Functional Gastrointestinal Disorders and Visceral Hypersensitivity in Children and Adolescents Suffering from Crohn's Disease

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Background: Symptoms of abdominal pain are reported by children with active Crohn's disease (CD). During remissions abdominal pain improves in most children but some of them continue to experience pain. We hypothesized that these patients may suffer from protracted abdominal pain related to functional gastrointestinal disorders (FGID) and visceral hypersensitivity. The objective was to characterize the symptoms and to measure the rectal sensory threshold for pain (RSTP) by barostat in CD children and adolescents suffering from abdominal pain despite remission.

Methods: Eight patients (median age 14.5 years; range 9.8–17) with quiescent CD but suffering from chronic abdominal pain were studied by rectal barostat. At the same time they completed validated questionnaires to assess FGID, anxiety, and depression. They were compared to 10 control children and 8 children with FGID also investigated in our laboratory.

Results: All patients fulfilled Rome II criteria for irritable bowel syndrome ($n = 5$), functional abdominal pain ($n = 2$), and functional dyspepsia ($n = 1$). RSTP was significantly lower in CD patients compared to the normal controls: median (range) 25 mmHg (15–29) versus 40 mmHg (30–48) ($P < 0.01$). RSTP was similar in patients and children with FGID. Rectal compliance was similar in patients, children with FGID, and controls. Seven of the 8 patients had scores indicating an anxiety problem.

Conclusions: Protracted abdominal pain that affects children and adolescents with quiescent CD is related to FGID associated with visceral hypersensitivity and anxiety. The incidence of FGID in children suffering from CD requires further investigation.

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Key Words: irritable bowel syndrome, functional abdominal pain, children, adolescents, Rome II criteria, rectal barostat, visceral sensitivity, Crohn's disease

Crohn's disease (CD) is an inflammatory disorder that manifests during childhood and adolescence in up to 25% of patients.[1] In affected patients abdominal pain is the most common symptom during the course of the disease.[2] Often, when the disease is quiescent and inflammation improves, the symptoms resolve and abdominal pain disappears. Sometimes abdominal pain remains chronic despite inflammation improvement and normalization of mucosal lesions, suggesting an association with functional gastrointestinal disorders (FGIDs). FGIDs are defined as recurrent digestive symptoms unexplained by structural or biochemical anomalies and Rome criteria describe with precision the various clinical pictures encountered.[3] Not uncommonly, they significantly impact similar to inflammatory bowel diseases (IBDs) a child's quality of life.[4] In the last few years studies have shown that FGIDs are highly associated with visceral hypersensitivity in adults and children.[5–9]

In adults, recent investigations have clearly revealed that the prevalence of irritable bowel syndrome (IBS)-like symptoms in IBD patients in long-standing remission is 2 to 3 times higher than in the normal population.[10] In pediatrics, according to a recent comprehensive review, no data are available on a possible association with FGID in children affected by CD.[11]

The aim of this study was to test the hypothesis that protracted abdominal pain in a group of children and adolescents with quiescent CD is related to FGID and visceral hypersensitivity.

MATERIALS AND METHODS

Patients

Eight children with CD were enrolled in the study. Their demographics are reported in Table 1. CD had been T1
diagnosed by the presence of segmental bowel inflammation (with or without granuloma on pathological examination of intestinal specimens) on colonoscopy or gastroduodenoscopy and/or the presence of inflamed lesions localized in the small bowel on small bowel follow-through.[12,13] All patients were considered to be in remission by their attending pediatric gastroenterologist at the time of barostat testing (i.e., normal abdominal and perineal examination; <2 liquid stools per day; erythrocyte sedimentation rate <20/hour; albumin >35 g/L; hemoglobin >120 g/L). Absence of active lesions on gastroduodenoscopy and colonoscopy were demonstrated in

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TABLE 1. Characteristics of the CD Study Population

Patient #	Gender	Age (y)	Age at Diagnosis (y)	Initial Extent of Crohn's Disease	Concomitant Medications	Endoscopic Assessement at the Time of the Barostat
1	F	13.6	13	Colon	prednisone	Normal
2	F	14.1	12.5	Stomach, ileum	6-mercaptopurine	Normal
3	F	9.8	8	Colon	prednisone + 6-mercaptopurine	Normal
4	F	15.5	15	Ileum, ascending colon	budesonide	Not done
5	F	15.2	14.5	Stomach	No	Normal
6	M	17	13	Stomach, ileum, ascending colon	budesonide + 6-mercaptopurine	Not done
7	F	14.0	13	Ileum, ascending colon	6-mercaptopurine	Normal
8	F	15.2	12	Ileum	5-ASA	Not done

Patients 1, 2, 3, 5, and 7 in the 3 months preceding the barostat. Because these subjects complained of chronic abdominal pain it was not possible to assess a validated activity index such as the pediatric Crohn's Disease Activity Index.[14]

Patients were referred for barostat assessment because of abdominal pain lasting for more than 3 months not explained by their CD. Parents and children gave informed consent and assent, respectively, before participating in the study. All medications affecting pain or gastrointestinal motility were discontinued at least 48 hours prior to the barostat procedure.

Controls

Data obtained in 10 control children (6 males, 4 females; median age 13.7 years, range 10.2–16.1) investigated under the same conditions in our laboratory were used as normal values. Details are reported elsewhere.[9] We also compared patients with 8 age- and sex-paired children with confirmed diagnosis of IBS or functional abdominal pain (FAP) according to Rome II criteria studied by rectal barostat in our laboratory. These control children with FGID were extracted from our patient database and corresponding data have never been published elsewhere.

Questionnaires

The participants completed the Questionnaire on Pediatric Gastrointestinal Symptoms in Children (QPGS), the State-Trait Anxiety Inventory for Children (STAIC), and the Child Depression Inventory (CDI). The QPGS was developed and validated in English and French at Hôpital Sainte-Justine.[15–17] It assesses symptoms associated with FGID in children, as specified by pediatric Rome II criteria.[3] This structured questionnaire includes sections on children's bowel habits, abdominal pain (pain duration and frequency), as well as limitations of activities (missed school days and missed activities with friends due to pain). The STAIC is a 20-item questionnaire validated in children for the assessment of anxiety symptoms. STAIC scores greater than 68 have been shown to reflect an anxiety state and/or trait.[18] The CDI is a 27-item questionnaire that has been validated in children for the evaluation of depression; CDI scores greater than 17 correlate with clinical depression.[19] French translations of both the STAIC and CDI have been validated in French-Canadian children.[18,19] All questionnaires were completed before the barostat procedure by the children or with the help of a parent if they were less than 10 years old.

Barostat Procedure

The rectal sensory threshold for pain (RSTP) was measured with an electronic barostat (G&J Electronics, Toronto, ON, Canada), according to published recommendations[14] and as described previously.[9] Briefly, after a 6-hour fasting period a double canal catheter of 18F diameter, on which a 600-mL spherical polyvinyl bag (MUI Scientific, Mississauga, ON, Canada) was fixed, was inserted into the rectum with the patient lying in the left lateral decubitus position. Five to 10 minutes were allowed for rectal accommodation. The barostat was programmed to deliver phasic intermittent stimuli lasting 60 seconds, followed by 60 seconds deflation according to the ascending method of limits with tracking. Maximal pressure was 48 mmHg. A 4-point scale served as a verbal descriptor for sensations felt during the barostat procedure. The RSTP was determined by averaging the pressures at which pain had been indicated. Rectal compliance was calculated according to a nonlinear model fitting the pressure-volume curves of each individual. Pressure-volume curves were constructed with average computed volumes during the 60 seconds of each consecutive pressure step. Compliance was calculated as the maximum slope in the pressure-volume curves.[20,21]

When pain was reported by the patient the sensation was evaluated as previously described.[9] Briefly, the localization of pain was specified with the help of a standardized

measurement method described and validated in children.[22] Prior to the barostat procedure the children were asked to indicate where they experienced pain on a human body diagram (seen from front and back). Then, during the barostat measurement, they were instructed to indicate on a separate human body diagram any painful sensations experienced during the procedure. At the end of the barostat procedure, just before the removal of the balloon catheter, the child had to answer "Yes" or "No" to the question: "Is the sensation you felt similar to what you usually feel at home?"

The barostat findings in our study population (RSTP, compliance, somatic referrals of visceral sensations) were compared to normal values established in our laboratory (see Materials and Methods).[9]

Statistics

Descriptive statistics were used to summarize the demographic characteristics of the study population, the questionnaire findings, and barostat exam results. Summary data are expressed as means (±standard deviation) of normally distributed data and medians (25th–75th percentile) for non-normally distributed data. The CD and control groups were compared by Student's *t*-test for the means of normally distributed continuous variables, by the Mann–Whitney *U*-test for non-normally distributed variables.

$P < 0.05$ values were considered statistically significant. All analyses were performed with Prism 4 software (GraphPad Prism, San Diego, CA).

RESULTS

Population

The 8 recruited children had a median age of 14.5 years (range 9.8–17 years) (Table 1). CD was diagnosed at a median age of 13 years (range 8–15), and median duration of the disease at the time of the study was 1.1 years (range 0.5–4). Remission was confirmed in all patients. Five patients fulfilled Rome II criteria for IBS, 2 for FAP, and 1 for functional dyspepsia, confirmed by symptoms reported in the QPGS.

Barostat Results

Median RSTP was 25 mmHg (20–29 mmHg; 25th–75th percentile) in patients with CD (Fig. 1). It was similar to children with FGID (median 23 mmHg; 16–35.2, 25th–75th percentile) but significantly lower than the RSTP values found in the control group (median 40 mmHg; 32–48, 25th–75th percentile) ($P < 0.01$).[9] Seven patients had rectal hypersensitivity as defined by RSTP ≤30.8 mmHg; this represents the 5th percentile of RSTP values measured in our control group, our cutoff score for rectal hypersensitivity.[9]

Similar to children with FGID, 7 of 8 patients referred their sensation to aberrant sites compared to the controls, i.e., with abdominal projections to dermatomes T8 to L1 when rectal distension-induced sensations refer to the S3 dermatome (perineal area) in controls.[9] Seven patients reported that the sensation they felt during the barostat procedure was the same as the pain they usually experienced at home.

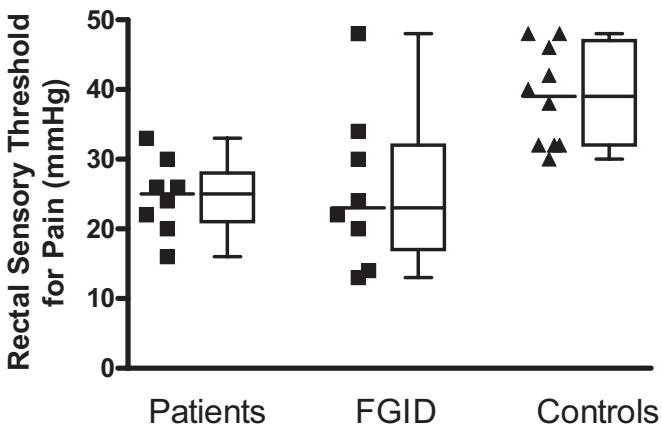

FIGURE 1. The rectal sensory threshold for pain (RSTP) in patients with quiescent CD and protracted abdominal pain (Patients), children with functional gastrointestinal disorders (FGID), and control children (Controls). Individual values are shown and, for each group, the horizontal bar represents the median value of each population with interquartile and 5%–95% ranges. The RSTP is lower in patients and in FGID than in control children ($P < 0.01$). The RSTP is similar in patients and FGID.

Rectal compliance was similar in patients (9.1 mL/mmHg, 6.6–10.9; 25th–75th percentile), children with FGID (9.2 mL/mmHg, 6.7–11.2; 25th–75th percentile), and controls (8.7 mL/mmHg, 6.0–10.1; 25th–75th percentile) (Fig. 2).

Role of Anxiety and Depression

Six of the 8 patients (75%) had a STAIC score indicating significant anxiety (median score for anxiety 75, range 66–93; normal <68).[18] Only 1 patient had a CDI score predictive of clinical depression. The median (range) score for depression was 10 (range 4–32; normal <17).[19]

DISCUSSION

The present study is, to our knowledge, the first report on the association of FGID in children with CD. This study reports a group of children and adolescents with quiescent CD suffering from chronic abdominal pain that is affected by FGID according to Rome II criteria. Barostat study in these patients demonstrate rectal hypersensitivity and abnormal somatic referrals of visceral sensation similar to children with IBS and FAP.[5,6,9]

The mechanisms of FGID appearance in patients with inactive IBD are currently unknown, but our data indicate that visceral hypersensitivity may be, at least partly, an explanation. In these patients, visceral sensitivity could be en-

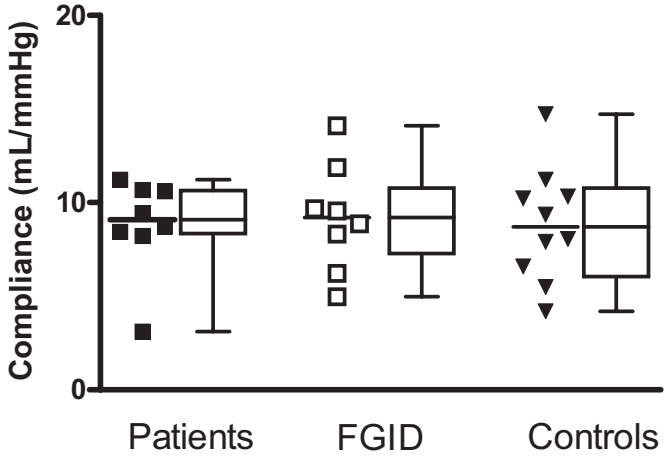

FIGURE 2. Rectal compliance in patients with quiescent CD and protracted abdominal pain (Patients), children with functional gastrointestinal disorders (FGID), and control children (Controls). Individual values are shown and for each group the horizontal bar represents the median value of each population with interquartile and 5%–95% ranges. Rectal compliance is similar in patients, FGID, and control children.

hanced by several mechanisms related either to mechanical factors affecting rectal compliance or to the long-term consequences of inflammatory processes on the intrinsic and/or extrinsic enteric nervous system (ENS). We did not find any difference in rectal compliance between the patient and control groups, suggesting that the elastic properties of the rectal wall were not modified in this group of CD patients. We cannot exclude that these pediatric patients had no mechanical changes in the rectal wall due to the relatively short duration of their disease (1.1 years) compared to adults with a long-standing evolution. Rectal compliance has been shown to be modified in adult patients with active or quiescent ulcerative colitis (UC).[23–25]

Animal models and studies performed in humans with CD or UC have both demonstrated and described the mechanisms of intestinal inflammation impacts on the ENS.[26] These consequences evoke profound structural[27] and functional[28] changes due to ENS plasticity. The alterations are not only restricted to the acute phase of inflammation, but are also seen in the noninflamed rectum of CD patients[29] and in an animal CD model.[30] Whether such modifications can explain the visceral sensitization in CD is currently being debated.[31] Animal models have provided contradictory results: in rats, acute inflammation has been shown to promote long-term effects on somatosensory functioning[32] but, on the other hand, dextran sodium sulfate-induced colonic inflammation does not affect rectal visceral sensitivity either in the short- or long-term in mice.[33] Chang et al[34] have demonstrated, by comparing patients with UC and mild inflammation and patients with IBS, that low-grade mucosal inflammation alone is unlikely to be responsible for symptoms in FGID. Moreover, recent data have disclosed that the immune system is a critical determinant of visceral nociception and that T lymphocytes have significant opioid-mediated antinociceptive influence in the gut.[35] Another hypothesis to explain the visceral sensitization in CD could involve central sensitization[36,37] or descending bulbospinal inhibition of sacral dorsal horn neurons in response to chronic intestinal tissue irritation.[38]

One could argue that the patients tested in the present study were not compared to paired patients with CD without any complaints in remission. For evident ethical reasons, we were not able to propose rectal barostat testing in asymptomatic children with a well-known diagnosis of CD. We thus compared the patients to a previously published group of control children[9] and to a group of children with FGID according to Rome II criteria assessed in our laboratory under the same conditions. We demonstrated a significant difference between this group of CD children and the controls but similar barostat values and somatic referrals as compared to children with FGID.

The precise mechanisms of FGID-associated symptoms in patients with inactive IBD are unknown, although psychosocial factors have been shown to greatly influence the occurrence of chronic complaints in these cases.[10] In this study we describe the high prevalence (7/8 patients) of anxiety disorders in children with FGID and CD compared to 48% in children with FGID only.[9] This is in accordance with recent data showing that anxiety is an independent predictor of FGID in adult patients with inactive IBD.[39] Other psychosocial factors may play a major role in the co-occurrence of FGID in pediatric patients with CD. Mother IBS status,[40] stress,[41] somatization,[42,43] attention to pain,[44,45] social threat,[45] parental reluctance to accept the diagnosis,[46] and family adaptation[47] are all factors that have been found to promote FGID development and were not evaluated in our study.

Overlapping of FGID with CD has several clinical implications. Differentiating among the causes of symptoms in patients with CD is of major importance to avoid the misdiagnosis of refractory IBD. Escalating therapy directed at disease activity may have no effect on functional symptoms other than to reinforce them. Second, it is well-recognized that quality of life alteration is similar in children with FGID and IBD.[4] Recognizing FGID in CD patients will allow us to better manage these patients by associating well-adapted treatments of CD with a comprehensive approach and adequate guidance for them and their families.[1] Reassurance and pathophysiological explanations on the nature and mechanisms of the symptoms to children and their parents should be provided with appropriate pharmacological[48] and/or psychological support.[49]

We conclude that children and adolescents with CD may suffer from recurrent abdominal pain related to FGID despite remission of their inflammatory disease. These symp-

toms result from biological and psychological alterations. The incidence of FGID in children suffering from CD and whether the changes demonstrated in the present study are specific to such patients requires further investigation.

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