Somatic Referral of Visceral Sensations and Rectal Sensory Threshold for Pain in Children with Functional Gastrointestinal Disorders

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Objective To test the hypothesis that abdominal pain related to functional gastrointestinal disorders is associated with visceral hypersensitivity and abnormal perception of visceral sensations.

Study design We examined 35 children (10-17.6 years old) fulfilling the Rome II criteria with irritable bowel syndrome (IBS; n = 21), functional abdominal pain (FAP; n = 8) or functional dyspepsia (FD; n = 6) compared with 10 control subjects (10.2-16.1 years). All underwent a rectal barostat examination. Painful sensations were reported on a human body diagram. The projections of sensations induced by rectal distension, the rectal sensory threshold for pain (RSTP) and the diagnostic value of RSTP measurements were measured.

Results Rectal distension induced sensations that projected to the S3 dermatome in the control subjects and FD and to aberrant sites in children with IBS and FAP. The RSTP was decreased in children with IBS and FAP compared with control subjects ($P < .002$) and was not different in children with FD compared with control subjects. At 30.8 mm Hg, the 5th percentile for the control subjects, the RSTP had a sensitivity rate of 89% and a specificity rate of 83% for IBS and FAP diagnosis.

Conclusion Children with IBS and FAP are characterized by the association of rectal hypersensitivity and abnormal pain referral after rectal distension. *(J Pediatr 2007;150:66-71)*

Functional gastrointestinal disorders (FGD), defined as recurrent symptoms unexplained by structural or biochemical anomalies, constitute a frequent problem in the pediatric population, affecting 15% of school-age children.[1,2] These disorders have important repercussions on the quality of life of patients and their family.[3-6]

The establishment of the Rome II criteria in 1999 represented major progress in the definition and diagnosis of FGD in children.[7] These symptom-based criteria identify the various clinical patterns encountered, namely irritable bowel syndrome (IBS), functional abdominal pain (FAP), and functional dyspepsia (FD).[8]

The role of anomalies of visceral sensitivity in FGD is well described in adults.[9] Numerous studies with the barostat have demonstrated rectal hypersensitivity in IBS; >70% of adult patients have a rectal pain threshold lower than control subjects.[10-12] Visceral hypersensitivity has been shown to be "organ-specific," with a low rectal sensitivity threshold in patients with IBS,[10-12] a low gastric sensitivity threshold in patients with FD,[13-15] and "diffuse" hypersensitivity in patients with both IBS and FD.[16] Two studies have evaluated visceral sensitivity in children with abdominal pain related to IBS and FAP; both studies found a subset of children with a low rectal sensory threshold for pain (RSTP).[17,18]

In addition to anomalies of visceral sensitivity, other studies suggest that the perception of painful abdominal sensations in adult patients with FGD differs from that in control subjects. During the inflation of a balloon in different parts of the colon, patients with IBS describe pain that is more diffuse and more often referred to extra-intestinal sites.[12,19,20]

This study was designed to test the hypotheses that: 1) rectal distension induces abnormal somatic projections in children with FGD; 2) the RSTP is low in children with

CDI	Child depression inventory	RAP	Recurrent abdominal pain
FAP	Functional abdominal pain	RSTP	Rectal sensory threshold for pain
FD	Functional dyspepsia	STAIC	State-trait anxiety inventory for children
FGD	Functional gastrointestinal disorders	VAS	Visual analog scale
IBS	Irritable bowel syndrome		
QPGS	Questionnaire on pediatric gastrointestinal symptoms in children		

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IBS and FAP, but not in children with FD compared with control subjects; and 3) RSTP measurements may help to confirm positively the diagnosis of IBS and FAP in children.

Our aims were therefore to evaluate the projections of the sensations induced by rectal distension in children with IBS, FAP, and FD in comparison to control children and to assess the reproducibility of pain by rectal distension in these children with IBS, FAP, and FD.

METHODS

Patients

Children aged 10 to 18 years were recruited from the tertiary care Pediatric Gastroenterology Clinic at Hôpital Sainte-Justine (University of Montreal, Montreal, Quebec, Canada). They had digestive symptoms of IBS, FAP, or FD according to the pediatric Rome II criteria.[7] Patients with severe psychiatric, neurological, or muscular problems, with a history of recto-colonic surgery, with encopresis or fecal impaction, or who were unable to collaborate to the study were excluded. All medications affecting pain or gastrointestinal motility were discontinued at least 48 hours before the barostat study.

Control Subjects

Eight children were recruited as control subjects from among the patients' siblings. None of them reported any gastrointestinal symptoms. Two girls with proven lactose intolerance and complete resolution of symptoms on a lactose-free diet were also included in the control group.

Ethical Considerations

The protocol was approved by the institutional ethics committee, and appropriate consent was obtained for the patients and control subjects. Consent was signed by the parents or legal guardian when the child was younger than 14 years and by the child when the child 14 years or older.

RSTP Measurement

RSTP was measured by means of an electronic barostat (G & J Electronics, Toronto, Ontario, Canada), according to published recommendations.[21] 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 tape, and 5 to 10 minutes were allowed for adaptation before beginning the procedure. The inflated bag was 11 cm long, and its maximal theoretical capacity was 600 mL. Its compliance is considered infinite. The bag was checked for leaks at the beginning of each experiment. The barostat was programmed to deliver phasic intermittent stimuli lasting 60 seconds, followed by a 60-second deflation according to the ascending method of limits with tracking. The starting pressure was 2 mm Hg, and the maximal pressure was fixed at 48 mm Hg. The rectal sensory threshold was established by averaging the pressures at which pain was reported by the subject during tracking.

Evaluation of Pain

When a sensation of pain was perceived by the patient, three precisions were targeted.

1) Quantification of pain—pain was quantified according to a standardized visual analog scale (VAS).[22]
2) Localization of pain—the localization of pain was specified with the help of a standardized measurement method described and validated in children by Savedra.[23] 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 scanned and processed for the measurement of areas of colored zones and the calculation of reproducibility between pain felt at home and pain felt during the barostat procedure. Colored areas were measured and quantified with ImageJ software (http://rsb.info.nih.gov/ij). Values are presented in pixels. An index of reproducibility was calculated by determining the percentage of similarity between pre- and per-barostat figures. The abdomen in each figure is divided in 9 squares, and when 1 square is colored pain is considered to be located in the zone delimited by that square. Pre- and per-barostat colored squares were compared for each patient, and the percentage of similarity was calculated as: total number of squares similarly colored on pre- and per-barostat figures/total number of colored squares on pre-barostat figure.
3) Qualification of pain—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?"

Questionnaires

The Questionnaire on Pediatric Gastrointestinal Symptoms in Children (QPGS) is used to evaluate the symptoms of FGD in children. The QPGS was developed and validated in English and translated to French at the Hôpital Sainte-Justine.[24] Form C was conceived for children aged 10 and older. We used questions linked to IBS, FAP, and FD and those concerning the impact of the disorder on everyday functioning (Form C-S).

The state-trait anxiety inventory for children (STAIC) provides scores reflecting the anxiety in everyday life.[25] Anxiety is measured in 2 components: state of anxiety and trait of anxiety. A French version of the STAIC validated in French-Canadian children is available.[26] For each component, a score >34 reflects a state or trait of anxiety.[26] The child depression inventory (CDI) provides scores reflecting the depression characterizing children in everyday life.[27] A French-Canadian

Table. Demographics of patients and control subjects

	Median age in years (range)	M:F ratio	Mean duration of symptoms in years
Patients with IBS	15.6 (10-17.6)	6:15	3.1
Patients with FAP	13.75 (10.3-17)	2:7	2.2
Patients with FD	15.7 (10.3-16.4)	2:4	1.3
Control subjects	13.7 (10.2-16.1)	6:4	-

M, Male; *F,* female.

version of the CDI is available.[28] A score >17, which is the 90th percentile of the healthy pediatric population, is predictive of clinical depression.[28] All questionnaires were administered before the barostat procedure.

Statistics

Values are expressed as median and range or 95%CI. Kruskal-Wallis 1-way analysis of variance with Dunn's multiple comparison was used for the comparison of variables in the IBS, FAP, and FD patient groups. The Student *t*-test was applied for continuous variables (RSTP, index of reproducibility, STAIC, CDI). To compare percentage values between different groups, we used a χ^2 test or Fisher exact test. Spearman's test correlated the different variables. Significance was expressed at the $P < .05$ level.

RESULTS

Clinical Characteristics

Thirty-five children, 21 of whom fulfilled the Rome II criteria for IBS, 8 for FAP, and 6 for FD, were included in the study (Table). The presence of the Rome II criteria was confirmed by the symptoms reported in the QPGS. There was no significant difference in age between the 3 groups of patients and the control subjects. In all groups of patients, girls were represented more than boys. However, in the control group, the sex ratio (M:F) was inverted ($P < .05$).

RSTP in Children with IBS, FAP and FD

RSTP was lower in patients with IBS (median value, 16 mm Hg; 95%CI, 13.7-22.1) and FAP (median value, 19.5 mm Hg; 95%CI, 11.9-27.1) than in control children (median value, 42 mm Hg; 95%CI, 34.6-46.3; $P < .002$ versus IBS and $P < .001$ versus FAP; Figure 1). Eighty-five percent (95%CI, 69-100) of patients with IBS and 88% (95%CI, 63-100) of patients with FAP had a RSTP ≤30.8 mm Hg, the 5th percentile of control children.

Children with FD had a RSTP similar to that of control children (median value, 41.5 mm Hg; 95%CI, 16.7-51.7; Figure 1).

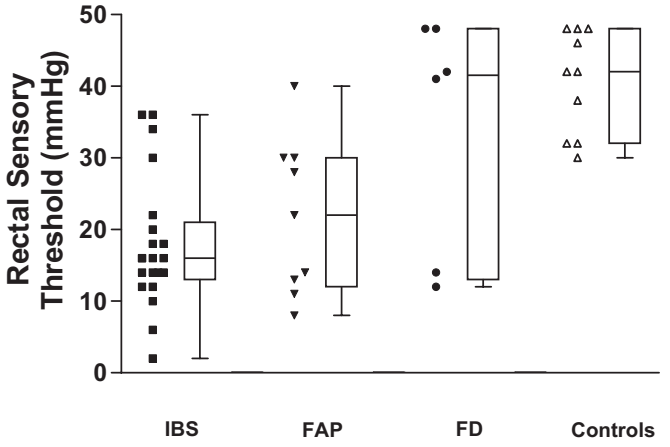

Figure 1. RSTP in patients with IBS, FAP, and FD and in control children. Individual values are shown, and, for each group, the horizontal bar represents the median value of each population with interquartile and 5% to 95% ranges. The RSTP is lower in patients with IBS or FAP than in control children ($P = .002$ and $P = .001$).

Somatic Referral and Characteristics of Pain Induced by Rectal Distension in Children with IBS, FAP, and FD

In all control subjects, rectal distension-induced sensations referred to the S3 dermatome (perineal area). In 5 of 6 children with FD, the sensation referred to the S3 dermatome.

In children with IBS and FAP, although in 4 patients the sensation referred partly to the S3 dermatome, the sensation of all 29 patients referred to aberrant sites compared with that of the control subjects (ie, with abdominal projections to dermatomes T8 to L1).

In patients with IBS, the value of the area colored during rectal distension was lower than the area representing the pain experienced at home (median value, 38,450 pixels; 95%CI, 32,240-60,000 versus 18,100 pixels, 95%CI, 15,740-41,750; $P = .002$). A strong correlation was found, however, between values of the colored area reported by the patients with IBS at home and those reported during the barostat procedure ($r = 0.7$, $P = .0004$).

The RSTP did not correlate with the value of the area colored for representation of the pain at home or during the barostat in patients with IBS, FAP, and FD.

There was no difference in the quantification of pain experienced during rectal distension on the VAS between patients with IBS (median value, 5.25; 95%CI, 3.8-5.8), FAP (median value, 4.5; 95%CI, 3.4-6.5), or FD (median value, 5.0; 95%CI, 0.4-8; $P > .05$).

No correlation was evident between the RSTP and pain intensity measured with VAS in any of the 3 patient groups.

Reproducibility of "Home" Pain by Rectal Distension

Ninety percent (20/22 patients) of the children with IBS and 87.5% (7/8 patients) of the children with FAP reported that the sensation they felt during the barostat pro-

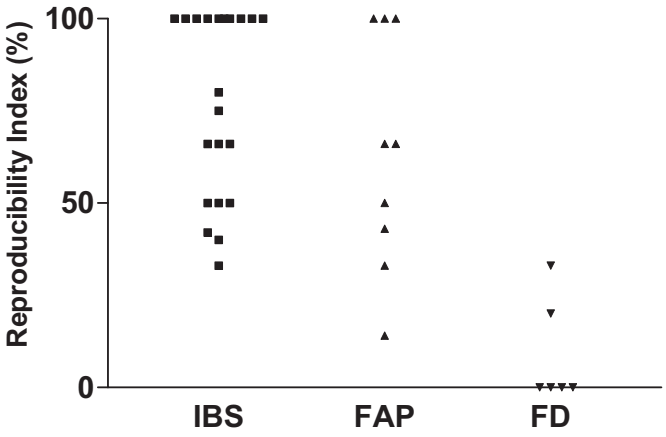

Figure 2. Individual values of reproducibility index (see text for definition and calculation) in patients with IBS, FAP, and FD. The index was higher in the children with IBS and FAP than in children with FD (P = .003 and P = .005).

cedure was the same as the pain they usually experienced at home. Conversely, only 1 in 6 children with FD reported experiencing the same sensation at home and during the barostat experience.

The index of reproducibility was higher in children with IBS (median value, 80%; 95%CI, 65.7-88.3; P = .003 versus children with FD) and FAP (median value, 66%; 95%CI, 39.2-87.2; P = .005 versus children with FD) than in children with FD (Figure 2).

Diagnostic Value of RSTP Measurement in IBS and FAP

At 30.8 mm Hg, the cutoff value corresponding to the 5th percentile of the RSTP in the control subjects, the RSTP measurement for the diagnosis of IBS and FAP had a sensitivity rate of 89% (95%CI, 77-100), a specificity rate of 83% (95%CI, 40-100), a positive predictive value of 96% (95%CI, 88-100), and a negative predictive value of 55% (95%CI, 15-96).

All patients with IBS and FAP except 1 were affected by rectal hypersensitivity, which associates at least 2 of these 3 features: RSTP <30 mm Hg; ectopic viscero-somatic referral of the pain induced by rectal distension; and reproduction of the usual pain reported by the patient interview, the index of reproducibility >66%, or both.

Role of Anxiety

Forty-eight percent of the patients had a state score indicating significant anxiety at the moment of the procedure, and 47% of the patients had a trait score considered as indicative of anxiety (scores >34).[26]

To assess the role of anxiety in rectal sensitivity, we examined the correlation between the RSTP and the anxiety scores. The value of the RSTP was not correlated to the STAIC score as a whole (r = 0.16; P = 0.38). We separately analyzed the 2 components of the STAIC score; no correlation was seen with both the state of anxiety (r = 0.07; P = .67) and the trait of anxiety (r = 0.18, P = .3).

No correlation was found between STAIC scores and the values of the area colored on the human body diagram pre and per-barostat in patients with IBS, FAP or FD.

Role of Depression

Two patients with IBS and 1 patient with FAP presented a CDI score indicative of depression (>17, or the 90th percentile according to Saint-Laurent[28]). Overall, the CDI score did not correlate with the RSTP (r = −0.15, P = .37).

No correlation was observed between the CDI score and the values of the area colored on the human body diagram pre and per-barostat in patients with IBS, FAP, or FD.

DISCUSSION

This study demonstrates that in children with IBS, FAP, or FD, as defined by Rome II criteria: 1) isobaric phasic rectal distension induces sensations that are different according to the different types of FGD; 2) phasic rectal distension induces a sensation similar to the usual pain in patients with IBS or FAP; 3) a low RSTP is highly suggestive of the diagnosis of IBS and FAP in children; and 4) in children the RSTP is lower in patients with IBS or FAP than in control subjects, and not different from the control subjects in patients with FD.

Visceral hypersensitivity is thought to have an important role in the pathophysiology of FGD in adults. Numerous studies have confirmed the notion of organ-specific visceral hypersensitivity in adult patients with FGD.[10-12,29-32] Van Ginkel et al examined with rectal barostat 16 children with FGD according to Rome II criteria, 8 children with IBS, 8 children with FAP, and 9 healthy control subjects.[17] They found that the RSTP was significantly reduced in children with IBS compared with children with FAP and healthy control subjects; 100% of the patients with IBS had a low RSTP. Di Lorenzo et al[18] used a rectal and gastric barostat in patients with IBS and patients with recurrent abdominal pain (RAP) according to the Apley criteria.[1] Although RSTP values are not reported in this study, patients with IBS and RAP had a threshold of pain perception lower than the control subjects at the rectal level. In our study, patients with IBS and FAP had a low RSTP compared with control subjects, but no significant difference was found between patients with IBS and patients with FAP. In children with FD, the RSTP is similar to that of control children, suggesting that in FGD the visceral hypersensitivity is "organ-specific" in children similar to how it is in adults.

This study indicates that the processing of sensation caused by rectal distension varies according to the different subtypes of FGD in children. We show that phasic rectal isobaric distension results in aberrant viscero-somatic projections on dermatomes different from S3, namely T8 to L1, in children with IBS or FAP, but not in children with FD. These results indicate that, in children, the mechanisms involved in the processing of painful sensation could follow

common pathways in IBS and FAP, but are different in FD. The absence of correlation between the level of the RSTP and the value of the area indicated during rectal distension also suggests that, at least in patients with IBS and FAP, rectal hypersensitivity and the abnormal projections of sensation may be related to different pathophysiological mechanisms. Abnormal somatovisceral projections have also been demonstrated in adults with IBS after colonic,[19] rectal,[12,20,33,34]or jejunal distension.[35] Phasic rectal distension excites local peripheral mecanoreceptors that induce viscero-somatic sensations. The viscero-somatic sensations involve splanchnic afferents that project to the thoraco-lumbar spinal cord[20] where visceral and somatic sensory neurons converge onto the same spinal sensory neurons.[36] Afferent nociceptive pathways include the spinomesencephalic, spinoreticular, and spinothalamic tracts, which project to midcingulate cortex, anterior cingulated cortex, and primary somatosensory cortex, respectively.[36,37] The spinothalamic pathway is important for sensory discrimination and localization of visceral and somatic stimuli.[38] Precise mechanisms involved in visceral hypersensitivity and in abnormal referrals of visceral sensations are unknown, but may involve sensitization of enteric neurons, sensitization of spinal cord neurons, abnormal modulation in ascending pathways, or abnormal integration at the cortical level. Descending inhibitory influx is also crucial in the modulation of the sensation of pain in patients with IBS.[39,40]

Anxiety disorders and anxiety scores were found to be significantly higher in children with RAP[41] or adolescents with IBS-like symptoms in a community-based study.[42] Whether the state of anxiety has a specific influence on the assessment of visceral sensitivity is important because some authors have demonstrated that the results of the measurement of visceral sensitivity are influenced by stress.[9,43] We separately assessed a state scale (ie, transitory anxiety reaction to particular situations) and a trait scale (ie, a stable predisposition to react anxiously, regardless of the situation).[26] We found that the RSTP did not correlate with the state of anxiety, suggesting that the anxiety generated by the procedure itself was not sufficient to bias the child's response to distension. We also show that the score measured on the trait scale of anxiety is not correlated to the level of the RSTP in our patients, similar to several studies in adults.[12,33,44] However, we confirmed the very high incidence of anxiety disorders in the population of children with abdominal pain-related FGD. The incidence of depression was also similar to the 8% to 10% of children reported by Hyams et al,[42] but we did not find any correlation between the RSTP and CDI score. Whether psychological factors, such as anxiety disorders or depression, are a cause (ie, a marker of vulnerability) or a consequence of visceral hypersensitivity in children requires further investigation.

Potential weaknesses of our study include the small number of children in the control group because of the difficulty of recruiting healthy children for such invasive studies. Second, most of the control subjects were recruited from the patients' siblings. This may introduce bias because genetic and environmental factors have been shown to influence the development of IBS.[45] Third, we included in the control group 2 children with lactose intolerance, the symptoms of which resolved completely during follow-up on a lactose-free diet. These children were thus not affected by FGD and could be considered to be control subjects because patients with lactose intolerance have been shown to have similar tolerance for rectal distension as control patients.[10]

In this study, we show that the determination of the RSTP has high sensitivity and specificity rates for the diagnosis of IBS and FAP in patients referred to a tertiary care center. Whether the determination of rectal sensitivity is a reliable biological marker of IBS is debated in the adult literature.[46,47] By providing a positive 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. However, children with IBS or FAP symptoms with a normal RSTP should be carefully re-examined to exclude any other diagnosis. One could suggest that a low RSTP in children with IBS or FAP reflects the state of intestinal "dysalgesia" that may be influenced by numerous factors, such as stress, attention to gastrointestinal sensations, and disease attribution, all of which may vary during periods of life according to the familial context, social learning, and reinforcement by parents.

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