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Scientific advances in the concept of the relationship between irritable bowel syndrome (IBS) and food intolerance

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ABSTRACT
Irritable bowel syndrome (IBS) continues to be a clinical challenge in the 21st century. It is the most commonly diagnosed gastrointestinal condition and also the most common reason for referral to gastroenterology clinics. 1It can affect up to one in five people at some point in their lives and has a significant impact on quality of life and healthcare utilisation. The diagnosis of IBS is not confirmed by a specific test or structural abnormality. Today, the Rome III Criteria are the gold standard for diagnosing IBS. Several mechanisms and theories have been proposed about its etiology, but the biopsychosocial model is currently the most accepted for IBS. However, about two-thirds of patients with IBS have clinical symptoms induced by food intolerance, including gastrointestinal symptoms such as abdominal pain, bloating, diarrhea, or constipation. Common types of food intolerance include lactose intolerance, gluten intolerance, FODMAP intolerance, and histamine intolerance, among which lactose intolerance and FODMAP intolerance are more common in IBS patients. The exact mechanism by which food intolerance is involved in IBS is not fully understood. The symptom complex would be the result of the interaction between psychological, behavioral, psychosocial and environmental factors. Recently, some studies have shown the possible role of histamine and its relationship with non-allergic intolerance as a mediator of digestive clinical manifestations in patients with IBS.3,4 In this chapter we will discuss the role of food intolerance in IBS through a summary of two articles published by our research group related to the role of food intolerance in the pathogenesis of IBS published in 2004 and 2010, respectively. 5,6 In these trials, we have already emphasized the importance and frequency of atopy and hyperreactivity in patients with IBS.

Keywords: Irritable bowel syndrome, Food intolerance, Histamine, Atopy, Digestive symptoms.

1 INTRODUCTION

Irritable bowel syndrome (IBS) remains a clinical challenge in the 21st century. It's the most commonly diagnosed gastrointestinal condition and also the most common reason for referral to gastroenterology clinics. 1Its can affect up to one in five people at some point in their lives, and has a significantly impact of life quality and health care utilization. The diagnosis of IBS is not confirmed by a specific test or structural abnormality. Today the Rome Criteria III is the current gold-standard for the diagnoses of IBS. Various mechanisms and theories have been proposed about its etiology, but the biopsychosocial model is the most currently accepted for IBS. However, about two-thirds of IBS

patients experience clinical symptoms induced by food intolerance , including gastrointestinal symptoms such as abdominal pain , bloating , diarrhea or constipation. Common types of food intolerance include lactose intolerance , gluten intolerance ,FODMAP intolerance , and histamine intolerance , among which lactose intolerance and FODMAP intolerance are more common in IBS patients. The exact mechanism by which food intolerance is involved in IBS is not fully understood. The complex of symptoms would be the result of the interaction between psychological, behavioral, psychosocial and environmental factors. Recently, some studies show the possible role of histamine and its relationship to non-allergic intolerance as a mediator of clinical digestive manifestations in patients with IBS.3,4 In this chapter we will discuss the role of food intolerance in IBS through a summary of two articles published by our research group related to the role of food intolerance in the pathogenesis of IBS published in 2004 and 2010 respectively. 5,6 In these trials we already emphasized the importance and frequency of atopy and hyperreactivity in patients with IBS.

1.1 CORRELATION BETWEEN SYMPTOMS OF THE IRRITABLE BOWEL SYNDROME AND THE RESPONSE TO THE FOOD EXTRACT SKIN PRICK TEST

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The relationship between the irritable bowel syndrome (IBS) and food intolerance is not clear. We studied the cutaneous response to food antigens in 43 volunteers who were students and employees of the Faculty of Medicine of Universidade Federal Fluminense. Subjects were divided into 3 groups after evaluation for Roma II criteria forfunctional disease of the gastrointestinal tract: group I, 14 volunteers with IBS; group II, 15 volunteers with functional dyspepsia; group III, 14 volunteers without habitual gastrointestinal symptoms. The subjects were submitted to the skin prick test with 9 food antigen extracts, for a total of 387 skin tests (9 per volunteer). Of the 126 tests applied to group I, 24 (19.4%) were positive (a 3-mm wider papule than the negative control) and of the 135 tests applied to group II, 3 (2.3%)were positive. Of the 126 tests applied to group III, 6 (4%) were positive. The number of positive responses obtained in group I (IBS) differed significantly from the other 2 groups ($P < 0.01$). None of the volunteers with IBS reported intolerance to any isolated food. The higher reactivity to food antigens in group I compared to groups II andIII suggests that intestinal permeability may be increased in patients with IBS.

Over the last decade, the study of functional diseases of the gastrointestinal tract (FGD), especially irritable bowel syndrome (IBS), has been gaining importance in the field of gastroenterology (1-3). Unlike most of the diseases of the digestive tract which can be diagnosed using biological markers (1,4), FGD can only be diagnosed using clinical approaches, presuming the absence of

structural or biochemical dysfunction in the generation of the symptoms (5-9). IBS is one of the most common diseases in clinical practice. Symptoms of IBS (episodes of abdominal pain associated with alterations in intestinal habits occurring more than six times a year), are observed in 10% of the general population. The prevalence estimates vary from 9 to 22% depending on the population studied (2,3,6). The mechanisms involved in the pathophysiological alterations found in FGD seem to be multiple and are still uncertain. A unifying hypothesis for the generation of these symptoms would be the phenomenon of visceral hypersensitivity identified in most of the patients with IBS (7). The phenomenon of visceral hypersensitivity may be related to an increased response of the neuroimmune circuits in the nervous system or gastrointestinal tract to external stimuli (for example environmental or psychosocial stimuli) or internal ones (tissue irritation, inflammation, infection) (4,5,7). This increased response may result in abnormalities of digestive motility, inducing symptoms compatible with the clinical picture of IBS. In synthesis, an abnormal neuroimmune interaction (genetic and psychosocial factors, food intolerance, bacterial microflora)may contribute to the phenomenon of visceral hypersensitivity frequently observed in the patients with IBS (1,4,5,6-9). Clinically, the frequency of IBS is higher among females and 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 surgeries(1,2,6,8,10). The pathogenesis of food intolerance, frequently associated with IBS symptoms, has been little studied.

The aim of the present study was to correlate symptoms of IBS with the response to food antigens using the skin prick test. Westudied the response to food antigens by the prick test in 43 volunteers, 27 women and 16 men, during the period from August 2002 to January 2003. The subjects were selected from 105 volunteers, students and employees of the Faculty of Medicine, Universidade Federal Fluminense, Niterói, RJ, Brazil, recruited through a poster affixed on the door of the group of study of intestinal diseases(outpatient unit), Hospital Universitário Antonio Pedro. The inclusion criteria were age above 18 years and volunteers from the general population. This approach was used in order to obtain a population sample that would not consist of ambulatory or hospital patients, but that would represent the population in general. The exclusion criterium was the diagnostic suspicion of organic disease of the gastrointestinal tract. The study consisted of 2 stages taking place over 2 consecutive weeks. Stage I. Clinical evaluation of the volunteers, including the application of Roma II criteria (1) for the determination of IBS (pain or abdominal discomfort accompanied by 2 or 3 symptoms, such as relief with defecation and/or with alterations in the frequency of evacuations or in the shape of the feces forat least 12 weeks, which need not be consecutive, in the preceding 12 months; in the absence of organic disease of the gastrointestinal tract and functional dyspepsia, persistent or recurrent symptoms, such as pain or discomfort in the upper abdomen at least 12 weeks earlier, not necessarily serial, during the preceding 12 months). Stage II. Application of skin tests using food

antigens by the prick test. Of the 105 volunteers, 30 were excluded because of a diagnostic suspicion of organic disease of the gastrointestinal tract and were scheduled for later outpatient consultation, 10 did not agree to be submitted to the skin tests, and 22 did not return the following week for the scheduled skin tests. The 43 selected volunteers were divided into 3 groups after clinical evaluation and the application of Roma II's approaches for IBS and functional dyspepsia. Group I consistedof 14 volunteers with a diagnosis of IBS (10 women and 4 men; mean age 25years), group II consisted of 15 volunteers with a diagnosis of functional dyspepsia (9 women and 6 men; mean age 26 years), and group III consisted of 14 volunteers without habitual previous symptoms of gastrointestinal tract disease (8 women and 6 men; mean age 28 years). The three groups were submitted to the skin tests with 9 food extracts (egg white,egg yolk, peanut, chestnut, wheat flour, cow milk, soy, crustaceans, and chocolate). We used the commercially available allergenic reagents (M. Queiroz Laboratory,Rio de Janeiro, RJ, Brazil) in 50% glycerin diluent. The antigens were applied on the volar surface of the forearm in droplets (25 ml of testing reagent) by the technique of percutaneous puncture (11) using identical needles and were discarded after each test to avoid cross-reactions due to allergen absorption at multiple skin sites. Twenty minutes after antigen application, the skin tests were read by measuringthe diameter of the papule in millimeters. A papule 3 mm wider than the negative control was considered to be a positive response,whereas any smaller value was considered to be negative (11). The study was approved by the Health Research and Post-Graduation Adviser Committee, Research and Pos-Graduation Department,UFF.

A total of 387 skin tests were applied to the 3 groups (9 for each volunteer). In group I, IBS, 24 positive responses were obtained, corresponding to 19.4% of the 126 tests performed. In group II, functional dyspepsia,3 positive responses were obtained, corresponding to 2.3% of the 135 tests performed. In group III, 6 positive responses were obtained, corresponding to 4% of the 126 tests performed (Table 1). The positive responses were not concentrated in 1 or 2 individuals in each group but were dispersed throughout the group. Ten volunteers with IBS presented a positive response to one or more food antigens but the positive response was not specifically associated with IBS crises in any of them. The number of positive response was not significantly different between groups II and III. In group I, IBS, the number of positive responses differed significantly from the values obtained in the other 2 groups ($P < 0.01$,Student t-test). The present results agree with those reported by others. The association between IBS and sensitivity to multiple foods has also been reported in most of the few available studies in the literature (10,12). None of the volunteers with IBS reported intolerance to any isolated food (10,13,14). This finding suggests that patients with IBS symptoms have difficulties with foods in general. It is very probable that IBS causes food intolerance and not the opposite (15- 19). Despite the small number of cases studied,the higher reactivity to food antigens in group I compared to groups II and III adds a new information and suggests the presence of a possible alteration in

intestinal epithelial function (20). The association between phenomena of food hypersensitivity and IBS symptoms is still open to question. Future clinical investigations on larger samples using tests of intestinal permeability will be useful for abetter understanding of the results obtained here.

The traditional pharmacologic management of IBS has been symptom based and several drugs have been used. However, the cornerstone of its therapy is a solid patient physician relationship. IBS has no definitive treatment but could be controlled by non-pharmacologic management eliminating of some exacerbating factors such certain drugs, stressor conditions and changes in dietary habits.

In this chapter we review the types of food intolerance in IBS and the role of food intolerance in the pathogenesis and intervention of IBS. Irritable bowel syndrome is a common functional gastrointestinal disorder, and more studies have found that food intolerance is involved in the pathogenesis of IBS.

This review will provide a summary of pathophysiology, diagnostic criteria and current and emerging therapies for IBS

1.2 THE PREVALENCE AND CLINICAL CHARACTERISTICS OF ATOPIC MANIFESTATIONS IN PATIENTS WITH IRRITABLE BOWEL SYNDROME IN A BRAZILIAN URBAN COMMUNITY

Irritable bowel syndrome (IBS) is a common chronic disorder characterized by recurrent abdominal pain, bowel movement changes, diarrhea, constipation, or both and affect approximately 10-20% of the general population. Today, IBS is considered a disorder of dysregulation of the so called brain-gut axis and evidence also suggests that gastrointestinal inflammation may be of great importance in the majority of cases of IBS. In addition to gastrointestinal symptoms, many patients have atopic symptoms. The aim of this study was to study the prevalence of atopic manifestations in volunteers with IBS in a Brazilian urban community. Volunteers over 18 years of age were enrolled and evaluated. The participants were evaluated by a gastroenterologist of the Group of Study of Intestinal Diseases at Hospital Universitario Antonio Pedro. All volunteers were evaluated to determine if patients had symptoms compatible with the diagnosis of IBS based on Rome III criteria. The identification of the atopic manifestations was based in a structured questionnaire for atopy. Three hundred and fifty volunteers were enrolled. Of them, 330 volunteers were evaluated: 78(23.6%) of the volunteers had symptoms compatible with IBS (Group I) and 252 (76.3%) without symptoms compatible with IBS (Group II). Atopic manifestations were present in 46 (65.3%) in Group I and 105 (41. 0%) in Group II(P=0.0107, OR-2.01 95%CI -1. 20-3. 37). The association between atopic manifestations and the presence of IBS was relevant in patients in this Brazilian urban community. This fact may have implications for diagnosis and treatment of patients with IBS.

Irritable bowel syndrome (IBS) affects 10- 20% of the general population and is the most common reason for patients to consult a gastroenterologist. It is often accompanied by gastrointestinal intestinal and extra-intestinal symptoms.1-6 The extra-intestinal symptoms associated to IBS may be correlated with an increase in seeking medical advice, a worse prognosis, and a reduced quality of life.7-11 The high prevalence of extra-intestinal symptoms or comorbidities in IBS patients has led investigators to develop a hypothesis regarding underlying pathophysiological mechanisms of these disorders.12-14 IBS has been associated with female gender, psychological distress, food intolerance (reproducible adverse reaction to a specific food or food ingredient which is not immune mediated or psychologically based), enteric infections, and previous abdominal surgery.15-21 Today IBS is considered a disorder of dysregulation of the so called brain-gut axis and there is evidence to also suggest that inflammation with the gastrointestinal tract may be of great importance in the majority of IBS patients.22,23Approximately 30% of patients with IBS identify acute infection as an initial trigger for their chronic intestinal infections.17,18,21 These findings led to speculation that the immune system may play a role in the pathogenesis of at least a subpopulation of IBS patients.24-27 In recent studies, excess prevalence of bronchial hyper-responsiveness has been verified among patients with irritable bowel syndrome. 27 Tobin et al. reported that adults with such atopic symptoms have a high incidence of IBS, suggesting a link between atopy and IBS.28 Studies of atopic symptoms or comorbidities are of great scientific interest. Such studies can contribute to the experimental development of a new pathogenesis of IBS.11-14 Assessment and improved understanding of atopic somatic symptoms in IBS patients might allow new sub-groups of IBS patients with special characteristics to be identified and therebylead to the creation of new therapeutic concepts.12,13 Distinguishing atopic IBS from nonatopic IBS could help design more appropriate clinical interventions.11, 14,28 This paper aims to study the prevalence of atopic manifestationsin volunteers with IBS in a Brazilian urban community.

2 MATERIALS AND METHODS

Adult volunteers aged 18 and over, residents in Niterói, RJ, Brazil were enrolled during a 2-year period from January 2006 to January2008. The study was approved by the local ethical committee (n. CAE 0109025800007) and by our institutional review board (IRB) at theFaculty of Medicine. The volunteers were selected from students and employees of the Federal Fluminense University, Faculty of Medicine, Computer Science and Social Sciences, Niterói, RJ, Brazil. They were recruited through a poster affixed on the door of the Group of Study of Intestinal Diseases(Outpatients Unit), Hospital Universitário Antonio Pedro. This approach was used inorder to obtain a population sample that would not consist of ambulatory or hospital patients and that would represent the population in general. The exclusion criteria included: those with the diagnostic suspicion of organic disease of the

gastrointestinal tract (including positive stool examination for ova and parasites)and those unable to complete the questionnaire. All participants were provided withan IRB-approved information sheet that described the purpose of the study, the voluntary nature of the study, the study aims, methods,and population, and were given opportunities to ask questions. The volunteers were evaluated in our outpatient's clinic at theUniversity Hospital Antonio Pedro (HUAP). After obtaining informed consent, the volunteers went through a complete clinical evaluation. Diagnosis of IBS was based on the Rome III criteria for IBS. These were recurrent abdominal pain or discomfort at least three days per month in the last three months associated with 2 or more of the following: i)improvement with defecation; ii) onset associated with a change in frequency of stool; iii) onset associated with a change in form (appearance) of stool. The volunteers were also asked questions to identify atopic manifestations(seasonal runny nose, nasal congestion,itchy eyes, asthma, food allergy, reactions that cause skin rash, food intolerance triggering digestive symptoms). A total of 330 volunteers completed the surveys. Twenty volunteers were excluded because they presented the diagnostic suspicion of organic disease of the gastrointestinal tract (including positive stool examination for ova and parasites). Statistical analysis :Analysis of categorical data was carried out using c2 or Fisher's exact test, and continuous data were analyzed using independent sample t-test. Odds ratios (OR) with 95% confidence intervals (CI) were used to measure the associations between the comorbid conditions. $P<0.05$ was considered significant. The analysis was performed using SAS version 9.1 (SAS)Institute, Inc., Cary, NC, USA).

3 RESULTS

Three hundred and fifty volunteers (177 women and 173 men) were enrolled in the study. Twenty volunteers who had diagnostic suspicion of organic disease of the gastrointestinaltract were excluded. A total of 330 volunteers completed the surveys. After evaluation of the 330 volunteers, 78 (23.6%, mean age 27.6±8.7 years, 60 female and 18 male) of them met the diagnostic criteria for IBS (Group I-GI). The other 252 (76.3%, mean age 32.4±10 years, 106 female and 146 male) were healthy without symptoms of IBS (Group II - GII). There was no significant difference in the mean age of the 2 groups ($P>0.05$). We also found that the number of female volunteers with diagnosis of IBS was significantly higher than that of male volunteers ($P<0.05$)

Atopic manifestations were present in 46 (65.3%) volunteers of group I and 105 (41.0%)in GII. Thirty (65.2%) of the volunteers with IBS had respiratory atopy (26 seasonal allergic rhinitis and 4 asthma), compared with 65 (61.9%) (55 seasonal allergic rhinitis and 10 asthma) of volunteers without IBS. In addition, 16 volunteers with IBS (34.7%) had allergic skin manifestations compared with 45 (42.8%)volunteers without IBS. The percentage of atopic manifestations in volunteers with IBS (GI) was significantly higher than that of GII ($P=0.0107$, OR-2.01 95%CI -1, 20-3, 37). Twenty-nine

(37.1%) volunteers with IBS reported that a particular food or multiple foods caused abdominal cramping, but the food intolerance was not specifically associated with IBS crises in any of them (Table 1). Sixteen (76.1%) of the 21 volunteers with IBS diarrhea predominant (D-IBS) and 11 (73.3%) of the 15 IBS constipation predominance(C IBS) volunteers had atopic manifestations. Seven (70%) of the 10 mixed IBS (m-IBS) volunteers had allergic complaints. The presence of atopic manifestations was similar between IBS sub-type groups (P>0.05). Discussion :Irritable bowel syndrome is a common disorder worldwide and estimates of prevalence ranged from 9-22% depending upon the population group studied. The prevalence of symptoms consistent with IBS in the present study, the female predominance and mean age were similar to that reported in the literature. IBS appears to be equally common in the Third World, and we suggest that it can be considered a transcultural functional disorder.1,2,4,6,15 In the present study, we investigated the prevalence of atopic manifestations in volunteer non-patients with IBS. We have shown that volunteers with IBS had a higher percentage of allergic symptoms when compared with those without IBS. This finding suggests that there is an association between IBS and allergy history.

The exact IBS pathophysiology remains unknown and the role of allergic reactions in the pathophysiology of IBS remains controversial. 21,23,24 However, recent interest has been directed to the possible participation of intestinal inflammatory mediators in the pathophysiology of IBS. Mucosal abnormalities such as colonic mastocytosis have been reported in some recent studies.19,21,22 Tobin et al.27 reported that adults with atopic symptoms report a high incidence of IBS suggesting a link between atopy and IBS. They proposed a new IBS subgroup of patients with atopic symtoms. Our results confirmed the association between IBS and atopic disorders in our study population. IBS is diagnosed by symptomatic criteria rather than biological markers. Clinical subtypes of IBS are based on the predominant symptoms, such as diarrhea predominant (DIBS) IBS, constipation predominant IBS (CIBS) and mixed IBS (M IBS).4,29 Dunlop et al.29 reported a significant correlation among atopy and increased intestinal permeability in a subset of IBS patients. We showed in a previous study that the number of positive responses to a skin prick test for food antigens was significantly greater in a D-IBS group of patients than in the other two groups (C IBS and M IBS).30 The report of a significant correlation among atopy and increased intestinal permeability suggests that the immune system may play a role in IBS pathogenesis of at least a subpopulation of IBS patients.30-33 In the current study, we didn't find a significant association between personal history of allergies and IBS clinical sub-type, but the present results confirm the association between allergy and IBS.23 Twenty-nine volunteers with IBS reported intolerance to multiple foods that caused abdominal cramping, but the food intolerance was not specifically associated with IBS crises in any of them. We could not find evidence that suggests a correlation between IBS crises and specific food intolerance in these subjects. This subjective report of adverse food reaction could represent a non-allergic immunological reaction. In a

previous study,24 we reported that volunteers with a diagnosis of IBS reported higher reactivity to food antigens when compared to patients with functional dyspepsia. We suspect that IBS causes the food sensitivity rather than food sensitivity causes IBS. It is still unclear whether diet is a key factor in exacerbating IBS symptoms and whether dietary manipulation is a valid treatment.34-39 Recent studies reported a high prevalence of bronchial hyper-responsiveness among patients with irritable bowel syndrome. The Atopic manifestations were present in 46 (65.3%) volunteers of group I and 105 (41.0%) in GII. Thirty (65.2%) of the volunteers with IBS had respiratory atopy (26 seasonal allergic rhinitis and 4 asthma), compared with 65 (61.9%) (55 seasonal allergic rhinitis and 10 asthma) of volunteers without IBS. In addition, 16 volunteers with IBS (34.7%) had allergic skin manifestations compared with 45 (42.8%) volunteers without IBS. The percentage of atopic manifestations in volunteers with IBS (GI) was significantly higher than that of GII (P=0.0107, OR-2.01 95%CI -1, 20-3, 37). Twenty-nine (37.1%) volunteers with IBS reported that a particular food or multiple association between IBS and asthma has also been reported by Ozol et al.40 These investigators hypothesized a shared respiratory and gastrointestinal pathopyisiological mechanism which produced smooth muscle hyperactivity. In our study, the number of IBS volunteers with asthma was not significantly higher than that of volunteers without IBS. In summary, the present results confirm the association between allergy and IBS and add new information about the possible participation of intestinal inflammatory mediators in the pathophysiology of IBS.17,20-22,34,35,39,40 Further studies are needed to clarify this association. The identification of IBS patients with different clinical sub-types could improve therapeutic options and prevention strategies of IBS.In summary, the present results confirm the association between allergy and IBS and add new information about the possible participation of intestinal inflammatory mediators in the pathophysiology of IBS.17,20-22,34,35,39,40 Further studies are needed to clarify this association. The identification of IBS patients with different clinical sub-types could improve therapeutic options and prevention strategies of IBS.

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