BREATH HYDROGEN TESTS IN THE DIAGNOSTICS OF BACTERIAL OVERGROWTH SYNDROME

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Key words: irritable bowel syndrome, bacterial overgrowth syndrome, lactulose hydrogen breath test, enteroseptics, probiotics

Introduction. In this paper we want to pay close attention to the combination of irritable bowel syndrome (IBS) and bacterial overgrowth syndrome (BOS) in the small intestine. Since IBS symptoms overlap with symptoms of BOS, several authors hypothesized that many patients with IBS had comorbidity with BOS [2, 17, 22, 24, 25]. This theory is supported by recent studies that have found that BOS, diagnosed using the hydrogen breath test with lactulose or glucose, is more common in patients with IBS than in patients with other physical symptoms that do not have symptoms of IBS.

In the gastrointestinal tract of human normally "live" from 300 to 500 different types of bacteria. Microbial landscape varies significantly in the proximal and distal small intestine. If the upper part of the small intestine has approximately 10^2 CFU/ml, the closer to the colon has 10^9 CFU/ml. In the proximal small bowel aerobic gram-positive bacterial species are the most common, while gram-negative, anaerobic bacteria are more often localized in the distal area. In healthy individuals the normal intestinal microflora is maintained by following major physiological mechanisms: hydrochloric acid pH in the stomach, the activity of the secretory function of the pancreas and cholepoiesis, intestinal motility and structural integrity of the gastrointestinal tract. Violation of any of these protective mechanisms can lead to the development of BOS in the small intestine.

If we assume that the presence of BOS can explain the development of IBS symptoms, it raises an interesting question whether BOS is one of the leading pathogenetic aspects of IBS development or it is a set of symptoms common in IBS patients [13, 17].

IBS is extremely common in the population and occurs with a frequency of 5 to 20% [13] depending on the criteria used for the definition of this diagnosis. Pathogenetic mechanisms of IBS determine the presence of the expressed painful abdominal syndrome [30], minimal signs of inflammation [3], abnormal gastrointestinal motility [32] and changes in the gut microflora [11]. Despite the recommendations of national and international guidelines that recommend the definition of the diagnosis of IBS in patients based on diagnostic criteria, diagnostics' important principle is not turn to invasive methods without need. But we can't ignore the fact that there are a number of other common organic gastrointestinal diseases, including celiac disease [41], with increasing cholepoiesis, malabsorption [39] and exocrine pancreatic insufficiency [36], which clinic corresponds to IBS. Bloating is one of the leading symptoms in IBS patients [26]. Several researchers describe the increase in the amount of exhaled hydrogen after receiving substrates, causing intestinal fermentation in IBS patients as compared to the examined healthy [18]. This symptom is due to the fact that patients who are identified by diagnostic criteria for IBS may have the presence of excess of enteric bacterial growth caused by the colonization of the proximal small bowel by bacteria that cause fermentation. Some researchers have studied therapeutic effects of such non-absorbable antibiotic as rifaximin in the treatment of IBS. A small, randomized, placebo-controlled study was published in 2006 [8], patients who participated in it took 400 mg of rifaximin three times a day for 10 days. During the study they identified a large percentage of patients feeling better, and flatulence symptoms decreased significantly. In recent years two randomized controlled studies have been conducted [34], patients received either 550 mg of rifaximin three times per day or placebo for two weeks. These studies obtained statistically significant reduction of IBS symptoms in patients receiving rifaximin in 4 weeks after cessation of therapy (40% of patients with active treatment as compared to 30% taking placebo). These data suggest the need for screening the patients with IBS symptoms for detection of enteric bacterial growth, in order to identify persons who should have enteroseptic therapy.

Hydrogen breath test (HBT) with the use of carbohydrates (glucose, lactulose, fructose, lactose, etc.) was carried out from the 70-ies of the last century. In one study, J. M. Rhodes et al. HBT studied with lactulose (LHBT) as a diagnostic test for BOS and used 14C-glycocholate breath test for comparison. LHBT was positive in 8 of 9 patients, the same patients had a positive 14C-glycocholate test. However, even in 6 patients with a positive 14C-glycocholate test LHBT was negative. Subsequent bacteriological examination of duodenal juice on bacterial overgrowth in these patients was also negative. Negative results were obtained from the LHBT of 12 patients, none of them subsequently showed bacterial overgrowth. LHBT was determined by a simple and promising diagnostic test for the detection of bacterial overgrowth in the small intestine. Unlike the C14-glycocholate test, LHBT has an advantage since the excess enables to detect bacterial growth various parts of small intestine [33].

Non-invasive technique for determining the excess of bacterial contamination of the small intestine using HBT was investigated by several other research groups. But unfortunately, the results of such studies are mixed, some researchers have reported that the positive HBT is more common in people with IBS in comparison with healthy [23], and others report that there are no significant differences in the use of HBT in IBS [4]. Systematic reviews and meta-analyzes published recently have considered this issue in detail [1, 4, 10, 40]. One was published in late 2009 and reported that a positive result in the diagnosis using the HBT using lactulose, glucose or sucrose usually was more common in patients with IBS, but the significance of the differences of this observation varies depending on the heterogeneity among research. The authors of the second study [21] reported that the probability of a positive HBT in patients with suspected IBS is more than four times higher than in healthy.

There are a few precautions of using these data in routine clinical practice:

- first, HBT themselves do not identify specific pathogen and are not screening;
- secondly, the lack of consensus as to what level of performance should be used for the definition of a positive test;

– thirdly, the gold standard for diagnosis of enteric bacterial growth remains bacteriological seeding of jejunal aspirate.

Today only one study used this technique [35] and revealed a statistically significant difference in the prevalence of BOS in cases with suspected IBS compared with control. Statement "whether to consider bacteriological seeding of jejunal aspirate as the gold standard in all cases of BOS" is also controversial. It is known that the technical preparation of aspirate for bacteriological examination of the distal parts of the small intestine is a very complex method. There are types of bacteria that can't yet be cultured by using the conventional methods. Finally, the research team suggested that a unifying explanation for high growth of HBT positive result in IBS patients might have been due to frequent and prolonged use of proton pump inhibitors [37], which are prescribed by the doctors empirically for many patients with gastrointestinal symptoms. Unfortunately, some of these studies, including meta-analyzes, reported prevalence of use of these drugs, but did not specify whether this was a significant factor for the development of BOS. Thus, there are some reasons to believe that bacterial contamination of the small intestine, diagnosed by using HBT in adults with symptoms that meet the diagnostic criteria for IBS, is very informative [12].

Thus, the initial studies revealed BOS high prevalence in persons with IBS, wherein subsequent investigations showed much lower incidence of this syndrome usually depending upon the diagnostic test used [24, 35]. Motility disorders of the small intestine have been proposed as one of the leading predictors of formation of IBS. A short course of antibiotic therapy can lead to improvement of symptoms, although the duration of this effect remains uncertain [8].

Over the past few years there has been some progress in the study of IBS. Studies have shown expressed disturbances of intestinal motility [19], peripheral [16] and central [31] sensory dysfunction, and severity of the pathological response to stress [9] in this syndrome. However, until now there is no single diagnostic test that determines IBS. As a result, researchers have created a range of diagnostic schemes such as the Rome criteria to help diagnose and classify the syndrome [14, 15]. One of

the compelling clinical symptoms of IBS is abdominal distension [5, 38]. A. Koide et al. detected the presence of gas in the small intestine, which significantly increased the amount of IBS patients compared to control ones [28], no matter what prevailed in the clinic — pain or diarrhea. Excessive gas production takes place in the small intestine by increasing the production of gas in the gut by bacterial fermentation. 78% of IBS patients have LHBT positive, indicating that they have BOS [24].

Another study showed that in 20% of patients IBS arises as a consequence of acute bacterial gastroenteritis, so called post-infectious IBS. Violation of bacterial fermentation in IBS patients explains such a symptom as bloating and is one of the factors causing increase in visceral hypersensitivity. The presence of excessive bacterial contamination of the small intestine allows exploring the new therapeutic options, including mainly the use of pre- and probiotics, and possibly antibiotics in IBS patients [7].

Study by S. C. Reddymasu et al. revealed that 36% of IBS patients had positive results of HBT pointing to BOS. The preponderance of exhaled hydrogen was detected more frequently in patients with diarrhea observed in IBS clinic, and exhaled preponderance of methane was found in patients with constipation in IBS. Predictors of BOS in IBS were age more than 50 and female gender. Identification of possible BOS predictors in IBS patients can help in choosing the tactics of successful treatment [29].

Study by S. Kumar et al. also determined that the positive hydrogen test was more frequent in patients with IBS as compared to healthy. Number of defecations per week correlated with the level of exhaled hydrogen in IBS patients [20].

Clinical problem is a certain group of IBS patients with the most probable BOS. Symptoms in these patients relative to many other factors (such as abnormal motility, visceral hypersensitivity, psychosocial distress factors) are also determined by increased intestinal bacterial contamination, which affects the clinical course of the syndrome. Unfortunately, there is no data to assist the clinician in the selection of diagnostic and therapeutic algorithms, so you can observe the following principles:

- to determine whether patient’s clinical profile of excess enteric bacterial growth corresponds to postprandial discomfort in abdomen, abdominal distention, and optionally a liquid feces;
- if clinical signs are absent, to conduct LHBT (if it is available);
- if the result of LHBT is positive, to prescribe antibiotic or enteroseptic of wide spectrum of action;
- after this treatment to prescribe a probiotic to restore the deficit of "good" bacteria;
- if the stool is normalized or upon tendency to constipation, to consider adding prokinetics to accelerate enteric transit;
- if symptoms recur, and the previous LHBT was positive, to repeat examination and course of antibiotics (enteroseptics) if LHBT is positive again;
- if LHBT is unavailable, the doctor should be conservative and should not repeat treatment if effect from conducted course antibiotics (enteroseptics) is preserved by at least several months [6].
- Material and methods. We examined 127 patients with IBS. The diagnosis was confirmed by exclusion of organic bowel disease using standard research methods. As a control group, we took 25 people with no signs of IBS and BOS, which was also held LHBT. All patients underwent IBS-BOS-depth clinical study, which included, besides general clinical methods, a set of techniques for detection of celiac disease, fecal antigen to Giardia CT colonoscopy or irrigoscopy, fibrocolonoscopy (by prescription), psychological testing, as well as each patient fills questionnaire IBS Quality of Life (IBS-QOL) [27]. The examination LHBT (device Gastrolyzer 2). Differences between the parameters of compBOSon were considered statistically different at $p \leqslant 0{,}05$.

Materials and methods. We examined 127 patients with IBS. The diagnosis was confirmed by exclusion of organic bowel disease using standard research methods. As a control group, we took 25 people with no signs of IBS and BOS, who

also underwent LHBT. All patients with IBS-BOS underwent in-depth clinical study, which included, besides general clinical methods, a set of techniques for detection of celiac disease, fecal antigen to Giardia, CT colonoscopy or irrigoscopy, fibrocolonoscopy (by prescription), psychological testing, as well as each patient filled in the questionnaire IBS Quality of Life (IBS-QOL) [27]. The examination of LHBT (device Gastrolyzer 2) was conducted for all the patients. Differences between the parameters of comparison were considered statistically different at $p \leqslant 0.05$.

Results. In 78 (61.4%) patients LHBT indicators exceeded normal, suggesting the presence of BOS. In constructing the general (average) test result chart in patients with IBS-BOS, we observed two peaks of increased exhaled hydrogen, which was typical for excessive bacterial contamination of the small intestine. In the control group only one peak is observed. It is known that lactulose is not normally metabolized in the small intestine (healthy), and it is metabolized in colon by normal anaerobic colonic microflora to short-chain fatty acids and excretion of molecular hydrogen. This hydrogen is recorded upon the exhalation from the lungs by a special device (in our study — Gastrolyzer 2). Patients with BOS in the small intestine have excess contamination colonic anaerobic, not physiological, microflora, so lactulose metabolism is observed much earlier, i.e. in the small intestine. This phenomenon is registered with LHBT, making it positive. The examination results are presented in Figure 1.

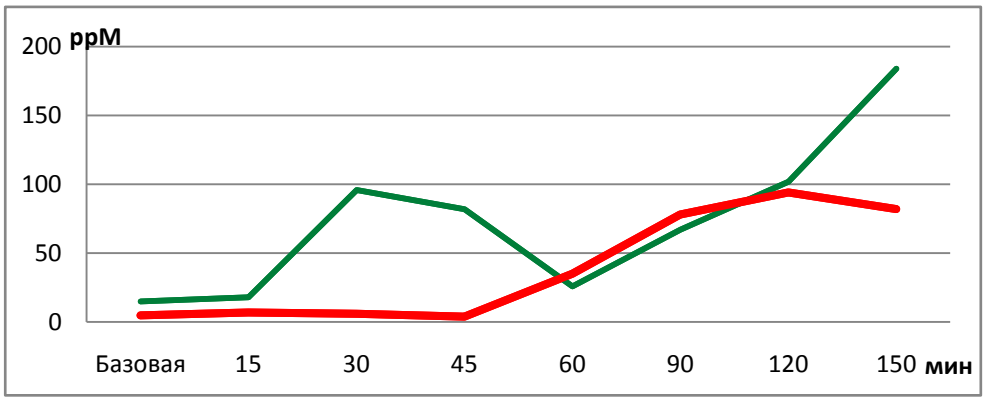

Fig. 1. Results of LHBT. The upper curve (green) — patients with IBS and BOS, the lower (red) — the control group ($p \leqslant 0{,}05$).

37 patients (group 1) with IBS-BOS and positive LHBT were prescribed the nitrofuran series nifuratel as enteroseptic 400 mg 3 times a day for a week. 51 patients with IBS-BOS (group 2) and with positive LHBT received drug rifaximin as enteroseptic 400 mg 2 times a day for 6 days.

After decontamination of the small intestine with the use of nifuratel, majority of patients (28 people — 78.4%) reported a significant reduction or complete relief of bloating, stool normalization or its decreasing frequency, complete or significant pain relief. The remaining 9 persons had intestinal dyspepsia symptoms decreased significantly, but the pain persisted, i.e. the psychosomatic component of IBS was expressed, these patients were assigned to treatment by antispasmodics, psychotropic drugs. Upon the dynamics of LHBT, in all the patients there was a statistically significant different positive dynamics. Pathological peak over the small intestine either was leveled completely, or decreased significantly; peak over the colon in some patients (16 people — 43.2%) also declined significantly. The latter index might have indirectly pointed to the inhibition of the normal microflora in the colon. The examination results in the dynamics are presented in Figure 2.

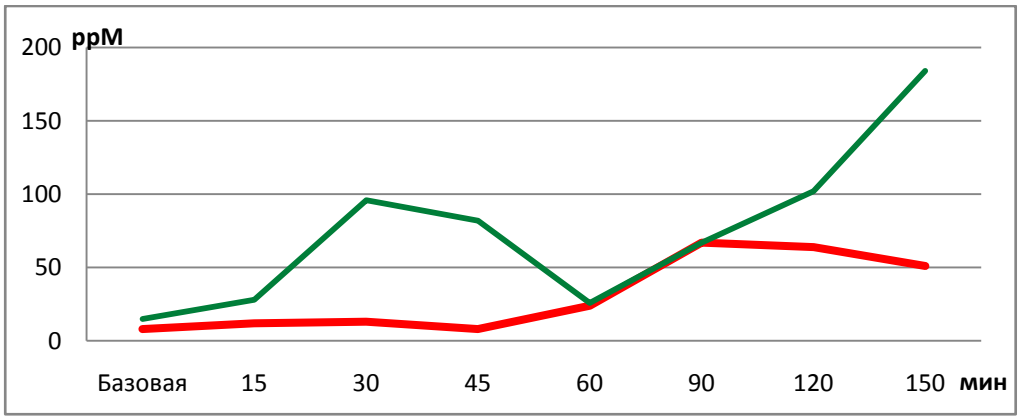

Fig. 2. Results of LHBT in dynamics. The upper curve (green) — patients with IBS-BOS before treatment, the lower (red) — after treatment with nifuratel ($p \leqslant 0,05$).

After decontamination of the small intestine with the use of rifaximin, the majority of patients (43 people — 84.3%) also reported a significant reduction or complete relief of bloating, stool normalization or its decreasing frequency, complete or significant pain relief. In the remaining 8 people intestinal dyspepsia symptoms

decreased significantly, pain also decreased, these patients were assigned to treatment by antispasmodics, psychotropic drugs, as well as patients receiving nifuratel. Upon the dynamics of LHBT, all the patients had statistically significant different positive dynamics. Pathological peak over the small intestine either was leveled completely, or decreased significantly; peak over the colon in some patients (28 people — 54.9%) also declined. The latter figure might have indirectly pointed to the inhibition of the normal microflora in the colon. The examination results in the dynamics are shown in Figure 3.

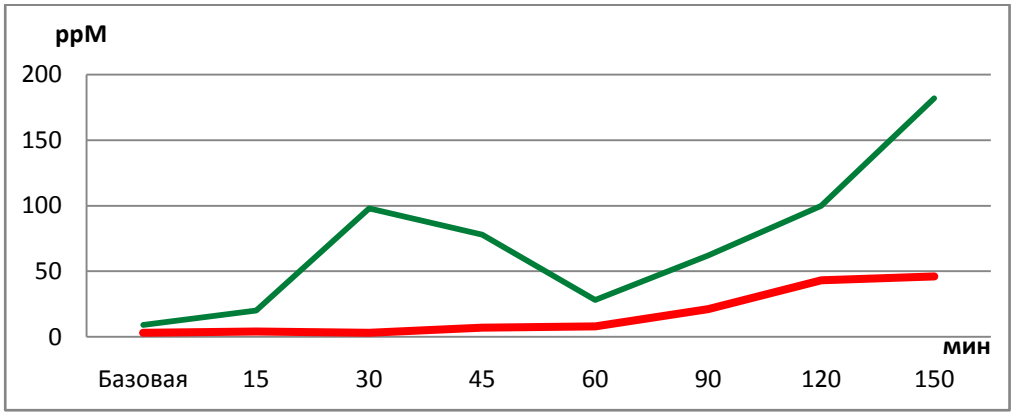

Fig. 3. Results of LHBT in dynamics. The upper curve (green) — patients with IBS-BOS before treatment, the lower (red) — after treatment with rifaximin ($p \leqslant 0,05$).

Conclusions. As a result, we were able to confirm the position of the different researchers that IBS was often associated with BOS — in this case, 61.4% of patients. After the treatment of patients with IBS-BOS, the clinical picture of the disease and the results of LHBT ($p \leqslant 0,05$) significantly improved. The objectives of the study did not include a comparison of enteroseptics that were used in the study, this stage of the analysis will be continued in the future. All patients after decontamination received probiotics — Linex or RioFlora balance, results of this stage being also monitored by using LHBT.

LHBT is a very affordable non-invasive method for diagnosing and monitoring the treatment. Its implementation does not require long-term specialized training of laboratory assistant, who conducts research, separate equipped premises, expensive reagents. It can be used in different situations — as a method of examination for

screening of medical examinations, for detection of bacterial contamination in certain groups of patients, for control of decontamination. All possibilities of the method have not yet been fully exploited, since it is very difficult to convey many physicians of related gastroenterology specialties that LHBT can extend their diagnostic capabilities, thereby increasing the effectiveness of their therapeutic interventions. And as a result, quality of life for patients will be improved, whose BOS will be promptly identified and treated.

We consider our primary task as the implementation of this technique not only in gastroenterology and therapeutic practices, but in pediatrics, gynecology, surgery and other related specialties. We are planning lectures, development of guidelines for these professionals. HBT with lactulose, lactose, glucose and other carbohydrates has very promising prospects of application in clinical practice.

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We examined 127 patients with IBS. Diagnosis was confirmed due to the exclusion of organic intestinal diseases by using standard methods. All the patients underwent hydrogen breath test with lactulose (LHBT) (device Gastrolyzer 2). Differences between the parameters of compBOSon were considered statistically different at $p \leq 0.05$. In 78 (61.4%) patients LHBT indices exceeded normal ones, suggesting the presence of BOS. All patients were prescribed to perform a decontamination of the small intestine — rifaximin (400 mg twice a day for 6 days) or nifuratel (400 mg 3 times a day for a week). Upon the LHBT dynamics, we observed a significant positive trend that was statistically significant ($p \leq 0.05$) in all the patients. Pathological peak over the small intestine was either completely leveled, or significantly reduced, peak over the colon also decreased significantly in some patients. Complaints of abdominal pain, bloating, unstable stool also decreased significantly ($p \leq 0.05$) in the majority of patients in this group, only 12 (15.1%) patients had complaints remained the same, despite the positive LHBT dynamics.

Patients with IBS need the examination for having BOS, whereas it is detected, it should be treated by the modern enteroseptics and probiotics.