Pediatric functional dyspepsia: A comprehensive review

Dispepsia funcional en niños

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ABSTRACT

Functional dyspepsia (FD) is a common but heterogeneous upper gastrointestinal disorder that causes recurrent and/or chronic epigastric symptoms, with an estimated prevalence in children between 3% and 27%. Etiologies include genetic predisposition and events that cause disruption of the brain-gut-microbiota axis, such as environmental and psychosocial stressors, disturbance of the gut microbiota, and early life events that lead to hyperalgesia such as cow's milk protein. FD results in impaired quality of life and increased health-care costs, with an estimated \$5 billion in annual costs. Unfortunately, treatment options are limited given the complexity of its pathophysiology and the fact that most therapies are studied in adults and not children, thus making FD difficult to manage in pediatrics.

Keywords: Functional dyspepsia. Pediatric abdominal pain. Motility. Microbiome. Pharmacology.

RESUMEN

La dispepsia funcional (DF) es un desorden común del tracto gastrointestinal superior que causa síntomas epigástricos recurrentes y/o crónicos, con una prevalencia estimada entre 3% al 27%. Las etiologías incluyen predisposición genética y eventos que conllevan a la disrupción del eje cerebro-intestino-microbiota, tales como estresores del ambiente y psicosociales, disrupción de la microbiota intestinal y eventos en la vida temprana que llevan a la hiperalgesia, como la alergia a la proteína de la leche de vaca. La DF puede conducir a una calidad de vida deteriorada y con elevados costos de cuidado de salud, los cuales se estiman en unos \$5 billones anuales a nivel global. Desafortunadamente, los tratamientos disponibles son limitados dada la complejidad de la condición y que la mayoría de estos han sido estudiados en adultos y no en niños, lo cual dificulta el tratamiento pediátrico.

Palabras clave: Dispepsia funcional. Dolor abdominal en niños. Motilidad. Microbiota. Farmacología.

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NeuroGastroLatam Rev. 2021;5:144-153

Received in original form: 07-07-2021

Accepted in final form: 28-10-2021

DOI: 10.24875/NGL.21000013

INTRODUCTION

Pediatric functional abdominal pain disorders are common, and they include functional dyspepsia (FD), irritable bowel syndrome, abdominal migraine, and functional abdominal pain not otherwise specified¹. FD is a common but heterogeneous upper gastrointestinal (GI) disorder that causes recurrent and/or chronic epigastric symptoms, with an estimated prevalence in children between 3% and 27%^{2,3}. FD prevalence has been increasing in recent years, and it is the second most common functional abdominal pain disorder after irritable bowel syndrome⁴. The pathogenesis for functional abdominal pain disorders is not clearly understood but numerous mechanisms have been implicated, including visceral hypersensitivity, delayed gastric emptying, psychosocial factors, dysfunction of the central nervous system, lifestyle factors, duodenal eosinophilia, and inappropriate gastric accommodation^{3,5-7}. Impaired gastric accommodation is the most common documented abnormality in adult patients with FD, estimated at around 40%^{8,9}.

FD can be further subdivided into epigastric pain syndrome and post-prandial distress syndrome; however, these two syndromes can overlap in clinical practice¹⁰. Postprandial distress syndrome is characterized by symptoms that are triggered by a meal, including post-prandial fullness and early satiety³. Impaired gastric accommodation is thought to play a role in the postprandial distress syndrome group³.

There are currently no biochemical markers or structural abnormalities used to diagnose FD. A study by Singh et al. found the majority of

children with a clinical diagnosis of FD lacked chronic or acute inflammation in the GI mucosa¹¹. However, 60% of children with FD have increased eosinophils in the antrum and duodenum (cutoffs of 10/high power field and 20/high power field were used, respectively)¹¹. The diagnosis of FD is clinical and based on the Rome criteria, which provides symptom-based guidelines by which children are diagnosed with functional GI disorders (FGIDs)¹². The most recent criteria, Rome IV, was issued in 2016¹³. Table 1 summarizes the Rome IV criteria used to diagnose FD.

The role of a diagnostic work-up, including labs and esophagogastroduodenoscopy (EGD) in pediatric FD, remains unclear. These patients tend to undergo extensive workup, with mostly minimal to no yield. The average cost per patient with functional abdominal pain disorder is around \$6,104 (range \$1,052-\$20,994)¹⁴. A study evaluating the charts of children > 4 years of age diagnosed with abdominal pain showed that complete blood cell count was the most commonly done investigation (92%), followed by a comprehensive metabolic panel (83%), with electrolytes abnormal in only one patient (sodium: 132 mEq/L, n = 122)¹⁴. In this same study, elevated inflammatory markers and celiac antibodies led to changes in management in only five cases¹⁴. Unfortunately, most studies assessing the use of EGD in children with abdominal pain have had multiple limitations, including a small sample size, bias, and lack of standardization¹⁵.

The Rome IV pediatric committee does not believe there is compelling evidence to require an EGD in order to make a diagnosis of FD, but does understand that physician

TABLE 1. Rome IV diagnostic criteria for FD

Must include 1 or more of the following bothersome symptoms at least 4 days per month

1. Post-prandial fullness
2. Early satiation
3. Epigastric pain or burning not associated with defecation
4. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

Criteria fulfilled for at least 2 months before diagnosis. Within functional dyspepsia, the following subtypes are now adopted

1. Postprandial distress syndrome includes bothersome postprandial fullness or early satiation that prevents finishing a regular meal. Supportive features include upper abdominal bloating, postprandial nausea, or excessive belching
2. Epigastric pain syndrome, which includes all of the following: bothersome (severe enough to interfere with normal activities) pain or burning localized to the epigastrium. The pain is not generalized or localized to other abdominal or chest regions and is not relieved by defecation or passage of flatus. Supportive criteria can include (a) burning quality of the pain but without a retrosternal component and (b) the pain commonly induced or relieved by ingestion of a meal but may occur while fasting

Criteria fulfilled for at least 2 months before diagnosis.

TABLE 2. Potential alarm features in children with chronic abdominal pain

Family history of inflammatory bowel disease, celiac disease, or peptic ulcer disease
Persistent right upper or right lower quadrant pain
Dysphagia
Odynophagia
Persistent vomiting
Gastrointestinal bleeding loss
Nocturnal diarrhea
Arthritis
Perirectal disease
Involuntary weight loss
Deceleration of linear growth
Delayed puberty
Unexplained fever

practice patterns and social considerations may affect the decision to do one¹². In addition, there are “red flags” that suggest further diagnostic work up should be done (Table 2)¹².

PATHOPHYSIOLOGY

Visceral hypersensitivity

Visceral hypersensitivity is based on the strong association between the enteric nervous system and the central nervous system and their common embryonic origin¹⁶. Multiple factors predispose individuals to visceral hypersensitivity, including genetic, environmental, psychosocial (early stressors in life), and diet. These factors can alter the brain-gut axis communication by altering descending inhibitory control, impairing stress response, and/or sensitizing primary sensory neurons

and central spinal neurons¹⁶. This leads to abnormal secretion of excitatory neurotransmitters such as serotonin, which can result in changes in the central nervous system and trigger symptoms such as headache, abdominal pain, and discomfort^{16,17}.

Early life events are known to be associated with the development of visceral hyperalgesia (cow's milk protein hypersensitivity, pyloric stenosis, umbilical hernia repair, and Henoch-Schönlein purpura)^{17,18}. Rat models have shown that exposure to nociceptive somatic stimuli in the early neonatal period predisposes to visceral hyperalgesia, suggesting that disruption of the nervous system during its early development can alter the brain-gut axis, resulting in FAPDs^{17,19}.

Carbone et al. used high resolution manometry to measure intragastric pressure in children and found that the intragastric pressure drop during

meal ingestion in healthy and dyspeptic children was similar²⁰. The authors suggest that increased sensitivity may be the reason why children with FD have decreased nutrient tolerance²⁰.

Visceral and somatic endogenous pain modulations are central in fine-tuning and integrating pain perception²¹. They are closely integrated with affective, autonomic, cognitive, homeostatic, immune, and motor responses²¹. FGIDs are associated with several factors that can lead to changes in these modulation pathways, including stress, anxiety, and chronic inflammation²².

ALTERED GI MOTILITY

Patients with FGIDs may present abnormal GI motility, leading to diarrhea, constipation, nausea, bloating, and distention¹⁷. As with visceral hypersensitivity, it is thought that early life events and psychological factors (e.g., abuse and hospitalizations) can lead to alterations in the gut microbiota that result in altered GI motility, including abnormal gastric myoelectrical activity, poor antral motility and gastric emptying and abnormal gastric accommodation¹⁷. In fact, multiple studies by Devanarayana et al. demonstrated that gastric emptying rate and antral motility parameters were significantly impaired in patients with Rome III criteria of functional abdominal pain, FD, and irritable bowel syndrome²³⁻²⁵. In addition, gastric emptying was found to negatively correlate with the severity of symptoms^{23,24}. In another study led by Hoffman and Tack, children with FD were found to have slower gastric emptying than obese children (89.7 ± 54.8 min vs. 72.5 ± 26.0 min, $p = 0.05$) using the octanoic acid breath test²⁶.

These findings argue in favor of a role for GI motility disturbances in patients with FAPDs.

Gastric accommodation to a meal consists of relaxation of the proximal stomach without a concomitant increase in intragastric pressure^{27,28}. Inappropriate gastric accommodation is the most common documented abnormality in adult patients with FD, estimated at around 40%^{8,9}. Hoffman et al. assessed fundic accommodation in children with FD using the gastric barostat and found that 69% had inappropriate fundic accommodation²⁹. Since the barostat test is invasive, few studies evaluating its use in children are available²⁹. In children with FD, ultrasound imaging of the antrum has shown enlargement of the antral area, likely related to either inappropriate gastric accommodation or low antral tone³⁰. Olafsdottir et al. showed that in children with recurrent abdominal pain, ultrasound revealed a smaller sagittal area and a higher emptying fraction of the proximal stomach 10 min after meal ingestion when compared to controls, likely due to inappropriate gastric accommodation³¹.

Children with FGIDs might also have abnormal gastric myoelectrical activity since muscular activity of the stomach is preceded by gastric electrical activity¹⁷. A study using electrogastrography found increased gastric electrical abnormalities in children with recurrent unexplained upper GI symptoms³². Further studies assessing these relationships are warranted.

GUT MICROBIOTA

The gut microbiome is recognized as a key player in the pathogenesis of functional

abdominal pain disorders, including FD. The microbiome is composed of approximately 10^{13} - 10^{14} microorganisms with 500 to 1000 different species³³. Under non-stressful, normal circumstances, intestinal bacteria maintain a homeostatic relationship with the host mucosa³⁴. However, alterations to this balance (“dysbiosis”) can lead to enhanced intestinal permeability, mucosal immune activation, altered gut motility, and visceral hypersensitivity³⁴.

PSYCHOLOGICAL FACTORS

Children with functional abdominal pain disorders report a greater number of stressful experiences in the months before pain onset³⁵. Common stress examples in children include failing an exam, separating from a best friend, loss of a parent's job, and/or moving to a new place¹⁷. A recent study found that psychological stressors were the most common etiology for FD in children³⁶. Abuse also predisposes to functional abdominal pain disorders, with one study showing that abdominal pain-predominant FGIDs were significantly higher in children who were abused sexually (34%), emotionally (25%), and physically (20%) when compared to those who were not abused³⁷. In addition, children with functional abdominal pain disorders are more likely to receive a diagnosis of a psychiatric disorder, including depression and anxiety³⁸. Adult studies have shown that stress induces chronic overactivity or underactivity of adaptive systems, including the hypothalamic-pituitary-adrenal axis, autonomic nervous system, metabolic, and immune systems, which affects bodily function and behavior³⁹. Thus, it is probable that stressful, adverse events in early life can result in long-lasting alterations in the brain-gut

axis, leading to the development of functional abdominal pain disorders.

Children with chronic abdominal pain have also been shown to be less confident of their ability to change or adapt to stress⁴⁰. In addition, mothers of children who suffer from functional abdominal pain were significantly more likely to have a lifetime history of IBS (odds ratio [OR], 3.9; 95% confidence interval [CI], 1.5-10.3), anxiety (OR, 4.8; 95% CI, 2.2-10.6), depressive (OR, 4.9; 95% CI, 2.2-11.0), and somatoform (OR, 16.1; 95% CI, 2.0-129.8) disorders when compared to mothers of controls⁴¹. Thus, how a child and family deal with stressors may be one of the key factors in chronic abdominal pain.

ALTERED INTESTINAL PERMEABILITY

The intestinal barrier includes surface mucus, epithelial layer, and immune defense⁴². Epithelial permeability can result from increased paracellular transport, apoptosis, or transcellular permeability⁴². Growing evidence indicates that increased intestinal permeability plays a role in functional abdominal pain disorders. Several entities are known to cause altered gut permeability, including infection, genetic predisposition, and stress⁴³.

HELICOBACTER PYLORI

H. pylori bacteria have been associated with many diseases such as FD, gastric and/or duodenal ulcer, gastric cancer, and gastric mucosa-associated lymphoid tissue lymphoma⁴⁴. However, most patients with *H. pylori* are asymptomatic. A meta-analysis evaluating symptom relief from *H. pylori* eradication in

patients with FD found a small effect size; and found no improvement in the quality of life for patients with FD⁴⁴. Eradication therapy was also associated with more side effects (vs. control). Thus, the decision to eradicate *H. pylori* should be individualized and preferred in patients with risk factors (i.e., peptic ulcer disease, gastric cancer, and Asian origin). A recent study in pediatrics found *H. pylori* to be present in 11% of the subjects with FD (n = 55)³⁶.

GENETICS

Growing evidence has shown FD to be influenced by hereditary factors. Several gene polymorphisms have been studied in FD, including serotonin transporter promoter, interleukin-17F, migration inhibitory factor, cholecystocynine-1 intron 1, cytochrome P-450 2C19, catechol-O-methyltransferase, transient receptor potential vanilloid 1 receptor, p22PHOX, Toll like receptor 2, SCN10A, CD14, and adrenoceptors⁴⁵. However, results are contradictory, mostly because of inconsistencies in the studies⁴⁵. Further, assessments are needed, as there could be genetic contributions to FD.

EPIDEMIOLOGY

Prevalence

Based on the new Rome IV criteria, 25% of infants and toddlers (0-3 years of age) and 25% of children and adolescents (4-18 years of age) met the criteria for one FGID⁴⁶. In this same study, children were more likely to qualify for FGIDs if their parents also qualified for FGIDs⁴⁶. The prevalence of FD

– post prandial distress syndrome is approximately 7% and of FD – epigastric pain syndrome it is 0.4%⁴⁶.

Sex and age

A meta-analysis reviewing functional abdominal pain in children aged 4-18 years of age found that girls had a significant higher proportion of functional abdominal pain disorders when compared to boys (15.9% vs. 11.5%, pooled OR 1.5, 95% CI 1.3–1.7, $p < 0.01$)⁴. This same study found no significant difference for their prevalence in children < 12 years of age compared to children ≥ 12 years old (12.4% vs. 13.8%, pooled OR 0.9, 95% CI 0.5–1.4, $p = 0.62$)⁴.

Another cross-sectional study in children found that FD-epigastric pain syndrome was more prevalent in males than females subjects (0.9% males vs. 0% females, $p = 0.04$)⁴⁶. In this study, no other differences were found by sex, race, or ethnicity with regard to FAPDs⁴⁶.

QUALITY OF LIFE AND COST

Pediatric patients with FD have more dyspeptic symptoms, greater functional disability, and poorer health related quality of life when they reach adolescence (vs. healthy controls)⁴⁷. Both depression and anxiety are common in this population, with anxiety being more chronic⁴⁷. FD-post-prandial distress syndrome is associated with higher anxiety and depression, whereas FD-epigastric pain is associated with lower depression rates by patient reports⁴⁸.

Sleep disturbances are highly prevalent in subjects with FGIDs compared to the rest of the population⁴⁹. Sleep disturbances in patients with FD are associated with worse symptom severity and higher levels of anxiety⁵⁰. A recent study in adults found that subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction were worse in patients with FD when compared with controls⁵¹. The same study found that subjects with longer-term FD (> 6 months) had worse sleep disturbances than those with shorter-term FD, suggesting that sleep quality may deteriorate with the development of FD⁵¹.

A recent retrospective study looking to estimate the annual evaluation cost for children with FD found the cost for all patients to be \$724.874 ± \$180.075. When divided into improved symptoms versus partial/no improvement in symptoms, \$544.799 ± \$87.995 and \$904.949 ± 79.083 were the costs, respectively⁵². An extrapolated annual cost of evaluation in children with FD would be close to \$5.8 billion⁵². As would be expected, the average number of clinic visits, use of imaging studies, and endoscopic procedures were significantly higher in patients with partial/no improvement in symptoms⁵². Thus, children with FD represent a significant financial burden.

TREATMENT

Treatments for FD should be aimed to one or more of the main mechanisms: Gastric emptying, gastric accommodation, and visceral

pain sensation⁵³. Unfortunately, currently there are no prognostic factors described in the literature that help predict response to treatment in these patients⁵². Patient education is essential and all patients must receive psychosocial support¹. Dietary changes can be implemented, including smaller meals and avoidance of fatty foods and carbonated beverages.

FD-post-prandial distress syndrome

Cyproheptadine is an antihistamine commonly used as first line in patients suspected of having FD-postprandial distress syndrome¹. Not many randomized trials exist in the pediatric population assessing its use for FAPDs despite its popularity. A double-blind randomized placebo-controlled trial led by Sadeghian et al. resulted in improvement in the intensity and frequency in abdominal pain among children treated with cyproheptadine when compared to placebo (n = 29)⁵⁴. Unfortunately, this study is limited by its small size and non-validated measurement tools. Further studies assessing the use of cyproheptadine are warranted.

Peppermint oil is known to relax the lower esophageal sphincter and relieve symptoms of dyspepsia and can be trialed in this population⁵⁵. If both of these options fail, prokinetics can be tried. A placebo-controlled trial using domperidone by Karunanayake et al. was able to show overall improvement (74% domperidone vs. 50% placebo; p = 0.013), decreased severity of abdominal pain (54% vs. 25%; p = 0.008), and overall improvement at the 6 months follow-up (88% vs. 66%; p = 0.009)⁵⁶.

Buspirone is a non-selective serotonin 5-HT_{1A} receptor agonist that inhibits the tone of the proximal stomach and delays gastric emptying rate in a dose dependent manner⁵⁷. Buspirone has been shown to be superior to placebo in alleviating early satiation, post-prandial fullness, and upper abdominal bloating in adults with FD⁵⁸. It has been trialed in children and adolescents with anxiety, proving to be generally safe and well tolerated at doses up to 30 mg BID⁵⁹. No studies have been done to assess its use for inappropriate gastric accommodation in children.

Antiemetics such as ondansetron, diphenhydramine, and prochlorperazine can be helpful in reducing nausea but unfortunately can be sedating¹. When all these treatments fail, neuromodulation and/or psychological interventions can be trialed. Modulating central pain pathways and consequently visceral hypersensitivity by the use of percutaneous electrical field stimulation (Neuro-Stim, Innovative Health Solutions, IN, USA) has been studied in randomized clinical trials. A randomized, sham-controlled trial in adolescents aged 11-18 years who met Rome III criteria for abdominal pain-related FGIDs found that Neuro-Stim had sustained efficacy for abdominal pain⁶⁰. Psychological interventions include cognitive behavioral therapy, hypnotherapy (including guided imagery), yoga, and written self-disclosures.

FD-Epigastric pain syndrome

Proton pump inhibitors (PPIs) are usually the first line therapy for this population¹. PPIs have shown to be effective and well tolerated

in randomized placebo-controlled trials in adults with FD^{61,62}. In children, only limited studies are available. Even though they have shown to be safe and well-tolerated short term in pediatric patients, PPIs used for long-term has shown to lead to biochemical, endoscopic and histological changes, and small bacterial overgrowth⁶². In children with FD, two clinical studies by Dehgani et al. (2011, n = 169) and See et al. (2001, n = 25) showed improvement in dyspeptic symptoms when using these medications (vs. placebo). However, these studies showed significant methodological flaws and heterogeneity, and thus results should be interpreted with caution⁶³. Of the PPIs, omeprazole seems to be the most effective⁶³.

Even though limited data shows improvement in symptoms of FD with PPIs, longitudinal studies are warranted. These medications should be prescribed with caution and physicians should perform regular assessment of the ongoing need for this medication.

If PPIs fail to resolve symptoms, subsequent therapies include cyproheptadine, herbal medications, or medications aimed on altering stomach sensitivity and accommodation, as stated above. Neuromodulation and psychological techniques are also indicated.

CONCLUSION

FD represents a difficult to manage entity in children. The extrapolation of adult data and lack of pediatric-specific data represents a limitation to treatment options. The medical, social, and economic impact of FD is rising,

affecting not only the child but the child's family. As Lu and Saps state, "Despite all we have learned during the past four decades, it is hard to argue that we are truly making progress"⁶⁴. Given what we know now as plausible early causes of functional abdominal pain disorders (disruption of the gut microbiota, early life events that lead to hyperalgesia such as cow's milk protein), maybe we should shift our focus towards prevention and try to better understand the epidemiology and pathophysiology of functional abdominal pain disorders.

FUNDING

The author received funding from the American Neurogastroenterology and Motility Society.

CONFLICTS OF INTEREST

None.

ETHICAL DISCLOSURES

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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