

RAPID COMMUNICATION

Discrepancies between the responses to skin prick test to food and respiratory antigens in two subtypes of patients with irritable bowel syndrome

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FA responses differed significantly from those for the other two groups ($P < 0.01$).

CONCLUSION: Despite the small number of cases studied, the higher reactivity to FAs in Group I compared to Groups II and III adds new information, and suggests the presence of a possible alteration in intestinal epithelial function.

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Key words: Atopy; Constipation; Diarrhea; Food intolerance; Irritable bowel syndrome; Skin prick test

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Abstract

AIM: To compare the response to skin prick tests (SPTs) to food antigens (FAs) and inhalant allergens (IAs) in patients with two subtypes of irritable bowel syndrome (IBS) and healthy controls.

METHODS: We compared the results of SPTs for IAs and FAs in 87 volunteers divided into three groups: diarrhea predominant IBS (D-IBS) Group I ($n = 19$), constipation predominant IBS (C-IBS) Group II ($n = 17$), and normal controls Group III ($n = 51$).

RESULTS: Of the 285 tests (171 for FAs and 114 for IAs) performed in Group I we obtained 45 (26.3%) positive responses for FA and 23 (20.1%) for IA. Of the 153 tests for FA in Group II, we obtained 66 (20.1%) positive responses, and of the 102 tests for IA, we obtained 20 (19.6%) positive responses. Of the 459 tests for FA performed in Group III, we obtained 39 (8.4%) positive responses, and of the 306 for IA, we obtained 52 (16.9%) positive responses. The numbers of positive responses were not significantly different between the three groups, but in the D-IBS group, the number of SPT

INTRODUCTION

Irritable bowel syndrome (IBS) is an extremely common disorder that affects about one in every 5-10 persons. Estimates of prevalence range from 9% to 22% depending upon population group studied^[1-7].

The exact pathophysiology of IBS remains unknown, although various mechanisms including gastrointestinal dysmotility and visceral hypersensitivity have been well studied in IBS^[8-10]. Recent interest has also been directed to the possible participation of the mucosa in the pathophysiology of IBS^[11-13]. Inflammatory mediators cause intestinal dysfunction and a consequent increase in permeability^[14-17]. However the role and interaction of inflammatory mediators with IBS remains to be determined^[17].

IBS is defined by symptomatic criteria rather than biological markers. No diagnostic tests are available, clinical subtypes of IBS are based on the predominant symptom:

IBS diarrhea predominant (D-IBS), IBS constipation predominant (C-IBS), and mixed (m-IBS), and treatment is selected based on the predominant symptom^[3,18,19].

Clinically, the frequency of IBS is associated with psychological stress, food intolerance (adverse reaction to a specific food or ingredient that is not immune mediated or associated with psychological phenomena), intestinal infections, and even previous abdominal surgery^[3,7,12,20-25].

Dunlop *et al.*^[16] have reported that patients with sub-type D-IBS (pos-infectious and non-infectious origin) have a more pronounced permeability increase in the proximal intestine compared with controls and those with C-IBS. Another aspect of that study was the detection of a significant correlation between atopy and increased intestinal permeability, which suggests that at least a subset of IBS patients may have a systemic immunological disorder. Other studies have reported a correlation between asthma, food allergy and IBS^[26-29], but the role of allergic reactions in the pathophysiology of IBS remains controversial^[7,13,27,29-31].

We have previously observed that volunteers with a diagnosis of IBS have reported higher cutaneous reactivity to food antigens than to inhalant allergens, when compared to patients with functional dyspepsia and normal controls^[30]. The association between food hypersensitivity and IBS symptoms is still open to question^[7,17,20,22-25]. New information is useful for a better understanding of the relationship between increased intestinal permeability, mucosal barrier defects, and intestinal inflammation in IBS patients.

The aim of this study was to compare the response to skin prick tests (SPTs) with food and inhalant antigens in two subtypes of IBS and healthy controls.

MATERIALS AND METHODS

We studied the response to SPTs with inhalant and food extracts^[32] in 87 volunteers, 36 patients with IBS (evaluated by a pre-designed questionnaire based on the Rome III criteria^[18] for functional gastrointestinal diseases), and 51 normal volunteers (school employees and medical students at Antonio Pedro University Hospital). They were evaluated between September 2006 and January 2007. The volunteers were first evaluated in outpatient clinics for functional gastrointestinal diseases at Antonio Pedro University Hospital. Subjects completed a questionnaire which included Rome III criteria for IBS, and were submitted to a clinical evaluation that included a careful history (age, duration of symptoms, psychosocial factors, alarm symptoms, personal history of atopy, family history of gastrointestinal disease), examination, and stool examination for ova and parasites (Brazil is an endemic area for parasitic infections). The inclusion criteria were age > 18 years old and a diagnosis of IBS, or volunteers from the general population. The exclusion criteria were clinical suspicion or diagnosis of organic disease of the gastrointestinal tract (including positives stool examination for ova and parasites) at least 12 mo prior to the study after clinical evaluation.

The subjects were divided into three groups. D-IBS,

Group I ($n = 19$; 14 female, five male; mean age 32.6 years), with IBS ROMA III Criteria for recurrent abdominal discomfort or pain at least 3 d per month in the last 3 mo, associated with two or more of the following: (1) improvement with defecation; (2) onset associated with a change in stool frequency; or (3) onset associated with a change in stool form (appearance). C-IBS, Group II ($n = 17$ subjects; 12 female, five male; mean age 31.8 years). Controls, Group III ($n = 51$ subjects; 31 female, 20 male; mean age 26.3 years) without previous or current significant gastrointestinal symptoms. The three groups, after informed consent (approved by the local Ethical Committee: number CAAE 00902580007) were submitted to SPTs with nine food extracts (ovalbumin, egg yolk, nuts, peanuts, wheat flour, cow's milk, soya, crustaceans and chocolate), and six inhalant extracts (*Dermatophagoides* spp., *Blomia tropicalis*, air dust, *Dermatophagoides pteronissimus*, house dust and *Dermatophagoides farinaceus*)^[14].

The contents of glycerinated food extracts (1:20), the positive control substance, histamine, and the negative control substance, saline, were commercially available (M Queiroz Laboratory, Rio de Janeiro, Brazil). They were applied by the prick technique (percutaneous) puncture through the standardized punter (discarded after use to avoid cross reaction), which allowed allergen absorption at multiple points in the skin. The test reading, done at the 20 min after the beginning were made by the measures of the wheel diameter eliciting by the test, obtained in millimeters. A wheal that was 3 mm greater than that of the negative control was considered positive. Anything less was considered negative^[14].

Statistical analysis

Data were analyzed using Pearson's χ^2 test. $P < 0.05$ was considered significant.

RESULTS

A total of 1305 SPTs (783 for the FAs and 522 for the IAs) (nine FAs and six IAs for each volunteer) were accomplished in the three groups. In the D-IBS Group I, we obtained 45 positive responses for food extracts, which corresponded to 26.3% of the 171 tests performed and 23 positive responses for IAs, which corresponded to 20.1% of the 114 tests performed. In the C-IBS Group II, we obtained 21 positive responses (13.7% of the 153 tests) for FAs and 20 positive responses (19.6%) for IAs. In the control Group III, 39 (8.4%) positive responses were obtained in 459 tests performed for FAs, and 52 (16.9%) for IAs.

The positive responses were not concentrated in one or two subjects, but dispersed throughout the populations examined. The numbers of positive responses to SPT for each antigen did not differ significantly between the three groups ($P > 0.05$).

Nine (52.9%) C-IBS and 11 (57.8%) D-IBS patients reported intolerance to several foods, but we did not find any correlation between positive SPTs and specific food intolerance in these subjects. Ten (58.8%) C-IBS and 12 (63.1%) D-IBS patients reported a personal history of

Table 1 Personal history of allergies and food intolerance, and SPT response to FAs and IAs in IBS patients and normal controls (%)

	D-IBS (<i>n</i> = 19)	C-IBS (<i>n</i> = 17)	Without gastrointestinal symptoms (<i>n</i> = 51)
Reported food intolerance	11 (57.8)	9 (52.9)	3 (5.8)
Personal history of allergies	12 (63.1)	10 (58.8)	26 (50.9)
No. of tests for FAs	171	153	459
Positive SPT for FAs	45 (26.3) ^b	21 (13.7)	39 (8.4)
No. of tests for IAs	114	102	306
Positive SPT for IAs	23 (20.1)	20 (19.6)	52 (16.9)

Papule 3 mm larger than the negative control was considered to be a positive response. ^b*P* < 0.01 compared to the other groups (χ^2).

allergies. Three (5.8%) volunteers without gastrointestinal symptoms reported food intolerance and 26 (50.9%) had a personal history of allergies. A personal history of allergies and the number of positive SPTs to IAs did not differ significantly between the three groups (*P* > 0.05). However, the number of positive SPTs to FAs in the D-IBS group differed significantly from that in the other two groups (*P* < 0.01) (Table 1).

DISCUSSION

In the present study, we observed that patients with a diagnosis of D-IBS had higher cutaneous reactivity to FAs than to IAs, when compared with those with C-IBS and healthy controls. An association between IBS and sensitivity to several foods was identified in two groups, but the SPT response was not specific for any type of food. None of the volunteers with IBS reported intolerance to an isolated food, and positive SPT responses also were not correlated significantly with a history of intolerance to a specific food. A positive SPT response for a specific food was not associated with the crises of IBS in any of the patients in Groups I and II.

IBS is a common disorder worldwide, but its exact pathophysiology remains unknown^[3]. Various mechanisms, including gastrointestinal dysmotility and visceral hypersensitivity, have been extensively studied in IBS^[8-10], but recent interest has also been associated with, or directed to the possible participation of the intestinal mucosa in the pathophysiology of IBS^[11-13,17]. Several lines of evidence suggest that IBS may be associated with inflammation in the ileal or colonic mucosa, and at least in a subset of patients with IBS, the mucosal immune system seems to be activated^[11,15-17]. Mucosal inflammation and immune system activation in IBS can be caused by many factors, including gastrointestinal infections, changes in the resident microflora, bile salts and FAs^[15-17].

FAs can activate the mucosal system when there is disruption of the gut barrier^[31,33-36]. It is hypothesized that mucosal immune activation by FAs may contribute to the development of food allergy and IBS^[9,11,13,15-17,21,25]. Clinically, the role of food-intolerance-induced symptoms in IBS frequently contrasts with that in food allergy^[20,22-25,29,37-42], and dietary elimination may be associated with symptom improvement^[31]. However, the interaction of food with

the gastrointestinal system is not completely understood^[13,17,20,22,23,25,29,33-37,39].

Our results demonstrate that patients with IBS symptoms have non-specific intolerance to foods, probably associated with generalized hypersensitivity. The lack of specificity suggests that people with IBS symptoms, associated or not with food intolerance, have difficulties with food in general and specific foods may not be involved in the pathogenesis of this condition. In agreement with other studies, we suspect that IBS causes food sensitivity rather than vice-versa^[5,22,37,38,41].

The mechanisms underlying these inflammatory responses are unclear, but recent studies have suggested that an alteration in the mucosal barrier function and a consequent increase in intestinal permeability are the basis for the increased inflammation in IBS^[14-17]. Dunlop *et al*^[16] have reported that patients with D-IBS have a pronounced permeability increase in the proximal intestine compared with controls, and those without a history of infection onset have a more severe defect. The increase in intestinal permeability could conceivably activate the release of neurotransmitters that stimulate afferent neurons^[13].

Scientific evidence of the functional interface between the immune and sensory motor systems of the gut and respiratory systems has been reported^[34,35,39]. Recent studies have reported that the prevalence of asthma and respiratory bronchial hyper-responsiveness are more common in IBS patients than in controls, and have suggested that at least a subset of IBS patients may have a systemic immunological disorder^[27,28]. We have previously noticed that IBS patients have greater cutaneous reactivity to FAs than to IAs, when compared to patients with functional dyspepsia or normal controls. An association between IBS and sensitivity to multiple foods and non-specific response to SPTs has also been identified^[30,42].

In the current study, the presence of diarrhea in IBS was a significant contributor to the greater cutaneous reactivity response to FAs. No patients with IBS, with or without diarrhea, presented with gastrointestinal infections over the 12 mo that preceded the study, including positive stool examination for ova and parasites. We did not find a significant association between personal history of allergies, IBS sub-type, food intolerance and SPT response. The discrepancies between the response to SPTs to FAs and IAs in the two subtypes of patients with IBS suggest disruption of the gut barrier in patients with D-IBS. Our findings are in agreement with other studies^[13,16,17,37,38,41].

We conclude that the lack of specificity to food SPT response and the greater cutaneous reactivity to FAs than to IAs may be associated with altered epithelial function and increase in intestinal permeability in D-IBS. Further studies are needed to clarify the potential pathogenic mechanisms underlying the association between IBS and allergy, and to determine if IBS is one or several disorders.

COMMENTS

Background

Irritable bowel syndrome (IBS) symptoms are frequently associated with the reporting of many food sensitivities. The role of food-intolerance-induced symptoms in IBS frequently contrasts with that in food allergy, but the pathogenesis

of this association is not completely understood. Food antigens (FAs) can activate the mucosal system when there is disruption of the gut barrier. The report of a significant correlation among atopy and increased intestinal permeability suggests that at least a subset of IBS patients may have a systemic immunological disorder.

Research frontiers

New information is useful for a better understanding of the relationship between increased intestinal permeability, mucosal barrier defects, and intestinal inflammation in IBS patients. Studies are needed to clarify the potential pathogenic mechanisms underlying the association between IBS and allergy, and to determine if IBS is one or several disorders.

Innovations and breakthroughs

The results of skin prick tests (SPTs) for IAs and FAs in two sub-types of IBS patients were compared. They confirmed a functional interface between the immune and sensory motor systems in the gut and suggest that in D-IBS, the epithelial function (intestinal permeability) in particular can be altered. Few studies regarding the subject are available in literature. This study provides valuable information about clinical and epidemiological aspects of IBS in Brazil.

Applications

The underlying cause of the pathophysiological changes encountered in IBS remains unclear. In clinical practice, the type and severity of symptoms determines the treatment of IBS. Our results add new information in answer to the question. Is IBS one or several disorders? Future clinical investigations will be useful for a better understanding of the results obtained here.

Peer review

The article gives a clear delineation of the research background and provides important data about pathophysiological changes in IBS. The references are appropriate and updated.

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