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Small intestinal bacterial overgrowth: could it be associated with chronic abdominal pain in children with allergic diseases?

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ABSTRACT

Background and aims: small intestinal bacterial overgrowth (SIBO) is a well-known cause of chronic abdominal pain (CAP) during the pediatric age. On the other hand, children with a history of some allergic disorder present CAP more frequently. The aim of this study was to determine the association between the presence of allergic diseases and SIBO in patients diagnosed with CAP.

Materials and methods: this was an observational, analytical, retrospective study. Children with CAP who had undergone a lactulose hydrogen breath test to determine the presence of SIBO were included in the study. All patients underwent an evaluation for allergies by means of a skin prick test or the determination of specific IgE, according to clinical diagnosis. The study groups were established according to the presence of SIBO and the results of the allergic evaluation were statistically compared between the groups.

Results: seventy patients were included (41 females and 29 males) and SIBO was diagnosed in 35 patients. In addition, 71.4% of children with SIBO were found to have an allergic disease, in contrast with 28.6% of children without SIBO (p = 0.001). The odds ratio for having any type of allergy in patients with SIBO was 5.45 (95% CI, 1.96-15.17; p = 0.001).

Conclusions: we found an association between SIBO and allergic disease, especially allergic rhinitis, cow's milk protein allergy and asthma. Thus, SIBO should be ruled out in pediatric patients with CAP and allergic disease.

Key words: Small intestinal bacterial overgrowth. Chronic abdominal pain. Allergic diseases. Breath tests.

INTRODUCTION

Children with chronic abdominal pain (CAP) comprise a heterogeneous population, which includes both organic and functional gastrointestinal disorders (1). In fact, there is a significantly higher prevalence of abnormal microbiota fermentation in children with CAP (2). Small intestinal bacterial overgrowth (SIBO) could explain this abnormal microbiota fermentation.

SIBO is defined by the microbiological presence of 10^5 or more colony forming units per milliliter of bacteria in the duodenal content (3). The condition is characterized by an increased number of endogenous bacteria in the small bowel, which can present with nonspecific signs such as abdominal pain, diarrhea, bloating or flatulence (4). The mechanisms restricting bacterial colonization in the small bowel can become disturbed that lead to an imbalance and ultimately SIBO. This includes congenital or acquired anatomical abnormalities, diminished gastric acid secretion, alteration of intestinal motility and immunodeficiency (3).

In addition, certain conditions that increase the risk of developing SIBO include chronic intake of proton pump inhibitors (PPI), alterations of intestinal motility, structural abnormalities of the gastrointestinal tract, Crohn's disease, cystic fibrosis, *Giardia lamblia* infection and immunodeficiency (3). Allergy related diseases are associated with an increased risk of CAP (5,6), maybe due to a low-grade inflammation in the gut (7). However, the mechanisms involved are not fully understood. The aim of this study was to determine

the association between the presence of allergic diseases and SIBO in patients diagnosed with CAP according to Rome IV criteria for functional disorders.

METHODS

Patients

A retrospective, observational and analytical study was performed between March 2018 and November 2018. Seventy consecutive patients were included, 41 females and 29 females, between the age of two and 18 years with CAP; 85% of patients were older than four years and were classified as functional abdominal pain according the Rome IV criteria for functional abdominal pain disorders (8) and possible SIBO based on symptomatology such as abdominal pain, diarrhea, bloating, and flatulence. Children seen in the outpatient clinic referred to our physiology and gastrointestinal motility unit in the Instituto Nacional de Pediatría (Mexico City, Mex) were included in the study. All patients had a normal coprology test, fecal culture, stool ova and were negative for parasites. Patients with structural abnormalities, functional constipation and CAP with an organic etiology were excluded.

Allergy diagnosis

The children were studied for some kind of allergic disease such as cow's milk protein allergy (CMPA), food allergy, allergic rhinitis, asthma, urticaria and atopic dermatitis by the departments of Gastroenterology, Immunology and Dermatology. All patients were attended by specialist experienced pediatricians in the area. The diagnosis of an allergy was established according to each disease. A skin prick test was performed in patients with CMPA, allergic rhinitis, asthma and urticaria. The determinations of specific IgE were requested in children with a food allergy. The diagnosis of atopic dermatitis was clinical.

Hydrogen lactulose breath test

A lactulose hydrogen breath test (LHBT) was performed in all patients for the diagnosis of SIBO. Parents were instructed to avoid any type of antibiotic for at least four weeks prior to the test and also to avoid complex-fermentable carbohydrates such as tubers, grains, beans and bran cereals for at least 24 hours prior to the test. All patients met the 12-hour fasting

period before the procedure. Lactulose was given at a dose of 0.5 g/kg, with a maximum dosage of 10 g. Breath samples were taken every 20 minutes for 180 minutes. PPI use was discontinued four weeks before LHBT in patients with a known PPI intake. A positive test for SIBO was considered when there was an elevation of 20 parts per million (ppm) above the baseline measurement. The breath test was performed with the Gastro+™ Gastrolyzer® device (Bedfont Scientific Ltd., JA England) and the methodology for the exhaled hydrogen test and cut-off point for SIBO diagnosis was followed, according to the recommendations of the North American Breath Testing Consensus (9).

Informed consent was obtained from all individuals who participated in the study.

Statistical analysis

Statistical analysis was performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Study groups were established according to the presence of SIBO and the existence of some allergic diagnosis (CMPA, food allergy, rhinitis, asthma, urticarial and atopic dermatitis) for the statistical comparison between both groups. The Student's t-test and Chi-squared test were performed to compare the findings in subjects with or without SIBO and also to determine an association between qualitative variables. The level of statistical significance was set at $\alpha = 0.05$.

The study was performed in accordance with the Declaration of Helsinki.

RESULTS

In the present study, 35/70 patients had a SIBO diagnosis. Of the children with a positive LHBT, 54.3% (n = 19) were female and 45.7% (n = 16) were male (p = 0.52). With regard to children with a negative LHBT, 62.9% (n = 22) were female and 37.1% (n = 13) male. The mean age in patients with SIBO was 83.3 ± 42.4 months and 114.7 ± 52.4 months in patients without SIBO (p = 0.008). The median percentile and z-score of body mass index (BMI) was 40.46 ± 31.6 and -0.48 ± 1.31 months and 56.8 ± 36.4 and 0.24 ± 1.42 months in patients with and without SIBO, respectively (Table 1).

Of the children with SIBO, 71.4% were found to have an allergic disease, in contrast with 28.6% of children without SIBO (p = 0.001, Chi-squared test). Allergic rhinitis was the most frequent related allergic disease, followed by CMPA and asthma (Table 2). A positive LHBT

(i.e., elevation of 20 ppm above baseline measurement) was observed in most patients during the fourth measurement (minute 60). Nevertheless, there were statistically significant differences between children with and without SIBO from the third measurement (minute 40) (Table 1).

There was a positive association between SIBO and any kind of allergy (OR = 5.45; 95% CI, 1.96-15.17; p = 0.001), allergic rhinitis (OR = 3.57; 95% CI, 1.27-10.01; p = 0.013), CPMA (OR = 1.34; 95% IC, 1.10-1.63; p = 0.001) and asthma (OR = 1.16; 95% CI, 1.01-1.36; p = 0.027). There were no statistically significant differences for urticaria and atopic dermatitis (Table 2).

DISCUSSION

In the present study, the relationship between SIBO and allergic disease was evaluated in pediatric patients with CAP. Certain types of allergies, including CMPA, allergic rhinitis and asthma were associated with SIBO. We found that patients with SIBO and allergic disease were younger, in contrast to patients with SIBO but without allergic diseases. This finding was also observed in the prevalence of allergic disease by age group, as there is a higher prevalence of allergic disease in children and a lower prevalence in adolescents (10).

Children with multiple allergy related diseases may have low-grade inflammation in the gut (7), resulting in barrier defects in the gastrointestinal tract and thus increasing the risk for disturbed motility and pain sensitivity (11). Lower gastrointestinal symptoms such as diarrhea and abdominal pain are common in children with allergic diseases such as asthma (12) and atopic dermatitis (13). Evidence shows that allergy related diseases are associated with CAP. Powell et al. found that gastrointestinal symptoms in adults were significantly more common in patients with a history of asthma (OR = 2.13; 95% CI, 1.39-2.56; p < 0.002) and in patients with allergic rhinitis (OR = 1.66; 95% CI, 1.02 to 2.7; p < 0.05) (5). Olén et al. reported the association between allergic diseases and CAP in a group of adolescents. They found that a greater number of allergic diseases such as asthma, allergic rhinitis, eczema and food hypersensitivity increased the possibility of CAP as follows: one allergic disease (OR = 1.57, 95% CI, 1.08-2.28); two allergic diseases (OR = 2.58, 95% CI, 1.69-3.94) and three or more allergic diseases (OR = 3.39, 95% CI, 1.99-5.80) (6).

Patients with SIBO may present some characteristics that predispose them to this condition. Rosen et al. reported that acid suppression in children results in gastric bacterial overgrowth and 46% of patients taking acid-suppressing medication had gastric bacterial growth, as compared with 18% of untreated patients (14). Mitre et al. described the association between the use of acid-suppressive medications or antibiotics in the first six months of infancy and the development of allergic disease in early childhood. They found an adjusted hazard ratio in children prescribed PPI of 1.44 (95% CI, 1.36-1.52) for allergic rhinitis and 1.41 (95% CI, 1.31-1.52) for asthma (15). This evidence showed a link between the chronic use of PPI and allergic diseases. As shown in animal studies, acid-suppressive medications may decrease protein digestion in the stomach (16), which consequently leads to an inhibition of the breakdown of ingested proteins and facilitates IgE antibody production (17).

Children with allergic disease are more likely to develop recurrent and persistent upper respiratory infections such as sinusitis, rhinitis and otitis media (18). Consequently, antibiotics are frequently prescribed in these children. Epidemiological studies have linked early antibiotic exposure with the development of atopic diseases later in life (19,20). Allergic and atopic disorders are primarily caused by impaired components of the adaptive immune system that rely largely on the gut microbiome (19). In fact, distinct compositions of infant gut microbiomes have been associated with the development of atopic diseases later in life (21-24). Antibiotics may play a role in the development of SIBO in children with allergies secondary to alterations in the intestinal microbiota.

Increasing evidence suggests that resident microbial communities in the human gastrointestinal tract, airway and skin contribute to health and disease (25). Environmental exposures to more diverse microbial communities or to certain bacteria in these diverse microbial communities may protect against the development of allergies (26,27). There are also perinatal factors associated with the development of CMPA, especially the use of antimicrobials during gestation and breastfeeding duration (28). The composition of the gut microbiome in early life and the subsequent development of allergic diseases has been studied in several recent longitudinal studies and birth cohorts. The findings suggest that intestinal dysbiosis may be associated with asthma phenotypes, CMPA, food allergies and other atopic disorders during the first years of life (29).

A delayed small intestinal transit time has been demonstrated in patients with SIBO. In fact, Roland et al. examined adult patients who underwent wireless motility capsule testing and LHBT. This study found that the subjects with positive LHBT had longer small bowel and whole gut transit times than those with normal LHBT (30). Kibune et al. showed a prolonged orocecal transit time in adult patients with irritable bowel syndrome; this abnormality appears to be a predisposing condition for the development of SIBO (31). Dysmotility likely plays a role in the pathogenesis of bacterial overgrowth, which is a protective mechanism against bacterial colonization in the small bowel.

The limited number of patients included in our study is a major limitation. Thus, a statistical analysis could not be performed of the effect of potential confounding variables such as cesarean delivery, diet, antibiotic intake and infections and the heterogeneity of patients in terms of age and symptoms that may be related to the existence of SIBO. However, to our knowledge, this is the first study to show an association between SIBO and allergic disease in pediatric patients. Therefore, future studies are warranted in order to strengthen this association.

In summary, we found an association between SIBO and allergic disease, especially allergic rhinitis, CPMA and asthma. Thus, SIBO should be ruled out in pediatric patients with CAP with concomitant allergic diseases.

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Table 1. Comparison of age, gender, nutritional status and LHBT in subjects with and without SIBO

	SIBO		*p-value*
	Negative n = 35	Positive n = 35	
Age (m)	114.7 ± 52.4	83.3 ± 42.4	0.008
Gender (female)	62.9%	54.3%	0.52
p-BMI	56.8 ± 36.4	40.46 ± 31.6	0.04
z-BMI	0.24 ± 1.42	-0.48 ± 1.31	0.03
Hydrogen breath test			
Basal measurement	4.1 ± 3.4	4.3 ± 4.4	0.88
20 minutes	4.1 ± 3.4	4.6 ± 4.1	0.88
40 minutes	3.8 ± 2.7	8.7 ± 7.6	0.001
60 minutes	5.2 ± 4.1	15.9 ± 12.9	< 0.001
80 minutes	7.3 ± 4.9	23.28 ± 10.4	< 0.001
100 minutes	8.11 ± 5.04	26.3 ± 8.0	< 0.001
120 minutes	10.2 ± 5.5	23.8 ±9.2	< 0.001
140 minutes	11.9 ± 6.3	24.3 ± 9.5	< 0.001
160 minutes	13.1 ± 5.7	25.0 ± 9.7	< 0.001
180 minutes	15.2 ± 6.0	24.2 ± 10.9	0.001

LHBT: lactulose hydrogen breath test; SIBO: small intestinal bacterial overgrowth; BMI: body mass index. p-value was calculated by the Student's t-test.

Table 2. Frequency of allergies in subjects with and without SIBO and the odds ratio of allergic disease in patients with CAP for SIBO

	SIBO				
Allergy	*Negative* *n = 35*	*Positive* *n = 35*	*OR*	*95% IC*	*p-value*
Any allergy	10 (28.6%)	25 (71.4%)	5.45	1.96-15.17	0.001
CMPA	0	9 (25.7%)	1.34	1.10-1.63	0.001
Food allergy	2 (5.7%)	7 (20%)	1.12	0.79-21.48	0.07
Rhinitis	8 (22%)	18 (51.4%)	3.57	1.27-10.01	0.01
Asthma	0	5 (14.3%)	1.16	1.01-1.36	0.02
Urticaria	1 (2.9%)	1 (2.9%)	1	0.06-16.64	0.75
Atopic dermatitis	3 (8.6%)	7 (20%)	2.66	0.62-11.30	0.15

SIBO: small intestinal bacterial overgrowth; CAP: chronic abdominal pain; CMPA: cow's milk protein allergy. Chi-squared test was performed.