

Combination of Allergic Factors Can Worsen Diarrheic Irritable Bowel Syndrome: Role of Barrier Defects and Mast Cells

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- OBJECTIVES:** Recent evidence suggests a role for increased colonic permeability and mucosal mast cell (MC) mediators on symptoms related to the irritable bowel syndrome (IBS). Whether allergic factors (AFs) are involved in the pathophysiology of IBS is unclear. We addressed the question of the possible influence of an allergic background on IBS symptoms.
- METHODS:** We assessed paracellular permeability, mucosal MCs counts, and spontaneous release of tryptase of colonic biopsy specimens in 34 IBS patients and 15 healthy subjects. The severity of IBS was assessed through self-reported questionnaires. All individuals were tested for the presence of AF, including self-perception of adverse reaction to food, personal and familial history of atopic disease, elevated total or specific immunoglobulin E against food/inhalant antigens, blood eosinophilia, and skin tests.
- RESULTS:** IBS patients had significant enhanced colonic permeability, higher number of MCs, and spontaneous release of tryptase than healthy subjects. The severity of IBS was significantly correlated with colonic permeability ($r=0.48$, $P=0.004$), MCs counts ($r=0.36$, $P=0.03$), and tryptase ($r=0.48$, $P=0.01$). In 13 IBS patients (38.2%) having at least three AFs, symptoms scores, colonic permeability, MCs counts, and tryptase release by colonic biopsies were significantly higher than in those with less than three AFs. IBS patients with at least three AFs were more prone to diarrhea or alternating symptoms. None AF was found to be predictive of IBS severity.
- CONCLUSIONS:** In IBS patients, the presence of an allergic background correlates with a more severe disease and diarrhea predominance, possibly by enhancing mucosal MC activation and paracellular permeability.

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INTRODUCTION

The irritable bowel syndrome (IBS) is characterized as a group of functional bowel disorders in the absence of an identifiable disease process (1). Increasing evidence suggests that mucosal immune activation contributes to the development of hypersensitivity and pain in IBS (2). Mucosal inflammation has been described in IBS patients, including various immune cells, mostly lymphocytes, mast cells (MCs), and enteroendocrine cells (3–5). Interestingly, MCs also interact with epithelial cells, which can affect inflammation and permeability of the epithelial barrier (6). Increased numbers of MCs have been documented throughout the gut mucosa

of IBS patients (7–9) and soluble mediators released by activated MCs, in particular tryptase, contribute to visceral hyperalgesia (10–12). Activation of MCs can be triggered by different pathways: they are key cells of innate immunity, being intermediate between innate and adaptive immunity, and also have a central role in immediate allergic reactions (13). They are particularly abundant in the gut mucosa and have been involved in pathomechanisms of various intestinal disorders, including inflammatory bowel diseases and food allergy (14). Increased intestinal permeability was documented in IBS patients including those having post-infective form or with adverse reactions to food (15–18). Even if increased

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intestinal permeability may lead to more severe symptoms in patients with diarrhea predominance and visceral hypersensitivity (19), whether increased colonic permeability correlates with both the elevated MCs count and the severity of IBS is unknown.

The contribution of allergic factors (AFs) in IBS has been controversial for many years (20). Patients with self-reported adverse reactions to food were found with high prevalence of IBS and atopic disease (21) despite discrepant sensitization test findings (15). Patients reporting atopic symptoms were more likely to fulfill the criteria for IBS (22). Food elimination diets based on high levels of specific immunoglobulin G (IgG) antibody were also effective to reduce IBS symptoms (23). Moreover, a significant association between the severity of referred clinical symptoms and the increasing of intestinal permeability index has been observed in IBS patients having food allergy (24).

Our aims were to (i) to evaluate the severity of IBS, colonic permeability, mucosal MC count, and tryptase in IBS with or without AFs and controls and (ii) to determine whether AFs may influence these pathophysiological mechanisms.

METHODS

Participants

Consecutive patients who met the Rome III criteria for the diagnosis of IBS were seen in the Department of Gastroenterology of the Centre Hospitalier Universitaire de Nice between March 2008 and June 2009. They were selected on the presence of abdominal pain and/or discomfort relieved by defecation or associated with change in stool frequency and consistency. Symptoms had to be present more than 25% of the time being evaluated by means of daily diaries completed during 15 days including a Bristol scale. IBS subtypes were divided as predominance of constipation (IBS-C), diarrhea (IBS-D), or with alternating symptoms (IBS-M). Patients were thoroughly examined and were submitted to biological tests to exclude an organic disease; celiac disease, lactose intolerance, severe depression and anxiety, and thyroid and renal dysfunction. Dietary habits were not changed during the three previous months before inclusion, and none followed hypoallergenic diet. None were taking anti-inflammatory drugs (including mast-cell stabilizers, histamine antagonists, anticholinergics, antidiarrhea medication, probiotics, or steroids). None were smokers or alcohol consumers.

Control patients were individuals without any digestive complaint enrolled in a colonoscopic surveillance program.

The study was conducted with local approval from the Ethic Committee (CCPPRB) and all patients gave their written informed consent.

IBS severity, quality of life, and psychological assessments

Patients were asked to score frequency and severity of their symptoms over the last 2 weeks before interview according to previously used questionnaires (18). Each subject completed the French validated IBS severity scoring system initially developed by Francis *et al* (25). Psychological variables were assessed through a set of questionnaires, including the fatigue impact scale, the Beck

depression inventory, and the hospital anxiety and depression scale.

Allergic factors

In the study, we aimed to identify not only a background of allergy including the criteria proposed by Bischoff *et al.* (26) to suspect intestinal food allergy, but also other stigma of general allergic or atopic background as a health condition in which MCs have a key role like in IBS. We defined a background of allergy when IBS patients fulfilled at least three criteria used in the management of allergic diseases (26), including self-reporting of food allergy, personal and familial history of atopic disease, elevated total or specific IgE (sIgE) against food or airborne antigens, blood eosinophilia, and skin tests.

The skin prick tests were based on commercial food extracts using the “prick test” technique: a drop of the specific food extract was placed in the inner forearm. Food allergens eliciting wheal reaction at least 3 mm or 50% greater than the negative control were considered as positive (15).

Serum samples were analyzed for total IgE and sIgE antibodies by using the ImmunoCAP technology (PHADIA AB, Uppsala, Sweden) with an ImmunoCap 250. Samples can be tested by using tests specific for a single allergen or screened by using multi-allergens tests targeting inhaled allergens (Phadiatop) or food allergens Trophatop fx5 (egg white, milk, fish, wheat, peanut, and soybean), fx24 (hazel nut, shrimp, kiwi fruit, and banana), and fx25 (sesame seeds, yeast, garlic, and celery). Results of multi-allergens tests are qualitative (negative or positive), with a sensitivity of 90% or more. Quantifications of sIgE antibodies targeting single allergen were performed by using monospecific ImmunoCaps, with a detection threshold for sIgE of 0.1 kU_A/l.

Collection of cecal biopsy specimens

All subjects underwent an ileocolonoscopy with 10 biopsies at the cecum site. Polyethylene glycol was used to provide adequate cleansing in preparation for colonoscopy. Four biopsy specimens were fixed in formol solution, and histopathological studies were performed on paraffin-embedded 4-mm thick sections. Four biopsy specimens were collected for assessment of paracellular permeability, whereas two specimens served to collect soluble mediators as described below.

Cell counting

Cell counts were performed twice by a pathologist (M.C.S-P), blinded for the diagnosis as previously described (9). Briefly, slides were incubated for 1 h with mouse monoclonal antibodies specific for CD3 and CD117. Sections were reincubated with secondary biotinylated anti-mouse/rabbit antibodies (Dako StreptABC complex, Glostrup, Denmark), followed by streptavidin/horseradish peroxidase conjugate. Conventional CD117 immunostaining was applied on the sections to calculate the absolute number of MCs within three nonoverlapping high power fields (hpf).

Colonic paracellular permeability

The colonic paracellular permeability was measured in the cecum as previously described (18). Four biopsy samples were mounted

Table 1. Clinical characteristics of IBS patients

IBS subtype	IBS	Controls	P value	IBS-C	IBS-D	IBS-M	P value
Sex (M/F)	6 M/28 F	9 M/6 F	0.02	1 M/9 F	2 M/11 F	3 M/8 F	0.5
Age (years)	51 (42–58)	54 (48.2–58.7)	0.4	54.5 (42–59)	44 (35.2–52.2)	57 (49.5–58)	0.5
IBS severity score	242 (162–328)	0	0.0001	207 (115–328)	271 (204–310)	225 (165–330)	0.4
IBS duration (years)	5.5 (3–10)	—		7.5 (4–10)	5 (3–10)	5 (3.2–9.5)	0.6
Abdominal pain frequency	2 (2–4)	0	0.0001	4 (2.5–4)	3 (2–4)	2 (2–2.7)	0.1
Abdominal pain severity	3 (2–2.2)	0	0.0001	2 (2–2.2)	2 (2–3.2)	2 (1.2–2)	0.3
FIS score	47 (21–110)	10 (0.7–10.7)	0.0001	38 (20–93)	87 (25.5–110.5)	33 (10.7–111)	0.8
HADS score	14.5 (10.5–22)	3 (1–4)	0.0001	16 (14–23)	15 (12–22)	11 (7.5–17)	0.3
BDI score	5 (3–9)	1 (0–1)	0.0001	8 (6.5–10)	6 (2.7–10)	4 (2.2–8)	0.2

BDI, beck depression inventory; F, female; FIS, fatigue impact scale; HADS, hospital anxiety and depression scale; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, IBS with mixed symptoms; M, male.

Data are medians and interquartile ranges.

in adapted Ussing Chambers (Transcellab; TBC, Paris, France), with an exposed surface area of 0.0314 cm². Biopsy specimens were bathed on each side with 3 ml of Ham's Nutrient Mixture (HAM's F12; Invitrogen, Cergy-Pontoise, France). Cultured media were continuously oxygenated and maintained at 37°C by a gas flow (95% O₂/5% CO₂). A 15-min baseline period was observed before 150 µl of apical medium was changed by the same volume of fluorescein-5.6 sulfonic acid (FITC-sulfonic acid; 10 mg/ml, 400 D, Invitrogen). The fluorescence level of basolateral aliquots of 150 µl was measured at 30-min interval during 180 min using a fluorimeter (Tecan Infinite F500; Tecan SA, Lyon, France). The values of fluorescence were converted to obtain concentrations of fluorescein (ng/ml) adapted through a standardized curve. Values of permeability are the mean value of four biopsies, with a calculated individual coefficient of variability <5%.

Tryptase assay in supernatant

Two biopsy samples were immersed in hard plastic tubes containing 1 ml of Hank's buffer saline solution (Invitrogen), continuously oxygenated (95% O₂/5% CO₂) at 37°C. After 20 min of incubation, the solution was removed and centrifuged at 200 g for 10 min before being filtered with centrifuge filters (200 µm, SPIN-X; Corning, NY) to remove bacterial components.

The amount of tryptase in the supernatant was measured using ImmunoCAP technology (PHADIA AB) with an ImmunoCap 250 as previously described. This assay measures both α-tryptase and β-tryptase from 1 to 200 µg/l.

Statistical analysis

Parameters of the study population were compared using χ^2 for qualitative variables, and Kruskal–Wallis and Mann–Whitney nonparametric tests for quantitative variables (medians, and 25th and 75th quartiles). The association between permeability, MCs, and the severity of IBS was a decision made *a priori* using linear regression. A *P* value <0.05 was considered statistically significant.

RESULTS

Clinical characteristics

In all, 34 IBS patients and 15 controls were included. Clinical characteristics are described in **Table 1**.

Histological findings

Histological findings are detailed in **Table 2** according to IBS subtypes. The count of MCs was significantly higher in IBS than in controls (*P*=0.001). This difference was observed for each IBS subtypes (IBS-C, *P*=0.003; IBS-D, *P*=0.001; and IBS-M, *P*=0.001), being more marked in IBS-D and IBS-M. The number of eosinophils and intraepithelial lymphocytes was similar between IBS and controls. In IBS, the number of MCs correlated significantly with the paracellular permeability (*r*=0.36, *P*=0.03; **Figure 1a**) and with the severity of IBS (*r*=0.62, *P*=0.0001; **Figure 1b**). Among all factors included in the IBS severity score, abdominal pain intensity correlated at best with MCs (*r*=0.54, *P*<0.001).

Paracellular permeability of cecal biopsies

Paracellular permeability was significantly higher in IBS (64 (48–101) ng/ml) than in controls (44 (33–70) ng/ml, *P*=0.006) and similar among IBS subtypes (86 (54.8–103.6) ng/ml for IBS-C; 55.7 (46.9–98.0) ng/ml for IBS-D; and 80 (45.4–99.9) ng/ml for IBS-M, *P*=0.6). In IBS, paracellular permeability correlated significantly with the severity of IBS (*r*=0.48, *P*=0.004; **Figure 1c**), without significant difference among IBS subtypes.

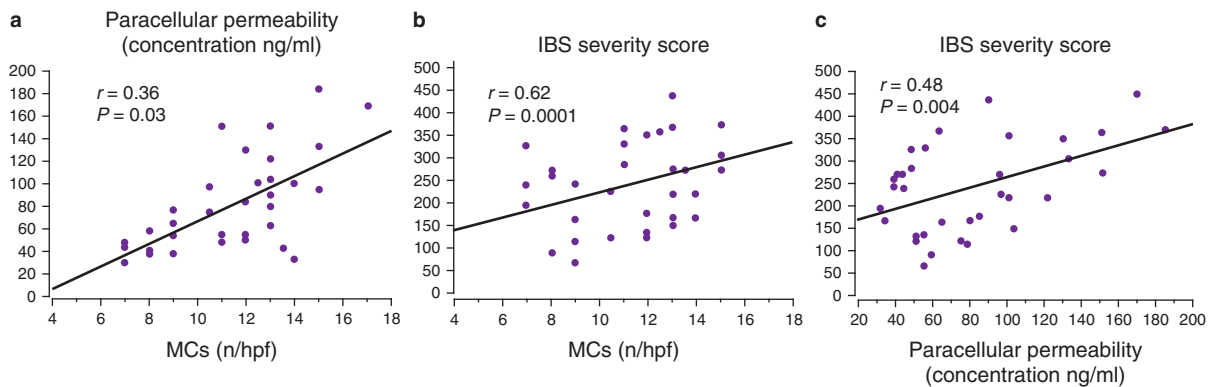
Tryptase release

In IBS, the release of tryptase correlated with the number of MCs (*r*=0.41, *P*=0.01). Significant higher amounts of tryptase were found in the supernatant from IBS (22.3 (12.5–55) µg/l) compared with controls (13 (8.1–14.7) µg/l, *P*=0.01). These amounts were significantly more elevated in IBS-D (51.5 (22.4–65) µg/l) and IBS-M (38 (19–52.5) µg/l) compared with IBS-C (7.2 (4.6–9.5) µg/l,

Table 2. Histological findings in colonic mucosal biopsy specimens of patients with IBS and healthy subjects

	IBS (34)	Controls (15)	<i>P</i> value	IBS-C (10)	IBS-D (13)	IBS-M (11)	<i>P</i> value
IELs	8 (6–12.1)	7 (6–9)	0.6	12 (8.3–14.2)	12 (4.5–8.3)	7 (5.5–9.5)	0.1
MCs	12 (9–13)	6 (5–8)	0.0001	10 (8–14)	12 (10.5–13)	12 (10.5–12.8)	0.5
Eosinophils	12.2 (10.5–14)	12 (7.5–11.5)	0.08	12 (11.6–13)	12 (9–14.2)	12.5 (10.5–14.1)	0.8

IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, IBS with mixed symptoms; IEL, intraepithelial lymphocyte; MC, mast cell. MCs and eosinophils are expressed as the number of cells per high power field and IELs per 100 epithelial cells. Data are medians and interquartile ranges.

**Figure 1.** Correlation between (a) the paracellular permeability of colonic biopsies and the number of mast cells (MCs); (b) the severity of irritable bowel syndrome (IBS) and the number of MCs; (c) the severity of IBS and the paracellular permeability.**Table 3.** Assessment of allergic factors according to IBS subtypes

	IBS-C (10)	IBS-D (13)	IBS-M (11)	Healthy (15)	<i>P</i> value
Trophatops ^a	0	7.6	18.1	0	0.2
Phadiatop ^b	20	46.1	54.5	0	0.007
Hypereosinophilia	0	15.3	9	0	0.3
IgE	0	23	22.2	0	0.2
Personal history of allergy	9	38.4	45.4	0	0.02
Familial history of allergy	12.5	38.4	9	0	0.03
Positive skin tests	20	61.5	54.5	26.6	0.07
Self-perceived suspected food	10	61.5	45.4	0	0.001

IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, IBS with mixed symptoms; IgE, immunoglobulin E.

^aTrophatops: multi-allergens biological screening tests targeting IgE directed against the most common food allergens for adults.

^bPhadiatop: multi-allergens biological screening tests targeting IgE directed against common inhaled allergens.

Data are expressed as percentages and comparisons were made using χ^2 -test.

$P=0.0007$ and $P=0.001$) or controls (13 (8.1–14.7) $\mu\text{g/l}$, $P=0.0004$ and $P=0.002$; **Figure 2**). The release of tryptase correlated with the severity of IBS ($r=0.48$, $P=0.01$).

Influence of AFs

Among 34 IBS patients, 38.2% presented at least three AFs, having significant higher symptoms scores ($P=0.001$), paracellular permeability ($P=0.04$), mucosal MCs ($P=0.01$), and release of tryptase ($P=0.01$) than those with less than three AFs (**Figure 3**). The group of 13 patients having at least three AFs was similar in age ($P=0.15$), gender ($P=0.5$), and bowel habits ($P=0.3$), as compared with IBS patients having no AF.

None of the seven AFs evaluated was predictive of the severity of IBS. IBS-D and IBS-M phenotypes were more frequent in IBS having at least three AFs (46.1% and 38.4%, respectively) compared with 21 IBS with less than three AFs (33% and 28.5%, respectively). In contrast, IBS-C was less common in IBS with at least three AFs (8.8%) compared with those with less than three AFs. Assessment of allergic factors according to IBS subtypes is detailed in **Table 3**.

DISCUSSION

A growing body of literature indicates that MCs have a key role in the pathophysiology of IBS. We addressed the question whether an allergic background, as a health condition in which MCs activation also has a central role, may influence IBS outcome. We showed that enhanced colonic paracellular permeability associated with increased number of mucosal MCs and tryptase release have a contributory role on the severity of IBS symptoms. Moreover, we found that patients with an allergic background

had more severe symptoms, with higher numbers of mucosal MCs and tryptase release. Interestingly, these patients were more prone to diarrhea. These findings suggest that a background of allergy may worsen IBS by promoting the activation of mucosal MCs and release of soluble factors, enhancing paracellular permeability.

Increasing evidence suggests the presence of functional activation of the inflammatory response at both systemic and mucosal level in IBS (3,4,9,12,27,28). In the present work, we retrieved an increased number of MCs infiltrating the mucosa of the cecum

that correlated with the severity of IBS symptoms. MCs are now recognized not only as effectors of allergic inflammation, but also as immunoregulatory cells contributing to the maintenance of gut barrier integrity (29). By contrast, a recent study showed no increase of MCs in rectal biopsies (30), which emphasizes that the inflammatory response and barrier functions of the distal colon are gradually different than in the proximal colon where we focused our biopsy specimens.

Interestingly, the severity of abdominal pain perception of IBS patients has been directly correlated to the close proximity between nerves fibers and MCs (12). It was previously demonstrated that the spontaneous release of tryptase from biopsy samples obtained in the distal colon was significantly higher in IBS than in controls (10,12), and that tryptase activity contained in supernatants could stimulate sensory neurons and hypersensitivity symptoms through the activation of PAR₂ receptors (10,11). In the present study, although similar numbers of MCs were found among IBS subtypes, the release of tryptase from biopsy samples was significantly higher in IBS-D and IBS-M compared with controls or IBS-C patients, which is in accordance with the findings of Buhner *et al* (10). The method that we used to measure tryptase takes into account both inactive α -tryptase, secreted in basal conditions, and functionally active β -tryptase released after MC activation (31). Therefore, the combination of similar number of MCs with different amounts of tryptase suggests that the level and/or pathway of MC activation are different between IBS-D and IBS-C. More patients with AF belonged to the IBS-D subtype and displayed more severe symptoms and higher disruption of the epithelial barrier. These findings suggest that common or different pathways leading to MC activation could be involved in both conditions

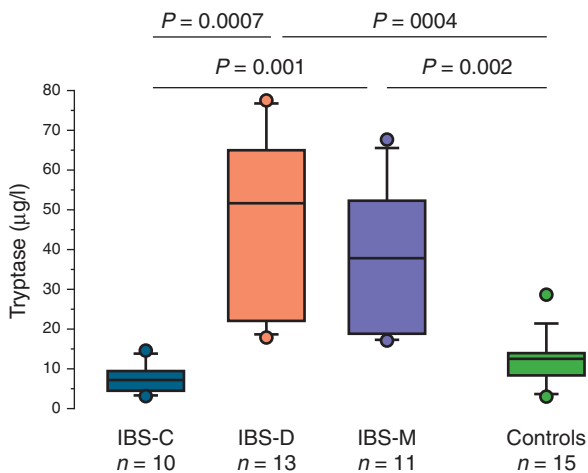


Figure 2. Spontaneous release of tryptase ($\mu\text{g/l}$) from colonic biopsies. IBS-C, irritable bowel syndrome with constipation; IBS-D, IBS with diarrhea; IBS-M, IBS with mixed symptoms.

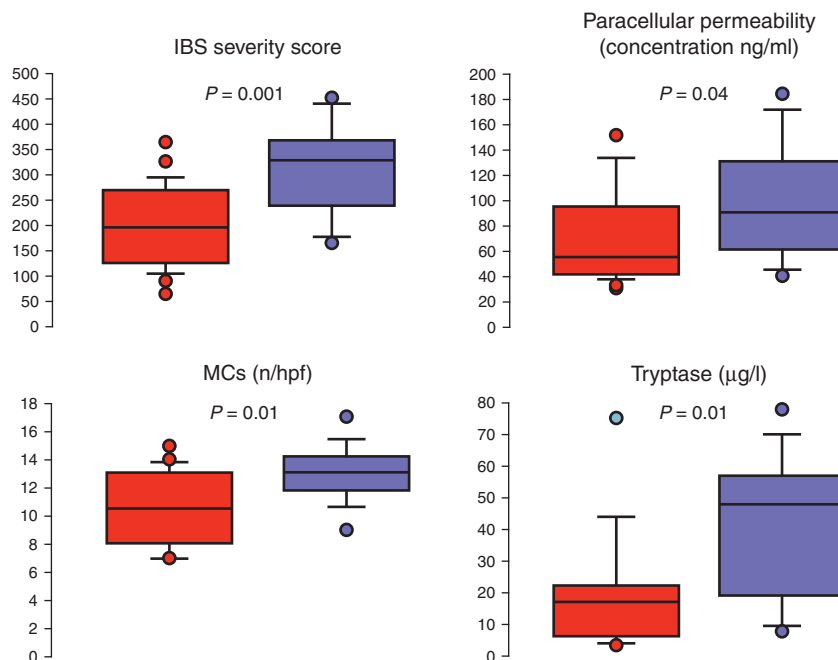


Figure 3. Comparison of irritable bowel syndrome (IBS) severity, paracellular permeability, mast cells (MCs) counts and tryptase release in IBS patients presenting with ($n=13$, blue) or without ($n=21$, red) criteria suggestive of allergy.

(e.g., IBS and allergy), with additive or synergistic effects. Indeed, MC activation can be triggered by a variety of immune and non-immune stimuli, including Toll-like receptor signaling activated by the microbiota, allergens via surface IgE, activation of C5a receptors, and many others (13).

MCs are also key effectors cells of allergy, and the question of a possible link between IBS and AFs is of particular interest. Symptom improvements have been observed in response to elimination diets and disodium cromoglycate treatments (32,33). Moreover, patients with asthma have increased prevalence of IBS compared with patients with other pulmonary disorders or healthy subjects (34). To date, the pathophysiology of food allergy and adverse immune response to foods that induce a variety of symptoms are far from clear with IgE-mediated and cellular non-IgE-mediated mechanisms involving MCs, eosinophils, and other immune cells (35). In the current study, we used a combination of criteria including, but not restricted to, those proposed by Bischoff *et al.* (26) to identify both type I hypersensitivity (e.g., total, sIgE, skin tests, and history of atopic disease) and food intolerance relying on IgE-independent mechanisms (e.g., history of food intolerance and eosinophilia). Although these criteria are clearly insufficient to diagnose food allergy in the absence of double-blind elimination diet or allergen reintroduction, combining these factors are helpful to identify an individual susceptibility to allergy. We did not focus on food allergy and included patients with a general background of allergy/atopy, regardless of the nature and way of entry of allergens into the system for different reasons. Allergy is mediated by highly motile immune cells that circulate throughout the body and interact with immune and mucosa cells located in distant organs and tissues. Moreover, antigens of different origins, such as food antigens and aeroallergens, can activate MCs in different locations through common activating antigenic determinants, which are responsible for the well-described oral syndrome (36). Therefore, allergy/atopy can possibly cause symptoms in distant organs and interfere with other pathophysiological mechanisms mediating MC activation. In addition, as aeroallergens enter the body via an aerodigestive crossing, it is likely that they are also partly ingested and can possibly bind and activate MCs in the gut. Using the above criteria, we found 38.2% of IBS patients presenting a background of allergy, which is a much higher proportion compared with the general population, as immune responses to foods affect approximately 3–4% of adults in westernized countries (35). This observation is also in accordance with a previous study based on the same criteria reporting that a diagnosis of intestinal food allergy could be suspected in 14.4% of patients with inflammatory and functional gastrointestinal disease (26). Moreover, patients with atopic symptoms were 3.20 times more likely to fulfill the criteria for IBS, which also suggests a link between IBS and non-food allergies (22). Altogether, these studies and our results strongly suggest that AFs contribute to the pathophysiology of IBS.

We also found a significant positive correlation between enhanced paracellular permeability and the severity of IBS. These data reinforce preliminary results obtained in a previous small cohort of IBS patients (18) and support the notion that paracellular permeability is a key factor contributing to IBS symptoms

(17,37). However, these correlations between permeability and symptoms are relatively weak, suggesting that other factors and/or route for allergen signal (e.g., transcellular permeability) could also be implicated in the occurrence of IBS symptoms. Interestingly, permeability values were similar among IBS subtypes, suggesting that barrier defects associated with mucosal inflammation may be a common mechanism underlying painful symptoms in all IBS subtypes. Moreover, the significant correlation between MCs and permeability levels measured at the same colonic site adds to the growing evidence that MCs and their secreted mediators alter paracellular permeability in IBS patients. We further observed that IBS patients with at least three AFs had more severe symptoms associated with more marked permeability defects, higher number of MCs, and amounts of tryptase, suggesting the contributory role of allergy mechanism to worsen IBS symptoms by activating MCs and enhancing paracellular permeability through an additive or synergistic effect of mediators released. Conversely, it can be speculated that barrier defects of IBS patients promote the entry of allergens into the mucosa and the occurrence of adverse reactions. Indeed, it is likely that any alteration of the gut barrier promotes the outcome of allergy, as suggested by the much higher prevalence of food allergy in young children whose mucosal barrier is immature or by recent findings showing that alteration of the physiological gastric barrier can lead to an augmentation of IgE sensitization in both children and adults (38). Whether AFs act as a cause or a consequence of barrier defects and/or inflammation in IBS remains to be determined.

Interestingly, most IBS patients with AFs had a diarrheic form of the disease, which is in accordance with previous findings (33). It was also shown that IBS-D patients had increased fecal serine protease activity (39). Many allergens have cysteine or serine protease activity, as well as other proteolytic activities that are in turn able to affect gut mucosal immunity (40). Whether IBS-D and IBS-M subtypes associated with food allergy have increased protease-activated receptors should be further evaluated.

In conclusion, our data indicate that increased mucosal MC activity, and release of soluble mediators, such as tryptase, together with enhanced colonic paracellular permeability, influence the severity of IBS symptoms. Moreover, our results suggest that IBS patients with an allergic background have more severe symptoms. This effect may be the result of augmented MC activation in the gut mucosa of patients with AF, through an additive or synergistic effect, with increased release of soluble mediators, such as tryptase, able to impair colonic epithelial barrier.

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CONFLICT OF INTEREST

Guarantor of the article: Thierry Piche, MD, PhD.

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performed skin tests and data acquisition: R. Dainese; data acquisition, technical support: R. Anty, N. Gonthier, S. Marjoux, and G. Frin-Mathy; performed permeability studies: J.L. Nano; performed histological assessments: M.C. Saint-Paul; material support acquisition: X. Hébuterne and A. Tran; study concept, data interpretation, manuscript preparation, and critical revision: V. Theodorou; study concept, obtained funding, manuscript preparation, and study supervision: T. Piche.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Epithelial barrier defects and mast cells (MCs) contribute to the pathophysiology of irritable bowel syndrome (IBS).
- ✓ The role of allergic factors on IBS symptoms is unclear.

WHAT IS NEW HERE

- ✓ The severity of IBS is associated with both enhanced colonic permeability and increased mucosal MCs.
- ✓ Individual susceptibility to allergy has the potential to worsen IBS symptoms, particularly in patients with diarrhea predominance.

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