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Gastroparesis in children

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Abstract

Historically, gastroparesis is characterized by delayed gastric emptying of fluids and/or solids without evidence of a mechanical gastric outlet obstruction. To provide a thorough, evidence-based overview of the diagnosis, treatment, outcome and future advances for gastroparesis in children, a web search (PubMed, Cochrane Database of Systematic Reviews, EMBASE, Clinical Evidence) was performed. Original articles and reviews were identified, examined and included as appropriate. The prevalence of gastroparesis is vague in adults and unknown in children. It is suspected on the presence of symptoms indicating gastric dysmotility (nausea, vomiting, early satiety, postprandial fullness, failure to thrive, weight loss) and is confirmed on the demonstration of delayed gastric emptying. It can be assessed with various methods from which gastric emptying scintigraphy of a radiolabeled solid meal is considered as the golden standard. Therapeutic approaches include: dietary modifications, medical treatment (prokinetics, antiemetics, intrapyloric injection of botulinum toxin, enteral feeds via jejunostomy, total parenteral nutrition) and surgical interventions (laparoscopic placement of gastric pacemaker) aiming at alleviating symptoms and maintaining optimal nutritional status. Gastroparesis in children can be challenging to diagnose and treat. Specific protocols for the evaluation of gastric emptying and for a stepwise management are required to optimise future outcomes.

Keywords Gastroparesis, gastric emptying, children, gastric motility disorders

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Introduction

Symptoms such as abdominal pain, nausea, vomiting and early satiety are quite common in everyday pediatric clinical practice. However, when they persist the diagnostic approach can become challenging because the physician has to differentiate among various clinical entities that include gastroesophageal reflux, peptic ulcer disease, malformations of the upper gastrointestinal tract, gastroparesis and functional dyspepsia (FD).

By definition gastroparesis is a gastric motility disorder characterized by delayed gastric emptying (GE) in the absence of mechanical obstruction [1]. The gold standard for the diagnosis of gastroparesis is GE scintigraphy [2]. For adults there is a consensus on the diagnostic approach and treatment of gastroparesis; the GE test is well standardized and the normal values for the latter are clearly defined [2-4]. On the contrary, there is no such position statement for the pediatric population. Furthermore, GE scintigraphy protocols vary across different institutions and lack normative values [5]. Additionally, only limited data are available on the epidemiology, etiology, pathophysiology, clinical presentation, treatment and outcome of gastroparesis in children [6,7].

The aim of this article is to systematically review the literature concerning the epidemiology, diagnosis and therapy of gastroparesis in the pediatric population including future perspectives in the overall management of this largely unknown entity.

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Epidemiology

The epidemiology of gastroparesis is still not well defined either in adults or in children [4]. One study showed that 7-15% of the adult population had symptoms indicative of gastroparesis [8]; however, another study demonstrated that the age-adjusted prevalence of definite gastroparesis in adults per 100,000 population was 9.6 for men and 37.8 for women [9]. Unfortunately there are no data available on

the prevalence of gastroparesis in children [10]. A recent retrospective study of a large cohort of pediatric patients revealed that there was almost equal distribution between females and males. The difference among genders increased with age, so that in patients older than 17 years almost two-thirds were females [10].

Etiology and pathophysiology

The integrity of gastric function relies on a fine coordination between the autonomic nervous system, smooth muscle cells and enteric neurons. Literally, any disease affecting the neuromuscular control of the stomach can lead to gastroparesis [11]. The classical teaching in adult gastroparesis has been that approximately one third of cases are related to type I or II diabetes mellitus [12]; one third is attributed to various causes including postsurgical conditions, neurological (e.g. Parkinson disease) [13], metabolic or gastrointestinal disorders and multisystemic diseases. Finally, one third is of unknown etiology, i.e. idiopathic [14].

In children, the majority of cases were considered either postviral or idiopathic [15]. Current literature reveals a predominance of idiopathic gastroparesis in children (70%), followed by drugs (18%) and postsurgical gastroparesis (12%). Additionally, a significant percentage (38.5%) presented concurrently with comorbidities (i.e. seizure disorders, cerebral palsy, developmental delay, prematurity) as well as with psychiatric disorders (28.4%) (e.g. attention deficit-hyperactivity disorder, anxiety, bipolar disorder, other behavioral problems) [10].

Drugs that could potentially cause delayed GE leading to gastroparesis include α-2 adrenergic agonists and tricyclic antidepressants which stimulate adrenergic receptors and thus decrease gastrointestinal motility. Also proton-pump inhibitors, antacids, H_2 receptor agonists, sucralfate, octreotide, β-adrenergic agonists, calcium channel blockers and diphenhydramine may delay GE leading to gastroparesis [16-20].

Viruses (rota virus, Epstein–Barr virus, cytomegalovirus) [15,21] have been implicated as causes of post-infectious gastroparesis. Although the exact mechanism of post-infectious gastroparesis is vague it seems that the infecting agent causes neuropathy by either direct damage of the autonomic ganglia or by indirect effect on the neurons via an immunologic or inflammatory response to the infection [22-24]. The post-infectious delayed GE is usually self-limited and resolves within 24 months [5,15].

Upper abdominal surgery (e.g. fundoplication for gastroesophageal reflux disease) or lung and heart transplantation can cause postsurgical gastroparesis for a number of reasons (e.g. vagal nerve injury leading to reduced antral contractions and pyloric spasticity or opportunistic viral infections due to immunosuppressive medications) [17,25].

Children with neurological conditions can develop gastroparesis possibly due to abnormal function of both the central and enteric nervous system [26,27]. Dysfunction of the autonomic nervous system plays a key role in diabetes-associated gastroparesis (loss of interstitial cells of Cajal, atrophy of gastric smooth muscle) and also in other conditions (e.g. Hirschsprung's disease) [28,29]. Gastroparesis has also been described in premature neonates [30], children with eosinophilic gastrointestinal disease, cow's milk protein allergy, celiac disease, cystic fibrosis, chronic intestinal pseudo-obstruction [10] and autoimmune disorders (dermatomyositis, Crohn's disease) [31,32], renal disease [33], and after corrosive ingestion [34].

Table 2 summarizes the most frequent causes of childhood gastroparesis.

Clinical presentation

Recent data support that the mean age of presentation of gastroparesis is school-age with males predominating among infants and females among adolescents [5]. It is associated with upper gastrointestinal symptoms: vomiting appears as the most common (68%) followed by abdominal pain (51%), nausea (28%), weight loss (27%), early satiety (25%) and postprandial fullness (7%) [10]. However the correlation between the presence and severity of symptoms and the degree of delayed GE is poorly defined. One study in children with gastroparesis found no correlation between symptom severity and the degree of emptying delay [5], whereas another study demonstrated an association between the severity of delayed GE and the frequency of nausea and abdominal pain [10].

Over the years several tools have been proposed for the assessment of the quality of life in patients with gastroparesis. The Gastroparesis Cardinal Symptom Index (GCSI) is believed to be one of the most reliable and valid modalities. It allows better symptom reporting from patients, higher correlation between symptoms and GE time and quantification of symptoms across various institutions. This instrument is used by adult services but is not validated for use in pediatrics [35].

Differential diagnosis

A detailed history and a careful physical examination can aid differentiation from other diseases which present with recurrent nausea, vomiting, abdominal pain, early satiety and postprandial fullness. Patients with gastroparesis may complain of nonspecific abdominal pain and on examination they could have epigastric or diffuse abdominal pain but often physical examination is unremarkable. Conditions that should be distinguished from gastroparesis include firstly esophagitis and peptic ulcer disease, which can be easily diagnosed endoscopically [36]. In cyclical vomiting syndrome GE time is normal in the free of symptoms periods [37]. Rumination syndrome shares common symptoms with gastroparesis but

is characterized by effortless regurgitation immediately or a short period (e.g. 30 min) after meal consumption [38,39]. Intestinal obstruction (e.g. pyloric stenosis, malrotation with volvulus, intestinal atresia or stenosis) are usually diagnosed with upper gastrointestinal contrast series or with transabdominal ultrasonography [40-42].

Interestingly, there is significant overlap between true gastroparesis, FD - as it is defined by the Rome III criteria - and the recently described gastroparesis-like syndrome [43,44]. Delayed GE is present in a subset of pediatric patients with FD [45] and as a result the differential diagnosis in this case can be challenging. Table 1 depicts the data from pediatric studies [10,46,47] regarding the prevalence of common symptoms in children with FD and gastroparesis. Abdominal pain and nausea are the predominant symptoms in FD, while vomiting is the cardinal symptom of gastroparesis. The differentiation between gastroparesis and FD with delayed GE can be difficult and the classification of these disorders as completely different clinical entities still remains controversial [48,49].

Medications that cause nausea and vomiting as side effects also need to be excluded (e.g. anti-neoplastic drugs) [50]. Other diseases that could potentially mimic gastroparesis include conditions affecting the gastrointestinal tract (pancreatobiliary disorders, celiac artery compression syndrome) [51,52], endocrine system (hyperaldosteronism), central nervous system (tumors) and the genitourinary tract (pregnancy, chronic pyelonephritis, uremia) [33].

Table 1 Occurrence of common symptoms in children with functional dyspepsia and gastroparesis

Symptoms	Functional dyspepsia (% of children)	Gastroparesis (% of children)
Nausea	70	28
Abdominal pain	70	5
Bloating	30	7
Vomiting	55	68
Early satiety	10	25

Table 2 The most common causes of gastroparesis in children

Etiological factors	Percent (%) *
Idiopathic	70
Drug-induced	18
Postsurgical	12.5
Postviral	5
Diabetic	4

*(Adapted from: Waseem S, Islam S, Kahn G, Moshiree B, Talley NJ. Spectrum of gastroparesis in children. J Pediatr Gastroenterol Nutr 2012;**55**:166-172.)*

**The numbers need to be interpreted by taking into account that there is overlap between the various categories of gastroparesis*

Diagnostic investigations

When gastroparesis is considered as a potential diagnosis an upper gastrointestinal contrast study or esophagogastroduodenoscopy are initially required in order to rule out mechanical obstruction. Subsequently a GE scintigraphy of a radiolabeled solid meal is performed as it remains the gold standard for the diagnosis of gastroparesis [1].

GE scintigraphy

During this test a radiolabeled meal is ingested and the percentage of the radioactivity, which correlates with the amount of the meal retained in the stomach, is calculated at various times. Scintigraphy is a physiological, cost-effective, non-invasive and quantitative method of evaluating GE time [53]. A consensus regarding the methodology of this test has been established for adults by the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine but not for the pediatric population. According to this protocol the patient ingests a technetium-99m sulphur colloid radiolabeled meal consisting of two large eggs, two slices of bread, jam and water. GE time is considered delayed if there is retention >90% at 1 h after meal ingestion, >60% at 2 h, and >10% at 4 h [2,3,54]. Of note, despite the fact that nuclear scintigraphy with solids is the standard criterion of determining GE time a study has been published indicating that GE of liquids can be abnormal in patients with normal GE of solids, suggesting therefore to perform the study for both the liquid and solid phase [55].

In children, the investigation is performed in accordance to various institution protocols. This limits the clinical utility of the test especially in terms of interpreting results from laboratories which follow a different methodology [56-59]. Apparently when the protocols are not the same between institutions or differ from published data then each laboratory needs to determine their own control values for their methodology.

Breath test

This is also a non-invasive method that indirectly measures GE time. The results from breath testing are similar to the ones measured by the GE scintigraphy [60,61]. The test is performed with a stable nonradioactive ^{13}C-isotope which is bound to a digestible substance and then mixed into a solid or liquid meal. The meal is ingested and then the isotope is absorbed by the small intestine and subsequently metabolized into ^{13}C-CO_2 which is exhaled and collected. The ratio $^{13}CO_2/^{12}CO_2$ in exhalation is used to evaluate the GE time [62,63]. This test has the advantage of not exposing the patient to radiation but it can be inaccurate in patients with specific conditions such as celiac disease and liver cirrhosis (impaired metabolism of the isotope to CO_2) [64].

Other methods

Other methods that assess the gastric motor activity and measure GE time include transabdominal ultrasonography, Magnetic Resonance Imaging (MRI) and antroduodenal manometry.

Both ultrasound and MRI are non-invasive techniques that measure not only GE time but also other parameters which affect the latter such as accommodation, antral contractility, and distribution of the meal. Few data are available and further validation of both techniques is required [65,66].

Antroduodenal manometry is an invasive technique that uses a water-perfused or solid-state catheter (placed intranasally or via a gastrostomy site) to measure intraluminal pressures in the stomach and small intestine. In gastroparetic children there is a disruption of the normal relationship between antral, pyloric and duodenal waves [67,68]. Antroduodenal manometry is particularly useful in differentiating between gastroparesis due to myopathy (presence of coordinated low amplitude contractions) or neuropathy (uncoordinated contractions with normal amplitude) [69,70].

Management

General approach

The pillars of treatment in gastroparesis include the diagnosis and management of an underlying disease, correction of fluid and electrolyte imbalances, alleviation of symptoms, and maintenance of optimal nutritional status. Patients with mild disease can be managed as outpatients whereas those with severe and life threatening manifestations (e.g. pronounced dehydration, electrolyte imbalances, intractable vomiting) need hospitalization and close monitoring.

Dietary and lifestyle modifications

Management of gastroparesis includes dietary and lifestyle recommendations such as small-volume and frequent meals with low content in fat and non-digestible fibers. Patients are advised to avoid carbonated beverages and lying down for 1 to 2 h following meals. A thorough dietary history must be obtained in order to enlighten the clinician about the caloric intake of the patient and the tolerance of solids and liquids. Referral to a dietician is always warranted.

In cases of severe and persistent symptoms the majority of calories are provided in a liquid form given that liquid emptying is often preserved. Enteral nutrition via nasojejunal tube or jejunostomy may be required for patients with severely impaired nutritional status. Total parenteral nutrition is reserved for the most complex patient who fails enteral feeds [71-73].

Pharmacologic treatment

There are many agents available for the management of gastroparesis.

a. Prokinetics

This category includes drugs such as metoclopramide, domperidone, and erythromycin. They promote GE by stimulating antral motility, correcting gastric dysrhythmias and enhancing antroduodenal coordination [74]. In one large pediatric cohort, promotility drugs were found to be effective in 55% of patients. A tendency towards a positive response to prokinetic drugs was also demonstrated in children in comparison to adolescents and infants and in patients with postviral gastroparesis. In the same study 26% of patients responded to metoclopramide with 24% reporting adverse effects (AEs), 74% responded to domperidone with 6% AEs and 51% responded to erythromycin with 10% AEs [5].

Metoclopramide and domperidone are dopamine antagonists. Metoclopramide has a central antiemetic and a peripheral prokinetic effect. Domperidone acts only as a peripheral dopamine antagonist because it does not cross the brain-blood barrier [75]. Although they are considered safe and effective drugs in the treatment of gastroparesis there are reports about potential side-effects such as galactorrhea for both drugs due to hyperprolactinemia, extrapyramidal dyskinetic reactions for metoclopramide, and cardiac arrhythmias or even sudden death for domperidone [74,76].

Erythromycin when administered in subtherapeutic doses (3-5 mg/kg/dose every 6 h) acts as a motilin agonist and has a significant prokinetic effect. Its safety and efficacy in improving feeding intolerance have been demonstrated in multiple studies with premature infants and children [30]. However, there are reports showing that early exposure to erythromycin in the neonatal period significantly increases the risk of pyloric stenosis in infants [10,77]. Interestingly prolongation of QT, a well-known side effect of erythromycin [78], was not reported as an AE in a recent large pediatric retrospective study on gastroparesis [5].

Cisapride and tegaserode both 5-HT_4 receptor agonists have been licensed in the past but then withdrawn from the market because of risk of arrhythmia-associated death [79] and cardiovascular ischemic events [80] respectively.

b. Antiemetics

This group includes phenothiazines (e.g. prochlorperazine), 5-HT_3 antagonists (e.g. ondasetron), dopamine antagonists (e.g. metoclopramide), histamine H_1 antagonists (e.g. diphenydramine), and benzodiazepines (e.g. lorazepam). They are prescribed in conjunction with prokinetic drugs in order to symptomatically alleviate nausea [81].

c. Proton pump inhibitors (PPIs)

Lansoprazole, omeprazole, esomeprazole and pantoprazole

are frequently used to address gastroesophageal reflux which is a common complication of gastroparesis in children [5].

d. Botulinum toxin

Botulinum toxin type A is endoscopically injected into the pylorus [82]. It blocks the release of acetylocholine from cholinergic nerve endings and as a result alleviates symptoms by promoting GE [83]. In pediatrics although botulinum toxin is occasionally used in children with refractory gastroparesis, sufficient data to definitively evaluate its use for this purpose are not yet available [84].

Gastric stimulation

This intervention is based on the laparoscopic implantation of two electrodes - connected to a pacemaker - into the seromuscular layer of the stomach. Two studies in children with gastroparesis demonstrated that gastric stimulation alleviated their symptoms and improved quality of life [85,86]. Despite the promising results the long-term efficacy and safety of this modality need to be established.

Surgical interventions

These include gastrostomy tube insertion, which may be required in order to facilitate gastric ventilation and symptomatic relief, and the placement of a jejunostomy tube. These therapeutic options are reserved for refractory cases that fail medical treatment [5,10,87]. Other sophisticated surgical techniques have also been proposed for complicated cases of gastroparesis [88]. Studies in both children and adults show favorable outcomes in terms of promotion of nutritional status, relief of symptoms and reduction of hospitalization frequency [5,89].

Alternative medical therapies

Apart from the therapeutic modalities that have been previously described, non-conventional medical treatments are also used to alleviate symptoms in patients with gastroparesis and FD [1]. Such interventions include the use of nutraceuticals (ginger, iberogast, rikkunshito), hypnosis and biofeedback as well as acupuncture [90-93]. The majority of published studies were conducted in adult populations and as a result their applicability in pediatrics needs to be further explored.

Figure 1 presents a summarized stepwise approach in the diagnosis and treatment of gastroparesis as proposed by the American Gastroenterological Association, based on the expertise of physicians who specialize in this field [1].

Outcome

Two retrospective studies in large pediatric cohorts provide useful data on the outcome of gastroparesis in children. The first study demonstrated resolution of symptoms in 52% of the patients after a median follow-up period of 18 months [5] and found that factors such as younger age, postviral etiology, shorter duration of symptoms, response to prokinetics and presence of nausea correlated with a favorable outcome. The second study revealed significant symptom improvement in 60% of the patients after a mean follow-up period of 24 months [10], and showed that favorable outcome was not related to gender, age, or degree of GE delay [10]. These data, although conflicting, further enrich our understanding of gastroparesis in children. Additionally, these studies differ from those performed in adults which show a high morbidity and mortality for this disease.

Future prospects

During the past few years our understanding of the etiology, pathophysiology, and management of gastroparesis has significantly improved. Current research on novel therapeutic agents: hemin [94], ghrelin agonist TZP-101 [95], muscarinic receptor antagonist acotiamide (Z-338) [96] and the motilin receptor agonist mitemcinal [97] just to name a few, along with recent advances in reprogramming of somatic cells and stem cell transplantation [98,99], create a whole new era of future treatment possibilities for gastroparesis.

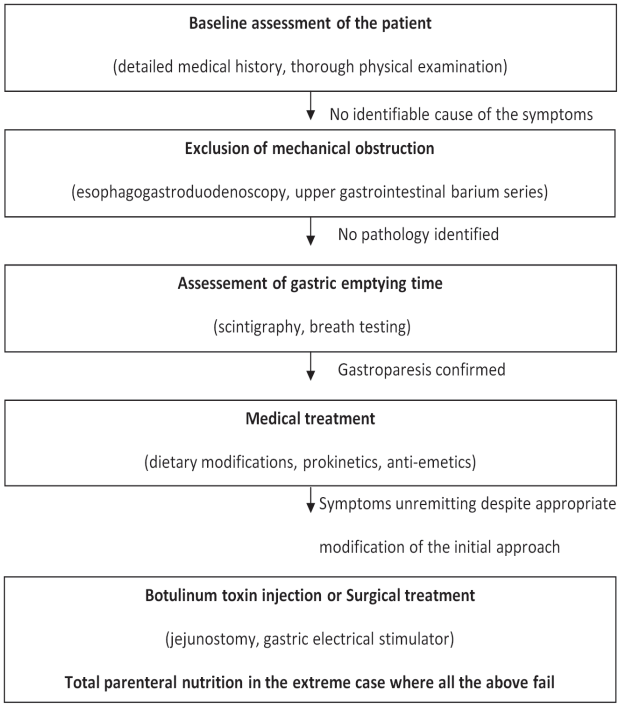

Figure 1 Stepwise approach in the diagnosis and treatment of gastroparesis

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