CLINICAL AND PATHOGENETIC SIGNIFICANCE OF BACTERIAL OVERGROWTH SYNDROME UPON CHRONIC PANCREATITIS

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Key words: chronic pancreatitis, bacterial overgrowth syndrome, pathogenesis, peculiarities of clinical manifestations, exocrine pancreatic insufficiency

Chronic pancreatitis (CP) — a group of chronic diseases of the pancreas (pancreatic) of various etiologies, inflammatory nature characterized by abdominal pain, development of irreversible structural changes in the parenchyma and ducts, their replacement by connective (fibrous) tissue and consequently the development of the exocrine and endocrine pancreatic insufficiency [7].

The pathogenesis of CP is increased disparity of pancreatic secretion (when taking alcohol, food, over-stimulating the secretion of the pancreas, etc.) and the outflow of pancreatic secretions into the duodenum (the pathology of major duodenal papilla duodenal hypertension, formation of protein "blocks" under the influence of alcohol and etc.), resulting in the activation of enzymes and intrapancreas prostate tissue autolysis. This is facilitated breach mechanisms of activation and inactivation of trypsin (destabilization of lysosomal and zymogen granules of acinar cells under the influence of alcohol and its metabolites in the casting pancreatic and bile ducts, etc.). Excessive synthesis of extracellular matrix proteins associated with the activation of pancreatic stellate cells by cytokines in inflammatory necrosis of the pancreatic parenchyma (the concept of sequential necrosis and fibrosis) or the direct effects of alcohol and its metabolites and oxidative stress (non-inflammatory mechanism of fibrosis) leads to fibrosis of the parenchyma. Against the background of progressive fibrosis and atrophy of the pancreatic parenchyma is formed and grows its exocrine and endocrine

insufficiency. Leading to the clinical picture of CP are abdominal pain syndromes, exocrine and endocrine pancreatic insufficiency.

Accepted provide several groups of causes of abdominal pain in CP. The leading ones are the inflammatory process in the prostate tissue, followed by stretching of the capsule body, perineural inflammation, irritation and/or compression of the nerve endings, and the complications of CP. Accepted provide several groups of causes of abdominal pain in CP. The leading ones are the inflammatory process in the prostate tissue, followed by stretching of the capsule body, perineural inflammation, irritation and/or compression of the nerve endings, and the complications of CP. In addition to these factors, pain may be associated with manifestations of exocrine pancreatic insufficiency — flatulence accompanied by an increase intraintestinal pressure, impaired motor skills of small and large intestine bacterial overgrowth in the small intestine.

Since the primary (absolute) exocrine insufficiency develops with the loss of 9095% of pancreatic acinar tissue in the later stages of CP, more often a secondary (relative) failure. In the duodenum (duodenal) receives a sufficient amount of enzymes, however, they do not take part in adequate digestion. Its major causes are [7]:

- inactivation of pancreatic enzymes in the duodenum when the pH drops below 5.5;
- violation of the mixing enzymes with food chyme due to motor disorders KDP, which is observed in asynchrony secretion of bile and pancreatic juice, gastroduodenal disorders transport chyme;
- destruction of enzymes in bacterial overgrowth in the small intestine;
- violation of the separation of gastrointestinal hormones in enteropathies (celiac disease, Crohn's disease);
- violation of the emulsification of fats, reducing the activation and the efficiency of lipase in the biliary disease (deficiency of bile acids).

Obviously, these same reasons may cause inefficiencies enzyme replacement therapy, so they require detection and correction.

From the above it follows that the bacterial overgrowth syndrome (BOS) in CP is one of the reasons for abdominal pain and secondary exocrine insufficiency. When you consider that BOS 40,0–44,7% observed in patients with CP [2, 9], it becomes apparent that his diagnosis and adequate treatment are essential to ensure the effectiveness of therapy CP.

BOS — is sowing proximal small intestine than 105 microbial cells (CFU)/ml of intestinal contents due to pathogenic microorganisms coming from the upper gastrointestinal tract (or upper respiratory tract infection) or due to retrograde translocation of opportunistic members of the microbiota of the colon [3].

There are a number of pathogenic mechanisms linking CP and BOS (Fig. 1). The trigger is a deficiency of pancreatic secretions and enzymes, followed by a failure of duodenal anti-bacterial barrier and a violation of the digestive cavity. As a result, the lumen of the intestine undigested nutrients accumulate primarily fats are substrates for bacterial overgrowth. Toxins are opportunistic pathogens are inactivated enzymes brush border membrane of the small intestine, resulting in impaired membrane digestion. Furthermore, microbial toxins through cAMP-dependent mechanism stimulates the secretion of water and electrolytes into the lumen, causing the secretory diarrhea. Secondary intestinal dysmotility is revealed clinically pain and diarrhea. The high osmolarity of the intestinal contents undigested leads to osmotic diarrhea. With the destruction of bacteria pancreatic enzymes in the duodenum and jejunum initial exacerbated secondary exocrine pancreatic insufficiency. Against deficiency of pancreatic lipase breaks down the digestion of fat, which on one hand is manifested steatorrhea, on the other hand, by reducing the pool of free fatty acids that have anti-bacterial effect, exacerbating BOS. Another consequence of the contamination of the small intestine and rapid transit of intestinal contents is early deconjugation of bile acids, the violation of their enterohepatic circulation, increasing the pool of free bile acids in the feces and the development of biliary insufficiency [4, 11].

If you suffer from biliary insufficiency emulsification of fat, reduced activation of the lipase and efficiency, adding to the secondary exocrine pancreatic insufficiency and steatorrhea. In addition, a decrease biliary insufficiency blood concentrations of cholecystokinin and secretin, leading to reduction of pancreatic secretion, including reducing the volume and concentration of bicarbonate. This results in a decrease in the pH in the duodenum, increased severity of pancreatic insufficiency, worsening of BOS, reduced absorption of bile acids in the intestine.

Significant role in the development and progression of CP violation plays the functional activity of immune cells, such as T-helper lymphocytes that produce cytokines. The last form in the body of the universal biological communication system, initiating and regulating inflammatory, immune, proliferative processes, the formation of fibrosis [6, 11].

Consequently, in the occurrence and progression of inflammation in CP significance attached to impaired immune response. One of the causes of these disorders is the BOS [5]. The greatest importance is attached to increased synthesis and translocation of endotoxin, which activates the immune inflammation in the prostate tissue. Endotoxin — specific lipopolysaccharide, which is synthesized by the bacterial membrane of gram-negative bowel flora, mostly E. coli. Endotoxin has a direct damaging effect on the acinar cells, exacerbating endotoxemia, upsets the balance between pro-and anti-inflammatory cytokines involved in the activation of lipid peroxidation, the process of apoptosis, activate stellate cells, fat cells, growth factors $TGF\beta_1$. The experiment showed that mice treated with alcohol, the introduction of endotoxin causes a pronounced inflammatory necrosis of the pancreas, and after repeated administration – fibrosis [10]. In this case, noted the mutual reinforcement of stimulating effects of alcohol and LPS on hepatic stellate cells [8]. All this increases the damage and contributes to the process of tissue fibrosis pancreatic.

Thus, the initial violation of the digestive cavity in CP leads to the formation of BOS, which becomes pathogenic factor in the progression of CP, and it exacerbates the symptoms. All the above mechanisms are closed in vicious circles.

Methods of diagnosis of bacterial overgrowth syndrome

Clinical manifestations of BOS are non-specific and allow only assume clinical diagnosis. These include pain or discomfort in the abdomen, bloating, diarrhea and / or symptoms of malabsorption, such as progressive weight loss, malabsorption of several important vitamins, especially folic acid and tsinakobalamina and minerals — calcium, iron.

Laboratory and instrumental methods of diagnosis BOS numerous, have different sensitivity, specificity and availability.

"Gold standard" diagnostic BOS is a direct method — intenstinoscopia with aspiration of the contents of the small intestine aspirate and sowing on fertile ground. The method allows a high degree of confidence BOS to identify, assess severity, determine the type of bacteria and to establish their sensitivity to antibiotics.

Bacterial overgrowth of bacteria diagnosed if the number of bacteria above 10^5 CFU/ml.

There are three severity BOS depending on the nature and quantity of microorganisms in the small intestine [4]:

Stage I — in the presence of increasing aerobic normal intestinal microflora ($>10^5$–10^6 CFU/g);

Stage II — an increase of aerobic intestinal microflora and the emergence of anaerobic bacteria ($>10^6$–10^7 CFU/g);

Stage III — the predominance of anaerobic flora (seeding at 10^9 CFU/g or more).

However, using this method, related to a number of difficulties. First of all, technical, since the operation intestinoscopy requires general anesthesia, the presence doublecylinder intestinoscopy, highly skilled endoscopist, a powerful germ service, fast delivery address biomaterial to the lab, etc. In addition, the rather long period of waiting

for the results, depending on the resulting culture, its growth rate, the ability to identify and carry out tests to determine the sensitivity to antibiotics. The high cost of research.

In this context, attention is drawn to indirect methods. These include tests, which are based on the study of metabolites of microorganisms. A large spread in the scientific and clinical purposes have breath tests with hydrocarbon-containing substrates (lactulose, glucose, xylose) [2]. They are based on the ability of enteric bacteria metabolize these compounds to release hydrogen and / or methane, which is registered in the exhaled air. Normally, hydrogen and methane metabolized to colonic bacteria, the appearance of these substances before they reach the colon, a marker BOS.

The method is applicable only for approximate determination of the degree of bacterial colonization of the small intestine. This figure is in direct proportion to the concentration of hydrogen in the breath empty stomach. One diagnostic problem during breathing test is the presence of two peaks in the hydrogen content in the exhaled air: early peak — enteric and late — colic. Time of occurrence of hydrogen peaks associated with individual characteristics of gut motor activity. The advantage of this test is the unlimited access to all of the bacteria of the gut, good correlation production rate of hydrogen in the digestive tract and the rate of release of hydrogen light. Breath test relates to non-invasive, rapid, and relatively cheap. The same method can monitor the results of treatment of a variety of drugs that suppress the growth of excess flora in the small intestine [1].

One method of diagnosing intestinal microbiocoenosis is to determine fatty acids, which are metabolites mainly anaerobic genera of microorganisms by gas-liquid chromatographic analysis. This method allows you to quickly and accurately assess the condition of the indigenous microflora, has a high sensitivity and specificity, provides high accuracy in the evaluation of the basic aerobic and anaerobic microbial populations with their tribal affiliation.

BOS diagnostic criterion in the small intestine is to increase the concentration of SCFA more than 0,078 mg/g and the change of their quality, indicating the activation of certain genera of microorganisms [1].

Gas chromatography and mass spectrometry based on the determination of bacterial cell components, appearing as a result they die or components of the immune system attack. Minor lipid components of microbial membranes are used as markers. 170 aerobic and anaerobic types of bacteria and fungi in various biological fluids can be determined according to their content. The disadvantages of this method are particularly computer diagnostics, the high cost of research [1, 2].

Treatment

CP treatment is aimed at eliminating pain, correction of exocrine and endocrine pancreatic insufficiency.

Main activities aimed at relief of pain:

- exclusion of alcohol and tobacco;
- nutritional therapy;
- the appointment of non-narcotic and narcotic analgesics;
- appointment of antisecretory (proton pump inhibitors (PPIs) and H_2-blockers) and antispasmodic drugs.

The use of analgesics is still one of the main methods of pain relief in patients with CP. The most commonly used drugs are ketanol, tramadol, metamizol, paracetamol. Relief of pain is most effective when combined with non-opioid analgesics, antispasmodics.

The leading mechanism of pain in CP is to increase the pressure in the duct system due to pancreatic secretion and increased difficulty of outflow of pancreatic juice. Blockade hydrochloric acid synthesis PPI or H_2-blockers increases the pH in the duodenum and, consequently, to reduce formation of natural pancreatic secretion stimulants — secretin and cholecystokinin, which provides a "functional rest" of the pancreas. At the heart of the analgesic effect of antispasmodics and anticholinergics

(drotaverine, mebeverin, papaverine, platifillin, etc.) is the resolution of spasm duct sphincter of Oddi, which prevents the outflow of pancreatic secretion.

Functional rest of the pancreas can also be provided with pancreatin preparations. This effect is associated with inhibition of pancreatic secretion by duodenopancreas negative feedback mechanism. It is based on — the destruction of releasing peptide, stimulates the secretion of cholecystokinin and secretin in the blood, and therefore the secretion of the pancreas. However, when expressed hyperenzymemia the use of drugs is not recommended pancreatin.

A key indication for prescribing pancreatin in CP is the correction of exocrine insufficiency. In the early stages of CP enzymes assigned courses mainly recurrence period for correction of dyspeptic symptoms that develop as a result of a secondary enzyme deficiency associated with inactivation or destruction of pancreatic enzymes at lower intraduodenal pH below 5.5 and/or result of microbial contamination of the duodenum. To overcome this difficulty, along with the enzyme preparations shows the assignment of antisecretory means (PPIs), pro-and prebiotics.

In the later stages of the CP needs constant replacement therapy using high doses of enzyme preparations. The most effective are the pancreatic enzymes are produced in the form of enteric minimicrospheres placed in gelatin capsules. The dose is adjusted individually, taking into account the severity of exocrine insufficiency, defined by the level of elastase-1 in stool. Pancreatic elastase-1 is specific to the human pancreas is not destroyed in transit through the intestines. To do this test does not require the interruption of enzyme replacement therapy, but the diarrhea is possible false positive result. The criterion of exocrine insufficiency and mild high is the level of pancreatic elastase-1 100-200 mcg/g of feces, with a decrease below 100 mcg/g of feces it is a severe. In severe pancreatic insufficiency recommended the appointment of a main meal at least 25000–40000 FIP lipase units in between meals — 10000–25000 FIP lipase units. Accordingly, the daily average dose is 100000–150000 FIP lipase units and more.

The lack of effectiveness of high doses of pancreatic enzymes should evaluate the role of the factors causing secondary exocrine pancreatic insufficiency and to act on them. The most important reason for the inefficiency enzyme replacement therapy is associated BOS [3]. In theory, the appointment of an adequate dose of enzyme digestion is restored and BOS additional correction is required. It was found that about half of what happens [11]. Therefore, the appointment of an adequate dose of enzyme preparations is the basic treatment for CP and exocrine pancreatic insufficiency. If you are still steatorrhea and flatulence can’t be shown additional prescriptions for the treatment of BOS. When expressed his symptoms begin with a decontamination treatment with antibiotics (rifaximin, ciprofloxacin, nifuroxazide, co-trimoxazole, furazolidone, etc.) that are assigned to the conventional therapeutic doses courses lasting 7–10 days. Be sure to include in the treatment of BOS pro- and prebiotics.

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Clinical and pathogenetic significance of bacterial overgrowth syndrome upon chronic pancreatitis

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Review represents data on the clinical and pathogenetic significance of the combination of chronic pancreatitis (CP) and bacterial overgrowth syndrome, the impact of the latter on the clinical course of CP, the severity of exocrine pancreatic insufficiency and efficacy of enzyme replacement therapy. It is shown that bacterial overgrowth syndrome contributes to the progression of CP. Methods of diagnosing the bacterial overgrowth syndrome are considered too. It is noted that detection and correction of bacterial overgrowth syndrome are required upon a treatment of patients with CP.

Fig. 1. Pathogenetic correlation between chronic pancreatitis and bacterial overgrowth syndrome