Chronic pancreatitis: etiopathogenesis, main clinical syndromes, diagnostics, treatment

Anatomical features of Oddi’s sphincter

1. sphincter of choledoch
2. sphincter of pancreatic duct
3. sphincter of major duodenal papilla’s ampulla

Composition of pancreas secretion

1. proteolytic enzymes
   - trypsin
   - chymotrypsin
   - carboxypeptidase A
   - carboxypeptidase B
   - elastase
   - kallikrein

2. lipolytic enzymes
   - lipase
   - colipase
   - phospholipase

3. amylolytic enzymes
   - amylase

4. other enzymes
   - RNAse
   - DNAse

5. bicarbonates

Chronic pancreatitis (CP) - a chronic (lasting over 6 months) polyetiological progressive inflammatory-dystrophic lesion of the pancreas, which can periodically take signs of acute inflammatory process; flows with formation of focal, segmental or diffuse destructive changes in the parenchyma, ducts and microvasculature; it is characterized by a gradual disorders increase in ductal system, development of parenchyma replacement fibrosis and exo- and endocrine functional insufficiency

Importance of the CP problem

- The occurrence of CP among digestive system diseases is 6-9% and tends to increase
- CP is one of those diseases whose treatment results often do not bring any solace neither to a patient nor to a doctor, as long as it is impossible to affect pain syndrome, risk of complications or mortality of the disease
A twenty-year-old anamnesis of CP increases the risk of pancreatic cancer fivefold.

For a period of 10 years 30% of CP patients dies, for 20 years - over 50% (N.B. Gubergrits, 2000).

The issue of terminology and connection with acute pancreatitis

Clinical and morphological manifestations of active pancreas inflammation, which first emerged and are within 3 months, should be considered as acute pancreatitis, from 3 to 6 months - subacute pancreatitis, and more than 6 months - transition to CP.

Popular in medical practice term "reactive pancreatitis" (which does not appear in standard classifications) is permissible to use as a temporary working diagnosis when unexpressed secondary structure (eg, edema) and function changes (hyperenzymemia, dyspancreatism), which are fully normalized by adequate treatment of a basic pathology (cholecystitis, peptic ulcer, etc.), are detected for the first time.

Chronization of acute pancreatitis (AP) is observed in 10-20% of patients.

However, there were cases when after an attack of AP, due to adequate therapy, pancreatitis was almost cured.

Sometimes between an attack of AP and emergence of CP clinical picture a long period of time passes (several years)

Latent (without acute onset of a disease and relapses) flow of CP is also possible

In some cases acute pancreatitis (or acute onset of CP) is concealed by clinical picture of concomitant disease (of biliary area, gastroduodenal area, intestines, spine, etc.).

Acute pancreatitis (by western criteria) - lesion of the pancreas, which manifests in different forms (from swelling to destruction of the parenchyma) of active inflammatory process (either in still unchanged gland, or at acute relapsing pancreatitis). It is characterized by acute pain attacks (primary or recurrent) and increased concentrations of serum amylase and/or lipase at least a factor of three.

Etiological factors

Among the causes of CP there are following factors:

1. Toxic factor:

a) alcohol abuse is considered one of the main causes of CP and is in 38-95% of cases of the disease. Pancreatitis of alcoholic etiology is characterized by apparent structural changes of parenchyma and ductal system, frequent calcification, more evident functional organ failure;

b) other toxic agents: organic solvents, dyes, pesticides, heavy metals, some drugs

Toxic agents:

- cause spasm of the Oddi`s sphincter by increase of ductal hypertension and permeability of ductal walls for enzymes;

- disturb synthesis and stability of cell membranes phospholipids;

- disturb microcirculation, promote fibrosis of small intrapancreatic vessels;
- cause hyperproduction and activation of pancreatic enzymes, while deteriorating their outflow;

- cause protein sedimentation with forming of protein plugs in the lumen of acini and small pancreatic ducts;

- inhibit biosynthesis in pancreatic cells and activity of antitoxic enzymes.

2. Hepatobiliary pathology:

various manifestations of dyscholia - microcholelithiasis, cholelithiasis, inflammatory and dyskinetic disturbances of biliary excretion system, other organic disorders of biliary patency, such as scars, strictures, rarely - acute and chronic liver diseases

- Recent data detected in 2/3-3/4 of patients with pancreatitis, which was considered idiopathic (of unknown origin), microcholelithiasis that have irritating effect on the tone of Oddi's sphincter and ductal epithelium of the pancreas when reflux

- Irritating effect of bile increases when it is infected (with "own" microbes, or with those from "sick" duodenum)

Biliary pancreatitis usually has an acute start and recurrent course, however, leads to less apparent (compared with toxic CP) structural and hypofunctional disturbances in time

Alcohol and biliary system diseases are considered major causes of pancreatitis development, both acute and chronic.

3. Gastroduodenal pathology (papillitis, strictures of the sphincter of Oddi, diverticulitis, duodenostasis of various genesis, peptic ulcer, gastroduodenitis, etc.)

4. Injuries of pancreas (external or as a result of operations or instrumental diagnostic manipulations) often cause development of AP, which might become chronic

5. Infectious agents also cause acute onset of the disease, which with presence of other pathogenic factors might become chronic. They are infections such as viruses (hepatitis A, B, C, epidemic parotiditis (mumps), Coxsackie virus, cytomegalovirus, AIDS), bacteria (different strains of helicobacter, mycobacteria of tuberculosis, mycoplasma, Legionella, toxoplasma, Cryptococcus, other pathogenic flora), parasitic infections (ascariasis, lambliasis, etc.).

6. Autoimmune disorders (in 5-6% of CP cases)

Autoimmune pancreatitis - manifestation of multiple organ autoimmune process induced by hyperproduction of IgG4, which is characterized morphologically by lymphoplasmocytic sclerotic changes and positive effect from treatment with corticosteroids. It is more common after 55 years

7. Hereditary factors

8. Hypercalc(in)emia (in 5-10% cases of hyperparathyroidism and when overdose of vitamin D) promotes formation of ductal calcifications.
9. Deficiency of certain diet components:

- protein and fat starvation (more common in underdeveloped tropical countries) = so-called tropical or nutritional pancreatitis;
- deficiency of antioxidant food components: vitamin E, vitamin C, β-carotene, vegetable bioflavonoids, lecithin, sulfur-containing amino acids, some trace elements and others

10. Local vascular disorders

11. Smoking (promotes tissue and vascular hypoxia)

12. Concomitant metabolic disorders (lipid metabolism disorder, obesity, diabetes) promote development of pancreatic dysfunction and degenerative processes, fat microembolism of pancreatic vessels

13. Pregnancy is an additional factor that promotes forming of CP if there are other etiological moments (especially in last trimester and in early postnatal period). Unfavorable moments: dishormonal metabolic fluctuations, changes in calcium metabolism, tendency to hypokinesia and dyscholia in biliary system.

Classification of chronic pancreatitis:

I. By etiology:

1. Toxic CP (alcohol, drug, etc.).
2. Biliary
3. Of other origin (indicate specific reason - secondary CP due to gastroduodenal pathology, infectious CP, ischemic CP, post-traumatic CP, autoimmune CP, protein deficiency = nutritional CP, heredity = "family" CP).
4. Of mixed origin

Classification of etiologic factors groups TIGAR-O:

Toxico-metabolic, Idiopatic, Genetic, Autoimmune, Obstructive.

II. By morphology (if present):

- Morphological variants of CP: calcific, obstructive, inflammatory-infiltrative, fibrotic (Marseille-Roman classification).
- Morphological degrees of CP severity: doubtful CP, light, moderate, severe CP - according to ERCPG, CT and ultrasound (Marseille- Cambridge classification)

III. By clinical features

Clinical forms:

1. Recurrent (recurrent CP) - with periodic exacerbations (with pain syndrome) and remissions.
2. Pain (pain CP) - with constant pain, no tangible remissions
3. Latent (latent CP) - no clear exacerbations, dull, monotonous course
4. Pseudotumor-like or icteric (pseudotumor-like CP) is like cancer of pancreatic head, is accompanied by jaundice.

**Division by the clinical features after N.B.Gubergrits (2002, 2006)**

1. **Pain CP**
   - with recurrent pain
   - with constant pain

2. **Pseudotumor-like CP**
   - with cholestasis
   - with subhepatic portal hypertension
   - with partial duodenal obstruction

3. **Latent CP**

**Phases of flow (for recurrent CP):**

1. aggravation
2. remission

**Degrees of severity:**

1. Easy (I).
2. Moderate (II).
3. Severe (III).

**IV. By functional condition:**

1. **Exocrine (excretory) function:**
   1.1. Increased (hypersecretion) - hyperenzymatic CP
   1.2. Reduced (excretory insufficiency) - hypoenzymatic CP
   1.3. Dyspancreatism - fluctuations in level of various enzymes

2. **Incretory function:**
   2.1. Increased (hyperfunction of insular apparatus)
   2.2. Reduced (incretory insufficiency, secondary pancreatic diabetes)

**V. By complications (if any):**

**Early:** jaundice, subhepatic portal hypertension, gastrointestinal bleedings, infection-toxic complications - abscess, parapancreatitis, extraperitoneal phlegmon, pancreatonecrosis (total or focal with formation of pseudocysts), peritonitis; systemic complications – DIC-syndrome, renal, respiratory, hepatic failure, encephalopathy and others.
Late: apparent maldigestion with systemic manifestations (hypovitaminosis, osteoporosis, anemia, hypotrophy, etc.), chronic encephalopathy, scars, strictures, duodenal stenosis, cancer.

Main clinical syndromes of CP:

- Pain syndrome
- Dyspeptic syndrome
- Dyskinetic syndrome – is distinguished separately when persistent diarrhea. Often it is united with dyspeptic syndrome
- Asthenoneurotic syndrome or syndrome of general symptoms

Pain syndrome

Causes of pancreatic pain:

- Ductal patency disturbance with increased intraductal pressure and irritation of baroreceptors. These are so-called "ductal" pains (more intensive, constant or recurrent).
- Irritation of nerve endings while stretching of pancreas capsule due to edema or destructive changes. These are so-called "parietal" pains of various intensity (from minimal to significant).
- Pancreatic interstitial ischemia (ischemic pains)
- In addition - solar plexus irritation when compression or transition of inflammatory process on it and irritant action of activated kinins (kallikrein and others) on pain receptors (in vessels, ducts, nerve ganglia, etc.), which provides more diffuse nature of pain

Clinical types of CP pains:

- So-called "great attacks" (1st type) - periodic sharp attacks of pain in the upper abdomen, usually occur due to eating disorder, alcohol intake, physical or emotional stress. Irradiation to sides, back (belting pain) and to heart is typical. These pains require prolonged complex drug therapy (inpatient treatment) and are typical for recurrent CP.
- So-called "small attacks" (2nd type) - moderate pains of same localization. Arise as a result of provoking factors or without clear reason, often irradiate. Condition of patient resemble "acute gastritis". Pains are cut short by diet and moderate drug intervention within 1-3 days. They are typical for light course of recurrent CP, when moderate course - may alternate with "great attacks".
- 3rd kind - constant, aching, dull or constricting pains in the upper abdomen of moderate or severe intensity. They are getting worse after eating disorder, alcohol intake, physical or mental overload. Usually irradiate and are typical for pain form of CP
- 4th kind – non-constant, dull, aching or constricting pains in the left hypochondrium or epigastric. Arise from eating disorder or without clear connection with it. Irradiation is not typical. Stop on their own or after minimal drug therapy (enzymes, antispasmodics, etc.). They happen when latent or recurrent CP

General features of pancreatic pains:

- Undulating character, i.e. fluctuations in intensity during the day
• Connection with eating disorder (spicy, fatty, "heavy" food, overeating)
• Nature and intensity of pains do not depend on body position and movements, as a rule
• Patient's condition relieves by abstinence from food, cold compress on mesogastrium
• Frequent irradiation. The direction of irradiation shows concomitant diseases, functional and organic
• Localization of pain depends on prevailing lesion of pancreas (head, body or tail)
• Expressed pain attack (first or recurrent) which lasts 3-5 hours and is accompanied by repeated vomiting that does not bring relief, diarrhea and blood pressure fall, is called pancreatic colic.

**Pain zones and points of CP**

1 - Chauffard's zone;
2 - Gubergrits-Skulskiy's zone;
3 - Desjardins' point;
4 - Mayo-Robson's point
A - line connecting the navel with the iliac cavity;
B - line connecting the navel with the middle of left costal arch

**Dyspeptic syndrome:**

• nausea - sometimes is the only clinical sign of a disease. Indicates increased pressure in ducts of pancreas
• vomiting - is less frequent, is observed when exacerbations of CP, does not bring relief.
• meteorism - in acute cases is due to intestinal paresis (sign of Gerbih). With prolonged course of CP is due to maldigestion and concomitant intestinal and bile excretion pathology;
• loss of appetite - among 1/3 of CP patients;
• stool disturbance - can be considered as a manifestation of dyspepsia and maldigestion or distinguished as a separate dyskinetic syndrome:
  a) moderate diarrhea, constipation or their alternation;
  b) increased stool volume even with absence of diarrhea (so-called "big pancreatic stool")

Dyspeptic disturbances are in clinical-laboratory syndrome of **pancreatic maldigestion.**

**Pancreatic maldigestion (PM)** - a syndrome of enteral digestion disturbance (maldigestion) due to absolute or relative production deficiency of pancreatic enzymes and/or disorders of their action realization.

**Primary (absolute) PM** - as a result of pancreas diseases, which are accompanied by production and/or excretion of pancreatic enzymes disorders;
Secondary (relative) PM - when excretory function of pancreas is not disturbed, but there are excessive "demands" to an organ (overeating) or problems with enteral realization of pancreatic enzymes action.

**Types of secondary PM:**

A) hepatogenic PM - with cholestasis or asynchronous excretion of pancreatic juice and bile;

B) gastrogenic PM - with hypoacid atrophic conditions that lead to reduced secretin stimulation of pancreas;

B) enterogenic PM - due to dysbiosis (change in intestinal pH, bile acids metabolism, enterocytes integrity and absorption disorders);

D) secondary PM of mixed origin

**Atypical clinical forms of CP** (are rare and usually against the background of concomitant disease, clinical picture of which is leading):

Infarction-like form – is like angina pectoris or infarct pains up to shock, collapse. More common among women with combined biliary and heart pathologies (metabolic cardiomyopathies, arterial hypertension). Reducing of pancreas inflammation leads to normalization of ECG (electrocardiogram)

Acute dyspeptic form – is like acute toxicoinfection, food poisoning (nausea, vomiting, bloating, heartburn, bitter taste in mouth, minimal pain syndrome). It happens with exacerbation of GERD (gastroesophageal reflux disease), gastroduodenitis, peptic ulcer

Diabetic form - clinical picture of diabetes is dominative. The disease starts with chronic latent pancreatitis with excretory insufficiency. Diabetes at CP has a benign course (except for cases after partial resection of the organ), does not always require insulin, is rarely accompanied by ketoacidosis and vascular disorders.

"Hypothalamic" form - hypothalamic paroxysmal chill-like conditions, sudden rise of blood pressure, sympathoadrenal crises (tachycardia, sweating, muscle weakness). It happens on the background of diencephalic syndrome of various origins, thyrotoxicosis. Symptoms of pancreatitis are not evident, but its diagnosis is confirmed by instrumental and laboratory data: changes in ultrasound picture, amylase level in the blood and urine, etc.

This statement is true for all atypical forms listed above.

**Diagnostic criteria of CP**

1. **Clinical features and medical history:** typical pain and dyspepsia; local painfulness of the abdomen in the area of the pancreas projection.

2. **Instrumental study of the pancreas structure:**

   - Ultrasound - detection of edema, destructive areas, pseudocysts, calcifications; with chronic changes - heterogeneous hyperechoic structure
with uneven contours and change in size, increase in diameter of the pancreatic duct;
- CT specify presence of calcifications, pseudocysts, pancreatonecrosis threat, makes differential diagnosis with pancreatic cancer;
- ERCPG specify condition of ductal patency (with questionable data of ultrasonography and CT);
- additional information can provide abdominal radiography, contrast duodenography, pancreas scanning.

3. **Laboratory tests:**

   a) tests on pancreas enzymatic activity are main in laboratory diagnostics of CP;

   - increase (with exacerbation) or decrease of α- amylase (blood, urine, duodenal contents);
   - blood lipase, test on proteolytic activity, fecal and blood elastase, breath tests on lipolytic activity of the pancreas, secretin-pancreozymin test at aspiration of duodenal contents;

   b) typical changes in coprogram " big pancreatic stool", steatorrhea, creatorrhea, amylorrhea, etc.

   c) tests on incretory pancreatic function: blood and urine sugar, glucose loading test, radioimmunological studies of insulin, etc;

   d) non-specific markers of pathological activity: leukocytosis, increased ESR (erythrocyte sedimentation rate), dysproteinemia, increase of ALT, AST, alkaline phosphatase, CRP and so on.

4. Final specification of the diagnosis is estimation of pancreatic biopsy by **histocytological methods.**

**Treatment of CP**

**Main therapeutic measures with CP:**

1. Causal treatment

2. Treatment in period of exacerbation of recurrent CP (like acute pancreatitis):
   2.1. Reduction of pain.
   2.2. Reducing of increased pancreas secretion and enzyme activity, correction of enzyme-inhibitory imbalance.
   2.3. Anti-inflammatory therapy.
   2.5. Reducing of common manifestations (intoxication, dehydration, electrolyte disorders, vascular insufficiency)

3. Keeping to a diet

4. Correction of exocrine pancreas insufficiency and maldigestion.
5. Correction of secondary disturbances of pancreas incretory function
7. Correction of immune disorders.
8. Treatment of concomitant diseases (of digestive organs, etc.).
9. Surgical treatment (if indicated).
10. Rehabilitating and maintaining therapy.

**Treatment in period of CP exacerbation:**

I. Basic therapy (base):

a) drugs for motility and tone correction while anesthesia:

spasm of sphincter of Oddi - no-spa, duspatalin, riabal, papaverine, baralgin intramuscularly 2 times a day, sometimes – aminophylline intravenously or nitrates orally;

insufficiency of the sphincter of Oddi and unidentified disturbances of its tone - prokinetics (metoclopramide intramuscularly 2 times a day, mosapryd or domperidone 1-2 tablets 3 times a day).

b) causal treatment - with known etiology of CP and its possible correction (alcohol refusal, treatment of biliary disorders); with signs of active gastroduodenal helicobacteriosis - triple or quadruple antihelicobacter therapy during 7-10 days, etc.).

II. Combined with basic therapy step-by-step (4 steps) sequential use of hypersecretion and enzyme-inhibitory imbalance correctors

**Treatment of pain due to pancreatitis**

(Transition to the next level if ineffectiveness of the previous level):

I step: base + gastrocepin or buscopan or PPI or H2-histamineblocker (pantoprazole, famotidine, etc.) orally + enzyme preparation (festal, pancreatin 1-3 doses 3 times a day, etc.) orally

II step: base + gastrocepin (buscopan) parenterally or proton pump blocker (pantoprazole, esomeprazole or other) + ε-aminocapronic acid intravenously drop-by-drop or dalargin + enzyme preparation

III step: base + atropine (buscopan) and proton pump inhibitor + natural inhibitor of kallikrein-kinin system (contrical ≥ 20-40 thousand units per day, hordox ≥ 50 thousand units per day).

IV step: medications of III step + 5-fluorouracil (on 5% glucose intravenously drop-by-drop 3-5 days) or sandostatin (50-100 mcg subcutaneously 2-3 times a day) or hemosorbtion, or radiotherapy; if no effect - surgical treatment.
Pancreatic enzyme preparations

Basic or single component is pancreatin, containing:

- amylase
- trypsin
- lipase

in different concentrations

Classification of enzyme preparations:

- Containing only pancreatic enzymes (amylase, lipase and trypsin) of animal origin: Pancreatin, Mezim forte, Mezim 10 000, Pangrol, Creon, Pancitrat, Likreaza, Pankreolan, Neo-panpur, Prolipaze
- Combined preparations (containing pancreatin in combination with additional components - bile, sorbents, antacids, extract of the gastric mucous coat, enzymes of fungal origin, etc.) Festal, Panzinorm forte, Enzistal, Digestal, Panpur, Pankurmen, Pankreoflat, Kotazim forte, Digestif Rennie, Merkenzim, Dipankrin, Kombizim compositum.
- Containing enzymes of fungal and vegetable origin (Solizym, Somilaza, Oraza, Nigedaza)

Indications for enzyme preparations

1. Diseases of the pancreas:
   - Chronic pancreatitis;
   - Conditions after pancreas or its part resection;
   - Other reasons lead to decrease of functioning parenchyma (large pseudocysts, tumors, etc.);
   - Obstruction of pancreas ducts (tumor, strictures, pseudocysts, etc.);
   - Diabetes;
   - Zollinger-Ellison syndrome;
   - Mucoviscidosis;
   - Genetically caused fermentopathies and hypoplasia or atrophy.

2. Gastroduodenal diseases:
   - Chronic atrophic gastritis, duodenitis with reduced secretory function of the stomach;
   - Condition after resection of the stomach;
   - Dumping syndrome.

3. Bowel diseases:
   - Chronic enteropathies (including enteritis);
   - The syndrome of excessive bacterial growth (small intestine dysbiosis).

4. Hepatobiliary diseases:
   - Extra- and intrahepatic cholestasis of various origins;
   - Condition after cholecystectomy.
5. Functional diseases of the digestive system:

- Functional gastric and intestinal dyspepsia;
- Gastroduodenostasis;
- Functional stool disorders;
- Biliary dysfunctions

6. Other indications:

- Condition after irradiation;
- "Age-related" enzyme deficiency;
- Episodes of overeating or monotony in food;
- Long bed or inactive mode;
- Preparation for an ultrasound

**Indications for enzyme preparations at chronic pancreatitis:**

1. Reduction of pain (pancreatic and enterogenic) syndrome.
2. Correction of pancreas exocrine insufficiency and related pancreatic maldigestion:
   
   2.1. "On demand" therapy - enzyme preparations

   2.2. Course (1-2 months) restoring of pancreas function after exacerbation of CP

   2.3. Long-term maintaining treatment of stable irreversible exocrine insufficiency of pancreas.