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REVIEW ARTICLE

Overlap between functional abdominal pain disorders and organic diseases in children☆

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Abstract Functional abdominal pain disorders are highly prevalent in children. These disorders can be present in isolation or combined with organic diseases, such as celiac disease and inflammatory bowel diseases. Intestinal inflammation (infectious and non-infectious) predisposes children to the development of visceral hypersensitivity that can manifest as functional abdominal pain disorders, including irritable bowel syndrome. The new onset of irritable bowel syndrome symptoms in a patient with an underlying organic disease, such as inflammatory bowel disease, is clinically challenging, given that the same symptomatology may represent a flare-up of the inflammatory bowel disease or an overlapping functional abdominal pain disorder. Similarly, irritable bowel syndrome symptoms in a child previously diagnosed with celiac disease may occur due to poorly controlled celiac disease or the overlap with a functional abdominal pain disorder. There is little research on the overlap of functional abdominal disorders with organic diseases in children. Studies suggest that the overlap between functional abdominal pain disorders and inflammatory bowel disease is more common in adults than in children. The causes for these differences in prevalence are unknown. Only a handful of studies have been published on the overlap between celiac disease and functional

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abdominal pain disorders in children. The present article provides a review of the literature on the overlap between celiac disease, inflammatory bowel disease, and functional abdominal pain disorders in children and establish comparisons with studies conducted on adults.

PALABRAS CLAVE
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Inflamación gastrointestinal

Sobreposición entre los trastornos funcionales de dolor abdominal y enfermedades orgánicas en niños

Resumen Los trastornos funcionales de dolor abdominal tienen una alta prevalencia en los niños. Estos trastornos pueden estar presentes por sí solos o en combinación con enfermedades orgánicas, tales como la enfermedad celíaca y las enfermedades inflamatorias intestinales. La inflamación intestinal (infecciosa y no infecciosa) predispone a los niños al desarrollo de hipersensibilidad visceral que puede manifestarse como trastornos funcionales de dolor abdominal, entre ellos el síndrome de intestino irritable. La aparición de síntomas de síndrome de intestino irritable en un paciente con una enfermedad orgánica subyacente, como la enfermedad inflamatoria intestinal, es un reto clínico, dado que la misma sintomatología puede representar un periodo de exacerbación de la enfermedad inflamatoria intestinal o un trastorno de dolor abdominal funcional sobrepuesto. Así mismo, puede ser que los síntomas del síndrome de intestino irritable en un niño con diagnóstico de enfermedad celíaca ocurran por un inadecuado control de la enfermedad celíaca o por la sobreposición con un trastorno de dolor abdominal funcional. Existe poca investigación acerca de la sobreposición de los trastornos funcionales abdominales y las enfermedades orgánicas en niños. Los estudios sugieren que la sobreposición entre los trastornos funcionales de dolor abdominal y la enfermedad inflamatoria intestinal es más común en adultos que en niños. Las causas de estas diferencias de prevalencia son aún desconocidas. Solo se han publicado unos cuantos estudios que tratan el tema de la sobreposición entre la enfermedad celíaca y los trastornos funcionales abdominales en niños. El presente artículo proporciona una revisión de la literatura acerca de la sobreposición entre la enfermedad celíaca, la enfermedad inflamatoria intestinal, y los trastornos funcionales de dolor abdominal en niños, además de establecer comparaciones con estudios realizados en adultos.

Introduction

Epidemiology and definition. Abdominal pain is common in children. In a prospective cohort study, ninety percent of American schoolchildren reported abdominal pain over a 6-month period and an average of 38% of schoolchildren had abdominal pain weekly.[1] Children that reported abdominal pain were more likely to miss school and social and physical activities, and have significantly higher anxiety and depression scores, as well as worse quality of life. Fifty-two percent of schoolchildren in that study had abdominal pain that lasted for 4 weeks and 24% of them had pain lasting for more than 8 weeks. Among the children that reported abdominal pain for 8 weeks, a subset of them met the Rome criteria for a functional abdominal pain disorder, a group of chronic functional gastrointestinal disorders, characterized by abdominal pain as the predominant symptom. The Rome IV criteria define functional abdominal pain disorders as the presence of abdominal pain that occurs at least 4 times a month, for 2 or more months, with some loss of daily function.[2–5] The criteria indicate that there should be ''no evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms'', but acknowledges the potential for coexistence of inflammatory disorders and functional abdominal pain. Those disorders are highly prevalent, with an estimated worldwide pooled prevalence of 13%. Some studies have found a prevalence as high as 40% in certain areas of the world.[4] The Rome IV criteria define 4 distinct functional abdominal pain disorders with specific diagnostic patterns: irritable bowel syndrome (IBS), functional dyspepsia, functional abdominal pain–not otherwise specified, and abdominal migraine, with the first 3 diagnostic categories being more prevalent than the last. The quality of life of children with those disorders is highly impaired. For example, symptoms related to functional abdominal pain and IBS account for 40 to 60% of variance in general health-related quality of life of those children.[6]

Risk factors. Gastrointestinal inflammation is a risk factor for the development of functional abdominal pain disorders.

More than 10% of adults and approximately 36% of children with acute infectious enteritis develop functional abdominal pain disorders that may last for several years.[7,8] Adults with infectious enteritis are more than 4 times as likely to develop IBS within one year after the infection.[7] Similarly, children that contract an acute gastroenteritis are at a 3 times greater risk for developing a functional abdominal pain disorder at least 6 months after the infection.[8,9] Other sources of gastrointestinal inflammation, including autoimmune disorders, have also been associated with the development of functional abdominal pain disorders.[10] Unlike acute gastroenteritis that clinically resolves by the time a functional abdominal pain disorder develops, symptoms of chronic autoimmune disease may coexist with functional abdominal pain disorders, despite treatment.

The coexistence of 2 conditions that can present with similar symptoms poses a diagnostic and therapeutic challenge for the clinician, who must decide whether the patient's symptoms are related to a functional abdominal pain disorder or a relapse of the underlying organic disease.[11,12] Celiac disease and inflammatory bowel disease (IBD) are 2 common autoimmune gastrointestinal diseases in children. The diseases are also found worldwide, with celiac disease affecting up to 1% and IBD up to 0.4%. Approximately one-fourth of patients with IBD are diagnosed in childhood and increasing awareness of celiac disease may result in earlier diagnoses being made. Active inflammation in either disease can be associated with abdominal pain, nausea, vomiting, change in bowel habits, and other systemic symptoms including fatigue, weakness, and weight loss. However, studies in adult patients have shown that patients with celiac disease frequently complain of gastrointestinal symptoms, including abdominal pain and diarrhea, despite maintaining a gluten-free diet. Multiple studies in adult patients have also shown that a large percentage of adult patients with ulcerative colitis and Crohn's disease have overlapping functional abdominal pain disorders, such as IBS.[13]

There have been few studies on the overlap of celiac disease and IBD with functional abdominal pain disorders in children. We present herein a review of the current literature in the pediatric population and contrast it with findings in adults.

Celiac disease

Celiac disease is an immune enteropathy that is associated with T lymphocyte-mediated inflammation in the mucosa of the small bowel. Symptoms of functional abdominal pain disorders may sometimes mimic celiac disease. Abdominal pain and diarrhea are frequently present in patients with both conditions.[14,15] The similarity of symptoms may lead to confusion in patients with undiagnosed celiac disease, as well as patients with celiac disease undergoing treatment. As a result, the Rome IV criteria recommend testing for celiac disease in children presenting with symptoms consistent with IBS with diarrhea, particularly when there is a family history of celiac disease.[14] Despite those recommendations, the question of whether patients with IBS are more likely to have celiac disease has not been definitively established. A meta-analysis found that adult patients with IBS were three times more likely to have celiac disease than those without IBS diagnosis, and that celiac screening tests were cost-effective.[16] However, that was not true for the general population or when only North American studies were considered.

Few studies have investigated the relation between celiac disease and functional abdominal pain disorders in children. A study in children found no association between recurrent abdominal pain and celiac disease diagnosed through antiendomysial antibody testing.[17] However, another study found that children with IBS were four times more likely to be diagnosed with celiac disease than the general population.[18] The relation between celiac disease and functional abdominal pain disorders is not exclusively limited to the time of diagnosis. A proportion of patients with celiac disease on a gluten-free diet continue to have gastrointestinal symptoms.[19,20] A follow-up study of a cohort of adults diagnosed with celiac disease in the US found that 48% of patients met the criteria for IBS at the time of diagnosis, whereas only 2% continued to meet the criteria 6 months later, and 95% of the patients had relief or resolution of abdominal pain shortly after the introduction of a gluten-free diet.[21] However, the findings of a Canadian study contradicted those results, indicating that symptoms frequently persist, despite adequate treatment.[19] The study found that a large proportion of patients continued to report gastrointestinal symptoms, such as abdominal pain (65%), diarrhea (78%), and constipation (54%), 5 years after initiating a gluten-free diet for celiac disease treatment. The authors of the study proposed that post-inflammatory functional abdominal pain disorder was a factor that could explain those symptoms.

Few studies have investigated the prevalence of functional gastrointestinal disorders in children with celiac disease on a gluten-free diet. It is a relevant clinical problem for pediatric gastroenterologists, because children on a gluten-free diet that still complain of gastrointestinal symptoms pose a management dilemma. Unnecessary testing or an unnecessary focus on improving dietary adherence can be avoided if there is awareness of the existence of a subset of children that, despite adhering to a strict gluten-free diet, may continue to report gastrointestinal symptoms. Those situations often frustrate families already compliant with the gluten-free diet and repeated questioning about dietary adherence can strain the relation between families, children, and providers. In 2011, Turco et al. conducted a prospective study to evaluate the association of celiac disease with functional gastrointestinal disorders in children.[22] They observed that celiac disease patients on a gluten-free diet had significantly more functional gastrointestinal disorders than controls. However, the clear majority of those children had functional constipation that could be explained by changes in diet, including lower ingestion of fiber. A cohort study of children with celiac disease that were compliant with a gluten-free diet found that children with celiac disease had a prevalence of abdominal pain and functional abdominal pain disorders similar to that of their healthy siblings.[23] Although the cohort was relatively small, the use of sibling controls in that study helped to adjust for potential confounding factors. A large international study also found that children with celiac disease and a gluten-free diet had a similar risk of abdominal pain and functional abdominal pain

disorders, compared with their healthy siblings and healthy, unrelated controls.[24] Despite chronic abdominal pain prevalence rates being higher in the Italian cohort versus the US cohort, comparisons between rates of pain in the celiac and control groups were not affected. Those results suggest that post-inflammatory functional pain disorders may not frequently occur in children and imply that not every type of inflammation, even if present for long-periods of time, predisposes to functional pain disorders. The pathogenesis of post-inflammatory functional pain disorders may differ in children and adults. It is not yet understood why a brief acute gastroenteritis, lasting only a few days, frequently leads to post-inflammatory functional pain disorders, whereas chronic inflammation due to celiac disease, present for months or years prior to diagnosis, does not.[8,25]

Inflammatory bowel disease

IBD is a chronic condition of immune dysregulation that presents in childhood and adolescence 25% of the time.[26,27] During remission, inflammation is reduced and gastrointestinal symptoms are expected to resolve. As in the case of celiac disease, the new onset of abdominal pain and diarrhea can be worrisome symptoms in patients with IBD thought to be in remission. Some of those patients, despite being in remission, meet the criteria for a functional pain disorder that overlaps with their underlying organic disease. Several studies have investigated the prevalence of IBS-like symptoms in adult patients with IBD in remission. All the studies concluded that said overlap was common. A systematic review of 11 studies found that 25-46% of adults with IBD in remission had IBS-like symptoms.[13] Higher rates of IBS were found in adults with IBD, compared with healthy controls, and rates were also increased in active IBD, compared with inactive disease. A more recent study not included in the systematic review supported similar conclusions in adults, finding that patients with IBD in remission had higher rates of IBS than healthy controls.[28] It was also noted that decreased quality of life and increased anxiety were found in IBD patients with concurrent IBS, compared with those that only had IBD. There are fewer studies on overlap between IBD and functional abdominal pain disorders in children. In 2013 Zimmerman et al. assessed the prevalence and impact of functional pain disorders in patients with quiescent Crohn's disease. The authors found that 6% of children with IBD in remission had functional abdominal pain.[29] Another study conducted in the Netherlands found that 6.4% of children with IBD in clinical remission had IBS-type symptoms (Crohn's disease: 4.5%; ulcerative colitis: 10.8%).[30] There was no difference in inflammatory markers (fecal calprotectin and CRP) between patients with or without IBS-type symptoms. In that study, IBD patients in remission that presented with IBS-like symptoms, were younger and used fewer medications, compared with those with no IBS-like symptoms. The prevalence of overlap functional abdominal pain disorders in both studies was grossly similar to the overall prevalence of functional abdominal pain and IBS in the population as a whole, and much lower than the prevalence of overlap found in adult patients.

A cross-sectional study conducted in the US using strict Rome III criteria found that up to 26% of children and adolescents with IBD in remission had functional abdominal pain disorders (Crohn's disease: 27.4%; ulcerative colitis: 22%).[31] Pediatric studies typically use the Pediatric Crohn's Disease Activity Index (PCDAI) to assess disease severity in children with Crohn's disease. A shortcoming of using the PCDAI in children with IBD in remission and overlapping functional abdominal pain disorders is that it may overestimate disease activity. Although that index helps categorize disease severity, its score can be impacted by symptoms that are common features in patients with functional abdominal pain disorders, such as abdominal pain and abdominal tenderness.[29] Similarly, the Pediatric Ulcerative Colitis Activity Index (PUCAI), commonly used in children with that pathology, may produce elevated scores in children with functional abdominal pain disorders.

Abdominal pain, frequent stools, and interference with daily activities may be present in patients with ulcerative colitis with functional abdominal pain, independent of the degree of activity of the underlying organic disease. However, inflammatory markers, such as fecal calprotectin, are abnormally elevated in patients with active IBD, whereas they are generally normal in patients with IBD in remission and overlapping functional abdominal pain disorders.[30,32] The criterion of interference with activity in the PUCAI can also be influenced by psychological disturbances that are frequently present in patients with IBD, with and without overlapping functional abdominal pain disorders. Gold et al. found that IBS patients had more depression and decreased quality of life than patients with IBD.[33] Depression was also higher in children with IBD and chronic abdominal pain, regardless of whether the pain was attributed to inflammation or a functional disorder.[29] In line with those findings, patients with overlapping IBD and functional abdominal pain disorders were shown to have more psychological internalizing disorders than patients with IBD in remission, alone. Patient health communication appears to be linked to gastrointestinal worry and IBD symptoms, as well.[34] In their study comparing patients with IBD with and without overlapping functional abdominal pain disorders, Watson et al. found that the patients with IBD-functional pain disorders had greater anxiety symptoms, significantly more depressive symptoms, and worse quality of life.[31] Studies in adult patients suggest that psychological disorders are also more common in patients with overlapping IBD and functional abdominal pain disorders. Adults with ulcerative colitis in deep remission commonly had IBS-like symptoms and the frequency of those symptoms was associated with poor psychological well-being that included anxiety, depression, and perceived stress.[35]

The pathophysiology of overlap of IBD with functional abdominal pain disorders is not completely understood. A study by Akbar et al. found increased TRPV1 (a receptor known to play a role in visceral hypersensitivity) nerve fibers in quiescent IBD with IBS-like symptoms, and that increase significantly correlated with abdominal pain severity.[36] Thus, TRPV1, or other mediators of visceral hypersensitivity found in inflammatory conditions, provide potential therapeutic targets for that group of patients, in addition to typical functional abdominal pain disorder treatments. Identifying the IBD patients that are more likely to develop functional abdominal pain disorders while in remission could also

help establish preventive measures. A study from Sweden on patients with ulcerative colitis, without a prior diagnosis of IBS, found that the severity of inflammation at diagnosis, measured by fecal calprotectin, CRP, and mucosal cytokine mRNA expression (IFN-γ, IL-17A and IL-8), did not determine which patients would develop IBS-like symptoms while in remission.[37] Psychological factors may also be involved in the development of functional abdominal pain disorders in patients with IBD. Stress and anxiety can increase intestinal permeability, alter intestinal mucosal immunity, and induce low grade intestinal inflammation with the release of inflammatory mediators, which in turn, leads to diarrhea and abdominal pain that manifest as IBS symptoms.[38]

Future directions

The overlap between inflammatory intestinal disease and functional abdominal pain is clearly exemplified by celiac and inflammatory bowel diseases. Although awareness and education regarding said overlap is paramount for enhancing clinical practice, improved understanding of the relationships and mechanisms involved is also warranted. Questions remain that merit investigation through rigorous clinical studies and the likely necessity of laboratory models. Broader cohorts of children analyzed prospectively (i.e. starting at the time of diagnosis of IBD and celiac disease) would greatly expand our knowledge and understanding of the relation of those diseases to functional abdominal pain disorders and help us understand the risk factors involved in the development of the overlap form. Some of the interesting questions to be explored are whether genetic predisposition, intestinal microbial content, dietary patterns, time of diagnosis, type of treatment, psychosocial factors including stressors, hormonal factors, and early adverse life events increase the risk of developing functional abdominal pain disorders in patients with celiac disease and IBD.

Delineating the role of anxiety and depression, parental and patient worries, and the mediators of those relations may help establish earlier intervention. Efforts should be invested in designing placebo-controlled trials addressing not only the treatment of that overlap form, but also its prevention. However, more information is required to enable us to propose well-designed studies for those purposes. Among the important data that should be investigated are the mechanisms involved in the development of the overlap form of organic and functional abdominal pain disorders. Although few functional MRI studies have been conducted on adults with IBD and IBS,[39,40] there are no published studies on children. Based on the abovementioned data showing the differences between children and adults, the findings of functional imaging studies conducted on adults may or may not be applicable to children.

The extent to which the onset of autoimmune intestinal inflammation modulates central or peripheral pain processing, alters intestinal electromechanical function, or affects behaviors that increase the likelihood of developing functional pain disorders in children, even after active inflammation resolves or becomes quiescent, should be further investigated. Augmenting the body of literature related to the overlap between functional and organic disorders could facilitate the development of new diagnostic criteria for those disorders, a task that may be considered in the next edition of the Rome criteria. Increasing awareness may lead to the proper and early identification of the overlap between functional abdominal pain disorders and organic diseases, resulting in better care of our patients and a consequent improvement in their quality of life. The additional unanswered questions of why there appear to be differences between adult and pediatric populations are not trivial ones. To the contrary, they can help us understand the pathogenesis of those disorders in both groups of patients. At present, we can hypothesize that the prolonged time course of inflammatory disease may increase the risk of developing functional pain disorders, but there are no pediatric data to substantiate that claim. It can only be resolved through comparative studies on adult and pediatric patients. Treatment adherence, coping mechanisms, perception of illness and related psychological comorbidities, and diet are other differences between adult and pediatric patients with inflammatory intestinal disease that may contribute to the development of functional pain disorders, but they have not been specifically evaluated in children.

In conclusion, we have limited data on the prevalence of functional abdominal pain disorders in pediatric patients with celiac disease, Crohn's disease, and ulcerative colitis in remission. A lower prevalence of overlapping functional abdominal pain disorders was found in the majority of pediatric studies, compared with studies conducted on adult patients, which could be related to the longer duration of disease and ongoing inflammation present in adults at the time of assessment. A heightened awareness of overlap is warranted, and further investigation of potential risk factors and mechanisms of overlap is needed. Pediatric gastroenterologists should be aware of the risk factors that predispose children with IBD to develop overlapping symptoms of a functional abdominal pain disorder. A multidisciplinary approach to inflammatory disease focused on potential biopsychosocial factors contributing to symptoms is necessary as part of a comprehensive treatment plan and may also concurrently prevent or treat overlapping functional pain disorders. Assessment of anxiety and depression, functional disability, and barriers to school attendance, as well as the teaching of coping strategies, are relevant to functional pain disorders and overlapping inflammatory diseases. Consideration of a functional abdominal pain disorder diagnosis and assessment using the Rome IV questionnaire are recommended when it is unclear if symptoms are related to celiac disease, ulcerative colitis, or Crohn's disease inflammation. Recognition of the overlap between functional pain disorders and intestinal inflammatory disease is paramount in preventing unnecessary diagnostic tests and initiating appropriate treatment. Patients, families, primary care providers, pediatric specialists, and the adult providers to whom patients transition should all be aware of potential overlapping disorders and the fact that prevalence may increase in adulthood.

Ethical disclosures

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

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

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

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Authorship

All the authors contributed to the critical revision and editing of the manuscript and to the approval of the final version. Licia Pensabene collaborated on the study concept. Amber Langshaw, John Rosen, and Miguel Saps were involved in all aspects of the study, including its design, literature review, analysis, and drafting.

Conflict of interest

The authors declare that there is no conflict of interest.

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