**Etiological significance of the hepatitis C virus among other infectious factors of chronic pancreatitis**

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**Key words:** pancreas, chronic pancreatitis, etiology, pathogenesis, infectious factors, hepatitis C virus

**Introduction.** The problem of chronic pancreatitis (CP) is one of the most urgent in modern medicine. In recent years, attention has increased to the infectious agent, which can cause the development of inflammatory process in the pancreas.

**Aim of study** is to assess the role of infection in the occurrence of pancreatitis on the background of studying literary sources.

**Main part**. CP is one of the topical diseases in modern medicine. It is liver and psoriasis that are the most serious pathologies of the gastroenterological profile, as they often lead to the disability of working-age patients, require long-term treatment and follow-up of patients for a long period of time. With a combined liver injury and a prognosis for recovery, it is rarely favorable for recovery, since treatment tactics are particularly complicated [3]. Significantly increased prevalence of pathology of the digestive system in recent years and in Ukraine. Thus, the prevalence of chronic hepatitis from 2008 to 2012 increased by 2.2 times, the incidence of pancreas — by 3.2 times. According to the Center for Medical Statistics of the Ministry of Health of Ukraine for 2006–2013, the rates of hospitalization in the chronic course of pancreatitis increased by 30.2%. At the same time, in the vast majority of patients, gastroenterological clinics are diagnosed with several diseases, and one of the most common diseases that occurs in association with chronic hepatitis and cirrhosis of the liver is the CP [3]. The adverse conditions that have emerged in recent decades, namely the epidemic of viral hepatitis, the increase in alcohol consumption, the prevalence of obesity and metabolic syndrome, and consequently non-alcoholic steatohepatosis, cause a further increase in the number of patients with terminal liver disease, the peak of which, according to epidemiological analysis, for 2010–2020 [2].

The basis of the development of chronic recurrent pancreatitis (CRP) is the damage of acinar cells of the pancreas by various exogenous and endogenous factors, among them the most commonly used chronic alcoholism (from 25 to 80%) and diseases of the biliary system (from 25 to 40%). In 5% of cases CRP refers to "idiomatic" diseases, the cause of which it is impossible to establish with the use of modern diagnostic methods [6].

In recent years, more and more attention is paid to the infectious agent, whose influence may lead to the development of inflammation in the pancreas. The reasons for its occurrence may be epidemic parotitis, hepatitis virus, enterovirus, adenovirus, Coxsackie viruses, mycoplasmosis, salmonella, helminthiasis, and other infections [7].

Over the past 25 years, experimental and clinical data have been accumulated confirming the involvement of herpes viruses, including cytomegaloviruses, in the pathogenesis of atherosclerosis, which is one of the factors of the onset of CP. This idea was first introduced in 1973 by E. Benditt and J. Benditt, who proposed the theory of "benign neoplasia", according to which the atherosclerotic plaque develops as a result of the clonal expansion of a single cell, the mutation of which is caused by the influence of the viral agent [7].

The main biological and pathogenetic features of herpesvirus are their lifelong persistence in the body at least once infected by humans, the strongest dependence of the course of the chronic infectious process on the state of immunity of the virus carrier and the tendency to relapse [7]. Recurrent herpetic infection of the maxillofacial area in 89% of cases is combined with erosive-ulcerative lesions of the gastroduodenal zone, 57% — with pathology of biliary tract, 68% — with intestinal diseases, 31% — in pancreas, 97% — ENT pathology, 62 % — diseases of the genitourinary system, in 42% of cases — with diseases of the respiratory system [1].

The role of cytomegalovirus infection (CMVI) in the occurrence of CRP is most likely to be considered. In recent years, it has been shown that specific CMVI antibodies are detected in 90% of the adult population. Matter is more rare than the antibody titer exceeds the critical values ​​characteristic of latent CMVI [6].

Principal and distinctive features of CMVI are the widest range of clinical and pathogenetic variants of infection and the possibility of lesion of any organs and systems of humans [6].

At present, many researchers associate the development of atherosclerosis with the immune-inflammatory process in the vascular wall, which occurs in response to damage to the endothelium by various agents and, in particular, cytomegalovirus, with subsequent alteration of the matrix of vessels with lipids [6].

It has been proved that CMVI can increase the atherogeny of low density lipoprotein, suppress the activity of enzyme systems that carry out the hydrolysis of cholesterol fats, and suppress the anticoagulant properties of the endothelium [6].

Consequently, the development and progression of coronary heart disease and CRP are characterized by similar pathogenetic mechanisms that undergo a stage of inflammation [6].

Cytomegalovirus damages the pancreas with the appearance of symptoms of CP. With the expanded clinical picture of herpesvirus infections (CMVI, Epstein-Barr virus), various clinical diagnoses, including hepatitis, pancreatitis, are presented by the therapists [7].

Nowadays, from known hepatitis viruses, the ability to chronic infection is proven for HBV, HCV, and HDV (which exists in the body only in the presence of HBV and HGV). For these viruses, identical ways of spread (including blood and blood products) and prolonged persistence in the body are characteristic. There were reports of individual cases of chronic hepatitis A, which indicate the possible persistence of HAV. One of the most important recent discoveries of recent years are the establishment of the fact of the replication of HBV and HCV in tissues of lymphatic and non-lymphatic origin. This contributed to the understanding of the pathogenesis of the multiplicity of lesions, which is observed in these infections, which makes it possible to consider viral hepatitis not as a liver disease, but as an infectious disease, or a systemic (generalized) infection [7].

The urgency of the problem of chronic viral hepatitis (HCV) is due to their widespread and progressive course, with the formation of part of patients with cirrhosis. At present, most cases of cirrhosis are due to hepatitis C virus, C and B + C [2]. A much more complicated situation arises in the case of the disease with viral hepatitis C, which is characterized by an asymptomatic (anesthetized) course with subsequent development of the chronic process in 80% of patients. HCV has a wide range of clinical manifestations — from forms with minimal activity to severe progressive with the development of cirrhosis and primary hepatocellular carcinoma. In part of patients, HVGS is formed after acute hepatitis C, with a clearly observed pattern: acute hepatitis — chronic hepatitis — cirrhosis — cirrhosis — liver cancer. In other patients, there is no episode of acute infection in the history. HVGS for a long time runs through the type of persistent with the minimum expressed clinical and biochemical signs of the activity of the process, which is the cause of late diagnosis [5]. Often, from the moment of infection to the first signs of infection, a long latent period passes. There are a number of factors that have a negative impact on the natural course of HVGS: age more than 40 years before the date of infection, male sex, race (non-European), alcohol abuse, obesity, metabolic disorders, metabolic syndrome [5].

Of particular importance is the development of pancreatitis against the background of the viral infection B and C. The pathogenesis of the lesion of pancreas, as well as the liver, consists of replication of viruses in these organs, heterogeneity of genotypes and mutation of genomes of viruses, direct cytopathic effect (for HCV), immunopathological changes in liver and pancreas, common immunological disorders. Thus, HBV antigens and HBV DNA in integrative and replicative forms are found in the acinar, duct, endocrine cells of the pancreas, and in HBsAg — and in pancreatic secretion. In 1998, a number of researchers identified HCV RNA in the tissues of pancreas in 3 out of 8 deaths due to various clinical variants of HCV infection. As for immunopathological changes, they, as with liver diseases, and in cases of a combination of these diseases with pancreatitis, can be represented by two variants: a combination of the reaction of HRT with immunocomplex processes and the pathology of predominantly immunocompetent genesis. In the first case, parenchymal dominated, in the second — vascular (vasculitis) changes, with special importance attached to mixed cryoglobulinemia (especially with HCV infection). In the part of patients with HBGS there is a syndrome of Sjogren ("dry" syndrome: sialoadenit + keratoconjunctivitis + pancreatitis with external secretion insufficiency of pancreas). Damage to pancreas for viral hepatitis B and C can be manifested in the form of diabetes mellitus associated with the replication of viruses in the endocrine cells of the body, as well as with the immunopathological process. More often, diabetes develops with chronic HCV infection. Moreover, in such patients in the blood increases the titer of autoantibodies to insulin and develops resistance to it [4].

It is possible to distinguish the following features of the course of HVG B and C:

* presence of markers of HCV- or HBV-infection;
* combination with chronic hepatitis or cirrhosis of the liver;
* absence or minimum severity of pain syndrome;
* absence of clear hyperenzymemia (cytolysis and acinar cells, hepatocytes);
* manifestation of minimal, slowly progressing symptoms of external secretion insufficiency of pancreas;
* often the damage to the pancreas runs through the type of indurational-fibrous ("pseudotumorosis") pancreatitis with extrahepatic cholestasis [4].

Since pancreas is a powerful source of digestive enzymes synthesis and the most sensitive to damage from the organs of the abdominal cavity, the violation of its function is manifested by the formation of external secretion insufficiency, and as a result — syndromes of maldigestion and malabsorption. In this case, the violation of the functional state of pancreas is not always accompanied by gross changes in its structure [9].

The Enterovirus RNA gene-flanked non-transmitted site (NTR) together with 5 'NTR coxackie virus B3 (CVB3) of type 1 forms a protozoal virus (poliovirus). The resulting "fantastic" virus (CPV / 49) is copied in pancreatic cysts and causes inflammation in the tissues of the pancreas. One vaccine with the introduction of CPV / 49 into experimental mice stimulates protective anti-CVB3 in neutralizing antibody titres, which completely protects animals from pancreatic disease [7].

There is an acute onset of type 1 diabetes after severe echovirus infection. The department of medical microbiology at the University Hospital Nijmegen (The Netherlands) believes that infectious diseases, in particular caused by enteroviruses, lead to the development of type 1 diabetes. Two possible mechanisms of this process were considered: the virus destroys β-cells by cytolysis or promotes the development of autoimmune events. The viruses were isolated and cultured from β-cells. Coxsackie viruses were actively reproduced in Serotype 3, and all ended in a rapid increase in their numbers and the massive death of β-cells. Ecoviruses did not multiply when cultured in β-cells, no antibodies to the components of the latter and direct cytolytic action on β-cells were detected. The authors conclude that enteroviruses cause diabetes mellitus using other mechanisms [7].

For insulin-dependent diabetes, seasonal morbidity is characteristic: recovery occurs in the autumn and winter months with peak in October and January, with a minimum of new cases of diabetes being noted in June and July. The maximum incidence of diabetes in children was noted at the age of 5 and 11, which is probably due to the possibility of influencing the development of various viral diseases. At present it is believed that in animals, the emergence of diabetes mellitus promotes the transmission of encephalomyocarditis, Coxsackie, type II meningitis, reovirus type 1 and type 2, rubella virus. In humans, the pathogenesis of insulin-dependent diabetes plays a role in the Coxsackie B-3 and B-4 viruses, type 3 retroviruses, mumps virus, cytomegalovirus and congenital rubella. Other viruses (hepatitis, etc.) are much less involved in the onset of diabetes if they are involved at all. The role of viral infection in the origin of diabetes is likely to be that viruses initially cause damage to β-cells in individuals with a genetic predisposition to such a deterioration. As a rule, from the moment of the appearance of a viral disease before the onset of diabetes occurs a certain period [7].

Pancreatitis often develops in AIDS, but because of its latent course, physicians do not pay attention to the state of the pancreas. In a survey of 86 HIV-infected people who did not have clinical manifestations of pancreatitis, 52 of them (60%) had hyperamilasemia or (i) hyperlipaemia. In 12 surveyed (14%), the indicators exceeded the norm more than 2 times [4].

The development of AIDS sclerosing cholangitis also creates the preconditions for the involvement in the pathological process of pancreas in the framework of multifocal fibrosis, through the stenosis of the pharyngeal papilla. In addition, cryptosporidia and cytomegalovirus are the potential cause of sclerosing cholangitis in AIDS. The latter, as already indicated above, is capable of causing pancreatitis [4].

The possibility of development of cholestatic diseases of the liver, pathology of the CP as a result of the influence of Helicobacter pylori and Helicobacter bilis is envisaged. A study is conducted to study the role of Helicobacter pylori (isolated from the human liver) and Helicobacter bilis (isolated from the human gall bladder) in the development of liver and protozoan diseases. One or both types of microorganism are found in liver tissues (in bile) in 75% of cases of primary sclerosing cholangitis, in 92% of cases of primary biliary cirrhosis and in 75% of hepatocellular carcinomas and cholangiocarcinomas. The aggravating effect of Helicobacter pylori infection on the course of chronic pancreatitis is proved. However, this information is even more recent [4].

The probability of development of invasive mycoses is determined by the main disease and a number of other factors, in particular: antibiotic therapy with two drugs and more, colonization of mushrooms of mucous membranes, skin. Relatively more invasive candidiasis develops with pancreatitis [7].

Often, in the autoimmune and non-immune pancreatitis (20.6% and 14.3% respectively), chronic pancreatitis is preceded by opisthorchiasis, which is the cause of the lesion of the pancreas. Clinical variants of the course of the early stage of the disease are diverse — from eroded forms to generalized allergic reactions with multiple lesions. The eroded form is limited to subfibrilitis, a slight eosinophilia with normal leukocyte contents. The chronic stage is associated with the activity of parasites in the bile ducts of the liver and the pancreas. There is a chronic proliferative inflammation in the duct system of the pancreas, accompanied by fibrosis of varying degrees with diffuse changes and retention cysts in the pancreas. Immunological methods of diagnosis of opisthorchiasis and clonal pharmacology are currently not sufficiently specific and sensitive, and sometimes it is expedient to use them only as additive to parasitological methods. Parasitologic diagnosis, based on the study and detection of eggs of helminths in feces and (or) duodenal contents, is currently the only means of confirming the diagnosis [7].

Ascaridosis can be the cause of the development of CP in the calcination of ascaris in the vysungal duct [7].

Changes typical for CP occur when tuberculosis of the intestines and parasitic diseases of it [7].

Described in giardiasis, CH is more benign than in its classical form, the course: the evidence of giardia etiology of the disease is the detection of these pathogens in the ducts of the gland and the effect of anti-parasitic treatment. The mechanism of malabsorption in giardiasis is due to a decrease in the intestinal absorption function, as well as a change in the enzymatic activity of the small intestine and in the pancreas [8].

**Conclusion**. Given the diversity of factors in the formation of CP, one can assume combined damage to pancreas by several factors simultaneously. The significance of the infectious factor should be taken into account when diagnosing CP and in the formation of adequate therapeutic tactics.

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The article presents a review of modern literature data on the role of various etiological factors in the development of chronic recurrent pancreatitis. Much attention is paid to infectious agents (viruses of epidemic parotiditis, hepatitis B and C, enteroviruses, adenoviruses, mycoplasmas, salmonellae) in the formation of the inflammatory process in the pancreatic tissue. The features of the pathogenesis of chronic pancreatitis associated with viral infection B and C are considered; it has been shown that the lesion of the pancreas is caused by the replication of viruses directly in the cells of this organ, immunopathological changes in the liver, and concomitant immunological disorders. The probability of developing diabetes mellitus, as one of the clinical manifestations of viral replication in pancreatic endocrine cells, is underlined. The clinical manifestations of exocrine and endocrine insufficiency of the pancreas during infection with various viruses, including Coxsackie B and enteroviruses, are described in detail; the features of the course of diabetes caused by infection of these pathogens are listed. The peculiarities of chronic pancreatitis in HIV-infected and AIDS patients, in patients with parasitic pathology (opisthorchiasis, clonorchosis, ascariasis, giardiasis) are considered; the role of helicobacteria in the development of a chronic inflammatory process in pancreatic tissue is characterized. It has been suggested that a given organ may be simultaneously affected by several infectious factors; the importance of identifying pathogens of infectious diseases for the timely formulation of the correct diagnosis and the selection of adequate therapy is emphasized.