



Atopic Patients Who Fulfilled Rome III Criteria for Irritable Bowel Syndrome Had Higher Animal Danders Sensitization

Kewin T H Siah,^{1,2*} Amelia Santosa,^{2,3} Cynthia K Y Cheung,⁴ Alex Y S Soh,^{1,2} and Paul L Bigliardi⁵

¹Division of Gastroenterology and Hepatology, University Medicine Cluster, National University Health System, Singapore; ²Yong Loo Lin School of Medicine, National University of Singapore, Singapore; ³Division of Rheumatology, University Medicine Cluster, National University Health System, Singapore; ⁴Department of Medicine, The University of Hong Kong, Hong Kong, China; and ⁵Department of Dermatology, Division of Dermato-Allergy, University of Minnesota, Minneapolis, MN, USA

Background/Aims

The relationship between animal exposure and irritable bowel syndrome (IBS) is debated. Epidemiological studies have shown that atopy is more prevalent in IBS patients and vice versa. We set out to examine the association between animal danders sensitization and IBS-like symptoms in atopic patients.

Methods

We recruited 69 consecutive atopic patients from the allergy clinic of a tertiary hospital. Subjects completed validated bowel questionnaires, underwent skin prick test, blood was collected for serum total immunoglobulin E, and ImmunoCAP immune solid-phase allergen chip (ISAC) IgE multiplex assay.

Results

Twenty-eight (41.0%) atopic patients fulfilled the Rome III IBS criteria (atopy-IBS). There were no differences in gender, age, pet ownership, total serum IgE, or food allergen sensitization between atopy-IBS group and atopy-non-IBS group. We found that atopy-IBS group had significantly higher number of positive skin prick test for cat dander (64.3% vs 24.4%, $P < 0.001$), dog dander (64.3% vs 41.5%, $P = 0.015$) and weed pollens (32.1% vs 14.6%, $P = 0.050$) compared to atopy-non-IBS group. Out of 112 components from 51 allergen sources (both aeroallergen and food allergens), only Fel d1 (a major cat dander antigen) IgE is significantly higher in atopy-IBS group than atopy-non-IBS group (21.4% vs 2.4%, $P = 0.029$). Majority of atopy-IBS patients had mixed-type IBS.

Conclusions

We demonstrated an association between animal danders sensitization, in particular cat dander sensitization, and IBS-like symptoms in atopic patients. Future studies are needed to explore the relationship between aeroallergen and functional gastrointestinal disorders. Sensitization may be related to the pathophysiology of IBS or it could be that we are missing aeroallergen-induced gut allergy.

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Key Words

Allergens; Allergy and immunology; Fel d1 protein; Irritable bowel syndrome

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*Correspondence: Kewin T H Siah, MD

Division of Gastroenterology and Hepatology, University Medicine Cluster, National University Health System, NUHS Tower Block, Level 10, 1E Kent Ridge Road, 119228 Singapore
Tel: +65-6779-5555, Fax: +65-6775-1518, E-mail: kewin_siah@nuhs.edu.sg

Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder (FGID), characterized by recurrent abdominal pain or discomfort associated with irregular bowel habits.¹ The reported mean prevalence of IBS ranges from 1.1% in France to 35.5% in Mexico.² The pathology underlying IBS is likely multifactorial resulting from a variety of mechanisms such as visceral hypersensitivity, motility disturbances, dysfunction of the gut-brain axis, genetic inheritance, low-grade inflammation, gut microbiome dysbiosis, and psychosocial disturbances.^{3,4} Increasing numbers of epidemiological research associate pet or animal exposure with the development of IBS.⁵⁻⁷ A recent systematic review and meta-analysis combining the result of 5 studies found that exposure to pets was found to be significantly associated with having IBS (pooled odds ratio of 1.264).⁵ In a prior community study performed in Singapore to investigate the environmental factors associated with IBS development, we found that pet owners were 2.5 times more likely to suffer from IBS.⁶ Similarly, Koloski et al⁷ also reported childhood animal exposure as a risk factor for the development of IBS later in life.

Multiple studies showed that patients with allergic diseases often also suffer from IBS, suggesting a link between atopic disorders and IBS.^{8,9} In 2008, Tobin et al⁹ showed that IBS was significantly more prevalent in patients with allergic rhinitis and allergic eczema. Atopic patients were also found to be 3.2 times more likely to fulfill IBS criteria compared to non-atopic patients, and were referred to as “atopic” IBS.⁹ Vivinus-Nebot et al¹⁰ showed that IBS patients with higher allergy-related factors like self-perception of adverse reaction to food, and blood eosinophilia were more prone to diarrhea than IBS patients with less allergy-related factors. In another study in Australia examining the relationship of atopy and FGIDs, self-reported animal allergy was significantly associated with IBS while pollen allergy was associated with functional dyspepsia.¹¹

Animal dander is one of many types of aeroallergens in addition to pollen, cockroach, and house dust mite (HDM). Aeroallergens have been shown to be involved in multiple gastrointestinal (GI) diseases. Allergic reactions to foods contaminated with HDM can cause oral mite anaphylaxis characterized by an immediate allergic reaction to mite in patients with IgE sensitization to HDM.¹² Eosinophilic esophagitis is an esophageal disease characterized by eosinophil-predominant inflammation. Intranasal instillation of dust mite, *Aspergillus fumigatus*, and cockroach causes the onset of experimental eosinophilic esophagitis.¹³ Patients allergic to birch

pollen often complain of both respiratory and GI symptoms during the birch pollen season. Studies of patients with birch pollen allergy have also shown that birch pollen exposure triggers a local inflammation in the duodenum with increased eosinophils and IgE-carrying mast cells (MCs).^{14,15}

However, not all studies reported positive results. Nybacka et al¹⁶ reported that IBS patients did not have more atopic disease compared to controls (55.0% in IBS vs 40.0% in controls, $P = 0.070$). They also showed that atopy status or total serum IgE level was not a good biomarker to identify IBS patients with allergic manifestation. Thus, instead of looking for atopy in IBS based solely on IgE levels, we decided to establish the correlation between the complex and heterogenous atopic and allergic diseases with bowel issues by performing skin prick tests (SPTs), evaluation of specific IgE in serum by immune solid-phase allergen chip (ISAC) multiplex assay, and relating all of these results to pertinent clinical symptoms. We hypothesize that atopic patients with IBS-like symptoms are sensitized to animal dander. We aim to compare the sensitization pattern of aeroallergens and food allergens of both atopic patients with and without IBS-like symptoms.

Materials and Methods

Study Population

Study subjects comprised of consecutive adult Chinese patients seen for atopic symptoms (asthma, rhino-conjunctivitis, and/or atopic dermatitis) at the allergy outpatient clinic of the National University Hospital, Singapore. Exclusion criteria included patients with red flags (nocturnal GI symptoms, blood in stool, weight loss, recurrent fever, family history of colon cancer, or inflammatory bowel disease) or known organic GI disease, psychiatric illness, or any patient who has taken antibiotic, corticosteroids or immunosuppressive agents in the past 2 months. Participating subjects completed the Bowel Symptoms Questionnaire validated in our local setting,¹⁷ underwent SPT and venipuncture for total serum IgE and specific IgE antibody tests. Blood was tested for occult parasitic infections to rule out their influence on total serum IgE level. Written informed consent was obtained from all subjects. The conduct of our study was approved by the local Institutional Review Board (NHG ROAM: 2011/02188).

Definition

Rome III IBS was defined as recurrent abdominal pain or discomfort for at least 3 days per month in the last 3 months associated

with at least 2 other criteria: (1) improvement with defecation; (2) onset associated with a change in frequency of stool; and (3) onset associated with a change in form of stool. Atopy was defined by the presence of atopic clinical symptoms (allergic rhinitis, asthma, and/or atopic dermatitis) plus either a positive SPT to at least one allergen and/or elevated total IgE in the presence of at least one positive specific IgE. Asthma was defined based on the criteria used in the European Community Respiratory Health Survey (ECRHS) II.¹⁸ Allergic rhinitis was defined according to the Allergic Rhinitis and its Impact on Asthma (ARIA)¹⁹ document, and allergic dermatitis was diagnosed based on the GA²LEN definition.²⁰ Pet ownership means the subject either currently or previously live in a home with indoor pet.

Skin Prick Test

SPTs were conducted by trained allergy nurses or physicians and evaluated by a board certified allergologist. All pricks were done on the volar aspect of the subjects' forearm and read 15 minutes after application. We used histamine (1 mg/mL) as our positive control, while physiological saline served as negative control (both from Allergopharma). The SPT was considered to be positive if the wheal diameter was larger than 3 mm. The SPT solutions used in our test panel were from Allergopharma (A), Germany and Stallergenes (S), France. They included: *Alternaria tenuis* (A), *Cladosporium herbarum* (A), *A. fumigatus* (A), *Penicillium notatum* (A), cockroach (A), grass mix (A; containing kentucky blue grass, meadow fescue, orchard grass, rye grass, timothy grass and velvet grass), tree mix I (A; containing alder, elm, hazel, poplar, and willow) and II (A; containing birch, beech, oak, and plane tree), grasses/cereals (A; containing grasses, barley, oat, rye, and wheat), weed pollens (A; containing [*Artemisia vulgaris*, *Urtica dioica*, *Taraxacum vulgare*, and *Plantago lanceolata*]), latex (A), *Dermatophagoides farinae* (A), *Dermatophagoides pteronyssinus* (A), *D. farinae* (S), *D. pteronyssinus* (S), *Blomia tropicalis* (S), dog (S), cat (S), prawn (S), curry (S), coffee (S), wheat (S), soya (S), and pork (S). HDM sensitization on SPT was measured using allergen extracts from Allergopharma and Stallergenes to compare the reproducibility of the standardized HDM allergens from different suppliers. The following drugs had to be avoided for at least 1 week before the SPTs: antihistamines, tricyclic antidepressants, cysteinyl leukotriene antagonists, benzodiazepines, and beta-blockers.

Specific Serum Immunoglobulin E Antibodies

Total serum IgE levels were measured using Phadia 100; results were reported in kIU/L. Specific serum IgE antibodies were

measured with the ImmunoCAP ISAC (Thermo Fisher Scientific, Waltham, MA USA). ImmunoCAP ISAC is a miniaturized immunoassay platform that allows for multiplex measurement of specific IgE antibodies to many allergen components using 20 μ L of serum or plasma. Allergens are immobilized on a microarray chip to allow simultaneous measurement of specific IgE antibodies to 112 components from 51 allergen sources.²¹ Test results were measured with a biochip scanner and results were reported in ISAC standardized units (ISU) and categorized based on the manufacturer's cutoff levels (< 0.3 ISU, undetectable or very low; 0.3-0.9 ISU, low; 1-14.9 ISU, moderate/high; and \geq 15 ISU, very high). Values above 1 ISU were considered positive.

Statistical Methods

The study sample size was chosen based on a previous population study from Singapore.⁶ Descriptive statistics for the categorical variables were reported as number (%). Normally distributed continuous data were presented as mean and standard deviation. Categorical data were presented as mean and proportion. Categorical and continuous data were analyzed using chi-squared, unpaired *t* and Mann-Whitney *U* tests depending upon the distribution. All *P*-values were two-sided with the level of significance specified at 0.05. All analyses were performed using IBM SPSS version 25 (IBM Corp, Armonk, NY, USA).

Results

Eighty-seven subjects who fulfilled the inclusion criteria were recruited. Sixty-nine subjects (female 52.2%) who fulfilled atopy criteria were included in the analysis. Twenty-eight (40.6%) atopic subjects fulfilled the Rome III IBS criteria (atopy-IBS). There was no difference in gender, age, type of housing, or education level between atopy-IBS and atopy-non-IBS group. There were more asthma patients in the atopy-IBS group (42.9% vs 14.6%, *P* = 0.014) but no difference in allergic rhinitis and allergic dermatitis (Table 1). There was a trend of increased pet ownership in the atopy-IBS group (75.0% vs 51.0% *P* = 0.068). There was no difference between types of animals at home and timing of the animals at home.

Skin Prick Tests

HDM antigens (*B. tropicalis*, *D. pteronyssinus*, and *D. farinae*) were the top 3 most sensitized antigens among all the participants. Thirty-five (50.7%) subjects were sensitized to dog dander and 28 (40.6%) to cat dander. Atopy-IBS patients had higher cat dander (64.3% vs 24.4%, *P* < 0.001), dog dander (64.3% vs

Table 1. Characteristics of Atopic Subjects With and Without Irritable Bowel Syndrome-like Symptoms

Variables	Atopy-non-IBS n (%)	Atopy-IBS n (%)	P-value
Total	41 (59.4)	28 (40.6)	
Female	19 (46.3)	17 (60.7)	0.270
Age (mean [SD], yr)	35.1 (12.3)	33.5 (11.3)	0.492
Type of housing ^a			0.074
Government flat	31 (75.6)	20 (71.4)	
Private apartment	2 (4.9)	6 (21.4)	
Land property	7 (17.1)	2 (7.1)	
Highest education			0.134
Primary	0 (0.0)	1 (3.6)	
Secondary	15 (36.6)	5 (17.9)	
Tertiary or higher	26 (63.4)	22 (78.6)	
Pet ownership	26 (51.0)	21 (75.0)	0.068
Asthma	6 (14.6)	12 (42.9)	0.014
Allergic rhinitis	36 (87.8)	25 (89.3)	0.200
Eczema	22 (53.7)	10 (35.7)	0.183
Serum total IgE (mean [SD], kIU/L)	148.8 (190.8)	211.5 (224.5)	0.232
Histamine size (mean [SD], mm)	4.8 (1.2)	5.0 (0.9)	0.274

^aMissing 1 entry for type of housing.

IBS, irritable bowel syndrome; IgE, Immunoglobulin E.

41.5%, $P = 0.015$), and weed pollens (32.1% vs 14.6%, $P = 0.050$) sensitization compared to atopy-non-IBS patients (Table 2). Only 10 out of 28 participants who were tested positive for cat dander did not have IBS-like symptoms. Eighteen atopy-IBS patients had cat dander sensitization, majority had mixed-type IBS (7/18), followed by diarrhea-predominant IBS (4/18), constipation-predominant IBS (4/18), and unsubtyped IBS (3/18). Sixteen of cat dander sensitized atopy-IBS subjects had AR, 8 had asthma and 7 had eczema. Majority of atopy-IBS with cat dander sensitization do not have animals at home. Only 4 had cats and 6 had dogs at home.

Specific Serum Immunoglobulin E Antibodies

Out of 112 components from 51 allergen sources, only Fel d1 (major cat dander antigen) sensitization was significantly higher in the atopy-IBS group (21.4% vs 2.4%, $P = 0.029$) (Table 3). Only 1 Fel d1 positive patient out of 7 had no IBS symptoms. All Fel d1 positive patients had allergic rhinitis, 50.0% of them had asthma and eczema. The only Fel d1 positive patient with no IBS symptoms had positive cat SPT, allergic rhinitis, and eczema, while the only positive GI symptom in this patient was hard stool.

Discussion

Comparing atopic patients with or without IBS-like symptoms,

we found a significant association between animal danders and weed pollen (*A. vulgaris*, *U. dioica*, *T. vulgare*, and *P. lanceolate*) sensitization and IBS-like symptoms. However only cat dander sensitization was significantly higher in both SPT and specific IgE tests. It is important to state early that the demonstration of animal dander sensitization purely based on positive SPTs and specific IgE is not sufficient to diagnose a clinically relevant allergy. A sensitized individual may be entirely asymptomatic upon exposure to the allergen in question. To prove causation, we will need to show that exposure to the culprit allergen reproduces IBS symptoms. Our study hinted that aeroallergens may have a more sinister role in the GI tract rather than just being an innocent bystander. Notably, our findings concur with the recent report by Koloski et al¹¹ that patients with self-reported animal allergy had higher prevalence of IBS.

Aeroallergens and the Gastrointestinal Tract

The possible role of aeroallergens in the distal area of the GI tract was first raised after the discovery of HDMs allergen in the colon by Tulic et al.²² The cysteine protease activity of Der p1 resulted in increased epithelial permeability.¹⁶ Previously, the role of aeroallergens was sidelined by food allergy in IBS studies. In retrospect, multiple studies that looked for food allergy or relationship of IBS and allergy often included aeroallergens as part of their routine investigation, and some had reported higher aeroallergen sensitiza-

Table 2. Frequency of Sensitization to Aeroallergens by Skin Prick Test

Aeroallergens	Total SPT positive (n = 69)	Atopy-non-IBS (n = 41)	Atopy-IBS (n = 28)	P-value
<i>Alternaria tenuis</i>	5 (7.2)	3 (7.3)	2 (7.1)	0.762
<i>Aspergillus fumigatus</i>	4 (5.8)	2 (4.9)	2 (7.1)	0.908
<i>Blomia tropicalis</i>	56 (81.2)	33 (80.5)	23 (82.1)	0.454
<i>Cladosporium herbarum</i>	5 (7.2)	3 (7.3)	2 (7.1)	0.762
<i>Dermatophagoides farinae</i>	54 (78.3)	30 (73.2)	24 (85.7)	0.172
<i>Dermatophagoides pteronyssinus</i>	56 (81.2)	32 (78.0)	24 (85.7)	0.439
<i>Penicillium notatum</i>	5 (7.2)	2 (4.9)	3 (10.7)	0.830
Cockroach	42 (60.9)	21 (51.2)	21 (75.0)	0.268
Dog dander	35 (50.7)	17 (41.5)	18 (64.3)	0.015
Cat dander	28 (40.6)	10 (24.4)	18 (64.3)	< 0.001
Weed pollen	15 (21.7)	6 (14.6)	9 (32.1)	0.050

SPT, skin prick test; IBS, irritable bowel syndrome; IgE, immunoglobulin E.
Data are presented as number (%).

Table 3. Frequency of Sensitization to Aeroallergens by Immune Solid-phase Allergen Chip^a

Common name	Latin name (allergen component)	Total ISAC positive (n = 68)	Atopy-non-IBS (n = 41)	Atopy-IBS (n = 28)	P-value
Aspergillus	<i>Aspergillus fumigatus</i> (rAsp f 3)	1 (1.5)	0 (0)	1 (3.6)	0.326
Bermuda grass	<i>Cynodon dactylon</i> (nCyn d 1)	2 (2.9)	0 (0)	2 (7.1)	0.337
Birch	<i>Betula verrucosa</i> (Betv1)	2 (2.9)	0 (0)	2 (7.1)	0.170
House dust mite	<i>Dermatophagoides farinae</i> (rDer f 1)	34 (50)	21 (51.2)	13 (46.4)	0.568
House dust mite	<i>Dermatophagoides pteronyssinus</i> (nDer p 1)	33 (48.5)	20 (48.8)	13 (46.4)	0.959
Timothy-grass	<i>Phleum pratense</i> (rPhl p 1)	4 (5.9)	2 (4.9)	2 (7.1)	0.696
Dog	<i>Canis familiaris</i> (rCan f 1)	4 (5.9)	2 (4.9)	2 (7.1)	0.856
Horse	<i>Equus caballus</i> (nEqu c 3)	1 (1.5)	1 (2.4)	0 (0.0)	0.817
Cat	<i>Felis domesticus</i> (rFel d 1)	7 (10.3)	1 (2.4)	6 (21.4)	0.029
Cat	<i>Felis domesticus</i> (rFel d 4)	3 (4.4)	1 (2.4)	2 (7.1)	0.553
Mouse	<i>Mus musculus</i> (nMus m 1)	2 (2.9)	1 (2.4)	1 (3.6)	0.807

^aMissing 1 subject's immune solid-phase allergen chip (ISAC) result.
IBS, irritable bowel syndrome.
Data are presented as number (%).

tion in IBS compared to their respective controls. Vivinus-Nebot et al¹⁰ showed that IBS patients had significantly higher aeroallergen sensitization, enhanced colonic permeability, a higher number of MCs, and spontaneous release of tryptase than healthy subjects. Though Nybacka et al¹⁶ did not find a higher prevalence of IBS in atopic patients, they showed that a higher proportion of atopic IBS patients tested positive for aeroallergens, as compared to non-atopic IBS patients.

Cat Dander Sensitization

Cats release proteins into the environment through excretion or as dander, minute scales from hair, skin, saliva, or urine. Fel d1,

a major cat allergen, is found in cat saliva, sebaceous glands, and urine. Fel d1 elicits IgE responses in 90.0% to 95.0% of patients with cat allergy. The prevalence of cat dander sensitization is in the range of 10.0% to 15.0% among adults worldwide.²³⁻²⁵ Exposure to cat allergens can happen without us knowing, as cat allergens are known to persist up to 6 months after the source is removed. They easily become airborne and attach themselves to hair or clothing. Generally, there is a direct relationship between exposure and immune response to allergens like pollen, cockroach, and HDM. Conversely, high exposure to cat dander has been associated with an induction of tolerance instead.²⁵⁻²⁸

High exposure to cat dander induces a tolerogenic signal medi-

ated by IL-10 and TGF- β secreted by T-regulators, which results in suppression of allergy effector cells including MCs, basophils, and eosinophils. It is postulated that increased gut permeability reported in some IBS patients may lead to higher concentrations of the allergen being delivered to antigen-presenting cells.²⁹⁻³¹ We postulate that IBS patients may have 2 reasons for high cat dander sensitization: (1) IBS patients have an impaired mucosal barrier thus enabling cat dander to cross the gut epithelium,^{32,33} and (2) IBS patients exhibit an immune imbalance favoring the production of pro-inflammatory TNF- α over the anti-inflammatory IL-10 cytokines leading to failure of developing “immunological tolerance.”³⁴⁻³⁶ The presence of sensitization to cat dander in these patients may be a reflection of these processes and may be a biomarker of disease, at least for a subtype of patients.

Effect of Anti-allergic Drugs on Irritable Bowel Syndrome

Anti-allergic drugs have previously been evaluated in IBS patients, though mostly by chance and not targeting the allergy process. A study by Lobo et al³⁷ showed that both MC activation and IBS symptoms decreased in diarrhea-predominant IBS patients treated with oral disodium cromoglycate compared to those without treatment. In a randomized control trial, ketotifen was shown to increase discomfort threshold in IBS patients with visceral hypersensitivity.³⁸ Ebastine, a second-generation H1-antihistamine, was effective in reducing visceral hypersensitivity and abdominal pain in IBS patients.³⁹

Our study is limited by the relatively small number of subjects. We also lack data on psychosocial factors which can shed light on the effect of psychological attributes on clinical severity. It would have been desirable to verify exposure-based symptoms to assess the clinical relevance of sensitization and its relationship with other allergic diseases. However, a single question is unlikely to ascertain the degree of animal exposure, and more thorough questioning on animal exposure had been suggested.

Conclusion

We demonstrated an association between aeroallergen sensitization, in particular animal dander sensitization, and IBS-like symptoms in atopic patients. This observation warrants further study to assess the clinical relevance of such sensitization through a more granular comprehensive clinical history and closer examination to assess whether exposure to cat allergen reproduces IBS symptoms or we have been missing aeroallergen-induced gut allergy.

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References

- Mearin F, Lacy BE, Chang L, et al. Bowel disorders. *Gastroenterology* 2016;150:1393-1407, e7.
- Sperber AD, Dumitrascu D, Fukudo S, et al. The global prevalence of IBS in adults remains elusive due to the heterogeneity of studies: a rome foundation working team literature review. *Gut* 2017;66:1075-1082.
- Ford AC, Lacy BE, Talley NJ. Irritable bowel syndrome. *N Engl J Med* 2017;376:2566-2578.
- Enck P, Aziz Q, Barbara G, et al. Irritable bowel syndrome. *Nat Rev Dis Primers* 2016;2:16014.
- Al momani L, Alomari M, Numan L, Patel AH, Olayan M, Young M. Sa1687 exposure to pets is associated with irritable bowel syndrome: a systematic review and meta-analysis. *Gastroenterology* 2019;156:S-366.
- Siah KT, Wong RK, Chan YH, Ho KY, Gwee KA. Prevalence of irritable Bowel syndrome in Singapore and its association with dietary, lifestyle and environmental factors. *J Neurogastroenterol Motil* 2016;22:670-676.
- Koloski NA, Jones M, Weltman M, et al. Identification of early environmental risk factors for irritable bowel syndrome and dyspepsia. *Neurogastroenterol Motil* 2015;27:1317-1325.
- Jones MP, Walker MM, Ford AC, Talley NJ. The overlap of atopy and functional gastrointestinal disorders among 23,471 patients in primary care. *Aliment Pharmacol Ther* 2014;40:382-391.
- Tobin MC, Moparty B, Farhadi A, DeMeo MT, Bansal PJ, Keshavarzian A. Atopic irritable bowel syndrome: a novel subgroup of irritable bowel syndrome with allergic manifestations. *Ann Allergy Asthma Immunol* 2008;100:49-53.
- Vivinus-Nébot M, Dainese R, Anty R, et al. Combination of allergic fac-

- tors can worsen diarrheic irritable bowel syndrome: role of barrier defects and mast cells. *Am J Gastroenterol* 2012;107:75-81.
11. Koloski N, Jones M, Walker MM, et al. Population based study: atopy and autoimmune diseases are associated with functional dyspepsia and irritable bowel syndrome, independent of psychological distress. *Aliment Pharmacol Ther* 2019;49:546-555.
 12. Takahashi K, Taniguchi M, Fukutomi Y, et al. Oral mite anaphylaxis caused by mite-contaminated okonomiyaki/ pancake-mix in Japan: 8 case reports and a review of 28 reported cases. *Allergol Int* 2014;63:51-56.
 13. Hill DA, Grundmeier RW, Ramos M, Spergel JM. Eosinophilic esophagitis is a late manifestation of the allergic march. *J Allergy Clin Immunol Pract* 2018;6:1528-1533.
 14. Magnusson J, Lin XP, Dahlman-Höglund A, et al. Seasonal intestinal inflammation in patients with birch pollen allergy. *J Allergy Clin Immunol* 2003;112:45-50.
 15. Rentzos G, Lundberg V, Stotzer PO, Pullerits T, Telemo E. Intestinal allergic inflammation in birch pollen allergic patients in relation to pollen season, IgE sensitization profile and gastrointestinal symptoms. *Clin Transl Allergy* 2014;4:19.
 16. Nybacka S, Öhman L, Störsrud S, et al. Neither self-reported atopy nor IgE-mediated allergy are linked to gastrointestinal symptoms in patients with irritable bowel syndrome. *Neurogastroenterol Motil* 2018;30:e13379.
 17. Gwee KA, Wee S, Wong ML, Phg DJ. The prevalence, symptom characteristics, and impact of irritable bowel syndrome in an asian urban community. *Am J Gastroenterol* 2004;99:924-931.
 18. European Community Respiratory Health Survey II Steering Committee. The European community respiratory health survey II. *Eur Respir J* 2002;20:1071-1079.
 19. Bousquet J, Khaltayev N, Cruz AA, et al. Allergic rhinitis and its impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;63(suppl 86):8-160.
 20. Frew AJ. GA²LEN-the global allergy and asthma European network. *Clin Exp Allergy* 2005;35:122-125.
 21. Canonica GW, Ansotegui IJ, Pawankar R, et al. A WAO - ARIA - GA²LEN consensus document on molecular-based allergy diagnostics. *World Allergy Organ J* 2013;6:1-17.
 22. Tulić MK, Vivinus-Nébot M, Rekić A, et al. Presence of commensal house dust mite allergen in human gastrointestinal tract: a potential contributor to intestinal barrier dysfunction. *Gut* 2016;65:757-766.
 23. Grönlund H, Saarne T, Gafvelin G, van Hage M. The major cat allergen, Fel d 1, in diagnosis and therapy. *Int Arch Allergy Immunol* 2010;151:265-274.
 24. Erwin EA, Woodfolk JA, Custis N, Platts-Mills TA. Animal danders. *Immunol Allergy Clin North Am* 2003;23:469-481.
 25. Brasó-Aznar JV, Pelaez-Hernandez A, Rochina-Puchades A, Morales-Rubio C, Burches Baixauli E. Etiologic role of unapparent exposure in cat allergy. *Allergy* 1995;50:447-450.
 26. Yilmaz I, Oner Erkeköl F, Secil D, Misirligil Z, Mungan D. Cat and dog sensitization in pet shop workers. *Occup Med (Lond)* 2013;63:563-567.
 27. Weber RW. Atopic persons sensitive to cat dander. *Ann Allergy Asthma Immunol* 2002;88:A4.
 28. Shargorodsky J, Garcia-Esquinas E, Umanskiy R, Navas-Acien A, Lin SY. Household pet exposure, allergic sensitization, and rhinitis in the U.S. population. *Int Forum Allergy Rhinol* 2017;7:645-651.
 29. Herre J, Grönlund H, Brooks H, et al. Allergens as immunomodulatory proteins: the cat dander protein Fel d 1 enhances TLR activation by lipid ligands. *J Immunol* 2013;191:1529-1535.
 30. Morris DO. Human allergy to environmental pet danders: a public health perspective. *Vet Dermatol* 2010;21:441-449.
 31. Saarne T, Grönlund H, Kull I, Almqvist C, Wickman M, van Hage M. Cat sensitization identified by recombinant Fel d 1 several years before symptoms—results from the BAMSE cohort. *Pediatr Allergy Immunol* 2010;21(2 Pt 1):277-283.
 32. Dunlop SP, Hebden J, Campbell E, et al. Abnormal intestinal permeability in subgroups of diarrhea-predominant irritable bowel syndromes. *Am J Gastroenterol* 2006;101:1288-1294.
 33. Li X, Kan EM, Lu J, et al. Combat-training increases intestinal permeability, immune activation and gastrointestinal symptoms in soldiers. *Aliment Pharmacol Ther* 2013;37:799-809.
 34. Bashashati M, Rezaei N, Bashashati H, et al. Cytokine gene polymorphisms are associated with irritable bowel syndrome: a systematic review and meta-analysis. *Neurogastroenterol Motil* 2012;24:1102-e566.
 35. Chen J, Zhang Y, Deng Z. Imbalanced shift of cytokine expression between T helper 1 and T helper 2 (Th1/Th2) in intestinal mucosa of patients with post-infectious irritable bowel syndrome. *BMC Gastroenterol* 2012;12:91.
 36. Macsharry J, O'Mahony L, Fanning A, et al. Mucosal cytokine imbalance in irritable bowel syndrome. *Scand J Gastroenterol* 2008;43:1467-1476.
 37. Lobo B, Ramos L, Martínez C, et al. Downregulation of mucosal mast cell activation and immune response in diarrhoea-irritable bowel syndrome by oral disodium cromoglycate: a pilot study. *United European Gastroenterol J* 2017;5:887-897.
 38. Klooker TK, Braak B, Koopman KE, et al. The mast cell stabiliser ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome. *Gut* 2010;59:1213-1221.
 39. Stanisor OI, van Diest SA, Yu Z, et al. Stress-induced visceral hypersensitivity in maternally separated rats can be reversed by peripherally restricted histamine-1-receptor antagonists. *PLoS One* 2013;8:e66884.