FUNTIONAL ABDOMINAL PAIN - PATHOGENESIS

MIGUEL SAPS M.D.[1]; PAPA ADAMS B.S.[1]

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 biopsicosocial 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 socioculturas, 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

1 Department of Pediatric Gastroenterology, Hepatology and Nutrition, Children's Memorial. Chicago, United States of America

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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.

EPIDEMIOLOGY

Chronic abdominal pain is one of the most common pediatric complaints, accounting for 2% to 4% all of 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[9,10].

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].

PATHOGENESIS

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. The biopsychosocial model, a framework that integrates the biological, psychological, and social processes, is the most accepted paradigm[15]. A continuous interplay of

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[16]. 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[17,18]. Abnormal contractions frequently coincide with episodes of abdominal pain[19]. Impaired intestinal gas propulsion and clearance are present in patients with IBS and bloating[20]. 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[21]. 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[22-24]. IBS patients develop pain with volumes of retained gas that are well tolerated by healthy controls[25]. Intolerance to gastric distention was also documented in FD[26,27] Adolescents with FD have delayed gastric emptying and report nausea and bloating after a meal[28]. 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[29,30]. 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[31-33], 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[34].

EARLY LIFE EVENTS

Neglect, abuse, loss of a parent, and life-threatening situations in childhood have been linked to FGIDs in adulthood[35,36]. Adults with IBS have a higher prevalence of conflicted maternal relationships, loss, and separation during childhood[36]. Studies suggest the existence of an early period of susceptibility of the nervous system associated with enduring neural plasticity and alterations of pain perception[37,38]. 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[37.38]. Minor colonic stimulation in the neonatal period in rats can produce long-term sensitization[39]. Mechanical or chemical colonic irritation in neonatal rats leads to the development of visceral hypersensitivity in adulthood[40]. Also in rats, maternal deprivation during the early postnatal period (a surrogate of stress) results in alterations in behavior and induces a stress response[41], visceral hyperalgesia, and increased colonic motility later in life[42]. 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[43]. 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[44]. Maternal deprivation in rats promotes similar long-term changes in colonic mast cells and nerve terminal distribution[45].

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[46]. 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[47]. 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[48-50]. 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[48]. Monozygotic twins are twice as likely to develop IBS as dizygotic twins[51]. Studies also show that having a parent with IBS is an independent and stronger predictor of IBS than having a twin with IBS[51]. 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[52-55]. 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[56]. In humans, the level of SERT mRNA and SERT protein in the intestinal epithelial cells of IBS patients decreased significantly[57]. However, these findings have not been replicated in a recent study[58].

Researchers have described a link between p11, a protein critical to 5-HT 1B receptor functions, and IBS[58]. The expression of p11 is increased in patients with IBS. 5-HT 1B receptor agonists reduce perception of gastric distention in patients with FD and hypersensitivity[59]. The protein p11 could modulate the response to stimulation of serotonergic receptors, including 5-HT 1B receptors[58], 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[60]. Children of adults with IBS have more gastrointestinal-related health care visits than children of parents without IBS[61]. Levy et al.[62] 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[36,63,64]. Whitehead et al.[63,65] 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[63.65]. 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[62,64].

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[66]. In addition, studies have shown that children with FAP have a poorer ability to cope with stressful situations than their peers[67]. 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[68]. 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 defi ned 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[69,70] and enhanced colonic motor activity[69]. Psychosocial stress seems to have an even greater physiologic response in patients with FGIDs[69]. There is evidence that stress plays a prominent role in the pathophysiology[70] and clinical presentation of IBS[71]. 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, proinfl amatory responses, and anxiety. R2 stimulation results in slowed gastric emptying, anti-inflammatory changes, and anxiolysis during stress in rats[72]. These responses can be blocked by CRF antagonists and reproduced by CRF administered intraventricularly[73,74].

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[75]. 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[76,77]. Mast cell degranulation caused by stress initiates polymorphonuclear cell influx, increased secretion, permeability, and propulsive motility, leading to pain and diarrhea[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[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[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[81]. Changes in gut flora may explain the increase in prevalence of IBS that has been found after antibiotic use[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[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[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[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 lowgrade 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[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[88,89]. Sixty-two percent of patients with IBS limit or exclude a particular food to avoid symptom onset[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[91].

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[92]. Studies have shown an increased number of mast cells in the ileocecal region of IBS patients[44]. 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[93]. 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[94,95]. The possible role of IgG4 is also controversial. IgG4 receptors are located on basophils and mast cells and are distinct from IgE receptors[96]. Although several studies suggest that IgG4 production may be part of a normal immunologic response to dietary antigens[97,98], other studies demonstrate elevated serum IgG4 levels in patients with a history of food allergy and IBS, suggesting a contributory role[93,94,99]. Elimination of foods selected by specific serum IgG4 testing resulted in symptom improvement[95,100-102]. 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[101]. 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[103]. 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[104].

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)[105]. 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[101]. 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[100].

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[83]. Germ-free rats have different spatial and temporal characteristics of migrating motor complexes in the small intestine than do conventional animals[106]. Anaerobic bacteria seem to be an important promoter of regular spike activity in the small intestine. Psychological stress results in quantitative alterations in bacteria[107,108]. Stressed mice exhibit a decrease in the relative proportion of *Lactobacilli* and *Escherichia coli*, changes that could be related to small intestine dysfunction[108]. 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[109]. Pimentel et al have found bacterial overgrowth in 78% of patients with IBS[110]. 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[82,111]. Probiotics and antibiotics have also been used to treat a proposed dysfunctional relation between the indigenous flora and the host in patients with IBS[110,112-114]. Verdu et al suggest a possible pathogenic mechanism linking changes in flora and IBS[115]. 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[44].

Pathogenic bacteria leading to acute gastroenteritis may also cause persistent GI symptoms and FGIDs including IBS[116] and dyspepsia[117]. Postinfectious IBS develops in 10% to 34% of adult patients following acute infectious enteritis[85]. A multicenter controlled study conducted by our group has recently demonstrated the presence of postinfectious IBS in children[86]. 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 phenomenon[87].

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 dysmotility[118]. Psychological and physical stressors may be involved in the onset and modulation of IBS symptoms. Stress can lead to mast cell activation, degranulation[78], 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 infections[119]. 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 pain[79]. 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 months[4,79,120]. 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 pain[67]. A study suggested different seasonal patterns of abdominal pain in children living in different latitudes[121]. 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 function[122]. 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 IBS[123]. Multiple clinical trials have shown a beneficial role of melatonin in the treatment of IBS[124] and dyspepsia even in the absence of sleep disturbances[125]. Melatonin has also been implicated in the treatment and pathogenesis of headaches[126], a common comorbidity in children with abdominal pain[60]. Headaches and IBS share the biopsychosocial model[60]. 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 FGIDs[124,127].

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[128,129]. 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[130]. 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[5]. 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[121].

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[51].

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-pituitaryadrenal 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[131].

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[132]. 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[5]. Psychosensory stimulation has shown to increase the perception of stimuli in the human colon[133]. 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[134]. 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[64]. Conversely, parental acceptance of FAP as a biopsychosocial illness has been shown to decrease recurrence of symptoms[135]. 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[111].

SCHOOL-RELATED STRESS

Chronic abdominal pain has been associated with disability and school absenteeism[135]. There is a higher incidence of hospital admissions for nonspecific abdominal pain during the academic year than during holiday periods[136]. 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[137].

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 States79 (79). 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.

INFECTIOUS 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[138]. 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[86]. Depression, anxiety, and stressful events in the previous months were demonstrated to be independent predictors of progression of gastroenteritis to PI-IBS in adults[139]. 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)[106]. 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[140].

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[111].

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[89]. 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[141].

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[88]. 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[142]. Intraluminal lipids inhibit gut propulsive motility and delay intestinal gas transport in IBS patients who report abdominal bloating[143]. Elimination of lactose from diet has not shown to be effective in improving symptoms of RAP in children[144].

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[145]. A randomized controlled trial has shown a beneficial effect of food elimination guided by IgG antibodies in reducing IBS symptoms[101]. 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[146]

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.

References

1. Veereman-Wauters G. The Quest for Light in the Misty Frontierland of Pediatric Functional Gastrointestinal Disorders: Act II: Rome III Criteria. J Pediatr Gastroenterol Nutr 2006;43:156-7.
2. Galler JR, Neustein S, Walker WA. Clinical aspects of recurrent abdominal pain in children. Adv Pediatr 1980;27:31-53.
3. Saps M, Saini J, Di Lorenzo C. Common GI Symptoms: Prevalence and Risk Factors. J Pediatr Gastroenterol Nutr 2006;43:E59-E60.
4. MacIver R, Mears C, Di Lorenzo C, Saps M. Seasonal Nurse Consultations for Abdominal Pain in an Adolescent Population. J Pediatr Gastroenterol Nutr 2007;45:E13.
5. Hyams JS, Burke G, Davis PM, Rzepski B, Andrulonis PA. Abdominal pain and irritable bowel syndrome in adolescents: a community-based study. J Pediatr 1996;129:220-6.
6. Faull C, Nicol AR. Abdominal pain in six-year-olds: an epidemiological study in a new town. J Child Psychol Psychiatry 1986;27:251-60.
7. Zuckerman B, Stevenson J, Bailey V. Stomachaches and headaches in a community sample of preschool children. Pediatrics 1987;79:677-82.
8. Saps M, Bolioli P, Espana M, Marshall BM, Di Lorenzo C. Cost and consultation patterns of abdominal pain in Uruguayan children. J Pediatr Gastroenterol Nutr 2008;46:159-63.
9. Apley J, Naish N. Recurrent abdominal pains: a field survey of 1,000 school children. Arch Dis Child 1958;33:165-70.
10. Oster J. Recurrent abdominal pain, headache and limb pains in children and adolescents. Pediatrics 1972;50:429-36.
11. Inadomi JM, Fennerty MB, Bjorkman D. Systematic review: the economic impact of irritable bowel syndrome. Aliment Pharmacol Ther 2003;18:671-82.
12. Walker LS, Garber J, Van Slyke DA, Greene JW. Long-term health outcomes in patients with recurrent abdominal pain. J Pediatr Psychol 1995;20:233-45.
13. Borge AI, Nordhagen R, Moe B, Botten G, Bakketeig LS. Prevalence and persistence of stomach ache and headache among children. Follow-up of a cohort of Norwegian children from 4 to 10 years of age. Acta Paediatr 1994;83:433-7.
14. Apley J, Hale B. Children with recurrent abdominal pain: how do they grow up? Br Med J 1973;3:7-9.
15. Ringel Y, Drossman DA. Irritable bowel syndrome: classification and conceptualization. J Clin Gastroenterol 2002;35:S7-10.
16. Kellow JE, Delvaux M, Azpiroz F, Camilleri M, Quigley EM, Thompson DG. Principles of applied neurogastroenterology: physiology/motility-sensation. Gut 1999;45 Suppl 2:II17-24.
17. van der Veek PP, Steenvoorden M, Steens J, van der Schaar PJ, Brussee J, Masclee AA. Recto-colonic reflex is impaired in patients with irritable bowel syndrome. Neurogastroenterol Motil 2007;19:653-9.
18. Fukudo S, Kanazawa M, Kano M, Sagami Y, Endo Y, Utsumi A, et al. Exaggerated motility of the descending colon with repetitive distention of the sigmoid colon in patients with irritable bowel syndrome. J Gastroenterol 2002;37 Suppl 14:145-50.
19. Chey WY, Jin HO, Lee MH, Sun SW, Lee KY. Colonic motility abnormality in patients with irritable bowel syndrome exhibiting abdominal pain and diarrhea. Am J Gastroenterol 2001;96:1499-506.
20. Salvioli B, Serra J, Azpiroz F, Malagelada JR. Impaired small bowel gas propulsion in patients with bloating during intestinal lipid infusion. Am J Gastroenterol 2006;101:1853-7.
21. Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. Gastroenterology 1997;112:2120-37.
22. Ritchie J. Pain from distension of the pelvic colon by inflating a balloon in the irritable colon syndrome. Gut 1973;14:125-32.
23. Whitehead WE, Holtkotter B, Enck P, Hoelzl R, Holmes KD, Anthony J, et al. Tolerance for rectosigmoid distention in irritable bowel syndrome. Gastroenterology 1990;98:1187-92.
24. Van Ginkel R, Voskuijl WP, Benninga MA, Taminiau JA, Boeckxstaens GE. Alterations in rectal sensitivity and motility in childhood irritable bowel syndrome. Gastroenterology 2001;120:31-8.
25. Serra J, Azpiroz F, Malagelada JR. Impaired transit and tolerance of intestinal gas in the irritable bowel syndrome. Gut 2001;48:14-9.
26. Lemann M, Dederding JP, Flourie B, Franchisseur C, Rambaud JC, Jian R. Abnormal perception of visceral pain in response to gastric distension in chronic idiopathic dyspepsia. The irritable stomach syndrome. Dig Dis Sci 1991;36:1249-54.
27. Mearin F, Cucala M, Azpiroz F, Malagelada JR. The origin of symptoms on the brain-gut axis in functional dyspepsia. Gastroenterology 1991;101:999-1006.
28. Chitkara DK, Camilleri M, Zinsmeister AR, Burton D, El-Youssef M, Freese D, et al. Gastric sensory and motor dysfunction in adolescents with functional dyspepsia. J

Pediatr 2005;146:500-5.
29. Mertz H, Morgan V, Tanner G, Pickens D, Price R, Shyr Y, et al. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. Gastroenterology 2000;118:842-8.
30. Mayer EA, Berman S, Suyenobu B, Labus J, Mandelkern MA, Naliboff BD, et al. Differences in brain responses to visceral pain between patients with irritable bowel syndrome and ulcerative colitis. Pain 2005;115:398-409.
31. Andresen V, Bach DR, Poellinger A, Tsrouya C, Stroh A, Foerschler A, et al. Brain activation responses to subliminal or supraliminal rectal stimuli and to auditory stimuli in irritable bowel syndrome. Neurogastroenterol Motil 2005;17:827-37.
32. Kwan CL, Diamant NE, Pope G, Mikula K, Mikulis DJ, Davis KD. Abnormal forebrain activity in functional bowel disorder patients with chronic pain. Neurology 2005;65:1268-77.
33. Bernstein CN, Frankenstein UN, Rawsthorne P, Pitz M, Summers R, McIntyre MC. Cortical mapping of visceral pain in patients with GI disorders using functional magnetic resonance imaging. Am J Gastroenterol 2002;97:319-27.
34. Ringel Y. New directions in brain imaging research in functional gastrointestinal disorders. Dig Dis 2006;24:278-85.
35. Biggs AM, Aziz Q, Tomenson B, Creed F. Effect of childhood adversity on health related quality of life in patients with upper abdominal or chest pain. Gut 2004;53:180-6.
36. Lowman BC, Drossman DA, Cramer EM, McKee DC. Recollection of childhood events in adults with irritable bowel syndrome. J Clin Gastroenterol 1987;9:324-30.
37. Porter FL, Wolf CM, Miller JP. The effect of handling and immobilization on the response to acute pain in newborn infants. Pediatrics 1998;102:1383-9.
38. Taddio A, Katz J, Ilersich AL, Koren G. Effect of neonatal circumcision on pain response during subsequent routine vaccination. Lancet 1997;349:599-603.
39. Winston J, Shenoy M, Medley D, Naniwadekar A, Pasricha PJ. The vanilloid receptor initiates and maintains colonic hypersensitivity induced by neonatal colon irritation in rats. Gastroenterology 2007;132:615-27.
40. Al-Chaer ED, Kawasaki M, Pasricha PJ. A new model of chronic visceral hypersensitivity in adult rats induced by colon irritation during postnatal development. Gastroenterology 2000;119:1276-85.
41. Levine S. Primary social relationships influence the development of the hypothalamic—pituitary—adrenal axis in the rat. Physiol Behav 2001;73:255-60.
42. Coutinho SV, Plotsky PM, Sablad M, Miller JC, Zhou H, Bayati AI, et al. Neonatal maternal separation alters stress-induced responses to viscerosomatic nociceptive stimuli in rat. Am J Physiol Gastrointest Liver Physiol 2002;282:G307-16.
43. Gareau MG, Jury J, Yang PC, MacQueen G, Perdue MH. Neonatal maternal separation causes colonic dysfunction in rat pups including impaired host resistance. Pediatr Res 2006;59:83-8.
44. Barbara G, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Santini D, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology 2004;126:693-702.
45. Barreau F, Ferrier L, Fioramonti J, Bueno L. New insights in the etiology and pathophysiology of irritable bowel syndrome: contribution of neonatal stress models. Pediatr Res 2007;62:240-5.
46. Anand KJ, Runeson B, Jacobson B. Gastric suction at birth associated with long-term risk for functional intestinal disorders in later life. J Pediatr 2004;144:449-54.
47. Smith C, Nordstrom E, Sengupta JN, Miranda A. Neonatal gastric suctioning results in chronic visceral and somatic hyperalgesia: role of corticotropin releasing factor. Neurogastroenterol Motil 2007;19:692-9.
48. Bode G, Brenner H, Adler G, Rothenbacher D. Recurrent abdominal pain in children: evidence from a population-based study that social and familial factors play a major role but not Helicobacter pylori infection. J Psychosom Res 2003;54:417-21.
49. Kalantar JS, Locke GR, 3rd, Zinsmeister AR, Beighley CM, Talley NJ. Familial aggregation of irritable bowel syndrome: a prospective study. Gut 2003;52:1703-7.
50. Locke GR, 3rd, Zinsmeister AR, Talley NJ, Fett SL, Melton LJ, 3rd. Familial association in adults with functional gastrointestinal disorders. Mayo Clin Proc 2000;75:907-12.
51. Levy RL, Jones KR, Whitehead WE, Feld SI, Talley NJ, Corey LA. Irritable bowel syndrome in twins: heredity and social learning both contribute to etiology. Gastroenterology 2001;121:799-804.
52. Svenningsson P, Chergui K, Rachleff I, Flajolet M, Zhang X, El Yacoubi M, et al. Alterations in 5-HT1B receptor function by p11 in depression-like states. Science 2006;311:77-80.
53. Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, et al. Serotonin transporter genetic variation and the response of the human amygdala. Science 2002;297:400-3.
54. Melke J, Landen M, Baghei F, Rosmond R, Holm G, Bjorntorp P, et al. Serotonin transporter gene polymorphisms are associated with anxiety-related personality traits in women. Am J Med Genet 2001;105:458-63.
55. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 2003;301:386-9.
56. Chen JJ, Li Z, Pan H, Murphy DL, Tamir H, Koepsell H, et al. Maintenance of serotonin in the intestinal mucosa and ganglia of mice that lack the high-affinity serotonin transporter: Abnormal intestinal motility and the expression of cation transporters. J Neurosci 2001;21:6348-61.
57. Coates MD, Mahoney CR, Linden DR, Sampson JE, Chen J, Blaszyk H, et al. Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome. Gastroenterology 2004;126:1657-64.
58. Camilleri M, Andrews CN, Bharucha AE, Carlson PJ, Ferber I, Stephens D, et al. Alterations in expression of p11 and SERT in mucosal biopsy specimens of patients with irritable bowel syndrome. Gastroenterology 2007;132:17-25.
59. Tack J, Caenepeel P, Corsetti M, Janssens J. Role of tension receptors in dyspeptic patients with hypersensitivity to gastric distention. Gastroenterology 2004;127:1058-66.
60. Levy RL, Olden KW, Naliboff BD, Bradley LA, Francisconi C, Drossman DA, et al. Psychosocial aspects of the functional gastrointestinal disorders. Gastroenterology 2006;130:1447-58.
61. Levy RL, Whitehead WE, Von Korff MR, Feld AD. Intergenerational transmission of gastrointestinal illness behavior. Am J Gastroenterol 2000;95:451-6.
62. Levy RL, Whitehead WE, Walker LS, Von Korff M, Feld AD, Garner M, et al. Increased somatic complaints and health-care utilization in children: effects of parent IBS status and parent response to gastrointestinal symptoms. Am J Gastroenterol 2004;99:2442-51.
63. Whitehead WE, Winget C, Fedoravicius AS, Wooley S,

Blackwell B. Learned illness behavior in patients with irritable bowel syndrome and peptic ulcer. Dig Dis Sci 1982;27:202-8.
64. Whitehead WE, Crowell MD, Heller BR, Robinson JC, Schuster MM, Horn S. Modeling and reinforcement of the sick role during childhood predicts adult illness behavior. Psychosom Med 1994;56:541-50.
65. Whitehead WE, Fedoravicius AS, Blackwell B, Wooley S. A behavioral conceptualization of psychosomatic illness: psychosomatic symptoms as learned responses. In: McNamara JR, editor. Behavioral Approaches to Medicine: Application and Analysis. New York: Basic Books; 1979. p. 65-99.
66. Walker LS, Heflinger CA. Quality of life predictors in pediatric abdominal pain patients: findings at initial assessment and five-year follow-up. In: Drotar DD, editor. Measuring Health-Related Quality of Life in Children and Adolescents: Implications for Research and Practice. London: Psychology Press; 1998. p. 237-52.
67. Thomsen AH, Compas BE, Colletti RB, Stanger C, Boyer MC, Konik BS. Parent reports of coping and stress responses in children with recurrent abdominal pain. J Pediatr Psychol 2002;27:215-26.
68. Nicholl BI, Halder SL, Macfarlane GJ, Thompson DG, O'Brien S, Musleh M, et al. Psychosocial risk markers for new onset irritable bowel syndrome—results of a large prospective population-based study. Pain 2008;137:147-55.
69. Rao SS, Hatfield RA, Suls JM, Chamberlain MJ. Psychological and physical stress induce differential effects on human colonic motility. Am J Gastroenterol 1998;93:985-90.
70. Tache Y, Martinez V, Million M, Rivier J. Corticotropin-releasing factor and the brain-gut motor response to stress. Can J Gastroenterol 1999;13 Suppl A:18A-25A.
71. Mayer EA. The neurobiology of stress and gastrointestinal disease. Gut 2000;47:861-9.
72. Fukudo S, Saito K, Sagami Y, Kanazawa M. Can modulating corticotropin releasing hormone receptors alter visceral sensitivity? Gut 2006;55:146-8.
73. Lechner SM, Curtis AL, Brons R, Valentino RJ. Locus coeruleus activation by colon distention: role of corticotropin-releasing factor and excitatory amino acids. Brain Res 1997;756:114-24.
74. Gue M, Junien JL, Bueno L. Conditioned emotional response in rats enhances colonic motility through the central release of corticotropin-releasing factor. Gastroenterology 1991;100:964-70.
75. Valentino RJ, Miselis RR, Pavcovich LA. Pontine regulation of pelvic viscera: pharmacological target for pelvic visceral dysfunctions. Trends Pharmacol Sci 1999;20:253-60.
76. Santos J, Yang PC, Soderholm JD, Benjamin M, Perdue MH. Role of mast cells in chronic stress induced colonic epithelial barrier dysfunction in the rat. Gut 2001;48:630-6.
77. Soderholm JD, Perdue MH. Stress and gastrointestinal tract. II. Stress and intestinal barrier function. Am J Physiol Gastrointest Liver Physiol 2001;280:G7-G13.
78. Bhatia V, Tandon RK. Stress and the gastrointestinal tract. J Gastroenterol Hepatol 2005;20:332-9.
79. Saps M, Blank C, Khan S, Seshadri R, Marshall B, Bass L, et al. Seasonal variation in the presentation of abdominal pain. J Pediatr Gastroenterol Nutr 2008;46:279-84.
80. Saps M. Ecology of functional gastrointestinal disorders. J Pediatr Gastroenterol Nutr 2008;47:684-7.
81. Pimentel M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. Am J Gastroenterol 2000;95:3503-6.
82. Maxwell PR, Rink E, Kumar D, Mendall MA. Antibiotics increase functional abdominal symptoms. Am J Gastroenterol 2002;97:104-8.
83. Camilleri M. Probiotics and irritable bowel syndrome: rationale, putative mechanisms, and evidence of clinical efficacy. J Clin Gastroenterol 2006;40:264-9.
84. Spiller R. Probiotics: an ideal anti-inflammatory treatment for IBS? Gastroenterology 2005;128:783-5.
85. Spiller RC. Postinfectious irritable bowel syndrome. Gastroenterology 2003;124:1662-71.
86. Saps M, Pensabene L, Di Martino L, Staiano A, Wechsler J, Zheng X, et al. Post-infectious functional gastrointestinal disorders in children. J Pediatr 2008;152:812-6, 6 e1.
87. Spiller RC, Jenkins D, Thornley JP, Hebden JM, Wright T, Skinner M, et al. Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute Campylobacter enteritis and in post-dysenteric irritable bowel syndrome. Gut 2000;47:804-11.
88. Simren M, Mansson A, Langkilde AM, Svedlund J, Abrahamsson H, Bengtsson U, et al. Food-related gastrointestinal symptoms in the irritable bowel syndrome. Digestion 2001;63:108-15.
89. Zar S, Kumar D, Benson MJ. Food hypersensitivity and irritable bowel syndrome. Aliment Pharmacol Ther 2001;15:439-49.
90. Monsbakken KW, Vandvik PO, Farup PG. Perceived food intolerance in subjects with irritable bowel syndrome—etiology, prevalence and consequences. Eur J Clin Nutr 2006;60:667-72.
91. Farup PG, Monsbakken KW, Vandvik PO. Lactose malabsorption in a population with irritable bowel syndrome: prevalence and symptoms. A case-control study. Scand J Gastroenterol 2004;39:645-9.
92. Park MI, Camilleri M. Is there a role of food allergy in irritable bowel syndrome and functional dyspepsia? A systematic review. Neurogastroenterol Motil 2006;18:595-607.
93. el Rafei A, Peters SM, Harris N, Bellanti JA. Diagnostic value of IgG4 measurements in patients with food allergy. Ann Allergy 1989;62:94-9.
94. Zar S, Benson MJ, Kumar D. Food-specific serum IgG4 and IgE titers to common food antigens in irritable bowel syndrome. Am J Gastroenterol 2005;100:1550-7.
95. Zuo XL, Li YQ, Li WJ, Guo YT, Lu XF, Li JM, et al. Alterations of food antigen-specific serum immunoglobulins G and E antibodies in patients with irritable bowel syndrome and functional dyspepsia. Clin Exp Allergy 2007;37:823-30.
96. Nakagawa T, de Weck AL. Membrane receptors for the IgG4 subclass on human basophils and mast cells. Clin Rev Allergy 1983;1:197-206.
97. Husby S, Oxelius VA, Teisner B, Jensenius JC, Svehag SE. Humoral immunity to dietary antigens in healthy adults. Occurrence, isotype and IgG subclass distribution of serum antibodies to protein antigens. Int Arch Allergy Appl Immunol 1985;77:416-22.
98. Johansson SG, Dannaeus A, Lilja G. The relevance of anti-food antibodies for the diagnosis of food allergy. Ann Allergy 1984;53:665-72.
99. Miyamoto T, Koya N, Suzuki S, Arita M, Matsumoto T, Tamura H, et al. [Clinical significance of specific IgG4 antibody in serum]. Arerugi 1991;40:215-23.
100. Zar S, Mincher L, Benson MJ, Kumar D. Food-specific IgG4 antibody-guided exclusion diet improves symptoms and rectal compliance in irritable bowel syndrome. Scand J Gastroenterol 2005;40:800-7.
101. Atkinson W, Sheldon TA, Shaath N, Whorwell PJ. Food

elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. Gut 2004;53:1459-64.
102. Drisko J, Bischoff B, Hall M, McCallum R. Treating irritable bowel syndrome with a food elimination diet followed by food challenge and probiotics. J Am Coll Nutr 2006;25:514-22.
103. Whorwell PJ. The growing case for an immunological component to irritable bowel syndrome. Clin Exp Allergy 2007;37:805-7.
104. Drossman DA. Gastrointestinal illness and the biopsychosocial model. J Clin Gastroenterol 1996;22:252-4.
105. Whorwell P, Lea R. Dietary Treatment of the Irritable Bowel Syndrome. Curr Treat Options Gastroenterol 2004;7:307-16.
106. Husebye E, Hellstrom PM, Sundler F, Chen J, Midtvedt T. Influence of microbial species on small intestinal myoelectric activity and transit in germ-free rats. Am J Physiol Gastrointest Liver Physiol 2001;280:G368-80.
107. Wang SX, Wu WC. Effects of psychological stress on small intestinal motility and bacteria and mucosa in mice. World J Gastroenterol 2005;11:2016-21.
108. Holdeman LV, Good IJ, Moore WE. Human fecal flora: variation in bacterial composition within individuals and a possible effect of emotional stress. Appl Environ Microbiol 1976;31:359-75.
109. Galatola G, Grosso M, Barlotta A, Ferraris R, Rovera L, Ariano M, et al. [Diagnosis of bacterial contamination of the small intestine using the 1 g [14C] xylose breath test in various gastrointestinal diseases]. Minerva Gastroenterol Dietol 1991;37:169-75.
110. Pimentel M, Park S, Mirocha J, Kane SV, Kong Y. The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome: a randomized trial. Ann Intern Med 2006;145:557-63.
111. Mendall MA, Kumar D. Antibiotic use, childhood affluence and irritable bowel syndrome (IBS). Eur J Gastroenterol Hepatol 1998;10:59-62.
112. Kim HJ, Vazquez Roque MI, Camilleri M, Stephens D, Burton DD, Baxter K, et al. A randomized controlled trial of a probiotic combination VSL# 3 and placebo in irritable bowel syndrome with bloating. Neurogastroenterol Motil 2005;17:687-96.
113. Quigley EM, Flourie B. Probiotics and irritable bowel syndrome: a rationale for their use and an assessment of the evidence to date. Neurogastroenterol Motil 2007;19:166-72.
114. Sharara AI, Aoun E, Abdul-Baki H, Mounzer R, Sidani S, Elhajj I. A randomized double-blind placebo-controlled trial of rifaximin in patients with abdominal bloating and flatulence. Am J Gastroenterol 2006;101:326-33.
115. Verdu EF, Bercik P, Verma-Gandhu M, Huang XX, Blennerhassett P, Jackson W, et al. Specific probiotic therapy attenuates antibiotic induced visceral hypersensitivity in mice. Gut 2006;55:182-90.
116. Gwee KA, Collins SM, Read NW, Rajnakova A, Deng Y, Graham JC, et al. Increased rectal mucosal expression of interleukin 1beta in recently acquired post-infectious irritable bowel syndrome. Gut 2003;52:523-6.
117. Mearin F, Perez-Oliveras M, Perello A, Vinyet J, Ibanez A, Coderch J, et al. Dyspepsia and irritable bowel syndrome after a Salmonella gastroenteritis outbreak: one-year follow-up cohort study. Gastroenterology 2005;129:98-104.
118. Hart A, Kamm MA. Review article: mechanisms of initiation and perpetuation of gut inflammation by stress. Aliment Pharmacol Ther 2002;16:2017-28.
119. Wood JD. Effects of bacteria on the enteric nervous system: implications for the irritable bowel syndrome. J Clin Gastroenterol 2007;41:S7-19.
120. Saps M, Di Lorenzo C. An Epidemiological Study of Common GI Symptoms in School-Age Children Gastroenterology 2007;132:A-325.
121. Saps M, Sztainberg M, Di Lorenzo C. A prospective community-based study of gastroenterological symptoms in school-age children. J Pediatr Gastroenterol Nutr 2006;43:477-82.
122. Konturek SJ, Konturek PC, Brzozowska I, Pawlik M, Sliwowski Z, Czesnikiewicz-Guzik M, et al. Localization and biological activities of melatonin in intact and diseased gastrointestinal tract (GIT). J Physiol Pharmacol 2007;58:381-405.
123. Bubenik GA. Gastrointestinal melatonin: localization, function, and clinical relevance. Dig Dis Sci 2002;47:2336-48.
124. Song GH, Leng PH, Gwee KA, Moochhala SM, Ho KY. Melatonin improves abdominal pain in irritable bowel syndrome patients who have sleep disturbances: a randomised, double blind, placebo controlled study. Gut 2005;54:1402-7.
125. Lu WZ, Gwee KA, Moochhalla S, Ho KY. Melatonin improves bowel symptoms in female patients with irritable bowel syndrome: a double-blind placebo-controlled study. Aliment Pharmacol Ther 2005;22:927-34.
126. Peres MF, Masruha MR, Zukerman E, Moreira-Filho CA, Cavalheiro EA. Potential therapeutic use of melatonin in migraine and other headache disorders. Expert Opin Investig Drugs 2006;15:367-75.
127. Elsenbruch S. Melatonin: a novel treatment for IBS? Gut 2005;54:1353-4.
128. Hyman PE, Milla PJ, Benninga MA, Davidson GP, Fleisher DF, Taminiau J. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology 2006;130:1519-26.
129. Rasquin A, Di Lorenzo C, Forbes D, Guiraldes R, Hyams JS, Staiano A, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology 2006;130:1527-37.
130. Campo JV, Bridge J, Ehmann M, Altman S, Lucas A, Birmaher B, et al. Recurrent abdominal pain, anxiety, and depression in primary care. Pediatrics 2004;113:817-24.
131. Sagami Y, Shimada Y, Tayama J, Nomura T, Satake M, Endo Y, et al. Effect of a corticotropin releasing hormone receptor antagonist on colonic sensory and motor function in patients with irritable bowel syndrome. Gut 2004;53:958-64.
132. Soderholm JD, Yang PC, Ceponis P, Vohra A, Riddell R, Sherman PM, et al. Chronic stress induces mast cell-dependent bacterial adherence and initiates mucosal inflammation in rat intestine. Gastroenterology 2002;123:1099-108.
133. Ford MJ, Camilleri M, Zinsmeister AR, Hanson RB. Psychosensory modulation of colonic sensation in the human transverse and sigmoid colon. Gastroenterology 1995;109:1772-80.
134. Ramchandani PG, Stein A, Hotopf M, Wiles NJ. Early parental and child predictors of recurrent abdominal pain at school age: results of a large population-based study. J Am Acad Child Adolesc Psychiatry 2006;45:729-36.
135. Crushell E, Rowland M, Doherty M, Gormally S, Harty S, Bourke B, et al. Importance of parental conceptual model of illness in severe recurrent abdominal pain. pediatrics 2003;112:1368-72.
136. Greco LA, Freeman KE, Dufton L. Overt and relational

victimization among children with frequent abdominal pain: links to social skills, academic functioning, and health service use. J Pediatr Psychol 2007;32:319-29.
137. Williams N, Jackson D, Lambert PC, Johnstone JM. Incidence of non-specific abdominal pain in children during school term: population survey based on discharge diagnoses. Bmj 1999;318:1455.
138. Neal KR, Hebden J, Spiller R. Prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome: postal survey of patients. Bmj 1997;314:779-82.
139. Dunlop SP, Jenkins D, Spiller RC. Distinctive clinical, psychological, and histological features of postinfective irritable bowel syndrome. Am J Gastroenterol 2003;98:1578-83.
140. Lin HC. Small intestinal bacterial overgrowth: a framework for understanding irritable bowel syndrome. Jama 2004;292:852-8.
141. Fernandez-Banares F, Esteve-Pardo M, de Leon R, Humbert P, Cabre E, Llovet JM, et al. Sugar malabsorption in functional bowel disease: clinical implications. Am J Gastroenterol 1993;88:2044-50.
142. Bijkerk CJ, Muris JW, Knottnerus JA, Hoes AW, de Wit NJ. Systematic review: the role of different types of fibre in the treatment of irritable bowel syndrome. Aliment Pharmacol Ther 2004;19:245-51.
143. Serra J, Salvioli B, Azpiroz F, Malagelada JR. Lipid-induced intestinal gas retention in irritable bowel syndrome. Gastroenterology 2002;123:700-6.
144. Lebenthal E, Rossi TM, Nord KS, Branski D. Recurrent abdominal pain and lactose absorption in children. Pediatrics 1981;67:828-32.
145. Caffarelli C, Deriu FM, Terzi V, Perrone F, De Angelis G, Atherton DJ. Gastrointestinal symptoms in patients with asthma. Arch Dis Child 2000;82:131-5.
146. Stapel SO, Asero R, Ballmer-Weber BK, Knol EF, Strobel S, Vieths S, et al. Testing for IgG4 against foods is not recommended as a diagnostic tool: EAACI Task Force Report. Allergy 2008;63:793-6.