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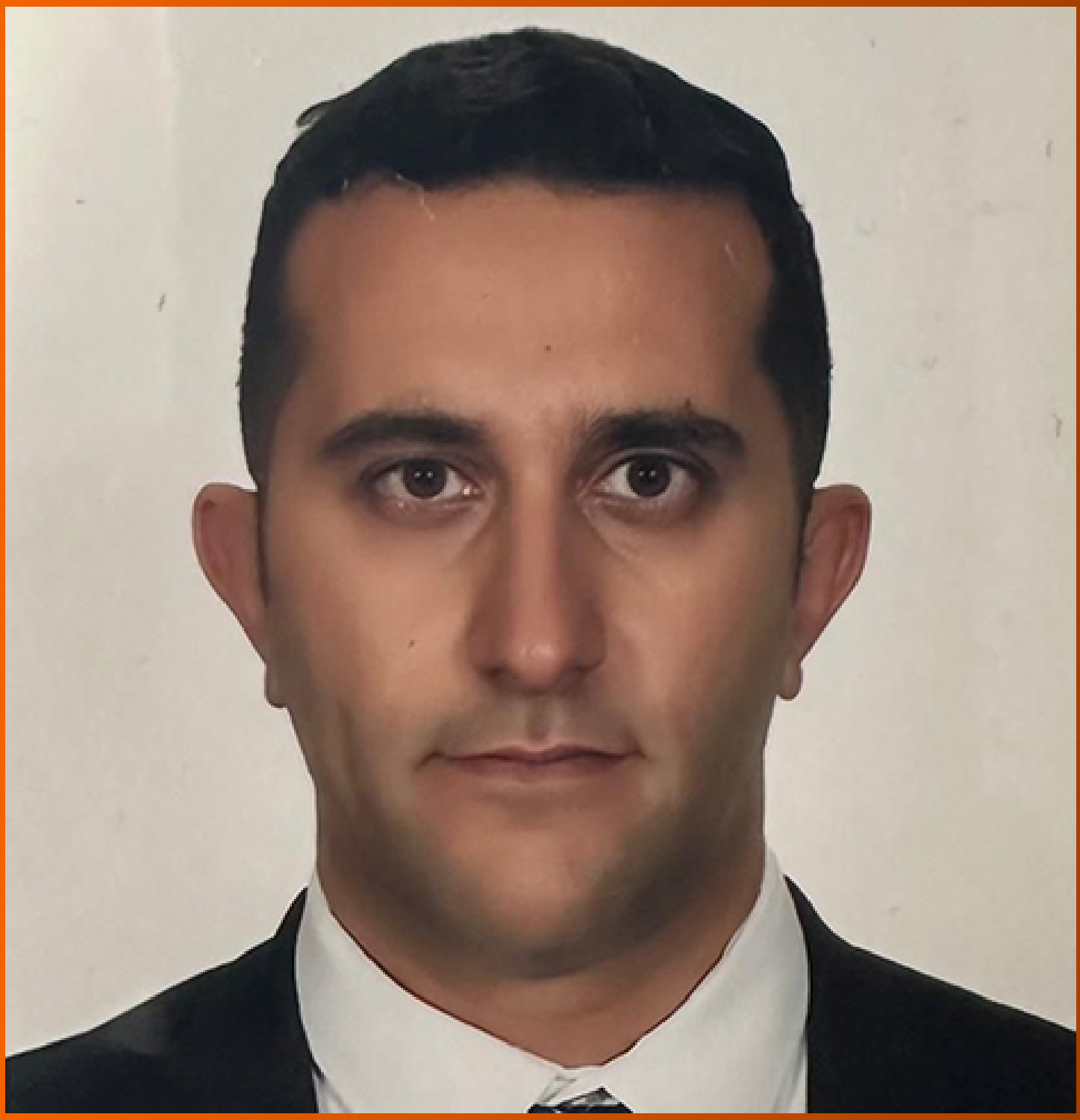

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EVIDENCE REVIEW

Use of endolumenal functional lumen imaging probe in investigating paediatric gastrointestinal motility disorders

Emily White, Mohamed Mutalib

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Abstract

Investigating gastrointestinal (GI) motility disorders relies on diagnostic tools to assess muscular contractions, peristalsis propagation and the integrity and coordination of various sphincters. Manometries are the gold standard to study the GI motor function but it is increasingly acknowledged that manometries do not provide a complete picture in relation to sphincters competencies and muscle fibrosis. Endolumenal functional lumen imaging probe (EndoFLIP) an emerging technology, uses impedance planimetry to measure hollow organs cross sectional area, distensibility and compliance. It has been successfully used as a complementary tool in the assessment of the upper and lower oesophageal sphincters, oesophageal body, the pylorus and the anal canal. In this article, we aim to review the uses of EndoFLIP as a tool to investigate GI motility disorders with a special focus on paediatric practice. The majority of EndoFLIP studies were conducted in adult patients but the uptake of the technology in paediatrics is increasing. EndoFLIP can provide a useful complementary data to the existing GI motility investigation in both children and adults.

Key Words: Endolumenal functional lumen imaging probe; Paediatric; Gastrointestinal motility

Core Tip: Manometries are commonly used to investigate gastrointestinal (GI) motility disorders albeit with acknowledged limitation to their diagnostic yield. Endolumenal functional lumen imaging probe (EndoFLIP), an emerging technology uses impedance planimetry to provide cross sectional area, distensibility and diameter of a hollow organ. EndoFLIP is increasingly used as an adjunct diagnostic tool to provide diagnostic information and to guide therapy for many GI motility disorders.

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INTRODUCTION

Investigating gastrointestinal (GI) motor function requires a careful assessment of muscle contractions and sphincters function[1]. Manometries can directly measure the lumen-generated pressure and are considered the gold standard to evaluate the strength and propagation of muscle contractions, peristalsis velocity and the integrity and coordination of different types of GI sphincters[2]. Sequential multi-channel impedances, in isolation or combined with manometry, will evaluate the directional flow and the bolus transit[3]. However, it has long been recognised that the competency of GI sphincters does not always relate to the tightness of their contractions[4-6]. Measuring the resistance to distension, also known as distensibility assessment, can provide an accurate geometric measurement of the sphincters and a plethora of diagnostic information[7].

Endolumenal functional lumen imaging probe (EndoFLIP) uses the principles of impedance planimetry, a technical term that describes the measuring of the cross-sectional area (CSA) of a distending bag by using an internal electrical impedance measurement[8,9]. EndoFLIP consists of 16 sensors and a solid state pressure transducer placed inside a distensible and compliant balloon to provide a measurement length of 8 or 16 cm[10]. EndoFLIP is used during endoscopy under the same anaesthesia. To obtain the desired data, the balloon is filled with a conducting fluid (in a predetermined volume) (Figure 1), then the system will run a constant alternating current and the voltage difference between the excitation and the detection electrodes is measured[11]. The voltage is mathematically proportioned to the CSA of the balloon, from which, the balloon diameter can easily be calculated[12]. The EndoFLIP data will be presented as geometric plots and will provide the following values: Distensibility is the resistance of the luminal wall to a distending force, compliance is the change in volume in response to a change in pressure, the CSA, the internal diameter of the balloon and the intra balloon pressure[13,14] (Figure 2A).

EndoFLIP has been increasingly used in clinical practice to study the lower oesophageal sphincter (LOS), the pylorus and the anal sphincters[11]. It has also been used to assess distensibility of the oesophageal body in conditions such as eosinophilic oesophagitis (EoE)[15] and to guide surgical interventions (*e.g.*, during and post fundoplication)[16]. Recently, EndoFLIP topography was developed allowing real life display of the balloon diameter continuum during volumetric distension. Oesophageal body contraction can then be visualised and analysed[17,18] (Figure 3).

In this article, we aim to review the use of EndoFLIP as a tool to investigate GI motility disorders with a special focus on paediatric practice. We searched PubMed database for English Language literature on the following keywords: EndoFLIP; Gastrointestinal Disorders; GI disorders; oesophagus; pylorus; rectum; anorectum; paediatric; children using AND/OR combination as appropriate. The extracted articles were reviewed and their salient findings were summarised and presented in the headings below.

Uses of EndoFLIP in the oesophagus

The oesophageal body, the LOS and the upper oesophageal sphincter were the most commonly studied part of the GI tract in regards to EndoFLIP measurement[19]. Normative values from healthy adults have been recently published in a meta-analysis[20].

Achalasia

Achalasia is an uncommon oesophageal motility disorder, characterised by impaired relaxation of the LOS and absent or spastic oesophageal body contractions[21]. It has three distinct types based on peristalsis patterns: Absent peristalsis in type I, pan-oesophageal body pressurisation in type II and an abnormal peristalsis with premature contractions in type III [22]. Impaired LOS relaxation is the hallmark of all three types. High resolution oesophageal manometry (HROM) is universally agreed on as the gold standard tool to diagnose and characterise achalasia[23].

In adults, EndoFLIP assessment of LOS can appropriately identify patients with achalasia who may have a normal integrated relaxation pressure but other features of achalasia[4,6]. EndoFLIP was able to bridge a gap in the understanding of the physiological behaviour of the LOS and the limitation of HROM as a sole diagnostic tool for major oesophageal motor disorders[24,25]. LOS distensibility index (DI) of < 2 mm^2/mmHg is strongly suggestive of an obstructive process and is significantly lower in patients with achalasia compared to healthy volunteers[21,26,27]. LOS DI also appears to correlate well with achalasia symptoms prior to and after therapeutic interventions; achieving a definitive increase in DI after pneumatic dilatation was reported to be associated with improved clinical response[26,28]. Using DI,

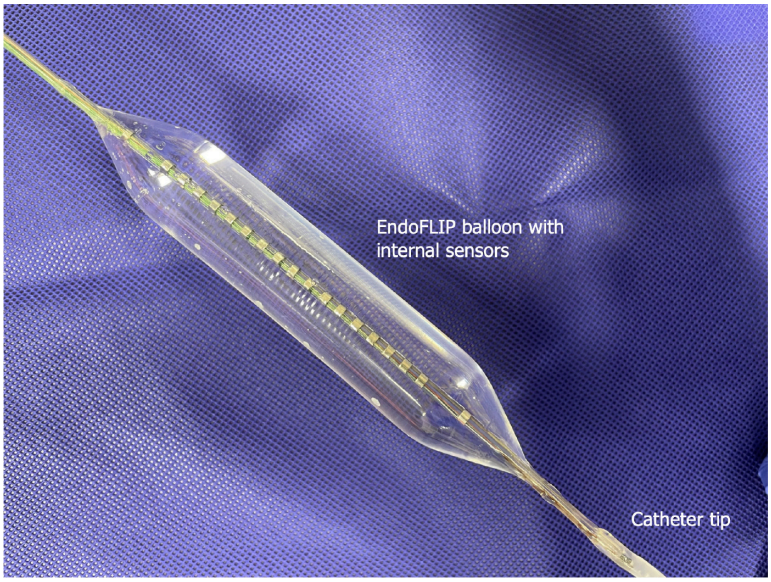

Figure 1 Endolumenal functional lumen imaging probe catheter (filled). EndoFLIP: Endolumenal functional lumen imaging probe.

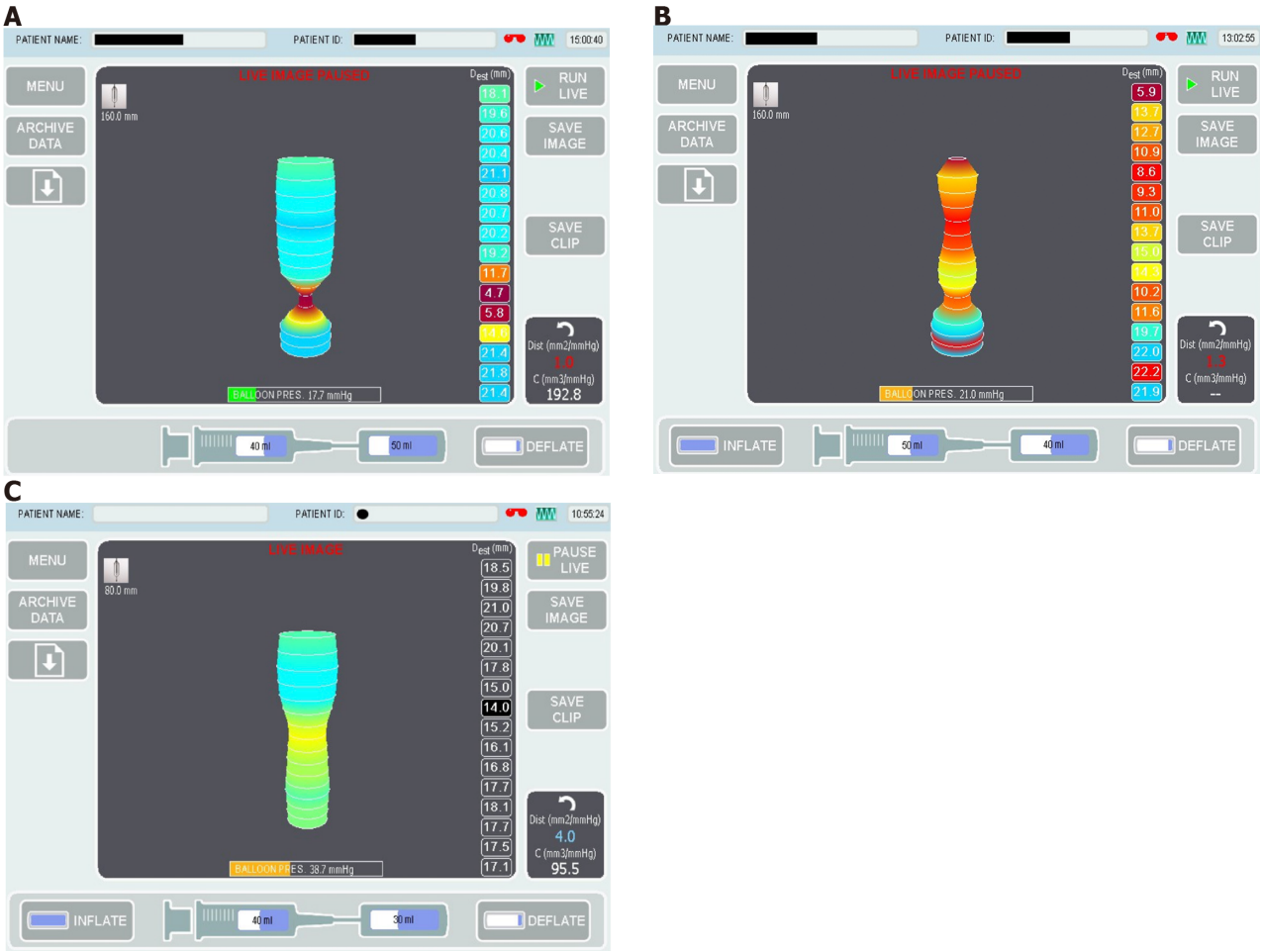

Figure 2 Endolumenal functional lumen imaging probe measurement. A: Endolumenal functional lumen imaging probe (EndoFLIP) measurement for a child with achalasia; B: EndoFLIP measurement from a child with eosinophilic oesophagitis; C: EndoFLIP measurement from a child with repaired oesophageal atresia.

CSA and balloon pressure as complementary data can help predict response to therapeutic interventions [Heller's myotomy and peroral endoscopic myotomy (POEM)] in patients with achalasia[29-31], however, the data on the use of EndoFLIP parameters as a predictor of pneumatic dilatation response is conflicting, Rohof *et al*[26] experience showed a

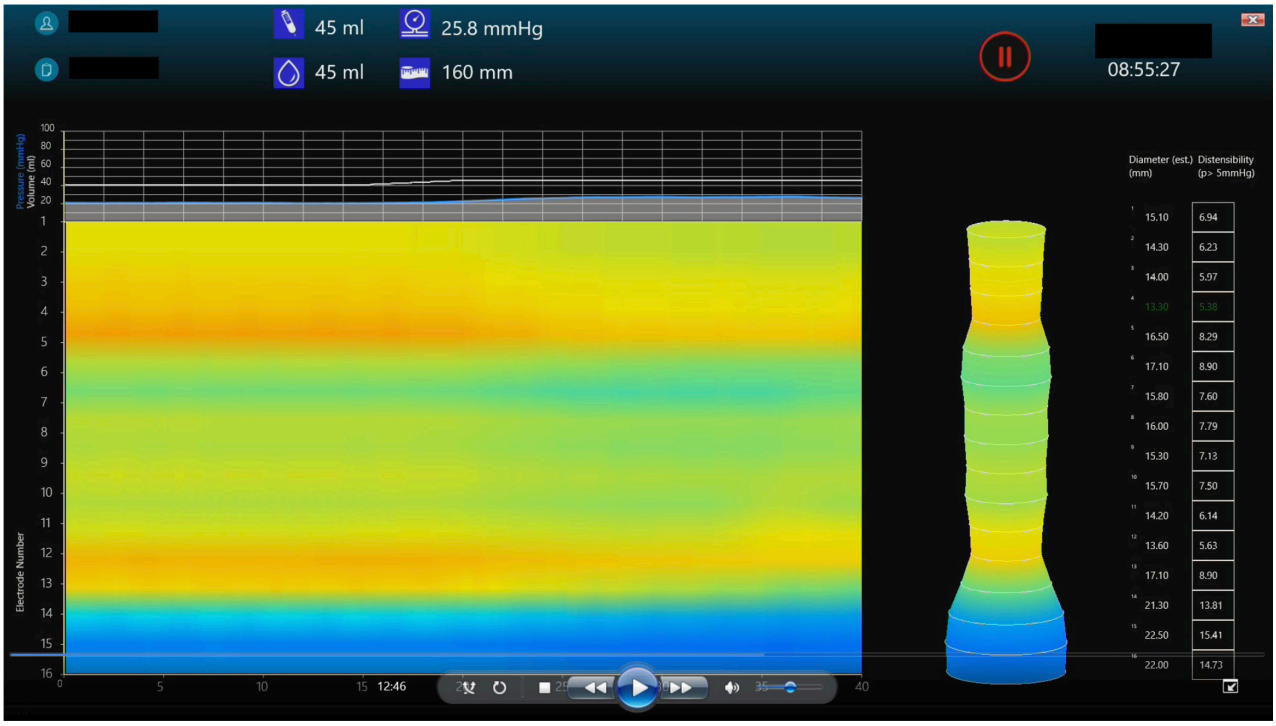

Figure 3 Endolumenal functional lumen imaging probe topography from a child with eosinophilic oesophagitis.

positive outcome while Smeets *et al*[32] reports no added therapeutic benefits.

In paediatrics, EndoFLIP has been used intra-operatively during POEM and laparoscopic myotomy to guide and assess the immediate post-procedural DI[33,34]. The authors have reported a significant improvement in DI from baseline and a successful clinical outcome. Howk *et al*[33] have reported on the use of intra-operative EndoFLIP with the balloon inflated throughout the procedure to guide the myotomy length and provide a real time feedback on DI and CSA. Their use of EndoFLIP resulted in a shorter operative time. Figure 2A is showing EndoFLIP data from a child with type 1 achalasia showing reduced LOS DI and diameter.

EoE

EoE is a chronic immune mediated and eosinophil predominant inflammation characterised by symptoms related to oesophageal dysfunction[35]. EoE is associated with many types of oesophageal motility disorders and often thought to be secondary to oesophageal remodelling and fibrosis[36,37]. Oesophageal strictures and luminal narrowing are also common in patients with EoE[38,39]. Early identification of lamina propria fibrosis is crucial in guiding therapeutic strategies and endoscopic assessment but mucosal biopsies have a poor correlation with the degree of oesophageal fibrosis[40,41]. HROM findings are not specific or sensitive to EoE motility disorders and they do not describe a characteristic pattern for EoE symptoms[42,43].

In adults, EndoFLIP can provide an accurate information in relation to oesophageal distensibility and compliance. Reduced oesophageal distensibility is reported in both children and adults with EoE and is associated with increased risk of food bolus impaction and the need for oesophageal dilatation[40,44]. Distensibility is also significantly reduced in children with active EoE compared to an age matched control and the natural increase in oesophageal distensibility normally observed with age, appeared to plateau in children with EoE[44,45]. This may represent a fibrotic remodelling or a separate EoE phenotype[44]. Figure 2B is a child with EoE and reduced diameter/distensibility.

In paediatrics, a reduced oesophageal distensibility was reported in children with EoE and high endoscopic reference score part of (EREF)[44]. In EREF, rings and strictures are considered as features of fibrosis and remodelling changes, while oedema, furrows and exudates are considered as features of inflammatory changes[46]. It is increasingly recognised that inflammatory features can progress to fibrosis and remodelling in the context of EoE and although children can predominantly present with inflammatory EoE phenotype, early fibrosis in paediatric patients is commonly described[44,45]. Oesophageal DI, but not CSA or diameter, has a strong correlation with endoscopic fibrostenotic severity and history of food bolus impaction in paediatrics independent of age, height or oesophageal inflammation[44]. Oesophageal DI < 4.5 mm^2/mmHg has been suggested as a predictor of the presence of grade II rings in children[44]. The association between EndoFLIP findings, particularly DI, and the degree of EoE inflammation in paediatric is conflicting and is in contrast to adult studies which showed no correlation between reduced DI and the degree of oesophageal inflammation[40]. This is likely to represent the small scales of paediatric studies and the difference in selection criteria.

Gastrooesophageal reflux disease

Limited data is available on the use of EndoFLIP for the assessment of patient with gastrooesophageal reflux disease (GORD) and is mostly from adult studies. In adults, there were contradicting results regarding DI of the gastrooeso-

phageal junction (GOJ) in the context of GORD[47,48]. In one study, GOJ DI was reported to be higher in patients with GORD compared to controls irrespective of the presence of distal oesophagitis, but the authors did not look for the presence of hiatal hernia[47]. Hiatal hernia is an important factor that may independently affect GOJ morphological studies, although in a separate study, Lottrup *et al*[49] have reported on the usefulness of EndoFLIP in identification and assessment of hiatal hernia. In another study, the authors did not find a statistically significant difference in the measurements of GOJ DI between patients with GORD and healthy volunteers but they did acknowledge the presence of many independent confounding factors (*e.g.*, obesity)[48].

EndoFLIP can provide a useful tool in the assessment of fundoplication and can be used intraoperatively during anti-reflux surgery. Using FLIP intraoperatively can provide a real time measurement of GOJ DI and diameter, although direct clinical outcome data is lacking, proxy data appeared to support the clinical outcome associated with certain EndoFLIP values[16,50,51].

Oesophageal atresia and oesophageal strictures

EndoFLIP offers a promising tool to study the oesophageal morphology post oesophageal atresia repair. One small paediatric study has reported on the use of EndoFLIP to assess the geometry of OGJ, oesophageal body distensibility and anastomotic strictures. They have reported a DI within published normal values for the oesophageal body and the OGJ, while their data on FLIP measurements of the anastomosis site were combined with other diagnostic modalities to help guide therapeutic and prognostic directions[52]. Figure 2C is a child with repaired oesophageal atresia showed a reduced diameter at the site of anastomotic scare and a dilated oesophageal segment above.

Another retrospective paediatric study has reported on the use of EndoFLIP and the FLIP dilatation catheter EsoFLIP in assessment and management of different types of oesophageal strictures in children. They reported a potential clinical benefit of reduction in procedural time and achieving a larger diameter changes post dilatation[53]. Both studies recruited a small number of children in a retrospective manner affecting their wider applicability. With such limited data, the use of EndoFLIP in the assessment of children with repaired oesophageal atresia and/or oesophageal strictures is to be explored.

Uses of EndoFLIP in the pylorus

In contrast to LOS, the pyloric sphincter did not receive the same level of diagnostic scrutiny. Although the pylorus plays a vital role in regulating gastric emptying (GE), the association between symptom severity and measured GE remains poor[54]. In part, this can be explained by the complex role of the pylorus sphincter compared to other GI sphincters. Detailed assessment of post prandial period reported that GE occurred during the relaxation of the pylorus and was driven primarily by the pressure generated by gastric tone and content (pressure pump) rather than the effect of antral contraction wave (peristalsis pump)[55]. On the other hand, contraction of the pylorus in the face of gastric peristalsis wave will lead to bolus retention and gastric content mixing. However, the pylorus pressure measurements did not differ in patients with normal or delayed GE[54,56].

In adults, geometric assessment of the pylorus by EndoFLIP has been widely studied in patients with gastroparesis or with symptoms suggestive of gastroparesis (such as nausea and vomiting)[57-59]. Pylorus DI has been found to correlate with GE and gastroparesis symptoms, a promising finding to identify a group of patients who may respond to targeted pylorus therapy[58,59].

EndoFLIP catheter is usually inserted *per os* under direct endoscopic vision and prior to endoscopic intubation of the pylorus. The effect of anaesthesia and sedation on the EndoFLIP findings are yet to be studied. Pylorus geometric measurements are often taken after the EndoFLIP balloon is filled with a predetermined volume of 20, 30, 40 and 50 mL. Pylorus DI was significantly lower in patients with gastroparesis compared to healthy volunteers, but there was no difference in DI between diabetic gastroparesis and other forms of the disorder[19]. Early satiety and postprandial fullness were inversely correlated to pylorus CSA and diameter, this has been the only clear association between a diagnostic investigation and symptoms of gastroparesis, in contrast to other investigative modalities such as GE scintigraphy and manometry[58]. Although the authors were unable to offer a concrete explanation of this association, and the absence of correlation with any EndoFLIP parameters and other gastroparesis symptoms, it is possible that the pylorus opening diameter rather than distensibility or compliance is the driving force behind these two symptoms but further research is needed to study this hypothesis.

EndoFLIP has also been used to predict clinical response to intra pylorus Botulinum Toxin injection[60]. Patients with gastroparesis and an abnormal pylorus EndoFLIP measurements appear to show sustained symptom improvement at 3 mo compared to gastroparesis patients with normal FLIP parameters[60]. A similar clinical response was also observed post pylorus dilatation and gastric POEM guided by EndoFLIP findings in patients with therapy refractory gastroparesis [59,61].

In paediatrics, Hirsch *et al*[62] have reported in a retrospective observational study in children with nausea and vomiting that the pylorus distensibility were lower in children with delayed GE compared to the normal GE group but the differences were not statistically significant. This is likely to be secondary to small sample size and patient selection. In the same study, EndoFLIP did not predict the symptomatic response to intra pylorus Botulinum Toxin injection[62]. A likely explanation is the selection criteria for included children as 44% had normal GE and previous adult studies did not show correlation between EndoFLIP and the reported symptoms of nausea and vomiting.

We have recently published our experience in using pylorus EndoFLIP in children with neuromuscular disorders and the response to Botulinum Toxin injection[63]. In our cohort, children with symptoms suggestive of gastroparesis had abnormal EndoFLIP measurements according to both adults and previous paediatric studies. We reported good symptoms improvement, weight gain and feed tolerance after Botulinum Toxin injections, a response that had been replicated after repeat injections 6-9 mo later. We did observe a trend of improvement in EndoFLIP measurements even

though the FLIP remeasurements were obtained due to symptoms recurrence. Our sample size was small and we did not measure GE due to the comorbidities present in our studied group[63]. Figure 4 is from a child with gastroparesis showed reduced pylorus distensibility. EndoFLIP usage in the assessment of pylorus sphincter is increasing and appear to show promising diagnostic data, symptom correlation with GE and most importantly, it can identify a subset of patients who can response to targeted pylorus therapy.

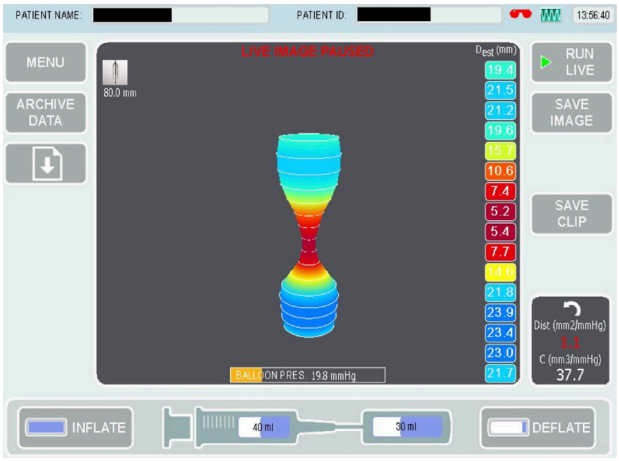

Figure 4 Endolumenal functional lumen imaging probe of the pylorus sphincter from a child with gastroparesis showing reduced pylorus distensibility.

Uses of EndoFLIP in the anal sphincter

There are very few studies reporting on the use of EndoFLIP in assessment of the geometry of the anal canal, all were from adult patient and healthy volunteers[64-66]. To date, there is no published paediatric study. Although there was a general harmony on the methods used in all published studies, there were no agreement on the relevant FLIP measurements or their applicability to clinical practice. All published studies have reported a higher anal distensibility in patients with faecal incontinence compared to healthy volunteers, however, the clinical utility of such a finding is yet to be explored.

CONCLUSION

EndoFLIP is a promising tool to further improve our ability to understand the motility function of the GI tract. By providing a detailed geometric assessment to the oesophageal lumen and various sphincters in the GI tract, EndoFLIP findings are complementary to the existing GI motility investigations, but the data does not support the use of EndoFLIP to replace standard GI motility investigations. EndoFLIP has been successfully used to aid diagnosis and to guide therapeutic interventions. EndoFLIP studies in paediatrics are lagging behind adult studies but they have replicated some of adult results. The absence of normative values for children may limit the wider uptake within paediatrics but with the increase in complexity and prevalence of paediatric GI motility disorders, EndoFLIP can provide a valuable diagnostic and prognostic data.

FOOTNOTES

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REVIEW

Role of gastrointestinal health in managing children with autism spectrum disorder

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Abstract

Children with autism spectrum disorders (ASD) or autism are more prone to gastrointestinal (GI) disorders than the general population. These disorders can significantly affect their health, learning, and development due to various factors such as genetics, environment, and behavior. The causes of GI disorders in children with ASD can include gut dysbiosis, immune dysfunction, food sensit-

ivities, digestive enzyme deficiencies, and sensory processing differences. Many studies suggest that numerous children with ASD experience GI problems, and effective management is crucial. Diagnosing autism is typically done through genetic, neurological, functional, and behavioral assessments and observations, while GI tests are not consistently reliable. Some GI tests may increase the risk of developing ASD or exacerbating symptoms. Addressing GI issues in individuals with ASD can improve their overall well-being, leading to better behavior, cognitive function, and educational abilities. Proper management can improve digestion, nutrient absorption, and appetite by relieving physical discomfort and pain. Alleviating GI symptoms can improve sleep patterns, increase energy levels, and contribute to a general sense of well-being, ultimately leading to a better quality of life for the individual and improved family dynamics. The primary goal of GI interventions is to improve nutritional status, reduce symptom severity, promote a balanced mood, and increase patient independence.

Key Words: Gastrointestinal disorders; Autism spectrum disorders, Children; Gut microbiota; Ketogenic diet; Gluten-free casein-free diet, Dietary management

Core Tip: Children with autism spectrum disorder often experience gastrointestinal (GI) disorders that can significantly impact their health, learning, and development. Various factors, including genetics, environment, and behavior, can cause these disorders. Common causes include gut dysbiosis, immune dysfunction, food sensitivity, digestive enzyme deficiencies, and sensory processing differences. Proper management can improve well-being, cognitive function, behavior, and educational abilities. GI interventions enhance nutrition, reduce symptoms, promote balanced moods, and increase independence.

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INTRODUCTION

The prevalence of autism spectrum disorders (ASD) has increased since Leo Kanner was first illustrated in 1943 and continues to rise[1]. ASD is a neurodevelopmental disorder, which includes, in addition to autism, Asperger's disorder, and pervasive developmental disorder-not otherwise specified. Pervasive developmental disorders, which include Rett's disorder, childhood disintegrative disorder, and overactive disorder, are also related. It may overlap with attention deficit hyperactivity disorder[2]. The prevalence of ASD varies from country to country, with an average of 1% worldwide. In the United States, the incidence of ASD can be as high as 1/59 in 2014, according to the centres for disease control and prevention[3], while it can reach 1/64 in the United Kingdom[4]. The prevalence of ASD may be underestimated in some parts of the world, such as Bahrain, where it is estimated to be 1/1000, due to missed diagnoses and lack of official recordings[1]. ASD is more common in boys than girls, with a higher prevalence in non-Hispanic white children and a lower prevalence in Hispanic and African American/black children, with variability in Asian/Pacific residents[5]. Although the exact cause of ASD remains unclear, it is widely accepted that the development of this condition is influenced by a complex interplay of various factors, including genetic predisposition, biological determinants such as advanced parental age, and environmental, immunological, and psychosocial factors[6].

ASD presents in various ways and is characterized by a combination of social, cognitive, sensory, motor, and perceptual symptoms that typically emerge before age three. Children with ASD exhibit behaviors, communication patterns, social interactions, and learning styles that differ from typically developing children. They may struggle with social communication and interaction, including difficulty giving eye contact, displaying limited expressions of emotion, and showing little interest in others or playing with them. They may also have restricted interests, such as playing with the same toys in the same way repeatedly, becoming agitated over minor changes in routine, and developing an obsessive interest in specific parts of objects, the environment, or the body. Additionally, they may engage in repetitive or stereotyped behaviors, such as repeating words, phrases, or sections of videos, flapping their hands, rocking their body, or spinning in circles. Children with ASD may also experience delays in language development, movement, sensory, and cognitive or learning skills[7,8].

It has been observed that children with ASD are at a higher risk of developing medical comorbidities than the general population. These medical conditions can adversely affect their overall health, hinder their learning abilities, and worsen their autistic symptoms. Among the common medical conditions observed in patients with ASD, gastrointestinal (GI) disorders are particularly prevalent[9]. In this review, we highlight the connection between GI issues and ASD, emphasizing the importance of understanding the role of GI health in managing ASD.

Prevalence of GI disorders in children with ASD

It has been observed that patients with ASD commonly experience GI problems, with a prevalence rate between 46% and 84% in children with ASD. These problems manifest in numerous ways, including food intolerance and/or sensitivities, nausea and/or vomiting, chronic constipation, chronic diarrhea, gastroesophageal reflux and/or disease, chronic flatulence, abdominal discomfort, ulcers, inflammatory bowel disease, colitis, and/or failure to thrive. Additionally, food allergies are more prevalent in children with ASD, with a rate of 20%-25% compared to only 5%-8% in children without ASD[10]. Several factors contribute to this higher prevalence (Figure 1). It is established that genetic factors participate in both ASD and GI disorders. Specific genetic mutations and variations are detected in individuals with ASD, which may impact the development and operation of the GI system[11]. One of the primary reasons is an imbalance and microbiota and dysregulation in the gut microbiota. Children with ASD often exhibit dysbiosis, resulting in GI issues[12]. Another factor is immune system dysfunction, which some children with ASD experience. This can lead to gut inflammation and further contribute to GI problems. Food sensitivities and allergies, particularly to gluten and casein, are also more common in children with ASD. These sensitivities can trigger symptoms like abdominal pain, diarrhea, and constipation. In addition, some children with ASD may have deficiencies in digestive enzymes, which can impact the breakdown of food components. This inadequate enzyme activity can lead to malabsorption and GI disturbances[13]. It's not uncommon for children with ASD to experience GI motility issues, which can lead to problems like constipation or diarrhea. These issues can arise from various factors, including abnormal serotonin levels linked to ASD and GI dysfunction[14]. Children with ASD frequently display selective and limited eating habits, leading to unbalanced diets that lack essential nutrients. These dietary restrictions may contribute to GI issues like constipation or diarrhea[15]. Additionally, individuals with ASD often exhibit sensory processing differences, making them hypersensitive or hyposensitive to sensory stimuli. These differences may affect their perception of GI sensations, resulting in discomfort or altered responses to normal digestive processes[16]. Unfortunately, the general public, some parents, and professionals may misinterpret sudden improper behaviors due to GI discomfort from children with ASD as lousy behavior that came up from nowhere or just to avoid activity. For instance, during an activity, the child might have severe abdominal or GI pain that forces him/her to scream and move from the place. Meanwhile, the adults may interpret the child's behavior as improper and escape trial. Children with ASD are more liable to have dysautonomia and abnormal dietary metabolites. Furthermore, gut and brain communications are bidirectional through the gut-brain axis. Children with ASD often have altered gut-brain communication, leading to an impaired gut-brain axis. This can contribute to digestive issues and affect GI function[17]. Children with ASD frequently display selective and limited eating habits, leading to unbalanced diets that lack essential nutrients. Their insistence on sticking to stereotypical diets can result in inadequate fiber and fluid intake, causing GI symptoms. These dietary restrictions may also contribute to GI issues like constipation or diarrhea[15]. Certain medications can also affect bowel function, such as stimulants causing abdominal pain and βeta-blockers causing constipation, diarrhea, and stomach irritation[18].

Children with ASD may experience pain and discomfort due to GI disorders, which can interfere with their learning. Children with ASD who are nonverbal may exhibit behavioral problems like posturing, self-injury, or outbursts without apparent causes due to unrecognized GI disorders, specifically reflux esophagitis and disaccharide malabsorption. However, these manifestations may be mistakenly overlooked as a behavioral problem instead of a medical condition since many children with ASD have difficulty expressing their symptoms or discomfort to their parents or physicians. Lactase deficiency, common in children with ASD and not associated with intestinal inflammation or injury, may also contribute to abdominal discomfort, pain, and obvious behavioral problems[19]. It can be challenging to diagnose GI symptoms in children with ASD due to the lack of established clinical guidelines that prioritize routine assessment of potential medical conditions or GI issues in this population. This is particularly challenging because many children with ASD are nonverbal and cannot convey pain or discomfort through language. Even those who can communicate verbally may have trouble describing subjective experiences or symptoms compared to their typically developing children. As a result, guidelines that specifically address this issue are crucial[20]. Healthcare professionals should know that children with ASD may experience GI dysfunction, mainly if they exhibit unusual postures or movements, have trouble sleeping, are intolerant to certain foods, or display aggressive or self-harming behaviors. To properly assess these issues, clinicians should gather a comprehensive GI and nutritional history covering the patient's eating habits, allergies or food sensitivities, and bowel movements in children with ASD[21].

It's essential to consider a child's sleep history when diagnosing underlying GI disorders, as they may manifest as disturbed sleeping patterns[22]. Healthcare providers should thoroughly review the child's medication, growth history, and sleep habits. Additionally, they should be able to identify vocal, sensory, or motor behaviors that may indicate the presence of pain related to GI disorders. Vocal behaviors associated with GI disorders may include throat clearing, guttural sounds, spitting up in infants, ear rubbing, habitual coughing, or difficulty swallowing. Motor behaviors related to GI disorders include seeking belly pressure, pointing behaviors, certain repetitive behaviors, abnormal neck or body posture, and aggressive or self-injurious behaviors. Studies have shown a strong correlation between aggressive behavior and underlying GI disorders[23], and more severe autistic features tend to be linked to severe GI symptoms. GI disorder symptoms are more likely associated with sleep disruptions and food intolerances. Therefore, clinicians should consider these associations when assessing and treating comorbidities and screening for constipation, diarrhea, or soiling of underwear in children with ASD with prominent rigid-compulsive symptoms[24].

If a child with ASD experiences eczema, vocal, sensory, or motor signs, aggressive or self-injurious behaviors, chronic constipation or diarrhea, or chronic spitting or vomiting, pediatricians should consider referring them for GI evaluation. It is common for children with ASD who exhibit GI symptoms to have increased intestinal permeability. One way to evaluate this is by measuring plasma zonulin level, a valuable blood marker[25]. Endoscopy can also reveal signs of allergic esophagitis, acid reflux damage, allergic changes, or evidence of inflammatory bowel disease in patients with ASD and abdominal manifestations[26]. Effective medical treatment of GI disorders may lead to improvements in

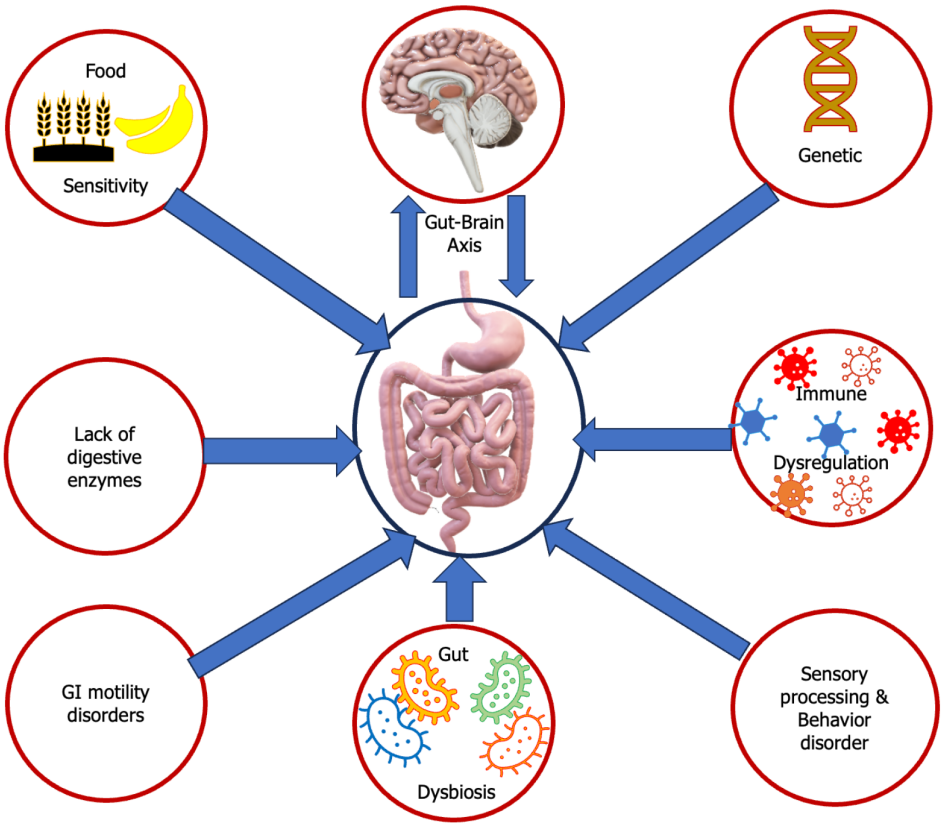

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Figure 1 Increase the prevalence of gastrointestinal disorders in children with autism spectrum disorders. These factors may include genetic variations, abnormal gut-brain axis, dysbiosis, immune dysfunction, food sensitivities, digestive enzyme deficiencies, sensory processing and integration differences, dysautonomia, and abnormal behaviors. GI: Gastrointestinal.

behavioral problems. If abdominal pain or discomfort is present, psychotropic medications may not be effective and may even worsen the problem due to GI adverse effects. The microbiota-gut-brain axis is an emerging concept that suggests modulation of the gut microbiota could lead to new therapeutic modalities for different complex central nervous system disorders[27].

While studies have not found a higher prevalence of celiac disease in ASD, it's important to note that one child out of 68 with celiac disease may develop ASD, and one child out of 130 with ASD may develop celiac disease. Even without GI symptoms, those with celiac disease have been found to have a strong association with epilepsy, cerebral calcifications, and positive responses to dietary changes. Investigating and treating celiac disease, non-celiac gluten sensitivity, and epilepsy could potentially lead to positive outcomes for those with ASD, even without typical GI symptoms or overt seizures[28]. It's crucial to consider non-celiac gluten or wheat sensitivity in children with ASD, especially if they have irritable bowel symptoms and a history of atopy and allergies[29]. Medical professionals should also be aware of the possibility of non-celiac gluten sensitivity in patients with ASD who present with atopic disease, migraine, mood, and anxiety disorders. While many children with ASD have experienced positive results from a gluten-free, soy-free, and dairy-free diet, it's crucial to have a celiac test performed before attempting any dietary changes. The gluten-free diet remains the only effective treatment for those with gluten sensitivity, regardless of the manifestations. It's essential to prioritize the overall health and well-being of patients with ASD, and understanding the potential impact of diet and gluten sensitivity can lead to better outcomes[30].

Understanding the gut-brain connection in children with ASD

The idea of the "second brain" pertains to the enteric nervous system, an intricate network of neurons in the GI tract's walls. The enteric nervous system is also known as the "gut brain" or "second brain" because it can function autonomously from the central nervous system. It has its own reflexes and sensory abilities[31]. The enteric nervous system consists of millions of neurons communicating with each other and the central nervous system *via* the vagus nerve and other nerve pathways. It plays a crucial role in regulating different digestion aspects, such as food movement through the digestive tract, secretion of digestive enzymes, and absorption of nutrients[32]. The connection between the brain and gut is a complex interconnection known as the gut-brain axis. This pathway allows for two-way communication between the central nervous and GI systems. It comprises various components, including the enteric nervous system, gut microbiota, immune system, and autonomic nervous system[33]. The gut-brain axis regulates physiological processes like digestion and metabolism, influencing cognitive function, behavior, and other brain functions. Communication between the gut and brain is facilitated through various mechanisms, such as neurocrine and endocrine

pathways[34]. Within the digestive system are trillions of microorganisms collectively known as the gut microbiota. These microorganisms are vital in maintaining gut health, digestion, nutrient absorption, and immune function and significantly impact human health, including their influence on brain development and function[35]. The gut microbiota is a crucial part of the gut-brain axis and is involved in signaling from the gut microbiota to the brain. The brain, in turn, can influence the composition of gut microbiota and control it through neurotransmitters such as serotonin and dopamine, neuromuscular control of peristalsis, stress-induced cortisol, and stimulation of mucus secretion. On the other hand, the gut affects the brain through vagus nerve activation, neuropeptides, and neurotransmitters like leptin and serotonin, immune signaling through secretory immunoglobulin A, and mucous membrane barrier integrity signaling through zonulin protein and short chain fatty acids (SCFAs) like butyrate[36,37]. Additionally, the microbiota can impact the brain through various mechanisms, like the production of neurotransmitters such as gamma-aminobutyric acid, serotonin, and dopamine, the production of SCFAs like butyric acid, propionic acid, and acetic acid, stimulation of the sympathetic nervous system, and induction of mucosal serotonin release, subsequently affecting memory and learning processes in the brain[38].

Children with ASD experience numerous changes that disrupt their gut-brain axis. One significant change is an imbalance in their gut microbiota composition, known as dysbiosis. This imbalance can disrupt the gut's normal functioning, potentially contributing to the development of ASD symptoms[39]. Research has shown that children with ASD have reduced microbial diversity, overgrowth of certain harmful bacteria, and imbalances in the beneficial to pathogenic bacteria ratio compared to neurotypical individuals. These changes can impact the production of essential metabolites, neurotransmitters, neuronal sensory processing and integration, and immune signaling molecules, affecting brain development and behavior. The gut microbiota also can produce and modulate neurotransmitters, including serotonin, dopamine, and gamma-aminobutyric acid[12]. These neurotransmitters are critical in regulating mood, sensory processing and integration, behavior, and cognition. Disruptions in the gut microbiota can lead to imbalances in neurotransmitter production, potentially impacting the neurodevelopmental processes associated with ASD. Serotonin, a hormone linked to social behavior and communication, has been found to have altered levels in individuals with ASD. In addition, imbalances in gamma-aminobutyric acid levels have been linked to anxiety and behavioral issues commonly seen in children with ASD[40]. Gut dysbiosis may contribute to GI symptoms commonly observed in children with ASD, such as abdominal pain, constipation, and diarrhea[41].

There is a link between the gut and brain in individuals with ASD that goes beyond microbial composition and neuroactive compounds. Children with ASD have been observed to experience GI inflammation and immune dysregulation, and chronic inflammation. When the immune system in the gut is activated, it can release pro-inflammatory cytokines that can communicate with the brain, causing changes in neural function[42]. Furthermore, immune dysregulation may lead to a compromised blood-brain barrier, which can allow immune cells and inflammatory molecules to enter the brain, resulting in additional effects on neurological processes[43]. Chronic inflammation in the gut can lead to a "leaky gut", which is an increased intestinal permeability. Increased gut permeability allows bacteria and their byproducts, such as lipopolysaccharides, to pass into the bloodstream, causing systemic inflammation and immune activation[44]. Such inflammation can affect the blood-brain barrier and contribute to neuroinflammation, impacting brain function and behavior and potentially contributing to the cognitive and behavioral symptoms observed in children with ASD[45]. The gut-brain connection is also influenced by metabolic and nutritional factors, which are critical components. Children with ASD often have altered metabolic profiles and frequent nutrient deficiencies. Deficiencies in vitamins, minerals, and essential fatty acids affect brain development and function. Additionally, the composition and diversity of the gut microbiota can be influenced by dietary factors, which can impact the gut-brain axis[46].

Research on the gut-brain connection in children with ASD presents new opportunities for diagnosis and treatment. By studying the composition and function of gut microbiota and examining gut permeability and immune markers, potential biomarkers for ASD diagnosis may be uncovered. Furthermore, interventions that target the gut microbiota, such as probiotics, prebiotics, and dietary adjustments, have shown promise in mitigating ASD-related symptoms and improving overall well-being[47]. To further understand the gut-brain connection in children with ASD, more comprehensive research is necessary. Longitudinal studies are required to determine whether gut dysbiosis precedes the onset of ASD symptoms or is a consequence of the disorder. Additionally, investigating the impact of early-life interventions, like breastfeeding and antibiotic exposure, on the gut microbiota and subsequent ASD risk is crucial. Technological advancements, such as metagenomics and metabolomics, will provide more comprehensive insights into the mechanisms underlying the gut-brain connection in ASD[48].

Common symptoms and common mechanisms for GI and ASD spectrum disorders

While GI disorders and ASD are distinct conditions, some overlapping symptoms and potential shared mechanisms exist (Figure 2). It's important to note that researchers are still studying these associations, and the exact nature of the relationship between GI disorders and ASD is not fully understood[20]. Some common GI symptoms include abdominal pain, diarrhea, constipation, bloating, and gastroesophageal reflux, observed in individuals with ASD and may contribute to their behavioral and sensory issues. Both GI disorders and ASD also involve sensory sensitivities, such as heightened responses to certain textures, physical pressure, movement, sounds, tastes, and smells. Additionally, many individuals with both conditions exhibit food selectivity, preferring specific foods while avoiding others, and may limit their diet due to food intolerances and/or sensitivities[49].

Common mechanisms between the two conditions include gut-brain axis disruptions, gut and systemic inflammation, altered serotonin levels, and genetic factors. For example, alterations in gut microbiota composition, intestinal permeability, and abnormal immune responses have been implicated in GI disorders and ASD[44]. Chronic low-grade inflammation in the gut may lead to systemic inflammation, which can affect brain function and contribute to cognitive, sensory processing and integration, and behavioral symptoms seen in ASD. Additionally, altered serotonin levels have

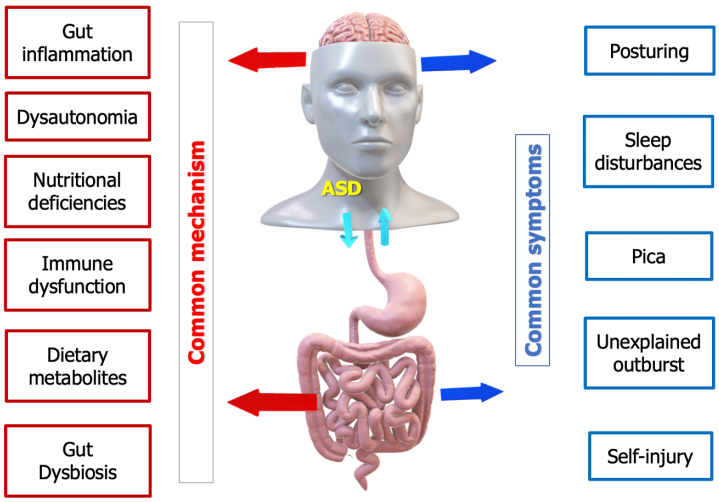

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Figure 2 The mutual interaction between autism spectrum disorders and gastrointestinal disorders. ASD: Autism spectrum disorders.

been found in both conditions, suggesting a potential link between them[50]. Furthermore, GI disorders and ASD have a genetic component, and certain genetic variations may make individuals more susceptible to developing one condition when the other is present[51].

Gastroesophageal reflux

Gastroesophageal reflux is a common GI issue where stomach acid and contents flow back into the esophagus. It can affect individuals with or without ASD, but studies suggest that those with ASD may have a higher prevalence of gastroesophageal reflux[52]. The exact reasons for this are not fully understood, but possible factors include delayed gastric emptying, abnormal esophageal motility, and differences in sensory processing[20].

Individuals with ASD who suffer from gastroesophageal reflux may exhibit abnormal behaviors due to various factors. Although the link between gastroesophageal reflux and abnormal behaviors in ASD is not entirely understood, sensory sensitivities are believed to play a significant role[53]. This is because discomfort related to gastroesophageal reflux can trigger physical discomfort and pain, leading to irritability, restlessness, or agitation, which may manifest as abnormal behaviors[54]. Communication challenges may also contribute to the problem, as patients with ASD may have difficulty expressing their discomfort or pain verbally. Instead, they may use unconventional ways of communicating their distress, such as self-stimulating or challenging behaviors[55]. Individuals with ASD thrive on routines and predictability, making gastroesophageal reflux significantly disrupt their daily routines. For instance, mealtimes or feeding schedules may be affected, leading to frustration or anxiety, which can trigger changes in behavior or increased rigidity in following established patterns. Heightened anxiety and stress levels can trigger or exacerbate abnormal behaviors to cope with physical and emotional discomfort[21].

Diagnosing gastroesophageal reflux in individuals with ASD can be difficult as they may exhibit atypical or subtle symptoms. These could include irritability, behavioral changes, eating refusal, gagging, choking, or discomfort during feeding. Communication difficulties may further hinder their ability to accurately express or describe their symptoms [52]. As such, it is crucial to identify the signs of gastroesophageal reflux and seek appropriate medical attention. A healthcare professional specializing in ASD can determine the underlying cause of gastroesophageal reflux and suggest treatments like dietary adjustments, medications to reduce acid reflux, or other interventions as required[56]. Managing gastroesophageal reflux in individuals with ASD involves following standard guidelines for gastroesophageal reflux treatment. These may include making lifestyle changes such as adjusting their diet, elevating their head during sleep, managing their weight, and refraining from lying down right after eating. Depending on the severity of the condition, medications like antacids, proton pump inhibitors, or histamine-2 receptor blockers may be prescribed to reduce acid production or neutralize stomach acid[57].

Helping individuals with ASD communicate their discomfort and pain can be achieved through various methods, such as alternative communication, visual aids, or assistive technology[58]. Additionally, sensory therapy plans and integration strategies can be implemented at home to manage discomfort related to gastroesophageal reflux. This can involve activities that provide sensory input, offering comfort items like weighted blankets or fidget toys, or creating a sensory-friendly eating environment[59]. Consulting certified occupational therapists with a sensory integration specialty can be beneficial in creating specific plans to address abnormal sensory processes that contribute to behaviors associated with gastroesophageal reflux. These plans may include using sensory tools, training alternative coping skills, providing visual schedules, or employing positive reinforcement techniques[60]. Establishing routines and maintaining predictability can also help individuals with ASD manage disruptions caused by gastroesophageal reflux. Precise visual schedules and social stories can assist them in understanding and preparing for changes in their daily routine[61]. Consistent monitoring, follow-up, and open communication between caregivers, healthcare professionals, and educators are essential for effectively managing gastroesophageal reflux in individuals with ASD[62].

Abdominal pain

Individuals with ASD commonly report experiencing abdominal pain, which can have varying severities and causes, including GI and non-GI factors. To determine the underlying cause, conducting a comprehensive differential diagnosis is significantly essential. Several GI causes may affect individuals with ASD. These include gastroesophageal reflux disease, constipation, irritable bowel syndrome, food intolerances or sensitivities, and inflammatory bowel disease[5]. Gastroesophageal reflux disease is caused by stomach acid flowing back into the esophagus and can cause discomfort and irritation. Constipation can be more prevalent in individuals with ASD and may lead to abdominal pain. Irritable bowel syndrome is a functional GI disorder characterized by changes in bowel habits, bloating, and abdominal pain. Some individuals with ASD may have specific intolerances or sensitivities to certain foods, such as gluten or lactose. Inflammatory bowel disease, including crohn's disease and ulcerative colitis, involves chronic digestive tract inflammation and can cause abdominal pain[63].

Aside from GI causes, other factors can lead to abdominal pain, such as sensory sensitivities, urinary tract infections, musculoskeletal issues, anxiety and stress, and medication side effects. Individuals with ASD may experience heightened sensory responses, leading to discomfort from certain sensations like pressure on the abdomen, clothing textures, or internal sensations. Urinary tract infections, including bladder infections, can also cause abdominal pain, especially for those with difficulty expressing or communicating their symptoms[64]. Muscle strain, spasms, or other musculoskeletal problems can result in abdominal pain. Emotional factors like anxiety and stress can also have physical manifestations like abdominal pain. Furthermore, some medications used to treat ASD symptoms or other co-occurring conditions may list abdominal pain as a potential side effect[65].

Diagnosing abdominal pain in children with ASD can be challenging due to various factors. Communication and behavioral differences associated with ASD can make it difficult to assess the severity and identify the potential underlying causes of the pain. Children with ASD may have difficulty expressing their symptoms verbally or have limited communication skills[66]. Describing the location, intensity, or nature of their abdominal pain can be challenging, making it difficult for healthcare providers to assess the severity of the pain and identify potential underlying causes. They may also have heightened sensory sensitivities that can affect their perception and response to pain[67]. They may exhibit atypical reactions or engage in self-injury as a response to pain, which can complicate diagnosis. In addition, abdominal pain can present with various underlying causes, some of which may overlap with common behavioral or GI symptoms seen in ASD. Differentiating between primary GI issues and pain-related behaviors associated with ASD can be complex[68].

Diagnostic overshadowing is another problem involving correctly identifying abdominal pain in children with ASD. Healthcare providers may attribute symptoms solely to a child's ASD rather than considering other potential underlying medical conditions[69]. Abdominal pain may be overlooked or dismissed as a behavioral issue related to ASD, leading to delayed diagnosis and appropriate treatment. Furthermore, children with ASD often experience high anxiety levels and have difficulty coping with medical procedures or assessments, making it harder to conduct thorough physical examinations, laboratory tests, or imaging studies to identify the cause of abdominal pain[70]. It can be challenging for some patients with ASD to access appropriate healthcare, as they may encounter various barriers. These barriers can range from difficulties in healthcare settings to sensory overload or difficulty adapting to new environments. Unfortunately, limited access to healthcare can lead to delays in diagnosis and appropriate treatment, especially when addressing abdominal pain[71].

When children with ASD experience abdominal pain, they may express their discomfort differently. They may resort to aggression or self-injurious behaviors if they cannot effectively communicate their pain or frustration. Additionally, they may become more agitated or irritable, exhibit social withdrawal or isolation, and display changes in eating habits or disruptive behaviors during mealtimes. Chronic abdominal pain can also increase anxiety and emotional dysregulation, leading to outbursts, meltdowns, or heightened anxiety levels. Furthermore, sleep disturbances can occur, which can further exacerbate behavioral challenges and affect overall well-being and functioning[66,72].

To address these challenges, healthcare professionals may employ various strategies. One method uses visual aids, such as visual pain scales or communication boards, to help children express their pain levels and location[73]. Another approach is closely observing behavioral changes or non-verbal cues that may indicate discomfort or pain. Involving parents, caregivers, or teachers familiar with the child's behavior patterns can also provide valuable insights into changes in behavior or routines. A multidisciplinary team of pediatricians, gastroenterologists, psychologists, and occupational therapists can provide a comprehensive assessment and accurate diagnosis in complex cases[56]. It is crucial to acknowledge that every person with ASD is unique, and their medical background, sensory processing profiles, and behavioral patterns differ. Individual situations must be considered when assessing and addressing abdominal discomfort[74].

Diarrhea

Diarrhea can occur in individuals with ASD, just as it can affect anyone else. While diarrhea is not directly related to ASD, individuals with ASD may be more prone to specific GI issues, including diarrhea. Diarrhea can affect individuals with ASD for various reasons, and certain factors may increase these patients' diarrhea risk. These factors include sensory sensitivities and dietary preferences, dietary changes and restrictions, food intolerances and sensitivities, GI disorders, medications and supplements, and anxiety and stress. Pica is also a significant risk factor for diarrhea in children with ASD[49]. Pica, which is eating non-food items, is a behavior sometimes exhibited by individuals with ASD. While pica itself may not directly cause diarrhea, there are several ways by which ingesting non-food substances can increase the risk of developing GI issues, including diarrhea. These include irritation of the digestive system, blockages in the digestive tract, bacterial or parasitic infections, and nutritional imbalances. It's important to understand that pica is a complex

behavior with various underlying causes and can occur in individuals with or without ASD[75]. Chronic diarrhea could result from immune dysfunction, irritable bowel syndrome, inflammatory bowel disease, intestinal infection, food allergies, celiac disease, lactose intolerance, or excessive intake of sugary liquids such as fruit juices. In some cases, fecal encopresis due to severe chronic constipation can be misdiagnosed as chronic diarrhea[76]. However, it is essential to remember that not all individuals with ASD will experience diarrhea or have an increased risk compared to the general population. Each person is unique, and other co-occurring conditions or individual factors may also play a role[8].

Sometimes, children with ASD may display behaviors that resemble or are mistaken for diarrhea. These behaviors can be categorized into four groups: Sensory-seeking behaviors, repetitive or ritualistic behaviors, communication difficulties, and sensory sensitivities[77]. Sensory-seeking behaviors involve playing with materials that may resemble the appearance or consistency of diarrhea, such as enjoying squishing or smearing substances like playdough, mud, or other malleable materials, which may appear similar to diarrhea but are not actual fecal matter[78]. Repetitive behaviors may involve movements or actions around the diaper area that can be mistaken for diarrhea. Still, it is crucial to differentiate between purposeful behaviors and physical neuro-sensory symptoms. Children with ASD may have difficulties expressing themselves verbally, leading to unconventional means of communication that may be misinterpreted as indicating diarrhea. Lastly, sensory sensitivities can cause discomfort or aversion to certain physical sensations around the diaper area, which may be misinterpreted as diarrhea[79].

Managing diarrhea in patients with ASD requires a personalized approach that considers both general strategies for diarrhea management and specific considerations for the individual's unique needs and challenges associated with ASD. Hydration is crucial to keep the individual hydrated, and a balanced diet that includes easy-to-digest and gentle foods is key. Probiotics can help restore the natural balance of gut flora and aid digestion; medications or supplements may be necessary in some cases. Visual and social support, sensory accommodation, communication support, and personalized strategies are crucial for managing diarrhea effectively. It's essential to collaborate with healthcare professionals, clinical occupational therapists specialized and certified in sensory integration, and caregivers familiar with the individual's abilities to provide tailored strategies for managing diarrhea[80,81].

Constipation

Constipation is a common GI problem that individuals with ASD may be more susceptible to. While there is no direct link between ASD and constipation, some studies suggest that individuals with ASD are prone to experiencing constipation 3.5 times more than the general population[82]. The reasons for this are unclear, but several factors could contribute. Many individuals with ASD have sensory sensitivities, including sensitivities to certain textures or tastes of food. This may result in a limited diet lacking fiber-rich foods, leading to constipation. Some individuals with ASD may have limited food preferences or engage in selective eating patterns that exclude fruits, vegetables, and other high-fiber foods necessary for regular bowel movements[83]. Individuals with ASD may have difficulty recognizing and responding to bodily cues, such as the urge to have a bowel movement. This can lead to a delay in seeking a restroom or actively avoiding using the bathroom due to sensory sensitivities or rigid routines[84]. Some medications commonly prescribed for individuals with ASD, such as antipsychotics or certain antiepileptic drugs, can have constipation as a side effect, which can exacerbate the problem. Differences in the gut microbiome of individuals with ASD have been found in some studies, and changes in gut microbiota can influence bowel function and potentially contribute to constipation[85].

For individuals with ASD, constipation can sometimes lead to or be interpreted as abnormal behaviors. Although the precise connection between constipation and such behaviors is not yet fully understood, several factors could contribute to this association. One factor is sensory sensitivities, as many individuals with ASD are sensitive to certain sensations, and this discomfort can extend to constipation[86]. The physical discomfort and pain caused by constipation may lead to increased irritability, restlessness, or agitation, which could manifest as abnormal behaviors[87]. Communication challenges can also be a factor, as some individuals with ASD may have difficulty verbally expressing their discomfort or pain. They may instead resort to unconventional methods of communicating their distress[66]. Furthermore, individuals with ASD rely heavily on routines and predictability, and constipation can interfere with their daily routines, causing frustration or anxiety, leading to changes in behavior or increased rigidity in following established patterns[88]. Finally, constipation can cause discomfort and pain, leading to increased anxiety and stress levels in individuals with ASD, which can trigger or worsen abnormal behaviors to cope with physical and emotional distress[89].

When evaluating constipation in children with ASD, a comprehensive investigation is necessary to identify root causes and appropriate interventions. It's crucial to obtain a detailed medical history to understand the child's bowel habits, diet, fluid intake, and any previous diagnoses or treatments related to constipation. A physical examination is necessary to identify signs of constipation and any physical abnormalities that could contribute to it. A bowel movement diary can provide valuable information about bowel patterns, triggers, and dietary habits[90]. A dietary assessment is also essential to identify potential dietary factors contributing to constipation and assess the intake of fiber-rich foods, fruits, vegetables, and fluids[91]. Toileting skills should be evaluated to determine any challenges or difficulties related to recognizing the need to use the bathroom or any routines that may interfere with regular bowel movements[92]. Additional medical tests may be necessary to determine the severity of constipation or rule out underlying conditions. Collaboration with specialists may be beneficial in complex cases or if there are concerns about underlying medical conditions. An individualized management plan can be developed to address sensory sensitivities, communication challenges, or behavioral factors that may impact the child's ability to manage constipation effectively[93].

When dealing with constipation-related behaviors in individuals with ASD, it's essential to consider several approaches. Firstly, recognizing the signs of constipation and seeking medical intervention is vital. It's advisable to consult a healthcare professional experienced in ASD, as they can help identify the underlying cause of constipation and recommend appropriate treatments such as dietary modifications, fiber supplements, stool softeners, or laxatives[88]. Secondly, encouraging and facilitating effective communication can help individuals with ASD express their discomfort

and pain. Alternative communication methods, such as visual aids or assistive technology, can enhance communication and reduce frustration[58]. Thirdly, sensory strategies can help manage discomfort related to constipation. This may include providing sensory input through appropriate sensory activities, offering comfort items like weighted blankets or fidget toys, or creating a sensory-friendly bathroom environment to make bowel movements more comfortable[94]. Fourthly, collaborating with behavioral therapists or professionals experienced in working with individuals with ASD can be helpful. They can develop behavior support plans that address the specific abnormal behaviors associated with constipation. Strategies may include teaching alternative coping skills, providing visual schedules, or implementing positive reinforcement techniques[95]. Lastly, maintaining established routines and predictability as much as possible can help individuals with ASD manage the disruptions caused by constipation. Clear visual schedules and social stories can help them understand and prepare for changes in their daily routine[96].

All the previous strategies should work hand in hand with strategies aimed at relieving constipation. One effective strategy is adjusting one's diet to include fiber, fruits, vegetables, and whole grains. Individuals with sensory sensitivities may need gradual food diversification and the introduction of new textures and tastes[97]. Staying hydrated by drinking plenty of fluids, especially water, can help soften the stool and ease bowel movements[98]. Establishing a regular bathroom routine, preferably after meals, can also help develop a consistent routine for bowel movements. Regular exercise and physical activity can stimulate bowel movements and promote healthy digestion. If constipation persists and is associated with medication side effects, consulting with a healthcare professional is essential to explore potential adjustments in medication or additional treatments[99]. Regular follow-up and monitoring are crucial to assess the effectiveness of interventions and make necessary adjustments.

Coeliac disease

Coeliac disease and ASD are two distinct medical conditions that can sometimes exist simultaneously in an individual. Coeliac disease is an autoimmune condition that is triggered by consuming foods that contain gluten. It affects the small intestine, leading to inflammation and damage to the lining, which may cause various GI symptoms and nutritional deficiencies[100]. Although some studies and case reports suggest a possible link between coeliac disease and ASD, the exact nature of this connection remains unclear. Some scientists suggest that shared genetic or immune system abnormalities might contribute to some individuals' co-occurrence of these conditions[101]. However, further research is necessary to understand this association's underlying mechanisms and prevalence. Despite studies finding no higher prevalence of coeliac disease in patients with ASD, one child per 68 children with coeliac disease will develop ASD, and one child per 130 children with ASD will develop coeliac disease[9]. There is a strong association between coeliac disease, even in the absence of GI symptoms, epilepsy, and cerebral calcifications, and positive responses to dietary changes in these patients. Investigation and treatment of coeliac disease, non-coeliac gluten sensitivity (NCGS), and epilepsy, even without typical GI symptoms or overt seizures, could yield positive outcomes for patients with ASD[28].

It is essential to consider the possibility of non-coeliac gluten or wheat sensitivity in children with ASD, who are more likely to have atopy and allergies, especially if they show symptoms of irritable bowel[29]. When neurological manifestations with probable autoimmune etiology are unclear, it is recommended to determine the transglutaminase-2 autoantibody titer to consider the possibility of gluten sensitivity[102]. The relationship between coeliac disease and abnormal behavior in children with ASD is complex and not yet fully understood. Both coeliac disease and ASD share some symptoms, such as GI issues, irritability, anxiety, and sleep disturbances[103]. Consuming gluten can lead to inflammation and other immune responses that may affect behavior and cognition. Coeliac disease can also cause nutrient deficiencies, such as deficiencies in vitamins and minerals, which might contribute to abnormal behavior or exacerbate existing behavioral challenges in children with ASD[104]. While implementing a gluten-free diet in children with ASD who have coeliac disease or gluten sensitivity may improve behavior, communication, and social interaction, the evidence in this area is limited. Not all studies have shown consistent results. It's important to note that the impact of coeliac disease on behavior can vary among individuals[102].

It's worth noting that having coeliac disease doesn't necessarily mean an individual has ASD, and vice versa. These conditions can occur separately. However, if a child with ASD experiences GI symptoms or other signs that suggest coeliac disease, it's crucial to seek advice from a healthcare professional. Diagnosing coeliac disease in children with ASD follows a similar process to diagnosing coeliac disease in the general population, such as measuring tissue transglutaminase antibody test, determining HLA typing, and performing intestinal biopsies[105]. The gluten-free diet is currently the only effective treatment available and should be recommended for all patients with gluten sensitivity, regardless of the type of manifestations. Medical professionals should be aware of the possibility of NCGS in some patients with ASD, particularly those with atopic disease, migraine, mood, and anxiety disorders. Although many children with ASD improve on a gluten-free, soy-free, and dairy-free diet, it is essential to perform a celiac test before attempting this diet[106].

Impact of GI disorders on children with ASD

GI disorders can significantly impact children with ASD. GI disorders can affect all the child's life aspects; behavior, quality of life and well-being, social interaction: Communication abilities, education capabilities, and sleep patterns, and increase the risk of epilepsy. There is a strong correlation between GI symptoms and the severity of ASD, indicating that children more severely affected by ASD are likely to have severe GI symptoms. Health professionals should consider the possibility of GI dysfunction in patients with ASD, especially those presenting with strange posturing or movements, sleep disorders, food intolerances, and aggressive or self-injurious behaviors[80]. Table 1 summarizes the impact of GI disorders on the various life aspects of patients with ASD.

Table 1 Impact of gastrointestinal disorders on children with autism spectrum disorders

Domain	The impact
Patient's behavior	Abnormal posturing, self-injury, sudden outbursts, social withdrawal or isolation, and changes in eating habits
	Self-stimulatory behaviors
	Toe walking, increased irritability, restlessness, and agitation
	Poor attention, reduced food intake, or avoidance of certain foods
	Poor response to psychotropic medications
Patient's social interaction	Difficult engagement in social interactions
	Anxiety, irritability, and withdrawal from social situations with social avoidance
	Decrease the ability to engage in social play, follow social cues, or maintain relationships with peers and family members
	Poor development of social skills
Patient's sleep	Disrupted sleep patterns
	Disruption of sleep-wake cycles regulation
Patient's epilepsy	Altered brain electrical activity
	Increased risk of epileptic tendencies
	Decrease epilepsy thresholds
	Interactions with anti-epileptic medications
Patient's education	Increase absenteeism and poor attendance
	Poor academic performance
	Poor participation
	Decreased ability to concentrate
	Poor engagement in learning activities
	Reduced motivation and participation in classroom activities
	Poor participation in group activities
	Poor participation in food-related activities
	Poor cognitive functioning
Patient's quality of life	Poor eating, sleeping, and social interactions
	Reduced appetite, causing poor nutrition and weight loss

Impact on the patient's behavior

GI disorders can cause pain-induced agitation and irritability in children, leading to abnormal behaviors in individuals with ASD. For instance, GI pain may be mistaken for behavioral issues like abnormal posturing, self-injury, sudden outbursts, social withdrawal or isolation, and changes in eating habits. Individuals with ASD and oesophageal ulcerations may exhibit self-stimulatory behaviors in response to the pain or discomfort they experience[79]. Additionally, gastroesophageal reflux can lead to frequent nighttime awakenings. If the patient is experiencing constipation, it can lead to a range of behavioral changes such as toe walking, increased irritability, restlessness, and agitation. The patient may also experience abnormal sleep patterns, such as difficulties falling asleep, frequent awakenings, or restless sleep, resulting in daytime irritability, fatigue, and behavioral challenges[107]. Constipation can cause poor attention, reduced food intake, or avoidance of certain foods. Additionally, toilet training problems could be caused by chronic diarrhea or constipation. If the patient with ASD frequently digs into the rectal area, it could indicate anal itching, which parasitic infestations like enterobiasis may cause. However, if the GI disorder is identified and treated with medical intervention, the behavioral problem may decrease. It's important to note that psychotropic medications may not be effective and could worsen the issue if they have adverse GI effects, especially when abdominal pain or discomfort is present[108]. Table 2 summarizes the different behavior changes associated with GI disorders in individuals with ASD.

Impact on the patient's social interaction

For individuals with ASD, GI disorders can significantly affect their social interactions. The GI disorders-related discomfort can make it difficult for individuals with ASD to engage in social interactions, leading to anxiety, irritability, or a desire to withdraw from social situations[109]. The sensory discomfort associated with GI issues, like nausea or GI

Table 2 The different behavior changes that result from various gastrointestinal disorders

GI disorder	Behavior changes
Gastroesophageal reflux with/without ulcerations	Self-stimulatory behaviors (commonly called stimming)
	Constant eating/drinking/swallowing (grazing behavior)
	Frequent nighttime awakenings, abnormal posturing, pushing out the jaw, straining the neck, and tapping the throat, increased self-injury, and other challenging behaviors
Abdominal pain	Increased anxiety levels and emotional dysregulation, leading to outbursts and meltdowns
	Repetitive rocking and other repetitive behaviors.
	Blinking, sudden screaming, spinning, and fixed look
	Agitation: Pacing, jumping up and down
	Sleep disturbances, exacerbating the behavioral challenges and affecting overall well-being and functioning
Constipation	Tip-toe walking
	Increased irritability, restlessness, and agitation
	Abnormal sleep patterns, such as difficulties falling asleep, frequent awakenings, or restless sleep
	Daytime irritability, poor attention, fatigue, and behavioral challenges
	Reduced food intake, or avoidance of certain foods
	Toilet training problems
Diarrhea	Social withdrawal if the child is experiencing discomfort or embarrassment due to diarrhea
	Increased self-stimulatory behaviors like engagement in repetitive or self-stimulatory behaviors to self-soothe, especially during the time of discomfort
	Toilet training problems
	Change appetite with changing eating patterns or food preferences

distress, can be overwhelming and make it challenging for individuals to focus on social interactions or be present in social environments. The discomfort or pain caused by GI disorders may also interfere with verbal communication or affect the individual's ability to engage in reciprocal conversation, leading to limited social interactions and potential misunderstandings[67]. In addition, GI disorders-related behavioral changes can impact social interactions by affecting their ability to engage in social play, follow social cues, or maintain relationships with peers and family members. Meanwhile, GI disorders can increase anxiety in individuals with ASD, leading to social avoidance. They may develop fear or anxiety related to social situations due to concerns about experiencing GI symptoms or being unable to manage them in public. This social avoidance can limit opportunities for social interaction and hinder the development of social skills[110].

Impact on the patient's sleep

Individuals with ASD spectrum disorder often experience disrupted sleep patterns due to GI disorders. Studies have found a higher prevalence of GI issues among those with ASD, although the exact relationship between the two is still being researched. Symptoms such as constipation, diarrhea, abdominal pain, and acid reflux can cause significant discomfort and pain, making it challenging for people with ASD to fall asleep and stay asleep[111]. Moreover, sensory sensitivities among people with ASD can exacerbate the discomfort caused by such symptoms, making relaxation and sleep difficult. As individuals with ASD rely on routines and predictability to feel secure, any disruptions caused by GI disorders can lead to increased anxiety and difficulty in transitioning to sleep[112]. Changes in diet, medication, or medical procedures can also contribute to sleep disturbances. Additionally, GI disorders can disrupt the regulation of sleep-wake cycles, affecting the production and regulation of hormones and neurotransmitters essential for sleep regulation[113]. Therefore, it is crucial to address GI issues in people with ASD to manage physical symptoms and improve overall well-being. Effective management strategies may involve dietary modifications, medication, behavioral interventions, and addressing sensory sensitivities. Pediatric gastroenterologists and ASD-specializing dietitians can collaborate to develop these strategies[114].

Impact on the patient's brain activities and epileptic tendencies

Individuals with ASD who experience GI disorders may be at risk of epileptic tendencies due to the potential influence on brain electrical activities. The gut-brain axis facilitates bidirectional communication between the gut and brain, meaning disruptions in the gut, such as inflammation, altered gut microbiota, or intestinal permeability, can impact brain function and neural electrical activities[115]. Therefore, GI disorders in individuals with ASD may contribute to dysregulation in brain electrical activities through this gut-brain connection[116].

GI disorders have the potential to cause inflammation in the gut, which in turn releases pro-inflammatory molecules that can affect the brain and lead to neuroinflammation. This neuroinflammation has been linked to various neurological conditions, including epilepsy, and can result in altered brain electrical activity and an increased likelihood of seizures [40]. Chronic inflammation in the gut may also contribute to developing or worsening epileptic tendencies. Interestingly, some individuals with ASD, epilepsy, and GI disorders may share genetic factors contributing to these conditions. Specifically, genetic variations and mutations related to GI function and neuronal excitability can increase the risk of epilepsy[117]. These shared genetic factors may influence brain electrical activities and contribute to the co-occurrence of GI disorders and epileptic tendencies in individuals with ASD[118].

Individuals with ASD who are prone to epilepsy may experience seizures triggered by GI disorders, especially when combined with sensory sensitivities. Specific triggers, including certain foods, GI pain, or changes in gut microbiota, can increase the likelihood of seizures in susceptible individuals[119]. GI discomfort or inflammation can lower the seizure threshold and cause abnormal brain electrical activities. It is crucial to consider potential interactions between medications used to treat GI disorders and those prescribed for epilepsy[120]. Some medications, such as antacids, proton pump inhibitors, or antibiotics, may affect the efficacy of antiepileptic drugs or increase the risk of adverse effects. Careful management and medication monitoring are essential to minimize potential interactions and ensure optimal treatment for both conditions[121].

It is crucial to understand how GI disorders affect brain electrical activities and epileptic tendencies in individuals with ASD to provide comprehensive care[44]. A multidisciplinary approach involving gastroenterologists, neurologists, and other healthcare professionals must address GI and neurological aspects. Treatment strategies may include dietary modifications, targeted therapies for GI disorders, antiepileptic medications, and lifestyle adjustments to manage both conditions effectively. It is important to note that while there is an association between ASD, GI disorders, and epilepsy, the exact mechanisms underlying these relationships are still being investigated[122]. The impact of GI disorders on brain electrical activities and epileptic tendencies can vary among individuals with ASD, making personalized care plans tailored to each person's unique needs and challenges essential for optimal outcomes[123].

Impact on the child's learning

For individuals with ASD, GI disorders can significantly impact their learning and education. These disorders can affect various aspects of a student's educational experience, including academic performance, attendance, participation, and overall well-being[124]. GI disorders can impact education for individuals with ASD in different ways. GI disorders often cause physical discomfort and pain, making it challenging for students to concentrate and engage in learning activities. Persistent abdominal pain, bloating, or other symptoms can distract and affect students' ability to focus on their studies [125]. GI disorders can cause fatigue and a lack of energy in individuals with ASD, reducing motivation and participation in classroom activities. This makes it difficult for students to actively engage in lessons, complete assignments, or participate in group activities. Many individuals with ASD have sensitivities/over-responsivity that extend to food textures, pressure, tastes, smells, and GI movement[126]. In the case of GI disorders, certain foods or dietary restrictions may be necessary, which can further limit food choices and cause additional stress or anxiety for the student. This can make it difficult for them to navigate school environments where food-related activities are common[127]. Severe GI symptoms may lead to increased absenteeism from school. Students with ASD who experience frequent GI distress may need to miss school days or leave early due to discomfort or medical appointments. This can result in missed instruction, reduced participation in classroom activities, and disruptions in educational progress[128]. GI disorders can contribute to behavioral changes and emotional distress in individuals with ASD. The discomfort and pain associated with GI issues can lead to increased irritability, anxiety, or even meltdowns. These behavioral and emotional challenges can disrupt the learning environment and entirely hinder the student's ability to engage in educational activities[129]. Research suggests that there may be a bidirectional relationship between GI health and cognitive functioning. GI inflammation and imbalances in gut bacteria may affect mental processes, including attention, concentration, memory, and executive functioning. Consequently, students with ASD and GI disorders may experience difficulties in sensory and information processing and integration, problem-solving, and academic achievement[130]. Some individuals with autism and GI disorders may require specific dietary modifications to manage their symptoms. These dietary restrictions may limit their food choices and require accommodations in school settings. Collaborating with school staff may be necessary to ensure meeting the student's nutritional needs while maintaining a safe and inclusive environment[131].

Collaboration is key in addressing the educational impact of GI disorders on individuals with ASD. Educators, school staff, and parents can work together to support these students by implementing various strategies. This includes maintaining open communication between all parties to comprehensively understand the student's needs and challenges [132]. It also involves creating a supportive and understanding school environment that considers the unique needs and challenges of students with ASD and GI disorders. Sensory-friendly strategies, like providing quiet spaces for breaks and accommodating sensory sensitivities related to food, can also be implemented. Developing individualized learning plans or 504 plans in collaboration with healthcare professionals and families is crucial to address the student's specific needs [133]. Providing access to appropriate healthcare interventions, such as medication management, dietary adjustments, or therapies to manage GI symptoms, is also essential. Communication and collaboration between healthcare providers and school personnel help ensure consistency in managing the student's GI issues[134].

Academic accommodations should be offered. These accommodations may include flexible schedules, extra time for assignments or tests, and access to support services like occupational therapy and clinical psychology counseling. Creating a supportive and inclusive classroom environment that promotes understanding, empathy, and tolerance for individual differences is also crucial[135]. Sensory needs can be addressed through sensory environments, breaks, or by utilizing personalized/customized sensory tools by occupational therapists-sensory integration specialists to alleviate discomfort or anxiety related to GI issues. By addressing the impact of GI disorders on education and providing

appropriate support, individuals with ASD can have a better chance of achieving their learning goals and maximizing their potential[67].

Impact on the patient's quality of life

Individuals with ASD may experience a significant decline in their quality of life due to GI disorders. These disorders, including constipation, diarrhea, acid reflux, and abdominal pain, can cause persistent physical discomfort and pain. The discomfort can be distressing and affect daily activities, such as eating, sleeping, and social interactions[136]. It can also reduce appetite, cause poor nutrition, and lead to weight loss, further affecting overall health and well-being. Many individuals with ASD have sensory sensitivities, and GI symptoms can exacerbate these sensitivities[137]. The discomfort caused by GI issues, such as bloating or stomach pain, can be overwhelming for individuals with heightened sensory sensitivity, leading to increased anxiety and challenges in daily activities. Individuals with ASD often rely on routines and predictability to feel secure and comfortable. GI disorders can disrupt daily routines, increasing stress and anxiety [67]. Changes in diet, medication regimens, or medical procedures related to managing GI issues may require adjustments to established routines, which can be challenging for individuals with ASD and impact their overall quality of life. GI symptoms can affect social interactions and participation in activities[138]. Individuals with ASD may experience embarrassment, anxiety, or discomfort due to GI issues, leading to social withdrawal or avoidance of certain situations. This can impact their ability to form and maintain relationships, participate in social events, and engage in educational or vocational settings. Living with GI disorders can affect the emotional well-being of individuals with ASD [139]. Chronic pain, discomfort, and the challenges of managing GI symptoms can increase stress, anxiety, and depression. These emotional factors can further impact the overall quality of life and make engaging in activities and enjoying daily life difficult[140].

Improving the quality of life for individuals with ASD requires addressing their GI disorders. Seeking medical evaluation and management from healthcare professionals, such as pediatric gastroenterologists, occupational therapists specializing in sensory integration, and dietitians specializing in ASD, can effectively treat GI symptoms. Treatment options may include dietary modifications, medications, behavioral interventions, and occupational therapy based on sensory integration[56]. Equally important is providing support and understanding within the individual's social environment, including family, friends, and educators. Creating a supportive and inclusive environment that accommodates the individual's needs and ensures access to appropriate healthcare and educational resources can significantly enhance their overall quality of life[141]. It is essential to recognize that each person with ASD and GI disorders is unique, and the impact on their quality of life may vary. Therefore, a personalized approach that considers the individual's specific needs, challenges, and strengths is essential for promoting their well-being and enhancing their overall quality of life[142].

GI tract as a key for the diagnosis and evaluation of ASD

There is no definitive way to diagnose ASD based on examining the GI tract. Healthcare professionals, like psychiatrists, psychologists, and developmental pediatricians, primarily rely on behavioral assessments and observations to diagnose ASD. These assessments evaluate a person's social interactions, communication skills, and repetitive or restricted behaviors[143]. Although some have claimed that specific tests, such as stool analysis or measurements of specific gut bacteria, could help diagnose ASD, no consistent scientific evidence supports these claims[144]. Therefore, these tests are not regarded as reliable diagnostic tools for ASD. However, specific GI tests may lead to a higher likelihood of developing ASD or experiencing more severe symptoms of ASD.

Gut microbiota print

Research suggests that changes to a child's intestinal microbiota during their early years can impact their emotional and cognitive development later on. Specifically, certain species of bacteria found in the gut microbiota (or the absence of others) may play a significant role in the development of ASD[145,146]. Jendraszak *et al*[147] showed that children with ASD have a distinct fecal microbiota pattern different from the neurotypically developed children with lower *Bifidobacterium* spp. Kang *et al*[148] conducted a study comparing the bacterial composition in fecal samples from 19 children with ASD who had varying GI symptoms and 20 neurotypical controls with minimal GI symptoms. They used high-throughput sequencing of the 16S rDNA gene. The study found that the presence of autistic symptoms, rather than the severity of GI symptoms, was associated with lower levels of the bacterial genera *Prevotella*, *Coprococcus*, and unclassified *Veillonellaceae*. Furthermore, in their research, Adam *et al*[149] discovered a significant correlation between the severity of ASD and GI symptoms. This suggests that children with more severe ASD are more prone to experiencing intense GI symptoms and vice versa. It is also possible that underlying GI issues could contribute to the severity of ASD symptoms. However, it is regrettable that two recent meta-analyses have revealed inconsistent outcomes in investigating the intestinal microbiota of children with ASD through cohort studies[150,151].

A study by Wu *et al*[152] aimed to confirm previous research on the gut microbiome's association with ASD. They utilized machine learning techniques to identify potential biomarkers for ASD through feature selection and classification evaluation in training, validation, and independent diagnosis cohorts. The results revealed that *Prevotella*, *Roseburia*, *Ruminococcus*, *Megasphaera*, and *Streptococcus* could be potential biomarkers for ASD. *Prevotella* showed significant differences between patients with ASD and typical neuro-developers. Qureshi *et al*[153] investigated the differences in gut microbial metabolites between children with ASD and GI disorders and typically developing children without GI disorders. They also examined the effects of gut microbiota transfer therapy (MTT) on the fecal metabolites of the group with ASD. Using machine learning, they created 5-metabolite fecal models for classification, which showed significant changes before and after gut MTT. The developed multivariate metabolite models can potentially categorize children

with ASD from typically developed children effectively. These machine-learning models can also diagnose children with ASD by comparing their gut microbiome data with subjects with and without ASD. However, these findings did not align with the prediction model established by Zhai *et al*[154]. Various factors, such as environmental conditions and calculation methods, may influence intestinal microbiota composition. Additionally, the quality control of sequencing data may also affect the prediction model's accuracy[155]. Further studies are necessary to explore the gut microbiome's characteristics in ASD, particularly regarding interventions.

Alternations in gut permeability

Research has found that patients with ASD often experience changes in the integrity of their intestinal barrier. In one study, 75% of patients with ASD showed a reduction in the expression of "tight junction" components that form the barrier in the intestine[156]. Zonulin is a protein that regulates the tight junctions between enterocytes and controls how permeable the intestines are. In patients with ASD, the zonulin levels were higher than in healthy controls, which was associated with the severity of ASD symptoms[157]. This suggests that zonulin could be a valuable biomarker for a subgroup of children with ASD who have GI issues related to changes in intestinal integrity. Still, not all studies have confirmed this[158].

GI Tract as a key component in the management of ASD

Effectively managing GI disorders in patients with ASD can significantly benefit their overall well-being, improving their quality of life, better behavior, cognitive function, and educational abilities[159]. Addressing underlying GI issues such as chronic constipation, diarrhea, or gastroesophageal reflux can help alleviate physical discomfort and pain experienced by individuals with ASD. This can, in turn, lead to better digestion, enhanced nutrient absorption, and improved appetite. Properly addressing GI problems can also positively impact mood, attention, irritability, and hyperactivity, potentially reducing challenging behaviors[20]. As individuals with ASD often face communication and social interaction challenges, relieving GI symptoms can improve comfort, reduce distress, and better regulate their sensory systems, creating a more favorable environment for communication and social engagement[21]. Promoting a balanced gut microbiota may also positively affect brain function and cognition in individuals with ASD[160]. Relief from GI symptoms can improve sleep patterns, increase energy levels, and contribute to a general sense of well-being, ultimately leading to a better quality of life for the individual and improved family dynamics[161]. Therefore, the main aim of GI interventions is not to treat ASD but to improve nutritional status, reduce concomitant symptoms, ensure a balanced mood with decreasing anxiety, impulse control, aggression, and stereotypy, and increase the patient's independence.

Dietary intervention: Treating ASD through dietary interventions has garnered attention and research, although there is limited and contentious scientific evidence to support their effectiveness. It is crucial to recognize that ASD is a multifaceted neurological condition with diverse symptoms and underlying causes, and there is no universally applicable treatment. Nonetheless, specific dietary interventions have been studied in the context of ASD. Many individuals with ASD turn to nutritional interventions, with or without clinical supervision, to help alleviate GI and behavioral symptoms [162]. Different types of dietary interventions can be used for ASD, grouped into four main categories: elimination dietary therapy [*e.g.*, gluten-/casein-free diet, oligoantigenic diet, and specific carbohydrate diet (SCD)], modification dietary therapy (*e.g.*, modified ketogenic diet), supplementation dietary therapy (*e.g.*, minerals, vitamins like Vitamin B6, high dose Vitamin B12, and Vitamin D, antioxidants/polyphenolic compounds, omega 3, omega 6, and camel milk), and exclusion dietary therapy (*e.g.*, excluding food additives)[163]. Although there is significant interest in nutritional interventions for individuals with ASD, there is currently no consensus on the optimal dietary approach to pursue[164]. A meta-analysis conducted by Yu *et al*[165] has revealed that implementing specific dietary therapies can effectively improve the core symptoms associated with ASD. Adopting a gluten-free diet has been shown to impact social behaviors positively. Despite the promising outcomes, it is essential to note that the small sample size of randomized controlled trials currently limits the effectiveness of dietary therapy for ASD. Therefore, further well-designed and high-quality clinical trials are required to validate these conclusions.

Gluten-free casein-free (GFCF) diet

Eliminating gluten and casein from the diet is a commonly discussed approach for managing ASD. These proteins are found in wheat, other grains, and dairy products. The belief is that they may exacerbate ASD symptoms in certain individuals. It has been observed that children with ASD may have a sensitivity or intolerance to gluten and casein and may exhibit elevated levels of antibodies against certain substances, namely anti-gliadin, anti-casein, and dipeptidyl peptidase 4-a digestive enzyme that plays a crucial role in the breakdown of gliadin into various peptides including gliadinomorphin-7 which has "opioid activity", able to increase gut membrane permeability, stimulate opioid receptors, and decrease social interaction observed in children with ASD. Gluten also induces a state of systemic inflammation, including neuroinflammation[166,167]. It should be noted that among individuals with ASD, some may also have celiac disease or non-celiac gluten sensitivity. A double-blind, randomized controlled study by Hyman *et al*[168] involved 14 children between the ages of 3 and 5 with ASD. These children were put on a GFCF diet, and after 6 wk, they were given "dietary challenges" in the form of weekly snacks containing either gluten, casein, gluten plus casein, or neither. The children were monitored for an additional three months after three months of challenges. The study's findings indicate that the dietary challenges did not significantly affect the children's sleep quality, hyperactivity, or ASD behaviors. According to a systematic review conducted by Piwowarczyk *et al*[169], there is little evidence to support the effectiveness of a GFCF diet in alleviating symptoms of ASD in children. A recent meta-analysis by Quan *et al*[170] suggests that a GFCF diet may effectively reduce stereotypical behaviors and improve cognition in children with ASD. Despite most studies being single-blind, the potential benefits of a GFCF diet are encouraging. There is a need for further studies

on a larger scale to confirm these findings.

SCD

A SCD is a dietary approach that limits the intake of complex carbohydrates and specific sugars such as grains, starchy vegetables, lactose, and most processed sugars that are difficult to digest and may negatively affect gut health. On the other side, it allows the intake of specific types of carbohydrates that are believed to be easier to digest, such as monosaccharides and certain disaccharides. It is commonly used to manage conditions such as inflammatory bowel disease and celiac disease. This diet is believed to improve gut health, reduce inflammation, and potentially alleviate some ASD symptoms associated with gut-related issues[171,172]. Although some anecdotes exist on individuals with ASD experiencing better behavior, digestion, and overall well-being through the SCD, scientific research on its effectiveness for ASD is limited. Most studies have been hindered by limitations such as small sample sizes, absence of control groups, and variations in study design, making it difficult to arrive at definite conclusions regarding its efficacy. Therefore, it is crucial to approach SCD for ASD with caution and under the guidance of healthcare professionals[173,174].

Ketogenic diet

The ketogenic diet is a high-fat, low-carbohydrate, and adequate-protein diet that has gained attention for its potential therapeutic effects in various neurological conditions, including epilepsy. The ketogenic diet aims to shift the body's metabolism into ketosis, which primarily relies on fat for energy instead of carbohydrates. This metabolic state is likely to affect brain function and neurotransmitter activity, which may have implications for individuals with neurological conditions[175]. There are some physicians and families who have looked into using the ketogenic diet as a way to improve symptoms of ASD. Research suggests that the ketogenic diet can positively affect children with ASD by improving energy metabolism, reducing oxidative stress, controlling neurotransmitters, inhibiting the mammalian target of the rapamycin signaling pathway, and modulating the gut microbiota. These neuroprotective benefits demonstrate the ketogenic diet's potential as a helpful intervention for children with ASD[176]. The effectiveness of the ketogenic diet in addressing ASD symptoms is highly individualized and varies greatly depending on the child and their family's unique situation[177].

Although there have been some reports of anecdotal evidence showing improvement in behavior, communication, and social interaction, there has not been much research done on the effects of this diet on ASD. It's worth mentioning that while the ketogenic diet has shown some promise as a treatment for ASD, the scientific evidence is limited and inconclusive due to small sample sizes and a lack of control groups in most studies[178]. This makes it difficult to draw definitive conclusions about its effectiveness. Additionally, the ketogenic diet is highly specialized and restrictive, requiring close monitoring and supervision from healthcare professionals such as registered dietitians or physicians specializing in ketogenic diets. It can be challenging to implement and maintain, and there are potential risks and nutritional concerns, particularly for growing children[179]. When considering using the ketogenic diet for managing ASD, monitoring and providing proper guidance is essential. This includes assessing the need for dietary modifications, monitoring nutritional adequacy, and ensuring overall health and well-being[180].

Camel milk therapy

Camel milk is a nutritious and healthy alternative to cow's milk. It contains essential vitamins, minerals, and immunoglobulins, providing hypoallergenic, antioxidant, antibacterial, and antiviral properties. Moreover, it is easier to digest than milk from other ruminants making it more appealing to a broader range of consumers[181]. Recently, there has been growing interest in using camel milk as a possible aid for ASD. Camel milk advocates believe that it possesses distinct properties that could benefit individuals with ASD. Both research and personal accounts have suggested that camel milk may contain certain properties that could benefit those with ASD. These include lower lactose levels, unique protein structures, higher levels of vitamins and minerals, possible immune-regulating effects, and the ability to reduce oxidant stress[182,183]. Many people with ASD and their families have reported experiencing better behavior, digestion, and overall health after incorporating camel milk into their diet. According to the research conducted by Al-Ayadhi *et al*[184], the consumption of camel milk for a period of two weeks has been found to enhance the Childhood Autism Rating Scale (CARS), Social Responsiveness Scale (SRS), and ASD treatment evaluation checklist in children with ASD, as compared to those who consumed a placebo. According to a meta-analysis conducted by Kandeel and El-Deeb[185], the use of raw and boiled camel milk in treating ASD led to significantly lower CARS scores compared to the use of a placebo. The use of camel milk may be limited due to its comparatively high cost and short shelf-life. When it comes to discussing the potential benefits of camel milk for ASD symptoms, it's crucial to be cautious. The current research in this field is insufficient and frequently relies on small-scale studies with methodological constraints[186]. To ascertain the actual impact of camel milk on ASD symptoms, we require more rigorous and controlled studies.

High-dose Methylcobalamin (Vitamin B12) therapy

Methylcobalamin, or Vitamin B12, is a crucial nutrient that occurs naturally in the body. It is vital in various biochemical processes, including DNA synthesis and maintaining the nervous system[187,188]. Recent studies have examined the potential use of high-dose Methylcobalamin therapy to help individuals with ASD. Supporters of this therapy claim that it can enhance language and communication skills, behavior, attention, and overall well-being. They suggest it may have neuroprotective and neurotrophic effects, influencing brain function and behavior in people with ASD[189-191]. Research has shown that methylcobalamin may affect the redox status and potentially improve the clinical symptoms associated with ASD[192]. Some individuals with ASD may also have metabolic or genetic issues that could impact their vitamin B12 levels or metabolism[193]. Therefore, they can get benefit from methylcobalamin therapy.

A study by Čorejová *et al*[194] found that a 200-d treatment with 500 μg methylcobalamin orally daily gradually improved the clinical and psychological condition of children and adults with ASD. The social domain showed the most significant improvement, followed by cognitive, behavioral, and communication characteristics. The study also established a strong correlation between the changes in the clinical and psychological status and the level of reduced glutathione and reduced/oxidized glutathione ratio. According to a meta-analysis conducted by Rossignol and Frye [195], administering subcutaneous injections of methylcobalamin Vitamin B12 (64.5-75 μg/kg/dose two-to-three times weekly) can effectively improve metabolic abnormalities and clinical symptoms of ASD. These symptoms include expressive communication, personal and domestic daily living skills, interpersonal, play-leisure, and coping social skills, as well as sleep disorders, GI symptoms, hyperactivity, tantrums, nonverbal intellectual quotient, vision, eye contact, echolalia, stereotypy, anemia, and nocturnal enuresis. However, it should be noted that some patients may experience mild non-serious side effects such as hyperactivity, irritability, trouble sleeping, aggression, and worsening behaviors [195]. However, there are limitations to these studies, such as small sample sizes, lack of control groups, and variations in study design, making it difficult to determine the effectiveness of Methylcobalamin therapy for ASD.

Omega-3 supplement

Omega-3 fatty acids are vital polyunsaturated fats crucial to brain function and development. They are commonly found in fatty fish like salmon, mackerel, and sardines, as well as in some plant-based sources such as flaxseeds and walnuts [196]. Studies suggest that omega-3 fatty acids have anti-inflammatory and neuroprotective properties, which may support cognitive and behavioral processes, brain health, and development[197]. Although researchers have shown interest in exploring the potential benefits of omega-3 fatty acids, specifically eicosapentaenoic acid and docosahexaenoic acid , as a dietary intervention for ASD, the scientific evidence in this area is still limited and inconclusive[198]. Some studies indicate that omega-3 fatty acid supplementation may help address deficiencies associated with certain omega-3 fatty acids in the blood of some individuals with ASD, potentially improving ASD symptoms[199]. According to a meta-analysis conducted by Cheng *et al*[200], it has been found that omega-3 fatty acid supplementation may have positive effects on hyperactivity, lethargy, and stereotypy in individuals with ASD. However, the results of studies investigating the effects of omega-3 fatty acid supplementation in individuals with ASD have been mixed, and more extensive, well-controlled studies are needed to establish the efficacy and optimal dosing of omega-3 fatty acids for ASD[201]. Although omega-3 fatty acids may have potential benefits, they should be considered as part of a comprehensive treatment plan for ASD that includes a range of evidence-based interventions, therapies, educational strategies, and support services tailored to the specific needs of each person with ASD[199].

Other nutritional supplements

Studies have been conducted to investigate the effects of dietary supplements like vitamin B6, selenium, and magnesium on patients with ASD. Vitamin B6, a water-soluble vitamin, is crucial in various physiological processes, such as synthesizing brain function compounds and metabolizing neurotransmitters and amino acids[202]. Vitamin B6 supplementation has been explored as a potential treatment for ASD, but the scientific evidence supporting its effectiveness is limited and inconclusive. The interest in vitamin B6 for ASD stems from its involvement in the metabolism of neurotransmitters like dopamine and serotonin, which play a crucial role in brain function and behavior[203,204]. Some studies have examined the effects of vitamin B6 and magnesium supplementation, known as the "B6-Mg protocol", on individuals with ASD. While some studies have reported improvements in certain behaviors like social interaction, communication, and sensory issues, others have shown no significant effects. Study results may be due to differences in study design, participant characteristics, and outcome measures[205]. When discussing dietary interventions for ASD, it is crucial to exercise prudence and consider the unique needs, preferences, and circumstances of each individual with ASD. A holistic treatment approach for ASD typically comprises a blend of therapies, educational interventions, support services, and customized strategies tailored to the specific requirements of the individual[206].

Oral antifungal gut decontamination: There has been research into the possibility of fungi overgrowth in the GI tract contributing to ASD. Some scientists and medical professionals believe that excessive growth of fungi in the gut (gut defungemia hypothesis) may affect the behaviors and symptoms associated with ASD. The toxins released by an overgrowth of Candida species, a type of fungi, can enter the bloodstream and impact the brain, potentially leading to ASD symptoms. However, it is essential to remember that there is currently limited and inconclusive scientific evidence to support this theory[207]. Baker and Shaw[208] tested this theory by treating a child with symptomatic ASD. They found heavy GI fungal colonization with *Aspergillus*. They used the antifungal probiotic *Saccharomyces boulardii*, followed by increasing doses of itraconazole for strong antifungal therapy. The child experienced complete recovery from all ASD symptoms and even developed excellent academic, athletic, and musical skills. The recovery was accompanied by a significant reduction in urine markers of *Aspergillus* colonization, supporting the theory[208]. In a systematic review conducted by Herman and Herman[209], it was found that there were no significant differences between patients with and without antifungal medication. Therefore, it cannot be confirmed that Candida overgrowth is linked to ASD in children or causes ASD. Additionally, their findings do not entirely support the theory that Candida overgrowth is associated with GI issues and impacts ASD-related behavioral symptoms. Although there have been reports of changes in gut fungal composition among individuals with ASD, such as higher levels of Candida species, the link between increased gut candidiasis and ASD has not been definitively established. Small sample sizes, methodological issues, and inconsistent results often limit these studies.

Modification of gut microbiota: Researchers interested in managing ASD have given a growing interest in microbiota-based interventions, which involve modifying the gut microbiota. The gut microbiota is a diverse community of microor-

ganisms that reside in the GI tract and play a crucial role in various aspects of health, including immune function, metabolism, and brain development[210]. Research studies have revealed that people with ASD may have different gut microbiota compared to those without the condition. This has prompted researchers to explore whether gut microbiota plays a role in developing and expressing ASD symptoms. The goal is to improve ASD-related symptoms by adjusting the gut microbiota to a healthier composition[47]. There are different approaches to modifying the gut microbiota, including: Antibiotics and dietary interventions, probiotic and prebiotic interventions, and fecal microbiota transplant (FMT) therapy.

Antibiotics and dietary interventions

There is a conflicting opinion regarding the beneficial use of antibiotics in restoring gut dysbiosis and reducing GI and behavioral symptoms in children with ASD. However, there are still ongoing debates surrounding the use of antibiotics. Antibiotics eliminate harmful and beneficial bacteria in patients with ASD, which may increase the likelihood of GI illnesses in affected children. As a result, antibiotic therapy may not be the most effective approach for restoring gut microbiota balance[211]. Studies have demonstrated that a Mediterranean diet can improve GI health, cardiovascular diseases, and neurobehavioral health outcomes[212]. The effectiveness of a ketogenic diet has also been explored, with positive results in mitigating neurobehavioral symptoms[213]. The gluten-free and GFCF diet is another popular approach, with some studies showing favorable results in improving symptoms such as communication, social interaction, and GI issues[214]. However, recent studies have shown that restrictive diets can potentially have harmful effects, resulting in nutrient deficiencies and high costs for families. The standard of dietary intervention is also strict and may not apply to all ASD patients[215].

Probiotic and prebiotic interventions

Probiotics are microorganisms that can provide health benefits when taken in sufficient quantities. There have been studies on using specific probiotic strains to balance gut bacteria and potentially improve symptoms in people with ASD [216]. However, the evidence for the effectiveness of probiotics in treating ASD is limited and inconsistent[217]. Prebiotics are non-digestible fibers that can promote the growth of healthy gut bacteria. By consuming prebiotics, the gut microbiota can become more balanced[218]. Some studies have looked into the effects of prebiotic supplements on individuals with ASD, but further research is required to determine the impact on ASD symptoms[219]. As the gut-brain axis has two-way communication, probiotic intervention may decrease the prevalence of ASD by affecting related gene expression in infants. However, the specificity of the gut microbiota in different patients suggests the need for precision medicine tailored to specific subpopulations of patients[220].

According to Sanctuary *et al*[221] pilot study, the intake of *Bifidobacterium infantis* probiotic and a bovine colostrum product for five weeks was well-tolerated and effectively lowered the occurrence of specific GI symptoms. Additionally, it reduced the occurrence of certain abnormal behaviors. Furthermore, a study by Kong *et al*[222] found that using a combination of *Lactobacillus plantarum PS128* probiotic for 28 wk and oxytocin for 12 wk resulted in significant improvement in the SRS, aberrant behavior checklist, and clinical global impression scale. The combination also led to the growth of favorable gut microbiome network hubs. The study also revealed that the effectiveness of the combination treatment in enhancing social cognition is highly linked to the abundance of the *Eubacterium hallii* group.

FMT therapy

A potential solution for gut dysbiosis in children with ASD is a FMT. This procedure transfers fecal microbiota from healthy donors into an individual's GI tract to balance their gut microbiota. FMT has shown promising results in treating certain GI conditions and can improve GI and neurobehavioral symptoms in younger children with ASD[223]. However, it may only work for some older patients. Despite its benefits, FMT can cause adverse reactions in some patients, so a modified protocol called MTT was developed. MTT involves oral vancomycin treatment, bowel cleansing, and oral or rectal administration of standardized human gut microbiota[224]. Studies have shown that MTT can improve behavioral symptoms and increase the diversity of gut bacteria in children with ASD. The effects of MTT can last for at least two years after treatment. These results suggest that overall gut microbe rebalancing may be a promising approach to treating gut microbiota dysbiosis in ASD[47]. However, FMT use in ASD is still in its early stages and requires further research to establish its safety and efficacy.

When seeking interventions for individuals with ASD, it is essential to remember that while microbiota-based treatments show promise, they are still a developing field. Further research is necessary to determine their effectiveness, optimal protocols, and long-term effects on those with ASD[225]. Healthcare professionals with expertise in this field are recommended to oversee these interventions. Additionally, a comprehensive approach that includes evidence-based therapies, educational interventions, support services, and individualized strategies tailored to the specific needs of each person with ASD should be considered. Modifying the gut microbiota should be viewed as a component of a more extensive treatment plan, and healthcare professionals should be consulted when deciding on specific interventions[226].

Limitations of the study

It's important to remember that there are some limitations to the article's findings regarding the association between GI health and ASD symptoms. While the article suggests a potential link, it cannot definitively establish a causal relationship. It's worth noting that many of the studies included in the review relied on observational data or retrospective analysis, which may introduce biases and confounding factors that can impact the results. Additionally, some of the studies were limited by small sample sizes or specific populations, making it difficult to generalize the

findings. To better understand the relationship between these factors, we need more large-scale studies with strong controls to minimize potential biases and confounding factors.

CONCLUSION

This review article delves into the extensive research on the connection between GI health and ASD. We have summarized the key findings from the literature, highlighted areas of agreement and disagreement, and examined the implications of these outcomes for future research. Children with ASD are more susceptible to GI disorders than the general population, which can significantly impact their health, learning, and development due to genetic, environmental, and behavioral factors. GI disorders can arise from gut dysbiosis, immune dysfunction, food sensitivities, digestive enzyme deficiencies, and sensory processing and integration differences. Current research suggests that numerous children with ASD experience GI disorders, and effective management is critical. Behavioral assessments and observations are the preferred methods for diagnosing ASD, and GI tests are not consistently supported by scientific evidence for reliable diagnostic tools. However, certain GI tests may increase the risk of developing ASD or experiencing more severe symptoms. Addressing GI problems in individuals with ASD can improve their overall well-being, leading to better behavior, cognitive function, and learning abilities. Properly addressing GI issues can relieve physical discomfort and pain, promoting better digestion, enhanced nutrient absorption, and improved appetite. Alleviating GI symptoms can improve sleep patterns, increase energy levels, and contribute to a general sense of well-being, ultimately leading to a better quality of life for the individual and improved family dynamics. The primary objective of GI interventions is to improve nutritional status, reduce symptom severity, promote a balanced mood, and increase patient independence.

Recommendation

It is essential to support research on GI disorders' causes, mechanisms, and treatments in children with ASD. Healthcare professionals should receive training on diagnosing and treating such conditions and implementing evidence-based interventions. Effective management of GI problems can be achieved through medical team intervention and management, occupational therapy based on sensory integration in all settings the child uses, communication, and behavior support plans. Early identification and treatment of these disorders can improve overall well-being and prevent long-term complications. A multi-transdisciplinary approach is often necessary to provide comprehensive care.

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Abstract

Neuromuscular diseases (NMDs) affect the development and growth of the neuromuscular system in children. The pathology can occur anywhere along the neuromuscular pathway, from the brain to the nerves to the muscle fibers. These diseases have a profound impact on the quality of life not only of children but also of their families. The predominant manifestation in NMDs is hypotonia, which leads to muscle weakness and fatigue, reduced mobility, and decreased physical performance. However, multiple organ systems can be affected, with resulting orthopedic, cardiac, infectious, respiratory, and nutritional problems. Children with NMD present an increased risk for several dietary and feeding difficulties because of their neuromuscular diagnosis, presentation, and severity. These problems include chronic gastrointestinal issues (constipation, dysphagia, gastro-esophageal reflux, and diarrhea), dysphagia, malnutrition, and body composition alterations. As a result, compared to the overall pediatric population, infants and children with NMD are more likely to be malnourished, ranging from failure to thrive to overweight or obesity. Disease-specific guidelines vary in level of detail and recommendations for dietary management. Overall, nutritional data available are sparse, with the exception of Duchenne muscular dystrophy, spinal muscular atrophy, and congenital muscular dystrophy. The purpose of this review is to describe the spectrum of nutritional challenges in children with NMD and to summarize the main dietary and gastrointestinal recommendations for each neuromuscular disorder to provide guidance for daily clinical practice.

Key Words: Neuromuscular disorders; Diet; Malnutrition; Overweight; Dysphagia; Gastrointestinal dysmotility; Gastrointestinal symptoms; Tube feeding

Core Tip: Pediatric neuromuscular disorders (NMDs) can be associated with a range of nutritional issues, such as insufficient or excessive weight gain, difficulty in swallowing, constipation, diarrhea, vomiting, gastroesophageal reflux disease, and micronutrient deficiencies. We herein discuss the spectrum of nutritional challenges in children with NMD and summarize the currently available dietary and gastrointestinal recommendations for each neuromuscular disorder to provide guidance for daily clinical practice.

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INTRODUCTION

Pediatric neuromuscular disorders (NMDs) include a variety of diseases where the peripheral nervous system is the main site of abnormalities or damage. These include disorders of the anterior horn cell (*i.e.*, spinal muscular atrophy, poliomyelitis, and amyotrophic lateral sclerosis), peripheral nerve (*i.e.*, Charcot-Marie-Tooth disease), neuromuscular junction (*i.e.*, congenital myasthenic syndrome), and musculature (*i.e.*, myopathies and muscular dystrophies)[1]. The main and most frequent symptom in NMDs is hypotonia, which leads to muscle weakness, fatigue, reduced mobility, and decreased physical performance. Furthermore, a deterioration of the quality of life for NMD patients and their families is frequently brought on by orthopedic, cardiac, infectious, and respiratory issues[2]. Nutritional and gastrointestinal complications are also frequent in NMDs, but they are sometimes underestimated[2]. Compared with the general pediatric population, infants and children with NMDs are at higher risk of malnutrition, ranging from failure to thrive to being overweight or obese (Table 1)[3,4].

Moreover, they present an increased risk of developing chronic gastrointestinal (GI) conditions such as constipation, gastroesophageal reflux disease (GERD), dysphagia, and delayed gastric emptying. Several aspects related to nutrition need to be considered when prolonging survival in patients with NMD, including the negative impact of overnutrition on glucose metabolism, mobility, respiratory, and cardiac function and the effects of undernutrition on muscle development and strength ventilation function. In addition, difficulty chewing and swallowing can lead to a higher risk of aspiration, which predisposes to infectious diseases and respiratory issues[2]. Micronutrient deficiencies, such as vitamin D and calcium deficiencies, can affect bone health, particularly in children with Duchenne muscular dystrophy (DMD) who receive steroids (side effects include bone loss and fractures)[4,5].

The importance of optimal nutritional and GI management lies in reducing complications and mortality and improving the quality of life in this group of patients[4,5]. A particular attention to these issues is required with an early and appropriate approach. The purpose of this review is to describe the spectrum of nutritional problems in children with NMD and to provide specific dietary and GI recommendations for each NMD.

MATERIALS AND METHODS

For this review, relevant studies published over the last 20 years were identified *via* a PubMed/Medline (http://www.ncbi.nlm.nih.gov/pubmed/) search using the following keywords or combinations of keywords: neuromuscular disorders, malnutrition, overnutrition, diet, GI symptoms, management, guidelines. All of the most common neuromuscular disorders were afterwards used as search terms to review literature data regarding the GI and nutritional issues. Particular emphasis was placed on evidence-based guidelines and all high-quality studies illustrating current management pathways. Additional papers were identified by reviewing reference lists of relevant publications. Non-English publications were excluded. A systematic approach to study selection was not implemented. Instead, data were extracted based on their relevance to the topic.

RESULTS

Duchenne muscolar dystrophy

DMD is an X-linked recessive disorder caused by out-of-frame mutations in the dystrophin gene (DMD; locus Xp21.2). These mutations result in a deficiency or absence of the protein dystrophin, leading to progressive muscle degeneration and the loss of the ability to walk independently[6]. The type of mutation and how it affects dystrophin synthesis are the primary factors in the different phenotypic expression[6]. There are also milder allelic forms of the disease, such as intermediate muscular dystrophy and Becker muscular dystrophy, which result in loss of walking ability by ages 13-16 and over 16, respectively[7]. DMD affects 1 in 3600-6000 male births and is the most common pediatric muscular dystrophy[7]. Initial presentation ranges from motor delay, walking slowly, and difficulty getting up from the floor (Gower's sign) to loss of the ability to walk and use of a wheelchair for mobility (since adolescence) without treatment[8].

Table 1 Neuromuscular diseases and Neuromuscular disorder-related nutritional issues

NMD	Potential nutritional issue(s)
Spinal muscular atrophy	Dysphagia, weight loss[a]
Duchenne muscular dystrophy	Overweight/obesity, dysphagia, weight loss[b]
Myotonic dystrophy type 1	Weight loss/underweight, feeding difficulties
Congenital myopathies	Underweight/growth failure, feeding and swallowing difficulty
Charcot-Marie-Tooth disease	Unknown
Limb-Girdle muscular dystrophy	Unknown

[a]Especially spinal muscular atrophy type I and II.
[b]In later stages of Duchenne muscular dystrophy (due to progressive muscle weakness).
NMDs: Neuromuscular disorders.

Glucocorticoids (GCs) (prednisone 0.75 mg/kg/d as first-line unless otherwise indicated) are the only drugs that currently supports children with DMD in maintaining muscle strength and functionality[1]. GCs are relatively well tolerated, although significant weight gain and small height gains are commonly observed. Other (rare) serious side effects include hypertension, glycosuria, osteoporosis, GI lesions, and adrenal crisis[1].

To help multidisciplinary care teams manage this complex pathology, the US Centers for Disease Control and Prevention (CDC) selected a working group in 2018 to develop DMD care recommendations, including consideration of diet and GI health[9]. The most important goals in nutritional and gastrointestinal management include: (1) Optimization of macronutrient intake to avoid growth failure or obesity; (2) management of feeding and swallowing issues; (3) treatment of the GI symptoms; and (4) monitoring micronutrient intakes such as vitamin D and calcium[9]. Nutritional and GI evidence for DMD children is summarized in Table 2.

Nutritional management

The purpose of nutritional management is to prevent overweight or obesity and under- or malnutrition through regular assessment of growth and weight and the promotion of a healthy, balanced diet. A registered dietitian, an essential member of the multidisciplinary DMD care team, should record the patient's weight and height on growth charts[9].

Unlike other NMDs, specific growth curves are available for DMD. In a sample of 26 patients with DMD, Griffiths *et al* [10] estimated total muscle mass using 24-h urine creatinine excretion and discovered a 4% loss in muscle mass per year.

The authors developed a weight *vs* age curve for DMD that would determine the appropriate percentile by initially identifying the percentiles on a standard percentile height table. Recent studies have revealed that urinary creatinine excretion is not a reliable predictor of skeletal muscle mass in DMD, which challenges the logic of these charts based on [11]. Using recurrent growth measurements in a cohort of 513 DMD individuals aged 2 to 12 years from the Muscular Dystrophy Surveillance, Tracking, and Research Network, West *et al*[12] created growth curves specifically for DMD. Based on the CDC clinical growth charts, these curves demonstrated that male DMD patients were shorter than unaffected boys and tended to be overweight. The same team, later, visited the Muscular Dystrophy Surveillance, Tracking, and Research Network cohort to survey it, and they recently presented growth data in a cohort of 324 outpatients receiving GC therapy for at least 6 mo[13]. In contrast to untreated patients, this cohort had shorter stature, more weight, and a higher body mass index[9].

After a correct interpretation of the anthropometric measurements, the dietician should offer a nutritional plan that includes recommendations for increasing, decreasing, or maintaining caloric intake and water requirement as well as suggestions for modifying food textures to promote secure and pleasurable chewing and swallowing[9].

In the case of DMD and other NMDs, patient obesity is often attributed to a reduction in calorie requirements coupled with a decrease in physical activity and resting energy expenditure. In addition, chronic treatment with steroids can increase appetite and promote excess caloric intake. Instead, patients in the late stages of the disease may be malnourished and underweight[2,9]. Muscle weakness and its sequelae (dysphagia, constipation, delayed gastric emptying, prolonged mealtimes, and dependent food intake) are the main causes of malnutrition, and the presence of respiratory failure can cause increased energy demands. The result of malnutrition and increased energy needs is a negative energy balance and progressive weight loss[9].

As the disease progresses, most patients begin to experience increasing difficulty with chewing and swallowing[14]. The onset of dysphagia symptoms can be gradual, and the impact of oral-pharyngeal dysphagia might be under-recognized and under-reported by patients[15]. Dysphagia may manifest as unintentional weight loss or a slowing of the normal age-related weight growth. Tube feeding *via* gastrostomy should be considered early in patients with DMD. In the absence of symptoms consistent with suspected GERD, a polymeric formula may be considered initially. Alternatively, bolus feeding with home-made foods can be suggested and effective in children with chronic constipation[9].

According to the 2018 DMD Care Considerations, serum calcium and 25-hydroxyvitamin D levels should be regularly monitored once a year as part of routine bone health management. Vitamin D and mineral supplementation should be considered in all children if levels cannot be maintained[15].

Table 2 Nutritional and gastrointestinal management in children with Duchenne muscular dystrophy

Issue	Evidence
Tube feeding	Low to high probability (based on the stage of the disease)
Energy needs	Meet DRI
Formula	No special diet or formula
ONS	Possible; consider a speech-language therapist evaluation
Gastroesophageal reflux	Proton pump inhibitors; consider hydrolyzed or natural food enteral formulas
Constipation	PEG; consider hydrolyzed or natural food enteral formulas
Delayed gastric emptying	Meet fiber and fluid needs; prokinetics may be used

DMD: Duchenne muscular dystrophy; DRI: Daily recommended intake; ONS: Oral nutrition supplements; PEG: Polyethylene glycol.

GI symptoms management

The most common GI symptoms in DMD patients are GERD and constipation. GER may be related to altered gastric smooth muscle cell emptying function. Treatment includes the early use of proton pump inhibitors. Regarding constipation, the use of polyethylene glycol after gastrostomy placement is recommended to prevent the use of high oral volumes, both of which are associated with the risk of bronchoaspiration[2]. Increasing fiber intake or using natural food enteral formulas could also be considered to treat constipation[16,17].

SPINAL MUSCULAR ATROPHY

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disease caused by a homozygous mutation or deletion in the survival motor neuron 1 (SMN1) gene. Defects in the SMN1 gene cause the selective destruction of alpha motor neurons in the anterior horn cells of the spinal cord and brainstem. Clinical manifestations include muscle atrophy and weakness, resulting in swallowing and feeding difficulties and respiratory complications. SMA affects approximately one in 6000-10000 newborns worldwide[18]. The classification of SMA consists of four subtypes based on age of onset and maximal functional ability: very weak infants unable to sit unsupported, onset < 6 mo of age (type 1), nonambulant patients able to sit independently, onset between 6 and 18 mo of age (type 2), ambulant patients with onset between 18 mo and 18 years (type 3), and adult onset SMA (type 4).

The SMA multidisciplinary care focuses on reducing complications and improving quality of life. Symptoms of GI dysfunction, including constipation, delayed gastric emptying, and GERD, are important determinants of mortality and morbidity, for example dysphagia and reflux can lead to pulmonary disease[19].

In 2007, a consensus statement was published by the International Conference on the Standard of Care for SMA. A two-part update of the topics covered in the prior recommendations was published in 2018 as a result of the more current data publications and more generally made advancements in the themes mentioned in the original version[20].

One of the nine topics included in this update focused on nutrition. The main nutritional goals, which are slightly different for each type of SMA, include weight control, swallowing and dysphagia management, and management of GI dysfunction. Regular growth checks are important for all SMA types. Growth and body composition are measured using a variety of methods, such as basic anthropometry, dual-energy X-ray absorptiometry, and bioelectrical impedance analysis[19,20].

Specific growth charts for SMA are not currently available. Due to modifying body composition in standardized SMA growth charts, it may be helpful to monitor growth trends rather than monitor weight. In contrast, children with SMA type III are prone to overeating and obesity from physical inactivity and have reduced energy needs due to lower basal metabolic rates[3].

For optimal care, a nutritionist assessment is recommended every 3-6 mo for younger children and annually for older children and adults[20]. In addition, a qualified dietician should also promote healthy nutrition and keep track of hydration, macronutrient, and micronutrient intake, particularly calcium and vitamin D intake for bone health. Calcium and vitamin D supplements are recommended if the levels are low. It's crucial to inquire and record the specifics of GI symptoms in all subjects, which could include GERD, constipation, use of bowel regulators, delayed gastric emptying, and vomiting.

Infants and children with SMA types I and II should receive gastrostomies in the first few months of life to avoid the risk of malnutrition. This approach is also recommended to reduce the risk of respiratory infections[20]. Nutritional and GI evidence for SMA children is summarized in Table 3.

Non-sitter patients

Some aspects of nutrition assessments and interventions can differ among non-sitters, sitters, and ambulant patients[20]. One of the most significant considerations to take into account for a non-sitting child is safe swallowing, as bulbar dysfunction can lead to aspiration and lung infections. Recent data suggest that children with SMA type 1 should have a

Table 3 Nutritional and gastrointestinal management in children with spinal muscular atrophy

Issue	Evidence
Tube feeding	High probability (type 1 and 2)
Energy needs	Meet DRI
Formula	No special diet or formula
ONS	Possible (type 3 and 4); consider a speech-language therapist evaluation
Gastroesophageal reflux	Proton pump inhibitors; consider hydrolyzed or natural food enteral formulas
Constipation	PEG; consider hydrolyzed or natural food enteral formulas
Delayed gastric emptying	Meet fiber and fluid needs; prokinetics may be used

DRI: Daily recommended intake; ONS: Oral nutrition supplements; PEG: Polyethylene glycol.

videofluoroscopic swallow examination soon after diagnosis and when there are clinical indications suggestive of dysphagia (weak sucking, fatigue, a wet voice, pneumonia) to assess bulbar function and prevent growth failure[21,22]. In type 1 patient, reduced caloric intake and the possibility of malnutrition are caused by respiratory issues, dysphagia, and weak masticatory muscles. In addition, tachypnea can increase energy expenditure and calorie needs, further increasing the risk of malnutrition[20].

Sitter patients

Sitter patients may have a higher risk of being overweight or obese as a result of reductions in physical activity due to weakness and altered body composition[3,23]. Obesity can lead to reduced mobility and increased risks for associated comorbidities, including the metabolic syndrome.

Walkers

Swallowing disorders and feeding problems are rare in walkers[20]. The main nutritional concern is the risk of obesity and overweight, as these conditions can impair mobility and raise the possibility of comorbidities like metabolic syndrome, hypertension, and diabetes[3,20].

CHARCOT-MARIE-TOOTH DISEASE

Charcot-Marie-Tooth disease (CMT) is the most common inherited NMD with an estimated prevalence of up to 40 in 100000 people, which corresponds to 200000 cases in the European Union[24]. The disease generally appears in the first two decades of life and progresses slowly over many years. It is a genetically heterogeneous disorder resulting from mutations in genes that encode proteins in various locations, which include compact and non-compact myelin, Schwann cells, and axons. These proteins are involved in a wide variety of functions, including myelin compaction and maintenance, formation of the cytoskeleton and axonal transport rich, as well as mitochondrial metabolism[25]. Since motor and sensory peripheral nerves are affected, CMT is also known as hereditary motor and sensory neuropathy. Distal weakness, hand and foot deformities, slow loss of sensory perception, and mild to moderate disability are the most common clinical phenotypes.

There is still no effective drug therapy for CMT. A multidisciplinary approach is necessary for therapeutic management; the neurologist should work closely with other professionals such as orthopedics for the surgical treatment of skeletal deformities and soft tissue anomalies[1,25].

There are no specific nutritional recommendations for this patient group, and the nutritional approach must be evaluated individually. Sometimes the use of oral nutritional supplements may be recommended. Skeletal deformities may be associated with an increased risk of GERD.

CONGENITAL MUSCULAR DYSTROPHIES

Congenital muscular dystrophies (CMD) are a group of genetic neuromuscular disorders defined by muscle weakness that appears at birth or in the first few months of life and the presence of dystrophic biopsies and/or increased creatine kinase, two markers that are diagnostic of a muscular dystrophy[26]. The identification of different CMD subtypes backed by precise gene identification has been made possible by developments in molecular genetics and histopathology techniques[27]. Despite rapid advances in basic research, clinical care for patients with CMD remains poor due to the rarity of this pathology and the difficulty of differentiating clinical phenotypes.

The International Standard of Care Committee for Congenital Muscular Dystrophy published a consensus statement in November 2009 on standards of medical care divided into 7 areas: Diagnosis, neurology, pulmonology, orthopedics,

gastroenterology and nutrition, speech, and oral care, cardiology, and palliative care[28]. Main topics are nutrition and growth, food intake, GI motility, and oral care[28]. There are no specific growth charts or data on the energy and nutritional needs of CMD children, and this makes monitoring nutrition and growth even more difficult[28]. Patients with CMD often have a growth trajectory that is below age, and one of the most typical childhood problems is malnutrition and poor weight gain. Instead, obesity should be considered in adults due to the limited mobility of these patients.

In this group of patients, special attention needs to be paid to feeding and swallowing problems, which should be evaluated regularly during routine clinic visits, asking about: (1) Length of meals; (2) frequency of meals; (3) frequency of lung infections; (4) difficulty chewing (choking and coughing); (5) change in the structure of food; (6) stress in the family or enjoyment of meals for the child and parents; and (7) ability to eat independently. Videofluoroscopy can reveal difficulties in the oral phase, a delay in pharyngeal swallowing, and increased risks with aspiration[28]. In the case of dysphagia and feeding problems, treatment strategies may include adjustments in standing positioning and sitting, support for self-feeding, which include adjustment of feeding utensils and devices, safe swallowing procedures, and texture modification. When symptomatic treatment is inadequate, the use of tube feeding must be considered.

GERD and GI dysmotility, *i.e.*, delayed gastric emptying and constipation, are common in CMD patients. In order to minimize the risk of gastroesophageal reflux and dysmotility, the frequency and volume of tube feeding should be adjusted and attention should be paid to adequate fluid intake, posture, and movement. Medical treatment includes use of proton pump inhibitors and treatment with antacids and laxatives for GERD and constipation, respectively[28]. Increasing fiber intake or using natural food enteral formulas could also be considered to treat constipation[16,17].

MYOTONIC DYSTROPHY

Myotonic dystrophy (MD) is the most common form of muscular dystrophy in adults, with an estimated prevalence of 1 in 8000[29]. Myotonia and muscular dystrophy were traditionally used to name this multisystem condition. Myotonic dystrophy type 1 (MD1, Steinert disease) is caused by a cytosine, thymine, and guanine repeat expansion in the 3rd untranslated region of the myotonic dystrophy protein kinase gene on chromosome 19[30]. MD1 patients range from asymptomatic or moderately severe, late adult onset to severe congenital variants, with an autosomal dominant inheritance pattern. In particular, congenital MD is the most severe form and may present prenatally with polyhydramnios and reduced fetal movements.

Respiratory failure, hypotension, feeding difficulty, weakness, and tented or fish-shaped upper lips are all frequent at birth[30]. Facial weakness, dysarthria, myotonia, low intellect, and cardiac conduction anomalies characterize the childhood-onset (1-10 years) phenotype[31]. Patients may gradually present with early cataracts, myotonia, muscle weakness or atrophy, fatigue, excessive daytime sleepiness, central or obstructive apnea, respiratory failure, cardiac arrhythmia, insulin resistance, dysphagia, GI dysmotility, cognitive impairment, cluster C personality traits, and/or mood swings.

No particular dietary risks are reported for MD patients, although each patient must be assessed on an individual basis. The major GI problems that arise during the course of the disease are dysphagia, postprandial bloating or abdominal pain, diarrhea, constipation, and/or fecal incontinence, and cholelithiasis[31]. Drug therapy for the treatment of GERD does not differ from that for other patient groups[32].

CONCLUSION

The management of children with NMDs, who frequently present with nutritional issues like inappropriate weight and body composition, difficulty swallowing and feeding, constipation, and GERD, places a high priority on nutritional care. Effective interdisciplinary management can considerably lower morbidity and mortality even though there is often no treatment available.

This present study is an unstructured, narrative review, so there are inherent limitations, such as the lack of direct comparison between studies. However, we described the methods for selecting and reviewing literature to make it possible to verify or replicate these results. Moreover, the heterogeneity of the published studies on the nutritional and GI care of pediatric patients with NMDs made it challenging to implement a systematic approach to study selection and interpretation. The aims of the present article were to report the spectrum of nutritional problems in children with NMD and to provide clinicians with specific dietary and GI directions for each NMD while highlighting the knowledge gaps in this topic. There are no specific nutritional and GI recommendations for all of the NMDs in the scientific literature currently available, especially in the pediatric age group. More nutritional and GI data are available for DMD and SMA. Future studies should focus on creating disease-specific treatment guidelines, including dietary recommendations based on age group, physical activity status, and swallowing problems. This patient population is at high nutritional risk, so a proactive attitude is recommended. The clinician should plan for the early use of tube feeding and the appropriate selection of the most appropriate formula, with a particular interest in enteral hydrolyzed formulas. In terms of GI symptoms, the greatest challenges lie in the treatment of GERD and chronic constipation. The use of drugs to inhibit acid secretion should be prompt. The possibility of increasing fiber intake or the use of natural food formulas in enteral feeding should also be considered to further assist in the management of constipation.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Accidental ingestion of foreign bodies/harmful materials in children from Bahrain: A retrospective cohort study

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Abstract

BACKGROUND

Children like to discover their environment by putting substances in their mouths. This behavior puts them at risk of accidentally ingesting foreign bodies (FBs) or harmful materials, which can cause serious morbidities.

AIM

To study the clinical characteristics, diagnosis, complications, management, and outcomes of accidental ingestion of FBs, caustics, and medications in children.

METHODS

We conducted a retrospective cohort study of all children admitted for accidental ingestion to the Department of Pediatrics, Salmaniya Medical Complex, Bahrain, between 2011 and 2021. Demographic data, type of FB/harmful material ingested, and investigations used for diagnosis and management were recorded. The patients were divided into three groups based on the type of ingested material (FBs, caustics, and medications). The three groups were compared based on patient demographics, socioeconomic status (SES), symptoms, ingestion scenario, endoscopic and surgical complications, management, and outcomes. The FB anatomical location was categorized as the esophagus, stomach, and bowel and compared with respect to symptoms. The Fisher's exact, Pearson's χ^2, Mann-Whitney U, and Kruskal-Wallis tests were used for comparison.

RESULTS

A total of 161 accidental ingestion episodes were documented in 153 children. Most children were boys (n = 85, 55.6%), with a median age of 2.8 (interquartile

range: 1.8-4.4) years. Most participants ingested FBs (n = 108, 70.6%), 31 (20.3%) ingested caustics, and the remaining 14 (9.2%) ingested medications. Patients with caustic ingestion were younger at the time of presentation (P < 0.001) and were more symptomatic (n = 26/31, 89.7%) than those who ingested medications (n = 8/14, 57.1%) or FBs (n = 52/108, 48.6%) (P < 0.001). The caustic group had more vomiting (P < 0.001) and coughing (P = 0.029) than the other groups. Most FB ingestions were asymptomatic (n = 55/108, 51.4%). In terms of FB location, most esophageal FBs were symptomatic (n = 14/16, 87.5%), whereas most gastric (n = 34/56, 60.7%) and intestinal FBs (n = 19/32, 59.4%) were asymptomatic (P = 0.002). Battery ingestion was the most common (n = 49, 32%). Unsafe toys were the main source of batteries (n = 22/43, 51.2%). Most episodes occurred while playing (n = 49/131, 37.4%) or when they were unwitnessed (n = 78, 57.4%). FBs were ingested more while playing (P < 0.001), caustic ingestion was mainly due to unsafe storage (P < 0.001), and medication ingestion was mostly due to a missing object (P < 0.001). Girls ingested more jewelry items than boys (P = 0.006). The stomach was the common location of FB lodgment, both radiologically (n = 54/123, 43.9%) and endoscopically (n = 31/91, 34%). Of 107/108 (99.1%) patients with FB ingestion, spontaneous passage was noted in 54 (35.5%), endoscopic removal in 46 (30.3%), laparotomy in 5 (3.3%) after magnet ingestion, and direct laryngoscopy in 2 (1.3%). Pharmacological therapy was required for 105 (70.9%) patients; 79/105 (75.2%) in the FB group, 22/29 (75.9%) in the caustic group, and 4/14 (28.8%) in the medication group (P = 0.001). Omeprazole was the commonly used (n = 58; 37.9%) and was used more in the caustic group (n = 19/28, 67.9%) than in the other groups (P = 0.001). Endoscopic and surgical complications were detected in 39/148 (26.4%) patients. The caustic group had more complications than the other groups (P = 0.036). Gastrointestinal perforation developed in the FB group only (n = 5, 3.4%) and was more with magnet ingestion (n = 4) than with other FBs (P < 0.001). In patients with FB ingestion, patients aged < 1 year (P = 0.042), those with middle or low SES (P = 0.028), and those with more symptoms at presentation (P = 0.027) had more complications. Patients with complications had longer hospital stays (P < 0.001) than those without.

CONCLUSION

Accidental ingestion in children is a serious condition. Symptomatic infants from middle or low SES families have the highest morbidity. Prevention through parental education and government legislation is crucial.

Key Words: Pediatric; Accidental ingestion; Foreign body; Caustic; Complication; Bahrain

Core Tip: Foreign body (FB) or harmful material ingestion is common in pediatric patients. These accidents occur more frequently among boys. Toddlers are at a higher risk of accidental ingestion because of their exploratory behavior. Batteries are the most commonly ingested FBs. Many ingestion incidents have occurred while playing and because of unsafe storage. The stomach is the most common anatomical location of FB loosening on radiography and endoscopy. Caregiver education regarding preventive methods and governmental execution of safe manufacturing of toys, magnets, and batteries is essential to prevent FB ingestion and the complications that might occur.

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INTRODUCTION

Children like to discover their environment by putting substances into their mouth[1]. Accidental ingestion of foreign bodies (FBs) or caustic materials is a common problem encountered by families with children. It is considered as one of the most common indications for emergency referral and hospital admission. There are diverse types of FBs or ingested materials that can be swallowed by children. Coins, toy parts, jewelry, button-type batteries, needles, and pins are the most frequently ingested materials[1].

Most ingested FBs pass spontaneously, and patients can be safely observed[2]. Although most ingestion incidents are insignificant in terms of consequences, a few can pose a challenging problem that may lead to serious life-threatening complications[2]. For example, numerous magnetic objects located at various sites in the bowel can attract one another, leading to pressure necrosis of the bowel wall and eventual perforation[1]. Furthermore, although batteries can pass easily through the digestive tract and are eliminated from the stool within a few days of ingestion, swallowing batteries is more dangerous than swallowing coins or other inert objects because of their electrochemical composition and high risk of local damage[3]. Moreover, batteries 20 mm or larger in size can affect the esophagus, especially in young children[3]. Strong exothermic reactions can lead to serious mucosal injuries that may appear as skin burns[3]. Caustic ingestion is also common in pediatric age groups, and most cases happen accidentally[4]. The seriousness of this ingestion is due to

the tissue injury and necrosis[4]. Tissue damage can start from the mucosa and extend to the muscular layers, causing multiple complications, such as burns, strictures, and perforations[4].

Prompt diagnosis of accidental ingestion, appropriate management, and a decision on whether the patient necessitates intervention are crucial for reducing morbidity[2]. The type of FB, anatomic location in which the FB is lodged, and clinical picture of the patient determine the timing of endoscopic removal of the swallowed FB[2,3]. In children with caustic ingestion, postoperative treatment remains controversial and includes entities such as antireflux therapy, antibiotic therapy, steroids, and interventions such as esophageal stenting[3]. Nonetheless, the implementation of preventive methods and safe storage of caustic materials is essential to avoid these accidents and their related consequences[4].

Although many studies on accidental ingestion in children have been published in several countries, no studies have been published on this issue in Bahrain. The aim of this study was to review the incidence, demographics, different types of FBs/harmful materials, diagnostic modalities, complications, and outcomes of accidental ingestion in a pediatric age group and compare patients with endoscopic or surgical complications with those without complications to identify the predicted risk factors.

MATERIALS AND METHODS

Study design, setting, and population

In this retrospective cohort study, all pediatric patients (aged < 18 years) who presented to the Department of Accident and Emergency with a history of accidental ingestion and were admitted to the Department of Pediatrics, Salmaniya Medical Complex, Bahrain from January, 2011 to August, 2021 were included. Patients who presented to the Department of Accident and Emergency and were subsequently discharged were excluded.

Data collection

Patient data were collected by reviewing electronic and paper-based medical records. Important missing data were retrieved through direct contact with the patients' parents or guardians *via* telephone. Demographic data, including year of admission, nationality, sex, age at presentation, and age at the time of the study, were collected. Data on families' socioeconomic status (SES) were collected, including paternal and maternal educational levels, occupation, number of children, and total family income. Accordingly, families were categorized into low-, middle-, and high-SES groups. Data on symptoms at presentation, including vomiting, abdominal pain, passing tarry stool, choking, dysphagia, drooling of saliva, shortness of breath, and coughing, were collected. Details related to accidental ingestion of FBs, including the type, number, and source of FBs, were collected. Additionally, the presence of witnesses at the time of accidental ingestion, time to presentation to the Department of Accident and Emergency, and spontaneous passage times were outlined. More details regarding the type of battery were collected from the patients who ingested batteries.

Radiological imaging findings, endoscopic findings, and extraction methods were also reviewed. Urgent endoscopy was considered if it was performed within 48 h of ingestion, whereas a longer time was considered a delayed endoscopy. Data on the patients' hospital management, including endoscopic removal and the use of medications, such as lactulose, enema, glycerin suppositories, and omeprazole, were gathered. Furthermore, data on patient outcomes, including length of stay, morbidity, mortality, and follow-up period, were assessed.

Statistical analysis

Patient data were initially collected and entered into an Excel sheet and then transferred to and analyzed using the Statistical Package for the Social Sciences Statistics ver. 21.0 (IBM Corp., Armonk, NY, United States). Categorical variables are presented as numbers and percentages. Continuous variables are presented as the mean and standard deviation or median and interquartile range (IQR), according to distribution normality using the Shapiro-Wilk test. To assess the trend of accidental ingestion episodes over the last 10-year period, the duration was divided into two periods of 5 years each (2012-2016 and 2017-2021), and the incidence of ingestion in both periods was compared. The incidence was calculated as the number of patients with accidental ingestion per year divided by the total pediatric population (less than 18 years), obtained from the Bahrain Health Statistics website (https://www.moh.gov.bh/Ministry/Statistics?lang=en). The patients were divided into three groups based on the type of ingested material (FBs, caustic chemicals, and medications). The three groups were compared based on patient demographics, family SES, clinical presentations, ingestion scenario, endoscopic and surgical complications, management, and outcomes. Based on radiological and endoscopic findings, the anatomical location of the FB was categorized into esophageal, stomach, and bowel locations and compared with regard to the presenting symptoms. Metallic FBs were divided into jewelry and other metal objects and compared based on sex. The Fisher's exact test or Pearson's chi-square test was used to compare categorical variables, while student's *t* test, Mann-Whitney *U* test, or Kruskal-Wallis's test was used to compare independent groups. Confidence interval (CI) was set to 95%. $P < 0.05$ was considered statistically significant.

Ethical approval

This study was conducted in accordance with the principles of the Declaration of Helsinki, and it was ethically approved by the Secondary Health Care Research Committee, Salmaniya Medical Complex, Government Hospitals, Kingdom of Bahrain (IRB number: 88300719, July 30, 2019).

RESULTS

During the study period, 161 accidental ingestion episodes were documented in 153 children admitted to the hospital, all of whom were included in this study. Eight (5.0%) patients had another episode of accidental ingestion following the initial episode; one of them had three episodes in total, and two patients ingested the same object (battery or hard food) during the two episodes. Of the eight patients with multiple ingestions, three (37.5%) had neuropsychiatric disorders, including autism, demyelination, and mild intellectual disability. The latter had iron-deficiency anemia associated with pica. The patient with three episodes had disc battery ingestion, followed by two repeated FB ingestions, and was referred to the child protection team because of suspected child neglect, as this patient also had repeated burn events.

The mean number of accidental ingestions was 13.9 ± 10.3 episodes per year. The annual incidence of accidental ingestion episodes is shown in Figure 1. The incidence of accidental ingestion increased during the study period. In 2012-2016, the mean incidence was 3.3 ± 2.8 compared to 4.2 ± 2.4 episodes in 2017-2021. However, this increase was not statistically significant (P = 0.610, 95%CI: -4.6 to 2.9).

The demographic data and clinical presentations are shown in Table 1. Most of the patients ingested FBs (n = 108, 70.6%), 31 (20.3%) ingested caustic chemicals, and the remaining 14 (9.2%) ingested medications. Most of the patients were boys (n = 85, 55.6%). Most patients were Bahraini children (n = 118, 77.1%), while non-Bahraini children accounted for 35 (22.9%) patients (10 from India, 5 from Saudi Arabia, 2 from Bangladesh and United States of America each, 1 from Egypt, Sri Lanka, Sudan, Yemen, and Syria each, while 8 patients had unspecified nationalities). The median age at presentation was 2.8 (IQR: 1.8-4.4) years, and the most frequent age group was 2-3 years old, accounting for 43.5%. Patients with caustic ingestion were younger than those who ingested medications or FBs at the time of presentation (P < 0.001). Most patients (n = 119, 77.8%) ingested one item, and most were symptomatic (n = 86, 57.3%). The most common symptom was vomiting (n = 44, 29.3%), followed by abdominal pain (n = 25, 16.7%). Patients with caustic ingestion (n = 26/31, 89.7%) were more symptomatic than those who ingested medications (n = 8/14, 57.1%) or FBs (n = 52/108, 48.6%) (P < 0.001). The caustic group had more vomiting (P < 0.001) and coughing (P = 0.029) than the other two groups. Most of patients with FB ingestion were asymptomatic (n = 55/108, 51.4%). Upon comparison of symptoms according to the location of FBs (esophagus, stomach, or bowel), most of the 16 patients with esophageal FBs were found to be symptomatic [14 (87.5%) *vs* 2 (12.5%)], while the majority of the 56 patients with gastric FBs [34 (60.7%) *vs* 22 (39.3%)] and the 32 patients with intestinal FBs [19 (59.4%) *vs* 13 (40.6%)] were asymptomatic (P = 0.002).

Five patients had underlying diseases that might have been related to accidental ingestion. Esophageal strictures after tracheoesophageal fistula repair were found in two patients with food bolus impaction; one patient had cerebral palsy with needle ingestion, one had mental retardation with coin ingestion, and one had autism with disc battery ingestion.

Out of 136 (88.9%) patients with available witness history, 58 (43.6%) were witnessed and 78 (57.4%) were unwitnessed. Of those witnessed, 55 (94.8%) patients had a known witness person, while 3 (5.2%) had an unknown witness. Three (5.2%) patients had more than one witness person. First degree relatives were witnesses in 47 (85.5%) patients, second degree relatives in 8 (14.6%), and unrelated people (teacher, housemaid, and family friend) in 3 (5.5%). The mother was the most frequent witness (n = 27, 49.1%), followed by other siblings [n = 11 (20%); seven of them were sisters and four were brothers] and fathers (n = 7, 12.7%).

There were no significant differences among the three groups with respect to sex, nationality, SES, maternal occupation, number of siblings, time to presentation, length of stay, number of ingested materials, or the presence of a witness.

The different types of ingested material are listed in Table 2. Battery ingestion was the most frequent FB type (n = 49, 32%); 48 of them were disc batteries, and 1 was a finger type. The sharp objects included earring, screw, and nail/nail hanger (n = 5 each), key/keyring/keychain (n = 4), needle (n = 3), hair clip/pin and sharp pin (n = 2 each), gold chain, leg accessories, necklace, pepsi cap, and zipper piece (n = 1 each). The chemicals and corrosive solutions included alkaline corrosives (n = 19; Clorox in 11 patients, detergents or disinfectants in 3 each, and nonspecific corrosives in 2 patients), acid corrosives (n = 5; keratolytic agents in three and toilet cleaners in two patients), and other chemicals (n = 6). The medications included paracetamol (n = 4), antihypertensives (n = 3, coversyl in two and angiotensin-converting enzyme inhibitor in one patient), antihistamines, hypoglycemic agents, oral contraceptives, nitrite, multivitamins, methylphenidate, and multiple medications (n = 1 each).

Even though there was no significant difference between boys and girls in terms of the type of FBs ingested (P = 0.217), in metal object ingestions, girls were found to ingest more jewelry items than boys, with seven (70%) *vs* three (30%), respectively (P = 0.006). Of the 49 (32%) patients who ingested batteries, 43 (87.8%) patients had the source of battery data available. Unsafe toys were the main sources of batteries (n = 22, 51.2%), followed by light torches (n = 10, 23.3%), remote-control devices (n = 2, 4.7%), artificial candles, baskets, electronic walking aids, headphones, laser pens, on car seats, on tables, and from watches and weighing scales (n = 1 each, 2.3%).

The accidental ingestion scenarios are presented in Table 3. Data regarding this scenario were available for 131 (85.6%) patients. Accidental ingestion mostly happened while the child was playing (n = 53, 40.5%). FBs were ingested more while playing (P < 0.001), caustic chemical ingestion was mainly due to unsafe storage (P < 0.001), and medication ingestion was mostly due to a missing object (P < 0.001).

Results of radiological imaging, including chest and abdominal radiography, were available for 123 (80.4%) patients: 108 (100%) for FB, 8 (25.8%) for caustic, and 7 (50%) for medication ingestion (P < 0.001) (Table 4). The remaining 30 (24.6%) patients with no radiological findings ingested either corrosives (n = 23, 76.7%) or medications (n = 7, 23.3%). The most common location of the ingested object was the stomach both radiologically (n = 54/123, 43.9%) and endoscopically (n = 31/91, 34%).

Table 1 Demographic data and clinical presentation of 153 children with accidental ingestion

Demographic data	Total, *n* = 153 (100)	FB, *n* = 108 (70.6)	Caustic, *n* = 31 (20.3)	Medication, *n* = 14 (9.2)	*P* value
Sex					0.513[a]
Male	85 (55.6)	58 (53.7)	20 (64.5)	7 (50)	
Female	68 (44.4)	50 (46.3)	11 (35.5)	7 (50)	
Nationality					0.260[a]
Bahraini	118 (77.1)	87 (80.6)	22 (71.0)	9 (64.3)	
Non-Bahraini	35 (22.9)	21 (19.4)	9 (29.0)	5 (35.7)	
Socioeconomic status (*n* = 95)					0.520[a]
Low	32 (33.7)	26 (34.7)	3 (20.0)	3 (60.0)	
Middle	31 (32.6)	25 (33.3)	5 (33.3)	1 (20.0)	
High	32 (33.7)	24 (32.0)	7 (46.7)	1 (20.0)	
Working mother	33/95 (34.7)	28/75 (37.3)	4/15 (26.7)	1/5 (20.0)	0.568[a]
Number of siblings, (*n* = 94)	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)	0.877[b]
Age at presentation (yr), (*n* = 152)	2.8 (1.8-4.4)	3.4 (2.0-5.6)	1.8 (1.5-2.5)	2.6 (2.1-2.8)	**< 0.001**[b]
Age categories (yr), (*n* = 152)					**0.001**[a]
0-1	41 (27)	22 (20.6)	17 (54.8)	2 (14.3)	
2-3	66 (43.4)	45 (42.1)	11 (35.5)	10 (71.4)	
4-5	31 (20.4)	27 (25.2)	2 (6.5)	2 (14.3)	
≥ 6	14 (9.2)	13 (12.1)	1 (3.2)	0 (0.0)	
Time to presentation (h), (*n* = 139)	2.0 (1.0-6.0)	2.0 (1.0-6.0)	1.0 (0.3-5.0)	2.0 (1.0-4.0)	0.306[b]
Length of stay (d)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-4.0)	1.0 (1.0-1.0)	0.063[b]
Length of stay categories (d), (*n* = 146)					0.102[a]
0-1	104 (71.2)	74 (71.8)	16 (55.2)	14 (100)	
2-3	20 (13.7)	15 (14.6)	5 (17.2)	0 (0.0)	
4-5	7.0 (4.8)	5 (4.9)	2 (6.9)	0 (0.0)	
≥ 6	15 (10.3)	9 (8.7)	6 (20.7)	0 (0.0)	
Number of ingested FBs/materials per patient					0.053[a]
1	119 (77.8)	81 (75.0)	30 (96.8)	8 (57.1)	
2-5	23 (15.0)	19 (17.6)	1 (3.2)	3 (21.4)	
6-10	3.0 (2.0)	2 (1.9)	0 (0.0)	1 (7.1)	
> 10	8.0 (5.2)	6 (5.6)	0 (0.0)	2 (14.3)	
Clinical presentations (*n* = 150)					
Symptomatic[1]	86 (57.3)	52 (48.6)	26 (89.7)	8 (57.1)	**< 0.001**[a]
Vomiting	44 (29.3)	23 (21.9)	18 (62.1)	3 (21.4)	**< 0.001**[a]
Abdominal pain	25 (16.7)	21 (20.0)	2 (6.9)	2 (14.3)	0.240[a]
Cough	13 (8.7)	7 (6.7)	6 (20.7)	0 (0.0)	**0.029**[a]
Shortness of breath	11 (7.3)	6 (5.7)	5 (17.2)	0 (0.0)	0.060[a]
Choking	11 (7.3)	8 (7.6)	3 (10.3)	0 (0.0)	0.475[a]
Dysphagia/drooling of saliva	9 (6.0)	5 (4.6)	4 (12.9)	0 (0.0)	0.139[a]
Convulsion	3.0 (2.0)	1 (0.9)	1 (3.2)	1 (7.1)	0.245[a]

Others[2]	16 (10.6)	11 (10.2)	4 (12.9)	1 (7.1)	0.831[a]
Asymptomatic	64 (42.7)	55 (51.4)	3 (10.3)	6 (42.9)	**< 0.001**[a]
Presence of witness (n = 136)	58 (43.6)	38 (40.4)	14 (50.0)	6 (42.9)	0.667[a]

[a]Pearson's χ^2 test was used for categorical variables.
[b]Kruskal-Wallis's test was used for continuous variables.
[1]Patients might have more than one symptom.
[2]Dizziness, chest pain, nausea, tarry stool, and throat discomfort, each in two patients; fever, fatigue, nose swelling, tongue and lips swelling, abdominal bloating, noisy breathing, cyanosis, drowsiness (chlorpheniramine ingestion), reduction in activity, and lip ulcer, each in one patient (two patients of them had two symptoms).
Boldface indicates a statistically significant difference with $P < 0.05$. Values are presented as number (%) or median (interquartile range). FB: Foreign body.

Table 2 Types of foreign bodies and harmful materials accidentally ingested by 153 children

Type	Patients, n (%)
Foreign bodies	108 (70.6)[1]
Battery	49 (32)
Metal/sharp object	31 (20.3)
Magnets	16 (10.5)
Coin	8 (5.2)
Others[2]	5 (3.3)
Chemicals/corrosive solutions	31 (20.3)
Alkaline corrosives	19 (12.4)
Acid corrosives	5 (303)
Others[3]	6 (3.9)
Medications	14 (9.2)

[1]One patient ingested both magnet and disc battery.
[2]Marble (n = 2), intact grape, olive, and pistachio nut (n = 1 each).
[3]Kerosene in two, and comfor oil, mercury, car oil, and superglue in one patient each.
Values are presented as number (%).

Table 3 Scenario of foreign body/material ingestion in children (n = 131)

Ingestion scenario	Total, n = 131[1] (100)	FB, n = 90 (68.7)	Caustic, n = 27 (20.6)	Medication, n = 14 (10.7)	P value[a]
While playing	53 (40.5)	50 (55.6)	3 (11.1)	0 (0.0)	< 0.001[b]
Unsafe storage	46 (35.1)	13 (14.4)	26 (96.3)	7 (50)	< 0.001[b]
Missing objects	18 (13.7)	12 (13.3)	0 (0.0)	6 (42.9)	< 0.001[b]
Told by patient/relative	13 (9.9)	12 (13.3)	0 (0.0)	1 (7.1)	0.118
Accidental ingestion	4 (3.1)	4 (4.4)	0 (0.0)	0 (0.0)	0.391
Incidental finding on X-ray	3 (2.3)	3 (3.3)	0 (0.0)	0 (0.0)	0.497
Food bolus impaction	3 (2.3)	3 (3.3)	0 (0.0)	0 (0.0)	0.497
Suicidal attempt	1 (0.07)	0 (0.0)	1 (3.7)	0 (0.0)	0.144

[1]Some patients had more than one scenario.
[a]Pearson's χ^2.
[b]Indicating a statistically significant difference with $P < 0.05$.
Data are presented as number (%). FB: Foreign body.

Table 4 Anatomical locations of ingested foreign bodies based on radiological and endoscopic findings

Foreign body location	On X-ray, *n* = 123/153 (80.4)	In endoscopy, *n* = 91/152 (59.9)
Esophagus	14 (11.4)	13 (14.3)
Stomach	54 (43.9)	31 (34.0)
Small intestine	18 (14.6)	22 (24.2)
Large intestine	16 (13.0)	1.0 (1.1)
Others[1]	2.0 (1.6)	0.0 (0.0)
Not seen/normal	19 (15.5)	24 (26.4)

[1]Nose and throat (*n* = 1 each).
Data are presented as number (%).

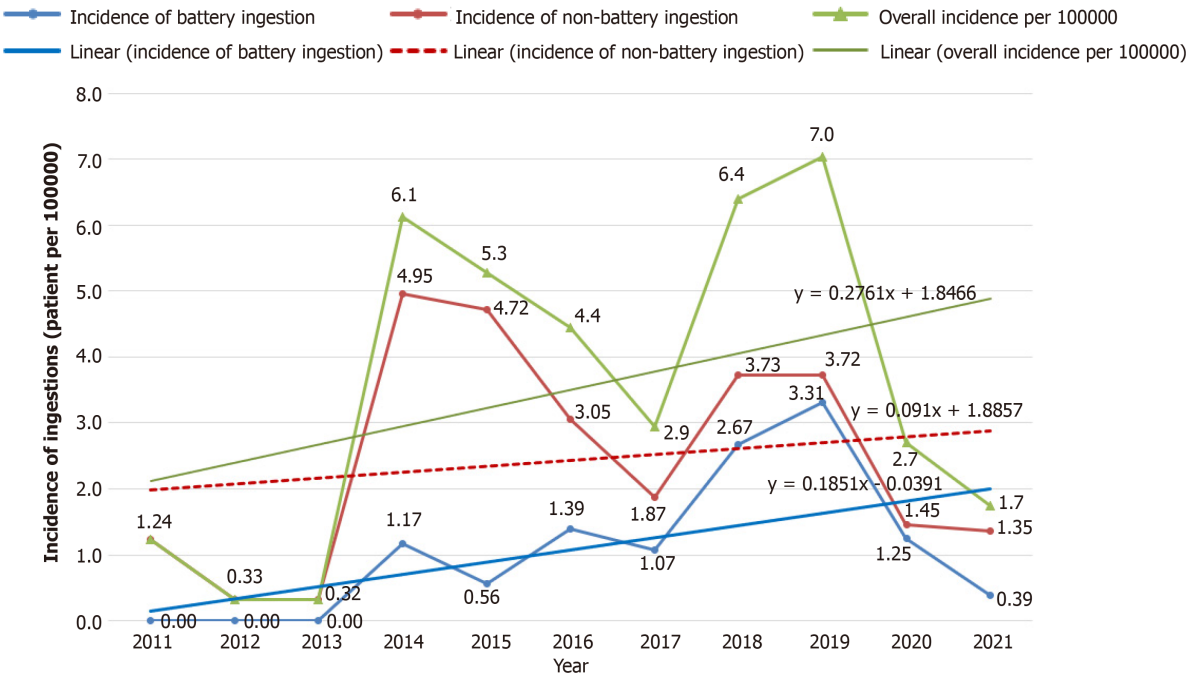

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Figure 1 Incidence of accidental ingestion episodes among children admitted to Salmaniya Medical Complex, Bahrain in 2011-2021.

Endoscopic procedures were performed in 91 (59.9%) of the 152 (99.4%) patients: 73/107 (68.2%) for FB ingestion, 18/31 (58.1%) for caustic ingestion, while no patient with medication ingestion underwent endoscopy ($P < 0.001$) (Table 4). Ninety patients (59.2%) underwent upper gastrointestinal endoscopy and one (0.7%) underwent colonoscopy. The common endoscopic location of the ingested objects was also the stomach (*n* = 31, 34%). The time from presentation to endoscopy was available for 81 (89%) patients; 78 (96.3%) of them had an emergency endoscopy (< 48 h), while 3 (3.7%) were delayed after 48 h. The first delayed patient was a 4-year-old girl who was brought by her parents with a history of fainting and vomiting streaks of blood after accidental ingestion of Clorox stored in a small water bottle. The second patient was an 8-year-old boy who ingested two attached magnets while playing a game. X-ray imaging revealed that the magnets had passed down to the large intestine. He was administered laxatives for 2 d without any progress; therefore, the magnets were removed endoscopically. The third patient was a 7-year-old boy who ingested a coin while playing, which was found to be in the stomach radiologically and remained there for 3 mo.

Data about the method of extraction were available in 107/152 (70.4%) patients with FB ingestion; spontaneous passage was noted in 54 (35.5%), endoscopic removal in 46 (30.3%), laparotomy in 5 (3.3%) (all after magnets ingestion), and direct laryngoscopy in 2 (1.3%); while in the remaining 45 (29.6%) patients nothing was removed as they ingested chemicals (*n* = 31, 20.4%) or medications (*n* = 14, 9.2%). Among patients who passed the FB spontaneously, 34 (59.7%) passed it within the first 24 h of admission, 13 (22.8%) passed it between 1 and 2 d, 10 (17.5%) passed it after 3 d, and one patient had missing data. Three patients underwent endoscopic removal of one FB and spontaneous passage of the other.

Pharmacological therapy was required for 105/148 (70.9%) patients; 79/105 (75.2%) in the FB group, 22/29 (75.9%) in the caustic group, and 4/14 (28.8%) in the medication group ($P = 0.001$). The commonest medication was omeprazole (*n* = 58; 37.9%), which was used more in the caustic group (*n* = 19/28, 67.9%) than in the FB (*n* = 37/104, 25.9%) and medi-

cation (n = 2/14, 14.3%) groups (P = 0.001). Phosphate/glycerin enemas, lactulose, and glycerin suppositories were used in 30 (19.6%), 28 (18.3%), and 24 (15.6%) patients, respectively. Laxatives and whole-bowel irrigation were administered to one patient who ingested mercury. Among the patients who ingested medication, two received gastric lavage, and two were given activated charcoal.

Seven types of endoscopic and surgical complications were detected in 39 (26.4%) out of 148 patients with available data (Table 5). Some patients experienced more than one complication. Overall, patients who ingested caustics had more complications than those in the other groups (P = 0.036) in the form of mucosal erythema (P = 0.005) and strictures (P = 0.019). Gastrointestinal perforation developed in the FB group only (n = 5, 3.4%) and was more with magnet ingestion (4 patients) than with other FB types (one with battery and none with others) (P < 0.001). Examples of complications caused by battery and magnet bead ingestion are shown in Figures 2 and 3, respectively. Patients who ingested the medications showed no endoscopic or surgical complications. Data from follow-up out-patient visits were available for 49 (32%) patients. Median follow-up period was 2 (IQR = 1.7-6.2) wk.

A comparison between the FB and caustic groups with respect to the presence or absence of endoscopic and surgical complications is shown in Table 6. In patients with FB ingestion, patients aged < 1 year (P = 0.042), those with middle or low SES (P = 0.028), and those with more symptoms at presentation (P = 0.027) had more complications. Both the FB and caustic groups with complications had longer hospital stays (P < 0.001) than those without. There were no significant differences in sex, nationality, maternal occupation, number of siblings, presence of witnesses, time to presentation, number and type of ingested FBs, or anatomical location.

DISCUSSION

This study observed an increasing trend in the incidence of accidental ingestion among children. This may be attributed to the increasing number of battery-powered electronic devices and the increased incidence of disc battery ingestion over the past several years[2,5].

The present study showed a male predominance among children with accidental ingestions, where boys accounted for 55.7%. Some accidental ingestion patterns may also be related to sex[6]. In fact, there was a consensus among all the reviewed studies that boys form the majority of children with accidental ingestion (Table 7)[2,4,6-17]. However, there were some variations in percentages. For instance, Dereci *et al*[13] from Turkey showed that boys accounted for 56%, which is similar to our study. However, Diaconescu *et al*[14] reported a male predominance, but with a lower percentage (52.45%), while Chan *et al*[9] reported a higher proportion of boys (80%). This finding may be explained by the fact that boys are more active and explore more[16]. However, some FBs are more accessible to girls than to boys and *vice versa*[6]. For instance, girls frequently consume jewelry and hair products[6]. This finding was confirmed in the present study. In a study by Orsagh-Yentis *et al*[6], girls were 2.5 times more likely to swallow jewelry than boys. Speidel *et al*[4] also found that girls were at higher risk of sharp object ingestion.

The current study found that the median age at presentation was 2.8 years, and the most frequent age group was between 2-3 years old, accounting for 43.4%. This finding is consistent with several other studies showing that the toddler age group is the most frequent risk factor for accidental ingestion[2,4,6-10,14,17]. This high prevalence of accidental ingestion in younger age groups can be attributed to the exploratory habits of these children[14]. Furthermore, children in the oral phase are prone to ingesting objects while crawling and playing[7]. Several studies have attributed the high prevalence of FB ingestion to the accessibility of FBs in a child's environment, especially because this age group has the desire to explore their surroundings[1,6,16,18]. However, few studies have reported older age groups up to adulthood[11,13,15,16,18].

In the current study, we evaluated families' SES as a risk factor for the increased incidence of accidental ingestion, as the child might be left alone at home unwitnessed by the parents/caregivers owing to their work obligations, as stated by Kalra *et al*[16]. Despite that, we did not observe an overall significant difference between families of different SES. However, in patients who ingested FBs, families with middle or low SES had more endoscopic and surgical complications than those with higher SES families (P = 0.028).

In this study, 57.3% (86/150) of the patients were symptomatic at presentation. This is comparable to the studies by Speidel *et al*[4] and Khorana *et al*[17], where the percentages of symptomatic patients were 51.6% and 55.67%, respectively. However, studies by Uba *et al*[7] and Diaconescu *et al*[14] reported higher percentages of symptomatic patients (85% and 70.5%, respectively). In contrast, Chan *et al*[9] and Lee *et al*[10] reported very low percentages of symptomatic patients, with 12% and 9.2%, respectively. This variation in the percentage of symptomatic patients who ingested FBs or other materials can be attributed to the differences in the time from ingestion to presentation and the shape, type, location, and amount of the ingested object[14,15].

Overall, the most frequent presenting symptom in our study was vomiting (29.3%). In the literature review, we found variations in the presenting symptoms depending on the type of FBs/materials ingested or the site of the FB impaction [15]. In terms of the type of ingestion, caustic materials exhibited the highest percentage of symptoms (89.7%) in this study. A lower percentage of symptomatic patients who ingested cleansers was reported by Speidel *et al*[4] (53.4%). In the FB group, 48.6% of our patients were symptomatic, and 21.9% had vomiting as the most common symptom. Khorana *et al* [17] reported a higher percentage of symptomatic patients with FB ingestion (55.67%), and vomiting was also the commonest presenting symptom (23.2%). Moreover, Diaconescu *et al*[14] reported symptoms in 70.5% of their patients with FB ingestion, yet they mainly presented with abdominal pain (55.73%), followed by vomiting (34.42%). Upon comparison of symptoms according to the lodgment site, most patients with esophageal FBs were symptomatic in our study (87.5%). This was comparable to the percentage reported by Uba *et al*[7] in patients with esophageal FBs (85%).

Table 5 Endoscopic and surgical complications in children with accidental ingestion based on type of ingested materials (*n* = 153)

Complication	Total, *n* = 148[1] (96.7)	FB, *n* = 104 (70.3)	Caustic, *n* = 30 (20.3)	Medication, *n* = 14 (9.6)	*P* value[a]
Erythema	16 (10.8)	8 (7.7)	8 (26.7)	0 (0.0)	0.005[b]
Ulcer	14 (9.5)	10 (9.6)	4 (13.3)	0 (0.0)	0.369
Mucosal erosions	9 (6.1)	9 (8.7)	0 (0.0)	0 (0.0)	0.132
Hemorrhage	6 (4.1)	6 (5.8)	0 (0.0)	0 (0.0)	0.266
Perforation	5 (3.4)	5 (4.8)	0 (0.0)	0 (0.0)	0.335
Airway edema	5 (3.4)	2 (1.9)	3 (10.0)	0 (0.0)	0.074
Stricture	2 (1.4)	0 (0.0)	2 (6.7)	0 (0.0)	0.019[b]
Total	39 (26.4)	28 (26.9)	11 (36.7)	0 (0.0)	0.036[b]

[1]Some patients had more than one complication.
[a]Pearson's χ^2.
[b]Indicating a statistically significant difference with $P < 0.05$.
Data are presented as number and percentage. FB: Foreign body.

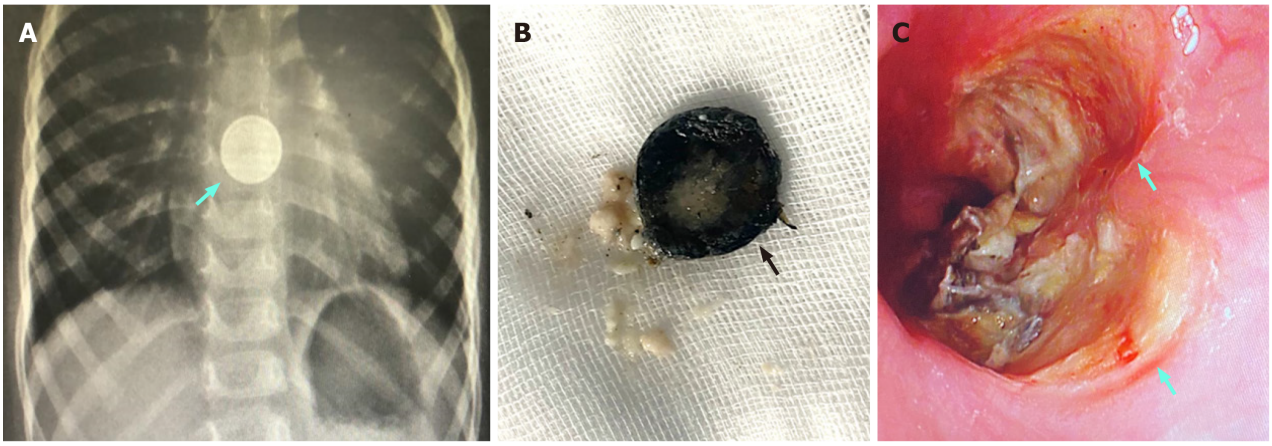

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Figure 2 Disc battery ingestion in children. A: Plain chest X-ray revealing the double hallow shadow of a disc battery impacted in the esophagus; B: Rusted and friable disc battery after endoscopic removal; C: Endoscopic picture of the esophagus showing two large kissing mucosal ulcers at the site of the disc battery impaction.

Drooling of saliva and dysphagia are the main symptoms in patients with esophageal FBs[8,13], while abdominal pain and vomiting are the main symptoms in patients with FBs found in the stomach[14,15]. Diaconescu *et al*[14] explained the wide variation in presenting symptoms among different studies based on the shape of the FB, duration between the ingestion event and time to presentation, and age of the patient.

In the current study, 42.7% of the children who ingested FBs, caustics, or medications were asymptomatic. This is comparable to the study by Speidel *et al*[4], who also included the three types of ingested materials, where the percentage of asymptomatic patients was 48.4%. Moreover, Lee *et al*[10] reported that most of the 76 patients with FB ingestions were asymptomatic (90.8%), which was also the case in our study, but at a lower rate (51.4%). Chan *et al*[9] also documented that most of the 25 patients with button battery ingestion were asymptomatic (88%). This high percentage of asymptomatic patients is of concern, as it may lead to delayed diagnosis in many cases, putting these children at risk of a higher rate of complications. Preventing complications and missed diagnoses, particularly in high-risk objects, such as batteries, is important. Early detection of an incident by parents leads to faster presentation, diagnosis, and intervention[3,19]. Nevertheless, doctors should consider FB ingestion scenarios in young patients who present with vague symptoms, such as abdominal pain and vomiting[3,19].

In this study, the majority of the ingestion scenarios were during the playing time (40.5%) and were unwitnessed (57.4%). Ingestion episodes while playing were also documented by Dereci *et al*[13] but at a higher rate (72%). Unwitnessed events were also found in other studies, such as those illustrated by Litovitz *et al*[19] who reported a comparable percentage to our study (56.2%). In contrast, most of accidental ingestions reported by Lin *et al*[15] were witnessed (89%). However, Kalra *et al*[16] found a low percentage of witnessed accidental ingestions (19%). The presence of a witness during the child's play is important for the early detection of ingestion episodes and might hasten medical management.

Table 6 Predictors of complications in children with accidental ingestion based on type of ingested materials (foreign body or caustic material)

Variable	FB complications, *n* = 104		*P* value	Caustic complications, *n* = 31		*P* value
	Yes, *n* = 28 (26.9)	No, *n* = 76 (73.1)		Yes, *n* = 11 (35.5)	No, *n* = 20 (64.5)	
Sex			0.661[a]			1.000[a]
Male	16 (57.1)	39 (51.3)		7 (63.6)	13 (68.4)	
Female	12 (42.9)	37 (48.7)		4 (36.4)	6 (31.6)	
Nationality			0.775[a]			0.199[a]
Bahraini	24 (85.7)	61 (80.3)		10 (90.9)	12 (63.2)	
Non-Bahraini	4 (14.3)	15 (19.7)		1 (9.1)	7 (36.8)	
Socioeconomic status (*n* = 74)			**0.028**[b]			0.059[b]
Low	9 (42.9)	16 (30.2)		2 (28.6)	1 (12.5)	
Medium	10 (47.6)	15 (28.3)		4 (57.1)	1 (12.5)	
High	2 (9.5)	22 (41.5)		1 (14.3)	6 (75.0)	
Working mother (*n* = 74)	4/21 (19.0)	24/53 (45.3)	0.061[a]	1/7 (14.3)	3/8 (37.5)	0.569[a]
Number of siblings, (*n* = 74)	3 (2-4)	3 (2-4)	0.355[c]	3 (1-5)	3 (3-4)	0.779[c]
Age at presentation (yr), (*n* = 103)	2.8 (1.5-4.2)	3.4 (2.2-5.7)	0.069[c]	1.5 (0.9-2.5)	1.9 (1.6-2.7)	0.185[c]
Age group (yr) (*n* = 103)			**0.042**[b]			0.181[b]
0-1	11 (39.3)	11 (14.7)		8 (72.7)	9 (47.4)	
2-3	9 (32.1)	35 (46.7)		2 (18.2)	8 (42.1)	
4-5	4 (14.3)	20 (26.7)		0 (0.0)	2 (10.5)	
≥ 6	4 (14.3)	9 (12.0)		1 (9.1)	0 (0.0)	
Presence of ingestion witness (*n* = 93)	12/27 (44.4)	25/66 (37.9)	0.643[a]	4/10 (40)	10 (55.6)	0.695[a]
Time to presentation (h), (*n* = 96)	3 (1-8.5)	2 (1-5)	0.325[c]	1 (0.3-3.0)	2 (0.5-6.0)	0.155[c]
Length of stay (d), (*n* = 102)	2 (1-4)	1 (0-1)	**< 0.001**[c]	7 (2-12)	1 (0-2)	**< 0.001**[c]
Number of ingested FBs/materials per patient[c]			0.372[b]			1.000[b]
1	18 (64.3)	60 (78.9)		11 (100)	18 (94.7)	
2-5	6 (21.4)	12 (15.8)		0 (0.0)	1 (5.3)	
6-10	1 (3.6)	1 (1.3)		0 (0.0)	0 (0.0)	
> 10	3 (10.7)	3 (3.9)		0 (0.0)	0 (0.0)	
Type of FBs			0.384[b]	NA	NA	NA
Battery	15 (53.6)	34 (44.7)	0.508[a]	NA	NA	NA
Metal/sharp object	6 (21.4)	23 (30.3)	0.464[a]	NA	NA	NA
Magnets	6 (21.4)	9 (11.8)	0.224[a]	NA	NA	NA
Coin	1 (3.6)	7 (9.2)	0.679[a]	NA	NA	NA
Food bolus[1]	0 (0.0)	3 (3.9)	0.562[a]	NA	NA	NA
Anatomical location			0.682[b]	NA	NA	NA
Esophagus	3 (11.1)	13 (17.3)	0.550[a]	NA	NA	NA
Stomach	16 (59.3)	38 (50.7)	0.504[a]	NA	NA	NA
Bowel	8 (29.6)	23 (30.7)	1.000[a]	NA	NA	NA
Clinical presentations			**0.027**[a]			1.000[a]
Symptomatic	19 (67.9)	32 (42.1)		9 (90)	17 (89.5)	

Asymptomatic	9 (32.1)	44 (57.9)	1 (10)	2 (10.5)

[a]Fisher's exact test was used for categorical variables.
[b]Pearson's χ^2 test was used for categorical variables.
[c]Mann-Whitney *U* test was used for continuous variables.
[1]Intact grape, olive, and pistachio nut (n = 1 each).
Boldface indicates a statistically significant difference with $P < 0.05$. Data are presented as number (%) or median (interquartile range). FB: Foreign body; NA: Not applicable.

Table 7 Summary of foreign body ingestion in children from neighboring counties and worldwide

Ref.	Country	*n*	Age (yr)[1]	Sex	Two most common FBs (%)	Two most common symptoms (%)	Two most common sites of FB (%)
Our study	Bahrain[2]	153	2.8 (1.8-4.4)	M > F	Battery (32), metals/sharps (21)	Vomiting (29), abdominal pain (16)	Stomach (44), small intestine (15)
Al-Salem *et al*[11], 1995	Kingdom of Saudi Arabia	40	8.5 (5 mo-8)	M > F	Coins (43), metallic dog toy	NR	Esophagus (60), stomach (38)
Dereci *et al*[13], 2015	Turkey	64	5.7 ± 4.6	M > F	Coin (37), pin (8)	Dysphagia (24), cough (8)	Esophagus (56), stomach (16)
Kalra *et al*[16], 2022	India	100	5.0 ± 14.4	M > F	Coin (65), battery cell (13)	FB sensation (55), vomiting (54)	Just below the cricopharynx (89)
Lee *et al*[10], 2016	Korea	76	3.1 ± 3.1	M > F	Coins (22), button battery (16)	Chest discomfort, abdominal pain (9)	FBs: Stomach (40), unknown (28). Batteries: Duodenum (50), stomach (42)
Chan *et al*[9], 2002	Taiwan	25	2.6 ± 1.8	M > F	Button battery	Abdominal pain (8), dyspnea (4)	Stomach (52), small intestine (8)
Lin *et al*[15], 2007	Taiwan	87	3.4 (6 mo-13)	M > F	Coins (57), button battery (22)	Odynophagia, cough (84)	Esophagus (51), stomach (45)
Khorana *et al*[17], 2019	Thailand	194	43.5 (21-72) mo	M > F	Coin (41), button battery (17)	Vomiting (45), dysphagia (27)	Esophagus (37), stomach (29)
Uba *et al*[7], 2002	Nigeria	108	3.0 ± 0.8	M > F	Coins (80), bottle caps (7)	Drooling (34), regurgitation (17)	Esophagus (52), hypopharynx (33)
Adedeji *et al*[12], 2013	Nigeria	28	32.1 (2-75)	M > F	Alkali (79), acid (14)	NR	NR
Diaconescu *et al*[14], 2016	Romania	61	3.3 ± 4.7	M > F	Coins (26), metals (13)	Abdominal pain (56), vomiting (34)	NR
Antoniou and Christopoulos-Geroulanos[2], 2011	Greece	675	3.3 (4 mo-14)	M > F	Coins (32), safety pins (21)	Retrosternal pain, drooling	Stomach (58), bowel (33)
Speidel *et al*[4], 2020	Germany	1199	3.3 ± 3.2	M > F	Coin (19), metal (16)	Retching and vomiting (30), coughing (8)	NR
Little *et al*[8], 2006	United States	555	3.2 (2 mo-19)	M > F	Coins (88), round batteries	Dysphagia (37), drooling (31)	Esophagus (99)
Orsagh-Yentis *et al*[6], 2019	United States	29893	< 6	M > F	Coins (62), toys (10)	NR	NR

[1]Age is presented as either median (range) or the mean ± SD.
[2]The present study.
FB: Foreign body; NR: No record; M: Male; F: Female.

In our study, the most frequently ingested FBs were batteries (32%), followed by chemical solutions (20.3%). The main source of ingested batteries was unsafe toys (51.2%). Unsafe toys are a source of danger, particularly if their batteries are not locked. This may be due to the ease of swallowing these objects and/or being within reach of the children. However, our findings are not compatible with those of many other studies on the most commonly ingested FBs. Most studies have reported that coins are the most common[2,6-8,10,11,13,14]. This can be explained by the strict inclusion criteria of our study, in which patients were admitted to the hospital for observation and for the inclusion of possible endoscopic procedures. Most patients who ingested coins at our hospital were seen in the Department of Emergency, and if the coin was in the stomach or beyond, the patient was discharged if he or she was asymptomatic. Because a significant number of patients with accidental ingestion present to the hospital without any symptoms, the implementation of specific investig-

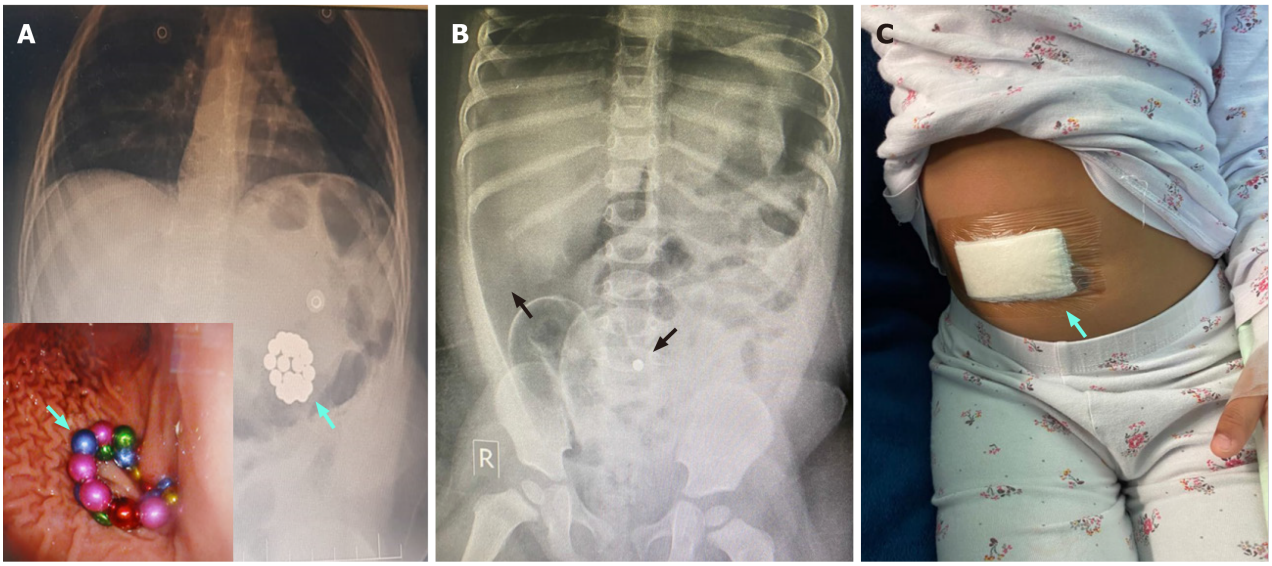

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Figure 3 Magnet bead ingestion in children. A: Plain chest and abdominal X-ray of a 13-mo-old girl who ingested multiple beads of magnet which shows a shadow of magnet beads that were found to be adherent to the gastric mucosa and were removed endoscopically; B: Plain post-endoscopy abdominal X-ray showing signs of gastric perforation (free air in the peritoneum) and one remaining magnet bead; C: A picture of the child's abdomen post laparotomy.

ations and diagnostic modalities, such as erect chest radiography, technetium-labelled sucralfate scan, and early esophago-gastroduodenoscopy, is important to establish any anatomical-internal injuries[4]. The decision to perform an endoscopic procedure to remove a FB depends on the time since ingestion, FB location, size, and shape, as well as the patient's age, symptoms, and complications[10]. In our study, both radiologically and endoscopically, FBs were mostly found in the stomach, followed by the small bowel, and then the esophagus, with 37.7%, 19.7%, and 14.7%, respectively. However, the study by Lin *et al*[15], which was conducted on 87 patients who underwent an endoscopic procedure, showed that the most common lodgment site of FBs was the esophagus (51.4%), followed by the stomach (44.6%) and finally the duodenum (4%).

Fortunately, most of our patients did not develop complications (73.6%). However, 26.4% had endoscopic and surgical complications, 10.8% developed mucosal erythema, 9.5% had ulcer, 6.1% had erosions, and 3.4% had gastrointestinal perforation (n = 5). Uba *et al*[7] illustrated that the most common comorbidities were hemorrhage (15%), perforation (3.7%), and aspiration pneumonitis (2.8%).

In our study, 38.2% (n = 58) of the patients had a spon-taneous passage of the FBs. However, higher rates of spontaneous passage have been documented. Chan *et al*[9] and Khorana *et al*[17] reported percentages of spontaneous passages that reached 92% and 60.31%, respectively. Accordingly, it was thought that the actual number of ingested FBs in children was higher than the documented number, since many cases had uneventful and symptomless spontaneous passage without the recognition and witnessing of the parents[13]. In our study, 30.3% of children underwent endoscopic procedures either to remove the FB or for the assessment/management of any complications. However, Dereci *et al*[13] reported a higher percentage of endoscopic procedures (n = 55, 85%). Fortunately, the overall need for surgical intervention reported in the literature is relatively low. In our study, five (3.3%) cases needed surgical intervention. Speidel *et al*[4] showed an even lower percentage (n = 4; 0.3%).

Limitations

This study had several limitations. As this was a retrospective study, missing data, such as patient contact number, presence of a witness, and details of the ingestion scenario, were expected. One of the limitations of this study was that we included only those who had been admitted to the hospital, excluding those who attended the Departments of Accident and Emergency and were discharged home, especially asymptomatic patients and those who ingested metallic coins found in the stomach or beyond. Moreover, the ingestion scenario of some patients was gathered *via* telephone calls to the child's parents/guardians after the ingestion episode, which was subject to recall bias. Some parents did not provide consent for endoscopy, especially for children who ingested corrosives, which made the assessment of local injury and gastrointestinal complications difficult. The ingestion of glass is a real challenge because it is radiolucent, and nothing was seen on the X-ray to determine the location. Despite these limitations, this study had many strengths. It is the first study from Bahrain to focus on accidental ingestion in children. This covered all types of accidental ingestion, unlike most other studies, which included the ingestion of only one type of hazardous material. The findings of this study are particularly important for health care providers dealing with this group of patients. They are also valuable for policy-makers as prevention guidelines and legislation are crucial for protecting children from avoidable risks.

CONCLUSION

Accidental ingestion of FBs/harmful materials in children is a serious problem. Our study showed that boys and toddlers were at a higher such risk. Most children were symp-tomatic at presentation, with vomiting being the predominant symptom. Batteries were the most commonly ingested materials, followed by metals and chemicals. Most accidents occur while children playing games unwitnessed. Patients who ingested chemicals had higher endoscopic morbidity than the FB or drug group. In patients with FB ingestion, younger age (less than 1 year), those from middle- and low-SES families, and those with more symptoms at presentation, were more prone to complications. Gastrointestinal perforation developed in the FB group only, and mainly after magnet ingestion. Further studies are required to assess the impact of parental education, government legislation, and ensuring a safe environment to prevent such serious accidents in children.

ARTICLE HIGHLIGHTS

Research background

Accidental ingestion of foreign bodies (FBs) or harmful materials is a common problem in families with children because of their exploratory behavior. This behavior puts them at risk and can cause serious morbidities.

Research motivation

While many studies on accidental ingestion in children have been published from several countries worldwide, no study has been published on this issue in Bahrain. This knowledge gap motivated us to study this health problem in Bahrain.

Research objectives

To evaluate the incidence, demographics, types of FBs/harmful materials ingested, diagnostic methods, management, complications, and outcomes of accidental ingestion in pediatric patients at the main tertiary hospital in Bahrain and compare patients with endoscopic or surgical complications with those without to identify the predicted risk factors.

Research methods

We retrospectively reviewed and collected the demographic data, clinical presentations, radiological and endoscopic findings, treatments, complications, and outcomes of accidental ingestions in children admitted to the Department of Pediatrics at the Salmaniya Medical Complex, Kingdom of Bahrain, from medical records between 2011 and 2021.

Research results

In total, 161 accidental ingestion episodes were documented in 153 children. Male predominance was noted (n = 85, 55.6%). The median age at presentation was 2.8 (interquartile range: 1.8-4.4) years. Most participants ingested FBs (n = 108, 70.6%), followed by caustic chemicals (n = 31, 20.3%) or medications (n = 14, 9.2%). Most patients were symptomatic (n = 86, 57.3%); vomiting was the common symptom (n = 44, 29.3%), followed by abdominal pain (n = 25, 16.7%). Batteries were the most commonly ingested FBs (n = 49, 32%). Unsafe toys were the main source of batteries (n = 22/43, 51.2%). Most episodes occurred while playing (n = 49/131, 37.4%) or unwitnessed (n = 78, 57.4%). Stomach was the common location of FB lodgment, both radiologically (n = 54/123, 43.9%) and endoscopically (n = 31/91, 34%). Of 107/108 (99.1%) patients with FB ingestions, spontaneous passage was noted in 54 (35.5%), endoscopic removal in 46 (30.3%), laparotomy in 5 (3.3%), and direct laryngoscopy in 2 (1.3%). Pharmacological therapy was required in 105 (70.9%) patients. Complications were detected in 39 (26.4%) patients, five of whom had gastrointestinal perforation. Patients who ingested FBs before the age of one year (P = 0.042), those with middle or low socioeconomic status (P = 0.028), and those with more symptoms at presentation (P = 0.027) had more complications.

Research conclusions

Accidental ingestion in children is a serious health problem. Symptomatic infants from families with middle or low families have the highest morbidity. Prevention through parental education and government legislation is crucial.

Research perspectives

Additional research is required to evaluate the influence of parental awareness, authority regulations, and the provision of safe environments to prevent such serious incidents.

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FOOTNOTES

Author contributions: Isa HM was the main contributor in study conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, original draft writing, and manuscript review and editing; Aldoseri SA, Abduljabbar AS, and Alsulaiti KA were responsible for literature review, data collection, and manuscript drafting and revision; and all the authors have read and approved the final manuscript.

Institutional review board statement: This study was conducted in accordance with the principles of the Declaration of Helsinki, and it was ethically approved by the Secondary Health Care Research Committee, Salmaniya Medical Complex, Government Hospitals, Kingdom of Bahrain (IRB number: 88300719, July 30, 2019).

Informed consent statement: Consent was not needed as the study was retrospective without exposure to the patients' data.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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ORIGINAL ARTICLE

Retrospective Study

Safety and efficacy of intravitreal anti vascular endothelial growth factor for severe posterior retinopathy of prematurity with flat fibrovascular proliferation

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Abstract

BACKGROUND

Intravitreal anti-vascular endothelial growth factor (IVA) injection is known to cause contraction of fibrovascular proliferation (FVP), when present in severe retinopathy of prematurity (ROP).

AIM

To assess the structural outcomes of IVA injection in the treatment of severe posterior ROP with significant FVP.

METHODS

It was a retrospective study in which 36 eyes of 18 preterm babies who developed > 4 clock hours of FVP in zone I or posterior zone II, were treated with either intravitreal 0.625 mg bevacizumab or intravitreal 0.2 mg of ranibizumab. Favorable structural outcome included resolution of plus disease and FVP without the development of tractional retinal detachment. Secondary outcome measure included either full retinal maturation at follow-up or development of recurrent disease requiring additional treatment. Adverse outcomes included progression to retinal detachment.

RESULTS

The mean gestational age of the 18 preterm babies was 30 wk (range 27-36), and mean birth weight was 1319 g (range 650-1980 g). Mean post-menstrual age (PMA) at the time of primary treatment was 35.5 wk (range 31-41 wk). All eyes showed regression of plus disease and FVP. 5 eyes of 3 babies showed reactivation of disease and were treated with repeat IVA (n = 2 eyes) or peripheral laser photocoagulation (n = 3 eyes) respectively. 16 out of 36 (44%) reached retinal vascular maturation at final follow up at 5 years.

CONCLUSION
There was good resolution of severe posterior ROP with FVP with IVA, with retinal maturity of 44% at 5 year follow-up and a reactivation rate of 13.8%. When the IVA injection is given prior to 37 wk PMA, while disease is in phase 2, it is less likely to cause contracture of pre-existing FVP.

Key Words: Retinopathy of prematurity; Anti-vascular endothelial growth factor injection; Contraction; Crunch phenomenon

Core Tip: This is a retrospective study to evaluate if anti-vascular endothelial growth factor injection could cause contraction of preexisting fibrovascular proliferation when present in severe retinopathy of prematurity.

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INTRODUCTION

Since the first description of retinopathy of prematurity (ROP) by Terry in 1942, the understanding of the disease has evolved vastly, especially over that last decade with wider armamentarium of treatment options[1,2]. There has been an increase in the popularity of intravitreal anti-vascular endothelial growth factor (IVA) injection as a treatment modality especially with the landmarks trails such as Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT–ROP) and Ranibizumab *vs* laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW), proving their safety and efficacy[3,4]. IVA injection has become the treatment of choice in aggressive and posterior diseases. Although dramatic effects are often noted after IVA injections, minimizing need for laser and related effects such as high myopia and peripheral field defect, reactivations are not uncommon and many of them may need re-treatment[5]. Therefore a through close follow up for these babies is mandatory. In cases associated with flat fibrovascular proliferation (FVP), there is often a risk of development or worsening of anteroposterior traction- also known as crunch phenomemon, especially in babies with higher post menstrual age[6,7]. The current study aims to show the safety and effectiveness of IVA injection in the treatment of severe type 1 ROP with more than 4 clock hours of flat FVP in zone I and posterior zone II.

MATERIALS AND METHODS

It is a retrospective study of babies with severe type 1 ROP as defined by the early treatment for retinopathy of prematurity study[8] with significant flat FVP in zone 1 or posterior zone II, who were treated with IVA injections between December 2013 to December 2016 and followed up for five years. The study was approved by the Ethics committee and the Institutional Review Board and adhered to the tenets of declaration of Helsinki. Significant FVP was defined as FVP spanning more than 4 clock hours. Relevant data of the baseline characteristics like gestational age, birth weight, post conceptional age at treatment, date of injection were collected from the electronic medical records. Zone of the disease and stage of the disease was defined as per the latest ICROP guidelines[9]. Informed consent was obtained from all the parents prior to the IVA, and the parents of the babies were offered to choose either Bevacizumab (Avastin; Genentech Inc, South San Francisco, CA, United States) or Ranibizumab (Accentrix; Novartis pharma Stein AG) after they were explained the possible side- effects, need for long follow up, and off label use. Dosage administered was 0.625mg of bevacizumab or 0.2 mg of ranibizumab given under aseptic precaution in operation theatre under topical anesthesia using 30 gauge needle about 1.5 mm from limbus. Two ophthalmologist reviewed fundus images pre and post injection. Documentation was done by taking images using 130 degrees lens using the Retcam 3 (Clarity Medical Systems, Pleasanton CA, United States).

All the babies were treated within 2 days of presentation. Concurrent bilateral injection were given under aseptic precautions for each eye separately, using drugs with different batch numbers for the two eyes. Patients were followed up weekly for two months, two weekly for next two months, monthly till 6 months, two monthly till 12 months and six monthly till 5 years of age.

Patients who demonstrated peripheral avascular retina (PAR), were followed up as per schedule and examination under anesthesia was performed wherever necessary. Reactivation was treated with either repeat IVA injection or peripheral laser photocoagulation depending on the location of the disease and family's preference. Rescue vitrectomy was planned in case of development of tractional retinal detachment/crunch phenomemon.

Primary outcome was measured in terms of regression of plus disease and absence of FVP. Secondary outcome was measured in terms of absence of reactivation of disease and vessels reaching maturity at the end of 1 year, which was considered as the minimum follow up period. Safety profile was assessed by lack of development of anteroposterior traction or crunch phenomenon. The results were tabulated in Microsoft excel version 2206, in which mean and percentages were calculated.

RESULTS

Thirty-six eyes of 18 infants were included in the study. The mean gestational age of the 18 preterm babies was 30 wk (range 27-36), and mean birth weight was 1319 g (range 650-1980g). Mean post-menstrual age (PMA) at the time of IVA was 35 wk (range 31-41 wk). 22 eyes (61.1%) had aggressive ROP (AROP) in zone I, 6 eyes (16.66%) had AROP in posterior zone II. Two eyes had stage 3 in zone I and 6 eyes has stage 3 in posterior zone II. Thirty two eyes (89%) received 0.625 mg of intravitreal bevacizumab and 4 eyes (11%) received 0.2 mg of intravitreal ranibizumab (0.2 mg). All eyes showed regression of plus disease and FVP. In 10 eyes (27%) this regression was within a week of IVA and in additional 25 (69%) eyes it occurred within a month and only in 1 eye regression occurred by 2 mo post IVA. Figures 1 and 2 show pre injection (Figure 1A and B) and post IVA regression of plus disease and FVP (Figure 1C and D). 2 eyes of 2 patients (5.5%) developed vitreous hemorrhage within one week post IVA, which showed resolution within a month. The neovascularization of iris (in 4 eyes) regressed within a week of injection. The regression of disease activity after IVA for each case is shown in Table 1.

In 14 out of 36 (39%) eyes the retinal vessels reached maturity uneventfully without intervention. In 4 eyes (11%) the vessels matured by 4 months, in 6 eyes (33%) by six months and in another 6 eyes (33%) by one year. Among the 20 (55.5%) eyes that did not reach maturation, recurrence of disease was seen in 5 eyes (13.8%). The mean time of recurrence was 10 weeks in our study (6 weeks for ranibizumab eyes and 12 wk for bevacizumab eyes). An additional dose of IVA was given in 2 eyes of 1 patient (post ranibizumab) at one and half months after initial injection. 3 eyes of 2 patients required peripheral laser photocoagulation. In 15 of 36 eyes, although there was no recurrence of ROP, babies were kept under follow-up with immature vessels/peripheral avascular retina in zone II or III. All eyes were followed up for a minimum period of 1 year at our centre. 12 out of 18 babies (24 eyes) (66%) completed 3 years follow up, and 11 out of 18 babies (22 eyes) (61%) completed 5 years.

At final follow up, vascular maturity was noted in 16 (44%) eyes, PAR was noted in 17(47%) eyes and peripheral laser scars in 3 (8%) eyes. Development of disc pallor was noted in 2 eyes. 4 eyes of 2 babies developed white without pressure in the area of PAR and 2 eyes of 1 baby additionally developed lattice degeneration in the PAR at 5 years follow up. Babies who were lost to follow up at our center due to the emergence of coronavirus disease 2019 outbreak, were followed up over telephonic conversation and directed to the closest ophthalmic center for follow up to rule out the possibility of development of any sight threatening ROP.

None of the babies developed anteroposterior traction or tractional retinal detachment or required rescue vitrectomy at any time until the last follow up. None of developed any systemic complications.

DISCUSSION

In this study we attempted to show the effectiveness of IVA in severe posterior type 1 ROP with over 4 clock hours of FVP. Trials such as the BEAT ROP[3] study has showed the effectiveness of bevacizumab in ROP in posterior disease, and the RAINBOW trial has showed the outcomes of ranibizumab *vs* laser in ROP[3,4]. However, its effectiveness in presence of flat FVP is not studied. The fate of the retinal vessels following bevacizumab follow certain scalloped pattern described by Chen *et al*[10] as having one of the following fate; vascular arrest alone with peripheral non perfusion in 43%, vascular arrest with persistent tortuosity in 38%, reactivated ROP in 18%, and full vascular maturation (by 60 week PMA) in 3%. [10] Although in our cohort we did not look into these patterns, 11% of the eyes had vascular maturation within 4 months post IVA, which appears to be greater than reported by them, and finally 39% eyes reached maturation in 1 year. Even in the RAINBOW trial, full peripheral vascularization (which they assessed only by indirect ophthalmoscopy) occurred in 32% by day 169 in both the combined ranibizumab groups[4].

It is known and has been emphasized even in landmark trails that the retinal vessels advance to the point at which the vascular precursors have ceased migration, with differentiation of the underlying retina, in case of IVA injection monotherapy[3]. Therefore a PAR is expected in majority of these cases. The rate of reactivation was 13.8% in our patients, which was low considering that presence of FVP is not the typical cohort of choice for IVA in most of the studies conducted. Infact, before the widespread use of IVA injections, early vitrectomy was recommended for such cases[11].

The timing of recurrence is influenced by the half-life of the drug in the vitreous cavity. For Ranibizumab, which is a 48 kDa Fab antibody fragment, the serum half-life is much lesser than bevacizumab, which is a 149 kDa monoclonal antibody. Therefore, an earlier recurrence is expected in Ranibizumab eyes[4]. The mean time of recurrence was 10 week in our study (6 week for ranibizumab eyes and 12 week for bevacizumab eyes). These results were similar to the recurrence at 16 week for bevacizumab in BEAT-ROP trial[3]. In the RAINBOW trial the median time to recurrence was 8 week for ranibizumab[4]. Reactivation have been reported with bevacizumab occurring upto 69 weeks after injection and there have been reports of very late reactivations, even as late as 2.5 years of age with tractional retinal detachment (TRD) after bevacizumab for AROP[12,13]. TRD in proliferative diseases like diabetic retinopathy[14] can worsen after IVA injection and studies have showed that similar phenomenon can also occur in advanced ROP, described as crunch effect

Table 1 Regression of disease activity after intravitreal anti vascular endothelial growth factor

S. No	Eye	GA	BW	PMA	Features	Follow up after IVA								
						1 wk	1 mo	2 mo	3-4 mo	6 mo	8 mo	12 mo	3 yr	5 yr
1	OD	30	1200	35	Zone 1 AROP	Regressing FVP	Complete FVP regression	PAR	Zone II stage 3 – Lasered	Stable	Stable	Stable	Stable	Stable (lasered)
	OS				Zone 1 AROP	Regressing FVP	Complete FVP regression	PAR	Zone II stage 3 – Lasered	Stable	Stable	Stable	Stable	Stable (lasered)
2	OD	32	1200	38	Zone 1 AROP	Regressing FVP	Complete FVP regression	PAR	PAR	PAR	Mature	Mature	Mature	Stable
	OS				Zone 1 AROP	Regressing FVP	Complete FVP regression	PAR	PAR	PAR	Mature	Mature	Mature	Stable
3	OD	30	950	35	Zone 1 AROP	Complete FVP regression	PAR	PAR	PAR	Mature	Mature	Mature	Mature	Stable
	OS				Zone 1 AROP	Complete FVP regression	PAR	PAR	PAR	Mature	Mature	Mature	Mature	Stable
4	OD	28	1235	36	Zone 1 AROP	Regressing FVP	Complete FVP regression	Zone II stage 3-repeat -R	PAR	PAR	PAR	Mature	Mature	Stable, disc pallor
	OS				Zone 1 AROP	Regressing FVP	Complete FVP regression	Zone II stage 3-repeat -R	PAR	PAR	PAR	Mature	Mature	Stable, disc pallor
5	OD	36	1800	41	Zone II P AROP	Regressing FVP	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere
	OS				Zone II P AROP	Regressing FVP	Complete FVP regression	PAR	Zone II stage 3 – lasered	PAR	PAR	Stable (Lasered)	FU elsewhere	FU elsewhere
6	OD	35	1700	41	Zone II P AROP	Regressing FVP	Complete FVP regression	PAR	PAR	Mature	Stable	Stable	stable	FU elsewhere
	OS				Zone II P AROP	Regressing FVP	Complete FVP regression	PAR	PAR	Mature	Stable	Stable	Stable	FU elsewhere
7	OD	28	1200	34	Zone II stage 3 P +	Regressing FVP	Complete FVP regression	PAR	Mature	Stable	Stable	Stable	Stable	Stable
	OS				Zone II stage 3 P +	Regressing FVP	Complete FVP regression	PAR	Mature	Stable	Stable	Stable	Stable	Stable
8	OD	32	1980	36	Zone 1 AROP	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere
	OS				Zone 1 AROP	Complete FVP regression		PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere

9	OD	29	2050	35	Zone 1 AROP	Regressing FVP	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere
	OS				Zone 1 AROP	Regressing FVP	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere
10	OD	28	1300	34	Zone 1 AROP (hge)	Regressing FVP	Complete FVP regression	PAR	PAR	PAR	PAR	Mature	Mature	Mature
	OS				Zone 1 AROP (hge)	Regressing FVP	Complete FVP regression	PAR	PAR	PAR	PAR	Mature	Mature	Mature
11	OD	29	1265	34	Zone II stage 3 P+	Regressing FVP	Complete FVP regression	PAR	PAR	Mature	Mature	Mature	Mature	Mature
	OS				Zone II stage 3 P+	Regressing FVP	Complete FVP regression	PAR	PAR	Mature	Mature	Mature	Mature	Mature
12	OD	29	1750	33	Zone 1 AROP	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	PAR	PAR, lattice, WWOP	PAR, lattice, WWOP
	OS				Zone 1 AROP	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	PAR	PAR, lattice, WWOP	PAR, lattice, WWOP
13	OD	27	650	33	NVI, Zone 1 Stage 3 +	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	PAR	PAR, WWOP	PAR, WWOP
	OS				NVI, Zone 1 Stage 3 +	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	PAR	PAR WWROP	PAR, WWOP
14	OD	30	1300	35	Zone 1 AROP	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere
	OS				Zone 1 AROP	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere
15	OD	28	1500	31	Zone 1 AROP	Regressing	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere
	OS				Zone 1 AROP	Regressing	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere
16	OD	28	1060	35	NVI, Zone II P AROP	regressing	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	PAR	PAR
	OS				NVI, Zone II P AROP	Regressing	Inomplete FVP regression	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	PAR
17	OD	29	1450	33	Zone II stage 3 P+	Regressing	Complete FVP regression	PAR	Mature	Mature	Mature	Mature	Mature	Mature
	OS				Zone II stage 3 P+	Regressing	Complete FVP regression	PAR	Mature	Mature	Mature	Mature	Mature	Mature
18	OD	29	1260	34	Zone II AROP	Regressing	Complete FVP	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere

			regression							
OS	Zone II AROP	regressing	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere

GA: Gestational age; OD: Right eye; OS: Left eye; BW: Birth weight; PMA: Post menstrual age; PAR: Peripheral avascular retina; FU: Follow up; AROP: Aggressive retinopathy of prematurity; FVP: Fibrovascular proliferation; NVI: Neovascularization of iris; WWOP: White without pressure.

[7].

Crunch effect is the term given to accelerated posterior/prepapillary fibrosis and contraction as one of the characteristic patterns of TRD which may occur following intravitreal injection of anti-vascular endothelial growth factor (VEGF) therapies in acute ROP, with 49% of detachments occurring within 4 week of the treatment, with older infants (by PMA) at higher risk[7].

In this American Academy of Ophthalmology 2019 interview[15], Dr. Capone Jr. describes his experience with crunch detachment where he states an inverse relationship of PMA with pace of developing detachment - older children are at a greater risk of crunch detachments because they typically have pre-existing fibrosis and an increased chance of abrupt contraction. He also described 2 unique types of crunch—arcuate and prepaillary contraction. Thus, the presence of extensive FVP presents a dilemma in treating zone 1 or posterior zone II disease with anti-VEGF injection. All babies in our study had no clinical evidence of antero-posterior traction unlike described by Honda *et al*[6] where avastin given to baby with stage 4A resulted in acute contracture of proliferative membrane resulting in worsening of the disease. A similar study by Kychenthal *et al*[16] showed that bevacizumab given in eyes with extensive neovascular tissue showed higher chances of development of fibrosis. However they also recruited cases with stages 4A and B, which already have established antero-posterior traction.

In a study by Wu *et al*[17], bevacizumab was injected for stages 3, 4A and stage 5 patients. 33% of eyes with 4A regressed after bevacizumab alone without the requirement of vitrectomy. Many studies have shown the outcomes of use of intravitreal bevacizumab prior to vitrectomy, where reduced vascularity not only aided the surgery but also induced contracture of proliferative membrane indicating earlier surgical intervention[18,19].

This phenomenon is likely to be secondary to a shift in the cytokine signalplex, with exacerbation of the unopposed activity of profibrotic cytokines such as transforming growth factor-beta (TGF-β); TGF-β, an antagonist of VEGF, rises in systemic and intravitreal concentration between 36 and 40 wk PMA, the time period during which many of these premature infants are being treated with anti-VEGF[20]. No contracture of FVP was seen in any of our cases, rather in 75% eyes there was disappearance of FVP within a month of injection, earliest being within a week.

In the attempted normal physiological vascularization in a preterm, various risk factors interrupt this process to and assist in the pathogenesis of ROP. In the Phase 1 or vaso-obliterative phase, there is a low level of VEGF as well as declining levels of circulating insulin like growth factor 1 (IGF-1) from the maternal source. With the maturation of the liver of the premature baby, IGF-1 production starts and its levels rise. This, along with the rise in VEGF levels in phase 2 of pathogenesis of ROP, aids in development of treatable ROP[21-24]. A late component of phase 2 can be described as Phase 3, which is the phase of development of fibrosis and TRD[25]. Increased VEGF activates plasminogen activators which converts plasminogen to plasmin which in turn activates transforming growth factor beta 1 (TGF-β1) which downregulates VEGF and promote fibrosis leading to excessive scarring in stages 4 and 5 ROP[26]. As the baby matures, the liver is able to produce the factors such as TGF-β1, and this allows exaggerated effects of the VEGF and subsequently the development of fibrous component, providing a scaffold for the high levels of VEGF to act and cause a contracture. This is why crunch phenomenon is often seen in babies with higher PMA[15].

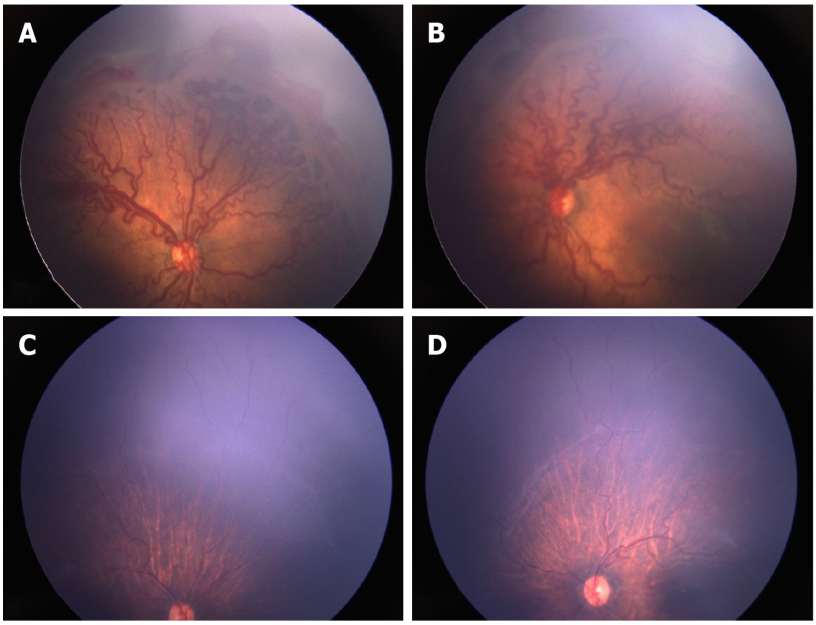

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Figure 1 Pre and post intravitreal anti-vascular endothelial growth factor injection fundus pictures showing disease regression. A: Fundus picture of right eye and; B: Fundus picture of left eye showing severe Zone 1 Aggressive retinopathy of prematurity with extensive fibro vascular proliferation; C: Fundus picture of right eye and; D: Fundus picture of left eye taken 4 months following anti-vascular endothelial growth factor injection showing marked resolution of disease with minimal residual fibrous tissue.

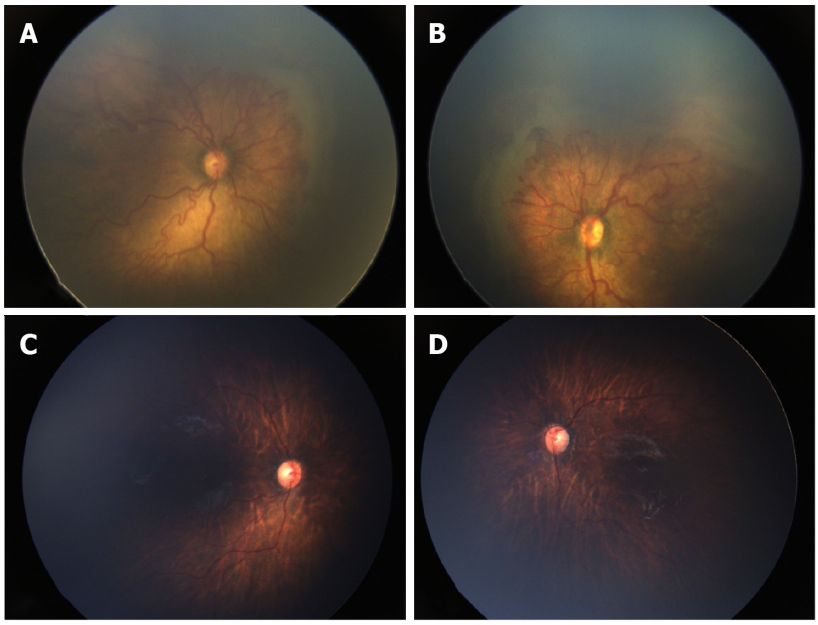

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Figure 2 Pre and post intravitreal anti-vascular endothelial growth factor injection fundus pictures showing disease regression. A: Fundus picture of right eye and; B: Fundus picture of left eye showing severe Zone 1 Aggressive retinopathy of prematurity with extensive fibro vascular proliferation; C: Fundus picture of right eye and; D: Fundus picture of left eye taken 3 months following anti-vascular endothelial growth factor injection showing marked resolution of disease.

The mean PMA at the time of injection in our cases was 35.1 week which explains the resolution of FVP in our series. In most of the reported cases of crunch phenomenon, the IVA has been given between 37-42 wk[6,27,28]. Thus, we can assume when the anti- VEGF injection given prior 37 week PMA, the baby is believed to be in phase 2 where the vascular component predominates and no contracture of FVP occurs. On the contrary, if anti-VEGF injection is given near or at term, then the disease is already in Phase 3 and anti-VEGF would hasten the already set-in fibrosis leading to contracture with progression of disease to stages 4b and 5. Although determining an exact cut off requires studies with larger sample size, it may still lack direct evidence to establish such a cut off, due to prior knowledge of crunch phenomenon in older babies and ethical considerations. However, it must be kept in mind that the timing of IVA is key and it is unlikely to

cause a contracture of pre-existing FVP prior to 37 week PMA, as per indirect evidence.

The effect of systemic absorption of IVA and effect on the other eye has been noted by the development of crunch effect in the fellow eye[28]. Theoretically a shorter acting IVA is preferred due to lesser suppression of systemic VEGF and we feel it could be preferred in cases with significant FVP as well, as this would limit the development of contracture or atleast shorten the critical time when contracture is likely to occur. In our cohort however, the choice of IVA was as per the patient's preference which in turn was mostly influenced by the cost of the injection. The drawback of this study includes comparison across different anti VEGF that are known to have different half-life in the vitreous cavity. Also, we included babies with significant FVP (> 4 clock hours) treated with IVA injections, without performing ultrasound B scan to rule out anteroposterior traction.

CONCLUSION

The subset of severe posterior ROP with FVP pose therapeutic dilemma. This study shows favorable outcomes when treated with IVA injections, in babies with PMA < 37 weeks. The present study also shows the importance of extended period of follow up post IVA injections, as we found a high percentage (55.5%) of babies having incomplete vascular maturity at 1 year follow up. However, none of the babies developed anteroposterior traction or tractional retinal detachment or required rescue vitrectomy at any time until the last follow up 5 years post IVA. But we advise caution, especially in a setting without vitreoretinal surgery back up, and recommend a multi-center prospective study with a larger sample size.

ARTICLE HIGHLIGHTS

Research background

There is always a dilemma whether or not intravitreal anti-vascular endothelial growth factor (IVA) injections can be given in severe retinopathy of prematurity (ROP) with fibro vascular proliferation (FVP).

Research motivation

The outcome of laser alone in treating severe posterior ROP with FVP is poor. Hence we wanted to test if IVA injections could be a better option for these subset of cases.

Research objectives

To test if early IVA injections in severe posterior ROP with FVP would cause worsening of the disease.

Research methods

It is a retrospective study which included 36 eyes of 18 babies, which were given IVA injections for severe posterior ROP with FVP and followed up till 5 years of age.

Research results

There was no contraction of the FVP in any of the eyes after the IVA injections. All eyes showed very good regression. The mean post menstrual age of injection was 35.5 wk. Five eyes showed disease reactivation on follow up which was treated by laser in 3 eyes and repeat IVA injections in 2 eyes.

Research conclusions

IVA injections can be tried as an initial treatment in severe posterior ROP with FVP, if the post menstrual age at the time if injection is < 37 wk.

Research perspectives

IVA injections could be used as a first line treatment in the management of severe posterior ROP with FVP.

FOOTNOTES

Author contributions: Shah PK and Narendran V designed the research study; Maitra P and Prema S performed the research; Narendran V contributed towards analytic tools; Maitra P, Prema S and Shah PK analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Aravind Eye Hospital Institutional Ethics Committee (Approval No. RET201300423).

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ORIGINAL ARTICLE

Retrospective Study

Radiation dose analysis of computed tomography coronary angiography in Children with Kawasaki disease

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Abstract

BACKGROUND

There is evolving role of computed tomography coronary angiography (CTCA) in non-invasive evaluation of coronary artery abnormalities in children with Kawasaki disease (KD). Despite this, there is lack of data on radiation dose in this group of children undergoing CTCA.

AIM

To audit the radiation dose of CTCA in children with KD.

METHODS

Study (December 2013-February 2018) was performed on dual source CT scanner using adaptive prospective electrocardiography-triggering. The dose length product (DLP in milligray-centimeters-mGy.cm) was recorded. Effective radiation dose (millisieverts-mSv) was calculated by applying appropriate age adjusted conversion factors as per recommendations of International Commission on Radiological Protection. Radiation dose was compared across the groups (0-1, 1-5, 5-10, and > 10 years).

RESULTS

Eighty-five children (71 boys, 14 girls) with KD underwent CTCA. The median age was 5 years (range, 2 mo-11 years). Median DLP and effective dose was 21 mGy.cm, interquartile ranges (IQR) = 15 (13, 28) and 0.83 mSv, IQR = 0.33 (0.68, 1.01) respectively. Mean DLP increased significantly across the age groups. Mean effective dose in infants (0.63 mSv) was significantly lower than the other age

groups (1-5 years 0.85 mSv, 5-10 years 1.04 mSv, and > 10 years 1.38 mSv) ($P < 0.05$). There was no significant difference in the effective dose between the other groups of children. All the CTCA studies were of diagnostic quality. No child required a repeat examination.

CONCLUSION

CTCA is feasible with submillisievert radiation dose in most children with KD. Thus, CTCA has the potential to be an important adjunctive imaging modality in children with KD.

Key Words: Computed tomography coronary angiography; Coronary artery abnormalities; Dual source computed tomography; Kawasaki disease; Radiation exposure

Core Tip: Dual source computed tomography (CT) scanners by virtue of high temporal resolution, faster gantry rotation, electrocardiography triggered tube current modulation, large area coverage, body adaptive automatic selection of tube current modulation and iterative reconstruction algorithm have largely addressed the issue of high radiation exposure when subjecting children with Kawasaki disease (KD) to CT coronary angiography. It is now possible to evaluate these patients using submilliseivert radiation exposure. This is a significant advance in management of KD.

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INTRODUCTION

Kawasaki disease (KD) is a common childhood medium vessel vasculitis with special propensity for coronary arteries. It typically affects children below 5, however, older children and young adults can also be affected. Diagnosis of KD is based on constellation of clinical features, and there are no pathognomonic laboratory tests. Children with KD fluffing the epidemiological case definition are known as complete KD. Incomplete and atypical forms of disease can constitute up to 50% of patients with KD[1-4]. Coronary artery abnormalities (CAAs) represent the major contributors to both acute as well as long term morbidity and mortality related to KD[4-8]. Timely treatment of KD reduces the CAAs incidence from 25% to < 5%. Timely and precise evaluation of CAAs is important for management of patients with KD[4]. 2D-echocardiography (ECHO) has hitherto been the first line imaging modality for evaluation of CAAs. However, it has some inherent limitations. These include operator dependency, poor acoustic window and lack of visualization of middle and distal segments of coronary arteries[6]. Further, it is difficult to visualize the coronaries in older children who have thick chest walls[9,10]. Catheter angiography (CA) is the gold standard imaging modality but has the disadvantages of being invasive and is associated with high radiation exposure[11-13].

Recently, multi-detector CT (MDCT) and dual source CT (DSCT) platforms have allowed imaging of coronary arteries at any heart rate with attempts at radiation optimization[14-18], which otherwise is a serious concern in children[19,20]. There are limited studies that to with small sample size on radiation dose in children with KD undergoing CTCA on DSCT (Table 1). Radiation dose in these studies was either more or comparable to our study. This study enumerates various methods to optimize the radiation exposure on CTCA in children with KD, an audit of the radiation dose and show that radiation exposure can be reduced to 1mSv or less in majority of children.

MATERIALS AND METHODS

Study design

Review of records was carried out during the period December 2013-February 2018. The manuscript has been approved by Departmental Publication Review Board (RDG/EC/Pub/27 dated July 03, 2020). Written informed consent was obtained from parents prior to CTCA.

Patient population

Children with KD who underwent CTCA were either at presentation or on regular follow-up with CAAs on ECHO were included in the analysis. As per International Commission on Radiological Protection-103 (ICRP 103) recommendations, children were grouped as per age into infants (< 1 year), 1-5 years, 5-10 years, > 10 years. System generated radiation exposure dose length product (DLP in milligray-centimeters-mGy.cm) was recorded and effective radiation dose (millisieverts-mSv) was calculated by applying age adjusted conversion factors recommended by ICRP 103[21] and analysis of

Table 1 Comparison of effective radiation dose on dual source computed tomography coronary angiography platforms in patients with Kawasaki disease

Ref.	Country	Number of cases	Platform	ECG triggering	Age	Radiation dose	Remarks
Duan *et al*[27], 2012	China	19	DSCT	Prospective	Range: 3 mo-5 yr	ED (mean ± SD): 0.36 ± 0.06 mSv	
Kim and Goo [28], 2013	Korea	51	DSCT: (1) 64-Slice: *n* = 49; and (2) 128-Slice: *n* = 2	Retrospective in most of the patients	Mean (range): 13.2 (1-24) yr	ED (mean ± SD): (1) 64-Slice: 2.6 ± 2.7 mSv; and (2) 128-Slice: 2.1 ± 0.6 mSv	ED was only 0.6 ± 0.5 mSV in 5 children < 2 yr of age, who underwent prospective ECG-triggering
Ghoshhajra *et al*[29], 2014	United States	52	DSCT: (1) 64-Slice: *n* = 16; and (2) 128-Slice: *n* = 36	Prospective	Range: 0-18 yr	Median (IQR) ED: (1) 64-Slice: 2.9 (0.9-4.1) mSV; and (2) 128-Slice: 1.0 (0.6-2.0) mSV	ED significantly reduced compared to 16 and 64-Slice Scanner platforms
Kantarcı *et al* [30], 2019	Turkey	17	128-Slice DSCT	Details NA	Mean (range): 3 yr (2 mo-11.3 yr)	ED range: 1.2-4.3 mGy depending on the patient's body weight	
van Stijn *et al* [26], 2020	Netherlands	70	DSCT: (1) 2 × 192-Slice: *n* = 56; and (2) Other CT scanners (64/128/320-Slice): *n* = 14	Prospective	Median (range): 15.1 (0.5-59.5) yr	Median (range) ED: (1) 2 × 192-Slice: 1.5 (0.3-9.4) mSv; and (2) Other CT scanner: 3.8 (1.7-20.0) mSv	This is the only study on 3rd generation DSCT platform
Borhanuddin *et al*[31], 2022	Malaysia	52	64-slice DSCT	Retrospective	Median (range): 5 (1-18) yr	Median (range) ED: 0.81 (0.4-5.8)	
Present study, Chandigarh	India	85	128-Slice DSCT	Prospective	Median (range): 5 yr (2 mo-11 yr)	Median (IQR) ED: 0.83 (0.68-1.01)	Largest study on 128-Slice platform which provides data that CTCA can be performed in sub-millisievert doses

CTCA: Computed tomography coronary angiography; DSCT: Dual source computed tomography; ED: Effective radiation dose; IQR: Interquartile range.

radiation exposure across groups was done (Table 2).

CTCA technique

CTCA was carried out on a second generation DSCT 128-slice scanner (Somatom Definition Flash, Siemens, Erlangen, Germany) using non-ionic contrast (Omnipaque 350, GE Healthcare, Ireland) with the following parameters: Temporal resolution- 75 milliseconds, gantry rotation time-0.28 s, slice thickness-0.6 mm. The scan was conducted in a craniocaudal direction from floor of carina to the diaphragm (till base of heart). CTCA was carried out with adaptive prospective electrocardiography (ECG) triggered sequence (CorAdSeq) tube current modulation to minimize radiation exposures without compromising image quality. With this technique the CT X-ray tube is switched on at the predefined range of R-R interval of ECG (in our study 30%-80% R-R interval) and provides images in systolic and diastolic phases.

Scanning parameters were customized to ensure minimal radiation exposure. Volume CT dose index (CTDIvol) was taken as adjusted by the CT scanner according to body-size adapted protocols-CARE Dose4D (Siemens, Erlangen, Germany). With this tube current-time product (mA.s) is automatically calculated for optimal automatic exposure depending on body weight and cross-sectional area. Automatic CARE kV was switched off and adjusted to 80 kilovolt (kVp) in all children. These modifications, along with CARE-Dose 4D tube current modulation, enabled us to further reduce the effective radiation dose. Lowest kVp and mAs values ensured optimal image quality with minimum possible radiation exposure. The current-time product ranged between 32-154 mA.s.

Statistical analysis

Parameters showing normal distribution were depicted as mean and standard deviation, while variables with skewed distribution were expressed as median and interquartile ranges (IQR). A P value of < 0.05 was regarded as significant. Statistical analysis was accomplished using SPSS statistical software version 20.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

Demographic characteristics

CTCA of 85 patients [71 (84%) boys; 14 (16%) girls] with KD were acquired. Median age of our cohort was 5 years [IQR: 5

Table 2 Conversion factors for chest in different age groups at 80 kV according to recent International Commission on Radiological Protection recommendations (20)

S.No.	Age group	Tube voltage (kV)	Conversion factor
1	< 1 yr	80	0.0823
2	> 1 - < 5 yr	80	0.0525
3	> 5 - < 10 yr	80	0.0344
4	≥ 10 yr	80	0.0248

(7, 2)]; range: 2 mo-11 years. As per ICRP 103 recommendations, children were grouped as per age into infants (< 1 year) (n-10; 12%), 1-5 years (n-29; 34%), 5-10 years (n-38; 45%), > 10 years (n-8; 9%).

Radiation dose

The median DLP and effective dose of all 85 patients in our study were 21.0 mGy.cm, IQR = 15 (13, 28) and 0.83 mSv, IQR = 0.33(0.68, 1.01), respectively. Details of DLP and effective CT radiation dose for children in study group are given in Table 3.

The mean DLP in infants, 1-5 years, 5-10 years, and > 10 years was 9.19, 18.82, 31.76, and 55.67 mGy.cm, respectively. The mean effective dose in infants, 1-5 years, 5-10 years, and > 10 years was 0.63, 0.83, 1.04, and 1.38 mSv. The DLP showed significant increase with increasing age. The difference in the DLP was statistically significant across all age groups (P value for infants *vs* 1-5 years, 1-5 years *vs* 5-10 years, and 5-10 years > 10 years; < 0.001, < 0.001, and 0.01, respectively. The mean effective dose in infants (0.63 mSv) was significantly lower than the other age groups (1-5 years 0.85 mSv, 5-10 years 1.04 mSv, and > 10 years 1.38 mSv) (P < 0.05). There was no significant difference in the effective dose among children in the other groups.

All the CTCA studies were of diagnostic quality. No child required a repeat examination.

DISCUSSION

We performed CTCA on 128-DSCT scanner with radiation optimized protocols (CorAdSeq tube current modulation, body-size adapted protocols and reduced tube kilovoltage settings at 80 kVp) to minimize radiation exposures. In total 85 children with median age of 5 years [IQR: 5 (7, 2)]; (range: 2 mo-11years) were scanned. The mean effective radiation dose was 0.83 mSv with radiation exposure significantly lower in infants (0.63 mSv) as compared to other age groups. CTCA can visualize CAAs along the entire course of coronary arteries[6].

KD is a medium vessels vasculitis with special predilection for involvement of coronary arteries[1-4]. ECHO has hitherto been considered the imaging modality of choice for diagnosis and follow-up of CAAs in patients with KD, but with many limitations related to comprehensive evaluation of coronary arteries. CA is the gold standard, but is associated with inordinate radiation exposure, is invasive and cannot be repeated often for follow-up. Moreover, mural abnormalities cannot be depicted on CA[9,22].

With the advent of new high MDCT and DSCT scanners, imaging of coronary arteries is possible. However, until recently the risk of high radiation exposure had precluded the use of CTCA in children with KD. This was probably the limiting factor that prevented its application in pediatrics when cardiac CT on single source 64-slice was made possible. CTCA with single source 64-Slice CT is associated with radiation exposure as high as 3.0-5.7 mSv[23]. Moreover, this technique resulted in sub-optimal image quality due to inability to acquire images at high heart rates in children. Though there are no criteria to define limits of radiation dose in children, authors are of the opinion that this is clearly unacceptable in children and every possible method should be used to reduce radiation exposure in children as per ALARA (as low as reasonably achievable) principle[24]. Higher slice and dual source CT scanners with improvised technologies have emerged as promising platforms for CTCA with possibility for radiation optimization providing a promising imaging modality for assessment of CAAs of KD vis-a-vis CA.

Various dose-saving strategies that can be adopted during CTCA on DSCT are body size-adapted protocols including low tube voltage techniques, ECG-controlled and attenuation-based tube current modulations, and prospectively ECG-triggered scanning[14-18]. Lowering the KVp values (to 80) results in a significant dose reduction with acceptable image quality[25]. We have used adaptive prospective ECG-triggered sequence with tube current modulation, lower tube voltage (80 kVp) and optimized system calculated tube current using CARE-Dose 4D for radiation reduction. Iterative reconstruction algorithm that was used in our protocol in addition provides excellent quality images even at low exposure.

van Stijn *et al*[26] recently published a study on coronary artery assessment in patients with KD using 3rd generation DSCT platform (2 × 192-Slice CT scanner) on 70 children. The authors achieved a radiation exposure of 1.5 mSv (range 0.3-9.4 mSv)[26]. The radiation dose in our cohort was lower. Median effective dose of radiation 0.83 mSv (0.68-1.01) in our study is amongst the lowest achieved so far on DSCT platform using 128-Slice CT scanner. Further, cohort sizes in the previously published studies have been much smaller than ours[26-31] (Table 1). Having achieved such low radiation exposures and given the fidelity of images acquired on these platforms, it may not be long before CTCA on a DSCT platform becomes the imaging modality of choice for detailed evaluation of CAAs in children with KD.

Table 3 Effective computed tomography radiation exposure according to age in adaptive prospective electrocardiography-triggered sequence computed tomography coronary angiography on 128-dual source computed tomography platform

S.No.	Age group	Mean DLP (mGy.cm)	Mean effective radiation dose (mSv)
1	0-1 yr (n = 10)	9.19 ± 2.21	0.63 ± 0.16
2	1-5 yr (n = 29)	18.82 ± 8.48	0.85 ± 0.41
3	5-10 yr (n = 38)	31.79 ± 14.14	1.04 ± 0.37
4	> 10 yr (n = 8)	55.67 ± 19.39	1.38 ± 0.48

DLP: Dose length product; mSV: Millisievert.

We recognize several limitations to our study. The data in the current study comes from a single center and more such studies are required for further validation of our results. Further, there were fewer children in individual age groups. The cumulative impact of radiation dose in children who may require follow up CTCA is not known. Though, all the scans were of diagnostic quality, it is desirable to assess image quality along with radiation dose. However, our study was not tailored to assess the image quality.

CONCLUSION

In conclusion, DSCT scanners by virtue of high temporal resolution, faster gantry rotation, ECG triggered tube current modulation, large field of view, body adaptive automatic selection of tube current modulation and iterative reconstruction algorithm have largely addressed the issue of high radiation exposure when subjecting children with KD to CTCA. It is now possible to evaluate these patients using submilliseivert radiation exposure. This is a significant advance in management of KD.

ARTICLE HIGHLIGHTS

Research background

There is evolving role of computed tomography coronary angiography (CTCA) in non-invasive evaluation of coronary artery abnormalities in children with Kawasaki disease (KD). Despite this, there is lack of data on radiation dose in this group of children undergoing CTCA.

Research motivation

There is paucity of literature on radiation exposure in children with KD undergoing CTCA for coronary artery assessment.

Research objectives

To estimate the radiation dose exposure in children with KD undergoing CTCA for coronary artery assessment.

Research methods

Children with KD who underwent CTCA were either at presentation or on regular follow were included in the analysis. System generated radiation exposure dose length product (DLP in milligray-centimeters-mGy.cm) was recorded and effective radiation dose (millisieverts-mSv) was calculated by applying age adjusted conversion factors.

Research results

Total 85 children with median age of 5 years were scanned. Mean effective radiation dose was 0.83 mSv with radiation exposure significantly lower in infants (0.63 mSv) as compared to other age groups. CTCA demonstrated coronary artery abnormalities along the entire course of coronary arteries.

Research conclusions

CTCA is feasible with submillisievert radiation dose in most children with KD.

Research perspectives

CTCA has the potential to be an important adjunctive imaging modality in children with KD. To confirm our results multicentric study with larger sample size would be required.

FOOTNOTES

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CASE REPORT

Transient hyperphosphatasemia in a toddler with COVID-19 infection: A case report and literature review

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Abstract

BACKGROUND

Transient hyperphosphatasemia (TH) is a condition characterized by elevated serum alkaline phosphatase (ALP) in the clinical setting with no evidence of bone or liver disease among children under the age of 5. Typically, it will resolve spontaneously in a few months in the majority of cases. TH has been found to be associated with viral infections. Two cases of TH associated with coronavirus disease 2019 (COVID-19) infection in toddlers have been previously reported.

CASE SUMMARY

A previously healthy 2-year-old boy presented with fever and positive real-time polymerase chain reaction for COVID-19. Prior to his illness, the patient had been in close contact with his grandfather, who later developed COVID-19. The physical examination on admission was unremarkable. He remained asymptomatic throughout 7 d of hospitalization. On the 5th day of his illness, blood tests showed markedly elevated serum ALP (4178 U/L). Results from the simultaneous testing of the remaining liver profiles and metabolic bone panels were normal. Two months after discharge from the hospital, the patient continued to thrive well. The skeletal surveys revealed no significant abnormalities. The serum ALP declined into the normal range adjusted for his age. This evidence is consistent with the diagnosis of TH.

CONCLUSION

TH can occur in COVID-19-infected toddlers. Serial measurements of ALP levels have been shown to gradually decline into the normal range within a few months. Therefore, being aware of this transient abnormality will help clinicians to avoid additional unnecessary investigations.

Key Words: Alkaline phosphatase; Coronavirus; Pediatric endocrinology; Case report

Core Tip: Transient hyperphosphatasemia (TH) is an unrecognized condition among children under the age of 5. The only abnormality demonstrated is markedly elevated serum alkaline phosphatase (ALP) without evidence of bone or hepatic disease and spontaneous resolution occurring in several months. Numerous reports have identified various viral infections as contributing factors to the etiology of this condition. TH should be considered in coronavirus disease 2019 -infected toddlers exhibiting isolated high serum ALP. Awareness of this condition will help to avoid unnecessary investigations.

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INTRODUCTION

Transient hyperphosphatasemia (TH) is a benign and self-limiting condition characterized by a marked increase in serum alkaline phosphatase (ALP) in the absence of liver or bone disease[1]. The elevated serum ALP level usually declines into the normal range within a few months[1,2]. TH is observed in either sick or healthy infants and children under the age of 5 by finding incidentally elevated serum ALP on routine laboratory investigation for other purposes[3-8]. Although its etiology remains unclear, the propensity of TH associated with various conditions, such as post organ transplantation, hematologic malignancy, rheumatologic disease[9-11], and, in particular, infectious diseases, has been reported in the literature[5,12,13].

Coronavirus disease 2019 (COVID-19) infection is a highly contagious infection that quickly became a global pandemic disease. Endocrinopathies associated with COVID-19 infection in children, such as thyroid diseases (subacute thyroiditis, hypothyroidism, hyperthyroidism), adrenal insufficiency, diabetes mellitus, vitamin D deficiency and hypopituitarism, had been previously reported[14,15]. TH observed with COVID-19 infection in toddlers is a new discovery that was recently described in two cases[16,17]. Here, we report a case of a 2-year-old boy who developed TH associated with COVID-19 infection.

CASE PRESENTATION

Chief complaints

A previously healthy 2-year-old boy was admitted to our hospital with an acute febrile illness of 4 d duration.

History of present illness

There was a history of the patient being in close contact with his grandfather, who was later diagnosed with symptomatic COVID-19 infection. The patient had a positive test of real-time reverse transcription polymerase chain reaction for severe acute respiratory syndrome coronavirus 2.

History of past illness

He was a full-term baby with a birth weight of 2800 g, requiring no medication since his birth.

Personal and family history

No special notes.

Physical examination

The physical examination upon admission revealed that the patient was in good general condition, with no sign of respiratory distress or dehydration, body temperature 37.6°C, pulse rate 90/min, respiratory rate 22/min and O_2 saturation in room air 99%. His weight and height were 12.1 kgs (-0.7 SDS) and 86.5 cm (+0.7 SDS), respectively. The skeletal examination revealed no wrist joint swelling, rachitic rosary, knock knee or abnormal gait to suggest definite skeletal disease. There were no clinical findings of jaundice or hepato-splenomegaly to indicate hepatobiliary disease.

Laboratory examinations

The initial laboratory results showed hemoglobin 13.3 g/dL, white blood cell 10100/μL with 61.6% lymphocytes and platelet count 196000/μL. Chest X-ray revealed no infiltration. The liver function test (LFT) on the 5th day of his illness

showed a markedly elevated serum ALP of 4178 U/L (normal range: 111-277). Additionally, the occurrence of bone or hepatobiliary disease was assessed, and the results were normal as follows: Blood urea nitrogen 12.4, Cr. 0.3, calcium 9.9, phosphate 4, magnesium 2.2 mg/dL, intact-PTH 21.3 pg/mL, 25-OHD 33.6 ng/mL and gamma-glutamyl transferase 12 U/L (Table 1). The serum ALP was repeated 4 d following the initial study. It remained elevated at 4662 U/L, but the rest of the LFT was normal.

Table 1 Laboratory tests of our patient during coronavirus disease 2019 infection and follow-up

Parameters	At admission		Follow-up after illness	
	5th day of illness	9th day of illness	2nd month	6th month
ALP (U/L)	4178	4662	252	229
AST (U/L)	35.8	30.8	37.7	29.3
ALT (U/L)	17	15.9	16.5	18.8
TP (g/dL)	7.1	6.8	6.7	6.8
Alb (g/dL)	4.9	4.8	4.6	4.6
TB/DB (g/dL)	0.25/0.12	0.17/0.11	0.37/0.12	0.24/0.11
GGT (U/L)	12	-	-	-
Cr (mg/dL)	0.3	-	-	-
Ca (mg/dL)	9.9	-	9.7	-
P (mg/dL)	4.0	-	4.9	-
Mg (mg/dL)	2.2	-	2.26	-
iPTH (pg/mL)	21.3	-	26.4	-
25-OHD (ng/mL)	33.6	-	23.4	-

ALP: Alkaline phosphatase (normal range: 111-277 U/L; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TP: Total protein; Alb: Albumin; TB: Total bilirubin; DB: Direct bilirubin; GGT: Gamma-glutamyl transferase; Ca: Calcium; P: Phosphate; Mg: Magnesium; iPTH: Intact parathyroid hormone.

Imaging examinations

No special notes.

FINAL DIAGNOSIS

At this point, the diagnosis of TH was strongly considered. The entire 7 d of his hospital course was uneventful without fever, diarrhea or respiratory tract symptoms.

TREATMENT

The management was symptomatic and supportive care with oral antipyretic, anti-emesis and oral rehydration solution.

OUTCOME AND FOLLOW-UP

Two months after discharge, the patient was re-evaluated at the outpatient endocrine clinic. His physical examination was normal. Serum ALP became normal at 252 U/L. The other investigations, including LFT, calcium, phosphorus, magnesium, 25-OHD and skeletal survey radiography, were completely normal. A six-month follow-up study with the same parameters as the 2-month follow-up study revealed that everything remained within the normal range (Table 2).

Table 2 Clinical characteristics and laboratory tests in hyperphosphatasemia associated with coronavirus disease 2019 infection: our patient and previous reports

Clinical characteristics	Our patient	Erat *et al*[16], 2020	Tchidjou *et al*[17], 2020
Ethnicity	Thai	Turkish	French
Gender	M	F	M
Age (mo)	26	16	9
Symptom of COVID-19 infection			
Fever	Yes	Yes	Yes
Upper respiratory tract symptom	No	Yes (Cough, oropharyngeal hyperemia)	Yes (Rhinitis)
Lower respiratory tract symptom	No	No	No
Gastrointestinal symptom	No	Yes (Nausea, diarrhea)	No
Laboratory tests			
Peak ALP (U/L)	4662 (Normal: 111-277)	1860 (Normal: 145-420)	3384 (Normal: 46-116)
ALP ratio[a]	16.8	4.4	29
Cr (mg/dL)	0.21	0.22	0.43
AST (U/L)	36	34	37
ALT (U/L)	17	14	39
GGT (U/L)	12	13	8
Ca (mg/dL)	9.9	9.8	NA
P (mg/dL)	4	5.5	6.8
iPTH (pg/mL)	21.3	28.1	NA
25-OHD (ng/mL)	33.6	32	NA
Resolution of TH			
Time turned to normal ALP level	Two months	One month	One month
ALP (U/L)	252	254	371

[a]ALP ratio: The measured ALP level divided by the upper limit of normal. ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; Ca: Calcium; COVID-19: Coronavirus disease 2019; P: Phosphate; Mg: Magnesium; iPTH: Intact parathyroid hormone; TH: Hyperphosphatasemia; NA: Not available.

DISCUSSION

ALP is a membrane-bound phosphomonoesterase enzyme consisting of four isoenzymes, three tissue-specific ALPs (intestinal, placental and germ cell) and the tissue-nonspecific ALP (TNSALP)[18]. TNSALP is abundant in the bone, liver and kidney and accounts for 95% of total ALP activity in serum[19]. Therefore, abnormally high ALP levels are an important marker for skeletal and hepatobiliary diseases.

TH is a benign self-limited condition that reportedly has a prevalence from 1.1% to 3.5% among infants aged 2-24 mo and affects both sexes equally[20,21]. This condition was first described in 1954 by Bach[22]. In 1985, Kraut *et al*[2] established the criteria for the diagnosis of TH in infancy and children, defined as an age group below 5 years, no evidence of bone or liver disease on physical examination or laboratory test, elevation of both bone and liver ALP isoenzymes and a return to normal serum AP values within 4 mo. Although the specific cutoff value of ALP level for diagnosis of TH had not been identified by the original criteria, recent studies have suggested that TH is considered when serum ALP is above 800[5,13], 1000 (6, 11, 21) or 2000 U/L[23]. However, the peak serum ALP of TH was distinctively higher than the serum ALP levels of other bone and hepatic diseases. In a review of 733 TH patients, the mean ALP level was 9 times above the upper limit of the normal range, and 71% of these patients had the highest ALP > 5 times above the upper limit of the reference value[4].

Numerous reports have identified various viral infections as contributing factors to the etiology of TH (Table 3)[13,23-27]. Suzuki *et al*[28] identified antibodies against enteroviruses, such as ECHO 22, entero-71 and coxsackie B4, in the serum of 50 TH children. Among these viruses, ECHO 22 antibody was most frequent, accounting for 32% of TH cases. Additionally, few but not all studies reported clusters of TH during the fall and winter seasons, which supported the assumption of the viral etiology[3,12,21].

Table 3 Viral infections associated with hyperphosphatasemia [13,23-27]

Respiratory syncytial virus
Influenza virus
Epstein-Barr virus
Adenovirus
Bocavirus
Cytomegalovirus
Rotavirus

The mechanism of TH is obscure. Several hypotheses have been postulated, including increased activities of ALP in plasma, increased production and impaired clearance of ALP. The most likely mechanism is decreased hepatic clearance due to the high sialic acid content of ALP, but the mechanism involved in excessive sialic acid content of the molecule is unknown[29]. Increased bone ALP production is thought to be a result of increased bone resorption triggered by virus infection, consequently increasing osteoblast activities and bone formation and hence increasing bone turnover. This was supported by evidence of transiently increased urinary hydroxyproline (bone resorption marker) excretion[30]. In contrast, the study by Kutilek *et al*[8] in 2012 showed a lack of elevated iPTH, Beta-CrossLaps and osteocalcin in TH patients. As such, the hypothesis of increased bone turnover leading to elevated ALP in TH remains controversial.

TH typically resolves without any treatment. A reduction in ALP level to the normal range occurs between 2 wk and 4 years with a median of 10 wk[4]. In 80% of cases, ALP returns to the normal level in 16 wk[4].

Our patient, who was confirmed to have an active COVID-19 infection, exhibited typical clinical features of TH, including high serum ALP levels and no clinical or laboratory evidence of bone or hepatic disease. His biochemical markers of bone metabolism were normal, including calcium, vitamin D and intact PTH. ALP isoenzyme assays were not available at our facility, nor were the other more specific tests for bone turnover markers. The markedly elevated ALP in our patient became normal within 3 mo of follow-up and remained stable at the 6-month follow-up. Given the reports of TH associated with other viral infections, we concluded that our patient developed TH related to COVID-19 infection. Recently, two cases of TH associated with COVID-19 infection in children have been reported[16,17]. All 3 cases, including ours, were aged under 3 years, in accordance with the preponderance (82%) of TH in patients aged < 36 mo in a previous report[4]. The peak level of ALP appears to have no association with the severity of the illness. In our patient, the peak ALP was at 4, 662 U/L (16.8 times to upper normal range), while his symptoms were mild only with low-grade fever. However, the other 2 previous cases had additional clinical symptoms of the upper respiratory tract and gastrointestinal symptoms, but peak levels of ALP appeared to be lower (Table 2). Nonetheless, the serum ALP levels of all 3 cases were similar to those in previous case reports, ranging from 805 to 16814 U/L[3,5,8]. Our patient had the serum ALP return to the normal range of 252 U/L at 2 mo after the acute illness, which is similar to most of the TH cases. In the 2 previous cases of TH associated with COVID-19 infection, their ALP levels declined to the normal range within a month (Table 2). This can be explained by their early schedule testing compared to ours.

In summary, we demonstrated a typical case of TH in a toddler who had been confirmed to have acute COVID-19. It is likely that a rising number of TH cases will be observed along with continuation of the COVID-19 pandemic.

CONCLUSION

Transient hyperphosphatasemia is a benign and self-limiting condition that occurs mainly in infants and children under the age of 5. This condition can be found in toddlers with COVID-19 who exhibit an isolated high level of serum ALP without evidence of bone or hepatic disease based on physical examination and laboratory testing. Therefore, follow-up monitoring of serum ALP levels to confirm the resolution of hyperphosphatasemia without additional extensive investigation and treatment is recommended.

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