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HEPATIC FAILURE IN PANCREONECROSIS AND THE DEVELOPMENT OF ABDOMINAL SEPSIS

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ПЕЧЕНОЧНАЯ НЕДОСТАТОЧНОСТЬ ПРИ ПАНКРЕОНЕКРОЗЕ И РАЗВИТИИ АБДОМИНАЛЬНОГО СЕПСИСА

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Abstract. It is well known that acute destructive pancreatitis, pancreonecrosis is accompanied by severe endogenous intoxication, often leading to the development of multiple organ failure syndrome, liver failure is one of the important links in this process. The mortality rate of patients with pancreonecrosis related to liver failure is as high as 83%, and approximately 5% of patients with pancreonecrosis have fulminant liver failure. Proven: liver function is closely related to the progression of purulent-necrotic complications in patients with acute destructive pancreonecrosis. The authors present the data of literature on the importance of liver failure in the course and prognosis of acute destructive pancreatitis. The pathogenetic role of lipid peroxidation processes are especially emphasized. The controversial issues of portal and systemic bacteremia and toxemia in the development of pancreatogenic abdominal sepsis are discussed, as well as the involvement of the lymphatic system. The authors' research aims to analytically dissect and summarize

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the processes underlying the clinical manifestations of liver failure in pancreatic necrosis and their underlying mechanisms, which may provide new insights for further understanding and better management of liver failure in patients with pancreatic necrosis and abdominal sepsis.

Аннотация. Известно, что острый деструктивный панкреатит, панкреонекроз сопровождается тяжелой эндогенной интоксикацией, часто приводящей к развитию синдрома полиорганной недостаточности; печеночная недостаточность является одним из важных звеньев этого процесса. Летальность больных панкреонекрозом, связанная с печеночной недостаточностью, достигает 83%, а примерно у 5% больных панкреонекрозом наблюдается фульминантная печеночная недостаточность. Доказано: функция печени тесно связана с прогрессированием гнойно-некротических осложнений у больных острым деструктивным панкреонекрозом. Авторы приводят данные литературы о значении печеночной недостаточности в течение и прогнозе острого деструктивного панкреатита. Особо подчеркивается патогенетическая роль процессов перекисного окисления липидов. Обсуждаются спорные вопросы портальной и системной бактериемии и токсемии в развитии панкреатогенного абдоминального сепсиса, а также участие лимфатической системы.

Keywords: acute destructive pancreatitis, liver failure, lipid peroxidation, kallikrein-kinin system, endogenous intoxication, bacteremia.

Ключевые слова: острый деструктивный панкреатит, перекисное окисление липидов, калликреин-кининовая система, эндогенная интоксикация, бактериемия.

According to modern concepts, severe purulent-necrotic forms of acute destructive pancreatitis (hereinafter referred to as ADP), including secondary purulent pancreatogenic peritonitis, retroperitoneal pancreonecrosis, septic phlegmon and retroperitoneal abscesses, are qualified as abdominal sepsis (AS) with multiple organ dysfunction syndrome (MODS) and septic shock [1].

In ADP in the reactive phase of the disease, the outcome depends on the accession of infection and the development of various purulent complications up to sepsis [2-4], which is observed in 40-70% of cases, and mortality is 70-85% [3-8].

The spread of the purulent process to the retroperitoneal fibre significantly aggravates the course of the disease and increases mortality from pancreatic shock and purulent-septic complications [9]. However, the main cause of mortality in this case is dysfunction of one or more organs/systems [4, 10, 11] due to the development of abdominal sepsis [12, 13].

There are review articles on the significance of liver failure in ADP and its significance in increasing the severity of the disease and mortality [14, 77], pancreonecrosis in 41.5% [7].

It is the cause of death in 40% of cases, and in destructive forms - in 90-95.2% [19-21, 69, 78]. In ADP, extra-organ complications are present in 60-95% of patients [15, 16]. Therefore, the study of mechanisms of liver failure development in destructive forms of pancreatitis, their role in the development of abdominal sepsis is an urgent task for surgeons.

Purpose of the study: to investigate and summarise the results of researchers for the last 10 years, devoted to the search and study of the pathogenesis of liver failure development in patients with destructive form of pancreatitis (pancreonecrosis).

Search Strategy of the study: we conducted a review of scientific papers of researchers for the last 10 years, using search resources of publications from journals in Europe, Canada and the USA (PubMed, Medline, Scopus, as well as CIS and RK countries).

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Influence of liver failure in acute destructive pancreatitis and its significance in increasing the severity of the disease and lethality: the characteristic feature of acute ADP is a high level of endogenous intoxication almost immediately during the transformation of acute pancreatic oedema into haemorrhagic/fatty pancreonecrosis [22, 23], in the structure of which the liver is present in 56.1% of cases [24, 25] and largely determines its severity [26-28].

In ADP, like pancreatogenic shock, MODS is formed during the first week of the disease (enzymatic phase) against the background of severe intoxication and marked haemodynamic disorders [29].

In acute destructive pancreatitis (ADP) the frequency of functional liver failure ranges from 18% to 83.9% [30-32] and is the main cause of death in 12.6-40% of cases [17-20].

According to the data of S. A. Alekseev et al. [33], based on 89 autopsies of persons who died from acute destructive pancreatitis, in 52.8% of cases there was hepatic failure with outcome in hepatorenal syndrome. In pancreonecrosis, the onset and development of acute HF often predetermines the severe course and prognosis of the disease, since it is the liver that is the first and the main barrier to the toxins coming through the portal vein from the pancreas and from the peritoneal cavity [34, 35].

The role of activation of lipid peroxidation (hereinafter referred to as LPO: endogenous intoxication is of a specific nature in ADP due to the fact that in the tissues of the pancreas, due to marked alteration and predominance of catabolic processes, there is a decompensation of regulatory systems with the accumulation of high concentrations of effector products. The amount of proelastase decreases, histamine, phospholipases are released in the presence of kallikrein and bile acids (in cholangiogenic pancreatitis), bradykinin and kallidin release occurs under the action of pancreatic kallikrein. The pathogenesis of liver cell damage is based on the activation of lipid peroxidation processes, electrolyte balance disorders, cascade enhancement of fat-dependent processes with the inability of cells to compensate for the necessary energy expenditure [25, 36].

In infected pancreonecrosis (abdominal sepsis), increasing metabolic disorders are accompanied by hypoalbuminemia, increased intoxication, immune system depression and bacteraemia [2,, 3, 68].

Damaging factors alter cell membranes with disruption of intracellular homeostasis and release of toxic products of incomplete and perverted metabolism with their entry into the interstitial space and blood [38, 39].

The amount of proelastase decreases, histamine and phospholipases are released in the presence of kallikrein and bile acids (in cholangiogenic pancreatitis), bradykinin and kallidin are released under the action of pancreatic kallikrein. Most authors believe that in pancreonecrosis activated pancreatic and lysosomal enzymes, biologically active substances, toxic decay products of pancreatic tissues at necrobiosis and activation of the kallikrein-kinin system enter the liver via the portal vein [25, 37, 41]; the result is hepatic failure. Although, V.S. Tarasenko et al. [42] indicate that in acute pancreatitis, exo- and endotoxins from the systemic circulation enter the liver. According to A. N. Plekhanov and D. N. Reshetnikov [19], significant changes in destructive pancreatitis occur in porto-hepatic haemodynamics. This is manifested by a reliable decrease in the diameter of the portal vein and linear velocity and volume blood flow in it. Similar data are established in relation to the superior mesenteric vein, whereas the volume blood flow in the hepatic artery does not significantly change. Moreover, the degree of reduction of porto-hepatic haemodynamics was in direct correlation with the severity of PH.

Cytokine and inflammatory cascade, inflammatory mediators: as a result of increasing endotoxicosis and direct action of toxins already at early stages of disease development they interact with endothelial cells of hepatic sinusoids and lead to a decrease in blood flow due to pre-capillary

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contraction due to increased production of alpha-actin by smooth muscle cells [44-46] microcirculatory disorders occur [47, 48, 72, 73].

At the same time, the production of pro-inflammatory cytokines increases, capable of releasing a large amount of H_2 O_2 and active oxygen radicals. The latter, acting on the cell membranes of hepatocytes, disrupt their integrity, i.e. have a cytolytic effect. In addition, the activating effect of cytokines leads to an increase in the procoagulant activity of the endothelium and intravascular hypercoagulation with aggravation of intrahepatic haemodynamic disorders [49]. According to V.S. Tarasenko et al. [42]: this subtle regulatory mechanism is aimed at temporary isolation of the liver parenchyma from the extraordinary stimulus. However, the state of hypertonus, which probably takes place in pancreonecrosis, from protective can become the basis for the development of pathological process as a result of ischaemia and hypoxia.

Studies of a number of authors testify: during the period of functional insufficiency of parenchymatous organs final and intermediate products of catabolism and other substances of toxic action accumulate. There is a disorder of macro- and microcirculation, which leads to a violation of virtually all types of metabolism: carbohydrate, fat, water-electrolyte, bile formation, protein-synthetic, detoxification, haemostatic. As well as reticulo-endothelial system, endocrine metabolism, immunological, etc. [43, 50], which leads to a sharp disturbance of blood circulation, hypoxia and morphological changes in the liver [42, 51].

Microcirculation disorders of the liver and pancreas: research results proved that gross microcirculatory disorders occur as a result of a decrease in the linear velocity of blood flow in capillaries, disturbance of blood rheological properties due to the aggregation of formate elements and platelets, thrombosis and haemocoagulation, the consequence of which is initially circulatory and then circulatory-metabolic hypoxia [35,52] with activation of lipid peroxidation (LPO) [53,].

Lefkowitch J. H., Saveliev V. S. in their works proved that as the inflammatory-destructive process in the PG progresses with the formation of necrotic and purulent forms, the second stage of intoxication development begins with the appearance in blood and lymph, mainly products of proteolytic and lipolytic necrosis. In the period of haemodynamic disorders (enzymatic phase), the main pathogenetic mechanisms are enzymeemia, activation of the kallikrein-kinin system and arachidonic acid cascade with the formation of prostaglandins and leukotrienes. A pronounced endotoxicosis syndrome - pancreatogenic toxaemia syndrome is formed [54].

There is an "evasion" of toxins into the portal vein tributaries into the blood and lymphatic vessels [54-56].

Thus, multicomponent pacreatogenic toxaemia, in the path of which the liver is the first target, is carried out due to highly toxic and aggressive pancreatic and lysosomal enzymes, biologically active substances, and decay products of PU tissues as a result of necrobiosis and activation of the kallikreinkinin system [15, 57, 58]. In half of the cases of PU develops against the background of functional inferiority of the liver. Endogenous intoxication, microcirculation disorders, decreased linear blood flow velocity in capillaries, deterioration of blood rheological properties, as well as sharp activation of catabolic processes increase tissue oxygen demand, which leads to the development of circulatory-metabolic hypoxia and intensification of lipid peroxidation processes not only in the liver, which is very sensitive to all types of hypoxia [59, 60], but also in all parenchymatous organs [18, 48, 52]. In this case, a significant role belongs to the sharply increased activity of the kallikreinkinin system in blood and lymph [52, 54, 61].

The lymphatic hypertension observed in this case increases the concentration of toxic products and protease activity in lymph [50].

There is an insufficiency of compensatory capabilities of the antioxidant system in the liver as a result of its degeneration, which leads to an increase in necrotic processes with the development

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of acute liver failure [15, 62, 71]. Steadily increasing endotoxaemia is accompanied by disturbances of macro- and microdynamics not only in PD itself, but also in the whole organism [18, 48], as it is believed to be a result of sharply increased activity of the kallikreinkinin system in blood and lymph [52, 54, 61].

Discussion

Thus, the leading mechanisms of functional liver disorders in acute pancreatitis are deep microcirculatory disorders, degenerative-dystrophic changes of hepatocytes and decompensation of reparative capabilities. There is purulent and putrefactive decay of the liver and adjacent retroperitoneal fibre with formation of phlegmon and abscesses.

So according to A. N. Plekhanov and D. N. Reshetnikov [19], the clinical and biochemical syndrome of PN includes: frequent hyperbilirubinaemia, increased activity of cytolytic enzymes, discoordination of carbohydrate and protein metabolism. Patients have jaundice (in 100% of cases), skin itching (in 43,3%), hepatosplenomegaly (in 41,6%), hepato-cerebral syndrome (in 5%). Diagnosis of PN is based on biochemical indicators of cytolysis (ALT, AST, LDH), cholestasis (bilirubin, alkaline phosphatase), synthetic liver function (total protein, albumin, triglycerides) [37, 40, 41].

However, according to M.A. Nartaylakov et al. [7], in infected pancreonecrosis there is a pronounced hypercatabolism syndrome, so the level of total protein and its fractions in blood serum is not an adequate marker of acute PN. In addition, in some patients laboratory indicators of cytolysis can remain above normal values for a long time - up to a month. In this regard, the authors, as well as other researchers [27, 37, 74.], consider the concentrations of total bilirubin, alkaline phosphatase and triglycerides in serum to be the most reliable.

According to V. I. Filin [63], in experimental acute haemorrhagic pancreatitis in the first 6-12 hours in the liver tissue there is irregular hemorrhage with congestion in some lobules, focal necroses around vessels, in some places focal destruction of cells with pronounced discomplexity. Already at early stages in patients with acute pancreatitis there are changes in the histological structure of the liver (hepatocytes and reticuloendothelial elements) - morphological picture of acute hepatitis [22, 30, 42, 54, 64].

Apoptosis of hepatocytes is observed. As a number of studies have shown - it is also one of the factors leading to liver failure [75, 76].

It is worth agreeing with the opinion of a number of authors: apoptosis is observed in the endoplasmic reticulum (ER) in cells. The endoplasmic reticulum is the largest membrane organelle in the cell and it controls the processing, modification and synthesis of a large number of proteins in the cell. When the environment in the ER, which is characterised by oxidation and high calcium concentration in severe endotoxicosis, it breaks down - this leads to the accumulation of misfolded proteins in the ER, resulting in severe ER stress. In patients who died as a result of acute pancreonecrosis at microscopy of liver tissue, dystrophic and degenerative changes (toxic fatty, protein, granular dystrophy), foci of necrobiosis and necrosis, infarcts are often found [22, 54, 63]. According to S. A. Alekseev et al. [33], there is edema of the interstitial space of hepatocytes (in 76.6% of cases), lymphoid-neutrophil infiltration of portal tracts (65.9%), centrilobular necrosis of hepatocytes (75.7%), microcirculatory channel disorder (75%). All dystrophic and degenerative changes of hepatocytes in pancreonecrosis are associated with massive apoptosis processes. Toxic damage to organs/systems (liver, kidneys, adrenal cortex, as well as nervous, cardiovascular, respiratory and immune systems) forms the MOD syndrome [17, 23, 50, 63, 65, 66].

In general, extra-organ complications in patients with DLD occur in 60.8-96.5% of cases [39, 54, 67, 70].

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Summarizing the research results, we can highlight the following points in the pathogenesis of the development of liver failure in abdominal sepsis:

1. Activation of lipid peroxidation processes plays an important role in the development of functional and structural disorders of pancreatocytes and the organism as a whole. The level of antioxidant activity of pancreas tissue is one of the lowest in the organism.

2. Functional liver failure significantly aggravates the course of acute pancreatitis and worsens the prognosis of the disease.

3. Excessive intensification of lipoperoxidation processes is an important pathogenetic link in the mechanism of damage to cell membranes and lysosomal structures in the development of cytolysis, which determines the severity of destruction in the liver.

4. In infected pancreonecrosis, abscesses and septic retroperitoneal phlegmon, i.e. complicated acute destructive peritonitis or abdominal sepsis, acute liver failure is accompanied by immune system depression, so-called secondary sepsis-induced immunodeficiency and bacteraemia.

5. Moreover, systemic toxaemia and bacteraemia may occur earlier or simultaneously with the breakthrough of the protective hepatic barrier, located on the path of microorganisms and their toxins to the liver via the portal vein. Since from the retroperitoneum resorption of infected and toxic exudate occurs in the retroperitoneal veins, which are tributaries of the inferior vena cava (lumbar, lower diaphragmatic veins, etc.) or superior vena cava (unpaired and semi-unpaired veins). In addition, in secondary purulent pancreatogenic disseminated peritonitis, everything that is absorbed into the blood vasculature by the parietal peritoneum is also transported into the systemic venous channel, bypassing the v. hornblende. Lymphatic vessels, which in the parietal peritoneum are located closer to the surface than blood vessels and perform purely drainage function. Lymph passing through the lymph nodes eventually flows into the thoracic duct and then into the left venous angle.

Main results

1. Activation of lipid peroxidation processes plays an important role in the development of functional and structural disorders of pancreatocytes and the organism as a whole. The level of antioxidant activity of pancreas tissue is one of the lowest in the organism.

2. Functional liver failure significantly aggravates the course of acute pancreatitis and worsens the prognosis of the disease.

3. Excessive intensification of lipoperoxidation processes is an important pathogenetic link in the mechanism of damage to cell membranes and lysosomal structures in the development of cytolysis, which determines the severity of destruction in the liver.

4. In infected pancreonecrosis, abscesses and septic retroperitoneal phlegmon, i.e. complicated acute destructive peritonitis or abdominal sepsis, acute liver failure is accompanied by immune system depression, so-called secondary sepsis-induced immunodeficiency and bacteraemia.

5. Moreover, systemic toxaemia and bacteraemia may occur earlier or simultaneously with the breakthrough of the protective hepatic barrier, located on the path of microorganisms and their toxins to the liver via the portal vein. Since from the retroperitoneum resorption of infected and toxic exudate occurs in the retroperitoneal veins, which are tributaries of the inferior vena cava (lumbar, lower diaphragmatic veins, etc.) or superior vena cava (unpaired and semi-unpaired veins). In addition, in secondary purulent pancreatogenic disseminated peritonitis, everything that is absorbed into the blood vasculature by the parietal peritoneum is also transported into the systemic venous channel, bypassing the v. hornblende. Lymphatic vessels, which in the parietal peritoneum are located closer to the surface than blood vessels and perform purely drainage function. Lymph passing through the lymph nodes eventually flows into the thoracic duct and then into the left venous angle.

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Conclusion

In acute purulent-necrotic destructive pancreatitis acute liver failure is an integral component of the multi-organ failure syndrome that develops to severe abdominal sepsis.

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