
Atopic irritable bowel syndrome: a novel subgroup of irritable bowel syndrome with allergic manifestations

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Background: Mast cells have a primary role in atopy. Mast cells may play a unique role in a subgroup of patients with irritable bowel syndrome (IBS). This observation suggests a link between atopic disorders and IBS.

Objective: To determine whether there is an association between atopic disorders and IBS.

Methods: We undertook a prospective study using structured questionnaires. We administered questionnaires to 125 consecutive patients seen in the following clinics from July 1 through October 31, 2001: allergy/immunology (AI) (n = 39), gastroenterology (n = 36), and general medicine (n = 50). The survey included questions detailing gastrointestinal and allergic symptoms. Diagnosis of IBS was based on Rome II criteria. Diagnosis of atopy was based on clinical parameters.

Results: The AI clinic reported a significantly ($P = .015$) higher rate of IBS than the general medicine clinic. The IBS incidence reported in the AI clinic was similar to that reported in the gastroenterology clinic. The likelihood of IBS was significantly higher in patients with seasonal allergic rhinitis (2.67 times; 95% confidence interval [CI], 1.10–6.49; $P = .03$), patients with allergic eczema (3.85 times; 95% CI, 1.72–8.60; $P = .001$), and patients with depression (2.56 times; 95% CI, 1.05–6.14; $P = .04$). Patients reporting atopic symptoms (seasonal allergic rhinitis, allergic eczema, and asthma) were 3.20 times (95% CI, 1.20–8.50) ($P = .02$) more likely to fulfill the criteria for IBS.

Conclusions: Adults with atopic symptoms report a high incidence of IBS, suggesting a link between atopy and IBS. We proposed a subgroup of patients with IBS (atopic IBS) who have typical IBS symptoms in association with atopic manifestations. Identifying atopic vs nonatopic IBS may help in identifying the underlying pathophysiologic mechanisms and therapeutic options.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a name given to a cluster of chronic functional bowel symptoms whose cause is frequently unknown. This syndrome affects 15% of the general population and is the most common reason for patients and generalists to consult gastroenterologists.¹ The Rome II criteria were developed to evaluate IBS and to provide a template for classification of IBS. Symptoms include abdominal pain for 12 weeks within the past year (not necessarily consecutively), change in stool consistency or frequency, and relief of the abdominal pain with defecation. Approximately 30% of patients with IBS identify acute infection as an initial trigger for their chronic intestinal symptoms (postinfectious IBS).² This suggests that environmental factors trigger symptoms of IBS in susceptible patients. In addition, IBS is often accompanied by extraintestinal symptoms, such as fatigue, anxiety, and asthma.³ This has led investigators to develop

hypotheses regarding underlying pathophysiologic mechanisms connecting these disorders.^{3–5}

Atopic disease, including allergic rhinitis, eczema, asthma, and food allergy, affects an estimated 20% of the population and can cause local end-organ dysfunction in the nose, lung, skin, or gut, and systemic symptoms through mast cell (MC) mediators released in response to multiple factors.⁶ Various findings suggest indirectly that allergen exposure, whether ingested or inhaled, may lead to IBS manifestations in some atopic individuals.^{7–11} First, in 1 study,¹¹ 7 of the 9 patients allergic to birch pollen also reported concomitant gastrointestinal symptoms that the authors described as consistent with criteria for IBS. Interestingly, 3 of the 7 patients reported that their gastrointestinal symptoms were directly related to the severity of the pollen season. Second, an increase in MCs has been documented in patients with IBS in the terminal ileum and colon.^{12,13} Third, patients with mastocytosis report significant abdominal pain and diarrhea that responds to treatment with antihistamines and cromolyn sodium.¹⁴

To our knowledge, the frequency of atopic disease with IBS has not been examined. We, therefore, undertook a pilot survey to determine whether IBS symptoms are common in unselected patients with atopic manifestations and, conversely, whether atopic conditions are common in unselected patients with IBS. If there is such a commonality, the pres-

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ence of shared manifestations may be evidence of a subgroup of patients with atopic IBS.

METHODS

This study was performed at Rush University Medical Center, Chicago, Illinois, during a 3-month period from July 1 to October 31, 2001, and was approved by our institutional review board. The study was conducted with 125 adult patients (≥ 18 years) composed of consecutive unselected patients from the gastroenterology (GI) clinic ($n = 36$), allergy/immunology (AI) clinic ($n = 39$), and general medicine (GM) clinic ($n = 50$). Questions were asked to determine if patients had symptoms compatible with the diagnosis of IBS (based on Rome II criteria). The questions to identify the atopic manifestations are given in Table 1. We also asked about other common medical and GI conditions, including gastroesophageal reflux disease (GERD), depression, fibromyalgia, and urinary tract infections, in a simple "yes" or "no" format. After obtaining informed consent and explaining the questionnaire to the subject, the subject was instructed to fill out the questionnaire. Patients were excluded from the study if they were not proficient in reading English or were unable to complete the questionnaire. The statistical analysis was performed using a commercially available software program (SPSS, version 11.5; SPSS Inc, Chicago, Illinois). Correlational studies were done to determine odds ratio (OR), perform χ^2 analysis, and develop a logistic regression model. $P < .05$ was considered statistically significant, and the 95% confidence interval (CI) was used to evaluate OR importance.

RESULTS

The demographic characteristics of the 125 patients in all 3 clinics were similar. Overall, 90 patients (72%) were female and 35 (28%) were male, and their mean $\pm$ SD age was 44.5 ± 1.5 years (range, 18–85 years). In the AI clinic, 27 patients (69%) were female and 12 (31%) were male, and their mean $\pm$ SD age was 41.0 ± 2.2 years (range, 18–72 years); in the GI clinic, 26 patients (72%) were female and 10 (28%) were male, and their mean $\pm$ SD age was 50.0 ± 2.9 years (range, 23–85 years); and in the GM clinic, 37 patients (74%) were female and 13 (26%) were male, and their mean $\pm$ SD age was 42.5 ± 2.4 years (range, 18–79 years) ($P = .07$ for the difference between groups). Of the 125 patients, 41 fulfilled the Rome II criteria for the diagnosis of IBS, with more women than men reporting IBS. This has been noted previously.¹⁵ Neither GERD nor non-GI disorders, such as recurrent urinary tract infections and fibromyalgia, showed a correlation with atopic IBS in our study population (Table 1).

The prevalence of IBS in patients attending the GI clinic (14 [39%] of 36 patients) and the AI clinic (17 [44%] of 39 patients) was similar, and each was significantly higher than the prevalence of IBS in patients attending the GM clinic (10 [20%] of 50 patients) (Fig 1). Of patients with IBS, 33 of 41 (80%) reported seasonal allergic rhinitis (SAR) compared with 51 of 84 patients without IBS (61%) ($P = .03$; OR, 2.67; 95% CI, 1.10–6.48). In addition, 21 of 41 of patients with IBS (51%) reported allergic eczema (AE) compared with

Table 1. Structured Questionnaire for Atopy

Question	All clinics (N = 125) ^a	AI clinic (n = 39) ^a	GI clinic (n = 36) ^a	GM clinic (n = 50) ^a	P value
Have you developed a seasonal runny nose, nasal congestion, or itchy eyes (SAR)?	87 (70)	38 (97)	22 (61)	27 (54)	<.001
Have you had asthma?	31 (25)	19 (49)	6 (17)	6 (12)	<.001
Have you had an allergic skin rash (eczema)?	38 (30)	19 (49)	12 (33)	7 (14)	.002
Have you developed a food allergy? If yes, which food?	42 (34)	22 (56)	10 (28)	10 (20)	.001
Have you developed a reaction to food that causes itching or swelling of your mouth, tongue, or throat (OAS)? If yes, which food?	23 (18)	13 (33)	3 (8)	7 (14)	.02
Have you developed a reaction to food that cause hives or a skin rash? If yes, which food?	17 (14)	10 (26)	4 (11)	3 (6)	.02
Have you developed a reaction to food that causes abdominal cramping and diarrhea? If yes, which food?	43 (34)	19 (49)	11 (31)	13 (26)	.07
Have you been diagnosed as having esophageal reflux? Have you taken medication for esophageal reflux?	42 (34)	14 (36)	17 (47)	11 (22)	.05
Have you been treated for fibromyalgia?	10 (8)	4 (10)	4 (11)	2 (4)	.40
Have you been treated for recurrent urinary tract infections?	13 (10)	3 (8)	4 (11)	6 (12)	.80
Have you been treated for depression?	26 (21)	8 (21)	7 (19)	11 (22)	.96

Abbreviations: AI, allergy/immunology; GI, gastroenterology; GM, general medicine; OAS, oral allergy syndrome; SAR, seasonal allergic rhinitis.

^a Data are given as number (percentage) of each group that responded "yes" to the question.

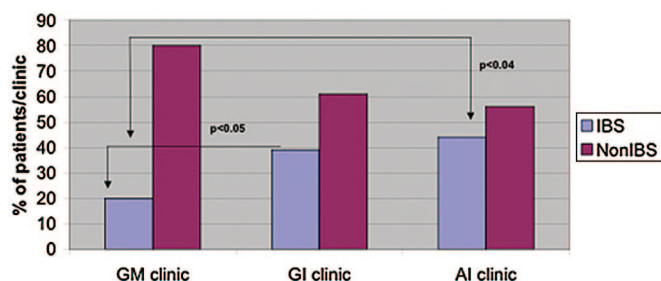


Figure 1. Percentage of patients with irritable bowel syndrome (IBS) in the 3 clinics surveyed: general medicine (GM), gastroenterology (GI), and allergy/immunology (AI). Significantly more patients with IBS were seen in the AI and GI clinics than in the GM clinic.

only 18 of 84 of patients without IBS (18%) ($P = .001$; OR, 3.85; 95% CI, 1.72–8.60). Seasonal allergic rhinitis and AE independently predicted the diagnosis of IBS (Table 2). Performing an analysis using a logistic regression model that included SAR, AE, and asthma, the OR for having IBS was 3.20 (Table 2). Food intolerance, described as abdominal pain, cramping, diarrhea, and depression, was also predictive of atopic IBS symptoms (Table 2).

In our patients with atopic IBS, 20 of 41 (49%) reported that a particular food or multiple foods caused abdominal cramping and diarrhea ($P = .03$; OR, 2.53; 95% CI, 1.16–5.50). Subjects were asked about food that caused symptoms of oral allergy syndrome and/or skin manifestations. The data are presented in Table 3.

DISCUSSION

Our data demonstrate a previously unappreciated association between reported IBS and reported atopic disorders and support the existence of a subgroup of patients with IBS whom we term *atopic IBS*. One important question is whether the observed association between IBS and atopic disorders is a nonspecific finding for 2 common disorders. To address this question, we also inquired about nonatopic symptoms, such as GERD and recurrent urinary tract infections, and we found no association between IBS and these common disorders.

Table 2. Summary of Predictors for Atopic IBS

Predictor	OR (95% CI)	P value
AE	3.85 (1.72–8.60)	.001
SAR	2.67 (1.10–6.49)	.03
ACD	2.53 (1.16–5.50)	.03
Atopy (AE, asthma, and SAR)	3.20 (1.20–8.50)	.02
Depression	2.56 (1.05–6.14)	.04
Food allergy	1.22 (0.56–2.67)	.62
Asthma	1.24 (0.54–2.86)	.61
Recurrent UTI	1.03 (0.33–3.23)	.96
GERD	1.43 (0.66–3.11)	.37

Abbreviations: ACD, abdominal cramping and diarrhea; AE, allergic eczema; CI, confidence interval; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; OR, odds ratio; SAR, seasonal allergic rhinitis; UTI, urinary tract infection.

Lack of correlation between these complaints and IBS suggests that our observed association between atopy and IBS is specific.

Our results showed that atopic manifestations, such as SAR and AE, are more commonly reported in subjects who report IBS symptoms. The association with SAR is intriguing in light of recent clinical studies that demonstrate an increase in IgE-bearing cells in the gut mucosa after seasonal inhalant allergen exposure.¹¹ Seasonal allergic rhinitis has a known link with oral allergy syndrome, and our data suggest that it is also associated with IBS.^{8,16} In SAR and oral allergy syndrome, pathogenesis-related proteins, accumulated by pollen in response to infections and stress, act as allergens that cross-react with similar proteins present in certain fruits, vegetables, and tree nuts.¹⁶ The allergic symptoms described in the mouth and throat may extend to the gut, as previous data suggest.¹⁶ Our subjects describe reactions to fruits and nuts that cause a range of gut symptoms from abdominal cramping and diarrhea to oral allergy syndrome to abdominal cramping and diarrhea with oral allergy syndrome. It is the description of these symptoms provoked by food that requires further clinician-directed evaluation. Food hypersensitivity in those with atopic IBS may be associated with class 2 food allergens, but skin testing with commercial allergens can be misleading.^{16–19} The other foods listed in Table 3 have been associated with hypersensitivity or intolerance reactions in IBS by others.²⁰ Some have proposed that IgG4 antibodies are more predictive of food-induced IBS. When subjects adhered to diets based on elimination of foods with high IgG4 antibody responses, they reported a reduction of IBS symptoms.^{21,22} Thus, further studies evaluating the role of class 2 allergens, such as pathogenesis-related proteins and specific IgG4 antibodies in atopic IBS, seem warranted.

The reported presence of allergic dermatitis was highly correlated to the presence of IBS in our population. In atopic disease, allergic dermatitis is the first step of the “atopic march.”²³ In early childhood, AE is frequently associated with gastrointestinal dysfunction and food allergy.⁸ A clinical history of AE may be a useful marker for patients with gut hypersensitivity and atopic IBS. Another study from an allergy clinic supports physician-diagnosed allergic dermatitis as a significant peripheral manifestation in adults for IBS.²⁴

In our study, 12 of 41 subjects (29%) reported asthma and IBS. This is similar to a previous report⁵ that used subjective and objective measures to diagnose asthma in 34% of the patients with IBS. The investigators hypothesized a shared respiratory and gastrointestinal pathophysiologic mechanism, which produced smooth muscle hyperactivity. In recent reviews of IBS and atopy, the authors^{3,25,26} propose that perceptual and visceral hypersensitivity is a common underlying factor, promoted by chronic stress on the immune system. Depression, the result of chronic stress, is a known independent predictor of IBS, as demonstrated in our study.²⁷ Atopic IBS and depression may result in alterations of the brain-gut axis via activation of corticotropin-releasing factor pathways promoting visceral hyperresponsiveness.^{26,28} The MC is per-

Table 3. Summary of Patient-Reported Food Reactions Classified According to Oral, Gastrointestinal, or Skin Symptoms^a

Food	Patients with ACD	Patients with OAS	Patients with OAS and ACD	Patients with hives with food
Milk	8	2	2	1
Dairy	4	1	0	0
Beef	2	0	0	0
Pork	4	0	0	0
Corn	6	1	1	2
Wheat	6	1	1	2
Nuts	3	3	3	2
Peanuts	1	1	0	1
Soy	4	0	1	0
Vegetables	2	2	1	0
Fruit	5	5	4	5
Eggs	2	0	0	1
Shellfish	4	6	3	4
Fish	1	3	2	3
Oregano	0	2	0	0
Eggplant	0	1	0	0
Unknown	0	0	2	5

Abbreviations: ACD, abdominal pain or discomfort, cramping, and diarrhea associated with food; OAS, oral allergy syndrome.

^a The number of patients with ACD was 43; those with OAS, 23; those with OAS and ACD, 14; those with hives with food, 17 (there were 56 total patients, including those with and those without irritable bowel syndrome). The total number of reactions was 52 in those with ACD, 28 in those with OAS, 20 in those with OAS and ACD, and 26 in those with hives with food. Some patients complained of different reactions with more than 1 food.

ceived on a cellular level as the key regulator of visceral hypersensitivity.^{3,26} The MC is positioned near enteric neurons, thereby allowing a quick response to MC-derived mediators, including the effects of tryptase on type 2 protein-activated receptors, which promote prolonged hypersensitivity.^{3,25,29} Further evidence that the MC is operative, even in innate short-term responses to stress in the gut, was shown by Santos et al,³⁰ who demonstrated an MC profile with cold stress similar to that evoked in food-allergic patients. Mast cells have also been shown to alter permeability in IBS.³¹ A recent report⁹ linked a fixed abnormality in small-bowel permeability of patients with diarrhea-predominant IBS with patients who described allergy symptoms, thus supporting our proposed atopic IBS subgroup.

The findings presented concerning atopic IBS are of clinical interest and warrant further attention. The true prevalence of this association can only be validated with standardized questionnaires and physician-diagnosed allergic conditions in subsequent studies of this population. We recognize that the subject's report of food allergy is problematic because it is not known what proportion of these adverse food reactions represent true allergic reactions or nonallergic immunologic reactions.

Treatment of IBS has been challenging. In a previous retrospective study of our patient population undergoing duodenal or colonic biopsies for chronic diarrhea, increased MCs were identified by immunohistochemistry for MC tryptase. The use of H₁- and H₂-blockers and an MC stabilizer produced symptomatic improvement.³² In addition, there are reports^{33,34} of improvement with cromolyn sodium (Gastro-

crom) in patients with IBS with positive allergen food skin test results. However, these interventions have given conflicting results.³⁵

In summary, we defined a subgroup of patients with IBS who also report atopic disorders. We propose that this subgroup of IBS (atopic IBS) be considered separately from patients with IBS without atopic symptoms, because they may have distinct pathophysiologic features and may benefit from specific therapeutic interventions. Indeed, the separation of postinfectious IBS was pivotal to further mechanistic studies in this group of patients and to a better understanding of the role of cytokines and other inflammatory pathways.¹⁵ Distinguishing atopic IBS from nonatopic IBS could result in designing more appropriate therapeutic interventions.

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