Towards an integrated psychoneurophysiological approach of irritable bowel syndrome

Veek, P.P.J. van der

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SYMPTOM SEVERITY BUT NOT PSYCHOPATHOLOGY PREDICTS VISCERAL HYPERSENSITIVITY IN IRRITABLE BOWEL SYNDROME

Patrick P.J. van der Veek[1], Yanda R. van Rood[2], and Ad A.M. Masclee[1]

Departments of [1]Gastroenterology and Hepatology and [2]Psychiatry, Leiden University Medical Center, Leiden, The Netherlands

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ABSTRACT

Background & Aims: Visceral hypersensitivity is a hallmark of irritable bowel syndrome (IBS), but the relationship with clinical symptoms and psychological factors has not been fully established. We aimed to 1) evaluate these variables in a large cohort of IBS patients, recruited from both hospital and general practice, and in healthy controls; 2) assess which of these factors predicts the occurrence of visceral hypersensitivity in IBS.

Methods: Rectal compliance and perception (intensity, perception thresholds; VAS 0-100 mm) were assessed by a rectal barostat study (ramp distension) in 101 IBS patients and 40 healthy volunteers. IBS symptom severity was scored using a 14-day 5-item diary. Anxiety, depression, somatization, vigilance, pain coping, dysfunctional cognitions, psychoneuroticism, and quality of life were assessed using psychometric questionnaires.

Results: Rectal compliance was significantly reduced in IBS patients compared to controls ($P<0.01$), as were thresholds for pain (27 ± 15 vs. 35 ± 8 mmHg; $P<0.01$) and urge ($P<0.05$). Levels of anxiety, depression, neuroticism, somatization and dysfunctional cognitions were significantly increased in IBS patients vs. controls while pain coping and quality of life were significantly worse. Hypersensitivity to rectal distension occurred in 33% of patients and was associated with increased symptom severity ($P=0.016$), but not with demographical characteristics or psychological disturbances.

Conclusion: Hypersensitivity to balloon distension occurs in 33% of IBS patients and is predicted by symptom severity but not by psychological or demographical characteristics.

INTRODUCTION

Irritable Bowel Syndrome (IBS) is characterized by recurrent abdominal discomfort or pain and disturbed bowel habits[1]. Several pathophysiological mechanisms have been suggested in symptom generation, including altered intestinal motility[2], autonomic dysfunction[3,4], inflammation[5,6], and immune system alterations[6-8]. Particularly, visceral hypersensitivity appears to play an important role[9,10] and has been proposed as a biological marker of IBS[11].

Visceral hypersensitivity may result from disturbances at different levels of the brain-gut axis, in which peripheral sensitization of intestinal nerve endings[12], hyperexcitability of spinal dorsal horn neurons[13] and altered central processing of visceral afferent information[14] are implicated. Abnormalities in regional brain activation, especially in areas involved in pain processing such as the anterior cingulated cortex and thalamus, have been reported in IBS patients in response to rectal balloon distension[15]. These regions belong to the emotional limbic system and are involved in psychological and cognitive events[16,17].

IBS symptomatology is associated with psychological factors and these may affect clinical outcome[18]. For instance, psychological distress is more prevalent among IBS patients who seek health care[19]. Little is known about the relationship between psychological variables and visceral hypersensitivity. Such information is relevant because it may provide a better understanding of the pathogenesis of IBS and its treatment. The few studies that explored this relationship have been criticized because of methodological shortcomings such as sample size and patient selection (tertiary referrals)[9,11,19].

The aims of the present study were to 1) explore in a large cohort of IBS patients the prevalence of rectal hypersensitivity, levels of psychological distress and IBS symptom severity, and 2) assess which demographical, clinical and psychological variables predict the occurrence of visceral hypersensitivity in IBS.

METHODS

Participants

This study was part of a large randomized controlled trial of psychological treatment in IBS, the results of which will be published elsewhere. IBS patients between 18 and 65 years of age were invited to participate. Baseline evaluation included detailed psychological assessment, rectal barostat measurements and IBS symptom severity scores.

To obtain a representative sample from the IBS population, patients were recruited from both the hospital IBS population (patients referred to the outpatient Department of Gastroenterology of the Leiden University Medical Center) and from the general population through local advertisement. Healthy volunteers were recruited through advertisement for comparison with the patient sample. All eligible participants were screened by one of the investigators (PvdV). Each patient met Rome II criteria for IBS[1]. Exclusion criteria were organic disease, previous abdominal surgery (except cholecystectomy and appendectomy), and pregnancy. Use of antispasmodics, laxatives, bulking agents and occasional use of analgesics was permitted. We used the Mini International Neuropsychiatric Interview (Dutch version 5.0.0)[20] to exclude patients with severe psychopathology (psychosis or risk of suicide). Informed consent was obtained from each participant. The Leiden University Medical Center ethics committee had approved the study protocol.

Barostat

An electronic barostat (Synectics Visceral Stimulator, Synectics Medical, Stockholm, Sweden) was used to assess rectal compliance and perception. This device measures rectal motor activity as volume changes in a rectal balloon, in which constant pressure is maintained by injecting air when the rectal wall relaxes and aspirating air during rectal contraction. Intrabag pressure is directly measured via a separate lumen. Maximal airflow is 38 mL/s. Pressure and volume are continuously monitored and recorded on a personal computer (Polygram for Windows SVS module, Synectics Medical, Stockholm, Sweden).

Visceroperception

Perception of urge to defecate and abdominal pain during rectal distension was quantified on a 100-mm Visual Analogue Scale (VAS). End points ranged from 'none' to 'intolerable'.

Demographical characteristics

The demographical group characteristics of interest were age, sex, and level of health care (general practice or referral).

Symptom severity

Patients and controls rated the severity of any abdominal discomfort, abdominal pain, constipation, diarrhea, and bloating, daily for 14 days, on a 5-point Likert scale (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe symptoms) using a symptom diary card. A composite score was computed by summing up the 14-day mean scores for each symptom (range 0-20).

Psychological assessment

A battery of questionnaires was administered to both IBS patients and control subjects to determine the following psychological characteristics of each group.

Anxiety and depression. We the used the Symptom Checklist 90 (SCL-90) to measure levels of anxiety (10 items) and depression (16 items). The SCL-90 is a validated survey and consists of 90 items addressing a range of physical and psychological problems[21].

Psychoneuroticism. The level of psychoneuroticism was determined by summing up all 90 items of the SCL-90.

Somatization. We used the abridged Dutch version (NVM) of the Minnesota Multiphasic Personality Inventory (MMPI) to measure somatization, which is 1 of 5 subscales on this questionnaire[22].

The role of the abovementioned psychological factors in IBS has been studied previously[9,10,19]. In addition, we considered the following psychological variables relevant, as they may confound the abovementioned determinants:

Vigilance. We used the previously validated 10-item Somatosensory Amplification Scale (SAS)[23] to determine the extent to which an individual is likely to report enhanced perception of physical symptoms (i.e. lower cognitive perception thresholds).

Cognitions. The recently developed 31-item Cognitive Scale for Functional Bowel Disorders (CSFBD) was used to measure patients' levels of dysfunctional cognitions concerning their IBS[24].

Pain coping. Pain coping was measured by 1 of 4 subscales of the Pain Coping and Cognition List (PCCL). This inventory has been widely used in The Netherlands and awaits future validation. Patients were asked to rate the extent to which they agreed with 11 statements concerning pain coping on a 7-point scale, ranging from "I completely disagree" to "I completely agree".

Somatic symptoms. The SCL-90 was also used to record non-IBS-related somatic symptoms. There are 12 items concerning general complaints, including headache, vertigo, backache, myalgia, difficulties with breathing, intolerance for high or low temperatures, dysphagia, etc.

Quality of life. Quality of life was assessed using the validated SF-36 questionnaire[25]. This survey measures quality of life in 8 domains, i.e. physical functioning, social functioning, role limitations due to physical problems and emotional problems, mental health, vitality, bodily pain and general health.

Experimental design

A small standardized, low caloric breakfast was permitted at 8.00 AM on the day of the barostat recordings. After arrival at our department at 10.00 AM, subjects filled

out all questionnaires consecutively. Each participant was allowed the necessary time to complete the questionnaires, which took 80-90 min on average.

After completion, the rectum was evacuated using a tap water enema. Participants were then placed in a hospital bed and with the subject in the left lateral position, a lubricated and tightly folded highly compliant, polyethylene bag (maximum capacity 1000 mL) tied to the end of a multilumen tube (19 Fr) was inserted through the anus and positioned in the rectal ampulla. Bag position was checked by manual inflation of 150 mL of air and subsequent retraction of the catheter until prevented by the external anal sphincter. After balloon deflation, the catheter was introduced an additional 2 cm, secured to the subjects upper leg by a piece of tape, and connected to the barostat. The hospital bed was placed in a 15° recumbent supine position (Trendelenburg) to avoid interference of abdominal mass with barostat measurements. Barostat measurements commenced approximately 4 hours after the light breakfast.

The experimental protocol consisted of a slow ramp distension to assess rectal compliance. Intrabag pressure was increased at a rate of 1 mmHg/min, starting at 5 mmHg, until a maximum of 30 mmHg. Patients rated the urge to defecate and level of abdominal pain on the 100 mm VAS scale at all even pressures (6, 8,…, 30 mmHg). After the experiment had ended, the rectal balloon was deflated and removed and each participant was provided with a 14-day symptom diary card and a stamped envelope to return the diary. Subjects were instructed to start filling out their symptom diary on the day after the experiment.

Barostat analysis

Dynamic compliance was assessed by calculating volume increments for each individual pressure step in each study participant. Compliance was defined by the largest volume increment (i.e., the steepest slope of the pressure-volume curve) for each participant and averaged over groups. Perception scores are expressed as the mean score at each pressure step. Perception thresholds were defined as the first pressure level at which perception scores exceeded 10 mm.

Visceral hypersensitivity

Patients with a pain perception threshold ≥ 2 SD below the mean threshold in controls were considered to be hypersensitive to balloon distension.

Statistical analysis

We aimed to enroll at least forty subjects in each group to be able to detect a 5 mmHg difference in mean pain threshold, which we considered clinically relevant, with a power of 0.80 and SD of 8 mmHg based on previous studies by our group.

All statistical analyses were carried out using SPSS for Windows, version 11.0.1 (SPSS Inc., Chicago IL, USA). Demographical characteristics were compared between groups by Student-t, Mann-Whitney or chi square analysis as appropriate. Differences in rectal compliance and visceroperception were analyzed for statistical significance using mixed models, using patient numbers as indicator for repeated measurements. One model analyzed pressure, volume, and pressure by volume interaction as separate contributors to the model; a second model did the same for pressure, visceral perception, and pressure by perception interaction. Compliance, perception of urge and pain at maximum rectal pressure (30 mmHg) and perception thresholds for urge were compared by Mann-Whitney (patients *versus* controls) or Kruskal-Wallis analysis (IBS subgroups). Because the pain threshold during ramp distension was not reached in all participants (see results), the best estimates for the mean pain threshold and SD was obtained by Maximum Likelihood Estimation using software for parametric survival models. Normal distribution for the pain scores was assumed. These estimates were compared by log rank analysis.

Finally, binary logistic regression and backward stepwise analysis (method Likelihood Ratio; entry at 0.05 probability, removal at 0.10 probability) was performed to identify demographical, clinical (symptom severity) and psychological characteristics that predict the occurrence of visceral hypersensitivity. Age, gender, health care level, predominant bowel habit, post-infectious symptom onset, rectal compliance, symptom severity, anxiety, depression, somatic symptoms, psychoneuroticism, dysfunctional cognitions regarding functional bowel disorders, vigilance, pain coping, somatization, and quality of life (general health subscale) were entered in the analysis as separate predictors. Data are expressed as mean ± SD. The level of significance was set at $P<0.05$.

RESULTS

Subject characteristics

We screened 130 patients, 26 of whom did not meet Rome II criteria, and 40 healthy volunteers. Two patients declined to participate in the barostat study, and one patient was diagnosed with conversion disorder. All healthy volunteers and 101 patients provided informed consent and were included in the final analysis. Thirty-one patients (31%) were recruited through the outpatient department and 70 patients (69%) were recruited through advertisement. All patients in the latter group had previously consulted a physician and had been evaluated for their abdominal symptoms. Healthy controls were also recruited through advertisement.

Demographical, clinical and psychological characteristics of patients and controls are listed in Table 1. Mean age and male to female ratio were not different between groups. Symptom severity and levels of anxiety, depression, psychoneuroticism, somatization, other somatic symptoms, and dysfunctional cognitions were all slightly but significantly increased in IBS patients compared to healthy controls. Pain coping scores were significantly reduced in IBS. Compared to controls, patients had

Table 1. Baseline demographical, clinical, and psychological characteristics of IBS patients and healthy controls

	IBS patients (n=101)	Healthy controls (n=40)
Demographics		
Age (yr)	42.0 ± 13.9	39.7 ± 15.0
Female sex (%)	73	63
Bowel habit (%)		
Diarrhea	34	0
Constipation	35	0
Alternating	24	0
Not specified/normal (controls)	8	100
Symptoms		
IBS symptom score (0-20)	4.4 ± 2.5*	0.43 ± 0.57
Psychological profile		
Anxiety (10-50)	13.4 ± 4.6†	12.2 ± 3.7
Depression (16-80)	22.5 ± 6.9*	20.7 ± 8.3
Somatic symptoms (12-60)	18.3 ± 5.6*	15.0 ± 3.7
Psychoneuroticism (90-450)	123.8 ± 31.9*	113.3 ± 30.7
Dysfunctional cognitions (31-217)	110.3 ± 35.8*	85.7 ± 37.3
Vigilance (0-40)	9.7 ± 5.8	7.7 ± 4.7
Pain coping (6-1)	3.4 ± 1.0†	3.7 ± 0.8
Somatization (0-2)	0.6 ± 0.4*	0.3 ± 0.3
Quality of life (0-100)		
Physical functioning	82.0 ± 20.4*	94.1 ± 10.5
Role limitations-physical	60.0 ± 42.0*	87.2 ± 28.6
Bodily pain	62.1 ± 19.6*	90.3 ± 16.1
Mental health	75.2 ± 16.3	78.5 ± 13.4
Role limitations-emotional	80.8 ± 35.3	91.0 ± 26.8
Social functioning	73.2 ± 23.7*	90.9 ± 14.3
Vitality	58.5 ± 16.9*	70.8 ± 15.8
General health	61.2 ± 18.8*	75.1 ± 14.6

Score ranges from best to worst are indicated after each parameter. Data are expressed as mean ± SD. * $P<0.01$ versus healthy controls; † $P < 0.05$ versus healthy controls.

Table 2. Psychological profile of patients recruited from the tertiary referral center and from the general population

	Referral center (n=31)	General population (n=70)
Anxiety (10-50)	12.9 ± 3.4	13.7 ± 5.0
Depression (16-80)	22.2 ± 5.1	22.7 ± 7.6
Somatic symptoms (12-60)	18.6 ± 4.0	18.2 ± 6.3
Psychoneuroticism (90-450)	122.1 ± 22.5	124.6 ± 35.7
Dysfunctional cognitions (31-217)	109.6 ± 34.2	110.6 ± 36.7
Vigilance (0-40)	8.2 ± 4.2	10.4 ± 6.3
Pain coping (6-1)	3.5 ± 1.0	3.4 ± 1.0
Somatization (0-2)	0.7 ± 0.3	0.6 ± 0.4

Score ranges from best to worst are indicated following each parameter. Data are expressed as mean ± SD.

impaired quality of life on 6 out of 8 SF-36 subscales. Psychological measures were not different between patients from the tertiary referral center and those from the general population (Table 2).

Rectal compliance and perception

Rectal compliance was significantly reduced in the IBS group compared to healthy control subjects (29.7 ± 12.6 ml/mmHg versus 41.8 ± 18.3 ml/mmHg, $P<0.0001$) (Fig 1A). Subgroup analysis showed that rectal compliance was particularly reduced in patients with a diarrhea predominant bowel habit (IBS-D; $P=0.04$) and those with alternating bowel habit (IBS-A; $P=0.05$) compared to constipation predominant IBS (IBS-C) (Fig 1B).

Urge perception at high rectal pressure distension (30 mmHg) was not significantly different between IBS patients (6.6 ± 2.7 cm) and controls (6.1 ± 2.6 cm) ($P=0.30$). The pressure-urge curves were also not significantly different between patients and controls (pressure by group interaction $P=0.82$; Fig 2). In contrast, pain perception at high rectal pressure was significantly increased in IBS patients compared to controls (2.5 ± 2.7 cm versus 1.0 ± 1.4 cm, $P=0.003$) and the pressure-pain curves differed significantly between groups (pressure by group interaction $P<0.0001$; Fig 3). No differences between IBS subgroups were found (Table 3).

Perception thresholds

Urge thresholds were reached in all participants, but were somewhat reduced in IBS patients (15.6 ± 6.1 mmHg) compared to controls (18.1 ± 6.0 mmHg) ($P=0.042$). No differences were found between IBS subgroups (Table 3). In contrast, only 10 of 40 control subjects (25%) compared to 55 of 101 IBS patients (54%) reached the threshold for rectal pain during balloon distension ($\chi^2=10.01$, $P=0.002$) (Fig 4). Maximum Likelihood Estimation of the mean pain threshold and SD in each group and subse-

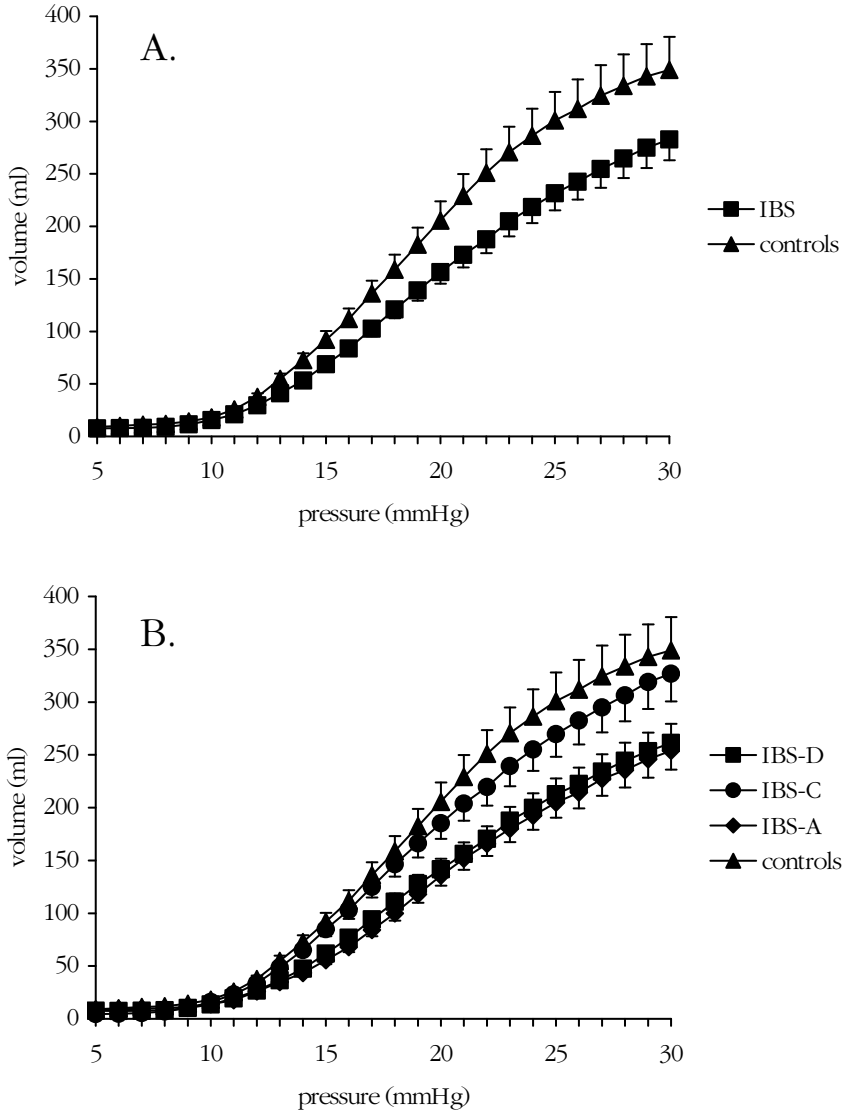

Figure 1. Dynamic rectal compliance (ml/mmHg) in IBS patients and controls (A.) and IBS-D, IBS-C and IBS-A patients and controls(B.). Compliance was significantly increased in all IBS patients compared to controls and in IBS-C compared to IBS-D and IBS-A. Data are expressed as mean ± SEM.

quent log rank analysis showed that the threshold was significantly reduced in IBS patients (27.5 ± 15.1 mmHg) compared to controls (35.3 ± 8.2 mmHg) (P=0.0009), but did not differ between IBS subgroups (Table 3).

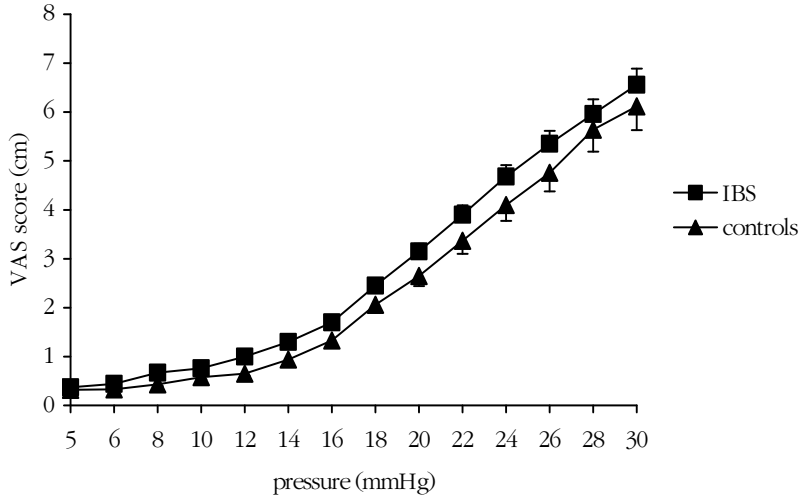

Figure 2. Intensity of urge perception in 101 IBS patients (squares) and 40 controls (triangles). Urge did not differ between patients and controls. Data are expressed as mean ± SEM.

Visceral hypersensitivity

The threshold for hypersensitivity to balloon distension was set at 18.9 mmHg (35.3 *minus* 16.4 mmHg). Thirty-three IBS patients (33%) compared to 0 controls were identified as hypersensitive to balloon distension (χ^2=17.06, P<0.0001) (Table 4). Thus, pain thresholds fell outside the range of control subjects in approximately 1 in 3 IBS patients.

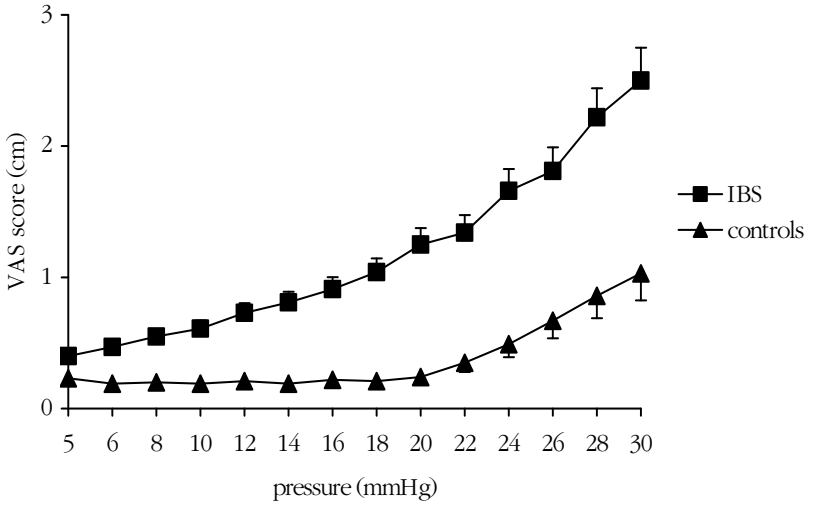

Figure 3. Intensity of pain perception in 101 IBS patients (squares) and 40 controls (triangles). Pain perception was significantly increased in patients compared to controls (pressure by group interaction, P<0.0001). Data are expressed as mean ± SEM.

Table 3. Rectal compliance and perception in IBS patients, IBS subgroups and healthy controls

	IBS patients				Controls
	IBS-D (n=34)	IBS-C (n=35)	IBS-A (n=24)	all patients (n=101)	(n=40)
Compliance (ml/mmHg)	27.2 ± 11	35.2 ± 14 †	26.6 ± 11	29.7 ± 13*	41.8± 18
Urge at 30 mmHg (cm)	6.5 ± 2.9	6.7 ± 2.6	6.7 ± 2.9	6.6 ± 2.7	6.1 ± 2.6
Pain at 30 mmHg (cm)	2.2 ± 2.6	2.9 ± 2.7	2.6 ± 3.0	2.5 ± 2.7*	1.0 ± 1.4
Threshold urge (mmHg)	16.9 ± 6.6	14.2 ± 5.6	15.6 ± 6.1	15.6 ± 6.1‡	18.0 ± 6.0
Threshold pain (mmHg)	31.3 ± 18	23.6 ± 13	29.6 ± 15	27.5 ± 15*	35.3 ± 8.2

* $P<0.01$ compared to controls; † $P<0.05$ compared to IBS-D and IBS-A; ‡ $P<0.05$ compared to controls. Data for the group with unknown bowel habit are not shown due to the small number of patients (N=8). Data are expressed as mean ± SD.

Predictors of visceral hypersensitivity

Of all tested variables, only IBS symptom severity remained as a predictor of visceral hypersensitivity in the logistic regression analysis (OR=1.25, 95% CI 1.04-1.50; P=0.016). Table 5 lists demographical, clinical and psychological characteristics in hypersensitive and normosensitive patients. IBS symptom scores were significantly higher in hypersensitive compared to normosensitive patients (5.4 ± 2.5 versus 4.0 ± 2.4, P=0.007). No other differences were found.

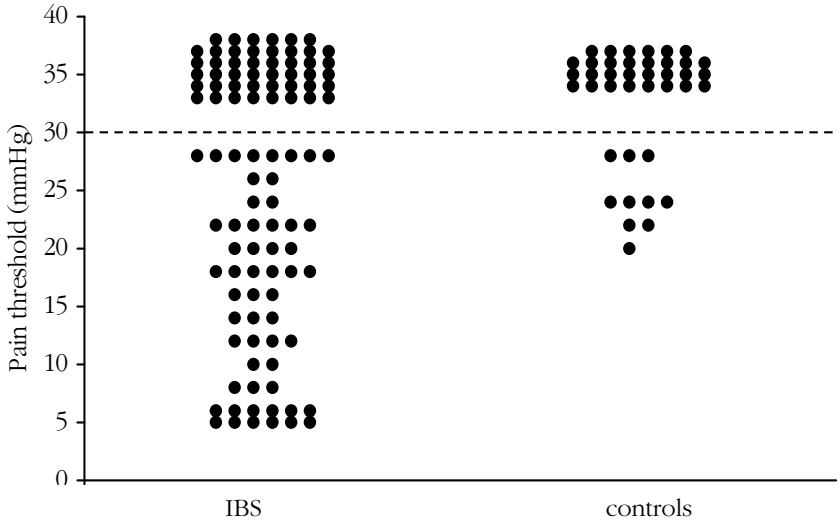

Figure 4. Individual pain thresholds in IBS patients and healthy controls. Significantly more patients (N=55, 54%) compared to controls (N=10, 25%) reached the pain threshold before the end of the ramp distension (dotted line, 30 mmHg).

Table 4. Visceral hypersensitivity in IBS patients and healthy controls

	Hypersensitive	Normosensitive
IBS (n=101)	33 (33%)*	68 (67%)
Controls (n=40)	0 (0%)	40 (100%)

* $P<0.001$ compared to controls.

Table 5. Demographical, clinical, and psychological characteristics of hypersensitive and normosensitive IBS patients

	Hypersensitive (n=33)	Normosensitive (n=68)
Age (yr)	40.7 ± 12.4	42.6 ± 14.5
Female sex (%)	73	74
Recruitment (%) advertisement	68	71
Bowel habit (%)		
Diarrhea	33	34
Constipation	46	29
Alternating	18	27
Not specified/normal	3	10
Post-infectious (%)	11	13
Dynamic compliance	31.8 ± 14.9	28.6 ± 11.3
IBS composite score	5.4 ± 2.5*	4.0 ± 2.4
Dyscomfort	1.38 ± 0.8‡	1.17± 0.62
Pain	1.34 ± 0.95†	0.98 ± 0.72
Constipation	0.73 ± 0.64†	0.37 ± 0.56
Diarrhea	0.45 ± 0.86	0.48 ± 0.69
Bloating	1.37 ± 0.79†	1.01 ± 0.75
General health	62.7 ± 16.4	60.5 ± 19.9
Anxiety	13.9 ± 5.0	13.2 ± 4.4
Depression	23.1 ± 6.5	22.3 ± 7.1
Somatic symptoms	19.0 ± 4.5	18.0 ± 6.1
Psychoneuroticism	126.5 ± 32.2	122.5 ± 32.0
Dysfunctional cognitions	106.8 ± 35.3	111.9 ± 36.1
Vigilance	9.2 ± 5.3	9.9 ± 6.1
Pain coping	3.5 ± 1.1	3.3 ± 0.9
Somatization	0.6 ± 0.4	0.6 ± 0.4
Antispasmodics (%)	15	12
Laxatives or bulking agents (%)	30	31

* $P=0.007$ *versus* normosensitive patients (range 0 (no symptoms) to 20 (worst imaginable)); † $P<0.02$ *versus* normosensitive patients; ‡ $P=0.072$ *versus* normosensitive patients.

DISCUSSION

The present study shows that 1) visceral hypersensitivity is an important feature of irritable bowel syndrome, but not present in all patients, and 2) hypersensitivity to rectal balloon distension is predicted by IBS symptom severity, but not by demographical or psychological characteristics.

Our data confirm previous findings that rectal compliance and pain thresholds are reduced and that the intensity of pain perception is increased in IBS patients when compared to healthy controls. Urge intensity at any given pressure was similar in patients and controls, with slightly lower thresholds for urge in IBS patients. Our observation that pain perception rather than urge is increased, is consistent with other reports demonstrating decreased perception thresholds in IBS only for noxious stimuli, and not for stool[11].

It is presumed that a phasic distension protocol (i.e. rapid balloon inflation to predefined pressure levels) is the preferred procedure to test visceral hypersensitivity, since this would elicit rectal sensations at lower volumes or pressures compared to slow ramp distension[26,27]. However, we chose to perform only ramp distensions because we considered rectal compliance to be an important factor in the model on predictors of visceral hypersensitivity, and compliance is best measured by means of slow ramp distension[27]. Phasic distensions were not performed, since assessment of sensory thresholds during phasic distensions after preceding ramp distension may introduce perceptual response bias, and phasic distensions prior to ramp distension may affect subsequent rectal compliance measurements. The pain thresholds we observed during ramp distension are similar to those reported by others using phasic distensions[10,28,29], which supports previous findings that the type of distension procedure (phasic, ramp, etc) does not affect perception[30].

One of our main findings is that hypersensitivity to balloon distension was less likely to occur in patients with milder symptoms. This challenges the view that visceral hyperalgesia is a biological marker of IBS[11], since hypersensitivity may be absent in Rome II positive patients with mild symptoms. The difference in the proportion of hypersensitive patients between that study (95%) and ours (33%) may in part be due to the use of different parameters to define visceral hypersensitivity. Mertz et al. used 3 parameters to score rectal perception simultaneously (i.e. perception thresholds, intensity of sensations and altered viscerosomatic referral), whereas we only identified patients having decreased pain thresholds and not those having decreased discomfort thresholds or altered pain referral patterns. It is, of course, essential to use equal definitions of visceral hypersensitivity when comparing its prevalence between studies. Since no accepted definition of visceral hypersensitivity is currently available, we decided to use a statistical point of view and consider patients with a

pain perception threshold ≥ 2 SD below the mean threshold in healthy controls as hypersensitive to rectal balloon distension. In general, this method is accepted to define 'outliers'. While this cut-off is arbitrary, our data suggest that hypersensitivity to rectal distension is not a suitable biological marker to identify patients with IBS.

The pathophysiology of visceral hyperalgesia in IBS remains poorly understood. Recent evidence suggests that disturbances may occur at different levels of the brain-gut axis. First, sensitization of peripheral nerve endings at the intestinal level may occur during or after acute inflammation[12,13], leading to higher excitability and/or increased firing of these neurons. Second, some studies suggest that alterations in the spinal dorsal horn neurons may provide an explanation for the extended viscerosomatic referral pattern that is often seen in IBS[11,12]. Third, altered processing of afferent visceral information in the brain, particularly in the prefrontal cortex, anterior cingulated cortex, and thalamus, has repeatedly been demonstrated in IBS patients[15,31]. These regions are not only involved in pain processing but are also part of the emotional limbic system and are therefore involved in numerous psychological and cognitive events[16,17]. Since nociception (becoming aware of a painful stimulus) and emotional pain management both occur in similar regions of the brain, we hypothesized that psychological disturbances are related to visceral hypersensitivity. However, our results do not support this hypothesis, as none of the psychological variables we studied predicted the occurrence of hypersensitivity to balloon distension. These findings substantiate previous observations that psychological characteristics as anxiety, somatization, and neuroticism do not correlate with sensory thresholds[9,11,19]. Similar results were obtained in recent study, in which multivariate analysis demonstrated that abdominal pain and bloating were significantly associated with altered rectal perception whereas psychological symptoms were not[32]. Our data also show that rectal hyperalgesia is not associated with other psychological factors (vigilance, dysfunctional cognitions, pain coping), demographical characteristics (age, gender), quality of life, or predominant bowel habit.

Previously Whitehead et al. proposed a model for psychological factors that influence pain perception in IBS[33]. It was suggested that low pain thresholds in IBS are influenced by two related cognitive traits, i.e. selective attention to gut sensations and a tendency to interpret these sensations as symptoms of disease. Our data show that neither vigilance (selective somatic attention) nor cognitions regarding functional bowel disorders (interpretation of normal sensations as symptoms of disease) were different between hypersensitive and normosensitive IBS patients. These findings suggest that hypersensitive patients do not perceive or manage their symptoms differently from normosensitive patients. Although vigilance and cognitions on functional bowel disorders differed significantly between patients and controls, these parameters were not associated with increased rectal sensitivity.

We aimed to obtain a representative sample from the IBS population by recruiting patients both from the outpatient clinic and by advertisement. Levels of psychological distress were low and did not differ significantly between groups. One may argue that low levels of psychopathology explain why we found no correlation between psychological variables and visceral hypersensitivity, since a certain degree of parameter variability is required for correlations to be detected. Although some studies found significantly more psychological disturbances in IBS patients recruited from tertiary care[18,19,34], one of these studies found no relation between psychological distress and visceral hypersensitivity in clinic patients with IBS[19], supporting our finding that visceral hypersensitivity is not affected by psychopathology, regardless of level of health care.

Allowing patients to take antispasmodics, laxatives and, occasionally, analgesics during barostat measurements is a limitation of this study as it may interfere with visceral sensitivity and affect sensory thresholds in general. While use of these medications was similar in hypersensitive and normosensitive patients (Table 5), prohibiting the use of these medications may have further increased the number of patients with hypersensitivity to balloon distension in both groups.

In conclusion, we found that patients with IBS have impaired rectal compliance and reduced sensory thresholds to rectal distension compared to controls. Visceral hypersensitivity is present in one third of our IBS population and is associated with increased symptom severity. Although psychological parameters do not predict the occurrence of visceral hypersensitivity, this does not exclude a common neuropsychological basis in the pathophysiology of IBS. Future studies should focus on the role of the brain-gut axis in the development of irritable bowel syndrome.

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