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Small intestine bacterial overgrowth in patients with irritable bowel syndrome

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Abstract. – Recent investigations in patients with irritable bowel syndrome (IBS) undergoing a breath test (BT) with lactulose, have shown inconclusive results on a possible association between IBS and a small intestine bacterial overgrowth (SIBO), as well as on the effective prevalence of SIBO in IBS patients, because of different geographic areas involved and different criteria adopted for the BT positivity.

The aim of this study was to estimate the prevalence of SIBO among IBS patients by means a lactulose BT.

Between January 2005 and December 2006, all the patients who were sent to our Gastroenterology Unit by general practitioners (GPs) for "functional" gastrointestinal (GI) symptoms, underwent a lactulose BT for diagnosis of SIBO. The test was considered positive if the hydrogen concentrations in the expired air increased more than 20 ppm over basal values within 90 minutes.

A total of 127 patients have been selected, 28 males and 99 females, aged between 17 and 76 (mean age: 41.4 years), with an IBS diagnosis based on the Roma II criteria. Fifty-five patients (43%) resulted positive to the lactulose BT. No significant difference was observed between IBS patients with (SIBO+) and without (SIBO-) an intestinal bacteria contamination.

In conclusion, our results indicate that SIBO is relatively frequent in IBS patients and that execution of a lactulose BT should be encouraged in all these patients, being the only way to make correct diagnosis of SIBO and establish a valid therapeutic treatment.

Key Words:

Small intestine bacterial overgrowth, Irritable bowel syndrome, Lactulose breath test, Prevalence.

Introduction

The irritable bowel syndrome (IBS) is a variable combination of gastrointestinal (GI) symptoms, either chronic or recurrent, in absence of biochemical or structural alterations of the intestinal wall. In the past, the diagnosis of IBS was mostly an "exclusion" diagnosis, i.e. once several laboratory or instrumental tests have excluded other diseases as a cause of GI symptoms. However, the introduction of new and more precise clinical criteria, i.e. the so-called "Criteria of Roma II", has allowed to limit the number of laboratory investigations and to make a diagnosis of IBS on the basis of symptoms only[1].

Thus, IBS is now defined by the presence of abdominal pain or discomfort that is associated with at least two out of thee "essential symptoms", i.e. changes in the alvus frequency, changes in the consistency of stools, and relief with evacuation. These symptoms should be present for at least 12 weeks, even not consecutive, in the last year and could be accompanied by some "additional symptoms", such as abdominal bloating and distension[2]. However, it is widely accepted today that three main physiopathological mechanisms underlie the genesis of IBS: psychological factors, an altered GI motility, and disturbances of visceral hypersensitivity[3].

Recent evidences indicate that endoluminal irritant factors, such as a quali- and quantitatively modified GI bacterial flora, and different infective and/or inflammatory factors, can participate in the genesis of IBS and be responsible for many of the GI motorial and sensitive disturbances observed in IBS patients[4,5]. A peculiar form of intestinal dysmicrobism is the "small intestinal bacterial overgrowth" (SIBO), in which the anaerobic bacteria are prevalent, thus explaining a clinical symptomatology that is mostly sustained by the peculiar metabolic characteristics of these bacteria[6].

Although the "gold standard" for diagnosis of SIBO is still the microbiological culture of a jejune aspirate, the "breath tests" (BT) are becoming more and more diffuse. They are based on the

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presence and assay of some metabolites of intestinal bacteria in the expired air. Among them, the BT with glucose (for high intestine) and the BT with lactulose (for low intestine) are became the most popular tests in gastroenterology.

Several studies have hypothesized an association of IBS and SIBO diagnosed by means of a lactulose BT[7-11]. The positivity of lactulose BT has been firstly defined as a presence of an early peak of hydrogen (> 20 ppm) caused by the bacterial flora of small intestine, which is shown at least 15 minutes before a second prolonged peak that is caused by the physiological metabolism of lactulose in the large intestine. Recently, some authors have introduced less restrictive criteria for positivity to lactulose BT, such as increased concentrations of hydrogen within 90 minutes since the oral ingestion of lactulose, or an increase larger than 20 ppm within 180 minutes[12].

Pimentel et al. (2000) have showed the presence of SIBO in 157 out of 202 patients (78%) with IBS according to Roma I criteria, which underwent a lactulose BT (with the original criteria of positivity). In addition, these patients showed an improvement of clinical symptomatology after a treatment with antibiotics that was followed by a normalization of the lactulose BT[13]. A further study performed by Pimentel et al. (2003) on 111 patients with IBS according Roma I criteria, which used less restrictive criteria for positivity of a lactulose BT, has also showed the presence of SIBO in an elevated percent of patients (84%) compared with a control healthy population for which the lactulose BT was positive in 20% of the cases. Also in this study, the normalization of the lactulose BT with the use of antibiotics was accompanied by a significant reduction of IBS symptoms[14].

Contrasting results were achieved by Walters et al[15], who studied 42 IBS patients (Roma II criteria) with lactulose BT by using the same criteria as by Pimentel et al[13] and have found a SIBO prevalence of about 10%. By applying to the same population the less restrictive criteria as by Pimentel et al[12] (except for a more rigorous reading of the hydrogen increase within 90 minutes that should be of at least 20 ppm over basal), the authors have observed a SIBO prevalence of 28% when only the hydrogen increase within 90 minutes was considered, and of 69% when the larger criterion (180 minutes) was considered. In a healthy population, the prevalence of SIBO was of 30% and 69%, respectively, with the two different criteria.

The aim of our observational, prospective study was to estimate the actual prevalence of SIBO in a population of IBS patients that general practitioners (GPs) have sent to our Gastroenterology Unit for a specialist medical advise in the period since January 2005 to December 2006.

Materials and Methods

In the concerned period, all the patients who were sent to our centre by GPs for "functional" GI symptoms were evaluated by means of an interview and a clinical questionnaire, including demographic and anamnesis data, characteristics of clinical symptomatology, concomitant treatments, and any laboratory and instrumental exam previously performed.

Patients of both sexes, aged between 17 and 80 years, with a diagnosis of IBS according to the Roma II criteria, were divided in three subgroups with an IBS diarrhoea-variant, constipation-variant and alternate alvus-variant. Patients have been excluded with diagnosis of other acute GI diseases than IBS, or severe diseases affecting cardiovascular and respiratory apparatus, kidneys, and central or peripheral nervous system. Patients with a positive anamnesis for abdominal surgery were also excluded (except for appendicectomy and cholecistectomy). Patients under chronic treatment with proton pump inhibitors for treatment of severe gastroesophageal reflux, were also excluded.

All the selected patients underwent a lactulose BT. Patients were required to avoid the use of antibiotics, probiotics, laxatives, proton pump inhibitors, H_2 antagonists, procinetics and antispastics, for two weeks before the test. At the evening before the examination, the patients were required to eat only boiled rise with no sausage or cheese, and grilled meat, and to drink only no-gas water; then, they were fasted for 12 hours before the test. If stipsis was present, the dietary prescriptions were extended to the three days preceding the exam. On the day of the test, the patient was completely fasted, and smoking was forbidden to all the patients (smokers included).

The lactulose BT was performed by measuring the hydrogen concentrations in the expired air in basal conditions, and after oral administration of lactulose 10 g; the measurements were done at 15-minute intervals for three hours. The test was considered positive for increases of hydrogen

concentrations of at least 20 ppm over basal values, within the first 90 minutes since oral administration of lactulose.

The hydrogen concentrations were measured by means of a Bedfond Gastrolizer gaschromatograph (Bedfond U.S.A., Medford, NJ, USA), which assays hydrogen by means of a sealed electrochemical sensor specific for hydrogen, and is not influenced by any change of pressure and temperature.

The demographic characteristics of the patients have been described as means and standard deviations (min-max ranges), or frequencies when appropriate. The frequencies of symptoms observed in patients with diagnosis of SIBO and IBS have been compared by means of the BT test.

Results

In the two-year period since January 2006 and December 2007, we have screened 127 patients with a diagnosis of IBS based on the Roma II criteria. They were sent to our Gastronterology Unit by 81 different GPs working in our geographical area (North-East Italy), and they were 28 males and 99 females, aged between 17 and 76 years (age mean ± s.d.: 41.4 ± 13.4); mean weight and height were, respectively, 62.6 ± 11.5 kg and 116.0 ± 9.1 cm. Ninety-four patients (74.0%) were scored with a diarrhoea-variant IBS, 21 patients (16.5%) with a constipation-variant, and 12 patients (9.5%) with alternate alvus variant (Table I).

The result of the lactulose BT was positive for 55 patients and negative for the remaining 72 (Table II); thus, we could estimate a prevalence of 43.3% of SIBO among the patients with IBS. Our value is between a 28% observed in similar IBS populations when only the hydrogen increase within 90 minutes was considered, and a 69% when the larger criterion (180 minutes) was considered[12]. In addition, we have performed a lactose BT in 30 patients who were suspected to have a lactose intolerance; the BT resulted positive in 21 of them, thus indicating a presence of lactose intolerance in about 16% of IBS patients.

It should be noted that, before the IBS population had been examined in our centre, a lactulose BT was required by GPs for only two patients, while glucose BT was never required. Thus, diagnosis of IBS and presence of SIBO and/or a lactose intolerance, as well as their relative treatments, were only based on a symptomatological approach.

Table I. Demography and clinical symptomatology associated with IBS in the survey population. The results are reported as frequency, mean ± SD, percentage and range as appropriate.

	Total patients (n = 127)
• Males/females	28 (22.0%)/99 (78.0%)
• Age (years)	41.4 ± 13.4 (17 – 76)
• Weight (kg)	62.6 ± 11.5 (41 – 91)
• Height (cm)	166.0 ± 9.1 (147 – 189)
• IBS diarrhoea-variant	94 (74.0%)
• IBS constipation-variant	21 (16.5%)
• IBS alternate alvus-variant	12 (9.5%)
Essential symptoms	
• Relieved by evaluation	116 (91.3%)
• Associated with a change in stool frequency	114 (89.8%)
• Associated with a change in stool consistency	119 (93.7%)
Additional symptoms	
• Altered stool frequency (< 3 weekly or > 3 daily);	78 (61.4%)
• Altered stool consistency;	118 (92.9%)
• Disturbances of evacuation;	117 (92.1%)
• Presence of mucus in the stools;	39 (30.7%)
• Abdominal bloating or distension.	107 (84.3%)

Table II. Results of BT with lactulose and BT with lactose.

	Total patients (n = 127)
BT with lactulose	Performed: 127 (100%)
• Positive	55 (43.3%)
• Negative	72 (56.7%)
BT with lactose	Performed: 30 (23.6%)
• Positive	21 (70.0%)
• Negative	9 (30.0%)

Discussion

The introduction of a lactulose BT should be encouraged in the diagnostic approach to patients with IBS, because SIBO is largely diffuse among these patients and responsible for a large part of symptomatology, while its presence can be demonstrated only by means of a BT. In our experience, the symptomatology was completely overlapping in IBS patients with and without SIBO, as it is shown by the distribution of symptoms in the two subpopulations (Figure 1). Therefore, symptomatology cannot be helpful in suggesting the presence of a bacterial contamination of the small intestine and/or a lactose intolerance.

In order to make diagnosis of SIBO, we have preferred the lactulose BT with a 90-minute "cut-off" rather than a glucose BT. Since glucose is absorbed from the proximal small intestine, it represents a good tool for diagnosis of high intestine (proximal) SIBO; on the contrary, lactulose is not absorbed through the small intestine and reaches unchanged the colon, where it is metabolised by the bacterial flora. Thus, the BT to lactulose is more specific than glucose BT to identify a low-intestine (distal) SIBO, which is the more frequent bacterial contamination observed in patients with IBS. The sensitivity and specificity of lactulose BT in the diagnosis of SIBO are actually estimated to be 68% and 44%, respectively, compared to values of 62% and 83% for the glucose BT[16].

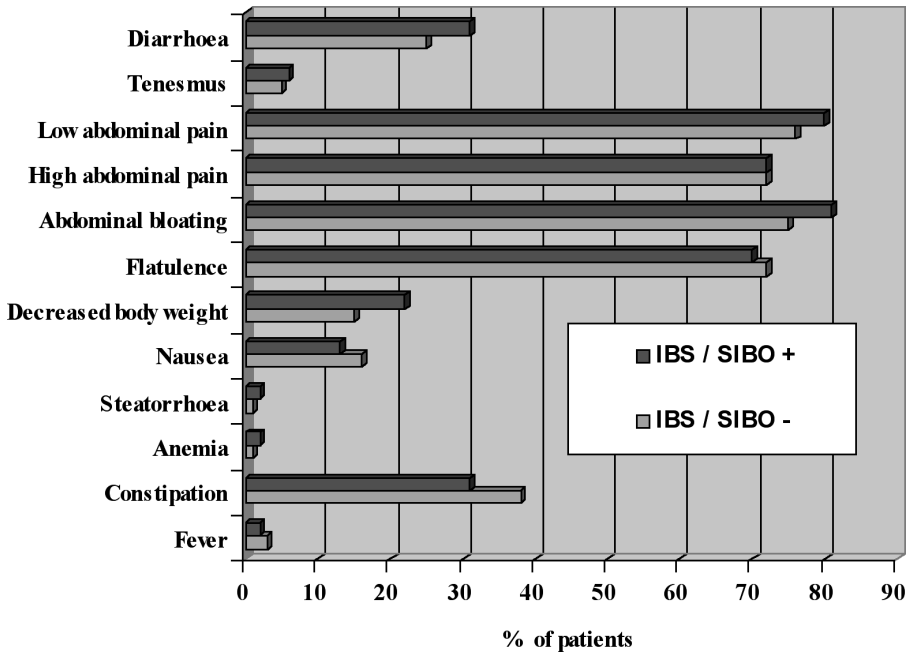

Figure 1. Frequency (% of patients) of symptoms in IBS patients with (IBS/SIBO +) or without (IBS /SIBO -) concomitant SIBO.

When the bacteria come in contact with lactulose, they metabolise it and produce intestinal gasses, such as methane and hydrogen, which can be detected and assayed in the expired air. In the healthy population, bacteria are present only in the colon and, therefore, at least two hours are needed for lactulose to reach the colon and be metabolised. Therefore, an increase of hydrogen concentrations in the expired air strongly suggests a bacterial overgrowth and contamination of the small intestine.

The positivity of lactulose BT has been firstly defined as a presence of an early peak of hydrogen (> 20 ppm) caused by the bacterial flora of small intestine, which is shown at least 15 minutes before a second prolonged peak that is caused by the physiological metabolism of lactulose in the large intestine. Recently, some Authors have introduced less restrictive criteria for positivity to lactulose BT, such as an increased concentrations of hydrogen within 90 minutes since the oral ingestion of lactulose, or an increase larger than 20 ppm within 180 minutes. It should be underlined that the variability of the orocaecal transit time might involve several difficulties in the interpretation of the test, keeping in mind the original definition of positivity in terms of double peak of hydrogen.

SIBO is due to a contamination of the small intestine by colo-fecal germs through an incontinent Bauhin's valve. The SIBO has various clinical and biological presentations: chronic diarrhoea, malabsorption syndrome and exudative enteropathy are the main criteria of diagnosis. The syndrome is characterized by an increase of overall bacterial burden in biotope $>10^5$ CFU/ml in adults and $>10^4$ CFU/ml in children, emergence of different species of *enterobacteria*, *bacteroides*, *clostridia* and *fusobacteria* in small intestine. Microecological changes are accompanied by B_{12} vitamin deficiency anaemia, hypovitaminosis, protein deficiency, translocation of bacteria and their toxins from intestine in blood, emergence of endotoxinemia and possible generalization of infection[17].

King et al[18] have provided indirect evidences for these alterations by showing an increased excretion of hydrogen and methane in post-prandial expired air in patients with IBS. Previous microbiological studies have also showed a reduced concentration of *colibacteria*, *lactobacilli* and *bifidobacteria* in the stools of IBS patients and an increased bacterial invasion of the colon mucosa by *E. Coli*, *colibacteria*, *enterobacteria*, *anaerobes* and *bacteroides*, in biopsies taken from patients with IBS[19].

The treatment of SIBO must be firstly focused on the correction of wrong food and dietary habits that usually underlying the disorder (e.g., excessive use of fast-food), and then to the reduction of bacterial colonization of small intestine by means of antibiotics[20-22]. In this regard the use of locally acting non-absorbable antibiotics, such as rifaximin[23,24], would be particularly useful in reducing immediately the bacterial count waiting for the slow-acting beneficial effects of dietary measures. Decontamination of the small intestine is more successful when probiotics are prescribed (both after antibiotics and independently), which suppress the opportunistic flora, protect the mucous coat, improve digestion and arrest diarrhoea[25].

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