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Irritable bowel syndrome: pathogenesis, symptoms, diagnosis and pharmacotherapy

Zespół jelita drażliwego: patogeneza, objawy, diagnostyka oraz farmakoterapia

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic disease of idiopathic origin, unconditioned organically or biochemically. This syndrome was first recognized and described by Osler in 1892 and named *mucous colitis*. Nowadays, 10-20% of the total population suffers from it, of which two thirds are women [15]. IBS can be classified as either diarrhea-predominant (IBS-D), constipation-predominant (IBS-C) or IBS with alternating stool pattern (IBS-A or pain-predominant). In some patients, IBS may be a consequence of the earlier bacterial gastroenteritis and then is called post-infectious IBS [5].

P a t h o g e n e s i s. There is no any specific cause of this condition. Possibly, people suffering from IBS are more sensitive to some kind of food or stress. It is believed that it may be also involved in the immune system. Recent studies have shown that patients with more severe symptoms of IBS have higher levels of T-lymphocytes expressing CD25, high number of intraepithelial lymphocytes in the colon (both diarrhea-predominant and alternating), and higher number of CD3+ in diarrhea-predominant and alternating than those with constipation. In addition, the number of MS in the gastrointestinal tract was high in patients with IBS-D without rectal hypersensitivity [12]. Also increase in the number of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8) and drop in the amount of anti-inflammatory cytokine IL-1O were observed [13].

Researchers have reported that IBS may be caused by a bacterial infection in the gastrointestinal tract. Studies show that people who have had gastroenteritis sometimes develop IBS, also called post-infectious IBS.

Recent studies show that the pathogenesis of IBS may also be associated with abnormalities in the serotonin (5HT). This neurotransmitter is closely related to normal functioning of the digestive tract. Ninety-five percent of serotonin in our body is located in the gastrointestinal tract (GI), and the remaining 5 percent is in the brain. In people with IBS, decreased activity of serotonin receptors in the gastrointestinal tract was observed, causing abnormal levels of serotonin. The result is a greater sensitivity to pain receptors 5HT located in the GI and gastrointestinal motility disorder [4].

S y m p t o m s a n d d i a g n o s i s. The primary symptom of IBS is abdominal pain, lasting at least 3 months, connected with diarrhea or constipation. Abdominal pain is constant or recurrent, usually intensifies after meals, it is relaxed after defecation. Patients can also feel urgency of bowel movements, upon the return of a feeling of incomplete bowel evacuation. The other symptoms are: abdominal bloating (with the normal amount of gas in the intestines), nausea, vomiting, headache and backache as well. People with IBS more often complain of gastroesophageal reflux [16]. In 70-90% of patients mental disorders such as depression and anxiety were also observed [6, 15].

There is no specific test for IBS. The diagnosis is usually based on an interview with the patient in question, and after doing a series of diagnostic tests, including blood count and erythrocyte sedimentation rate (ESR), blood biochemical examination, general physical examination and bacteriological urine and feces. Diagnosis is made after excluding other diseases. Diagnostic criteria are the Rome III guidelines, if the symptoms occurred within the last 3 months:

1) IBS with constipation (IBS-C) – hard or lumpy stools ≥25% and loose (mushy) or watery stools <25% of bowel movements;
2) IBS with diarrhea (IBS-D) – loose (mushy) or watery stools ≥25% and hard or lumpy stool <25% of bowel movements; 3) Mixed IBS (IBS-M) – hard or lumpy stools ≥25% and loose (mushy) or watery stools ≥25% of bowel movements; 4) Unsubtyped IBS (IBS-U) – insufficient abnormality of stool consistency to meet criteria IBS-C, D or M [3].

Celiac disease is often diagnosed as IBS, so it is recommended that physicians prior to the issue of diagnosis also carry out a study to rule out celiac disease.

Long-term use of certain sedative-hypnotics drugs, especially benzodiazepines can also cause symptoms similar to IBS [1].

T r e a t m e n t. The first step in treating IBS should be changing the diet, especially in constipation. It is recommended to increase the amount of fiber consumed. The first effects are visible only after 2-3 weeks of use. Dietary fiber (for example seed Plantago ispaghula) may reduce overall symptoms, but will not decrease the pain. The study shows that the optimal dose of fiber is 20g. Based on research carried out, an increase in stool weight, decreased symptoms of IBS, but no changes in intestinal transit were confirmed [8]. Also studies on the effectiveness of soluble and insoluble fiber have been carried out. Insoluble fiber is probably no better than placebo and may in some patients, even worsen the clinical outcome, while the soluble fiber proved to be beneficial to the overall improvement of symptoms [2].

Treatment of IBS is based on the alleviation of symptoms in spite of changes in diet and psychotherapy. Diarrhea is often treated with loperamide (2-4 mg) if needed. Diphenoxylate with atropine (2 tablets 3 times a day) and cholestyramine (4 grams in a meal) are also effective. With postprandial pain oksyfenonium bromide (5-10 mg 3 times per day) or hyoscine (10-20 mg) before meals is recommended. For chronic pain amitriptyline is used, and it is also used for depression and insomnia. The alternative is a selective serotonin reuptake inhibitor e.g. paroxetine [4].

Another common symptom of IBS-bloating is treated by simethicone (a mixture of polydimethylsiloxane and silica gel – 80 mg 3x a day) or dimethicone (one of several types of silicone oil- 10-20 mg before meals) [15].

In patients who do not respond to treatment with dietary fiber, there are used osmotic laxatives, such as propylene glycol, sorbitol, lactulose, and lubiprostone.

Serotonin partial agonist.

Tegaserod (Zelnorm) was the first partial agonist at 5-HT4 receptor, which allowed for the treatment of constipation in women diagnosed with IBS. The drug reduced the symptoms associated with IBS by a significant acceleration of gastric emptying and small bowel transit time and colon, but also decreased the sensitivity to rectal distension [17]. Efficacy was no observed in men. Effective dose was 6 mg tegaserod twice daily for 12 weeks. Reduction in symptoms was observed after the first week of use compared to placebo. Unfortunately, in March 2007, Zelnorm was removed from the market in the United States because it has been shown that it may increase the risk of heart attack, angina pectoris, or stroke. In July 2007 the U.S. Food and Drug Administration (FDA) announced that Zelnorm would be available to persons who meet certain criteria under an investigational new drug (ING) protocol, however, since April 2, it is no longer available [4]. Despite the withdrawal of Zelnorm in USA, clinical research on the effectiveness of this drug is still underway [17].

Lubiprostone (Amitiza) was approved by the FDA in 2006 at the dose of 24 μg twice a day for the treatment of chronic constipation for both men and women and in 2008 at the dose of 8μg twice a day for treatment of women with irritable bowel syndrome with constipation (IBS-C). Lubiprostone has not been approved for patients less than 18 years of age, since research is ongoing. Although there has been no evidence of toxicity in human fetuses, it has three classes of toxicity and can be used if the potential benefit outweighs the harm.

Lubiprostone is a bicyclic fatty acid (prostaglandin E1 derivative), that selectively activates type 2 chloride channels in the apical membrane of the intestinal epithelial cells, hence stimulating chloride secretion, along with passive secretion of sodium and water, inducing peristalsis and laxation, without stimulating gastrointestinal smooth muscle. Animal studies have shown that lubiprostone is metabolized within the gastrointestinal tract, particularly in the stomach and the jejunum, by the microsomal carbonyl reductase system. Ninety-four percent of the drug is bound to plasma proteins. There is an active metabolite, M3, which unlike the parent compound is systemically absorbed. The half-life of this metabolite is estimated to be 0.9-1.4 hours. Because of its metabolism, lubiprostone has few side effects and is well tolerated by patients. Most reported side effects are nausea, headache and diarrhea [9-11].

Serotonin agonist. Alosetron, which is a selective agonist at 5-HT3 receptor, decreases the motility of the colon. Clinical trials have shown that it causes inhibition of diarrhea, relieves pain, controls bowel urgency and improves the quality of life in diarrhea-predominant IBS patients. The results were more satisfying for women. Effective dose was 1 mg of alosetron twice a day. Paradoxical reduction in stool frequency occurred despite the increase in amplitude of contractions of the intestine [4]. Studies of brain activity showed that alosetron reduces the activity of the bilateral frontal cortex and different areas of the limbic system in response to colorectal distension. Despite high efficacy, unfortunately, side effects of this drug led to its withdrawal, as the patients experienced an increased incidence of ischemic colitis (leading even to death), and constipation. GlaxoSmithKline (GSK)

withdrew the drug from the market in November 2000, while in 2002 the FDA authorized its use only in specific cases. When prescribing this drug it is required to inform the patient of both the risks and benefits of this drug. In addition, serious adverse events are required to be reported to GSK or the FDA. The drug can be prescribed only for women who suffer from diarrhea-predominant IBS, who suffer from other diseases of the digestive tract, or do not respond to other treatments. In addition, starting dose of 1 mg once daily, may be increased to 1mg twice a day, if the drug is well tolerated [4].

Newer agents.

A number of new 5HT receptors has been steadily increasing, but in the treatment of IBS, renzapride, cilansetron and ramosetron are taken into account. The first one is a derivative of benzamide, showing the action of a 5HT3 receptor antagonist and 5HT4 receptor agonists. Phase III clinical trials of this drug are still ongoing, but the relationship between dose and the reduction in intestinal transit so far as well as the improvement of bowel function in female IBD-C patients have been observed.

Cilansetron is 5-HT3 antagonist and is investigated for treating diarrhea as well. It reduces pain and diarrhea but a few patients experienced ischemic colitis and constipation, and therefore it has not received FDA approval for treatment of IBS-C so far. Ramosetron- 5-HT3 antagonist with antiemetic properties and newer partial agonists of the 5-HT3 receptor like ME3412 (5-chloro-2-(1,4-diazacycloheptan-1-yl)-7-methylbenzoxazole), are being investigated in Japan [7].

Selective serotonin reuptake inhibitor (SSRI).

SSRI are often used in patients with IBS as antidepressants, if the disease is accompanied by anxiety, panic, sleeping disorders. Paroxetine and fluoxetine are the most commonly used ones. In addition to the antidepressant function, fluoxetine increases sensitivity to distention of the bowel after 6 weeks of use. In susceptible individuals it reduces abdominal pain compared to placebo and those susceptible to colorectal distension. Subsequent research has confirmed that fluoxetine is more effective compared to placebo in reducing abdominal pain, reducing bloating, improving peristalsis and decreasing consistency of stool [4].Patients treated with paroxetine reported no improvement in symptoms, but it affected the improvement of wellbeing and living standards both in patients diagnosed with depression and not suffering from depression. Citalapram reduced the severity of IBS symptoms, especially pain in people not suffering from depression. Improvement of pain symptoms in patients without depression may suggest that SSRIs have also additional benefits [4].

Antibiotic - Rifaximin.

Recent studies showed that rifaximin can be useful in treating IBS. Rifaximin is a semisynthetic antibiotic, derivative of rifamicyn, a small amount of which is absorbed from the gastrointestinal tract after oral administration. Studies have shown that short-term use of rifaximin improves quality of life of patients without constipation even 10 weeks after treatment. The recommended dose is 550mg 3x rifaximin per day for 14 days. Literature also provides that up to 5-times repeated treatment does not shorten the time when you have no symptoms or reduce the efficiency. Rifaximin action suggests that the cause of IBS may be the changes in bacterial flora, since it inhibits the production of metabolites of bacteria inhabiting the intestinal wall and decreases the immune response of host cells [14].

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SUMMARY

Nowadays irritable bowel syndrome (IBS) is a big problem for 10-20% of the population, of which two thirds are women. The study does not explicitly define the cause of this condition, but takes into account the impact of diet, stress, previous bacterial gastrointestinal infections, serotonin and immunological factors. Characteristic symptoms of IBS are abdominal pain lasting at least 3 months, and constipation or diarrhea, flatulence. Often, patients with IBS also have depression and anxiety disorders. SSRIs (paroxetine, fluoxetine and citalapram) used in these cases, not only affect the improvement of well-being and quality of life, but as have been observed also as having a positive influence on gastrointestinal motility and reducing abdominal pain. This may prove that in the pathogenesis of IBS serotonin plays an important role and may constitute a starting point for a newly discovered and studied agonists/antagonists of 5HT-3 receptors (tegaserod, lubiprostone, alosetron, renzaprid, cilansetron, ramosetron, ME3412), as potential drugs for irritable bowel syndrome. Study on rifaximin showed that IBS may be a consequence of early bacterial infection, because the antibiotic in therapeutic doses causes a reduction of symptoms associated with IBS, and now is considered one of the best in the treatment of IBS, since even treatment repeated 5 times does not reduce its effectiveness. The theory of immune response is only at the stage of research and, if confirmed, could become an effective alternative in the treatment of irritable bowel syndrome.

Keywords: irritable bowel syndrome, IBS, rifaximin, paroxetine, fluoxetine, citalapram

STRESZCZENIE

Zespół jelita drażliwego (IBS) jest w dzisiejszych czasach sporym problemem medycznym, dotyczącym 10-20% populacji, z czego 2/3 stanowią kobiety. Badania jednoznacznie nie określiły przyczyny tego schorzenia, ale pod uwagę bierze się wpływ diety, stres, wcześniejsze zakażenia bakteryjne przewodu pokarmowego, zaburzenia serotoninowe w układzie pokarmowym, a także czynniki immunologiczne. Objawami charakterystycznymi IBS są bóle brzucha trwające co najmniej 3 miesiące, a także zaparcia lub biegunki, wzdęcia. Częstym objawem u pacjentów cierpiących na IBS są również zaburzenia nastroju i lęk. Stosowane leki z grupy SSRI (paroksetyna, fluoksetyna, oraz citalapram) nie tylko wpływają na polepszenie samopoczucia i poprawę jakości życia, ale jak zaobserwowano, wpływają również pozytywnie na motorykę przewodu pokarmowego, zmniejszają bóle brzucha. Dowodzić to może, że w patogenezie IBS znaczącą rolę odgrywa serotonina, która może stanowić punkt zaczepienia dla nowo odkrywanych i badanych agonistów/antagonistów receptorów 5HT (tegaserod, lubiprostone, alosetron, renzaprid, cilansetron, ramosetron, ME3412), jako potencjalnych leków w IBS. Badanie nad rifaximiną pokazały, że IBS może być konsekwencją wcześniejszej infekcji bakteryjnej, gdyż antybiotyk ten w zastosowanych dawkach wykazywał zmniejszenie objawów towarzyszących IBS i obecnie uznawany jest za jeden z lepszych w leczeniu tej choroby, gdyż nawet 5-krotne przeleczenie nie powoduje zmniejszenia jego efektywności. Teoria immunologiczna jest dopiero na etapie badań i jeśli zostanie potwierdzona klinicznie, być może stanie się skuteczną alternatywą w leczeniu tej jednostki chorobowej.

Słowa kluczowe: zespół jelita drażliwego, IBS, rifaximina, paroksetyna, fluoksetyna, citalapram