Rectal Sensory Threshold for Pain is a Diagnostic Marker of Irritable Bowel Syndrome and Functional Abdominal Pain in Children

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Objective To evaluate the diagnostic value of the rectal sensory threshold for pain (RSTP) in children and adolescents with chronic abdominal pain.

Study design Fifty-one patients (25 girls; median age 14.2 years; range 8.4-17.6) with abdominal pain >2 months underwent a series of rectal distensions with an electronic barostat. RSTP and viscerosomatic referrals were assessed. Three months after the barostat, the final diagnosis was documented.

Results Thirty-five patients had a functional gastrointestinal disorder (FGID) (irritable bowel syndrome or functional abdominal pain), and 16 had an organic disease. RSTP was lower in the FGID group than in the organic disease group (25.4mm Hg vs 37.1mm Hg; $P = .0002$). At the cutoff of 30mm Hg, the RSTP measurement for the diagnosis of FGID had a sensitivity of 94% and a specificity of 77%. Both groups similarly reported aberrant viscerosomatic projections.

Conclusion In children, RSTP is a diagnostic marker of irritable bowel syndrome and functional abdominal pain. Viscerosomatic referrals are similar in children with FGID and organic diseases. *(J Pediatr 2010;156:60-5)*.

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Visceral hypersensitivity is defined as an exaggerated perceptual response to peripheral events, such as controlled visceral distensions, as compared with control subjects. Hence, subjects with visceral hypersensitivity report painful sensations at lower distending pressures than control subjects. In the last 15 years, rectal hypersensitivity has been associated with irritable bowel syndrome (IBS) in adult patients.[1] Similar data have since been reported in children with IBS and functional abdominal pain (FAP).[2-4] These findings support the hypothesis that visceral hypersensitivity plays a major etiologic role in IBS, FAP, and other functional gastrointestinal disorders (FGID) in addition to other factors such as anomalies of pain perception, anxiety, depression, and somatization.[5] Parallel to visceral hypersensitivity, abnormal somatic referrals in response to rectal distension have been reported in patients with IBS and FAP as compared with control subjects.[2,6] Whether visceral hypersensitivity is a biologic marker of FGID is debated in the literature largely because no prospective study has been attempted to measure rectal sensory threshold for pain (RSTP) in a cohort of patients suffering from symptoms of abdominal pain.[7]

Chronic abdominal pain affects up to 25% of children in the community.[8] In children suffering from abdominal pain, the diagnosis of IBS and FAP is based on the use of the Rome criteria that provide clear definitions of the various FGID.[9] However, the diagnostic value of these criteria has not yet been validated, and currently the diagnosis of a FGID is made after eliminating, by means of a sometimes invasive and expensive evaluation, organic disease. In the community, an organic disease is found only in 10% of children with chronic abdominal pain.[10] This study was designed to test the hypothesis that in children with abdominal pain, RSTP is lower in patients with IBS or FAP than in patients with organic disease and that RSTP measurement is sensitive and specific for the diagnosis of FGID.

The main objective was to evaluate the sensitivity and specificity of RSTP measured with a barostat for the diagnosis of IBS and FAP, as defined by the Rome III criteria, in children with complaints of abdominal pain for more than 2 months. The secondary objective was to compare the distribution of viscerosomatic referrals and depression and anxiety scores in the FGID and organic disease groups.

CDI	Child depression inventory
CI	Confidence interval
FAP	Functional abdominal pain
FGID	Functional gastrointestinal disorders
IBS	Irritable bowel syndrome
QPGS	Questionnaire on pediatric gastrointestinal symptoms in children
ROC	Receiver operating characteristic
RSTP	Rectal sensory threshold for pain
STAIC	State-trait anxiety inventory for children

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Methods

Children aged 8 to 18 years were recruited from the tertiary care Pediatric Gastroenterology Clinic at Hôpital Sainte-Justine (University of Montreal). The included subjects reported abdominal pain (not exclusively epigastric in location) for more than 2 months. Patients with severe neurologic or muscular problems, with a history of rectocolonic surgery, with encopresis or fecal impaction, with acute enteric infection (gastroenteritis), or those unable to collaborate with the study procedures were excluded. Patients with rectal bleeding or active perineal lesions were not eligible for the barostat study and were therefore also excluded from the study. The protocol was approved by the institutional ethics committee, and appropriate consent was obtained from all participants; consent was signed by the parents or legal guardian and by the child himself/herself if 14 years or older.

The participants completed the Questionnaire on Pediatric Gastrointestinal Symptoms (QPGS), State-trait anxiety inventory for children (STAIC), and Child Depression Inventory (CDI). The QPGS is a questionnaire that was developed and validated in English and French at the Hôpital Sainte-Justine.[11] It assesses symptoms associated with FGID in children and has been adapted to the pediatric Rome III criteria.[9,12] This structured questionnaire includes sections assessing bowel habits, abdominal pain (pain duration and frequency), as well as limitations in activities (missed days of school and missed activities with friends because of pain). The STAIC is a 20-item questionnaire validated in children that assesses symptoms of anxiety. STAIC scores greater than 68 have been shown to reflect a state or trait of anxiety.[13] 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.[14] French translations of both the STAIC and CDI questionnaires have been validated in French-Canadian children.[14,15] All questionnaires were completed before the barostat procedure by the child or with the help of a parent if the child was less than 10 years old.

RSTP was measured with an electronic barostat (G & J Electronics, Toronto, Ontario, Canada), as previously described[2] and according to published recommendations.[16] After a 6-hour fasting period, a double-canal catheter of 18F diameter—on which a spherical polyvinyl bag (Mui Scientific, Mississauga, Ontario, Canada) was fixed—was inserted into the rectum. The catheter was then secured with a tape, and 5 to 10 minutes were allowed for adaptation before beginning the procedure. The barostat bag was then slowly inflated with 30 mL of air, and the pressure was allowed to equilibrate for 3 minutes. The average bag pressure during the last 15 seconds defined the individual operating pressure, which is the minimum pressure required to overcome mechanical forces and inflate the bag with 30 mL of air.

The length of the inflated bag was 11 cm, and its maximal theoretical capacity was 600 mL. Its compliance is considered infinite. The bag was checked for leaks at the beginning and at the end of each experiment. The barostat was programmed to deliver phasic intermittent stimuli starting at the individual operating pressure progressively increased in steps of 4 mm Hg lasting 60 seconds followed by 60-second deflation according to the ascending method of limits with tracking. A 4-point scale was used as a verbal descriptor for sensation felt during the barostat procedure. The rectal sensory threshold was determined by averaging the pressures at which pain had been indicated. The maximal pressure was 48 mm Hg.

When a sensation of pain was perceived by the subject, the following measures were documented: (1) Pain was quantified according to a standardized visual analog scale. (2) The localization of pain was specified with the help of a standardized measurement method.[17] Before 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. The figures were visually processed for the localization (abdominal projections, sacral projections) of the pain. (3) At the end of the barostat procedure, just before the removal of the balloon catheter, the child was asked, "Is the sensation you felt similar to what you usually feel at home?," with 4 possible answers: (1) "Yes, it is the same;" (2) "Yes, it is the same but less painful;" (3) "Yes, it is the same but more painful;" and (4) "No, it is different."

After the barostat study, the patient was followed up by his/her attending physician, who was blinded to the results of the barostat study. Supplementary investigations were done at the discretion of the attending physician. The physician, an experienced pediatric gastroenterologist, member of the Pediatric Gastrointestinal team of Sainte-Justine Hospital, had a 3-month period to monitor the patient and order more investigations to determine the origin of the symptoms. This time period makes it unlikely that an organic diagnosis would be missed.

All patients were reassessed 3 months after the barostat study to determine their final diagnosis. At this time, each subject was classified as having a FGID according to the Rome III criteria[9] assessed by the QPGS or an organic disease.

For the sample size calculation for this study, we assumed that the minimum proportion of children presenting with chronic abdominal pain who would be diagnosed with an organic disease was 10%. Also, on the basis of a previous study performed in our laboratory showing that mean (SD) RSTP was 17.9 mm Hg (9.1) in patients with IBS, 19.5 mm Hg (9.0) in patients with FAP, and 37.6 mm Hg (8.6) in control subjects,[2] we estimated a difference in the mean RSTP between the FGID and organic disease groups of 12 mm Hg, and the standard deviation was set at 9 mm Hg. With these parameters and an α level of 0.05 and study power of 80%, the estimated sample size was a total of 50 children with recurrent abdominal pain.

Appropriate descriptive statistics were used to summarize the general features of the population, questionnaire findings,

Table I. Demographics of patients

	Age (years; median, range)	M:F
Functional gastrointestinal disorder	14.4 (8.4-17.6)	19:16
IBS (n = 20)		
FAP (n = 11)		
Rome III criteria not fulfilled (n = 4)		
Organic disease	14.5 (11.2-17.4)	7:9
Lactose intolerance (n = 8)		
Crohn's disease (n = 5)		
Celiac disease (n = 1)		
Esophagitis (n = 1)		
Pancreatitis (n = 1)		

M, Male; *F*, female.

RSTP values, and final diagnoses. Comparisons between the "functional" group (IBS and FAP) and the "organic" group used the Student *t* test or Mann Whitney U test to compare means or medians, respectively, for the continuous variables, and the χ^2 or Fisher exact test for count data. Significance was expressed at the $P < .05$ level. Anxiety and depression scores were converted to dichotomous variables on the basis of previously defined cutoff values. A receiver operating characteristic curve (ROC) was used to evaluate the diagnostic value of RSTP by estimating the area under the ROC curve with a 95% confidence interval (CI). Multivariate logistic regression models were used to determine the predictive value of RSTP (dichotomous variable by use of cutoff point determined by examination of ROC), location of viscerosomatic referrals, and anxiety and depression scores with respect to the final diagnosis, FGID versus organic disease. Variables were retained in the model if their *P* value was <.05 or if they resulted in a 10% change in the estimate of the other variables (confounding effect). The fit of the model was evaluated with the Hosmer and Lemeshow test.

Results

Fifty-one patients (25 girls; median age 14.2 years, range 8.4-17.6) were included in the study. At the end of the study period, 35 patients (69%) had a FGID; 31 fulfilled the Rome III criteria (IBS, n = 20; FAP, n = 11). The remaining 4 patients did not fulfill the frequency of abdominal pain episodes criteria reporting pain as "1 per week" and not "many times a week." They fulfilled the remaining Rome criteria with regard to localization of pain, changes in stool frequency and consistence, and improvement with defecation and had "no evidence of an inflammatory, anatomic, metabolic, or neoplastic process."[9]

Sixteen (31%) had a diagnosis of an organic disease (Table I). The diagnosis of lactose intolerance was confirmed in patients with a positive lactose breath test result whose symptoms resolved completely during follow-up on a lactose-free diet. Other diagnoses (Crohn's disease, celiac disease, esophagitis, and pancreatitis) were established by appropriate endoscopic, radiologic, and biologic investigations.

Symptoms, Anxiety, and Depression

Symptom duration, intensity, limitation in activities, and STAIC and CDI scores for patients of each group are detailed in Table II (available at www.jpeds.com). As reported in other studies, 11% of patients with FGID were clinically depressed, and 51% had anxiety.[8,18] However, there were no significant differences found between patients with FGID and patients with organic disease with regard to these variables. Nevertheless, patients with an organic disease tended to report lower intensity of pain and fewer limitations in their school attendance and social activities than patients with FGID.

Barostat Results

RSTP. RSTP was similar in patients with IBS (median value 25.5 mm Hg, 95% CI 21.7-30.9), those with FAP (median value 19.5 mm Hg, 95% CI 14.5-32.5), and patients with FGID not fulfilling the Rome III criteria (median value 25.1 mm Hg, range 12-48). Patients with a FGID had a RSTP lower than children with an organic disease (median value 24.5 mm Hg, 95% CI 21.3-29.3 vs 37.1 mm Hg, 95% CI 33.9-40.3; $P < .002$) (Figure 1).

Somatic Referral of Pain Induced by Rectal Distension. Forty-six patients (32 with FGID and 14 with an organic disease) reported pain during the barostat procedure. Because previous reports have shown that phasic rectal isobaric distension in patients with FGID results in aberrant viscerosomatic projections as compared with control subjects, we sought to determine whether somatic referral varied according to final diagnosis. The localization of rectal distension–induced sensation referral is reported in Table III.

There was no difference between the 2 groups of patients regarding the proportion of children with aberrant referrals in response to rectal distension. The proportion of patients who reported a similar sensation during the barostat procedure compared with their usual sensation was also not different in the 2 groups.

Diagnostic Value of RSTP

The calculation of sensitivity and specificity for the diagnosis of FGID for different cutoffs of RSTP is reported in Figure 2. At the cutoff of 30 mm Hg, the RSTP measurement for the diagnosis of IBS and FAP had a sensitivity of 94% and a specificity of 77%, and correctly classified 82% of patients for their final diagnosis. The area under the corresponding receiver operating characteristic curve (ROC) was 0.82 (95% CI 0.72-0.94). The odds of a diagnosis of IBS or FAP was 24 times greater if the RSTP was less than 30 mm Hg (95% CI 4-127) than for a RSTP greater than 30 mm Hg.

Role of Anxiety, Depression, and Barostat-Induced Pain Characteristics. There was no significant relation between the scores of anxiety and depression and the final diagnosis (for anxiety: OR 1, $P = 0.91$, 95% CI 0.95-1.06 and for depression: OR 0.97, $P = .63$, 95%CI 0.87-1.08). Anxiety and depression did not affect the predictive value of RSTP for the final diagnosis (no confounding effect). Similarly, the location and the qualification of the pain induced by the rectal distension did not predict the final diagnosis (OR 1.03, $P = 0.95$, 95% CI 0.31-3.42) or influence the RSTP estimate.

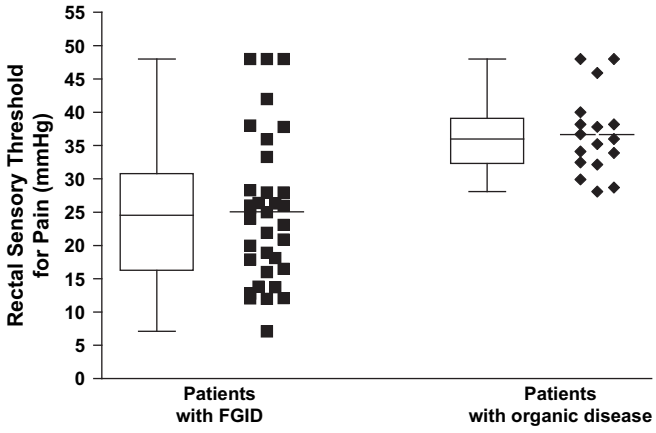

Figure 1. Rectal sensory threshold for pain (RSTP) in patients with functional gastrointestinal disorders (FGID) and patients with a final diagnosis of organic disease. Individual values are shown and, for each group, the *horizontal bar* represents the median value of each population with interquartile and 5%-95% ranges. The RSTP is lower in patients with FGID than in children with an organic disease ($P < .001$).

Discussion

We have shown that rectal sensory threshold for pain in response to phasic rectal distension is lower in children with IBS or FAP than in children with abdominal pain secondary to organic disease. More importantly, we have demonstrated that a RSTP value of 30 mm Hg or less is a sensitive and specific test for the diagnosis of functional gastrointestinal disorders in children prospectively evaluated for chronic abdominal pain. We also show that in children with chronic recurrent abdominal pain, irrespective of the origin of the symptoms, viscerosomatic referral of pain induced by phasic rectal distensions is not different between children with functional or organic disorders.

This study was a prospective evaluation of the utility of the rectal barostat procedure in the work-up of patients with chronic abdominal complaints. Bouin et al[19] have reported a large retrospective series of 86 adult patients with IBS and examined the sensitivity and specificity of rectal barostat procedures with phasic distensions for separating patients with IBS from 25 healthy control subjects and other patients with functional constipation (n = 25), those with functional dyspepsia (n = 21), and 31 patients with miscellaneous conditions that included only 7 subjects with an organic disease. They found an 80% specificity and a 90.7% sensitivity at a threshold of 40 mm Hg for separating IBS and control subjects.[19] We have reported similar results in a study comparing children aged 10 to 17.6 years with IBS or FAP with healthy control controls: at 30.8 mm Hg, the fifth percentile for the control subjects, the RSTP had a sensitivity rate of 89% and a specificity rate of 83% for IBS and FAP diagnosis.[2] However, in both of these studies patients were initially recruited and classified into subgroups according Rome criteria and the comparisons of rectal sensory thresholds were made between homogeneous diagnostic groups. Here we report the diagnostic value of the rectal barostat procedure, in which we evaluated the subjects with rectal barostat before the patients' diagnosis of a functional or organic disease.

Whether the determination of rectal sensitivity is a reliable biological marker of IBS is debated in the literature because the reporting of the sensation by the subject is influenced by several psychological and/or organic parameters that could lead to a non linear relationship between the actual stimulus and the reported perception.[1] To be a reliable biologic marker, rectal sensitivity as measured by barostat should encompass several characteristics, namely it should (1) have a high sensitivity and specificity; (2) be proportional to the measured symptoms/disease; (3) vary proportionally with the efficacy of treatments; and (4) be predictive of response to treatment. This study brings a definitive answer to the first assessment. Because this study was powered and designed to measure the sensitivity, specificity and effectiveness of the rectal barostat, we were not able to definitely demonstrate a correlation between RSTP and symptom severity in patients with FGID. However, several other groups have recently reported the relationship between visceral hypersensitivity and pain[6] and bloating[20] in adults with IBS and in children with functional dyspepsia.[21] The effect of drugs on visceral sensitivity remains controversial because some drugs provide an improvement in hypersensitivity, and others, although effective, do not modify the sensory threshold.[1,22] Previously, it was demonstrated that patients with visceral hypersensitivity may respond differently to treatment compared with subjects with normal visceroperception.[23,24]

Is visceral hypersensitivity a more reliable marker in children than in adults? This study clearly demonstrates that rectal sensitivity measurement is highly sensitive and specific for IBS and FAP in children. In adults, visceral hypersensitivity is considered a hallmark of IBS, but its prevalence varies from 20%[25] to 94%[26] across studies. Conversely, previous reports in children show that rectal hypersensitivity is found in 75%[4] to 100%[3] of patients with IBS, suggesting that FGID are less heterogeneous in children than in adults. This could be due to the protracted history of FGID in adults that may affect and alter the initial pathophysiological mechanisms. Further studies in children are warranted to confirm this hypothesis and further validate rectal hypersensitivity as a biomarker of IBS and FAP.

Surprisingly, we found that abnormal viscerosomatic referrals were reported similarly by the subjects irrespective of their final diagnosis. Previous studies have reported that in control subjects without any gastrointestinal complaints, rectal isobaric distension provokes sensations mainly referred to the S3 dermatome (perineal area), and most patients with IBS refer their sensation to aberrant sites (abdominal projections to dermatomes T8 to L1).[2,26] We hypothesize that subjects with protracted complaints of abdominal pain not related to FGID may have a normal visceral sensitivity but in contrast to "true" control subjects may have an abnormal

Table III. Characteristics of pain induced by phasic rectal distension in patients reporting pain during the barostat procedure

	Functional gastrointestinal disorders (n = 32)	Organic diseases (n = 14)
Abdominal referral, n (%)	26 (81%)	11 (79%)
Sacral referral, n (%)	6 (19%)	3 (21%)
VAS mean (SD)	6.2 (1.9%)	5.2 (2.5)
Reproduction of pain		
Yes, n (%)	22 (69%)	9 (64%)
No, n (%)	10 (31%)	5 (36%)

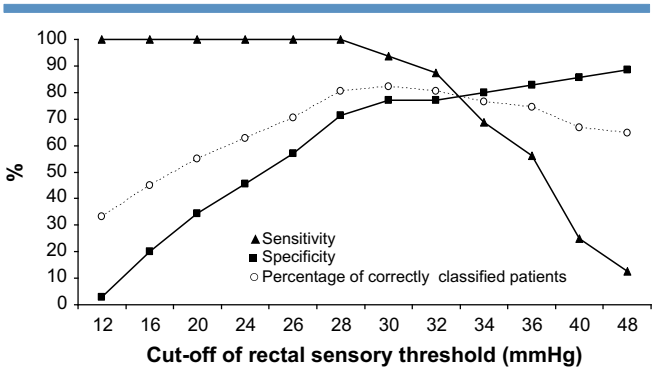

Figure 2. Sensitivity and specificity of rectal sensory threshold for pain measurement for diagnosis of irritable bowel syndrome and functional abdominal pain in children and percentage of correctly classified patients (functional gastrointestinal disorder or organic disease) after measurement of rectal sensory threshold for pain. Values are depicted for each cutoff of pressure distension tested.

perceptual response to distension (ie, abnormal interpretation and sensation in response to rectal distension). Dorn et al have reported that the perceptual response was abnormal in IBS patients compared with controls but no data are currently available on perceptual response in patients with organic complaints.[27] Another hypothesis is that dysregulation of afferent nociceptive pathways involved in the visceral sensation in response to rectal distension may result from the chronic abdominal pain.[28,29]

Anxiety and depression are frequently associated with FGID.[30] However, in this study, although the incidence of anxiety (~50%) and depression (~11%) in children with FGID was similar to that previously reported,[18,30] we did not find any differences in anxiety and depression scores between patients diagnosed with FGID or organic disease. In fact, significant anxiety and depression may also occur in children with chronic pain, or chronic conditions such as IBD, asthma, and sickle cell disease,[30-34] making psychological evaluation a poor predictor of the diagnosis of FGID.

One limitation of our study is the absence of a standardized procedure for the evaluation of the study participants. All participants were evaluated as per the study protocol (medical interview and physical examination, questionnaires, and barostat procedure). More invasive investigations were not included in the protocol primarily because of ethical concerns. Therefore supplementary procedures were performed at the discretion of the treating physician. The physician, an experienced pediatric gastroenterologist and a member of the pediatric gastroenterology team, had a 3-month period to monitor the patient and order more investigations, making it unlikely that an organic diagnosis was missed.

Another significant limitation of our study is its vulnerability to tertiary center bias. All participants were recruited from a tertiary pediatric center and therefore may be at the more severe end of the spectrum of FGID disorders. If this is related to increased visceral hypersensitivity, it may result in an overestimation of the difference in RSTP values between organic and functional diseases. In this tertiary referred population of children with chronic abdominal pain, 35 of 51 patients (68%) had a diagnosis of FGID, which is in keeping with previous studies at our center.[35] However, we can not conclude that these findings are generalizable to all patients in the community. These findings are not applicable to patients with abdominal pain exclusively located to the epigastric area, because previous reports have shown that patients with functional dyspepsia have normal rectal sensory thresholds for pain. We report that among the 35 patients with FGID, 4 of them did not strictly fulfill the Rome III criteria; these 4 subjects reported a frequency of pain episodes of "1 per week," but the Rome III criteria require "many times a week." All the other criteria (localization of pain, changes in stool frequency and consistence, and improvement with defecation) were met for the diagnosis of IBS (n = 3) or FAP (n = 1). This is similar to the 11% of FGID unclassified by Rome III criteria found in another report.[36]

What could be the role of RSTP measurement in clinical practice? By providing an objective criterion in addition to the clinical symptoms of IBS or FAP, the determination of a low RSTP may give a pathophysiological explanation to children and their parents, making it possible for them to understand the nature and mechanisms of the symptoms. This may be helpful to reassure patients, their parents, and physicians by confirming the clinical symptom–based diagnosis of IBS or FAP. On the other hand, children with IBS or FAP symptoms with a normal RSTP should be carefully reexamined to exclude other diagnoses. Further studies should be undertaken to assess whether RSTP measurement impacts the outcome of patients with FGID, specifically procedures ordered by the physician, long-term prognosis, and response to drugs. ■

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Table II. Symptom severity variables in the study population

	Functional gastrointestinal disorders (n = 35)	Organic diseases (n = 16)
Pain frequency		
≤Once a week	4 (11%)	5 (31%)
Many times a week	19 (54%)	8 (50%)
Everyday	12 (34%)	3 (19%)
Duration of pain		
2-3 months	1 (3%)	0 (0%)
4-11 months	12 (34%)	8 (50%)
≥ 1 year	22 (63%)	8 (50%)
Description of pain*		
"A little"	1 (4%)	4 (29%)†
From "a little" to "a lot"	4 (15%)	5 (36%)
"A lot"	22 (82%)	5 (36%)
Duration of pain episodes*		
0-4 hours	16 (59%)	11 (79%)
Most of the day	5 (19%)	3 (21%)
≥ 1 day	6 (22%)	0
Missed days of school		
Never or <once/month	10 (29%)	9 (56%)
1-4 times/month	11 (31%)	6 (38%)
Many times a week	14 (40%)	1 (6%)†
Missed social activities		
Never or <once/month	12 (34%)	11 (69%)†
1-4 times/month	17 (49%)	4 (25%)
Many times a week	6 (17%)	1 (6%)
STAIC score (median, 25th-75th percentile)	70 (60-78)	70 (61-76)
STAIC >68	18 (51%)	8 (50%)
CDI score (median, 25th-75th percentile)	10 (5-13)	9 (4-17)
CDI >17	4 (11%)	3 (19%)

*Data available for 27 patients with FGID and 14 patients with organic disease.
†$P < .01$ versus patients with FGID (Fisher's exact test); no correction for multiple testing.