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Disturbance in the Composition of the Intestinal Microflora in the Mechanisms of the Formation of Clinical Manifestations in Patients with Chronic Pancreatitis

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Annotation
The purpose of the study: To determine the role of a violation of the composition of the intestinal microflora in the formation of clinical manifestations and in structural changes of COD in patients with CP and to evaluate the effect of therapy aimed at restoring intestinal microbiosenosis on the course of the disease
Keywords: Microflora, Clinical Manifestations

The relevance of the topic. Chronic pancreatitis (CP) is an important socio-economic problem in terms of prevalence, increased morbidity, temporary disability and disability. Over the past 30 years, the number of patients with acute and chronic pancreatitis has doubled in the world (95), while primary disability of patients reaches 30% (138).
In the structure of diseases of the gastrointestinal tract, it ranges from 5.1 to 9%, and in general clinical practice - from 0.2 to 0.6% (61).
However, the role of disorders of the intestinal microflora, in particular, excessive bacterial growth, remains unexplored in the small intestine, in the mechanisms of formation of clinical manifestations, as well as in the development of structural changes in the mucous membrane (CO) of the duodenum (duodenum) in patients with chronic pancreatitis.
There are practically no publications in the literature devoted to the peculiarities of therapy of patients with chronic pancreatitis with a violation of the normal composition of the intestinal microflora. A complex therapy has not been developed, including antibacterial drugs for intestinal decontamination, and its effect on the course of CP has not been studied.

Materials And Methods Of Research

1.1 Clinical characteristics of patients

The present study included 50 patients with chronic pancreatitis who were repeatedly treated at the gastroenterology department of the Tashkent Medical Academy"Clinical Hospital" The criteria for inclusion of patients in the study were:
1. The presence of CP, confirmed by the results of clinical and instrumental research methods;
2. The age of patients is from 18 to 70 years old;
3. The patient's informed consent to participate in the study.
Patients who had the following cases were excluded from the study:
1. Complications of chronic pancreatitis requiring surgical intervention;
2. Oncological processes of any localization;
3. Surgical interventions on abdominal organs, excluding cholecystectomy and appendectomy;
4. Chronic calculous and stone-free cholecystitis in the acute phase;
5. Papillitis with signs of biliary hypertension;
6. The presence of signs of cholestasis and cytolysis in biochemical liver samples;
7. Diseases of other organs and systems that may be accompanied by motor-secretory and dyspeptic disorders of the gastrointestinal tract, the development of abdominal pain syndrome;
8. Diseases requiring constant intake of medications that affect the condition of the gastrointestinal tract.
Patients were included in the study only after receiving informed consent, which was of an open prospective nature.

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All information about the course of the disease was entered into a specially designed map. The duration of CP disease, the duration and frequency of exacerbations per year, the time of onset of symptoms, and their dynamics were evaluated. The assessment of clinical, laboratory and instrumental parameters was carried out: upon inclusion in the study, after 3 and 12 weeks. The clinical manifestations of the disease were analyzed (abdominal pain, diarrhea with fatty or watery feces, flatulence, nausea, vomiting, belching of air, bitterness in the mouth, constipation). The duration of the disease was determined by the time from the moment of occurrence of the clinical symptom (dyspepsia, abdominal pain syndrome) to the inclusion of the patient in the study. The degree of severity of clinical symptoms and their correlation with the results of laboratory and instrumental studies were studied.

To confirm the diagnosis of CP, a standard set of modern diagnostic measures was used, which included: analysis of clinical signs, laboratory methods (clinical blood and urine analysis, biochemical blood analysis - liver functional tests, determination of blood and urine a-amylase levels).

anamnesis of the disease was collected in all patients, general clinical, laboratory and instrumental studies were conducted, including:

physical examination; clinical blood test; biochemical blood analysis;

clinical urine analysis; general clinical stool analysis (coprogram);

examination of pancreatic elastase 1 in feces; bacteriological examination of feces; esophagogastroduodenoscopy (EGDS) with examination of the Fater's nipple; ultrasound examination of the abdominal cavity;

Characteristics of research methods

Clinical methods of investigation of the observed patients

When analyzing abdominal pain syndrome, we distinguished:

Pain caused by damage to the pancreas (hereinafter referred to as pancreatic pain). In the mechanisms of development of this type of pain, the leading role belongs to the development of inflammation in the pancreatic tissue, compression of nerve endings and increased intracranial pressure associated with edema and inflammatory infiltration of the organ.

The pain is constant or paroxysmal, localized in the

center of the epigastrium, radiating into the back, not clearly associated with food intake, does not decrease when taking antispasmodics;

Pain caused by ductal hypertension. They are based on a functional disorder of the Oddi sphincter, which is characterized by the presence of recurrent attacks of severe or moderate pain lasting 30 minutes or more, localized in the epigastrium, right, left hypochondrium, possibly with irradiation in the back. The pain is associated with eating; it often appears at night and is accompanied by nausea and, less often, vomiting. Taking antispasmodics relieves or reduces the intensity of pain syndrome (12).

Pain caused by duodenal hypertension, localized in the epigastric region, intensifying immediately after eating, accompanied by bitterness in the mouth, nausea, episodic vomiting, which brings relief. Palpation determines soreness and often rumbling or transfusion along the course of DNA.

Pain caused by impaired intestinal function, localized in meso - and hypogastria, in combination with stool disorders, fecal shape, flatulence and palpatory soreness along the course of the small and/or large intestine.

In the analysis of dyspeptic disorders, the following were evaluated: 1) bitterness in the mouth; 2) air burps; 3) nausea; 4) vomiting; 5) bloating; 6) diarrhea; 7) constipation.

The severity of abdominal pain and leading dyspeptic disorders (diarrhea, flatulence, nausea and/or vomiting) was assessed using a score scale. The severity of the symptom ranged from 0 to 3 points:

- 1 point (mild degree). The symptom does not disrupt the patient's activity and does not require medication;
- 2 points (average degree). The symptom does not significantly disrupt the patient's activity, but requires "self-help" (taking medications, changing the rhythm of intake and quality of food, etc.);
- 3 points (severe degree). The symptom disrupts the activity of the patient, medical assistance is required.

According to the literature, the key clinical symptoms of chronic pancreatitis are abdominal pain, belching, bloating, various stool disorders (diarrhea, increased stool mass and discoloration, the presence of undigested food particles and so-called "fatty" feces), less often constipation (4, 8, 12) Themethodology for assessing the severity of subjective manifestations of diseases in points is widely used in scientific research and allows

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objectifying subjective manifestations of the disease and studying the dynamics of the process in quantitative terms (4, 7).
The physical examination of the observed patients included: examination of the abdomen, palpation of the abdominal organs.

Laboratory research methods
Biochemical blood examination included determination of serum levels of total protein and protein fractions; liver enzymes (alanine aminotransferase, aspartic aminotransferase, gammaglutamyltranspeptidase, alkaline phosphatase); bilirubin; amylase, blood glucose, urine diastases. A clinical blood test was performed. Laboratory test data made it possible to clarify the functional state of the organs of the hepatobiliary zone 8].

Determination of amylase content in blood and urine
The amylase test was performed according to the classical method. If chronic pancreatitis was suspected, a three-time study was conducted: on the 1st day of hospitalization with exacerbation of pain (the so-called "enzyme evasion" detection test). It was taken into account that the maximum concentration of a - amylase is noted 24 hours after the onset of pain syndrome and persists for 2-3 days (11,13). A short-term increase in the level of amylase in blood and urine by 2 or more times was considered to be diagnostically significant, indicating a violation of outflow (due to duct obstruction or stagnation of secretion) or inflammation of the pancreas

Table 1
Degrees of dysbiosis of the colon

The degree of dysbiosis	**Data from microbiological examination of the contents of the colon**
I	A decrease in the total number of the main representatives of the anaerobic microflora (bacteroids, bifidobacteria and lactobacilli) to 10-10 microbial cells in 1 g of feces; A decrease in the number of E. coli with normal enzymatic activity to 106 microbial cells in 1 g of feces against the background of a decrease in the total number of bacteria of this species.
II	A decrease in the total number of the main representatives of the anaerobic intestinal microflora to 105 microbial cells in 1 g of feces against the background of an increase in colibacterium flora; a decrease in the number of escherichia with normal enzymatic activity while increasing (up to 104-105 microbial cells in 1 g of feces) the number of their lactose-negative forms; an increase in the level of opportunistic enterobacteria (proteus, klebsiella, citrobacter and up to 104 microbial cells in 1 g of feces and (or) the appearance of staphylococcus aureus, fungi of the genus Candida up to 104 microbial cells in 1 g of feces
III	A decrease in the total number of the main representatives of the anaerobic intestinal microflora to 103-104 microbial cells in 1 g of feces or even a complete absence in the studied material; the absence of escherichia with normal enzymatic activity against the background of an increase in their number (up to 10b microbial cells in 1 g of feces and more) the number of their lactose-negative and hemolytic forms; an increase in the level of opportunistic enterobacteria (proteus, Klebsiella,

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	Citrobacter, etc.), Staphylococcus aureus, fungi of the genus Candida to 105-106 microbial cells in 1 g of feces
IV	Absence of the main representatives of anaerobic microflora; absence of Escherichia with normal enzymatic activity; overwhelming superiority of opportunistic enterobacteria, Staphylococcus aureus, Candida fungi and their associations - more than 106 microbial cells in 1 g of feces

Instrumental research methods

To clarify the diagnosis of the underlying disease in the observed patients and assess the condition of the digestive organs, the following instrumental research methods were used:

• Ultrasound examination of the abdominal cavity;

• Esophagogastroduodenoscopy with examination of the large duodenal papilla;

Ultrasound examination of abdominal organs

Despite the improvement of laboratory and instrumental research methods, the diagnosis of pancreatic diseases is difficult enough. This is especially true for mild forms of chronic pancreatitis. According to various authors, the echographic picture of chronic pancreatitis coincides with the final diagnosis in 75-92% of cases. Echography of the pancreas in the diagnosis of chronic pancreatitis is one of the most common hardware research methods (6, 13). The sensitivity of the method ranges from 60% to 85%, and the specificity is 80-90%. With an exacerbation of pancreatitis, an increase or decrease in the organ is more often noted. In addition, there is a violation of the echostructure of the gland with a decrease or increase in its echogenicity (3, 5). With a prolonged course of CP, the organ has a homogeneous structure with increased echogenicity.

The generally accepted ultrasound signs of chronic pancreatitis are:

1. Early signs: a homogeneous diffuse increase in the echogenicity of the parenchyma with a preserved pattern; a picture of a "cobblestone pavement", which is given by echoes of medium intensity; medium and dense echoes, unevenly distributed on a normal background.

2. Late signs: inhomogeneous distribution of echoes with alternating dense and cystic areas;' extreme variability in the amplitude of the echo signals; an increase in the size of the organ by 1.5-2 times (anteroposterior dimensions: head more than 3 cm, body more than 2.5 cm, tail more than 3 cm); calcification of the gland tissue; concretions in the pancreatic duct; pseudocysts; expansion of the pancreatic duct (more than 2.5 mm); deformation of the organ; increased density of the pancreas; decreased mobility of the pancreas when the diaphragm moves; expansion of the common bile duct in combination with an increase in the head of the pancreas (7, 5, 10).

Esophagogastroduodenoscopy

During esophagogastroduodenoscopic examination, attention was paid to the postbulbar sections of the DNA and the presence of changes,

traditionally designated as indirect signs of chronic pancreatitis: duodenitis, duodenogastric reflux, semolina symptom (small lymphangiectasia of the duodenal mucosa), changes in the large duodenal nipple (12). Various models of endoscopes from the Japanese Olympus company were used for endoscopic examination: the GIF-1T30 esophagogastroduodenoscope, the GIF V 70, Q150 videogastroscope and the Fujinon FG-IZP esophagogastroduodenoscope.

Endoscopic examination, conducted according to methods developed by Russian scientists (6), made it possible to visually assess the nature and extent of the pathological process.

Special attention was paid to the condition of the large duodenal nipple (LDN), reflecting the involvement of the terminal choledochus in the pathological process. Signs of LDN lesion were considered to be: hyperemia, edema and swelling (papillitis) LDN (64, 14). In assessing inflammatory changes in the duodenum, the classification of P.Y. Grigoriev and co-authors was used (11).

Endoscopic examinations were performed in all patients upon admission.

Complex conservative therapy of patients with CP with excretory insufficiency and the presence of excessive bacterial growth in the small intestine

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The effectiveness of therapy aimed at normalization of intestinal microflora was studied in 31 patients with chronic pancreatitis with excretory insufficiency and the presence of excessive bacterial growth in the small intestine and dysbiosis of the colon. Depending on the treatment regimen used, the patients were divided into two groups. The main group consisted of 16 patients who used the first scheme, the control group consisted of 15 patients who were prescribed the second therapy scheme. The groups were comparable in age, gender and duration of the disease.

The first treatment regimen included diet, basic therapy aimed at:

1) correction of external secretory pancreatic insufficiency - pancreatin (creon) with lipase content of 20 LC units for mild and moderate and 40 LC units

- with severe pancreatic insufficiency, taken during breakfast, lunch and dinner constantly;

2) to normalize the tone of the Oddi sphincter and motility of the duodenum: with hypertension of the Oddi sphincter, trimebutin 200 mg was prescribed 3 times a day for 3-4 weeks, if duodenostasis due to hypomotor dyskinesia of the duodenum was detected, domperidone 10 mg 3 times a day for up to 2 weeks;

3) to reduce gastric and mediated pancreatic secretion - proton pump inhibitor pantaprasole 20 mg 1-2 times a day 2- 3 weeks;

4) for the relief of pancreatic type pain - nonsteroidal anti-inflammatory drugs - diclofenac 75 mg intramuscularly 1-2 times a day for 3-5 days.

Simultaneously with the basic treatment, decontamination therapy was performed to normalize the intestinal microflora, including nifuroxazide 200 mg 3 times or rifaximin 200 mg 3 times for 7-10 days, followed by the appointment of the probiotic enterol 1 capsule 2 times a day for 2 weeks.

The second treatment regimen included only diet and basic therapy. '

The effectiveness of therapeutic regimens was evaluated 3 and 12 weeks after the start of therapy based on the dynamics of clinical manifestations, indicators of a coprogram. In assessing the effectiveness, remission of the disease was highlighted, in which clinical symptoms were completely stopped; improvement when the severity of clinical symptoms decreased by 1 point or more; lack of improvement, in which the clinical picture remained unchanged; a relapse in which, after improvement or remission, the condition worsened, symptoms appeared or their severity increased by 1 point or more.

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