

Association between Allergic Diseases and Irritable Bowel Syndrome: A Retrospective Study

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Keywords

Irritable bowel syndrome · Allergy · Urticaria · Rhinitis · Gastrointestinal symptoms · Immune reaction

Abstract

Background: The relationship between allergic disease and irritable bowel syndrome (IBS) is poorly understood. We aimed to investigate the potential association as well as the underlying immunological mechanisms. **Methods:** A retrospective case-control study of 108 atopic patients from among outpatients in an allergy clinic (allergic rhinitis [AR], $n = 49$; chronic urticaria [CU], $n = 59$) and 74 controls from among ward companions was conducted from November 2016 to March 2017. The detection rates and related gastrointestinal (GI) symptoms of IBS, as well as immunological indices, were calculated. **Results:** CU patients had a trend of increase in the detection of IBS compared to controls (OR = 4.846; 95% CI 0.967–24.279, $p = 0.077$). Loose stools (OR = 2.406; 95% CI 1.075–5.386, $p < 0.05$) and viscous stools (OR = 2.665; 95% CI 1.250–5.682, $p < 0.05$) were more common in CU patients. Atopic patients positive for serum total immunoglobulin E (IgE) (OR = 3.379; 95% CI 1.088–10.498, $p < 0.05$) or house dust mite (HDM)-specific IgE (OR = 3.640; 95% CI

1.228–10.790, $p < 0.05$) were more likely to have abdominal bloating. Besides, a positive association between levels of total IgE and severity of abdominal bloating was observed ($p < 0.05$). An HDM-specific IgE-positive reaction was independently associated with abdominal bloating in atopic patients ($p < 0.05$). **Conclusions:** Allergic disease has a clear clinical association with IBS with more frequent and severe symptoms of IBS. CU patients have a tendency to suffer from IBS, usually with diarrhea. Serum total IgE and HDM-specific IgE are positively correlated with GI symptoms in atopic patients.

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Introduction

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder that presents as recurrent abdominal pain associated with defecation or a change in bowel habits. The worldwide prevalence of IBS is 11.2%. The incidence of IBS is 1.35–1.5% [1]. The prevalence of IBS reached

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5.9% in South China in 2016 [2]. IBS is a multifactorial disorder with a complex pathophysiology [1].

Allergic diseases, including allergic rhinitis (AR), asthma, urticaria, eczema, atopic dermatitis, and food allergy, implicate approximately 20% of the population. Allergic disease can cause local end-organ dysfunction and even systemic symptoms [3]. Previous studies have suggested that specific allergen exposure may contribute to IBS-related gastrointestinal (GI) symptoms in allergic individuals [4, 5]. Preschoolers with allergic diseases have an elevated risk of IBS [6]. On the other hand, patients with IBS have a higher risk of allergy than patients without IBS [3, 7].

T-helper 2 (Th2) immune activation has been associated with allergy and IBS. The pathology of active wheals in patients with chronic urticaria (CU) has shown a large number of degranulated mast cells [8]. Relevant allergen exposure causes relief of inflammatory mediators of hypersensitivity through cross-link of immunoglobulin E (IgE) on mast cells in patients with AR [9]. In addition, increased mast cells in the duodenal and colonic mucosa have been found in patients with IBS [7].

However, the relationship between allergy and IBS remains controversial. The pathophysiological mechanisms of the association are still unclear. To investigate the relation between allergic disease and IBS, we conducted a retrospective case-control study to evaluate the detection rates of IBS and IBS-related GI symptoms and the association of immunity and GI symptoms in atopic patients.

Materials and Methods

Participants

This study was carried out at the Affiliated Hospital of Zhejiang University School of Medicine during a 4-month period from November 2016 to March 2017. Atopic patients were referred to the Allergy Clinic of The Second Affiliated Hospital. Those who had history of allergen exposure or possible exposure, like seasonal onset, were recruited into the allergy group, and among them those with AR or CU were recruited into the AR subgroup or the CU subgroup, respectively. The diagnosis of AR is based on the Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 guideline [10]. The comorbidity was calculated, and 6 cases of eczema and 2 of conjunctivitis were found among the AR patients, according to ARIA 2008 and JDA 2009 [10, 11]. The diagnosis of CU was made according to the EAACI/GA²LEN/EDF/WAO guideline [12]. Healthy controls were recruited from ward companions and excluded if they had: (1) a history of any known chronic diseases involving the respiratory, GI, cardiological, urinary, hematological, endocrine, or nervous system; (2) any acute infection in the last 3 months; (3) a history of any documented allergic diseases or related allergic symptoms; or (4) a history of any medication of known diseases. Informed consent was obtained from all of participants in our study. All of the patients and controls included in

this study gave their written informed consent that the study protocol was approved by the Research Ethics Committee of the First Affiliated Hospital of Zhejiang University.

IBS Evaluation and GI Complaints

All participants completed the IBS questionnaire (Rome IV criteria [1]). Individuals diagnosed with IBS should meet the following criteria based on Rome IV: recurrent abdominal pain, on average, on at least 1 day a week in the last 3 months, associated with 2 or more of the following criteria: related to defecation, associated with a change in stool frequency, and associated with a change in stool consistency. Then, patients who fulfilled the criteria were followed by the gastroenterologists for differential diagnosis of IBS and other related GI diseases. The individuals also answered questionnaires about IBS-related GI complaints. Abdominal discomfort (abdominal pain or bloating) and habits and characteristics of defecation were assessed in all of the participants. Incidence, frequency, and severity were evaluated. GI symptoms had to have been experienced during the last 3 months with symptom onset at least 6 months before consulting. The frequency of abdominal discomfort was divided into the following 5 grades: "never," "occasionally" (once or twice a month), "sometimes" (once or twice a week), "usually" (3 or 4 times a week), and "always" (every day). The severity of abdominal discomfort was divided into the following 4 grades: "none," "mild," "moderate" (tolerable), and "strong" (unbearable). The severity of hard stools was described as: "none," "lumpy," or "nut-like." The severity of loose stools was described as: "none," "soft," "mushy," or "watery."

Cellular and Immunological Examination

The blood eosinophil counts, serum total IgE, house dust mite (HDM)-specific IgE, and food-specific immunoglobulin G4 (IgG4) of the allergic group and the eosinophils and total IgE of the controls were analyzed using the ImmunoCAP system [13]. A positive reaction to total IgE was defined as levels increasing to more than 100 KU/L. A positive reaction to HDM-specific IgE was defined as levels increasing to more than 0.35 KU/L. A positive reaction to food-specific IgG4 was defined as increased levels of IgG4 (≥ 250 U/L) to at least one food allergen.

Statistical Analysis

Statistical analyses were performed using Statistical Product and Service Solutions, version 22 (IBM SPSS Statistics 22, Inc., Chicago, IL, USA). An unpaired-samples Student's *t* test and the Mann-Whitney *U* test were used to test differences between groups. The χ^2 test was used for comparisons of categorical variables. Correlation analysis was performed using Spearman's correlation test and linear regression models. Multivariate logistic regression analysis was performed to assess the factors independently associated with GI symptoms. $p < 0.05$ was considered statistically significant.

Results

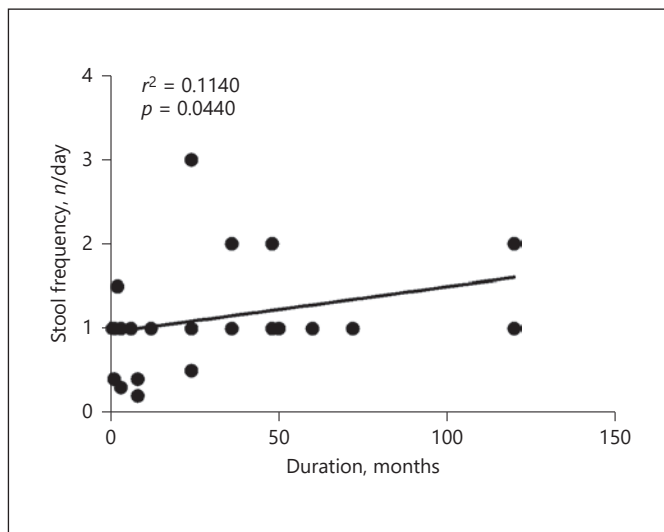
Demographic Characteristics and Detection Rates of IBS

In all, 108 atopic patients were identified, including 49 patients with AR and 59 patients with CU. A total of 74 subjects were included as controls. The demographic

Table 1. Demographic and IBS-related characteristics in allergy and controls

Characteristic	Allergy	AR	CU	Controls
Total, <i>n</i>	108	49	59	74
Males	43 (39.8)	24 (49.0)	19 (32.2)	35 (47.3)
Age, years	33.25±15.78	30.59±16.02*	35.52±15.35	38.97±16.46
Total IBS	9 (8.3)	2 (4.1)	7 (11.9)	2 (2.7)
IBS-related symptoms				
Bloating	23 (20.5)	9 (18.4)	14 (23.7)	17 (23)
Abdominal pain	27 (24.1)	9 (18.4)	18 (30.5)	13 (17.6)
Stool frequency, <i>n/day</i>	1.07±0.54	1.02±0.35	1.12±0.65	1.06±0.36
Hard stools	27 (24.8)	13 (26)	14 (23.7)	28 (37.8)
Loose stools	30 (27.5)	10 (20)	20 (33.9)*	13 (17.6)
Viscous stools	36 (32.1)	11 (22.4)†	25 (42.4)*	16 (21.6)

Values are presented as numbers (%) or means ± SD unless otherwise stated. IBS, irritable bowel syndrome; AR, allergic rhinitis; CU, chronic urticaria. * $p < 0.05$ compared with controls; † $p < 0.05$ compared with CU.

**Fig. 1.** Correlated analysis of disease duration and stool frequency in patients with chronic urticaria.

characteristics and detection rates of IBS for the allergy group and its subgroups compared to controls are shown in Table 1. There was a female predominance in all groups. The AR group was younger than the controls ($p < 0.05$). Nine of the 108 (8.3%) patients with allergic disease reported IBS. Among the patients with CU, 7 out of 59 (11.9%) reported IBS compared to 2 out of 74 (2.7%) controls (OR 4.846; 95% CI 0.967–24.279, $p = 0.077$).

IBS-Related GI Symptoms

The occurrence, frequency, and severity of IBS-related GI symptoms were analyzed in patients with allergy, AR, or CU compared to controls (Table 1). Loose stools were found in 33.9% of patients with CU and in only 17.6% of the controls (OR 2.406; 95% CI 1.075–5.386, $p < 0.05$). The severity of the symptoms also increased in patients with CU compared to controls ($p < 0.05$). In addition, viscous stools were found in 42.4% of patients with CU but in only 21.6% of the controls (OR = 2.665; 95% CI 1.250–5.682, $p < 0.05$) and in 22.4% of patients with AR (OR = 2.540; 95% CI 1.089–5.924, $p < 0.05$). With adjustment for age and sex, patients with CU had higher odds of viscous stools compared to controls ($p < 0.05$) and AR patients ($p < 0.05$). Moreover, loose stools were modestly more common in patients with CU compared to controls ($p < 0.05$). However, GI symptoms did not differ significantly between atopic patients and controls.

In correlation analysis, the frequency of stools was positively correlated with the disease course of urticaria in patients with CU ($p < 0.05$, $r = 0.3849$). Linear fit results are shown in Figure 1.

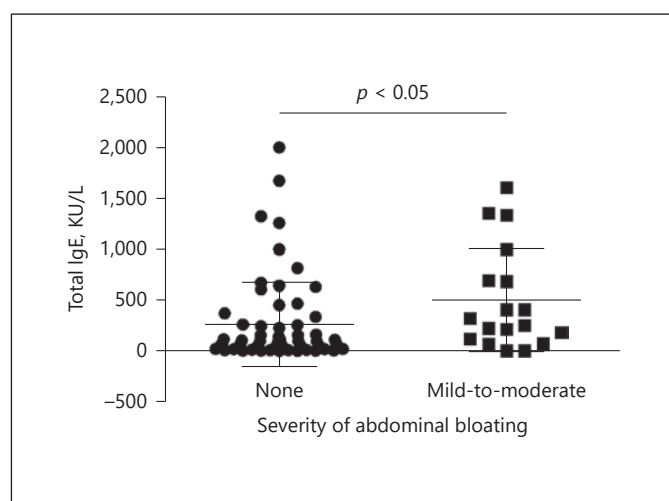
Immunity and GI Symptoms in Allergic Patients

Blood eosinophil counts, serum total IgE, HDM-specific IgE, and food-specific IgG4 were measured in allergic patients (see online suppl. Table S1; see www.karger.com/doi/10.1159/000489611 for all online suppl. material). Patients positive for total IgE had higher odds

Table 2. Effect of total IgE and HDM-specific IgE on bloating

Group	Total IgE positive		HDM-specific IgE positive	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Allergy	3.379 (1.088–10.498)	0.038	3.640 (1.228–10.790)	0.02
Allergic rhinitis	4.667 (0.507–4.923)	0.222	4.55 (0.5–41.417)	0.227
Chronic urticaria	4.667 (0.990–22.008)	0.066	9.750 (1.880–50.556)	0.007

HDM, house dust mite.

**Fig. 2.** Total IgE levels in patients with allergic disease with different degrees of severity of abdominal bloating.

of abdominal bloating compared to negative patients in the allergy group (OR = 3.379; 95% CI 1.088–10.498, $p < 0.05$; Table 2). Moreover, there was a significant increase in total IgE levels along with an increase in the severity of abdominal bloating in atopic patients (259.23 ± 415.18 and 501.91 ± 504.07 , $p < 0.05$; Fig. 2). Additionally, patients positive for HDM-specific IgE were more likely to have abdominal bloating than negative patients in both the allergy (OR = 3.640; 95% CI 1.228–10.790, $p < 0.05$) and the CU groups (OR = 9.750; 95% CI 1.880–50.556, $p < 0.01$; Table 2).

In the multivariate adjusted analysis with adjustment for age and sex, a positive reaction to HDM-specific IgE, rather than total IgE, was independently related to abdominal bloating in atopic patients ($p < 0.05$).

Discussion

In the present study, we investigated the association between allergy and IBS-related symptoms, while further exploring the underlying immunological mechanism.

Our study first revealed more frequent and severe IBS symptoms in allergic patients, especially in the subgroup of CU patients. In recent decades, several studies have investigated the relationship between allergy and IBS. A previous study showed a greater risk of subsequent IBS in children with antecedent allergic disease [6]. Lower GI symptoms such as diarrhea are common in children with allergy [14, 15]. Intestinal permeability was significantly increased in patients with atopy compared to nonatopic patients [16]. Seasonal inhalation of birch pollen has been suggested to cause a duodenal increase in IgE-bearing cells [5]. However, the association between AR or CU and IBS has rarely been identified. Jones et al. [7] reported a significantly higher prevalence of any atopic condition in patients with IBS. They found an elevated prevalence of hay fever/rhinitis with an OR of 2.98 (95% CI 2.63–3.37, $p < 0.0001$) in IBS patients compared to controls. Tan et al. [6] conducted a population-based case-control study and found the highest OR (i.e., 1.78) for IBS in patients with AR (95% CI 1.69–1.87) among all antecedent allergies in children, followed by an OR of 1.56 (95% CI 1.40–1.73) in children with urticaria. In our study, we used the detailed categories for symptom detection and thus proved a clear association between CU and IBS. However, we failed to show a significant association between allergy and IBS, as well as between AR and IBS. This study merely shows a tendency toward a difference between allergy patients and controls in symptoms of loose or viscous stools, whereas there was no tendency toward a difference between AR patients and controls, which might have affected the significance between allergies and controls. These inconsistent findings pro-

pose the need for additional large-scale population-based investigations.

The mechanisms underlying this association are still unclear. An IgE-mediated immune reaction might be the bridge under this association, supported by the positive correlation among serum total IgE, HDM-specific IgE, and abdominal bloating in atopic patients. As is known, dysregulated immune activation on the epithelial barrier surfaces is common in both allergy and IBS [17]. Lillestol et al. [16] reported earlier that elevated numbers of IgE-positive cells in duodenal mucosa were found in patients with atopy compared to nonatopic patients. Besides, numbers of IgE-positive cells in duodenal mucosa were significantly correlated with levels of serum total IgE. Vara et al. [18] reported that complaints of mild to moderate GI were positively associated with higher total IgE levels, and this was confirmed in our study, as the severity of bloating in subjects in our analysis was mostly mild to moderate. Recent studies reported 2 cases of a positive clinical response to omalizumab in patients with IBS-D and concomitant CU and asthma, respectively [19], which further confirmed this viewpoint.

On the other hand, the GI mucosal immune system probably has an effect on allergic disease. Local inflammation may influence the systemic immune homeostasis. Degranulation of mast cells in the intestinal mucosa is associated with the release of bioactive mediators, such as histamine, tryptase, chymase, and prostaglandin D₂, which may indirectly affect the activation of immune responses [20]. Other inflammatory cells, including lymphocytes, neutrophils, eosinophils, and basophils, can be found migrating to end-organs of allergic lesions. Neurotransmitters participating in regulation of the intestinal barrier, like substance P, help to perpetuate and further the allergic inflammation [21]. Moreover, it has recently been suggested that imbalances in the composition of the intestinal microbiota might trigger allergy. The intestinal microbiota not only regulates the intestinal mucosal immune system but also takes part in systemic inflammatory responses [22]. It has been found that a reduced gut microbial diversity in infancy is associated with an increased risk of allergic manifestations in school-aged children [23]. In an animal model, it was shown that microbial colonization induces appropriate maturation of the Th2 response and IgE regulation during the early developmental window time [24].

CU is a complex disease with multiple etiologies including chronic infections, autoimmune reactions, allergy, and even tumors in rare conditions. The pathological mechanism is still unclear. Most cases of CU have spon-

aneous provocations of symptoms and do not show direct connections to specific allergens. However, atopy characterized as an increase in total IgE can be found in many patients with CU, and the present study is the first to observe the connections between clinical symptoms and serum immunologic indices like specific allergen IgE and total IgE. The results did show this connection, although further studies are needed to explore the mechanism of this connection.

Our study showed that this clinical association was more prominent in CU and IBS-related symptoms. It is in agreement with the recent discovery of Magen and Chikovani [19] of a strong association between IBS and CU in a cross-sectional study of a large cohort (11,271 patients). Data that CU patients were more likely than controls to have loose or viscous stools suggested the association between CU and diarrhea. We subsequently found that the disease course of urticaria was positively correlated with the frequency of stools, which identified the association between CU and lower GI symptoms. The mechanisms of the association of CU and diarrhea are still unclear. Minnei et al. [25] suggested that CU is associated with gastroduodenal mast cell infiltration. In addition, CU is often aggravated by the intake of pseudoallergen-containing foods, which might be associated with mast cell infiltration in the GI mucosa. Dunlop et al. [26] reported that diarrhea-predominant IBS was associated with increased lamina propria mast cells and T lymphocytes. Moderately increased mucosal mast cells were positively correlated with visceral hypersensitivity and intestinal permeability in patients with D-IBS [27, 28]. Therefore, we supposed that intestinal mast cell infiltration was associated with diarrhea in CU patients. However, the pathological mechanisms of CU were complicated, including IgE-mediated, autoimmune, and nonimmunologic etiologies, whereas they were predominantly IgE mediated in AR [29]. So whether the underlying mechanism of CU and diarrhea involves more than one type of immune response (e.g., IgG mediated) needs further investigation. Besides, AR was usually associated with upper GI diseases, like oral allergy syndrome triggered by pollen, food, or eosinophilic esophagitis [30, 31].

The role of food allergy in IBS has been reported in previous studies. A portion of clinical trials of exclusion diets based on food-specific IgE and IgG4 have been reported successfully [32]. In addition, the relationship between food allergy and other allergic diseases, such as urticaria and AR, has been shown in previous studies [33, 34]. Food-specific IgG4 is actually one immunologic index connected to many diseases including allergic dis-

eases. It is not the direct etiology provoking the symptoms, but studies have indicated that it might play roles in recurrent attacks of allergic diseases [35]. Previous studies have presented the role of allergen-specific IgG4 in inducing the release of histamine from eosinophils, as IgE did in allergic diseases [36]. However, Antico et al. [37] reported that 62% of patients with allergic dermatosis were food-specific IgG4 positive and did not have any acute or delayed adverse reactions towards specific foods. It is suspected that IgG4 has an effect of the diagnosis of food allergy. The role of food-specific IgG4 in allergic diseases needs further research. However, our study failed to observe an obvious association between food-specific IgG4 and IBS or IBS-related GI symptoms in atopic patients. Besides, there was no significant difference in food-specific IgG4 positivity rate between AR and CU patients. The role of food-specific IgG4 in IBS is still controversial.

There are some limitations to our study. First of all, the number of samples was limited. The number of patients with IBS was not adequate for prevalence examination or further studies of subtypes of IBS. Secondly, we did not analyze allergen-specific IgE and food-specific IgG4 in controls, so we were not able to identify the role of IgE and IgG4 in GI symptoms in controls. Thirdly, not all of the allergic conditions of CU were confirmed by IgE assays or the skin prick test. Fourthly, respondent bias existed in the diagnosis of IBS. In addition, exclusion of ab-

dominal organic diseases lacked confirmation via a relevant imaging examination. Lastly, psychological and social factors, diet habits, obesity, and seasonal variation might have confounded our results.

In conclusion, patients with CU have a tendency to suffer from IBS, usually with diarrhea. Allergic patients positive for serum total IgE or HDM-specific IgE are more likely to have abdominal bloating, suggesting a role of IgE-mediated immune reaction in the effect of allergy on GI symptoms. HDM-specific IgE positivity is an independent risk factor for bloating, indicating the relation between HDM inhalation and GI symptoms. It is interesting to investigate the common pathological mechanisms between allergy and IBS, and the potential therapeutic value of anti-IgE therapy on IBS. Further research is necessary to deeply explore the association between allergic diseases and IBS.

Statement of Ethics

The study protocol was approved by the institute's committee on human research.

Disclosure Statement

The authors report no conflict of interests.

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Supplementary material

Supplementary Table 1. Patient immunological assays in allergy and controls

Characteristic	AD	AR	CU	Controls
Eosinophils				
Subjects submitted	45	24	21	17
Value($10^9/L$)	0.257±0.257	0.348±0.297 ^{*,†}	0.153±0.150	0.128±0.080
Total IgE				
Subjects submitted	81	40	41	17
Value(KU/L)	317.73±443.22 ^{**}	408.77±519.30 ^{***}	228.91±337.03 [*]	42.17±25.97
HDM-specific IgE positive				
Subjects submitted	84	43	41	NS
Value(%)	39(46.4)	28(65.1) ^{†††}	11(26.8)	
Food-specific IgG4 positive				
Subjects submitted	58	12	46	NS
Value(%)	29(50)	7(58.3)	22(47.8)	

IBS, irritable bowel syndrome; AD, allergic disease; AR, allergic rhinitis; CU, chronic urticaria; HDM, house dust mite.

* $P<0.05$ compared with controls; ** $P<0.01$ compared with controls; [†] $P<0.05$ compared with CU; ^{†††} $P<0.001$ compared with CU.

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