence of male-specific low BMD in adolescent stone formers[82].

Recently, Perez-Suarez *et al*[83] (2021) evaluated 34 hypercalciuric pediatric patients in a longitudinal study conducted over 20 years through three bone densitometry studies. Patients underwent a third densitometry study in adulthood (10.5 ± 2.7 [BMD1], 14.5 ± 2.7 [BMD2] and [BMD3] 28.3 ± 2.9 years of age). The authors observed a gradual decrease in calcium/creatinine and citrate/creatinine ratios and suggested that it would be related to improvement in osteoblastic activity and especially reduction in osteoclastic activity. They concluded that in patients with IH, BMD improves with time. This improvement may be related especially to the female gender, increment of body mass, and reduction in bone resorption. Urine calcium and citrate excretion tend to decrease upon the patients reaching adulthood[83].

At this point, it is known that IH and reduced BMD are closed entities. However, the precise mechanisms of reduction in bone mass loss or failure of normal bone mass gain remain not entirely known.

IMPORTANCE OF HYPERCALCIURIA FOR PEDIATRICIANS

The peak bone mass and its accumulation are achieved by late adolescence, peaking at the end of the second decade of life[84]. This accumulation should occur without interference in order to achieve the peak of optimal bone mass. The bone mass acquired during childhood and adolescence is a major determinant of adult bone health, and its accumulation should occur without interference[85]. This raises the important question of whether adult osteoporosis is initiated during childhood in IH patients[84]. However, interferences in childhood bone mass acquisition would not affect bone mass in late adulthood because there is a homeostatic system that seeks to return to the normal situation after any transient change[85].

Studies have emphasized that a persistent disturbing factor would, therefore, compromise the final bone mass in adulthood[85]. According to these studies, "any continuous and persistent interference may be a determining factor for low BMD with increased risk of osteopenia, osteoporosis and fractures in adulthood"[85].

An important point is how to assess and interpret BMD in children. According to the ISCD official position, DXA is the preferred method. Bone mineral content (BMC) and areal BMD results should be adjusted for absolute height or height age or to pediatric reference data that provide specific *Z* scores. The terms osteopenia and osteoporosis should not be used in pediatric patients. The correct term for them is "low bone mineral content" or "low bone mineral density" for age, when the *Z* scores are less or equal minus two[86].

There are few studies showing the association between decreased BMD and fractures in children. Data suggest that children with abnormal BMD are at risk for fractures. However, none of those included a biochemical analysis to assess other potential causes of low BMD[87,88]. In a case-control study, Olney *et al*[88] showed that BMD values were lower for the case subjects with fractures compared with the control subjects. The authors decided to evaluate these patients because both pediatricians and orthopedists are often unsure whether to consider further evaluation in children with repeat fractures[88].

CONCLUSION

Considering all the aforementioned, it is imperative that pediatricians have the knowledge and ability to diagnose and manage pediatric patients with IH with or without UL. They should advise parents and/or caregivers that children and adolescents must always have a healthy diet with a regular intake of calcium, proteins, calories and sodium, according to RDA; practice daily physical exercises; adequate fluid intake, especially water as well as regular sun exposure. If regular sun exposure is not possible, the serum levels of 25OH Vit. D should be assessed. The control of risk factors and adequate treatment (pharmacological or not) are essential for great bone structure and bone mass throughout life, decreasing the risk of osteopenia, osteoporosis and fractures later in life.

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ORIGINAL ARTICLE

Retrospective Study

Pediatric firearm-associated fractures: Analysis of management and outcomes

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Abstract

BACKGROUND

Firearm-associated injuries (FAIs) are among the leading causes of morbidity and mortality in children living in the United States. Most victims of such injuries survive, but may experience compromised function related to musculoskeletal injuries. Although complex firearm-associated fractures (FAFs) often require specialized orthopaedic, vascular, and plastic surgical intervention, there is minimal research describing their management and outcomes. The purpose of this study is to describe the epidemiology and presentation of pediatric FAFs, as well as evaluate the management and outcomes of these injuries.

AIM

To describe the epidemiology and presentation of pediatric FAFs, as well as evaluate the management and outcomes of these injuries.

METHODS

A retrospective chart review was performed at a major, pediatric level 1 trauma center. The study included patients aged 18 or younger who presented with FAIs between 2008-2018. Additional data was collected on patients with FAFs including demographic and clinical data such as age, sex, race, payor type, fracture location, injury severity score (ISS), and radiographic and clinical outcomes. The management of FAFs was analyzed as well as need for readmission and reoperation. Descriptive statistics were used to summarize the results and univariate analyses were performed to assess differences between groups.

RESULTS

Specialty type: Orthopedics

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Grade D (Fair): 0
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Between 2008 and 2018, there were a total of 61 patients who presented with FAIs. In this cohort, 21 patients (34%) sustained FAFs (25 fractures) with a mean age of 11 (Range: 10 mo to 18 years old) at the time of presentation. Approximately 52% (n = 11) of patients with FAFs were male, 76% (n = 8 and n = 8, respectively) identified as black or other, and 71% (n = 15) had government insurance. FAFs were most commonly noted in the upper extremity (n = 7) and lower extremity (n = 6). In patients with FAFs, the mean ISS at presentation was 11.38 (Range: 2-38), and 24% of patients (n = 5) were classified as having a major trauma. There were no significant differences in age, sex, race, and payor type in FAF patients that presented with and without major trauma (P > 0.05). When comparing FAF and non-FAF patients, there was a statistically significant difference in ISS (11.38 *vs* 14.45, P = 0.02). In total, 33% (n = 7) of patients with FAFs required orthopaedic surgical management, which was most commonly comprised of debridement (n = 6/7, 86%), and 14% (n = 1/7) of these patients required coordinated care with plastic and/or vascular surgery. There were no significant differences in age and payor type in patients with FAFs treated with and without orthopaedic surgery. Of the patients with FAFs, 52% (n = 11) had a minimum 90-d follow-up, and 48% (n = 10) had a minimum 2-year follow-up. Two patients were readmitted within 90-d, while one patient required a reoperation within 2-years.

CONCLUSION

Over 25% of FAIs in pediatric patients result in FAFs. FAFs often present to pediatric trauma centers and the majority of these injuries occur in non-Caucasian males with government insurance. Most FAFs do not need orthopaedic surgical management; 14% of these injuries require subspecialty care by orthopaedic surgery, vascular surgery, or plastic surgery. Patients with FAFs also have lower ISS compared to patients who sustained FAIs without fracture. Thus, these patients should be treated at pediatric trauma centers with specialty care and additional research is needed to focus prevention efforts, understand reasons for poor follow-up, and evaluate outcomes after injury.

Key Words: Firearm; Fracture; Adolescent; Gunshot; Injury; Pediatric

Core Tip: Over 25% of firearm-associated injuries (FAIs) in pediatric patients result in firearm-associated fractures (FAFs). FAFs often present to pediatric trauma centers and the majority of these injuries occur in non-Caucasian males with government insurance. Most FAFs do not need orthopaedic surgical management; 14% of these injuries require subspecialty care by orthopaedic, vascular, or plastic surgery. Patients with FAFs have a lower injury severity score compared to patients who sustained FAIs without fracture. These patients should be treated at pediatric trauma centers with specialty care. Additional research is needed to focus prevention efforts, understand reasons for poor follow-up, and evaluate outcomes after injury.

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INTRODUCTION

Firearm-associated injuries (FAIs) are among the leading causes of morbidity and mortality in children living in the United States. Recently, the injuries and fatalities associated with firearms have come to the forefront of public discourse in the United States. These injuries account for almost twenty pediatric hospitalizations per day across the country[1], and represent the cause of death for a quarter of adolescents 15-19 years old[2].

Despite the large number of children affected by firearm-related violence, there is a paucity of literature focusing on the rates of firearm associated fractures (FAFs) as well as the orthopaedic management of these injuries. Additionally, there are few studies focusing on concomitant injuries that occur with FAFs, such as vascular and soft tissue injuries. In a study by Blumberg *et al*[3], the incidence of FAFs in patients < 20 years of age between 2003 to 2012 was 90.7 per 100000 admissions. These patients were more likely to be male, African American, and older in age. The authors also noted an increase in overall incidence of FAFs during the study period, with the largest increase in children ages 0-4. These findings underscore the need for additional research focusing on the epidemiology, management, and outcomes of FAFs so that health care professionals are better able to counsel and manage patients, as well as inform policy makers to allocate resources and focus on prevention programs.

The aim of this study was to describe the epidemiology and presentation of fractures secondary to firearm injuries among children and adolescents at a major metropolitan trauma center over a ten-year period. In addition, we aimed to assess the management and outcomes of these complex musculoskeletal injuries. We hypothesized that these injuries would be rare, and the majority of patients would not require orthopaedic surgical intervention.

MATERIALS AND METHODS

A retrospective chart review was performed at a major pediatric level 1 trauma center. This study included patients aged 18 or younger that presented with a FAI between 2008 and 2018. Additional data was collected on patients specifically presenting with a FAF. Patients with isolated fractures of the hand, spine, skull, face, or ribs were excluded. This study was approved by our institutional review board.

Patients were identified from an institutional trauma database, which provided initial demographic and clinical data. This database captures all patients with FAIs seen in the emergency room. Charts for patients with FAFs were reviewed to collect additional clinical and radiographic data. Demographic data included patient age, sex, race, and payor status. Clinical data included year of presentation, fracture location, injury severity score (ISS), surgical management, need for other surgical services, rates of 90-d and 2-year follow-up, as well as 90-d and 2-year radiographic and clinical outcomes. The data were summarized using counts, percentages, ranges, and means. Univariate analyses comprised of student's t-test and chi-square analysis were performed to compare differences in patients with and without FAFs, with and without other major trauma, and patients that were or were not treated with orthopaedic surgery. All data was stored in a password protected file and analyses were performed in Microsoft Excel (v2016.).

RESULTS

Demographics

During the ten-year study period, we identified a total of 61 patients who sustained FAIs (Figure 1). Of these, 21 patients (34%) suffered FAFs and presented for care at our institution. The average age at time of presentation for all FAIs was 11 years, and approximately 70% of patients (n = 43) were male. Approximately 80% of patients identified as black or other (n = 25 and n = 24, respectively), and 59% (n = 36) had government insurance (Table 1). The mean ISS for all FAIs was 14.48 (Range: 4 to 50).

Fractures and management

There were 25 FAFs in 21 patients over the study period. Of the patients who sustained FAFs, the average age at time of presentation was 11 years, and 52% were male (n = 11). Approximately 76% identified as black or other (n = 7 and n = 9, respectively), and 67% (n = 14) had government insurance. The most common fracture locations included the upper extremity (n = 7) and lower extremity (n = 6), specifically in the scapula and femur (n = 3 and n = 3, respectively). Four patients had multiple fractures, of which two patients had both FAFs in the foot; one patient had both FAFs in the pelvis; and one patient had FAFs in the pelvis and lower extremity. The mean ISS at presentation was 11.38 (Range: 2 to 38), and 24% of patients (n = 5) were classified as having a major trauma, defined as an ISS greater than 15. There were no statistically significant differences in age, sex, race, and payor between patients with

Table 1 Demographics of patients with firearm-associated fractures

	Number
Age at injury	
0–12 years old	9 (43%)
13–18 years old	12 (57%)
Sex	
Male	11 (52%)
Female	10 (48%)
Race	
Asian	2 (10%)
Black	8 (38%)
White	2 (10%)
Other	8 (38%)
Unknown	1 (5%)
Insurance payor	
Government	15 (71%)
Non-government	6 (29%)
Location of fracture	
Upper extremity	7 (28%)
Lower extremity	6 (24%)
Foot	5 (20%)
Pelvis	5 (20%)
Unknown	2 (8%)
AO fracture classification	
14.A1	61A1.3
14A3	61A2.2
14B1	61A2.3
14B2	62A2.1
21.B1	81.1.C3
2R2C3	82.C3
31.3A3	82C1
32.C3	84B
33A3.2	87.C3
34B1.2	
42.A2	
Injury severity score	
≤ 15	16 (76%)
> 15	5 (24%)
Treatment	
Orthopaedic surgical management	7 (33%)
Debridement[1]	6 (86%)
Internal fixation[1]	5 (71%)
Both[1]	4 (57%)

No orthopaedic surgical management	10 (48%)
Unknown	4 (19%)

[1]The percentages are out of the total number of patients treated with orthopaedic surgical management.

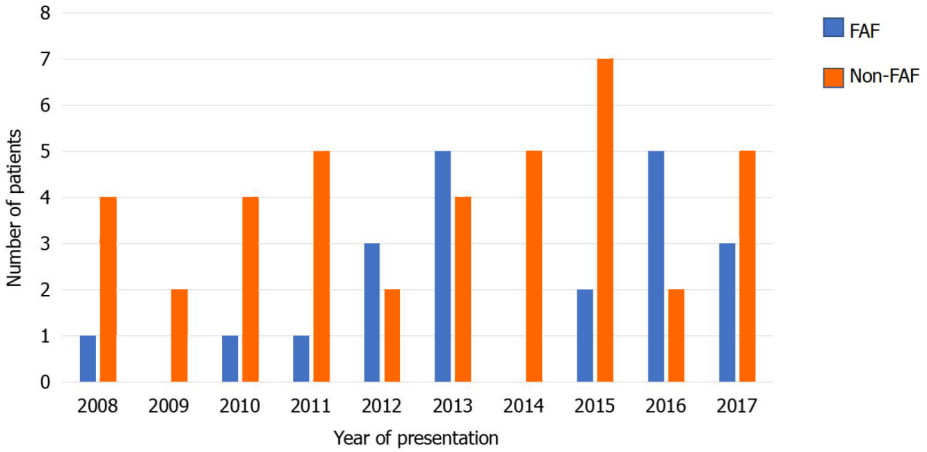

Figure 1 Number of patients with firearm-associated fractures versus non-firearm-associated fractures per year from 2008 to 2018.

and without major trauma ($P > 0.05$).

In total, 33% of patients ($n = 7$) required orthopaedic surgical management, which was most commonly comprised of debridement ($n = 6$, 86%) and internal fixation ($n = 5$, 71%). Internal fixation consisted of a variety of methods, including Kirschner wires, intramedullary devices, and plating (Table 1). Intramedullary devices were commonly used for lower extremity FAFs and k-wires or plate fixation was commonly used for upper extremity FAFs. There were no significant differences in sex and payor between patients treated with and without orthopaedic surgery.

In this cohort, approximately 14% of patients ($n = 3/21$) needed coordinated care with plastic and/or vascular surgery. Of the remaining patients, 48% of patients ($n = 10$) were treated non-operatively with modified weight-bearing, bracing, or splinting.

Follow-up and outcomes

Among all FAF patients, 52% ($n = 11$) had a minimum 90-d follow-up and 48% ($n = 10$) had a minimum 2-year follow-up. Of the 7 patients treated with orthopaedic surgery, 5 patients (71%) had 90-d follow-up, and 5 patients (71%) had two–year follow-up. All patients with radiographs at two-years had evidence of radiographic healing. In this cohort, 1 patient (14%) was readmitted within 90-d for ulnar nerve reconstruction, and 1 patient (14%) required a reoperation within 2-years for a hardware removal and a subsequent reoperation for revision fixation for malunion.

FAF and non-FAF patients

In our study, 66% patients ($n = 40$) had a FAI without an associated fracture. In this group, the average age at time of presentation was 11 years. Eighty percent ($n = 32$) of these patients were male, and 85% identified as black or other ($n = 18$ and $n = 16$, respectively). 50% of these patients had government insurance. There was no statistically significant difference in age, sex, race, and payor between our FAF and non-FAF group ($P > 0.05$). However, there was a statistically significant difference in average ISS between FAF and non-FAF patients ($P = 0.02$) with average scores of 9.5 for FAF patients and 14.5 for non-FAF patients.

DISCUSSION

The United States Center for Disease Control and Prevention estimates that 3443 fatalities and 18227 nonfatal FAIs occurred in patients below 19 years old in 2017 alone [4]. In a retrospective analysis of emergency department and ambulatory visits from the National Hospital Ambulatory Medical Care Survey, Srinivasan *et al*[5] calculated

an annual rate of FAIs of 23.9 per 100000 children between 2001 and 2010. A similar trend was noted for FAFs by Blumberg *et al*[3] with a recent increase in the number of such fractures.

Our study identified a total of 61 patients affected by FAIs over the last 10 years. Of this group, 21 patients experienced a total of 25 fractures. The majority of FAFs occurred within the last 5 years of the study period. The increasing incidence of FAFs in the last 5 years as well as the affected patient population is consistent with previous studies[3,5-10]. A previous study noted an increase in nonfatal FAFs over a 10-year period, and another study noted an overall increase in FAFs over time[3,5]. Additionally, FAFs often affect both the upper and lower extremity, with the scapula and femur being the most commonly affected anatomic location. Twenty-five percent of patients were classified as having a major trauma. In this study, there was a statistically significant difference between ISS in FAF and non-FAF patients. This may be because FAFs are commonly found in the extremities and as a result, they are not associated with major trauma since they are distal to critical organs and structures.

The majority of FAIs in this study were noted to occur in non-Caucasian males and patients with government insurance. This trend was also found in our FAF patients and is representative of our patient population. These findings are consistent with findings from a large database study, which noted FAFs were more commonly found in patients who were male, black, and uninsured in comparison to children who were being evaluated for non-firearm related complaints[5]. This pervasive trend underscores the importance of interventions targeting these demographic groups and focusing our efforts on reducing the morbidity and mortality associated with FAIs in these populations.

In general, many patients with FAFs do not need orthopaedic surgical management, but orthopaedic, vascular, or plastic surgical care may be required in up to half of all patients with FAFs. This is consistent with our hypothesis and the current literature, which supports the use of local wound care and antibiotics among low-velocity gunshot wounds with stable fracture patterns[11]. However, injuries caused by high-energy weapons or those with an unstable fracture pattern, vascular injury, or significant soft tissue defects may require formal surgical irrigation and debridement, fixation, vascular repair, or grafting, with intravenous antibiotics. In addition, a recent study by Berg *et al*[9] noted that FAFs were 1.9 times more likely to be associated with vascular and nerve injury, which may require care coordination across specialties.

In our study, approximately a third of our patients required orthopaedic surgical management, and approximately 14% of these patients needed coordinated care with plastic and/or vascular surgery. There were no significant differences in sex and payor between patients treated with and without orthopaedic surgery. Despite the lower rates of operative intervention, this finding highlights the importance of multispecialty care and a practice of having these patients managed at major trauma centers. This finding may be critical for those patients requiring orthopaedic surgical management.

This study has several limitations. This is a single center study and our sample size is small, which may affect the generalizability of our findings as well as our ability to perform analyses that are adequately powered. However, our institution serves a racially and socioeconomically diverse population, and it is the only level 1 pediatric trauma center in this geographic region. Additionally, this study only has short and long-term follow-up for approximately half of the cohort, and it has limited clinical and functional data for evaluation. This limitation may be due to the high rate of referrals to our institution, but it could also reflect the need for continued emphasis on follow-up for this patient population. Although we have a low rate of patient follow-up, readmission and reoperation were noted to occur. Thus, this finding emphasizes the need for closer follow-up to monitor for complications such as infection, malunion, and nonunion, which have been well-documented in the literature[11-13]. Lastly, we do not have any patient-reported outcome measures, which limits our ability to compare outcomes to other patients or populations.

CONCLUSION

In conclusion, FAFs are noted in approximately a third of all FAIs. FAFs have become increasingly more common at our institution, and there is a high rate of FAFs among certain demographic and socioeconomic groups. While these injuries can cause lasting effects on these patients, they may not be associated with major trauma. These findings are consistent with previous studies and should serve as a call to providers, administrators, and policy makers to investigate and propose ways to address this

issue. The findings from this study also underscore the need for multidisciplinary care and close follow-up to minimize the risk of readmission, reoperation, and poor outcomes. Patients with FAFs often have complex needs and should be treated at pediatric institutions with specialty care. Additional effort is needed to maintain follow-up and decrease the risk for readmission after this injury. The identification of factors, which may prevent follow-up in this population, could provide areas to target future interventions to ensure adequate care and optimize outcomes in these patients.

ARTICLE HIGHLIGHTS

Research background

Firearm-associated injuries (FAIs) are among the leading causes of morbidity and mortality in children living in the United States. Recently, the injuries and fatalities associated with firearms have come to the forefront of public discourse in the United States.

Research motivation

Most victims of such injuries survive, but may experience compromised function related to musculoskeletal injuries. Although complex firearm-associated fractures (FAFs) often require specialized orthopaedic, vascular, and plastic surgical intervention, there is minimal research describing their management and outcomes.

Research objectives

The purpose of this study is to describe the epidemiology and presentation of pediatric FAFs, as well as evaluate the management and outcomes of these injuries.

Research methods

A retrospective chart review was performed at a major, pediatric level 1 trauma center. The study included patients aged 18 or younger who presented with FAIs between 2008-2018. Additional data was collected on patients with FAFs including demographic and clinical data such as age, sex, race, payor type, fracture location, injury severity score (ISS), and radiographic and clinical outcomes. The management of FAFs was analyzed as well as need for readmission and reoperation. Descriptive statistics were used to summarize the results and univariate analyses were performed to assess differences between groups.

Research results

Between 2008 to 2018, there were a total of 61 patients who presented with FAIs. In this cohort, 21 patients (34%) sustained FAFs (25 fractures) with a mean age of 11 (Range: 10 mo to 18 years old) at the time of presentation. FAFs were most commonly noted in the upper extremity (n = 7) and lower extremity (n = 6). In total, 33% (n = 7) of patients with FAFs required orthopaedic surgical management, which was most commonly comprised of debridement (n = 6/7, 86%), and 14% (n = 1/7) of these patients required coordinated care with plastic and/or vascular surgery. Of the patients with FAFs, 52% (n = 11) had a minimum 90-d follow-up, and 48% (n = 10) had a minimum 2-year follow-up. Approximately 2 patients were readmitted within 90-d, while one patient required a reoperation within 2-years.

Research conclusions

Over 25% of FAIs in pediatric patients result in FAFs. FAFs often present to pediatric trauma centers and the majority of these injuries occur in non-Caucasian males with government insurance. Most FAFs do not need orthopaedic surgical management; 14% of these injuries require subspecialty care by orthopaedic surgery, vascular surgery, or plastic surgery. Patients with FAFs also have lower ISS compared to patients who sustained FAIs without fracture. Thus, these patients should be treated at pediatric trauma centers with specialty care and additional research is needed to focus prevention efforts, understand reasons for poor follow-up, and evaluate outcomes after injury.

Research perspectives

Additional effort is needed to maintain follow-up and decrease the risk for readmission after this injury. The identification of factors, which may prevent follow-up in this population, could provide areas to target future interventions to ensure adequate

care and optimize outcomes in these patients.

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ORIGINAL ARTICLE

Observational Study

Healthcare staff as promoters of parental presence at anesthetic induction: Net Promoter Score survey

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Abstract

BACKGROUND

Surgical intervention is usually a traumatic event that causes stress and anxiety in the pediatric patient and the family environment. To reduce the harmful effects of presurgical anxiety, parental presence during induction of anesthesia (PPIA) is one of the more notable interventions used in medical centers. However, data on this measure are difficult to evaluate and often face resistance from healthcare staff.

AIM

To analyze the perception of the healthcare workers after the implementation of a PPIA program.

METHODS

A survey was developed and sent by email to all the healthcare staff working in the children's area of a tertiary hospital. It consisted of 14 items divided into positive aspects of PPIA and negative aspects of PPIA evaluated with the use of a Likert scale (1 to 5). The demographics of the respondents were included in the data collected. The answers to the questions were interpreted through the Net Promoter Score (NPS). The statistical analysis compared the differences in the responses to each question of the survey made by the different groups of health personnel included.

RESULTS

A total of 141 surveys were sent out, with a response rate of 69%. Of the total number of responses, 68% were from women and 32% from men. The average age

enrollment.

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of the participants was 42.3 ± 10.6 years. As for the positive questions about the PPIA, 83% had an NPS > 50, and only one had a score between 0 and 50, which means that the quality of the service was rated as excellent or good by 100% of the respondents. On the other hand, 100% of the negative questions about the PPIA had a negative NPS. Responses to the question "PPIA increases patient safety" were significantly different (P = 0.037), with a lower percentage of pediatric surgeons (70%) thinking that PPIA increased patient safety, compared with anesthesiologists (90%), nursing (92%), and other medical personnel (96%).

CONCLUSION

The personnel who participated in the PPIA program at our center were in favor of implementation. There were no validated arguments to support worker resistance to the development of the PPIA.

Key Words: Parental presence; Survey; Anesthesia induction; Patient-centered care; Anxiety; Surgery

Core Tip: Surgical intervention is usually a traumatic event that causes stress and anxiety in the pediatric patient and the family environment. To reduce the harmful effects of presurgical anxiety, the parental presence during induction of anesthesia (PPIA) is one of the more notable interventions used in medical centers. However, data on this measure are difficult to evaluate and often face resistance from healthcare staff. With our work, we want to emphasize the acceptance and support of the health personnel of the application of PPIA in our center and the importance of family involvement in achieving a comprehensive approach for our patients.

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INTRODUCTION

Surgical interventions are traumatic events that causes stress and anxiety in the pediatric patient and the family environment. Several studies have shown that this type of anxiety is related to undesirable events such as negative results of anesthetic induction, increased pain in the postoperative period, increased postsurgical delirium, decreased adherence to subsequent medical treatment, and behavioral changes including sleep disorders, nutritional problems, enuresis, fear of separation, and aggression[1-4]. Various strategies have been developed to mitigate presurgical anxiety in both children and their family environment, with variable results that are controversial and difficult to evaluate. The use of pharmacological interventions remains one of the most widely used tools. However, in recent years, the use of nonpharmacological measures has gained great relevance in this field, with parental presence during induction of anesthesia (PPIA) being one of the most discussed[5].

It has been reported that families prefer to participate and be present during high-stress procedures such as surgery, and those who are present generally report favorable experiences and even consider it a right[6,7]. This trend, along with the increasing development of patient- and family-centered care (PFCC), the basic concepts of which include participation and collaboration, is often objectionable to those who do not favor active participation of the patient and family in the surgical experience. Critics usually argue that a PPIA program requires additional staff and new infrastructure, increased surgical time and therefore decreased operating room efficiency, increased costs, and possible medical-legal issues[9,10]. However, there are no validated data to support those arguments, and an increasing number of hospitals are implementing this measure, with good acceptance by health staff. The objective of

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this study was to evaluate the perceptions of health care personnel regarding the implementation of the PPIA program in our center.

MATERIALS AND METHODS

PPIA implementation program

Implementation of the PPIA program was motivated by the pediatric surgery and child anesthesia and resuscitation services at our center to achieve more patient- and family-centered medicine and after having positive experience with the same program in other centers at our medical center.

The program was implemented in June 2019 after approval by the ethics committee. The necessary space for the different phases of the program were set up, all the necessary material for the entrance to the operating room was obtained, and all the personnel involved were properly instructed in every step of the process. A pilot phase was initiated with 57 patients undergoing major outpatient surgery without the need for hospitalization (*e.g.*, epigastric herniorrhaphy, umbilical herniorrhaphy, inguinal herniorrhaphy, circumcision, hydrocelectomy, orchidopexy, and other minor surgical procedures). A future objective of this measure is potentially extending it to children undergoing conventional inpatient surgery and invasive diagnostic-therapeutic tests such as magnetic resonance imaging, computed tomography, and interventional radiology. The participating patients were between 2 and 12 years of age, were classified as American Society of Anesthesiologists status I, and 48% were premedicated with oral midazolam depending of the criteria used by the responsible anesthesiologist.

Process

The possibility of PPIA was offered to all parents or legal guardians of children cited for major outpatient surgery. The decision to be present or absent was made voluntarily by the parents or legal guardians, as was the choice of the person who would accompany the patient if there were several companions. Those who agreed to be present during anesthetic induction were given a set of rules and instructions to follow. (1) The dress code required a surgical suit, surgical cap, shoe covers, and face mask; (2) Do not touch anything, only the child, the bed, or the anesthetic mask in case of receiving the order from the anesthesiologist. (3) The phases of the process included preparation in the day hospital; moving to the presurgery room and the operating room, anesthetic induction, which includes an excitation phase with possible involuntary patient movement and hypotonia; and finally leaving the operating room. (4) The immediate postoperative phase included giving advice and instructions to understand and assist in patient recovery. The benefits and positive points of the process, such as the importance of focusing all attention on the child and the help and cooperation received from the family member at a critical time such as anesthetic induction, were reinforced at all times.

Survey

An internal survey was sent by email to all healthcare personnel involved in the process (*i.e.* pediatric surgeons, pediatric anesthesiologists, nursing and other medical staff) during the month of November 2019. The survey was composed of 14 items that were subdivided into positive aspects for PPIA and negative aspects for PPIA. The responses were graded on a Likert scale that ranged from totally disagree (1) to totally agree (5). The same questionnaire collected the demographic data of the respondents including age, gender, and the health group to which they belonged. The survey results were interpreted by the Net Promoter Score (NPS), which is a quality indicator that measures customer loyalty to companies based on recommendations. In the original version, each item has a score of from 0 to 10 where 0 is very unlikely to be recommended and 10 is strongly recommended. Scores between 9 and 10 are classified as promoters, those between 7 and 8 are passive, and those ≤ 6 are detractors. The final score is obtained by subtracting the detractors from the promoters and obtaining a percentage ranging from −100 to 100 that measures the quality of service, where an score > 0 is good, a score > 50 is excellent and a negative NPS is not a recommendation [11].

After obtaining the Likert scale scores for each item, these were transformed into values used by the NPS. Thus, scores of 4 or 5 on the Likert scale were considered as 9 or 10 in the NPS and were therefore promoters. Scores of 1 or 2, were considered as ≤ 6 and were therefore detractors. Finally, scores of 3 on the Likert scale were considered

as 7 or 8 on the NPS, were passive, and were not taken into account in the study. After the total numbers and percentages of promoters and retractors in percentage for each item of the questionnaire were obtained, the percentage of promoters was subtracted from the percentage of retractors of each item of the survey. An NPS > 0% indicated good quality, an NPS > 50% indicated excellent quality, and an NPS < 0% indicated poor quality. Finally, a statistical analysis was comparing the demographic characteristics and survey responses of each group was performed. Responses of < 75% were excluded.

Statistical analysis

The data were collected using Microsoft Excel version 16.35. Statistical analysis was performed with the IBM SPSS 25.0 statistical package. Quantitative variables were reported as means and standard deviation and qualitative variables as absolute frequencies and percentages. After checking the normality of distributions of the variables with the Kolmogorov-Smirnoff test (corrected by the Lilliefors test), quantitative variables were compared with the *t*-test and categorical variables with the chi-square test or the *F*-test. A P value of < 0.05 was considered significant; all intervals were calculated with 95% confidence.

RESULTS

The survey was sent to 141 people; the response rate was 69%. The group with the highest participation was nursing, with 30% of the total respondents, followed by pediatric surgeons (27%), and other medical staff (27%), and pediatric anesthesiologists (16%, Figure 1). Of the total number of responses, 68% were women and 32% were men. The average age was 42.3 ± 10.6 years. The demographic data for each group are shown in Table 1.

Answers to the survey sent to the healthcare staff

Table 2 shows the percentages of promoters, retractors and passive respondents as well as the NPS results. Table 3 shows the percentage of promoters in each group for each question and the comparative analysis of group responses. Questions rated positive for PPIA had NPS values > 50 (excellent service quality), except for the question "PPIA decreases use of presurgical medication" which had an NPS of between 0 and 50 (good service quality), meaning that 100% of respondents agreed fully and agreed with the positive aspects of PPIA. On the other hand, all questions considered negative for PPIA had a negative NPS (poor quality of service), meaning that the respondents all disagreed that PPIA has negative aspects for the patients, their families, and for the development of surgical care activities. Comparing the results by group, statistically significant differences were found only for the question "PPIA increases patient safety," with a lower percentage of pediatric surgeons who think that PPIA increases patient safety, compared with anesthetists (69.6% *vs* 90%), nurses (69.6% *vs* 92%), and other medical staff (69.6% *vs* 90% *vs* 96%, $P = 0.037$).

DISCUSSION

The results of our survey showed full approval of the implementation of the PPIA program at our center. The intervention was considered by pediatric surgeons, anesthesiologists, nurses, and other medical staff as an excellent quality service by more than 80% of the respondents. This conclusion is in line with other recent studies that showed that pediatric surgery departments and other healthcare providers approved of PPIA and consider it beneficial for the patient[7,12]. To our best knowledge, this is the first study to investigate whether sex and age were possible conditioning factors in answering this type of survey. According to our results, women were more prone to respond than men, but we did not find any differences regarding the age of the respondents. That finding might be explained by the higher percentage of women in the group with more survey participants (93% women *vs* 7% men), and not as a factor involved in support or resistance to PPIA.

We launched the project because we consider the presence of parents during anesthetic induction as part of a comprehensive, family-centered approach that respects their requirements and decisions. That was not always the case in pediatric healthcare. In 1895 D'Arcy Power wrote: "When an operation has been decided upon,

Table 1 Demographic data of each group

	Pediatric surgeons	Pediatric anesthesiologists	Nursing	Other medical staff	*P* value
Age, yr	40.8 ± 11.5	43 ± 8.5	41.7 ± 9.8	44.2 ± 11.7	0.56
Age subgroups, yr					
< 50	70	83	79	73	0.77
> 50	30	17	21	27	
Gender					
Male	46	44	7	38	0.006
Female	54	56	93	62	

Data are means ± SD or percentages.

Table 2 Percentages of promoters, retractors, and passive responses in each group for each question and the Net Promoter Score (promoters − retractors) for each question

Survey question	Promotors	Retractors	Passive	NPS (promotors − retractors)
Positive for PPIA				
PPIA improves the child's surgical experience	83.5	13.4	3.1	70.1
PPIA improves the parent's surgical experience	81.4	6.2	12.4	75.2
PPIA improves the relationship of the patient and his/her environment with health professionals at all levels	81.4	4.2	14.4	77.2
PPIA increases parental satisfaction	82.5	3	14.4	79.5
PPIA increases patient safety	71.1	11.3	17.5	59.8
PPIA decreases the use of presurgical medication	47.4	19.6	33	27.8
Negative for PPIA				
PPIA decreases surgical efficiency	5.1	71.1	23.7	-66
PPIA should be exclusive por patients in ambulatory surgery	12.4	71.1	6.2	-58.7
PPIA increases parental anxiety	23.7	54.6	21.6	-30.9
PPIA increases child's anxiety	3.1	86.6	10.3	-83.5
PPIA increases the duration of anesthetic induction	16.5	54.6	28.8	-38.1
PPIA increases the number of infections	4.1	63.9	32	-59.8
PPIA increases the cost of health care	20.6	59.8	19.6	-39.2
PPIA increases fear of legal problems	24.7	52.6	23.7	-27.9

NPS: Net Promoter Score; PPIA: Parental presence at anesthetic induction.

it will generally be seen that better results are obtained if the child is removed from his usual environment and placed in the care of those who have special experience in the care of sick children"[13]. The idea of separating the pediatric surgical patient from the family environment was maintained during the first half of the 20th century. Later, Gross[14] and Caniano *et al*[15] emphasized and assumed the role of the family in the child's surgical experience. It has been in recent decades that PFCC has grown and evolved to become a goal to be achieved in all medical areas including pediatric surgery[8]. Participation and collaboration are the basic concepts of PFCC, and numerous studies have tested strategies such as preoperative family preparation or the impact of the PPIA. The data on family preparation for the reduction of preoperative anxiety are positive[16,17]; in contrast, the results obtained regarding the impact of PPIA are controversial and not clear, as the latest Cochrane review showed[5]. However, even though Sadeghi *et al*[18] and Hussain and Khan[19] found no benefit of

Table 3 Percentage of promoters in each group for each question and comparative analysis by group

Survey question	Pediatric surgeons	Pediatric anesthesiologist	Nursing	Other medical staff	*P* value
Positive for PPIA					
PPIA improves the child's surgical experience	95	100	92	100	0.36
PPIA improves the parent's surgical experience	83	100	92	100	0.07
PPIA improves the relationship of the patient and his/her environment with health professionals at all levels	86	100	96	100	0.11
PPIA increases parental satisfaction	85	100	100	96	0.07
PPIA increases patient safety	70	90	92	96	$P < 0.05$
PPIA decreases the use of presurgical medication	62	80	55	88	0.11
Negative for PPIA					
PPIA decreases surgical efficiency	12	8	0	12	0.45
PPIA should be exclusive por patients in ambulatory surgery	13	23	8.3	22	0.52
PPIA increases parental anxiety	38	31	36	14	0.27
PPIA increases child's anxiety	0	0	7	3	0.45
PPIA increases the duration of anesthetic induction	29	21	23	22	0.94
PPIA increases the number of infections	5	10	11	11	0.91
PPIA increases the cost of health care	19	25	36	19	0.50
PPIA increases fear of legal problems	37	21.4	37	32	0.77

PPIA: Parental presence at anesthetic induction.

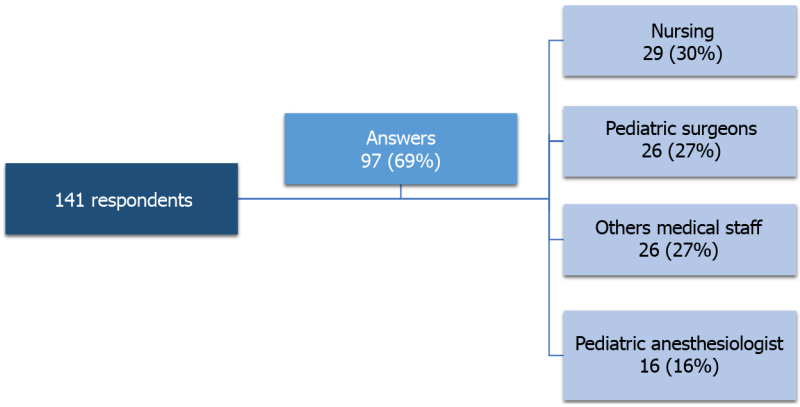

Figure 1 Survey participants. Ninety-seven of 141 healthcare workers who were sent the survey (69%) returned it with answers. The total number of participants and total number of participants in each group are shown.

PPIA with respect to preoperative anxiety, they did find other positive aspects, such as improved patient cooperation at the time of anesthetic induction, better acceptance of the face mask, or increased parental satisfaction, suggesting that PPIA may improve those aspects. In line with those findings, we found that the group with the highest percentage of promoters in most of the positive questions for PPIA was pediatric anesthesiologists, probably because behavior of children during anesthetic induction was better when a parent was present. However, Luehmann *et al*[7], showed that the median response to PPIA was most favorable for perioperative nurses, who are involved in all aspects of patient care and can give a more comprehensive opinion. The findings reinforce the support to the program from different points of view of the same process.

Many prejudices had to be overcome before the project could be launched. There are still common points of contention against this measure on the part of the medical staff, who believe that the presence of the parents could be disturbing, the induction of anesthesia and surgical intervention delayed, and the possibility of generating medical-legal problems. For example, Paice *et al*[6] reported significantly less support from medical staff for the presence of parents during invasive procedures compared with parents. In our results, pediatric surgeons were less positive than other groups when asked whether PPIA increased patient safety, which could be explained by fear of unwanted events. However, no related adverse effects were found in other studies, and there are no valid arguments to justify medical staff resistance to the implementation of this measure.

Unfortunately, despite the rationale and supporting evidence, PPIA is far from being a widespread and applicable procedure for all surgical procedures and invasive testing. Pediatric surgery has changed enormously over the last century, and we believe that family involvement in day-to-day clinical practice will eventually become a well-established part of pediatric surgical patient care. Finally, the acceptance and commitment of the healthcare personnel in the application of the PPIA at our center is highlighted. We suggest that all surgical centers should have programs that include family involvement, such as parental presence at anesthetic induction.

Limitations

Our study has the typical limitations of a qualitative survey. We cannot draw objective conclusions that can be tested if we do not offer an in-depth understanding of the acceptance of PPIA at our center with the belief in its expansion to other centers. Although we included the sex and age of respondents, other influential factors such as years of experience or previous experience with PPIA programs were not included in the analysis. We also did not take passive responses into account, assuming that they would not be relevant to the results. Finally, we are aware of the difficulty of applying a quality score from the business world to a measure of preoperative anxiety, but we believe in it here.

CONCLUSION

The results highlight the acceptance and commitment of healthcare personnel in the application of the PPIA in our center. We suggest that all surgical centers should have programs that include family involvement, such as parental presence at anesthesia induction.

ARTICLE HIGHLIGHTS

Research background

Medicine is getting closer and closer to the human side of the patient and family. Family knowledge, understanding, and accompanying their children, offers them an opportunity to contribute in the surgical process, and helps to reduce the stress caused by those situations.

Research motivation

We were motivated by the importance of avoiding the anxiety and stress that a surgical intervention causes in pediatric patients and their family environment, improving our relationship with them, and promoting their welfare.

Research objectives

The objective was to analyze the responses of healthcare workers to the implementation of a program in which parents accompany their children to the operating room to mitigate and reduce the anxiety and stress produced in the patient and their family environment by surgical interventions.

Research methods

A survey was designed and sent to the personnel involved in the process. It was analyzed and reinterpreted by applying a novel "Net Promoter Score".

Research results

The personnel involved in the process support the implementation of the program

Research conclusions

Based on the good acceptance of the program in our center, we suggest the development and implementation of the program by other centers.

Research perspectives

More studies are needed to demonstrate the effectiveness of parental presence during the induction of anesthesia (PPIA) and the support of healthcare workers for measures such as PPIA or similar programs. We must demonstrate the importance and involvement in achieving patient and patient- and family-centered care as one of the goals of present and future medicine.

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ORIGINAL ARTICLE

Observational Study

Association of breastfeeding with tidal breathing analysis in infants with bronchiolitis

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Abstract

BACKGROUND

Tidal breathing flow-volume (TBFV) analysis provides important information about lung mechanics in infants.

AIM

To assess the effects of breastfeeding on the TBFV measurements of infants who recover from acute bronchiolitis.

METHODS

In this cross-sectional study, TBFV analysis was performed in infants with bronchiolitis prior to hospital discharge. The ratio of time to peak expiratory flow to total expiratory time (tPEF/tE) at baseline and after the administration of 400 mcg salbutamol was evaluated.

RESULTS

General Hospital of Alexandroupolis provided approval for this study (IRB No. 23927/2382/02.01.2017).

Informed consent statement: Parental approval was obtained prior to inclusion for all involved infants.

Conflict-of-interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data sharing statement: The authors confirm that the data supporting the findings of this study are available within the article and its tables/figures. Raw data, without patient's personal information, are available upon reasonable request from the corresponding author.

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A total of 56 infants (35 boys), aged 7.4 ± 2.8 mo, were included. Of them, 12.5% were exposed to tobacco smoke and 41.1% were breastfed less than 2 mo. There were no differences in baseline TBFV measurements between the breastfeeding groups; however, those who breastfed longer than 2 mo had a greater change in tPEF/tE after bronchodilation (12% ± 10.4% *vs* 0.9% ± 7.1%; $P < 0.001$). Moreover, there was a clear dose-response relationship between tPEF/tE reversibility and duration of breastfeeding ($P < 0.001$). In multivariate regression analysis, infants who breastfed less (regression coefficient -0.335, $P = 0.010$) or were exposed to cigarette smoke (regression coefficient 0.353, $P = 0.007$) showed a greater change in tPEF/tE after bronchodilation, independent of sex, prematurity, and family history of asthma or atopy.

CONCLUSION

Infants who recover from bronchiolitis and have a shorter duration of breastfeeding or are exposed to cigarette smoke, have TBFV measurements indicative of obstructive lung disease.

Key Words: Tidal breathing analysis; Lung function; Bronchiolitis; Breastfeeding; Cigarette smoke; Infants

Core Tip: Assessment of lung function using tidal breathing could be beneficial for infants and preschoolers in whom forced respiratory maneuvers cannot be performed. We examined the correlation between breastfeeding and tidal breathing analysis in infants with bronchiolitis, and demonstrated that those who were exposed to cigarette smoke and/or had a shorter duration of breastfeeding showed tidal breathing alterations indicative of obstructive pulmonary disease.

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INTRODUCTION

Bronchiolitis is a viral infection of lower airways that is characterized by substantial inflammation, increased mucus production, and necrosis of small airway epithelial cells[1]. It is the leading cause of infant morbidity and mortality worldwide[2], and represents a significant burden for the healthcare system, the family, and society[3]. Infants with co-existing conditions, such as prematurity and cardiopulmonary disorders, are at higher risk of developing more severe bronchiolitis[3]. Moreover, environmental factors such as smoking exposure, indoor and outdoor pollution[4], and lack of breastfeeding[5] may significantly increase susceptibility to the disease.

The favorable effects of breastfeeding are indisputable, and no other practice can drastically promote infant's health in the short- and long-term[6]. Comprehensively, there is some evidence of the consistent advantageous impact of breastfeeding on increasing forced vital capacity (FVC)[7]. Early life nutrition with breast milk as the initial food for newborns is considered 'the best' due to its beneficial effects on overall health, along with improved lung function. A previous study showed a link between breastfeeding and lung function in school-age children, namely, greater forced expiratory flow at 50% (FEF50), particularly in those who breastfed longer than 3 mo including children of mothers with asthma[8]. Regarding bronchiolitis, current evidence suggests that breastfed infants have a clear immunological advantage compared with their formula-fed peers[9]; exclusive breastfeeding has been shown to decrease the requirement for oxygen supplementation, the length of hospital stay, and the risk of respiratory failure in infants with more severe forms of the disease[9]. However, despite the clear clinical advantages, less is known about the effects of

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breastfeeding on the pulmonary function of infants with acute bronchiolitis.

There is some evidence indicating that tobacco smoke exposure in children decreases lung function and augments airway hyperresponsiveness, predisposing infants to a more severe clinical course of infection compared to unexposed peers[4]. Similarly, studies have shown that maternal smoking during pregnancy is related to bronchiolitis[4,10]. Overall, pregnancy and subsequent parenthood can become major motivators for mothers and caregivers to permanently quit this detrimental practice.

Although lung function testing at bedside is notoriously difficult in infancy[11], recent evidence suggests that tidal breathing flow-volume (TBFV) measurement and analysis are feasible[11,12]. In particular, the ratio of time to peak expiratory flow to total expiratory time (tPEF/tE) decreases in obstructive lung disorders[10], providing important information on the underlying pathophysiological mechanisms and extent of lung injury[11,12].

The aim of this study was to assess the effects of breastfeeding on the lung function of infants who recovered from acute bronchiolitis. We hypothesized that breastfeeding may have favorable effects on baseline tPEF/tE values and/or tPEF/tE reversibility after bronchodilation, independent of other confounding factors.

MATERIALS AND METHODS

Patients

This observational, cross-sectional study was performed between September 2016 and April 2018 in the Pediatric Department of the University General Hospital of Alexandroupolis (Alexandroupolis, Greece). All infants aged 2-12 mo and hospitalized with bronchiolitis were eligible to participate. Bronchiolitis was defined according to the relevant history and physical examination (fever, cough, tachypnoea, chest recession, wheeze or crackles during auscultation)[3]. Infants with genetic disorders, neuromuscular disorders, craniofacial abnormalities, congenital heart disease, a history of significant prematurity (born at < 32 wk gestational age), or requiring intubation and mechanical ventilation after birth were excluded. The study was approved by the local ethics committee, and parental informed consent was obtained prior to enrollment.

Procedures

On the day of hospital discharge, eligible infants underwent TBFV measurements in the pediatric lung function laboratory using the MasterScreen pediatric respiratory system (Jaeger/CareFusion, Hoechberg, Germany). All infants were tested according to relevant European Respiratory Society/American Thoracic Society guidelines[13-15] during natural sleep after feeding. A minimum of 30 s of natural breathing was recorded to acquire a set of at least 10 regular breaths. The ratio of tPEF/tE was automatically calculated by the system at baseline and 10 min after the administration of 300 mcg salbutamol inhaler *via* an appropriate holding chamber. The metadata of the study population were obtained from the medical records. The weight-for-length *z*-scores were estimated using Centers for Disease Control and Prevention/National Center for Health Statistics norms[16].

Statistical analyses

Continuous variables are expressed as the mean ± SD standard deviation and compared with the Student's *t*-test or one-way analysis of variance (multiple comparisons). Multivariate regression analysis was used to determine the outcome of breastfeeding in terms of gender, history of prematurity, and family history of atopy. All analyses were performed using IBM SPSS version 25 (IBM Corp., Armonk, NY, United States).

RESULTS

A total of 56 infants (35 boys), aged 7.4 ± 2.8 mo, were included in this study. Their characteristics are presented in Table 1. Of them, 21.4% were born prematurely, 12.5% were exposed to tobacco smoke (during pregnancy and/or after birth), and 16.1% had a family history of asthma or atopy. No breastfeeding was reported in 7 infants (12.5%), whereas 23 infants (41.1%) were breastfed less than 2 mo (Table 1).

There were no differences in baseline TBFV measurements between infants who did not breastfeed or breastfed less than 2 mo (Group 1) and those who breastfed longer

Table 1 Characteristics of the study population

Characteristics	
n	56
Age (mo)	7.4 ± 2.8
Male sex, *n* (%)	35 (62.5)
Body weight, kg	7.3 ± 1.6
Body length, cm	65 ± 8.1
Weight-for-length *z*-score	-0.2 ± 2.0
Gestational age, wk	37.9 ± 1.5 (range 35-41)
Prematurity (< 37 wk)	12 (21.4)
Breastfeeding	
No	7 (12.5)
< 2 mo	16 (28.6)
2-6 mo	12 (21.4)
> 6 mo	21 (37.5)
Smoking exposure	
In pregnancy	5 (8.9)
After birth	7 (12.5)
In pregnancy and/or after birth	7 (12.5)
Family history of asthma/atopy	9 (16.1)

Values are mean ± SD or number of cases (%).

than 2 mo (Group 2) (Table 2). Conversely, infants in Group 1 had a significantly higher change in tPEF/tE after bronchodilation compared with those in Group 2 (12% ± 10.4% *vs* 0.9% ± 7.1%; $P < 0.001$) (Figure 1A). The tPEF/tE reversibility was also higher in infants exposed to tobacco smoke during pregnancy and/or after birth (Figure 1B). There was a clear dose-response relationship between the reversibility of tPEF/tE and the duration of breastfeeding ($P < 0.001$) (Figure 2).

Multivariate regression analysis showed that infants who breastfed less (beta -0.335, $P = 0.010$) or were exposed to cigarette smoke (beta 0.353, $P = 0.007$) had a greater change in tPEF/tE after bronchodilation, independent of sex, prematurity, and family history of asthma or atopy (Table 3).

DISCUSSION

In this study, we demonstrated that infants who recovered from acute bronchiolitis and had a shorter duration of breastfeeding or were exposed to cigarette smoke, had TBFV measurements indicative of obstructive lung disease. Specifically, these infants had a greater percent change in tPEF/TE after bronchodilation, and this effect was independent of other confounding factors such as premature birth and family history of asthma or atopy. Interestingly, there was a clear dose-response relationship between tPEF/tE reversibility and the duration of breastfeeding. Moreover, infants who were exposed to cigarette smoke showed a greater change in tPEF/tE after bronchodilation, independent of sex, prematurity, and family history of asthma or atopy.

Early life exposures may affect the outgrowth of pulmonary system, resulting in an immediate impact on later lung function. Previous studies have highlighted the key role of breastfeeding in terms of larger lung volumes at school age[8,17], suggesting the influence of breastfeeding on respiratory health. In addition, studies have shown that extended and exclusive breastfeeding reduces the risk of wheezing and asthma during infancy, early childhood[17-20], and even in youth[21], functioning as a shield against allergic predisposition. In a recent study of 555 children, forced expiratory volume in 1 s and FVC markedly increased in accordance with breastfeeding duration

Table 2 Baseline tidal breathing flow-volume values according to breastfeeding duration

	BF < 2 mo (*n* = 23)	BF ≥ 2 mo (*n* = 33)	*P* value
Tidal volume, mL/kg	8.6 ± 1.8	8.3 ± 2.1	0.580
Respiratory rate, bpm	46.8 ± 20	44.7 ± 18.4	0.687
Expiratory time, s	0.57 ± 0.21	0.55 ± 0.22	0.735
tPEF/tE, %	35.4 ± 15.5	41.3 ± 13.7	0.139

Values are mean ± SD. BF: Breastfeeding; TBFV: Tidal breathing flow-volume; tPEF/tE: Time to peak expiratory flow to total expiratory time.

Table 3 Factors affecting the % time to peak expiratory flow to total expiratory time change after bronchodilation

	Regression coefficient β	*P* value
Breastfeeding duration	-0.335	0.010
Cigarette smoke exposure	0.353	0.007
Male sex	0.005	0.974
Prematurity	0.031	0.833
Family History of asthma/atopy	0.121	0.379

Multivariable linear regression analysis; the effects of the independent variables were adjusted for each other. tPEF/tE: Time to peak expiratory flow to total expiratory time.

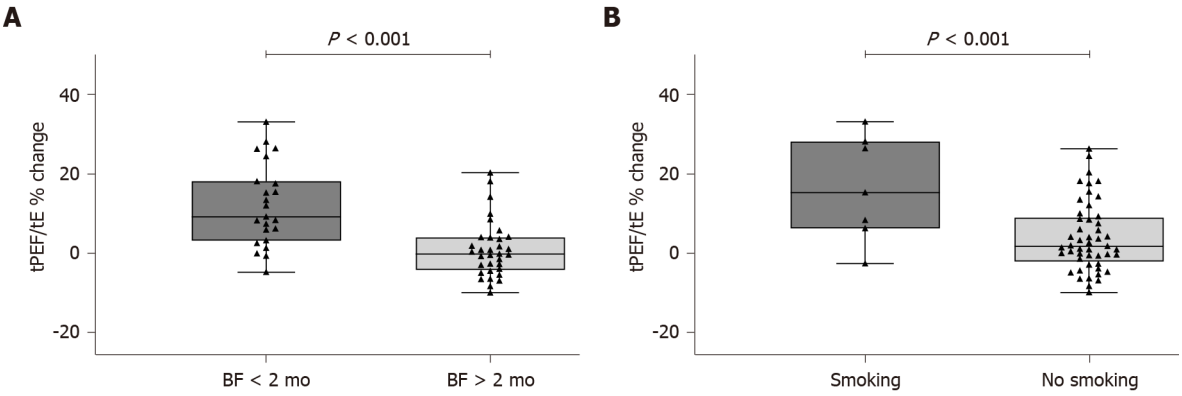

Figure 1 Percent change in time to peak expiratory flow to total expiratory time after bronchodilation in relation to breastfeeding and smoking exposure. A: Breastfeeding; B: Smoking exposure. BF: Breastfeeding; tPEF/tE: Time to peak expiratory flow to total expiratory time.

in those with asthma group[20]. However, in a novel birth cohort of 377 healthy term infants, a link between breastfeeding duration and obstructive or restrictive lung function was not shown[22]. Similarly, in a birth cohort of 620 infants, lung function was assessed at 12 and 18 years of age; duration of breastfeeding did not greatly influence lung function in children with a positive family history for allergic diseases [23]. Thus, whether breastfeeding protects against allergic disease in childhood remains a subject of debate, although exclusive breastfeeding for a duration of 6 mo is the keystone for the promotion of allergy health.

The evaluation of pulmonary function by TBFV analysis has certain benefits in infants in whom forced respiratory flows cannot be performed. Several studies have examined the application of TBFV measurements in a variety of lung disorders and have shown that a reduction in tPEF/tE ratio is suggestive of airway obstruction[11,12,15,24-26]. Zedan *et al*[25] reported that wheezing infants with a positive family history of asthma or who had never been breastfed, displayed significantly lower tPEF/tE compared with healthy controls. Similarly, children and infants with wheezing disorders have a reduced tPEF/tE ratio compared with control subgroups[27,28]. Moreover, studies of infants with chronic lung disease showed impaired lung

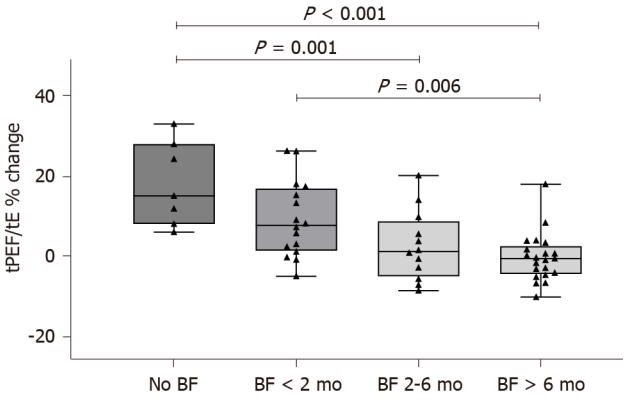

Figure 2 Percent change in time to peak expiratory flow to total expiratory time after bronchodilation in relation to the duration of breastfeeding. BF: Breastfeeding; tPEF/tE: Time to peak expiratory flow to total expiratory time.

compliance and reduced resistance during the first 12 mo of life[29].

Qi *et al*[30] found that wheezing infants had reduced lung function compared with those who were not wheezing, and that tPEF/tE was negatively associated with later poor respiratory outcomes; the deficit in tPEF/tE ratio remained after clinical improvement. However, a study in school-age children with asthma[24] showed no difference in tidal breathing parameters compared with control groups.

In accordance with our main findings, in a preliminary Norwegian study of infants with acute bronchiolitis, the tPEF/tE was reduced but improved after the administration of inhaled adrenaline[31]. By contrast, in another study in infants with bronchiolitis, the researchers did not find any significant differences in tPEF/tE after the administration of nebulized albuterol[32]. In a recent cross-sectional study, tPEF/tE was inversely related to the length of hospital stay and disease severity in infants with bronchiolitis[33], and was also significantly reduced in children exposed to parental smoking[33]. In another study of preschool wheezers, family history of asthma, breastfeeding duration less than 3 mo, and passive smoking, were all significant risk factors for bronchial hyperresponsiveness, defined as tPEF/tE increase > 20% following salbutamol administration[34].

Our study had a number of limitations. First, it was a single-center study with a small sample size; thus the findings cannot be generalized to all populations. Second, a control group was not included in the study design; consequently we could not compare our results with a subgroup of healthy peers. Third, the study design did not include some relevant confounding factors that could affect lung function, such as air pollution.

CONCLUSION

Infants who recovered from acute bronchiolitis and had a shorter duration of breastfeeding or were exposed to cigarette smoke, had TBFV measurements indicative of obstructive lung disease. Tidal breathing is undeniably a complex process, but its measurement during infancy appears promising. To understand the mechanisms by which acute bronchiolitis may affect lung function in infancy and beyond, additional large-scale research is required.

ARTICLE HIGHLIGHTS

Research background

Bronchiolitis is a common viral infection of lower airways and a major cause of morbidity and mortality globally, especially among infants with concomitant medical conditions. The positive effects of breastfeeding are uncontested in infant's health in the short- and long-term.

Research motivation

There are sufficient data suggesting the advantageous effects of breastfeeding on pulmonary function, but less information regarding the influence of breastfeeding on lung function in infants with acute bronchiolitis.

Research objectives

To assess the effects of breastfeeding on tidal breathing flow-volume (TBFV) measurements of infants who recovered from acute bronchiolitis.

Research methods

TBFV analysis was conducted in 56 infants with bronchiolitis prior to hospital discharge. The ratio of time to peak expiratory flow to total expiratory time (tPEF/tE) at baseline and after the administration of 400 mcg salbutamol was assessed using a MasterScreen pediatric respiratory system (Jaeger/CareFusion, Hoechberg, Germany). All infants were tested according to European Respiratory Society/American Thoracic Society guidelines in the middle of natural sleep following feeding. Multivariate regression analysis was used to investigate the outcome of breastfeeding in terms of gender, history of prematurity, and family history of atopy. All analyses were conducted in IBM SPSS version 25.

Research results

There were no differences in baseline TBFV measurements between breastfeeding groups; however, children who breastfed less than 2 mo had a greater tPEF/tE change after bronchodilation (12% ± 10.4% *vs* 0.9% ± 7.1%; $P < 0.001$). Additionally, a distinct dose-response relationship between tPEF/tE reversibility and duration of breastfeeding was shown ($P < 0.001$). In multivariable regression analysis, infants who breastfed less (beta -0.335, $P = 0.010$) or were exposed to cigarette smoke (beta 0.353, $P = 0.007$) exhibited a higher tPEF/tE change after bronchodilation, irrelevant of sex, prematurity, and family history of asthma or atopy.

Research conclusions

Infants who recovered from acute bronchiolitis and had a shorter duration of breastfeeding or were exposed to cigarette smoke, had TBFV analyses indicative of obstructive lung disease, independently of other confounding factors. Tidal breathing is undoubtedly a complicated procedure, but its measurement during infancy is promising.

Research perspectives

Additional large-scale studies are required to determine the mechanisms by which acute bronchiolitis may affect lung function in early infancy as well as later in life.

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META-ANALYSIS

Prevalence of pulmonary hypertension among children with Down syndrome: A systematic review and meta-analysis

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Abstract

BACKGROUND

Pulmonary hypertension (PH) has serious short- and long-term consequences. PH is gaining increasing importance in high risk groups such as Down syndrome (DS) as it influences their overall survival and prognosis. Hence, there is a dire need to collate the prevalence rates of PH in order to undertake definitive measures for early diagnosis and management.

AIM

To determine the prevalence of PH in children with DS.

METHODS

The authors individually conducted a search of electronic databases manually (Cochrane library, PubMed, EMBASE, Scopus, Web of Science). Data extraction and quality control were independently performed by two reviewers and a third reviewer resolved any conflicts of opinion. The words used in the literature search were "pulmonary hypertension" and "pulmonary arterial hypertension"; "Down syndrome" and "trisomy 21" and "prevalence". The data were analyzed by Comprehensive Meta-Analysis Software Version 2. Risk of bias assessment and STROBE checklist were used for quality assessment.

RESULTS

Of 1578 articles identified, 17 were selected for final analysis. The pooled prevalence of PH in these studies was 25.5%. Subgroup analysis was carried out for age, gender, region, year of publication, risk of bias and etiology of PH.

CONCLUSION

This review highlights the increasing prevalence of PH in children with DS. It is crucial for pediatricians to be aware of this morbid disease and channel their

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efforts towards earlier diagnosis and successful management. Community-based studies with a larger sample size of children with DS should be carried out to better characterize the epidemiology and underlying etiology of PH in DS.

Key Words: Down syndrome; Pulmonary hypertension; Prevalence; Trisomy 21; Persistent pulmonary hypertension; Congenital heart disease

Core Tip: The objective of this review is to provide quantitative data on the prevalence of pulmonary hypertension (PH) in pediatric patients with Down syndrome (DS). In addition, we also wish to address the lack of consensus on screening guidelines for PH in DS, as it is frequently missed unless associated with an underlying congenital heart disease. We conclude that children with DS require early echocardiography irrespective of an underlying congenital heart disease. We, therefore, by means of this systematic review would like to increase the vigilance for PH in DS, with the ultimate goal of reducing the morbidity due to PH in these children.

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INTRODUCTION

Down syndrome (DS) was first clinically observed and described by Dr. Down[1] in his report on the "Observations on an ethnic classification of idiots" in 1866. The incidence of DS is approximately 1 in every 733 live births, which makes it the most common human malformation[2,3]. Children with DS are at an increased risk of developing pulmonary hypertension (PH). DS is the most common genetic syndrome associated with PH (with or without congenital heart disease), the others being DiGeorge syndrome, Scimitar syndrome, Noonan syndrome, Dursun syndrome and Cantu syndrome[4]. Regardless of the underlying etiology, PH has debilitating consequences on the health of the child and also reduces life expectancy. Approximately 75% of all deaths in DS may be attributed to pneumonia and infectious lung disease, congenital heart disease (CHD) and circulatory disease (vascular diseases such PH)[5]. There have been no studies estimating the precise disease burden of PH in children with DS even though PH is independently associated with death among children with DS[6]. This reflects the need to provide a multidisciplinary approach for children with DS and PH for better management. Recent recommendations from the pediatric task force of the 6th World Symposium on Pulmonary Hypertension (WSPH) have defined PH in the pediatric age group as a resting mean pulmonary artery pressure (mPAP) > 20 mmHg (decreased from 25 mmHg) in children greater than 3 months of age at sea level and includes children with pulmonary vascular resistance (PVR) ≥ 3 WU[4,7]. PH is classified into 5 groups on the basis of each category sharing similar hemodynamics, pathological findings as well as similar management strategies: pulmonary arterial hypertension (PAH; group 1), PH due to left heart disease (group 2), PH due to lung disease and/or hypoxia (group 3), chronic thromboembolic PH (group 4) and PH with unclear/multifactorial mechanisms (group 5)[8].

The risk factors associated with the development of PH in DS are multifactorial. Chromosomal abnormalities such as trisomy 21 have been attributed to an increased risk of developing PH with an odds ratio of 36 (95%CI: 4.15-312.24), implying a genetic contribution to PH development using univariate logistic regression[9]. The presence of congenital heart disease (CHD) is a major contributing factor to PH in the DS population. Other risk factors include defects in lung development (due to overexpression of anti-angiogenesis genes on chromosome 21)[10], pulmonary hypoplasia [11], endothelial dysfunction[12,13], pulmonary diseases[14-18], gastrointestinal diseases[19] and endocrine abnormalities[20]. At the molecular level, it has been proposed

that increased gene dosage of four interferon receptors encoded on chromosome 21 results in increased interferon activation which may contribute to various disease processes in DS[21]. In addition, high interferon gamma levels have also been observed in pulmonary hypertension and are believed to be responsible for pulmonary vascular remodeling[22]. This probable relationship, however, requires further study.

Herein, we describe the first systematic review and meta-analysis which consolidates our existing knowledge on the prevalence of PH in DS. Our objective was to establish the prevalence of PH in children with DS. This systematic review also aims to provide sufficient evidence which could guide policy-making aimed at the prevention and effective management of PH as well as underpin further research.

MATERIALS AND METHODS

Meta-analysis of observational studies in epidemiology (MOOSE) guidelines were followed for this systematic review[23]. The protocol for this systematic review and meta-analysis was registered at the International Prospective Register of Systematic Reviews (PROSPERO # CRD42020204914).

Search strategy

A two-stage search strategy was used for this study.

Bibliographic database search

Electronic databases (PubMed, Cochrane library, EMBASE, Scopus, Web of Science) were searched. The search was restricted by English language with published studies including human subjects only, but not restricted by date or publication types. Studies with insufficient data such as abstracts only, studies with adult participants, conference papers and duplicate publications were excluded. Studies whose data could not be accessed even after a request from the authors were also excluded. The process of data extraction and quality control was performed independently by two reviewers (DP and PZJ). In the event of a conflict, a third reviewer's (AT) opinion was sought. The last electronic search was carried out on 30th June, 2020. The search strategy included the following: ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("down syndrome"[MeSH Terms] OR ("down"[All Fields] AND "syndrome"[All Fields]) OR "down syndrome"[All Fields] OR ("downs"[All Fields] AND "syndrome"[All Fields]) OR "downs syndrome"[All Fields]) AND prevalence.

Searching other sources

An individual manual search was also performed which included examining the references of all the eligible papers and other related review articles as well as recent conference proceedings or recommendations on PH. Additional studies from these sources were then included in the review, provided they fulfilled the inclusion criteria.

All studies were handled by the literature management software Endnote X7. This was carried out to ensure no duplication. A preliminary screening of studies was performed by 2 independent authors (AT and PZJ). Screening of all titles and abstracts was done, and the full text was studied for any article considered relevant. After the initial round of screening, sorting was carried out again by re-reading all the articles. Methods were adapted as per PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) guidelines for meta-analyses[24].

Eligibility criteria for studies

Any observational study which determined the prevalence of PH in DS was considered for the analysis. These studies needed to mention the number of patients with PH and the number of children with DS who had PH.

Inclusion criteria

(1) All cross-sectional, case–control or cohort studies including children with DS reporting the prevalence of PH; (2) Studies must use either right heart catheterization for diagnosis with the cut-off being mPAP ≥ 25 mmHg or a 2D echocardiogram for determination of pulmonary arterial systolic pressure (PASP) (> 25 mmHg); and (3) All published studies from 1st January 1980 to 30th June 2020 were included.

Exclusion criteria

(1) Studies performed in non-human subjects; (2) Case series, reviews, letters, commentaries and editorials; (3) Studies with insufficient data, abstracts, adult studies, conference abstracts and duplicate publications; and (4) Studies whose key data were not accessible even after a request from the authors.

Selection of studies

Two investigators (PZJ and DP) separately reviewed articles and screened them for eligibility. Full texts were downloaded for any articles which were deemed eligible. The investigators also checked the full texts of each study and studies which met the inclusion criteria were included. A third author (AT) was consulted to resolve any disagreements. A screening test was used to ensure that all review authors reliably applied the selection criteria. Agreement was measured using the kappa (κ) statistic [25].

Data extraction and management

A standard data extraction form was used to retrieve relevant information. Two review authors (PZJ and DP) participated in data extraction independently. PZJ and DP extracted data which included general information (authors, year, and country), study design, diagnostic criteria for PH, and prevalence of PH. In studies where only preliminary data were provided, such as sample size or number of outcomes, other required data were calculated based on these values. Data were extricated using a preconceived and standardized data abstraction form. Studies with un-interpretable data were excluded from the analysis. Level of agreement was ascertained by the κ statistic[25].

Quality appraisal of the studies included

Each included study was evaluated for quality of methodology and risk of bias by two investigators (PZJ and DP) using an adapted version of the Risk of Bias Tool for Prevalence Studies developed by Hoy *et al*[26]. The STROBE checklist[27] was utilized to assess the reporting quality of each study. Reporting of Observational Studies in Epidemiology (STROBE) was performed by two authors. The STROBE statement has a total of 22 items on the checklist. These items relate to various parts of the study such as the article's title and abstract (item 1), the introduction (items 2 and 3), methods (items 4–12), results (items 13–17) and discussion sections (items 18–21), and other information (item 22 on funding). Agreement was measured using the κ statistic[25].

Statistical analysis

Each included study reported the prevalence of pulmonary hypertension as a probability of binominal distribution. Forest plot was used to determine the combined prevalence from the studies and extent of heterogeneity between them. As there was a large difference in the clinical data of patients across the studies, a random-effects meta-analysis was used to pool the data on prevalence[28], after stabilizing the variance of individual studies utilizing the Freeman-Tukey double arc-sine transformation[29]. Heterogeneity of the included studies was tested by Cochran's *Q* test and I^2 index[30]. The degree of heterogeneity was categorized into 3 categories under the I^2 index: heterogeneity lower than 25%, heterogeneity between 25% and 75% and heterogeneity more than 75%. While combining the prevalence of PH, a random effects model was used due to the wide heterogeneity among the studies. The impact of each study was also evaluated by sensitivity analysis. Subgroup analysis of PH was carried out to ascertain the cause of heterogeneity. Sub-group analysis was performed on the basis of geographical distribution (Asia *vs* non-Asia), age, sex, etiology, quality of the studies, year of publication and diagnostic methods. Meta-regression model (method of moments) was performed on the basis of the year of publication of studies[31]. Publication bias was identified by Egger and Begg's tests. Data were analyzed using Comprehensive Meta-Analysis Software Version 2 and values lower than 0.05 were considered to be significant. High-resolution forest plots, with random effects, were separately created[32].

RESULTS

Characteristics of the included studies

Initially, a total of 1578 articles were identified (Figure 1). After elimination of dup-

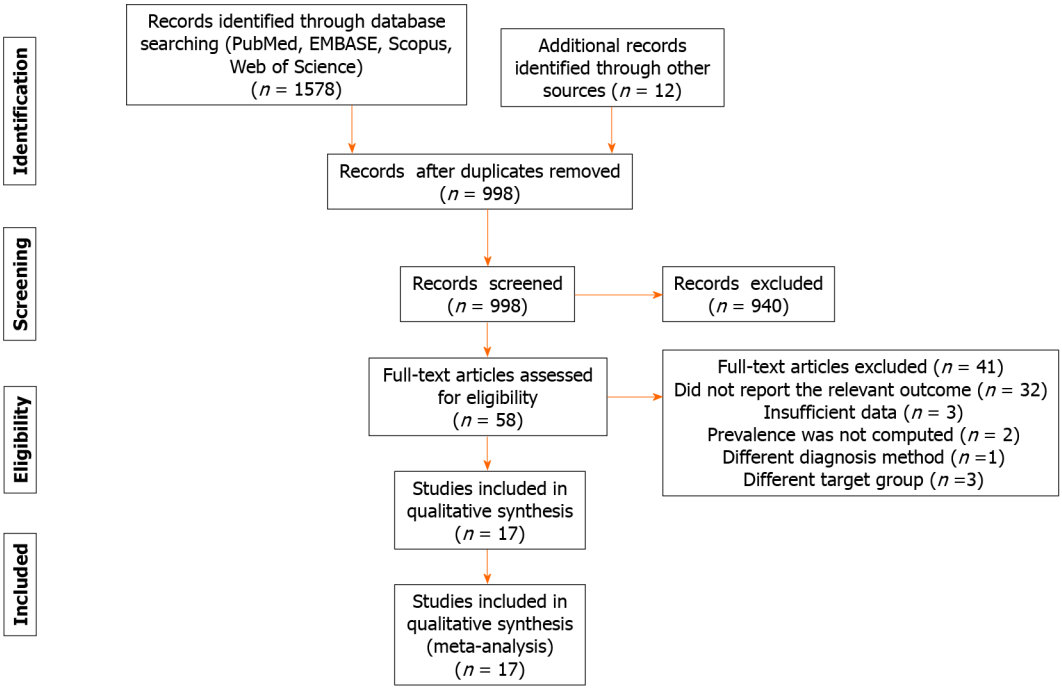

Figure 1 PRISMA flow chart diagram describing the process of identification and selection of studies for inclusion in the review.

licates, screening titles and abstracts, 940 papers were found to be completely irrelevant and excluded. Agreement between investigators on abstract selection was high ($\kappa = 0.90$, $P < 0.001$). Full texts of the remaining 58 studies were scrutinized for eligibility, among which 41 studies were excluded for various reasons. The investigators were in complete agreement for full text selection. Overall, seventeen studies were included for review in the meta-analysis (Figure 1).

All 17 studies noted the prevalence of PH without any analysis and no study reported the incidence of PH. The studies included were published from 2003 to 2020. Ten studies collected data retrospectively and seven studies collected the data prospectively. Study characteristics are summarized in Tables 1 and 2. The age of the patients ranged from neonate to 21 years. The studies differed in sample size varying from 35 to 1252 subjects with a summated sample size of 5393.

Quality of studies

The quality assessment results are presented in Table 3. No study met all criteria of the quality assessment score. Study quality varied from 10 to 17 as per the STROBE criteria. A score of < 14 was considered low quality, and > 14 was considered good/fair quality. The quality of reporting was low for two studies[33,34] and was good/fair for the remaining 15 studies. The most common limitations faced during STROBE assessment were inability to gauge the required sample size and poor projection of the results to the general population.

Risk of bias and heterogeneity

Quality assessment was also conducted for each study using the risk of bias assessment tool[26]. Among the 17 included studies (Table 4), there was low risk of bias for six studies (35.30%)[34-39], moderate risk for eight studies (47.05%)[40-47] and high risk for three studies (17.652%)[6,33,48]. Investigators' agreement on quality assessment of studies was high ($\kappa = 0.88$, $P < 0.001$). High heterogeneity was seen amongst the included studies according to Cochrane Q test (Q test; $P = 0.00001$) and I^2 test (98.4%).

Prevalence of pulmonary hypertension in DS children

Prior studies have estimated the prevalence of PH in children with DS to be as high as 6% and 15% at 1 and 10 years of life, respectively, but data from large populations are lacking[44]. A wide disparity was seen among the various studies for PH prevalence. The heterogeneity was high ($I^2 = 97.20\%$, $P < 0.001$). The overall prevalence of the meta-analysis of 17 studies, according to the Der Simonian-Laird random-effects model, revealed that the pooled prevalence of PH among children with DS was 25.5%

Table 1 Characteristics of studies included in the meta-analysis

Ref.	Year	Timing of data collection	Study design	Country	Population size	Cases with PH	Prevalence of PH
De Rubens *et al*[48]	2003	Retrospective	Observational	Mexico	275	41	14.90909
Shah *et al*[33]	2004	Retrospective	Observational	Canada	175	24	13.71429
Cua *et al*[35]	2007	Retrospective	Observational	USA	58	7	12.06897
Weijerman *et al*[40]	2010	Prospective	Cohort	Netherlands	820	25	3.04878
Banjar *et al*[41]	2012	Retrospective	Observational	Saudi Arabia	59	44	74.57
Mourato *et al*[42]	2013	Retrospective	Cross-sectional	Brazil	138	42	30.43478
Sharma *et al*[43]	2013	Prospective	Observational	India	35	18	51.42857
Shrestha *et al*[36]	2013	Prospective	Observational	Nepal	50	21	42
Espinola-Zavaleta *et al*[44]	2015	Prospective	Observational	Mexico city	127	102	80.31496
Bermudez *et al*[34]	2015	Retrospective	Observational	Brazil	1207	57	4.722452
Zonouzi *et al*[45]	2015	Prospective	Cross-sectional	Iran	110	23	20.90909
Joffre *et al*[6]	2016	Retrospective	Observational	France	66	19	28.78788
Okeniyi *et al*[37]	2017	Prospective	Observational	Nigeria	70	14	20
Bush *et al*[38]	2018	Retrospective	Cohort	USA	1252	346	27.63578
Martin *et al*[39]	2018	Retrospective	Cohort	Ireland	121	41	33.8843
Zahari *et al*[46]	2019	Retrospective	Cohort	Malaysia	754	160	21.22016
Alsuwayfee *et al*[47]	2020	Prospective	Cross-sectional	Iraq	76	23	30.26

PH: Pulmonary hypertension.

(95%CI: 17.4%–35.8%). The forest plot is shown in Figure 2.

Stability of the meta-analysis was assessed by sensitivity analysis. The observations remained largely the same. This similarity between the results showed the stability of our meta-analysis. Also, no significant factor influencing the heterogeneity was identified by the sensitivity analysis.

Subgroup analysis was used to reduce heterogeneity. The pooled prevalence of different subgroups is illustrated in Table 5. There were noteworthy differences for subgroups of gender, age group, region, year of publication, risk of bias and etiology of PH ($P < 0.05$). Four articles[35,38,45,47] presented prevalence linked to gender, with a prevalence of 24.3% among males and 26.2% among females. Some studies reported age distribution while others reported prevalence relating to each age group, which made the results difficult to compare. According to age group, 16 studies were sub-grouped into two categories: studies conducted in infants (less than one year) (4 studies), and studies conducted in infants and children (12 studies). The prevalence of PH among studies including infants and children (33.7%; 95%CI: 22.6%-47%) was higher than studies including only infants (13.4%; 95%CI: 6.6%-25.4%). The prevalence of PH among children with DS from the Asian continent (38.4%; 95%CI: 23.7%-55.7%) was higher than non-Asian continents (19.8%; 95%CI: 10.9%-33.2%). The prevalence of PH was higher in studies published after 2011 (29.8%; 95%CI: 20.2%-41.7%) than those published before 2011 (0.09%; 95%CI: 0.04%-20.0%). Subgroup analyses showed the prevalence of PH among children with DS in studies with moderate risk (34%; 95%CI: 16%-57%) and low risk (20%; 95%CI: 9%-37%) to be higher than studies with high risk of bias (17.8%; 95%CI: 11.6%-26.5%). According to the etiology of PH, 7 studies included were divided into two categories *i.e.* with CHD and without CHD. The prevalence of PH attributable to CHD (14.4%; 95%CI: 7%-26.1%) was higher than in those without CHD etiology (8.9%; 95%CI: 4.4%-17.5%). Only one study, Bush *et al*[38] classified the etiologies as per WHO classification[8]. The diagnosis of PH was made in 82% of children, with 45% being associated with CHD, and 38% having persistent pulmonary hypertension of the newborn (PPHN). The Egger weighted regression statistics ($P = 0.94$) and Begg rank correlation statistics ($P = 0.45$) indicated no evidence of publication bias. There was no sign of publication bias and asymmetry in the funnel plot (Figure 3). The meta-regression model in Figure 4 shows that the prevalence of PH among children with DS has increased in recent years. However, this relationship was

Table 2 Screening methodology of the included studies

Ref.	Diagnosis established by	Age group, (mean ± SD, yr)	Sex (M:F)	Diagnostic criteria for PH
De Rubens *et al*[48]	Echocardiography	Less than 16 yr	1:1	NM
Shah *et al*[33]	Echocardiography	Newborn	10:7	Right to left shunting at ductal or atrial level in the absence of severe pulmonary parenchymal disease
Cua *et al*[35]	Echocardiography	Neonate	25:33	Right-to-left shunt at the ductal level or flattening of the IVS in the absence of a PDA
Weijerman *et al*[40]	Echocardiography	Neonate	NM	Right-to-left shunt at the ductal level
Banjar *et al*[41]	Echocardiography	3.3 ± 3.9	34:25	> 50% of systolic systemic pressure
Mourato *et al*[42]	Echocardiography	Infant	61:77	mPAP > 25 mmHg
Sharma *et al*[43]	Echocardiography	Less than 12 yr	4:3	mPAP >25 mmHg
Shrestha *et al*[36]	Echocardiography	4 mo to 12 yr	1:1.4	NM
Espinola-Zavaleta *et al*[44]	Echocardiography	Up to 18 yr	64:63	mPAP > 30 mm Hg
Bermudez *et al*[34]	Echocardiography	Up to 11 mo	NM	mPAP > 25 mmHg
Zonouzi *et al*[45]	Echocardiography	1 mo-20 yr	53:57	NM
Joffre *et al*[6]	Echocardiography	1mo-16 yr	2:1	NM
Okeniyi *et al*[37]	Echocardiography	3 mo-9 yr	3:4	NM
Bush *et al*[38]	Echo or catheterization	Birth to 21 yr	688:564	mPAP > 25 mmHg; IVS flattening, RV dilation, or presence of RV hypertrophy
Martin *et al*[39]	Echocardiography	Neonate	62:59	Right to-left shunt across the PDA, IVS bowing into the left ventricle, or the presence of a TR jet
Zahari *et al*[46]	Echocardiography	Newborn	189:225	IVS flattening, a dilated main pulmonary artery, and dilated right cardiac chambers
Alsuwayfee *et al*[47]	Echocardiography	< 15 yr	0.85:1	mPAP > 25 mmHg

PH: Pulmonary hypertension; IVS: Interventricular septum; PDA: Patent ductus arteriosus; TR: Tricuspid regurgitation; PAP: Pulmonary artery pressure; NM: Not mentioned.

not statistically significant (meta-regression coefficient: 0.0947, 95%CI: -0.035 to 0.22, P = 0.153).

DISCUSSION

Children with DS are known to be at a higher risk of developing pulmonary hypertension (PH). This can be attributed to underlying CHDs, idiopathic PH and partly due to upper airway obstruction[49]. Other factors which may contribute to a higher risk include genetics, anatomical characteristics of the pulmonary vasculature, pulmonary hypoplasia, obstructive airway diseases, chronic infection and neuromuscular underdevelopment. Increased pulmonary blood flow due to underlying heart disease with left to right shunt increases the sheer stress on the endothelial lining and may induce endothelial dysfunction, eventually resulting in pulmonary vasculature remodeling. The sheer stress also leads to pathologic changes in the vessel wall such as endothelial cell proliferation and thickening of the vessel wall. The pathologic changes also include alveolar under-development. The production of prostacyclin and nitric oxide is diminished in DS, but endothelin-1 and thromboxane are elevated[50]. The lifetime incidence of PH in children with DS remains unknown [38]. Patients with DS have increased mortality due to pulmonary vascular disease with a standardized mortality odds ratio of 3.83 (95%CI: 3.60-4.07)[51].

In light of this, this is the first systematic review evaluating PH in children with DS. Despite extensive literature, there is large heterogeneity in the prevalence of PH in DS. The heterogeneity arises from multiple overlapping etiologies which are commonly associated with DS. The present study found the overall prevalence to be 25.5%

Table 3 Quality assessment of the included studies

STROBE quality of reporting						
Ref.	The title and abstract (Item 1)	Introduction (Item 2-3)	Methods (Item 4-12)	Results (Item 13-17)	Discussion and other information (Item 18-22)	Quality score (0-22)
De Rubens *et al*[48]	1	2	6	4	2	15
Shah *et al*[33]	0	2	5	2	3	12
Cua *et al*[35]	1	2	5	3	4	15
Weijerman *et al*[40]	1	2	4	4	4	15
Banjar *et al*[41]	1	2	4	4	4	15
Mourato *et al*[42]	1	2	5	2	4	14
Sharma *et al*[43]	1	2	5	3	4	15
Shrestha *et al*[36]	1	2	4	4	4	15
Espinola-Zavaleta *et al*[44]	1	2	5	3	3	14
Bermudez *et al*[34]	1	2	4	2	4	13
Zonouzi *et al*[45]	1	2	4	3	5	15
Joffre *et al*[6]	1	2	5	2	4	14
Okeniyi *et al*[37]	1	2	5	3	3	14
Bush *et al*[38]	1	2	5	3	5	16
Martin *et al*[39]	1	2	5	4	4	16
Zahari *et al*[46]	1	2	5	3	4	15
Alsuwayfee *et al* [47]	1	2	5	4	4	16

(95%CI: 17.4%-35.8%) from a pool of 17 studies which met the inclusion criteria. This finding has shown concordance with multiple studies[6,37,38,45,46]. In order to reduce heterogeneity, subgroup analysis was carried out according to age, gender, region, etiology of PH and bias. In neonates, the incidence of PH is estimated at 2 per 1000 live births, which is notably less when compared to that observed in neonates with DS[52]. Earlier studies assessing PH in children with DS report an incidence ranging from 1% to 5%, with the majority of these infants being classified as having pulmonary arterial hypertension (PAH). More recent studies, however, have noted a much higher figure ranging between 27% and 34%[38]. Additionally, children with DS have an increased risk of developing PPHN even in the absence of structural heart disease and should be followed up until resolution of PH[33].

According to age group, 16 of the included studies were divided into 2 subgroups: studies conducted in children < 1 year of age (7 studies) and studies conducted in children > 1 year of age (9 studies). The prevalence of PH in DS was highest in children followed by infants and neonates. This contrast was highlighted because of the identification that infants with DS have a higher prevalence of PPHN and abnormalities of developmental lung disorders (*e.g.*, reduced alveolarization, decreased vessel density, persistence of the double-capillary network and hypertensive arterial remodeling). This finding enforces that increasing age is a distinct risk factor for developing PH and its complications. Late PH is also important in contributing to adverse outcomes in children and adults with DS[38]. In the current review, 4 studies analyzed the prevalence of PH according to gender. The overall prevalence in females was 26.2% and in males it was 24.3%. Although, the prevalence was higher in females the difference was not statistically significant. When country of origin was considered in the analysis, it was noted that Asian countries showed a higher prevalence as compared to non-Asian countries (38.4% *vs* 19.8%). Studies published before 2011 recorded a pooled prevalence of only 9.4%, whereas after 2011 the prevalence was found to be 33%. This increased prevalence can be attributed to reasons such as increased survival of children with DS and CHD and increased birth rates. In a study conducted by Yang *et al*[51], among 17,897 patients with DS, the median age at death had increased from 25 years in 1983 to 49 years in 1997. A large percentage of PH in DS

Table 4 Risk of bias assessment of included studies using the Hoy *et al*[26] 2012 tool

Ref.	Representation	Sampling	Random selection	Non response bias	Data collection	Case definition	Reliability and validity of study tool	Method of data collection	Prevalence period	Numerator and denominator	Summary assessment
De Rubens *et al*[48]	HR	HR	HR	HR	HR	HR	LR	LR	HR	LR	HR
Shah *et al*[33]	HR	HR	HR	HR	HR	HR	LR	LR	HR	LR	HR
Cua *et al*[35]	LR	LR	LR	LR	LR	LR	LR	LR	HR	LR	LR
Weijerman *et al*[40]	HR	HR	HR	HR	HR	LR	LR	LR	HR	LR	MR
Banjar *et al*[41]	HR	HR	LR	HR	LR	HR	LR	LR	LR	LR	MR
Mourato *et al*[42]	HR	HR	HR	HR	LR	LR	LR	LR	HR	LR	MR
Sharma *et al*[43]	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	LR
Shrestha *et al*[36]	LR	LR	LR	HR	LR	LR	LR	LR	HR	LR	LR
Espinola-Zavaleta *et al*[44]	LR	LR	LR	HR	HR	HR	LR	LR	HR	LR	MR
Bermudez *et al*[34]	LR	LR	HR	HR	LR	HR	LR	LR	HR	LR	MR
Zonouzi *et al*[45]	HR	HR	HR	HR	LR	HR	LR	LR	HR	LR	MR
Joffre *et al*[6]	HR	HR	HR	HR	HR	HR	HR	HR	LR	LR	HR
Okeniyi *et al*[37]	LR	LR	LR	HR	HR	LR	LR	LR	HR	LR	LR
Bush *et al*[38]	LR	LR	LR	HR	HR	LR	LR	LR	HR	LR	LR
Martin *et al*[39]	LR	LR	LR	HR	HR	LR	LR	LR	HR	LR	LR
Zahari *et al*[46]	HR	LR	HR	HR	LR	HR	LR	LR	HR	LR	MR
Alsuwayee *et al*[47]	HR	HR	HR	HR	LR	LR	LR	LR	LR	LR	MR

HR: High risk; LR: Low risk; MR: Moderate risk (LR: 0-3; MR: 4-6; HR: 7-9).

can be attributed to the concomitant presence of CHDs. Laursen *et al*[53] in 1976, found that the incidence of PH in patients with DS and CHDs to be just 2%, whereas a study conducted by Bush *et al*[38] in 2018 found the incidence of PH in DS to be as high as 28%. The incidence was noted to increase to 45% in the presence of a co-morbid CHD. They also noted that the higher age group in their study may be responsible for the higher incidence.

The risk of bias was high in 3 studies with the prevalence of PH being 17.8%, 6 studies had low risk of bias with a prevalence of 20% and 8 studies with moderate risk showed a prevalence of 34%. There were 7 studies which assessed the prevalence of PH in children with DS with an underlying CHD. These studies had a prevalence of 14.4% while studies having no underlying CHD (7 studies) had a prevalence of 8.9%. Patients with an underlying CHD showed a higher prevalence of PH. Other studies have observed similar findings. Smith *et al*[54] reported that DS patients had a higher prevalence of PH with or without an underlying CHD and the difference between the

Table 5 Prevalence in different subgroups

Stratification group	Number of studies	Total number of subjects	Total number of events	I^2	*P* value	Prevalence	95%CI
Sex							
Male	4	801	210	28.22	0.243	24.3	18.8-30.6
Female	4	695	189	56.44	0.076	26.2	18.8-35.3
Age							
Infant (< 1 yr)	7	3273	356	95.35	0.000	13.4	6.6-25.4
Children (> 1 yr)	9	2061	607	94.68	0.000	33.7	22.6-47.0
Region							
Asia	6	1084	289	93.68	0.000	38.4	23.7-55.7
Not Asia	11	4309	718	97.92	0.000	19.8	10.9-33.2
Studies published							
Before 2011	4	1328	97	93.79	0.000	9.4	4.1-20.2
2011 - 2020	13	4065	910	97.13	0.000	33.0	22.5-45.4
Risk of bias							
High risk	3	516	84	76.20	0.015	17.8	11.6-26.5
Moderate risk	8	2119	437	97.91	0.000	34.0	16.6-57.1
Low risk	6	2758	486	97.63	0.000	20.0	9.3-37.7
Etiology							
Cardiac	7	724	372	97.06	0.000	14.4	7.4-26.1
Non-cardiac	7	724	352	96.63	0.000	8.9	4.4-17.5

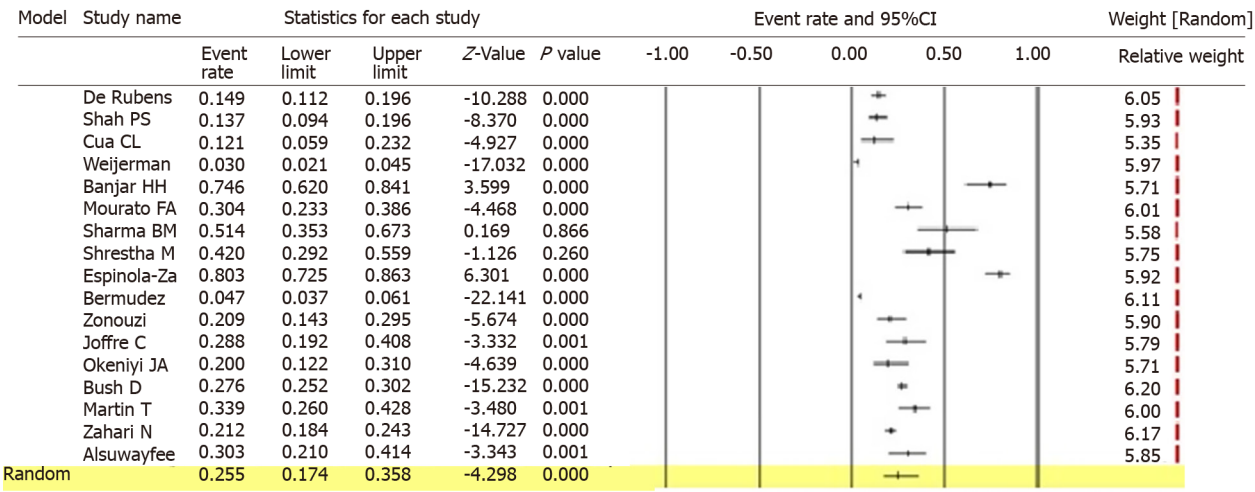

Figure 2 Forest plots of pulmonary hypertension prevalence among children with Down syndrome.

two groups lies in the underlying etiology and the age of presentation. Iwaya *et al*[55] reported a lower pulmonary arterial compliance in individuals with CHD in DS when compared to CHD without DS. A noteworthy association was found between low pre-operative pulmonary compliance in DS and the need for postoperative oxygen therapy after discharge.

Study strengths and limitations

This is the only systematic review and meta-analysis assessing the prevalence of PH in the pediatric population with DS. A comprehensive search was undertaken wherein we included any study that reported the prevalence of PH in children with DS. Despite considerable heterogeneity between studies, our review provides the most

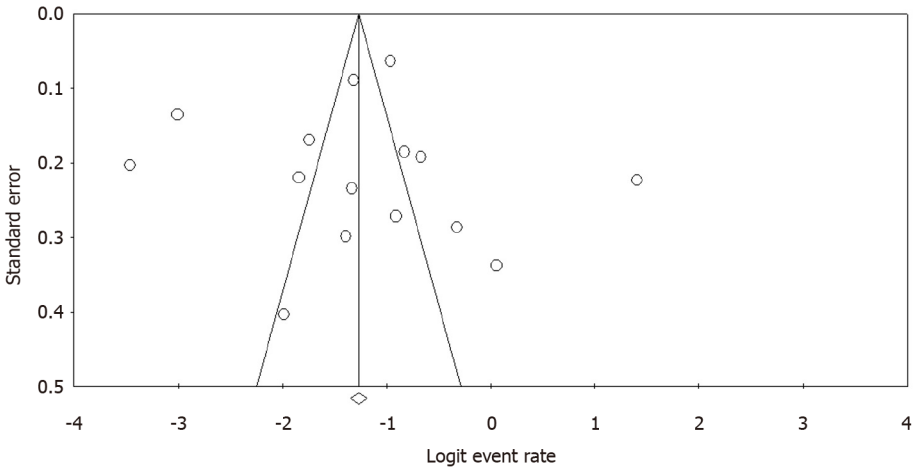

Figure 3 Funnel plots of pulmonary hypertension prevalence among children with Down syndrome.

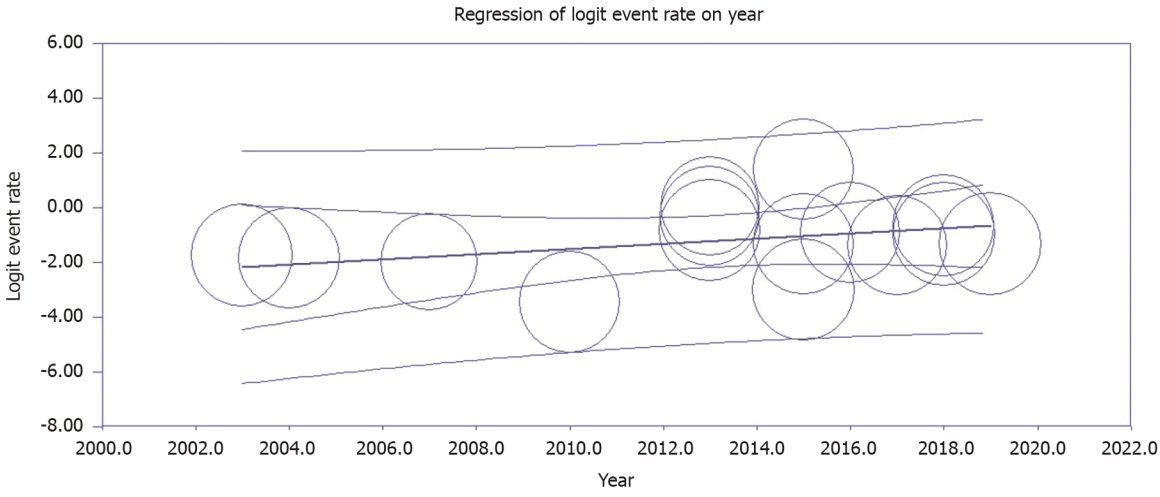

Figure 4 Meta-regression of pulmonary hypertension prevalence based on the year of the study.

comprehensive estimate of PH prevalence in children with DS to date, and most importantly, allows the comparison of prevalence between various groups of interest. Heterogeneity may arise from the data sources, populations examined and subjects with different ages, sex, risk of bias *etc*. This is not unexpected in view of the different populations studied and the nature of variations associated with the different methods used in estimating the prevalence. However, the sensitivity analysis showed that the heterogeneity had no significant impact on the pooled prevalence and a meta-analysis might still provide insights on the overall prevalence. The quality of the results and risk of bias of the studies included was at most, moderate, further highlighting that further such research may have a significant impact on our confidence in the estimate and might also change it. All included studies were observational; therefore, a cause effect relationship cannot be concluded between PH in children with DS. Longitudinal and interventional studies are still needed to determine the nature of any cause and effect relationship. Finally, some methodological limitations of the current meta-analysis were inevitable and should be taken into consideration while interpreting the results. Our study, although strengthened by rigid quality assessment, was limited by the fact that not all studies had classified all the etiologies of PH as per the WHO classification. The paucity of etiological data made it difficult to delineate individual causes of PH in patients with DS. This added to existing heterogeneity while analyzing the exact prevalence of PH in DS. More studies, specifically, ones with community screening for PH in DS are required to come to an exact estimate.

CONCLUSION

This article highlights the increasing prevalence of PH in children with DS. In order to improve the care given and reduce the disease burden, the attending pediatrician has a crucial role in being aware of this morbid disease and to channel his/her efforts towards routine screening of PH, earlier diagnosis and successful management. In addition, there should be early routine echocardiographic screening in children with DS even in the absence of CHDs. Community-based studies with a larger sample size of children with DS may be carried out to better characterize the epidemiology and underlying etiology. Our study reinforces what is already known and provides, in addition, reliable information about the prevalence of PH in DS.

ARTICLE HIGHLIGHTS

Research background

Children with Down syndrome (DS) have an increased likelihood of developing pulmonary hypertension (PH) with serious short- and long-term consequences. Approximately 75% of all deaths in DS may be attributed to pneumonia and infectious lung disease, congenital heart disease (CHD) and circulatory disease (vascular diseases such PH). Despite the overwhelming evidence of morbidity, there have been no studies estimating the precise disease burden of PH in children with DS.

Research motivation

Additional information is required to collate the prevalence rates of PH in order to undertake definitive measures for early diagnosis and management.

Research objectives

The objective of this study is to determine the prevalence of PH in children with DS.

Research methods

The electronic databases (PubMed, Cochrane library, EMBASE, Scopus, Web of Science) were searched. Any observational study which determined the prevalence of PH in DS was considered for the analysis. Data were extricated using a preconceived and standardized data abstraction form. The data were analyzed by Comprehensive Meta-Analysis Software Version 2.

Research results

Of 1578 articles identified, 17 were selected for final analysis. The pooled prevalence of PH in these studies was 25.5% (95%CI: 17.4%–35.8%). Subgroup analysis was carried out for age, gender, region, year of publication, risk of bias and etiology of PH.

Research conclusions

This article highlights the increasing prevalence of PH in children with DS. This is accounted for by the high prevalence of underlying CHDs in these children. In order to improve the care given and reduce the disease burden, the attending pediatrician has a crucial role in being aware of this morbid disease and to channel his/her efforts towards routine screening of PH, earlier diagnosis and successful management. In addition, there should be early routine echocardiographic screening in children with DS even in the absence of CHDs. Community-based studies with a larger sample size of children with DS may be carried out to better characterize the epidemiology and underlying etiology of PH in DS. Our study reinforces what is already known and provides, in addition, reliable information about the prevalence of PH in DS.

Research perspectives

Further studies are required to better characterize the epidemiology, underlying etiology, pathogenesis and risk factors of PH in children with DS.

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CASE REPORT

Treatment of alopecia totalis/universalis/focalis with vitamin D and analogs: Three case reports and a literature review

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Author contributions: Papadimitriou DT was the patient's treating pediatric endocrinologist and contributed to the drafting and editing of the manuscript; Bothou C reviewed the literature and contributed to drafting the manuscript; Dermitzaki E performed the clinical follow-up; Alexopoulos A performed the dermatological evaluations; Mastorakos G reviewed and supervised the manuscript drafting and interpreted the clinical implications; All authors issued final approval for the version to be submitted.

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Abstract

BACKGROUND

Alopecia areata (AA) is an inflammatory disease with autoimmune, environmental, and inherited components directed at the hair follicle, either limited to patchy hair loss over the scalp (Focalis, AF), total loss of scalp hair (Totalis, AT), or total loss of both scalp and body hair (Universalis, AU). Despite multiple treatment modalities, no therapy exists. Vitamin D deficiency in patients with AA/AT/AF influences disease severity and duration, inversely correlating with inflammation histologically.

CASE SUMMARY

Three girls presented with AT (P1), AU (P2), and AF (P3) at the ages of 1, 5, and 5 years, respectively. For P1-P2, all available treatments implemented for 2 years had failed. We started an initial 6-mo repletion with oral cholecalciferol 2000/4000 IU/d, with no apparent effect. Then we attempted immunomodulation using oral calcitriol and its analog paricalcitol. On calcitriol, 0.5 mcg/d P1 regrew hair within 6 mo. After 4 years, a relapse with loss of eyebrow hair was resolved after doubling the calcitriol dose to 0.5 mcg × 2/d; the results have been maintained for 6 years to date. On calcitriol, 0.25 mcg × 3/d P2 led to the development of asymptomatic hypercalcemia-hypercalciuria, which was immediately resolved by

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switching to paricalcitol 2 mcg × 3/d; mild tolerable hypercalciuria was maintained. Hair regrowth was observed at 6 mo, stabilizing only as fur at 12 mo. AF in P3 was resolved completely within 3 mo on a daily high dose (8000 IU) of cholecalciferol.

CONCLUSION

Vitamin D may have immunomodulating therapeutic impact on AT/AU/AF, which needs to be explored with further pilot clinical trials.

Key Words: Alopecia totalis; Alopecia universalis; Alopecia focalis; Calcitriol; Paricalcitol; Vitamin D; Case report

Core Tip: Alopecia areata (AA) is an inflammatory disease with autoimmune, environmental, and inherited components directed at the hair follicle, either limited to patchy hair loss over the scalp (Focalis, AF), total loss of scalp hair (Totalis, AT), or total loss of both scalp and body hair (Universalis, AU). Despite multiple treatment modalities, there is no current therapy. Three girls aged 3, 7, and 5 years with AT, AU, and AF were treated with oral calcitriol, paricalcitol, and cholecalciferol, showing hair regrowth at 6, 6, and 3 mo, respectively but only as fur for P2 with AU. Vitamin D may have an immunomodulating therapeutic impact on AT/AU/AF, which needs to be explored with further pilot clinical trials testing the effectiveness and establishing the optimal form and dosage of vitamin D.

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INTRODUCTION

Alopecia areata (AA) is a non-scarring T-cell mediated autoimmune disease directed at the hair follicle (HF), either limited to patchy hair loss over the scalp (Focalis, AF), total loss of scalp hair (Totalis, AT), or loss of both scalp and body hair (Universalis, AU). Its prevalence among the young and adult population is 0.7%-3.8%, significantly affecting patients' lives and having psychosocial implications. Management of the disease can be challenging, and despite multiple treatment modalities, no successful treatment is available. Pediatric age and more extensive disease with resistance to initial therapies with corticosteroids may sometimes benefit from a cocktail of established therapies. The likelihood of complete spontaneous regrowth in AA is estimated to be less than 10%, but even then, relapses are common and frustrating[1].

HF is a micro-organ with its own immune and hormonal microenvironment. During the anagen segment of the hair cycle, HF epithelium generates and maintains an area of immune privilege, which is mainly characterized by the low expression of major histocompatibility complex class Ia antigens and local production of immunosuppressive agents. This HF immune privilege (HFIP) is important for the protection of anagen- and melanogenesis-associated antigens from immune recognition by autoreactive CD8+ T cells. The collapse of mechanisms that maintain the HFIP renders the HF susceptible to inflammatory assault, contributing to the development of AA, while growing evidence implicates interferon gamma in triggering HFIP collapse[2].

The role of vitamin D in the proliferation and differentiation of keratinocytes has been extensively studied and well established in the literature. Vitamin D is synthesized in the epidermal keratinocytes from 7-Dehydrocholesterol by ultraviolet B light (290-315 nm) or is acquired through the diet and dietary supplements[3,4]. Further hydroxylation in the liver leads to 25-hydroxyvitamin-D3 (25OHD3) and subsequently in the kidney to the active hormone 1-25-dihydroxyvitamin-D3 (1-25(OH)2D3, calcitriol). The role of the vitamin D receptor (VDR) in the hair cycle was

first suggested by the observation of alopecia in patients with type II vitamin D dependent rickets (VDDR IIA), an autosomal recessive disorder that, due to a defect in the VDR, is characterized by hypokalemia, hypophosphatemia, hyperparathyroidism, rickets, osteomalacia, dental caries, and alopecia universalis[5]. Patients with VDDR IIA have normal hair at birth, possibly because they have normal HF morphogenesis, but they lose their hair between 1 and 3 mo of age. Histological results of VDDR IIA alopecia include a normal infundibular portion of the HF but the lower two-thirds of the HF, below the level of the sebaceous gland, is replaced by irregular epithelial structures and dermal cysts.

Recent studies in mice and *in vitro* support the pivotal role of VDR in the postnatal maintenance of the HF. In the late anagen and catagen phases, there is an increase in VDR expression, which is associated with the decreased proliferation and increased differentiation of keratinocytes, making the presence of VDR a prerequisite for maintenance of the normal hair cycle[6]. However, the roles of vitamin D and the VDR in the hair cycle have not been completely elucidated, and clinical therapies for hair disorders have not been established. However, vitamin D is an important immunomodulator, and vitamin D deficiency has been reported in many autoimmune diseases [7]. Recent retrospective studies among AA patients compared to controls reveal significantly reduced vitamin D levels among patients[8,9].

We present three cases with AT/AU/AF that emphasize the pivotal role of treatment with cholecalciferol, the active hormone calcitriol, and its analogue paricalcitol.

CASE PRESENTATION

Chief complaints

Sudden and total hair loss in the scalp, both the scalp and body, and in multiple focalized areas of the scalp in three girls aged 1, 5, and 5 years, respectively.

History of present illness

Two girls diagnosed with AT and AU based on clinical examination[10], who experienced sudden (within 3 mo) and total hair loss at the age of 1 and 5 years, presented to our pediatric endocrine unit at the ages of 3 (patient #1, P1) and 7 years (patient #2, P2), respectively. For 2 years, all available local and systemic treatments including oral methotrexate had been tried by pediatric and adult dermatology clinics with no results.

A third girl aged 5 years (patient #3, P3) presented with sudden (within the last month) hair loss compatible with AF.

History of past illness

None of the patients were suffering from other chronic dermatological diseases (vitiligo and psoriasis) or other systemic diseases such as diabetes mellitus, anemia, hypothyroidism or hyperthyroidism, systemic lupus, rheumatoid arthritis, chronic renal or liver disease, also autoimmune polyendocrinopathy type 1 was also excluded with the necessary laboratory testing. In P3, although there was normal thyroid function with negative anti-thyroid peroxidase (TPO) and anti-thyroglobulin (Tg) antibodies, signs of Hashimoto's thyroiditis were shown in thyroid ultrasonography (U/S) performed by a pediatric radiologist. All three girls were vitamin D-deficient with vitamin D levels (25OHD3) of 60 nmol/L (24 ng/mL) in P1, 50 nmol/L (20 ng/mL) in P2, and 42.5 nmol/L (17 ng/mL) in P3, and normal calcium metabolism and parathyroid hormone (PTH) (PTH < 45 ng/mL)[11]. Zinc, B12, vitamin A, vitamin E, and ferritin levels were within normal range in all patients, also with negative celiac serology.

Personal and family history

None of the patients nor any first-degree family members were suffering from other chronic dermatological diseases (vitiligo and psoriasis).

Physical examination

In P1, there was complete absence of scalp hair and eyebrows. In P2, there was complete absence of body hair. In P3, five localized areas had complete hair loss at the scalp, with a diameter of 3-5 cm, along with a palpable goiter (Figure 1). An experienced pediatric dermatologist found no apparent focal or systemic dermatological

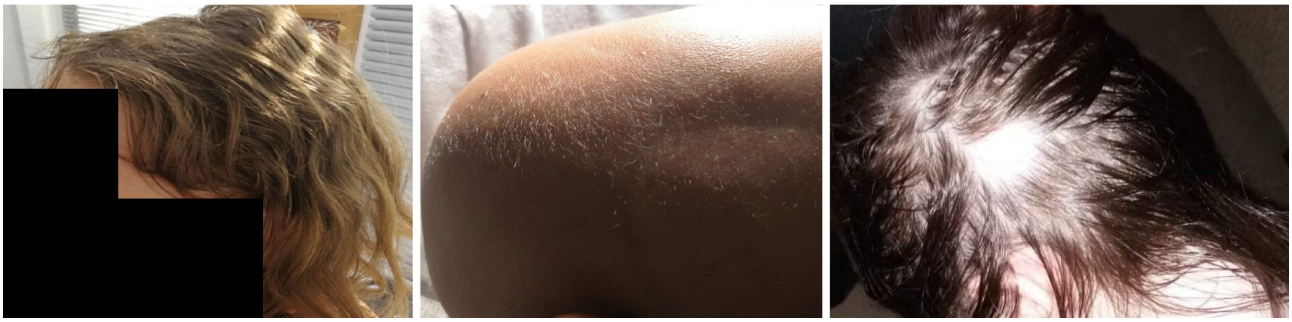

Figure 1 Hair regrowth in the alopecia totalis case (P1, top) and the alopecia universalis case (P2, middle); and presentation of the alopecia focalis case (P3, bottom).

cause in any of the girls, with absence of signs of skin or nail candidiasis, to exclude the possibility of autoimmune polyglandular syndrome.

Laboratory examinations

All three girls were vitamin D-deficient with vitamin D levels (25OHD3) found 60 nmol/L (24 ng/mL) in P1, 50 nmol/L (20 ng/mL) in P2 and 42.5 nmol/L (17 ng/mL) in P3, with the rest of the calcium metabolism and PTH being normal (PTH < 45 ng/mL)[11]. Zinc, vitamin B12, vitamin A, vitamin E, and ferritin levels were within normal range in all patients, also having a negative serology negative for celiac disease.

Imaging examinations

A thyroid ultrasound was performed by a pediatric radiologist. In P3, although there was normal thyroid function with negative anti-TPO and anti-Tg abs, signs of Hashimoto's thyroiditis were found.

FINAL DIAGNOSIS

P1 had AT, P2 AU and P3 AF.

TREATMENT

As P1 and P2 were vitamin D-deficient, we started an initial 6-mo repletion with oral cholecalciferol 2000/4000 IU/d at the upper tolerable daily dose, according to the Endocrine Society Clinical Practice Expert Guideline Committee, *i.e.* infants < 1-year 2000 IU daily and children 1-18 years 4000 IU daily[12] (https://www.endocrine.org/clinical-practice-guidelines/vitamin d deficiency), with no apparent effect on hair growth. Then, based on the previous experience of our group we attempted to induce immunomodulation by oral calcitriol[13-15] in P1 and P2, while both girls were continuously supplemented with cholecalciferol 2000 and 4000 IU p.o., respectively.

Active forms of vitamin D, such as calcitriol (1,25(OH)2 D, the biologically active form of vitamin D), and its up to 10 times less calcemic analog paricalcitol[16], are used to treat secondary hyperparathyroidism occurring in patients with kidney disease, leading to bone disease. Since they have different effects on calcium metabolism, experience in their use as well as special precautions are required (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c3d5546b-ccd4-4988-9d86-9f0b29e12128; https://www.mayoclinic.org/drugs-supplements/paricalcitol-oral-route/precautions/drg-20073059?p=1).

OUTCOME AND FOLLOW-UP

Treatment with 0.5 mcg/d P1 grew hair within the first 6 mo of treatment (except a small region at the rear of the scalp; Figure 1). After 4 years, there was a relapse with loss of eyebrow hair, which was resolved within 3 mo after raising calcitriol dose at 0.5

× 2 mcg/d. The result has been maintained for 7 years now since treatment initiation with normal calcium metabolism: calcium (Ca) 10.1 mg/dL (normal range: 8.5-10.5 mg/dL), phosphorus (P) 5.1 mg/dL (normal range: 3.5-5.5 mg/dL), alkaline phosphatase (ALP) 318 IU/L (normal range: 199-440 U/L), parathyroid hormone (PTH) 26 pg/mL (normal < 45 pg/mL), 25OHD3 41 ng/mL (normal range: 30-150 ng/mL), 1-25 (OH)2D3 30 ng/mL (normal range: 18-80 pg/mL) and normal 0.08 Ca/Cr ratio in a 2 h morning urine sample (normal range: < 0.22).

Treatment with 0.25 mcg × 3/d p.o. P2 developed asymptomatic hypercalcemia – hypercalciuria (Ca 14 mg/dL, Urine Ca/Cr 1.37 in a 2-h morning sample) within 1 mo and was immediately switched to an even higher corresponding dose of paricalcitol [17] at 2 mcg × 3/d p.o. Then calcium metabolism normalized: Ca 9.8 mg/dL, P 3.8 mg/dL, ALP 146 IU/L, PTH 22.4 pg/mL, 25(OH)D 152.5 nmol/L (61 ng/mL), 1-25 (OH)2 D3 38 ng/mL, apart from mild hypercalciuria (Ca/Cr 0.5 in a 2-h morning urine sample), closely monitored and with normal kidney U/S every 6 mo. Hair regrowth including scalp hair, eyebrows and eyelashes was noted by 6 mo but maintained at 12 mo only as fur (Figure 1). With no further improvement, paricalcitol treatment was discontinued at 12 mo with a complete subsequent relapse of AU.

In P3, treatment with high dose cholecalciferol p.o. (8000 IU/d) completely resolved all focalized alopecia areas within 3 mo with normal hair regrowth at all sites and 25(OH)D levels restored at 155 nmol/L (62 ng/mL). At 6 mo dermatological examination of the scalp was completely normal. Cholecalciferol substitution was continued with a maintenance dose of 4000 IU/d, which does not require medical supervision according to the Endocrine Society Expert Committee guidelines, in order to maintain 25(OH)D levels 100-150 nmol/L[12]. Subsequent follow-ups for 2 years were uneventful.

DISCUSSION

We present three cases of AT/AU/AF treated with oral calcitriol, its analogue paricalcitol, and high-dose cholecalciferol. Almost complete hair regrowth including scalp hair and eyebrows was accomplished in the girl with AT on calcitriol treatment. A relapse was avoided by raising the calcitriol dose and the patient can be considered cured, with the result being maintained for 7 years now, having a beneficial effect on the girl's well-being. Treatment with calcitriol is being continued though, as calcium metabolism is completely normal, and the family wishes to maintain it being afraid of a possible relapse. In the AU case, calcitriol caused hypercalcemia – hypercalciuria and was switched to paricalcitol, a less calcemic analog. While hair regrowth was noted by 6 mo of treatment with even eyelashes being temporarily restored, at 12 mo scalp hair was still as fur, leading to treatment discontinuation and subsequent complete AU relapse. In the AF case, early onset high dose daily cholecalciferol treatment was successful, restoring completely alopecia areas with no further relapses. Undoubtedly, just three cases do not suffice to suggest generalized use of the presented approach. Nevertheless, the possible implications of vitamin D in the clinical care of patients with AT/AU/AF, as in autoimmune disorders in general, are being examined and discussed. Using high dose cholecalciferol, calcitriol and paricalcitol, we aimed to exert immunomodulatory effects on T-cells while upregulating the expression of VDR on HF and epidermal keratinocytes. For the safety of the off-label use of calcitriol and paricalcitol we based our approach on the previous experience of our group[13,14] and also on published experience of pediatric patients with chronic kidney disease and hyperparathyroidism[18,19], closely monitoring our patients.

It is well established that vitamin D reduces the function and differentiation of T-helper 17 cells, down-regulates the T-helper 1 cells and increases the action of T-regs, resulting in immunomodulation[7,20]. AT/AU, as an inflammatory disease with autoimmune, environmental, and inherited components, is characterized by imbalance of the above-mentioned parts of the immune system. Previous work of our group has shown the negativation of Type 1 associated autoantibodies after treatment with oral calcitriol[13] but also practically the cure of severe atopic dermatitis, also an autoimmune disease, with calcitriol and its analogue paricalcitol[21] a synthetic analogue with 3 times less binding affinity to the VDR but 10-times less effect on calcium metabolism per se[16].

Regarding the role of vitamin D and its receptor (VDR) in hair, it is well established that VDR is expressed in the outer root sheath (ORS), HF bulb, and the sebaceous gland in the HF and participates in differentiation of HFs[6]. VDR knock out mice (VDR KO) have been proved to suffer from alopecia areata[22]. VDR expression is

decreased in HF and epidermal keratinocytes in AA leading to suppression of Wnt/beta catenin signals and cell differentiation[23]. This downregulation of VDR could be explained either due to the local inflammation that leads to loss of the VDR expression or due to the vitamin D deficiency. This is supported by the hypothesis that vitamin D deficiency is a stimulus for the local inflammation and vice versa, which could lead to a vicious cycle in the chronic status of the disease. Re-appearance of the VDR on HF was detected after topical calcipotriol treatment, a synthetic derivative of calcitriol, used in the treatment of psoriasis[24]. Similarly with other studies presenting small series of patients, using local treatments containing calcipotriol, over 50% experienced improvement of the alopecia manifestations[9,25].

On the other hand, vitamin D deficiency among AA patients is a common finding. Many studies reveal significantly reduced 25(OH)D concentrations among this population[26,27]. Another recent prospective study comparing 30 patients with AA with 30 controls showed that vitamin D deficiency in AA influences disease severity and duration[28]. Simultaneously, VDR expression was reduced in AA and as hypothesized, was inversely correlated with inflammation histologically. These finding suggest, not only the possible relation of vitamin D deficiency with the pathogenesis of the disease but also the potential use of vitamin D as a therapeutic approach. The fact that patients with vitamin D deficiency run a longer course of disease and it takes longer for autoimmunity to regress despite multiple immunosuppressive therapies enhance the hypothesis of a vitamin D role in pathogenesis of AA. Patients with AA have a higher prevalence of vitamin D deficiency and lower 25(OH)D levels than the control groups[29], although further research is needed to elucidate the underlying mechanisms and assess the efficacy of vitamin D in treating AA, as vitamin D may suppress autoimmunity and VDR down regulation.

The study from Daroach *et al*[28] was – to the best of our knowledge – the first effort of systematic supplementation of the vitamin D deficient AA. They used oral cholecalciferol 60.000 IU once weekly for 12 wk and detected clinical improvement and VDR upregulation, even though statistically significant results were not acquired[28]. The reason for this might be that, according to many studies, serum 25(OH)D above a certain cut-off may be required for its immunomodulatory actions but also a minimum duration of treatment for the upregulation of the VDR expression is required[7]. The dosage that has been used in this study would assure normal (30-150 ng/mL) 25(OH)D concentrations, above or around 40-60 ng/mL, as in our AF patient. Though, as in our cases, a pharmacological therapeutic intervention, as the individualized schemes with the active hormone calcitriol and its analog paricalcitol we used, may be required to obtain positive therapeutic results. This is because cholecalciferol is subjected to internal transformation to the active hormone calcitriol to exert most of its' immunomodulatory actions and this counterbalance has its limitations[30].

Even if not finally successful in resolving AU in our case, the active hormone calcitriol and its analog paricalcitol had some undeniable and visible effect on scalp and body hair – even as fur -, on eyebrows', and eyelashes' regrowth, indicating that vitamin D possesses an immunomodulating capability that interferes with the mechanism of disease in AA, opening the perspective of more powerful, less calcemic, and potentially more specific calcitriol analogs in the future. Thus, in addition to the cumulative evidence of vitamin D deficiency among alopecia patients, new therapeutic horizons in the complex management of this disease may be envisioned, especially now that newer more potent calcitriol analogues are being tested as anti-cancer and anti-metastatic agents. MART-10 for instance, has 3 times more VDR-binding affinity and much more resistance to CYP24A degradation compared to calcitriol, sparing the side effect of hypercalcemia[31].

CONCLUSION

Treatment with vitamin D in the form of cholecalciferol, as well the active hormone calcitriol and its analogs, such as the already marketed paricalcitol, may be envisioned for patients with AA/AT/AF, however with close monitoring of Ca metabolism parameters. Pilot clinical trials and RCTs are required to prove the effectiveness and safety of this therapeutic approach, as to establish the optimal form and dosage of vitamin D administration, alone or in combination with other treatments.

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