FUNCTIONAL ABDOMINAL PAIN - PATHOGENESIS
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RESUMEN
Los trastornos gastrointestinales funcionales (TGF), frecuentemente afectan a los niños y están asociados con morbilidad a corto y largo término. Estos TGF asociados con dolor incluyen el Síndrome de intestino irritable (SII), la Dispepsia funcional (DF), el Dolor abdominal funcional (DAF), el Síndrome de dolor abdominal funcional (SDAF), y la Migraña abdominal. Aunque la patogénesis de dolor asociado a los TGF es poco clara; la mayoría de los investigadores están de acuerdo, en una etiología multifactorial y la presencia de una interacción alterada intestino-cerebro. Una continua inter-relación de factores ambientales y genéticos, parece que hacen parte del desarrollo del sistema nervioso central y entérico. El modelo biosicosocial es el arma operacional común para los niños con TGF, y reconoce la interacción entre las influencias sociales y ambientales y los procesos psicológicos y fisiológicos. El modelo biosicosocial propone que los cambios específicos de susceptibilidad genética, las experiencias tempranas de la vida, los cambios socioculturales, y los mecanismos de imitación, podrían explicar la variabilidad en la presentación clínica y los resultados entre los individuos.

Palabras clave: Trastornos gastrointestinales funcionales, Síndrome de intestino irritable, Dispepsia funcional, Dolor abdominal funcional, Síndrome de dolor abdominal funcional, Migraña abdominal, Niños

SUMMARY
Functional gastrointestinal disorders (FGIDs) commonly affect children and are associated with short- and long-term morbidity. FGIDs associated with pain include irritable bowel syndrome (IBS), functional dyspepsia (FD), childhood functional abdominal pain (FAP), childhood FAP syndrome, and abdominal migraine. Although the pathogenesis of pain-related FGIDs remains incompletely understood, most investigators agree on a multifactorial etiology and the presence of an altered brain–gut interaction. A continuous interplay of genetic and environmental factors appears to shape the development of the central and enteric nervous systems. The biopsychosocial model is the current operational framework for children with FGIDs, as it recognizes the interaction between social and environmental influences and psychological and physiologic processes. The biopsychosocial model proposes that specific permutations of genetic susceptibility, early life experiences, sociocultural issues, and coping mechanisms could explain the variability in clinical presentation and outcome among individuals.

Key words: Functional gastrointestinal disorders, Irritable bowel syndrome, Functional dyspepsia, Functional abdominal pain, Functional abdominal pain syndrome, Abdominal migraine, Children

INTRODUCTION
Functional gastrointestinal disorders (FGIDs) are a variable combination of chronic or recurrent symptoms not explained by structural or biochemical abnormalities. They can involve any part of the gastrointestinal tract, including the esophagus, stomach, and bowel. A common feature of these conditions is the lack of biologic markers and the
inability to find characteristic pathologic findings on conventional endoscopy. Abdominal pain associated FGIDs includes functional dyspepsia (FD), irritable bowel syndrome (IBS), childhood functional abdominal pain (FAP), childhood FAP syndrome, and abdominal migraine.

In 1991, a group of experts designed diagnostic criteria—the Rome criteria—to provide clinicians and researchers with a method for standardizing FGIDs based on clinical symptoms. The third edition of the Rome criteria, published in 2006\(^1\), divided functional disorders of children and adolescents into disorders with vomiting, defecation, and pain.

Before the Rome criteria were published, there was great confusion regarding the terminology of this group of disorders. In children, *recurrent abdominal pain* (RAP) was used as a wastebasket term for all cases of chronic or intermittent pain. Although new specific nomenclature intended to include only functional conditions has been substituted for RAP, a few researchers continue to use the old term. This review uses the term RAP as equivalent to FAP.

**IMPORTANCE**

Childhood FAP may be self-limited and brief or long lasting and taxing. This condition’s perceived benign nature frequently leads to underestimation of its impact on life function. Long-term follow-up studies reported persistence of FAP into adulthood in up to one half of affected children\(^7,11\). Childhood FAP also has been associated with long-term psychological comorbidity, including depression, anxiety, social phobia, and somatic complaints\(^12\). Children with FAP reportedly visit at least three different health care providers for evaluation of unexplained abdominal pain\(^13\).

Patients with IBS have substantially poorer quality of life than those suffering from asthma or migraines\(^10\). Children with FAP miss significantly more school than healthy children\(^10,13\). FAP negatively affects the family budget directly and indirectly when one includes the cost of missed working days, laboratory studies, medical visits, and drug therapies\(^11\). In adults, medical expenses associated with IBS are estimated to total up to $30 billion per year. These costs are comparable to those of asthma, stroke, hypertension, and arthritis\(^14\). Although no cost studies have been conducted in children in the United States, clinical practice indicates that medical expenses incurred by evaluation and treatment of chronic abdominal pain are enormous. A study conducted in Uruguay showed that the costs involved with a single pediatric abdominal pain consultation account for 4% of the total per capita annual health care spending\(^8\).

**EPIDEMIOLOGY**

Chronic abdominal pain is one of the most common pediatric complaints, accounting for 2% to 4% of all pediatric office visits\(^2\). Two prospective, school-based studies investigated the prevalence of abdominal pain in American children at the community level\(^3,4\). These studies demonstrated that 46% of school-aged children experienced abdominal pain each week and that 12% of all children complained of weekly abdominal pain for at least 8 consecutive weeks. A cross-sectional community study revealed symptoms consistent with IBS in 14% of high school students and 6% of middle school students\(^5\). The prevalence of FAP increases with age into adolescence\(^5-8\). Abdominal pain has an equal gender distribution in early childhood\(^6-8\), whereas female complaints predominate in late childhood and adulthood\(^6,10\).
genetic and environmental factors appears to shape the development of the central and enteric nervous systems. It has been proposed that the specific permutations of genetic susceptibility, early life experiences, sociocultural issues, and coping mechanisms could explain the variability in clinical presentation and outcome among individuals.

ALTERATION IN MOTILITY

Gastrointestinal motility results from the integration of various elements, including myoelectrical activity, contractility, compliance, tone, and intestinal transit. Multiple investigations in adults have evaluated whether alterations in motility were present in patients with FGIDs and whether those could explain their symptoms. The studies have demonstrated dysmotility and alterations in transit through the small bowel and colon. The number and amplitude of colonic contractions are greater in IBS patients than in controls. Balloon distention of the rectum is also associated with abnormal motor responses. Abnormal contractions frequently coincide with episodes of abdominal pain. Impaired intestinal gas propulsion and clearance are present in patients with IBS and bloating. However, the physiologic and clinical significance of alterations in motility in IBS patients remains unclear. Some of the motility patterns found in the colon and small intestine are qualitatively similar to the contractions seen in healthy controls. Moreover, dysmotility is not universally present in patients with similar symptoms, and the temporal correlation between motility changes and symptoms is inconsistent. These findings seem to indicate that other mechanisms likely participate in the genesis of the symptoms.

VISCERAL HYPERSENSITIVITY

Studies on visceral sensation, an important aspect of gut function, have shed new light on the pathophysiology of FGIDs. Currently, visceral hypersensitivity is the leading hypothesis explaining most of the clinical findings in IBS. Adult and pediatric studies have shown that IBS patients are more sensitive than healthy individuals to colonic balloon distention. IBS patients develop pain with volumes of retained gas that are well tolerated by healthy controls. Intolerance to gastric distention was also documented in FD. Adolescents with FD have delayed gastric emptying and report nausea and bloating after a meal. These findings seem to implicate a topographical relation between the symptoms and the organs involved.

Imaging techniques, such as positron emission tomography and functional MRI, provided new insight in the study of brain–gut interactions and the understanding of the physiologic and psychological characteristics of patients with FGIDs. In vivo studies showed differences in activation in the limbic and emotional motor systems in patients with FGIDs. The level and extent of activation of the affective and cognitive regions during rectal distention differ between IBS patients and controls. Studies found that dorsal anterior cingulated cortex activity during painful rectal distention was higher in IBS patients. These differences in brain activation may explain the upregulation of visceral input to the brain and its abnormal affective and cognitive response found in patients with IBS. Although other studies could not replicate these findings, there is general agreement that there are alterations in brain activation in patients with IBS mostly in areas related to response selection and emotional reaction.

EARLY LIFE EVENTS

Neglect, abuse, loss of a parent, and life-threatening situations in childhood have been linked to FGIDs in adulthood. Adults with IBS have a higher prevalence of conflicted maternal relationships, loss, and separation during childhood. Studies suggest the existence of an early period of susceptibility of the nervous system associated with enduring neural plasticity and alterations of pain perception. One theory suggests that early life events, including those involving the gastrointestinal tract, can contribute to
abnormal neural processing of sensory information in adulthood. Studies have shown that circumcision and routine procedures such as nurse handling and immobilization modify the behavioral response to pain. Minor colonic stimulation in the neonatal period in rats can produce long-term sensitization. Mechanical or chemical colonic irritation in neonatal rats leads to the development of visceral hypersensitivity in adulthood. Also in rats, maternal deprivation during the early postnatal period (a surrogate of stress) results in alterations in behavior and induces a stress response, visceral hyperalgesia, and increased colonic motility later in life. Neonatal separation in rats also leads to persistent disruption of colonic mucosal barrier function, resulting in increased penetration of antigens and microbes and immune stimulation. Reuptake of these antigens later in life could lead to inflammation and visceral hypersensitivity. A high density of mast cells in the intestinal mucosa and greater proximity of mast cells to nerve fibers were found in adult IBS patients. Maternal deprivation in rats promotes similar long-term changes in colonic mast cells and nerve terminal distribution.

A cohort study comparing the outcome of human neonates with and without gastric suction at birth showed that those who underwent gastric suction had increased prevalence of FGIDs later in life. The authors suggest that this maneuver may promote the development of long-term visceral hypersensitivity. A controlled study in rats found somatic and visceral hyperalgesia in adulthood in animals that were subject to repeated orogastric suctioning during the neonatal period. These results were not present in rats without orogastric suction. The authors prevented visceral hyperalgesia by preemptive administration of antalarmin, a corticotropin-releasing factor (CRF) receptor antagonist. This suggests that stress could be involved in the pathogenesis of these alterations in sensation.

**GENETICS**

Studies have shown a familial clustering of FGIDs. Multiple studies suggest the coexistence of a genetic predisposition and social influences in the development of FGIDs. Children complaining of RAP are significantly more likely to have a parent with gastrointestinal complaints. Monozygotic twins are twice as likely to develop IBS as dizygotic twins. Studies also show that having a parent with IBS is an independent and stronger predictor of IBS than having a twin with IBS. Although multiple genes have been investigated, the data are still preliminary and inconclusive. Studies have focused on two proteins that influence the function of serotonin and serotonergic receptors: serotonin transporter protein (SERT) and p11.

Both proteins have been linked to comorbid psychological conditions that are frequently present in patients with IBS. SERT is responsible for inactivating serotonin, which plays a role in pain modulation and communication between the enteric nervous system and the central nervous system. Mice that lack SERT exhibit increased colonic motility and water in stools. An alternating pattern of diarrhea and constipation similar to the one present in patients with IBS was also described. In humans, the level of SERT mRNA and SERT protein in the intestinal epithelial cells of IBS patients decreased significantly. However, these findings have not been replicated in a recent study.

Researchers have described a link between p11, a protein critical to 5-HT1B receptor functions, and IBS. The expression of p11 is increased in patients with IBS. 5-HT1B receptor agonists reduce perception of gastric distention in patients with FD and hypersensitivity. The protein p11 could modulate the response to stimulation of serotonergic receptors, including 5-HT1B receptors, and increased p11 may be involved in delayed colonic transit through activation of serotonergic receptors. The significance of these findings is not yet known.

**PSYCHOLOGICAL FACTORS**

Psychological and social factors influence the
perception of symptoms, clinical presentation, and outcomes in patients with FGIDs. Familial and peer response affect the illness experience, school absenteeism, and health care use. Children of adults with IBS have more gastrointestinal-related health care visits than children of parents without IBS. Levy et al. demonstrated that pain severity and maternal distress were independent predictors of consulting behavior among children with RAP. Positive reinforcement and modeling are two examples of social learning frequently reported in children with IBS. Whitehead et al. have proposed that parents who provide gifts or special privileges to children complaining of gastrointestinal symptoms reinforce those complaints. Parents avoiding unpleasant tasks or expecting special consideration when they are ill provide a model of illness behavior that their children emulate. Retrospective and prospective studies also have shown that children whose mothers reinforce illness behaviors describe more severe stomachaches and miss school more often than other children.

Children with RAP have higher levels of anxiety and depression than healthy children. Anxiety or depression is also more severe in children with longer duration of gastrointestinal symptoms. In addition, studies have shown that children with FAP have a poorer ability to cope with stressful situations than their peers. A recent prospective study in adults without IBS investigated the relation between the psychosocial markers and IBS development. The study showed that higher levels of illness behavior, somatic symptoms, sleep problems, anxiety, depression, psychological distress, and health anxiety were predictors of IBS onset. Although this study seems to indicate that psychological factors predict IBS onset in certain patients, most patients developing FGIDs cannot be characterized as having any prior psychological condition. On the contrary, most such psychological conditions arise after the onset of gastrointestinal symptoms and are part of the impact of FGIDs.

**STRESS**

Stress is defined as an acute physical, immune, or psychological threat to the homeostasis of an organism. Gut sensitivity appears to be augmented by stress and reduced by relaxation. Anger, fear, pain, and anxiety can all lead to delayed gastric emptying and enhanced colonic motor activity. Psychosocial stress seems to have an even greater physiologic response in patients with FGIDs. There is evidence that stress plays a prominent role in the pathophysiology and clinical presentation of IBS. Early life events and stress sensitize central stress circuits, leading to the development of FGIDs.

The enteric nervous system is linked bidirectionally to the brain by parasympathetic and sympathetic pathways forming the brain–gut axis. The activation of brain CRF pathways plays an important role in the visceral and behavioral responses to stress. CRF is released in the paraventricular nucleus and stimulates adrenocorticotropic hormone secretion from the pituitary gland. CRF ligands and receptors are widely expressed, including in the brain and the gastrointestinal tract. Two CRF receptor subtypes, R1 and R2, have been described. R1 mediates increased colonic motor activity, proinflammatory responses, and anxiety. R2 stimulation results in slowed gastric emptying, anti-inflammatory changes, and anxiolysis during stress in rats. These responses can be blocked by CRF antagonists and reproduced by CRF administered intraventricularly.

The existence of colonic sensitization and increased colonic motility in patients with IBS has been explained by the upregulation of CRF-containing neurons and CRF-R1 receptors. Stressful events and food activate the hypothalamic-pituitary-adrenal axis and stimulate colonic motor activity through the activation of the sacral parasympathetic nervous system and cholinergic enteric mechanisms. Ascending projections from the locus ceruleus to the forebrain are thought to be responsible for the visceral hyperalgesia observed in patients with IBS.
Enteric mast cells are innervated by projections from the central nervous system and can be activated by neurons releasing CRF and/or acetylcholine\textsuperscript{76,77}. Mast cell degranulation caused by stress initiates polymorphonuclear cell influx, increased secretion, permeability, and propulsive motility, leading to pain and diarrhea\textsuperscript{78}.

**ENVIRONMENTAL INFLUENCES**

Children report more abdominal pain in certain winter months than during the summer. Coincidentally, a multicenter study has shown a higher frequency of consultations for abdominal pain during the same months\textsuperscript{79}. That this seasonal pattern of higher consultation is not present throughout the school year may indicate that factors other than school stress are involved. Based on the multifactorial origin and proposed interrelation among different factors, the authors hypothesized that the seasonal pattern may result from the interaction of stress, infectious agents, and the inability to participate in outdoor activities at certain times of the year\textsuperscript{80}. Recreational activities may help children cope and handle psychological and physical stressors, and those may be more prevalent in certain months.

**GUT FLORA AND PATHOGENIC AGENTS**

Alterations in indigenous flora and pathogenic bacteria have been linked to the pathogenesis of FGIDs. Qualitative and quantitative changes in gut flora have been described in patients with IBS. Bacterial overgrowth was found in up to 78\% of patients with IBS\textsuperscript{81}. Changes in gut flora may explain the increase in prevalence of IBS that has been found after antibiotic use\textsuperscript{82}. Although there is a persistent debate regarding the diagnostic methods used in these studies and the inability to replicate the results by other groups, changes in gut flora likely are present in at least a subset of IBS patients. This evidence has led to a surge in the use of probiotics to treat patients with IBS. The complexity of the various diagnostic methods, rationale, and analysis of the data on the use of probiotics is beyond the scope of this article and has been well described by other authors\textsuperscript{83,84}.

Acute gastroenteritis has been linked to the new onset of FGIDs. Adult studies have shown evidence of postinfectious IBS in 10\% to 34\% of patients after an acute gastrointestinal infection\textsuperscript{85}. Persistent symptoms of IBS have been found in up to 50\% of adult patients following an acute bacterial infection 6 years after the infectious episode. An outbreak of acute gastroenteritis of viral origin in adults resulted in postinfectious IBS lasting for 3 months. In children, a multicenter study demonstrated the presence of postinfectious IBS after an episode of acute bacterial gastroenteritis\textsuperscript{86}. The pathogenesis of postinfectious IBS remains unclear. Changes in gut mucosal function and structure have been proposed as possible mechanisms. The presence of a low-grade inflammation and immune activation resulting in increased mucosal permeability and altered sensorimotor dysfunction are among the possible mechanisms involved in the pathogenesis of postinfectious IBS\textsuperscript{87}. Infiltration of enteroendocrine cells and an increased number of lymphocytes and macrophages at the level of the colon and rectum have been described in these patients.

**FOOD**

Perceived adverse reactions to food triggering gastrointestinal symptoms are reported by 25\% to 65\% of adult patients with IBS\textsuperscript{88,89}. Sixty-two percent of patients with IBS limit or exclude a particular food to avoid symptom onset\textsuperscript{90}. The relation between perceived food adverse reactions and FGIDs remains unclear. Food adverse reactions include food intolerance, food allergy, and food aversions. All of those could be present in patients with FGIDs. Food intolerances are mediated by nonimmunologic reactions such as toxins, pharmacologic agents, enzyme deficiencies, or idiosyncratic responses. Some of the food items commonly implicated in adverse
reactions in patients with IBS stimulate gut motility (eg, coffee, alcohol, chewing gum, soft drinks). Fructose and lactose intolerance is frequently reported but rarely demonstrated. A case-control study showed that although milk-related symptoms were present in 40% of IBS patients and 12% of controls ($P < 0.001$), proven lactose malabsorption was equally present in both groups. Fructose and lactose intolerance is frequently reported but rarely demonstrated. A case-control study showed that although milk-related symptoms were present in 40% of IBS patients and 12% of controls ($P < 0.001$), proven lactose malabsorption was equally present in both groups. Food allergies result from immunologic reactions to certain foods. There are provoking and intriguing data regarding a possible relation between food allergies and IBS symptoms. The mechanism linking food allergies to IBS remains unclear. It is hypothesized that mucosal immune activation caused by food antigens may contribute to the pathogenesis of FD and IBS. Studies have shown an increased number of mast cells in the ileocecal region of IBS patients. It has been proposed that sensitized mast cells could induce secretory and sensorimotor abnormalities of the gut, resulting in IBS symptoms. Elevated serum IgE and IgG4 antibodies have been demonstrated in patients with atopic conditions induced by food hypersensitivity. Although a similar mechanism has been proposed in IBS, studies on IgE-specific food antibodies and skin testing have been disappointing. The results failed to demonstrate a consistent relationship between food antibodies and symptoms in most patients with IBS. The possible role of IgG4 is also controversial. IgG4 receptors are located on basophils and mast cells and are distinct from IgE receptors. Although several studies suggest that IgG4 production may be part of a normal immunologic response to dietary antigens, other studies demonstrate elevated serum IgG4 levels in patients with a history of food allergy and IBS, suggesting a contributory role. Elimination of foods selected by specific serum IgG4 testing resulted in symptom improvement. Double-blind studies also showed recurrence of symptoms when the offending food was reintroduced and a better response in patients who were more compliant with the diet. However, the number and type of foods to which IBS patients have had their circulating antibodies measured vary among studies, and no consistent pattern of antibody profile has emerged. Thus, although food allergies represent an interesting field of research, there are no well-established and accepted guidelines on how to study and manage patients with possible adverse reactions to food.

**CONCLUSIONS**

FGIDs in children result from the complex interaction among motility and sensation, early life events, environment, and psychosocial factors. The biopsychosocial model proposes that symptoms may be triggered by insults that directly or indirectly affect the gastrointestinal system through the dysregulation of the brain–gut axis. Further research should be conducted to advance the understanding of the multiple factors involved in the pathogenesis of this group of conditions and to provide evidence for its therapy.

**ECOLOGY OF FUNCTIONAL GASTROINTESTINAL DISORDER**

Ecology is the science that studies the interactions of organisms with their environment and each other. Two important principles of ecology characterize environmental relations. First, all living organisms have a continual interrelation with other living and nonliving elements that comprise their environment. Second, each of these ecosystems and their components are connected and affect one another. Sixty years ago, the World Health Organization provided a new dimension to the concept of human health by including physical, psychological, and social components to its definition. In keeping with this holistic concept of health, the biopsychosocial model underscores the relation and equilibrium among biological, physiological, and psychological systems to determine susceptibility to functional gastrointestinal disorders and explain the clinical variability and different responses to treatment.
This model proposes that illness and disease result from biological, psychological, and social subsystems that interact at multiple levels. In this context, psychosocial factors have direct physiological and pathological consequences. This framework differs from the classical view of a single etiology for each condition. Equilibrium between organ systems and ecosystems results in health, whereas imbalance is experienced as illness.

Our interaction with the environment can be loosely characterized as an interdependent relation between 2 ecosystems. Food antigens and gut flora are examples of the complex internal ecosystem. Relevant examples of the external ecosystem are the surrounding social and physical environment.

Adverse reactions to food are frequently reported by patients with functional gastrointestinal disorders (FGIDs). There are intriguing but still preliminary data indicating a possible role of food hypersensitivity in the pathogenesis of irritable bowel syndrome (IBS). A trial of food elimination based on serum immunoglobulin G4 antibodies in patients with IBS has shown a significant decrease in symptoms, compared with patients receiving a sham diet. In line with these findings, another study showed improvement in rectal compliance in patients with IBS undergoing a food-specific immunoglobulin G4 antibody-guided exclusion diet.

The gut flora influences our body functions in multiple ways. The flora forms a barrier against pathogens, stimulates the host immune system, limits the adhesion of pathogenic bacteria to the epithelium, and controls the proliferation and differentiation of epithelial cells. Germ-free rats have different spatial and temporal characteristics of migrating motor complexes in the small intestine than do conventional animals. Anaerobic bacteria seem to be an important promoter of regular spike activity in the small intestine. Psychological stress results in quantitative alterations in bacteria. Stressed mice exhibit a decrease in the relative proportion of Lactobacilli and Escherichia coli, changes that could be related to small intestine dysfunction. Qualitative and quantitative changes in gut flora have been described in patients with IBS. A study of fecal samples has shown qualitative differences between healthy controls and IBS patients and between IBS patients with constipation or diarrhea predominant. The study showed that although patients with constipation-predominant IBS had higher concentrations of Veillonella spp., patients with diarrhea-predominant IBS had lower levels of Lactobacillus spp. Galatola et al found evidence of bacterial overgrowth in 56% diarrhea-predominant IBS and 28% of the constipation-predominant type. Pimentel et al have found bacterial overgrowth in 78% of patients with IBS. Changes in gut flora, resulting from the use of antibiotics, have also been proposed as a pathogenic mechanism of IBS. Studies have shown that patients who received antibiotics in the previous months were approximately 3 times more likely than patients who did not receive antibiotics to develop functional symptoms. Probiotics and antibiotics have also been used to treat a proposed dysfunctional relation between the indigenous flora and the host in patients with IBS. Verdu et al suggest a possible pathogenic mechanism linking changes in flora and IBS. Perturbations in gut flora and inflammatory cell activity may modify the sensory neurotransmitter content in the colon, leading to altered visceral perception, dysmotility, increased gas production, and changes in bowel habits. Increased numbers of inflammatory cells in the lamina propria, proximity of mast cells to nerves, and production of substances that activate receptors involved in visceral sensation have been shown in patients with IBS.

Pathogenic bacteria leading to acute gastroenteritis may also cause persistent GI symptoms and FGIDs including IBS and dyspepsia. Postinfectious IBS develops in 10% to 34% of adult patients following acute infectious enteritis. A multicenter controlled study conducted by our group has recently demonstrated the presence of postinfectious IBS in children. This study showed a significant increase in prevalence of abdominal pain in patients experiencing acute gastroenteritis of bacterial origin several years after the initial episode subsided. Although the
pathogenesis of postinfectious IBS remains unclear, some authors propose that changes in gut mucosal function and structure, increased mucosal permeability, infiltration of enteroendocrine cells, and persistent neuroimmune interactions leading to continuing sensorimotor dysfunction could explain this phenomenon87.

The different organ systems also live in an integrated equilibrium with each other. The enteric nervous system has a bidirectional dialogue with the brain via parasympathetic and sympathetic pathways that integrate the brain–gut axis. Stress, defined as an acute threat to homeostasis, may lead to intestinal inflammation, increased intestinal permeability, visceral hypersensitivity, and dysmotility118. Psychological and physical stressors may be involved in the onset and modulation of IBS symptoms. Stress can lead to mast cell activation, degranulation78, and release of mediators that alter the gut motor response and visceral perception through its effect on enteric neurons and smooth muscle cells. Mast cells may constitute the final pathway of various mechanisms sensitizing the GI tract such as stress, food allergies, and infections119. School-related stress may play a role in explaining the seasonal variation of abdominal pain and other somatic complaints described in healthy children at the community level and in consultations for abdominal pain79. Three independent pediatric studies conducted in different settings have concluded that there is a higher prevalence of complaints and consultations for abdominal pain during winter months in comparison with summer months4,79,120. However, the analysis of the monthly pattern of gastrointestinal complaints in different schools and cities showed that those complaints do not occur during the whole school year, whereas school-related stress should be present during the entire academic year. The presence of a significant decrease in somatic complaints at the end of winter and beginning of spring suggests a possible involvement of factors other than school stress. Minor or subclinical infections in certain months of the year could play a role in this seasonal pattern. A decreased ability to cope was described in children with recurrent abdominal pain67.

A study suggested different seasonal patterns of abdominal pain in children living in different latitudes121. Limitations in outside activities due to weather conditions may result in a decreased ability to cope through play during certain months of the year. The possible effect of hormones with an important environmental underpinning should also be considered. Melatonin production illustrates the integration between ecosystems and organ systems. Melatonin, initially thought to be found only in the pineal gland, was then shown to be present in a much greater concentration in the gut, mainly in the enterochromaffin cells. Melatonin serum levels vary according to the daylight cycle and weather (external ecosystem). Melatonin is also produced by the gut flora and its intestinal concentration is modulated by meals (internal ecosystem). Multiple studies have shown an important effect of melatonin on gastrointestinal function122. Melatonin affects GI circadian entrainment, has antioxidant and cytoprotective activity, and anti-inflammatory effects. Melatonin also regulates gut motility and sensation, important factors in the pathogenesis of IBS123. Multiple clinical trials have shown a beneficial role of melatonin in the treatment of IBS124 and dyspepsia even in the absence of sleep disturbances125. Melatonin has also been implicated in the treatment and pathogenesis of headaches126, a common comorbidity in children with abdominal pain60. Headaches and IBS share the biopsychosocial model60. The evidence derived from these studies, the physiological implications of melatonin on the GI tract, and the presence of feedback mechanism between melatonin and serotonin justifies further investigation on the effects of this hormone on the GI tract and its possible role in the treatment of FGIDs124,127.

In summary, health, illness, and the various phenotypic expressions of each condition may be viewed as the results of multiple internal and external factors interacting and mutually affecting each other. We should be open to explore novel factors that could advance our understanding of the pathogenesis of FGIDs.
ENVIRONMENTAL FACTORS OF ABDOMINAL PAIN

Functional abdominal pain includes a group of clinical conditions characterized by chronic or recurrent abdominal pain that occurs in the absence of recognizable physiologic, infectious, structural, or biochemical abnormalities. The term functional abdominal pain (FAP) now replaces the old term of «recurrent abdominal pain,» a vague term. According to the most recent Rome criteria III classification of functional gastrointestinal disorders (FGIDs), functional abdominal pain conditions encompass four different well defined clinical entities: functional dyspepsia (FD), irritable bowel syndrome (IBS), childhood FAP, and abdominal migraine. The etiology of FAP in children is complex and incompletely understood. The most accepted pathophysiologic framework proposes that they result from the interaction of biological, psychosocial, and environmental factors in a predisposed individual. This article focuses on the role of many components of the child’s environmental setting that influence the development of functional abdominal pain.

EPIDEMIOLOGY

Functional abdominal pain is common in children. Office-based and community studies have shown a high prevalence in children of all ages peaking at approximately 9 years. Functional abdominal pain accounts for 2% to 4% of all primary care pediatric visits. A community study by Hyams et al reported that 13% and 17% of middle-school and high-school students experience weekly abdominal pain, with 8% students having consulted a physician for that complaint in the prior year. Saps et al have shown a 46% weekly prevalence of abdominal pain in pre-teen school-age children with 23% reporting persistence of abdominal pain for 4 weeks and 8% for more than 12 weeks.

BIOPSYCHOSOCIAL MODEL

The biopsychosocial model provides the conceptual basis for the understanding of FGIDs including abdominal pain. This holistic theory proposed by George Engel in 1977 proposes that illness results not from a single etiology, but from simultaneously interacting biological, psychological, and social subsystems. This model theorizes that the complex multi-tiered interplay of early life factors may influence later psychological experiences, physiologic functioning, and susceptibility to develop a FGID. Biological, behavioral factors or a combination of both would trigger the clinical onset of a FGID in predisposed individuals. Studies substantiate the biopsychosocial model by demonstrating that, although heredity contributes to the development of IBS, social factors have an equal or greater influence. Twin studies have shown that genetic makeup modulates the susceptibility to environmental factors. An analysis of 6,060 twins demonstrated concordance for IBS in 17% of monozygotic twins and 8.4% in dizygotic twins and that having a parent with IBS is an independent predictor for development of this condition.

STRESS

Stress is a demand made upon the adaptive capacities of the mind and body. Psychological stress places predisposed children at risk for the development of functional gastrointestinal disorders. Brain and gut have a continuous and complex bidirectional interaction («braingut» axis). Central nervous system modulates the motor response, pain sensation, and immune function of the GI system. Stress has been shown to alter the function of the GI tract and GI symptom perception by various mechanisms including the activation of the hypothalamic-pituitary-adrenal axis via neuroendocrine regulatory peptides such as corticotropin-releasing factor. Peripheral actions of neuropeptides may affect...
motility, secretion, and immune response of the GI tract.

Stress can cause alteration of the fecal flora in humans and animals. It has been shown that mucosal inflammation can develop in animals subjected to stress. The effect of emotions on GI physiology demonstrates that the brain plays a critical role in modulating GI functions. Healthy individuals frequently report that psychological stress influences their bowel function. Anxiety is correlated with the severity, frequency, and duration of abdominal pain. Psychosensory stimulation has shown to increase the perception of stimuli in the human colon. In IBS patients, emotions have also been shown to affect the patient’s motility and perception of rectal distension. The demonstrated beneficial effect of cognitive behavior therapy in the treatment of IBS and of hypnosis in reducing pain and rectal sensation further supports the interaction of psychological factors.

FAMILIAL FACTORS

Living in a single-parent household and having a parent with GI complaints have been found to be associated with increased prevalence of FAP in children. Children of parents with anxiety, depression, somatization, or other pain disorders are more likely to exhibit FAP. Maternal and paternal anxiety in the first year of a child’s life are associated with chronic abdominal pain later in life. Anxious parents may contribute to the recurrence of their child’s symptoms and sick behaviors by reinforcing them with encouraging responses. Greater parental reinforcement of children’s pain has been associated with greater functional disability, independent of stress and pain severity. Conversely, parental acceptance of FAP as a biopsychosocial illness has been shown to decrease recurrence of symptoms. All these factors underscore the therapeutic importance of familial education and reassurance during the medical consultation for FGIDs.

SOCIOECONOMIC STATUS

Socioeconomic status of the family influences the incidence of IBS. Although FAP affects children of all socioeconomic classes, a higher socioeconomic status is an independent predictor of IBS. Mendall and Kumar showed a significant association between IBS and having more rooms than family household members during childhood.

SCHOOL-RELATED STRESS

Chronic abdominal pain has been associated with disability and school absenteeism. There is a higher incidence of hospital admissions for nonspecific abdominal pain during the academic year than during holiday periods. Stressors at school including a school exam, dance, sports competition, or an encounter with a peer can contribute to the manifestation of abdominal pain. Children who are high achievers and those who are bullied at school have a higher reported incidence of FAP than their unaffected peers.

SEASONAL VARIATION

Higher prevalence of abdominal pain complaints at the school level has been found in children during winter months as compared with summer months. Increased prevalence of GI consultations in the winter months was also noted in a study of six pediatric tertiary care centers in the United States. Although the reasons are unknown, we hypothesize that the combination of school-related stress, minor infections, and fewer outdoor activities resulting in decreased ability to cope may make children more susceptible to abdominal complaints during the wintertime.

INFECTIONOUS AGENTS

Infectious agents may play a role in the pathogenesis of FGIDs. Studies have shown that IBS can develop as sequelae of an acute GI infection in 4% to 36% of
adult patients. Post-infectious IBS (PIIBS) has been found to occur after infectious colitis involving Salmonella, Escherichia coli, Shigella, and Campylobacter. The relation between viral infections and PI-IBS is less clear. A significant increase of postinfectious FGIDs including IBS and dyspepsia was found in children exposed to GI infections as compared with controls. Depression, anxiety, and stressful events in the previous months were demonstrated to be independent predictors of progression of gastroenteritis to PI-IBS in adults. These findings emphasize the proposed interactions of various biological and psychosocial factors in the pathogenesis of FGIDs.

ALTERED INTESTINAL FLORA

Colonization of the gut begins at birth with the first exposure to the maternal flora of the birth canal. Within hours, a large number of species of bacteria establish themselves in the GI tract. The gut flora are involved in the metabolism of nutrients, the maturation of the intestinal epithelium, vasculature and lymphoid tissue, immune regulation, and protection from pathogens. Less well known, the intestinal microflora induce development and maintenance of gut sensory and motor functions (regular spike burst activity and transit of the small intestine). These findings have led investigators to speculate that quantitative and qualitative changes in intestinal microflora may contribute to sensory-motor dysfunction in FGIDs. Although some investigators propose a link between small bowel bacterial overgrowth (SBBO) and IBS, this hypothesis remains controversial. Although some studies found SBBO in up to 80% of IBS patients, a recent large study showed that culture-confirmed SBBO could be detected in only 4% of IBS patients.

ANTIBIOTICS

Several studies have shown an association between administration of antibiotics and IBS symptoms. Alterations in gut flora could explain the increased prevalence of IBS following antibiotic use. In a study by Mendall, 22% of patients previously exposed to antibiotics had experienced IBS symptoms at least once a week during the previous 6 months, compared with 6% of those who had not received antibiotics.

FOODS

The role of adverse reactions to food in the development of FGIDs has been proposed but remains controversial. Perceived reactions to food causing GI symptoms were reported by 25% to 65% of adult IBS patients. Monsbakken et al found that 62% of IBS patients reported limiting or excluding various food items. Selective elimination of dietary sugars led to symptomatic improvement. No correlation between improvement of symptoms and breath hydrogen tests was noted.

The role of diet including fiber, lactose, and fructose in IBS is still a matter of controversy. Patients with IBS frequently complain of flatulence following the ingestion of foods high in dietary fiber. A systematic review of 17 RCTs found soluble fiber (compared with insoluble fiber) to be more effective than placebo in the reduction of global symptoms of IBS and constipation with no effect on abdominal pain. Intraluminal lipids inhibit gut propulsive motility and delay intestinal gas transport in IBS patients who report abdominal bloating. Elimination of lactose from diet has not shown to be effective in improving symptoms of RAP in children.

There is emerging evidence that food allergy and immune sensitization of intestinal mucosa may play a role in FGIDs. An increased incidence of GI symptoms has been reported in children with allergy and atopy. IBS affects significantly more adult patients who have allergic diseases, such as asthma and allergic rhinitis. A randomized controlled trial has shown a beneficial effect of food elimination guided by IgG antibodies in reducing IBS symptoms. However, a recent study concluded that there is no demonstrable utility of IgG4 in identifying food allergy.
The presence of IgG4 may only indicate immunological tolerance rather than hypersensitivity to the particular food.145

**CONCLUSION**

This article attempts to bring together the various environmental pieces of the FAP puzzle. FAP is a common clinical problem encountered by healthcare professionals and parents alike. FAP is a multidimensional entity influenced by many domains of the child’s environmental milieu. A thorough patient and family history might provide clues to the role of modifiable environmental factors that may contribute to the development of FAP. Accordingly, a comprehensive tailored treatment plan can be offered to the patient. Parents are often confused about the exact pathogenesis of FAP. Effective explanation of the various risk factors will help to educate parents about this disease condition and alleviate their anxiety. More research is needed to clarify the role of these various environmental components and the biologic basis in development of the distinct disease phenotypes defined in the Rome III criteria.

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