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Small intestine bacterial overgrowth in chronic pancreatitis

Przerost bakteryjny jelita cienkiego w przewlekłym zapaleniu trzustki

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Summary

Chronic pancreatitis (CP) is a serious disease that has a significant impact on the quality of life. The consequence of exocrine and endocrine pancreatic insufficiency is an abdominal pain, diabetes mellitus and malnutrition. Factors predisposing to CP, course of disease, as well as iatrogenic factors may lead to disorders in intestinal microbiota. Small intestine bacterial overgrowth (SIBO) is excess of bacteria in the small intestine. Its prevalence in adult patients with CP is approximately 36%. Many non-specific symptoms occur in SIBO, and in severe cases, it can lead to steatorrhea, malnutrition and weight loss. Furthermore, symptoms not only imitate those occurring in CP, but often aggravate them and hinder the treatment. "Golden standard" in SIBO diagnostics is a qualitative and quantitative assessment of aspirate from the small intestine, but this procedure is invasive, expensive and not widely available. The response are commonly used hydrogen breath tests with glucose. The disorder concerns intestinal microbiota, therefore the treatment is mainly based on its modification. Rifaximin is the best studied antibiotic, used in SIBO. Probiotics help to fight opportunistic intestinal pathogens, not causing disruption in gut ecosystem. It is equally important to treat nutritional disorders associated with SIBO. Regardless of therapy, the risk of bacterial overgrowth recurrence should always be considered. Due to the increasing awareness of microbiota's influence on the course of many diseases, it is necessary to further develop diagnostics and treatment of its disorders, also in chronic pancreatitis.

Streszczenie

Przewlekłe zapalenie trzustki (PZT) jest poważną chorobą, która ma istotny wpływ na jakość życia. Konsekwencją niewydolności zewnątrz- i wewnątrzwydzielniczej trzustki są: ból brzucha, cukrzyca i niedożywienie. Czynniki predysponujące do PZT, przebieg choroby oraz czynniki jatrogenne mogą prowadzić do zaburzeń mikrobioty jelitowej. Bakteryjny przerost jelita cienkiego (ang. *small intestine bacterial overgrowth* – SIBO) to zwiększona liczba bakterii w jelicie cienkim. Częstość jego występowania u pacjentów z PZT wynosi około 36%. W jego przebiegu występuje wiele nieswoistych objawów, a w ciężkich przypadkach może dochodzić do biegunki tłuszczowej, niedożywienia i utraty masy ciała. Ponadto, objawy nie tylko imitują te występujące w PZT, ale często nasilają je, utrudniając leczenie. „Złotym standardem" w diagnostyce SIBO jest jakościowa i ilościowa ocena aspiratu z jelita cienkiego, ale procedura ta jest inwazyjna, kosztowna i nie wszędzie dostępna. Odpowiedzią są szeroko stosowane wodorowe testy oddechowe z glukozą. Choroba dotyczy mikrobioty jelitowej, dlatego leczenie opiera się głównie na jej modyfikacji. Rifaksymina jest najlepiej zbadanym antybiotykiem stosowanym w SIBO. Probiotyki pomagają walczyć z oportunistycznymi patogenami jelitowymi, nie powodując jednocześnie zakłóceń w ekosystemie jelit. Równie ważne jest leczenie zaburzeń odżywienia związanych z SIBO. Niezależnie od terapii, zawsze należy rozważyć ryzyko nawrotu przerostu bakteryjnego. Ze względu na rosnącą świadomość wpływu mikrobioty na przebieg wielu chorób, konieczny jest dalszy rozwój diagnostyki i leczenia jej zaburzeń, także w przewlekłym zapaleniu trzustki.

Conflict of interest
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None
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INTRODUCTION

Chronic pancreatitis (CP) is an serious inflammatory process that develops in individuals with genetic, environmental and other risk factors, leading to progressive, irreversible organ injury. The disease proceeds with periods of remission and exacerbation. Gradual

changes in the form of atrophy and fibrosis of pancreatic parenchyma are the cause of exocrine and subsequent endocrine pancreatic dysfunction. The consequence of this is recurring abdominal pain, which in advanced chronic pancreatitis may be constant, diabetes mellitus and malnutrition. Patients life expectancy and its quality are reduced due to progression of the disease, its association with other systemic illnesses and pancreatic cancer (1, 2).

Disturbed secretion of pancreatic juice, which apart from its essential digestive function also acts antibacterially, altered gastrointestinal motility, alcohol abuse and medicines taken in the course of CP leads to the proliferation of pathogens in the intestinal lumen. Disorders of composition, amount of bacteria in the small intestine and accompanying symptoms are defined as small intestine bacterial overgrowth (SIBO). Manifestation of this disorder include non-specific gastrointestinal symptoms such as abdominal pain, flatulence, bloating, diarrhoea and more severe complications such as vitamins and other microelements deficiencies as well as growth disorders in children. Furthermore, symptoms caused by bacterial fermentation in SIBO not only imitate those occurring in chronic pancreatitis, but often aggravate them and hinder the treatment. The problem of bacterial overgrowth affects about 1/3 of people suffering from CP (3-5).

CHRONIC PANCREATITIS

Chronic pancreatitis is a serious disease that has a significant impact on the quality of life, which exacerbations and late sequelae can endanger patient life. In Europe, the incidence of CP range from 5 to 10 cases per 100,000 inhabitants. With median survival of 20 years, the prevalence is about 120 cases per 100,000 inhabitants. Pancreatitis is a rare childhood disease, but recent years have seen an increase in its incidence, which is explained by increased recognition (6, 7).

The causes of chronic pancreatitis, according to the TIGAR-O system, include toxic/metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis and obstructive aetiology. Alcohol abuse remains the dominant cause of chronic pancreatitis in adults. In Western countries, it is attributed to 40-70% of all cases. Smoking is also an independent risk factor for chronic pancreatitis. Other than alcohol and tobacco etiologic factors of CP are responsible for 20-50% of remaining cases of the disease. In the paediatric population, the most common causes of CP are gene mutations, anatomical defects of the pancreatic duct, and dyslipidemia (2, 8, 9).

Recurrent episodes of acute pancreatitis and chronic inflammation cause persistent damage to the exocrine and endocrine tissues, which is the basis of chronic pancreatitis. The greater the severity of the disease, the more intense is fibrosis process and the calcification of the pancreatic parenchyma. There is a distortions of the pancreatic ducts in the form of stricture and dilatation. Regardless of origin, injury to exocrine tissue is associated with an increase in intracellular levels of activated pancreatic enzymes (also in the blood). The accompanying inflammation and stenosis of ducts can damage the surrounding endocrine cells leading to the development of carbohydrate metabolism disorders, including diabetes mellitus eventually. The consequences of exocrine insufficiency are maldigestion and malabsorption. They manifest i.a. with abdominal pain, bloating, steatorrhea, weight loss, vitamin and microelements deficiencies. In addition to the clinical picture of exocrine and endocrine failure, pain is the most debilitating and disabling symptom that occurs in the majority of patients with chronic pancreatitis.

Symptomatic treatment in CP is of primary importance. The aim of therapy is also to prevent further progression of the disease and complications. CP significantly increases the probability of developing pancreatic tumors. Where possible, risk factors that may aggravate the course of illness such as alcohol consumption or cigarette smoking should be modified. Nutritional therapy aims to improve the general condition of the patient. Changing habits will help to avoid exacerbations caused by dietary errors. In the treatment of pain apply i.a. drugs throughout the analgesic ladder, procedures to reduce the pressure in the pancreatic duct and parenchyma, invasive endoscopic and surgical methods. The latter two are also used in the prevention and treatment of complications of CP. Digestive disorders caused by exocrine insufficiency require pancreatic enzyme replacement therapy administered with meals. Carbohydrate metabolism disorders, initially, can be controlled with the help of oral hypoglycaemic drugs such as metformin. Usually, however, for the treatment of diabetes type 3c, which is associated with injury to the pancreas, insulin supplementation is required. It is recommended to use long-acting preparations along with on-demand short acting insulins (8, 10, 11).

SMALL INTESTINE BACTERIAL OVERGROWTH

The number of microorganisms that colonize the digestive tract significantly exceeds the number of human body cells (10^{14} and 10^{13} cells, respectively). The greatest bacterial concentration is in the terminal section of the small intestine and colon (even 10^{12} bacteria per ml of intestinal contents). Due to the presence of mechanisms protecting against excessive microflora growth, the upper gastrointestinal tract (stomach, duodenum) has a significantly lower bacterial count (up to 10^3 bacteria per ml of intestinal contents). The further down, through alimentary tract, the greater the number of bacterial cells. Different conditions in each segment of the intestine cause differences not only in the number but also the type of microorganisms that inhabit them.

Upper digestive tract is occupied by gastric acid-resistant organisms, such as *Helicobacter pylori* or *Lactobacillus*. Coliforms, which are Gram-negative, non-spore-forming, lactose-fermenting bacteria, are characteristic for the colon. Disorders in intestinal microbiota are called dysbiosis. Changes in the number of microorganisms, their location, or changes in the proportion of particular types of bacteria can contribute to the development of certain diseases. The definition of SIBO still evolves, but it is usually referred to as the excess of bacteria in the small intestine. A total of 10^5 CFU/ml (colony-forming units per ml) of aspirate is generally accepted, although some postulate lower values. Due to the imperfection of diagnostic tests, "discussion" on the diagnostic criteria is still ongoing. Prevalence of bacterial overgrowth is not easy to determine. It is detected in up to 15.6% of healthy individuals, and this number increases with age and associated illnesses (12-14).

Many mechanisms are responsible for the stability of the intestinal flora, including appropriate gastric, pancreatic juices and bile secretion, undisturbed intestinal motility, proper structure of gastrointestinal tract, especially the ileocecal valve, functioning immune system of the intestinal mucosa. Disturbance of the aforementioned mechanisms may lead to excessive bacterial colonization and development of SIBO. Changes in bowel anatomy can be congenital or acquired. Among these of intrinsic origin are the obstruction, diverticula and fistulae. The course of the digestive tract can also be changed iatrogenically as a result of surgery or postoperative sequelae. Motility disorders occur i.a. in a variety of systemic diseases or during pharmacotherapy. Parkinson's disease, systemic sclerosis, hypothyroidism, diabetes are known to change the peristalsis and are related to the development of SIBO. Opioids, which are widely used in therapy, strongly inhibit intestinal peristaltic movements. Exocrine disorders, that influence the microbiota accompany liver cirrhosis and chronic pancreatitis. Achlorhydria occurs now, mainly due to the abuse of proton pump inhibitors. SIBO complicates also obesity, inflammatory bowel diseases, immune deficiencies, celiac disease. The relationship between SIBO and irritable bowel syndrome has not yet been clarified (13, 15).

Small intestine bacterial overgrowth is often taken into account in the differential diagnosis. This is because of the non-specific symptoms that it causes. Classic picture includes steatorrhea, abdominal pain, weight loss. However, this is not a frequent presentation. Patients are more likely to report bloating, belching, flatulence, abdominal pain and loose stools. Malnutrition and weight loss are a consequence of malabsorption, which accompany only very severe and persistent SIBO, most often associated with a change in bowel anatomy. In such cases, there may be numerous insufficiencies, not only caloric but also of fat soluble vitamins A, D, E, or B_2, B_6, folic acid, B_{12} and microelements i.a. iron. The deficiency of specific nutrients can lead to polyneuropathy, bone metabolic diseases, micro and macrocytic anaemia, and in children impairs growth and development (5, 16).

SMALL INTESTINE BACTERIAL OVERGROWTH IN CHRONIC PANCREATITIS

Prevalence of SIBO in patients with CP is approximately 36%. However, considerable heterogeneity in the results of respective studies should be noted, ranging from 14-92%. To date there are no studies on the prevalence of SIBO in children with CP (4).

Mechanism of bacterial overgrowth in patients with chronic pancreatitis is multifactorial. In its pathogenesis may participate factors predisposing to CP, the course of underlying disease, as well as iatrogenic factors associated with therapy. Alcohol abuse is still one of the most common causes of CP. Not only excessive, but also moderate alcohol consumption is a risk factor for SIBO (17, 18). Exocrine pancreatic insufficiency (EPI) is described as reduced pancreatic enzyme and/or bicarbonate secretion. Although the cause of this phenomenon is not fully explained, it appears that pancreatic juice of patients with CP has a significantly weaker antibacterial effect than the secretion of healthy people (19). Bowel motility disorders in patients with CP are certainly one of the important causes of bacterial overgrowth in the small intestine. They can result from action of undigested fats passaged through the bowel, due to impaired secretion of enzymes. They, also may compound with autonomic neuropathy, which is a serious complication of type 3c diabetes, developing in the course of endocrine pancreatic insufficiency. Opioids, used to control pain, also have impact on the gastrointestinal passage (20-23). In patients with CP, proton pump inhibitors are applied frequently. They are co-administered with an NSAID to prevent the development of peptic ulcer disease, and also with the pancreatic enzyme replacement therapy in order to improve its effectiveness. Meta-analysis of studies assessing the relationship between PPI and SIBO suggests a moderately increased risk of intestinal flora disorders (6, 24). SIBO is also more common in patients who underwent gastrointestinal surgery (4).

Pain reported by patients with CP has often different from primary disease, origin. When considering its cause, factors not directly related to inflammation of the pancreas should always be excluded, i.a. SIBO. It should also be noted that the abdominal pain often occurring in these patients is not only associated with unpleasant symptoms, but also with the necessity of expanding diagnostic tests (serum amylase and lipase, urine amylase) to exclude exacerbation of pancreatitis. In the course of SIBO, there are many non-specific symptoms like bloating,

flatulence, belching, diarrhoea. A similar clinical picture may also occur in case of EPI and be the result of replacement therapy failure (8, 23).

Certainly, in severe cases, SIBO can lead to malabsorption and malnutrition. Bacterial overgrowth can worsen, often abnormal, nutritional status of patients with CP, however there is still not enough studies documenting this phenomenon (4, 12).

SMALL INTESTINE BACTERIAL OVERGROWTH DIAGNOSTICS

Methods of testing in SIBO can be divided into directly and indirectly assessing the presence of overgrowth. First evaluate the bacterial flora in terms of composition and the number of bacteria. The second group appraise disorders on the basis of microbial metabolism products. Each method has its limitations and advantages. According to the definition, "golden standard" in SIBOs diagnostics is a qualitative and quantitative assessment of aspirate from the small intestine. However, due to the limitations of this method, it is no longer indicated as the best diagnostic tool in SIBO. However, due to disadvantages of this technique, it is no longer indicated as the best tool in bacterial overgrowth searching. Typically, $> 10^5$ CFU/mL was considered as evidence of overgrowth. Currently, since in healthy subjects the number of bacteria in the small intestine content rarely exceeds the level of 10^3 CFU/mL, this value is postulated instead. It may also be more clinically relevant in case of collecting content from the proximal intestine, where many of the mechanisms protecting against SIBO are active. The main problems of this procedure are its high invasiveness, cost and low availability. Culture-based research may also give false positive results, because of contamination with oral flora. False-negative results occur due to the limited range of endoscopy, which does not allow to sample content from the distal segments of the small intestine, and because of the difficulty in the culture of anaerobic bacteria (12, 25-27).

The response to invasive endoscopic examinations are inexpensive, widely available and safe, hydrogen and methane breath tests. This method uses the fact that human body cells do not produce hydrogen and methane, but are produced by the intestinal flora. Their presence in the exhaled air indicates the bacterial fermentation of chyme (ex. carbohydrates given during the test) in the intestinal lumen. In approximately 20% of the patients, microbiota contains bacteria producing methane. Hydrogen is used in its production, which can result in negative breath tests. Now generally available tests are mainly hydrogen-based, and measuring equipment that can detect methane in the exhaled air are not yet sufficiently widespread. In SIBO diagnostics, breathing tests with glucose and lactulose are primarily used. Because the glucose test (GBT) is characterized by higher sensitivity and specificity, this test is recommended. In relation to the culture of duodenal content, it is has low sensitivity but high specificity. In this test, patient is given a glucose solution at a dose of 2 g/kg bw, max. 75 g. Measurements are made every 15 minutes in 2 hours. A score of more than 20 ppm (parts per million) of hydrogen is considered positive. The greatest difficulty with breathing test is appropriate preparation for the study. Restrictions apply among other things, to diet on the day of test and the preceding day or medications that may affect the bacterial flora (15, 25, 28-30). Other methods, such as 13C/14C glycocholic acid breath test, molecular methods are also used for diagnosis of SIBO. However, high cost, necessity to use appropriate equipment and the lack of established standards make them not widely used in clinical practice (12, 15).

TREATMENT OF SMALL INTESTINE BACTERIAL OVERGROWTH

Therapy in patients with bacterial overgrowth covers several issues. If possible, primary cause of the disease should be eliminated. In case of CP, it is not possible to do it completely because of the multifactorial ethology of SIBO and direction of the treatment for primary disease, which aims to prevent exacerbation and maintain the function of pancreas. The disorder concerns intestinal microbiota, therefore the treatment is mainly based on its modification. For this purpose, we have three pathways to follow: antibiotics and/or probiotics. In treatment many broad spectrum antibiotic, encompassing Gram-positive, Gram-negative, aerobic and anaerobic bacteria, are applied. Their superiority over placebo has been demonstrated in normalization of breath tests, with a normalization rate of 51.1% for antibiotics and 9.8% for placebo. In best case, antibiotics should only act in the intestinal lumen and have no side effects. Rifaximin is the best studied and most closely similar to this profile, substance. These features make it a good choice also for pediatric patients. The effectiveness of rifaximin increases with enhancing the dose. The most commonly used dosage is 400 mg three times daily for 7-14 days (5, 12, 31, 32). Although the antibiotics in SIBO are rather used to modify the bacterial flora than its eradication, their excessive use may lead to disturbances in the intestinal ecosystem. The advantage of probiotics is that they not only help to fight opportunistic intestinal pathogens but also do not cause disruption in intestinal microbiota. According to a published meta-analysis (33), which evaluated the effectiveness of probiotics in SIBO, the preventive effect of their use, although positive, is not statistically significant. However, efficacy of therapy with probiotics in SIBO is comparable to antibiotics. The degree of decontamination (represented by bacterial density measurement, HBT normalization rate, or SIBO improvement rate) was 53.2% for probiotics

and 51.1% for antibiotics, respectively. There are no clear recommendations for the use of specific bacterial strains or whether multicultural preparations have advantage over monocultural. It should also be noted that probiotics used in insufficient dose or transported and stored inappropriately may have no therapeutic effect. It is significant that the combination of probiotics and antibiotics reached a higher degree of decontamination, of 85.8%. Nevertheless, more research is needed to assess the synergistic effect of these formulations (33).

Likewise, it is important to treat nutritional disorders associated with SIBO. In the case of deficiency of vitamins and micronutrients, the appropriate substances should be supplemented. Patients with bacterial overgrowth, often present symptoms of secondary intolerance of lactose or other fermentable carbohydrates. In this case, a temporary introduction of an elimination diet may be beneficial. The diet needs to be wholesome and cover the calorie requirements. In patients with exocrine pancreatic insufficiency, adequate replacement therapy with enzymes cannot be omitted (12).

Regardless of use of appropriate therapy, the risk of recurrence of bacterial overgrowth should always be considered. There are currently no recommendations for preventive management. Reappearance of symptoms should induce to perform tests for SIBO and if necessary repeat the treatment (12).

CONCLUSIONS

Chronic pancreatitis is a disease of increasing incidence and recognition. Genetic testing allows early identification of individuals with high risk of developing CP. Monitoring, diagnostics and appropriate treatment can prolong the life of patients. Small intestine bacterial overgrowth is relatively common in chronic pancreatitis and symptoms associated with it, especially abdominal pain and malabsorption, have a significant impact on patient's quality of life. They are even more important in children whose nutrient deficiencies can significantly affect growth, development and consequently their adult life. Due to the increasing awareness of microbiota's influence on the course of many diseases, it is necessary to further develop diagnostics and treatment of its disorders, also in chronic pancreatitis. This is particularly important in the pediatric population.

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