Pathomorphism of chronic pancreatitis: novelty in habitual

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Key words: abdominal pain, chronic pancreatitis, diagnostics, treatment, enzyme preparations

The annual incidence of chronic pancreatitis (CP) is growing every year in the world and is 16-23 cases per 100 thousand of population in the EU countries, 12.4 per 100 thousand of males and 45.4 per 100 thousand of females in Japan, 27,4-50 cases per 100 thousand in Russia [5, 8]. About 1/3 of patients can't work on their specialization, 40% — have a temporary or permanent disability [9], 10-year survival rate is 70%, 20-year — 45% [14].

Chronic pancreatitis is a group of chronic diseases of the pancreas, in which recurrent episodes of inflammation lead to the replacement of pancreatic parenchyma by fibrous tissue with the development as a result of this exocrine and endocrine organ failure [4].

Etiological factors. In 2007, German scientists proposed ethological classification of chronic pancreatitis M-ANNHEIM (A. Schneider et al., 2007) [15] (A — alcohol, N — nicotine, N — nutritive factors: hyperlipidemia, H — hereditary factor SPINK1, CFTR, PRSS1, E — violation of the ductal system (split duct, tumor), I— immunological factors, M — rare multiple factors (hypercalcemia)).

Alcohol and tobacco use are the most common causes of the disease. Smoking accelerates the progression of the disease process [16]. The reasons that lead to the development of obstructive pancreatitis: the sphincter of Oddi dysfunction; duct obstruction (tumor, stone); post-traumatic scars pancreatic duct, preampullar duodenal wall cysts; pancreas divisum (doubling of the pancreas).

The prevalence of hereditary pancreatitis is 1 case per 300 000. About 68% of patients with hereditary chronic pancreatitis have a gene mutation of the cationic trypsinogen (PRSS1). Several less make registration trypsinogen gene mutation inhibitor (SPINK1) and the gene for cystic fibrosis transmembrane regulator (CFTR) [13].

Hereditary pancreatitis should be suspected in the presence of one or two first-degree relatives with idiopathic pancreatitis, two or more episodes of acute pancreatitis with no particular reason, at the age of 25 years or idiopathic form of chronic pancreatitis with the beginning of the age of 25 years. Patients with a positive family history should be tested for the presence of gene mutations PRSS1, SPINK1, CFTR.

The diagnosis of chronic pancreatitis is made on clinical, morphological traits, radiological methods and functional tests.

Chronic pancreatitis is characterized by a triad of symptoms:

- abdominal pain;
- symptoms of exocrine pancreatic insufficiency;
- endocrine insufficiency (diabetes mellitus).

The course of chronic pancreatitis is defined by phasic flow and sequence of onset of clinical signs. In the early stages it is dominated by acute pain attacks. A few

years later joined symptoms of exocrine pancreatic insufficiency, malabsorption, and manifestations of diabetes.

The classification of M-ANNHEIM (A. Schneider et al., 2007)

CP Asymptomatic phase

• 0 — subclinical CP:

a) the period without symptoms (determined by chance, for example, at autopsy);

b) acute pancreatitis (AP) — the first episode (probably the beginning of CP);

c) AP with severe complications.

CP with clinical manifestations

• I stage — without pancreatic insufficiency:

a) AP recurrence (no pain between AP episodes);

b) recurrent or persistent abdominal pain (including pain between AP episodes);

c) abdominal pain with severe complications.

• II stage — exo- or endocrine pancreatic insufficiency:

a) isolated exo- or endocrine pancreatic insufficiency without pain;

b) isolated exo- or endocrine pancreatic insufficiency with pain;

in) II a / b with severe complications.

• III stage — exo- or endocrine pancreatic insufficiency in conjunction with pain:

a) exo- or endocrine pancreatic insufficiency (with pain, requiring analgesic treatment);

b) IIIa with severe complications;

• IV stage — reduction of pain intensity (stage of the "burnout" of the pancreas)

a) exo- or endocrine pancreatic insufficiency without pain and serious complications;

b) exo- or endocrine pancreatic insufficiency without pain, with severe complications.

Pain is the main symptom of chronic pancreatitis. The mechanism of pain in pancreatitis is multifactorial. The most common causes of pain are: inflammatory infiltration of the pancreatic parenchyma and nerve (optic neuritis), increased pressure in the pancreatic duct caused by stenosis or the presence of stones [10]. A number of other factors: the formation of pseudocysts, duodenal stenosis, strictures of the biliary tract, pancreatic cancer, peptic ulcer disease may be the cause of pain and determine the different treatment policy (Fig. 1).

Fig. 1. Causes of abdominal pain in chronic pancreatitis.

After anamnesis and physical examination includes an initial study of transabdominal ultrasonography of the pancreas. If there is clinical evidence of chronic pancreatitis, but according to transabdominal ultrasound (US), there is no conclusive evidence of organ damage (heterogeneous structure, pancreatic duct normal width), it is obligatory endoscopic ultrasonography (EUS). EUS is the most sensitive (80-100%) and specificity (80-100%) diagnostic test for chronic pancreatitis. Comparative studies have shown that EUS is superior to magnetic resonance cholangiopancreatography (MRCP) in the diagnosis of early forms of disease. Fine-needle biopsy is used for cytological or histological examination in the presence of lesions. Computed tomography (CT) and magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography are additional diagnostic methods to further evaluate ambiguous changes of the pancreas. MRCP to be performed to get detailed information about the pancreatic ductal system.

Radiography of the abdomen. In 30-40% of cases of plain radiography reveals calcification of the pancreas or intraductal calculi, especially in the study of oblique projection. This eliminates the need for further examination to confirm the diagnosis of CP. Calcification of the pancreas is most common in alcoholic pancreatitis, hereditary and rare in idiopathic.

Ultrasonography. Transabdominal ultrasound has insufficient sensitivity and specificity, and rarely provides sufficient information for the diagnosis of CP. The main value of the method lies in the exclusion of other causes of abdominal pain. Transabdominal ultrasound reliably detects concretions size >5 mm, especially when their localization in the pancreatic head. However, the resulting image has a lower spatial and contrast resolution than CT. Thus, the negative US does not exclude the presence of stones.

Computed tomography. CT sensitivity in the diagnosis of CP is 75-90%, specificity — 85%. Currently, it is the method of choice for primary diagnosis and an

exacerbation of the disease. Standard research is multidetector CT. Data CT pointing to CP, are pancreatic atrophy, the presence of stones in the ducts, dilation of MPD, intra- or peripancreatic cysts, thickening peripancreatic fascia and splenic vein thrombosis. Other features include the heterogeneity of the structure and an increase in prostate size. Reduction of the image density is characteristic for fibrosis, while the structure with the same intensity indicates its absence.

CT with intravenous contrast can detect prostate necrosis (no accumulation of contrast medium). CT is the most effective method of determining the topography and localization of the concrements of the pancreas.

Endoscopic ultrasonography. EUS is increasingly used for the diagnosis of CP. It is comparable to the sensitivity of CT in determining the localization of the prostate stones, even small sizes (<3 mm). This minimally invasive imaging technique used with curative intent.

EUS and magnetic resonance cholangiopancreatography (MRPHG) with secretin test are the most reliable methods of visualization of the parenchyma changes and pancreatic ducts in the early stages of the disease. However, interpretation of the data difficult lack of "gold standard" diagnostic criteria and the large variability of the threshold values, and the results from different researchers, as well as the lack of standard terminology.

ERCP method is associated with the presence of complications risk (generally 5-10%), the risk of acute pancreatitis — 3.47%, mortality — 0.3%, and is not currently recommended as a purely diagnostic procedure [3]. ERCP is shown in those cases where both studies: MRI and EUS/MRCP were performed, but a diagnosis has not been established.

The signs of exocrine pancreatic insufficiency are signs of steatorrhea and malnutrition. Severe manifestations of exocrine insufficiency logged about 10 years after the debut of chronic pancreatitis, when the secretion of lipase is reduced by more than 90% [7]. The presence of exocrine insufficiency markedly increases the risk of osteoporosis, fractures and deficit of fat-soluble vitamins, especially vitamin D and E.

Functional tests for the diagnosis of exocrine pancreatic insufficiency:

• Direct:

- secretin- cholecystokinin test; secretin test;
- Lundh-test;

• Indirect:

- quantitative determination of fats;
- qualititative determination of fatss;
- chymotrypsin;
- fecal elastase-1;
- breath test labeled ^{13}C-triglycerides;
- pancreolauryl test.

In 30-60% of patients with chronic pancreatitis develop complications requiring endoscopic or surgical treatment:

- stricture of the common bile duct;
- pancreatic pseudocysts;

- stones;
- pancreatic cancer.

The relative risk of pancreatic cancer in patients with chronic pancreatitis was 13.1% (95% confidence interval [95% CI] 6,1-28,9%); in patients with hereditary pancreatitis risk is 69% (95% CI 56,4-84,4%). Continued smoking of tobacco in the presence of chronic pancreatitis significantly increases the risk of pancreatic cancer: a long history of the disease increases the risk of cancer by a factor of 16, in patients who continue to smoke, — the coefficient of 25 [9].

Factors associated with an increased risk of pancreatic cancer:

- age: 80% of cases occur in patients aged 60-80 years. Only 10% of cases of pancreatic cancer occurs in patients under the age of 50 years;
- male: the overall risk of death from pancreatic cancer before 64 years of age is 0.2% for men, 0.1% for women;
- smoking;
- diabetes mellitus.

Retrospective analysis of 9200 cases of pancreatic cancer showed that with a history of diabetes for more than 5 years, the risk of having a low pancreatic cancer: OR = 1.5; 95% CI, 1.3-1.8. With a history of diabetes less than 5 years, the risk increased: OR = 2.1 95% CI 1.9-2.3. Debut diabetes after the age of 50 years at 1% is associated with pancreatic cancer [6]. If you suspect a resectable pancreatic cancer treatment should be surgical. Non-operated patients with carcinoma of the pancreas have a life expectancy of less than one year after successful resection of the probability of survival five years — 20-25% [1].

Identification of endocrine pancreatic insufficiency should be started immediately with suspected chronic pancreatitis, regularly checking the level of glycated hemoglobin A_{1c} (HbA_{1c}), fasting blood glucose, conducting a test for glucose tolerance.

It is emphasized that the use of HbA_{1c} for diagnosing diabetes is more sensitive laboratory test.

Aims of therapy:

1) cessation of alcohol consumption and cigarette smoking;
2) diet;
3) determination of the cause of pain and its treatment (conservative, endoscopic or surgical);
4) treatment of exocrine pancreatic insufficiency;
5) detection and treatment of endocrine insufficiency.

Treatment of pain in chronic pancreatitis includes:

1) relief of inflammatory infiltration of pancreatic parenchyma and neuritis;
2) reducing the pressure in the ducts of the pancreas.

With intense pain shown periodically or course assignment narcotic analgesics — paracetamol or non-steroidal anti-inflammatory drugs, with the ineffectiveness of tramadol should be preferred. Preparations should be taken 30 minutes before a meal to minimize the amplification of pain after meals.

Persons who have to constantly take pain medications shown endoscopic or surgical treatment [17].

An important component of therapy is to block the synthesis of hydrochloric acid proton pump inhibitors (PPI) or histamine blockers H_2 receptors. Therapy leads to an increase in pH in the duodenum and, as a consequence, to a reduction of the natural stimulators of pancreatic secretion — secretin and cholecystokinin, which provides "functional rest" of the pancreas [1].

Surgical drainage demonstrates the best results in terms of long-term pain relief [17].

Obstruction of the pancreatic duct stones or stenosis, which is accompanied by pain, violation of the outflow of pancreatic secretion, development of recurrent bouts of illness, supporting the presence of pseudocysts or causing other complications, should be seen as indications for endoscopic or surgical treatment.

Pseudocyst, which cause complications such as stomach obstruction, bleeding, pain, cholestasis, or vascular stenosis should be treated endoscopically or surgically. Surgical treatment of pseudocysts tends to have higher success rates than endoscopic drainage of pseudocysts, but is associated with a slightly higher mortality. If there are symptomatic pseudocysts regardless of size, endoscopic or surgical treatment is prescribed.

Asymptomatic pancreatic pseudocysts larger than 5 cm in diameter, which do not disappear within six weeks, also must be treated using these methods. Cysts larger than 5 cm have a complicated course in 41% of cases (rupture, infection, jaundice, bleeding).

Pseudocyst with a size less than 4 cm have favorable prognostic factor for spontaneous regression.

When the distal bile duct stenosis with development of cholestasis should be performed surgery or endoscopic stenting. If there is intrapancreatic calcification of pancreas, surgical method is preferred.

Surgical treatment is the most effective long-term relief of pain in chronic pancreatitis.

In cases where the pain is caused by increasing the pressure in the main pancreatic duct of the pancreas and no evidence of the patient for endoscopic or surgical treatment, antispasmodic drugs are assigned.

Classification of antispasmodics

1. Acting on the stage of the nerve impulse (neurotropic).
    1.1. Cholinolytics — M-cholinergic receptor blockers (atropine, platifillin, belladonna preparations, hyoscine butylbromide).
    1.2. Opioid receptor agonists (trimebutine).
2. Acting on smooth muscle cells (myotropic).
    2.1. Non-selective:
    - phosphodiesterase inhibitors (drotaverinum, papaverine, alverin, bentsiklan (Halidorum), otilone bromide).

    2.2. Selective:
    - sodium channel blockers (mebeverine).

Mebeverin (Duspatalin®) is a selective myotropic antispasmodic, drug of choice spasm associated with biliary or pancreatic disease. Effectively eliminates the clinical manifestations: pain and heaviness in the right upper quadrant, nausea, bitter

taste in the mouth, has a high affinity for sphincter of Oddi, and normalizes motility of the duodenum, lowers duodenal hypertension, duodenal and duodenopancreatic reflux, normalizes the flow of bile. The drug acts selectively on the smooth muscle cells of the gastrointestinal tract, spasms eliminates without affecting normal intestinal peristalsis. The drug has a dual mechanism of action: blocking Na^{+} channel opening and prevents the development of spasm, blocking Ca^{++}-depot, limiting the output of K^{+} out of the cell, preventing the development of hypotension.

Patients who have expressed steatorrhea (more than 15 grams of fat per day in stool) should receive pancreatin preparations. If steatorrhea is in the range (7-15 g/day), pancreatin preparations should be used if there are signs of an eating disorder, such as weight loss. Empirical treatment for 4-6 weeks is shown if there are symptoms. The dose of pancreatin is selected depending on the activity of lipase.

Currently, global pharmaceutical industry produces large amounts of enzyme preparations, which differ from each other as the dose contained therein digestive enzymes and various additives. Enzyme preparations produced in various forms — in the form of tablets, powder or capsules.

The choice of drug for the treatment of exocrine pancreatic insufficiency should be based on the following indicators:

- high content of lipase in the formulation (as exocrine pancreatic insufficiency in digestion of fat is broken in the first place);
- presence of a shell, protecting the enzymes from being destroyed by gastric juice (the main components of enzyme preparations — lipase and trypsin rapidly lose activity in an acidic medium: lipase — at a pH<4, trypsin — at pH<3, before entering the drug into the duodenum can be destroyed up to 92% lipase);
- small grain size, filling capsules (together with food preparation gastric emptying takes place only when its particle size exceeds 2 mm);
- rapid release of enzyme into the upper small intestine;
- lack of bile acids in a preparation (bile acids induce increased secretion of the pancreas, which is generally undesirable during exacerbation of pancreatitis, in addition, high levels of bile acids in the intestine, which is produced by intensive enzyme therapy causes cholangiogenic diarrhea).

The initial dose of lipase is 20,000-40,000 lipase units for basal meal and 10,000-20,000 lipase units for additional meals. In case of insufficient effectiveness of enzyme dosage should be increased by two to three times.

If efficiency is insufficient, pancreatin pellets should be recommended to acid inhibitor. If this does not lead to the desired success, it is necessary to look for another cause.

One of the most effective enzyme preparations having sufficient evidentiary basis to correct maldigestion and malabsorption syndrome, is a drug Creon®. The characteristics of the drug for optimum effect on the correction of digestive disorders of various origins. Capsules, containing enteric-coated minimicrospheres, rapidly dissolve in the stomach, releasing large amounts of minimicrospheres containing a high concentration of the digestive enzymes. The small grain size (less than 2 mm) ensures uniform mixing of the chyme and, ultimately, a better distribution of enzyme

when released into the gut lumen. When minimicrospheres reach the small intestine, and enteric coat is destroyed, there is a release of enzymes with lipolytic, proteolytic, aminolytic activity and leading to disintegration of fat, starch and lipids.

Creon® advantage over other drug enzyme preparations is the high activity of enzymes. The enzyme composition of the drug Creon® is optimally balanced for the replacement of exocrine pancreatic insufficiency of varying severity, produced in three variants Creon® 10000, Creon® 25000, Creon® 40000 units of lipase, respectively.

As for screening adenocarcinoma of the pancreas, it is currently recommended that patients with hereditary pancreatitis should be included in the screening program, starting at age of 40.

Screening should be carried out annually (collecting complaints, physical examination, imaging techniques, laboratory tests, including the level of glycated hemoglobin).

Visualization options include: EUS, multislice CT or MRI with magnetic resonance cholangiopancreatography. The use of ERCP is controversial, given the invasive nature of this investigation.

Selecting imaging method will be determined depending on the capabilities and medical facilities.

The value of screening for other forms of chronic pancreatitis remains unclear and is not currently recommended.

Considering that the presence of chronic pancreatitis (regardless of etiology) is a known risk factor for cancer, so any change in symptoms should prompt a doctor for the extended investigation.

As part of the dynamic monitoring should be assessed tumor markers (carbohydrate antigen (CA 19-9), carcinoembryonic antigen (CEA)).

Conclusion

Patients with chronic pancreatitis are the most difficult category of patients for supervision in internist’s practice. The disease is characterized by progressive course and is associated with the development of severe complications: endocrine and exocrine pancreatic insufficiency, pseudocysts, cholestasis. Patients have an increased risk of pancreatic cancer. Twenty years after the diagnosis of mortality in patients with chronic pancreatitis was 38.4%, significantly higher than in the general population [11].

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Etiologic factors and classification of chronic pancreatitis are reviewed, as well as the approaches to diagnostics and treatment of patients, principles of preparations selection for the treatment of exocrine pancreatic insufficiency.