PATHOGENIC ASPECTS OF THE CHRONIC PANCREATITIS OF BILIARY GENESIS AFTER CHOLECYSTECTOMY

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Introduction. Lately chronic pancreatitis (CP) has become one of the most common diseases in the practice of medicine, one of the most problematic for the diagnostics, determining treatment strategy and prognosis. This disease has become most problematic among multidisciplinary pathologies, which often overlap interests of physicians and surgeons, gastroenterologists and endocrinologists, where intervention of nutritionists, therapists and other professionals is necessary. In the last 30 years in the world, an increase in the incidence of CP and acute pancreatitis (AP) is more than 2 times, the prevalence of diseases of the pancreas in the adult population over the last 10 years has increased 3 times, and among teenagers — more than 4 times. On average, the incidence of CP in the world is 4-10 cases per 100,000 of population per year, and prevalence — 26.7-50 cases per 100,000 of population and varies by country, race, nutritional habits. In Europe — 25 diagnosed cases per 100,000 population. In Germany — over 20,000, while in Russia — more than 60,000 population of patients with CP. Patients with CP accounted for 25% of all numbers that apply to gastrointestinal departments of clinics Ukraine [6]. In 30% of patients with CP, early complications are being developed (suppurative-septic, bleeding from gastroduodenal ulcers plot thrombosis in the portal vein system, choledochal stenosis or duodenal ulcer (DU), and others). Mortality rate is 5.1%.

Consolidated global statistics data show that up to 5% of patients with CP have a high probability of developing pancreatic cancer, and in patients with hereditary pancreatitis risk increases tenfold. Twenty-year anamnesis increases the risk of developing cancer of the pancreas 5 times. CP leads to functional failure of the

pancreas, as well as complications, which are associated with disability. As a result, 30% of patients with CP die for 10 years, and more than 50% die for 20 years [6].

CP is a group of chronic pancreatic diseases of various etiologies, mainly inflammatory nature of the progressive phase-focal, segmental or diffuse degenerative and destructive changes of exocrine tissue, atrophy of glandular elements (pancreocytes) and their replacement by connective tissue; changes in the ductal pancreatic system with formation of cysts and concretions, with varying degrees of violation of exo- and endocrine functions of the pancreas [10]. CP is divided into primary and secondary one. The most frequent causes of CP include: diseases of the biliary system, stomach, duodenum, alcoholism. Less often the cause of CP is an injury of the pancreas, allergy and autoallergy, vascular lesions and ischemia of the pancreas, hyperlipoproteinemia, hyperparathyroiditis, hemochromatosis.

The aim of research is to analyze the literature on the pathogenetic aspects of influence of done cholecystectomy (CE) in the anamnesis on CP course.

Among the causative factors of CP, pathology of biliary tract occurs in 35-56% of cases. In Europe, gallstone disease (GSD) is the cause of 30-50% of AP. Inclusion of the pancreas in the pathological process upon chronic cholecystitis and gastrointestinal diseases depends on disease duration and location of calculus, is more common in women. Moreover, the cause of biliary pancreatitis (BP) is a congenital anomaly of bile ducts, choledochal cyst, pathology of major duodenal papilla (MDP).

The basis of this CP etiologic variant is a hypothesis of "common duct" suggested by E. Opie in 1901. Anatomical proximity of the confluence of the bile and pancreatic ducts into the duodenum for various reasons can lead to reflux of bile into the pancreatic duct, causing damage of the pancreas by detergents contained in the bile. Due to obstruction of ducts or ampulla of duodenal papilla, hypertension in the main pancreatic duct (MPD) develops, followed by the rupture of small pancreatic ducts. This leads to the separation of secretion to the pancreatic parenchyma, activation of digestive enzymes, resulting in the developing destructive and degenerative changes in the pancreas.

One of the mechanisms of CBP is a lymphogenous damage of the pancreas, mostly its head. The source of affection is considered to be a chain of enlarged lymph nodes, followed from inflamed gallbladder (GB) to the pancreatic head.

In the last few years, biliary sludge has become more and more important in the development of BP, which incidence in patients with idiopathic CP, according to different authors, is up to 33-75%. As a result of destabilization of physical and chemical composition of bile, precipitation of its main components and the formation of sludge in GB occur. An important factor in the formation of sludge is GB hypotonia and hypertonicity of Oddi's sphincter (OS). Continuous passage of biliary sludge in the tract causes damage to the mucosa, mostly in the area of OS, by the microlites that make up the bulk of the sludge. Consequently, the first is a developing secondary OS dysfunction, and stenosing papillitis is formed later. All these conditions result in the development of stenosis of the terminal part of the common bile duct, MDP, the mouth of the MPD, which leads to sustained hypertension in the common bile duct and MPD [12]. Frequent BP relapses occur upon migration of small and very small stones (microlites). Among the most dangerous microlites are stones up to 4 mm, the presence of stones in GB less than 5 mm in diameter increases the risk of pancreatitis 4 times. Choledocholithiasis is one of the main causes of CBP; according to different authors, the incidence of CP on the background of choledocholithiasis varies between 25.0-65.3%. It is believed that not every choledocholithiasis leads to the development of CBP, more often an ampullar lithiasis and MDP concremets.

Recently in Europe and North America there has been a tendency to reduce the incidence of CP, which is probably due to the conduction of the earlier operations in exacerbations of chronic calculous cholecystitis and fairly extensive use litolityc therapy [18]. However, any operation performed on the gastrointestinal diseases or their consequences is associated with the development of further pathophysiological processes leading to disruption of digestion and absorption of food, which is often caused by existing or first emerged CBP.

It is believed that the development of CP needs pathological changes of the bile, which is called toxic or aggressive. This penetration of such bile in MPD is a pathological mechanism that supports the inflammatory process in the pancreas, and is the main cause of CBP. However, the exact mechanisms that activate enzymes in the cells of acini with obstruction are still unknown. It is believed that upon cholelithiasis bile contains large amounts of lipid peroxidation that give it the aggressive action upon reflux in the pancreatic ducts.

In accordance with the opinion of O. Y. Gubergrits, biliary tract disease is the cause of CP in 63% of patients. The basic mechanisms of CP development upon diseases of the biliary tract are: 1) the transition of infection from bile ducts to the pancreas by common lymphatics; 2) complications of outflow of pancreatic secretion and the development of hypertension in the pancreatic duct, followed by the development of edema in the pancreas. This situation arises in the presence of stones and constrictive process in common bile duct; 3) biliary reflux into the pancreatic ducts. Thus, bile acids and other components of bile duct damage epithelium and parenchyma of the pancreas and contribute to the development of inflammation in it [4].

Some Western scholars do not emit BP in a separate nosological group and consider the case of pancreatitis in patients with cholelithiasis without other etiologic factors as idiopathic pancreatitis. At the same time, recent data has confirmed the importance of biliary pathology in CP occurrence due to the functional and organic changes in OS and MDP ampoules.

Every 5th women and 10th men on the planet suffer from gastrointestinal diseases. Gastrointestinal diseases are found in a quarter of the world’s population over the age of 60 and in one-third of the population over the age of 70. The disease occurs in 10-15% of the population of Western Europe [13]. Higher incidence in industrialized countries along with rising prevalence of gastrointestinal diseases with age has been marked. So, at the age of 21-30, 3-4% of the population suffers, 41-50 — 5%, over 60 — up to 20%, over 70 — up to 30% of the population. In secondary pancreatitis causal treatment is of importance that is usually limited to surgical

removal of the causes of the disease. We can't but mark the gastrointestinal diseases as one of the most common causes of pancreatitis. GSD is a cause of 30-50% of AP [19] and choledocholithiasis is one of the main etiological factors of CBP, the incidence of which within the range 25.0-65.3% [9]. There is evidence that biliary concretions, diameter of which is less than 5 mm, increase the risk of pancreatitis 4 times. Therefore, it is CE performed in time in patients with chronic calculous cholecystitis can be considered as a preventive measure of AP and CP of biliary etiology. Causal treatment for choledocholithiasis is the only CE. Surgical invasions include the traditional (open) or laparoscopic CE (LCE) upon gastrointestinal diseases, immediate removal of choledocholithiasis, papillostenosis. The only method of etiotrop treatment of CBP is conducting CE with rejection of choledoch or without it. Recently, LCE has been considered the gold standard of treatment, especially in the elderly patients [17]. In most cases, CE is planning, although in complicated cases it can be performed as emergency surgery. Laparoscopic technology led to a significant reduction in the number of open CE. Today, about 86% of CE are performed laparoscopically. Providing the secret outflow from the pancreas is performed by using the endoscopic techniques when disorders are of organic nature (stenosing papillitis) or by medical treatment when existing disorders are of functional nature (duodenostasis, OS spasm or failure) [5]. Accumulated surgical experience and advances in endoscopic technology have expanded the indications for LCE and allowed to include patients with complications of gastrointestinal diseases.

Until now a certain amount of research has been accumulated, the results of which show that open CE is always associated with some risk of complications in both the intervention and in the postoperative period. CE is accompanied by significant soft tissue injuries of the anterior abdominal wall. Furthermore, even in uncomplicated postoperative course, the term of rehabilitation is quite long.

In the early 70s CE was introduced by mini-incision. As the cuts upon mini-CE were smaller, the number of complications was brought down, respectively — the patients recovered faster [20]. At present, LCE is recognized as the gold standard of treatment of gastrointestinal diseases, although evidence of the benefits of this

intervention with respect to mini-CE is absent. LCE combines radical (deleted pathologically altered GB with concrements) and low invasiveness (almost completely preserved integrity of the soft tissues of the abdominal wall, especially aponeurosis and muscles), thus significantly decreasing term of rehabilitation of patients. Given that gastrointestinal diseases are often detected in women, often under the age of 30-40, implications of cosmetic surgery are of great importance — small skin incisions (5-10 mm) usually heal with subtle scar formation [11].

According to global statistics, GSD frequency tends to increase among children and among middle-aged and elderly, that is why number of CE is growing significantly. Each year in the world they perform more than 2.5 million CE, i.e. the frequency of executing this surgery is the second only after appendectomy. However, surgery does not always solve the problem of improving the health status of patients: 20-30% of them still complain of feeling unwell. In addition, the surgery itself leads to various disorders of the digestive system. According to the literature, after discharge from the hospital almost every second patient with AP needs rehabilitation and continuation of treatment, which increases the economic costs and complicates the recovery process and further changes the quality of life of patients. It is believed that the scheduled CE in terms of a highly skilled surgical hospital leads to full recovery and rehabilitation and quality of life in most patients [7]. In this regard, there is still a perception that patients who underwent CE without requiring further medical therapy and GB removal automatically eliminate factors that contribute to the development and progression of the disease. However, unfortunately, this is not the case. According to different authors, after CE gastrointestinal complaints occur in 5-40%, 3-48% or even in 74.3% of patients. After CE only a minority of patients (46%) marks alleviation, 25% indicate no change, 29% of patients point out the deterioration, about a third of patients complains on recovering attacks of pain in the abdomen [16].

In the majority of patients (58%) cause of complaints after CE is functional impairment, in 40-42% — organic. Only 1.5% of organic disorders are the result of the operation, and only 0.5% of patients with postcholecystectomical syndrome

(PCES) approach to repeated surgery. In most operated patients, polymorphism of clinical manifestations and complaints after CE is usually not a result of errors in the operation, and it is predetermined by functional or organic disorders in the biliary area, occurring after GB removal. CE worsens quality of life, although some studies have shown improvement. The rate of recovery of quality of life depends on the type of CE (traditional open, laparoscopic or mini-CE) [2]. After CE annually disabilities are found in 2-12% of patients.

The concept of PCES remains unclear because of different views: what states should be included in this concept? Some authors distinguish true PCES — as a result of tactical and technical errors during surgery and continued biliary tract diseases — and untrue one that develops as a result of pathological conditions that are not related to the biliary tract syndrome (satellite) [1]. You can mark at least 4 groups of major reasons that cause development of clinical symptoms after CE: 1) diagnostic mistakes in the preoperative stage, examination of the patient or during surgery; 2) technical and tactical errors made during transactions; 3) functional states associated with GB removal; 4) exacerbation or progression of existing disease before surgery, primarily in hepatopancreatobiliary areas and the development of new pathological conditions resulting from the restructuring of the adaptation of the digestive system due to CE. The first two groups of causes belong to the surgical aspects of the problem and are highlighted in details in the relevant literature. Internists and family physicians facing a patient who has had surgery need to understand the nature of the pathophysiological processes caused by CE for a correct evaluation of clinical symptoms and selecting the most optimal therapy to correct the disorders.

GB rejection due to the loss of GB physiological functions leads to functional reorganization of bile-excreting system, including complex neurohormonal interactions and being effective compensatory mechanism that contributes to the current slowdown and the concentration of bile in the ducts. In violation of adaptive-compensatory abilities of hepatobiliarypancreatoduodenal system due to GB lack, there are prerequisites for progression of PCES. Some operated patients do not note such an adaptation, a variety of clinical manifestations of PCES are being developed.

In our view, PCES is a functional disturbance that develops after CE due to GB lack. According to renowned gastroenterologist Y. S. Zimmermann, "the term "PCES" in the true sense of the word should be used only in cases where it is caused by deposition of GB functions in connection with its disposal". Experimental and clinical observations revealed that loss of GB function is reflected in the work of sphincter apparatus of the biliary tract. There is no consensus on the nature of the functional state of OS upon CE. Some authors point to increased tonus of MDP sphincter, and this explains the expansion of the common bile duct after surgery. Others believe that as a result of CE its insufficiency develops, since OS can’t maintain over time a high pressure of the liver. Currently there is a prevailing view that OS hypertonicity is being developed after CE, and in the first month after surgery this pathology is found in 85.7% of patients.

According to the Rome Consensus on functional disorders of the digestive system (1999), instead of the term "PCES" it is recommended to use the term "SO dysfunction". PCES is considered as dysfunction of OS caused by a violation of its contractile ability that prevents the normal outflow of bile and pancreatic secretions into the duodenum in the absence of organic interference.

According to the Rome criteria III, the following functional biliary disorders are distinguished: functional GB disorders, functional biliary OS disorders and functional pancreatic OS disorders. OS is a fibro-muscular sheath covering the final section of common bile and pancreatic duct and common channel in place of their passage through the wall of the duodenum. The main functions of OS include: adjusting the frequency and secretion of bile and pancreatic juice into the duodenum, preventing reflux of duodenal contents in the choledoch and pancreatic duct, providing the accumulation of hepatic bile in GB. GB rejection leads to disruption of deposition of bile and SO motility. Duodenitis is accompanied with duodenal dyskinesia, hypertension and reflux of content in common bile and pancreatic ducts. Dyskinesia of OS, as well as its components, is being developed — the sphincters of the bile and pancreatic ducts. Development of OS dysfunction after CE is almost inevitable. Pankreozymin-cholecystokinin (CCK-PZ) is a hormone produced by cells

of the mucous membrane of the duodenum and proximal jejunum, which stimulates GB contraction and OS relaxation during digestion. Out of digestion reversible change occurs — GB relaxing and filled with bile, and the tone of OS increasing, preventing the continuous penetration of bile into the duodenum. GB mucosa produces CCK-PZ antagonist — anticholecystokinin hormone that limits the effect of CCK-PZ and decreases in inter-digestion period GB relaxation and increased tone of OS [15]. After CE, when production of this hormone stops, CCK-PZ stays active longer, and therefore SO dysfunction is formed, usually with a predominance of spasm, at least — because of insufficiency of "chaos", impairment of regulatory mechanisms [14]. Many studies demonstrated reduction of reaction of OS on cholecystokinin after CE. This operation is a prerequisite for OS hypertonus, expanding extra- and intrahepatic bile ducts. In some cases, after surgery the tone of OS can be lower and insufficiently concentrated bile can enter the intestine regardless of the phase of digestion. In addition to CCK-PZ and anticholecystokinin, other gastrointestinal hormones, such as secretin, motylin, somatostatin, vasoactive intestinal peptide, pancreatic polypeptide enteroglucagon et al. are involved in the regulation of contractions and tone of GB, OS and other biliary sphincters (Lyutkens, Mirizzi).

The formation of functional OS impairment is promoted by psycho-emotional state of the patient, neurohumoral dysregulation of motor function of the biliary system, change of viscero-visceral response with increasing pain sensitivity, disturbance of duodenal tone, MDP irritation, OS spasm, spasm of smooth muscles of the walls of the gastrointestinal tract, and others. Due to the loss of contractile GB function, gastroduodenal motility worsens. GB serves as a kind of pump, with a reduction of which not only the release of bile happens, but normal intraduodenal pressure is maintained. In the absence of the "pump", duodenostasis and discoordination of gastroduodenal motor complex are being developed. Duodenitis is accompanied with duodenal dyskinesia, hypertension and reflux of content in common bile and pancreatic ducts.

Secretory GB function is evident in secretion of biliary mucus, and the tank one — in maintaining bile, most of which (50-90%) gets into GB in concentrated form. Consequently, the dilatation of the bile duct is possible. Of course, stretching of its walls causes pain. With GB removal, above-mentioned functions disappear. Absorption GB feature is closely related to its concentration function. GB is able to absorb 10-30% of the contents as a result of the active absorption of NaCl and NaHCO3 with water. This leads to the 50-times increased concentration of remaining constituents (bile salts, lipoprotein complex, pigments).

In 70-80% of patients after CE signs of high bile lithogenicity with low cholato-cholesterol coefficient are diagnosed. Loss of GB physiological function (concentration of bile in inter-digestion time and its release into the duodenum during digestion) is accompanied by the passage of bile into the intestine, digestive disorders, the emergence of diarrheal disorders (diarrhea, constipation, bloating, symptoms of duodeno-gastric reflux, gastroesophageal reflex disease). These manifestations occur after CE due to changes in the chemical composition of bile and its chaotic entering the duodenum. Digestion and absorption of fat and other substances of lipid nature is reduced, bactericidal duodenal contents is reduced too, resulting in microbial contamination of the duodenum, growth of normal flora is reduced. Under the action of microorganisms, bile acids are exposed to premature deconjugation accompanied by damage to the mucous membrane of the duodenum, small and large intestine with the development of duodenitis, colitis, gastritis reflex.

GB rejection demands restructuring the processes of bile formation and biliary excretion. After CE choleresis is increased by both acid and acid-dependent fraction. Increased bile occurs just in two weeks after CE. Increasing holeresis is the main cause of diarrhea after cholagenic CE. Among the organs of hepatopancreatoduodenal area, GB rejection has the most pronounced effect on the function of the pancreas. Development of CP with biliary pathology contributes to the functional disorders (dysfunction of the sphincter apparatus of bile ducts), which are quite common in patients undergoing CE. A variety of forms of CP and severity of objective assessment of the pancreas leads to the fact that in some patients the disease

is not diagnosed, and in some cases there is an overdiagnosis. In this regard, the incidence of CP after CE is quite wide and is equal to 5-90%. The longer is stones-carriage, the more common is CP, the heavier is its course.

Long existing pathological changes that occur in the pancreas upon the diseases of the biliary tract, leading to swelling of the intermediate tissue due to the inflammation as a result of subsequent degenerative disorders that can lead to a restructuring of tissue with the development fibrosis. These changes are reflected in the functional state of the pancreas: volume of secretion of enzymes and bicarbonate production rate is reduced, and this occurs in the early stages of the disease. In this regard, one of the causes of unsuccessful results of operations is sustained breach of enzyme-producing function of the pancreas. Well-timed and technically well-made CE, particularly in the early stages of gastrointestinal diseases, does not affect the functional status of the pancreas. It should be noted that the full restoration of patency of the bile and pancreatic ducts helps to eliminate or reduce the severity of pathological changes in the pancreas. Regeneration of pancreatitis comes with their increased activity. Reparative processes begin with the stroma and are characterized by regression of connective tissue, then move on to the parenchyma, which helps restore the functional activity of the organ. CE improves or normalizes exocrine pancreatic function in 62.5% of patients with GSD. Secretion of trypsin (up to 6 months) is primarily renewed, while the normalization of amylase activity comes much later, only in 2 years. However, in the long course of the pathological process, the full restoration of damaged tissues does not occur. Clinical manifestations of CP can appear at any time after surgery. Most often, they occur in the first 6 months and did not differ from the clinical picture of the disease itself.

In patients with GSD after CE the process of lithogenesis in biliary tract continues: biliary sludge is stored, and incidence of microlites increases by almost half. This leads to the violation of the outflow of bile, the occurrence of dyskinesia OS and scarring in the area, increasing pressure in this area and choledochal and Wirsung’s duct dilatation. Finally, as a result of these changes comes the

development of more severe structural changes in the pancreas, its fibrosis. In general, all these abnormalities contribute to the progression of CBP [3].

Patients with GSD and after CE have manifestations of syndrome of bacterial overgrowth in the small intestine. This is because after CE the concentration of bile acids and its antibacterial properties is reduced. To restore normal outflow of bile in GB absence of OS patency, the pressure in the duodenum is of great importance. The main mechanism of duodenal hypertension is excessive detention of liquid and gas in the lumen of the duodenum as a result of putrefactive fermentation processes due to microbial contamination [8].

Conclusions:

1. In patients with chronic pancreatitis clinical manifestations after cholecystectomy may be associated with: 1) a change in the chemical composition of the bile; 2) a violation of its passage into the duodenum; 3) Oddi's sphincter dyskinesia; 4) development of bacterial overgrowth in the gut.
2. Upon postcholecystectomical syndrome, development and progression of exocrine pancreatic insufficiency occurs not only due to the initial decrease in pancreatic enzymes production, but also because of cholagenic pancreatic insufficiency, secretory cholagenic diarrhea, bacterial overgrowth syndrome in the intestine, enterogenic pancreatic insufficiency.

Conducted analysis shows the perspective of reasonability of in-depth studying the dependence of clinical course and trophological disorders upon CP on the present done CE or other surgical invasions.

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Pathogenic aspects of the chronic pancreatitis of biliary genesis after cholecystectomy

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This article presents an analysis of the literature on the pathogenetic aspects of the influence of cholecystectomy on the course of chronic pancreatitis. It is stated that in patients with chronic pancreatitis clinical manifestations after cholecystectomy may be associated with: 1) a change in the chemical composition of the bile; 2) a violation of its passage into the duodenum; 3) Oddi's sphincter dyskinesia; 4) development of bacterial overgrowth in the gut. Upon postcholecystectomical syndrome, development and progression of exocrine pancreatic insufficiency occurs not only due to the initial decrease in pancreatic enzymes production, but also because of cholagenic pancreatic insufficiency, secretory cholagenic diarrhea, bacterial overgrowth syndrome in the intestine, enterogenic pancreatic insufficiency.