Clinical and morphological variants of chronic pancreatitis: basic pathogenetic links, diagnostic algorithm and principles of treatment

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Key words: chronic pancreatitis, clinical and morphological forms, diagnostics, treatment, pathogenesis, algorithm

Chronic pancreatitis (CP) consistently ranks among the highest in the structure of digestive diseases, affects people of working age and is one of the most difficult to study diseases of the digestive system, because of objective difficulties it ineffective diagnosis and existing treatments [1, 2, 3, 4].

Attracted the attention of many researchers, this pathology, but today there are still many questions regarding the development and course of morphological forms of CP: obstructive, calcificating, fibro-parenchymatous and CP complicated pseudocyst formation.

In SI "Institute of Gastroenterology Medical Sciences of Ukraine" according to the plan of research carried out research work "To study the mechanisms of complications of chronic pancreatitis and to develop methods for diagnosis and surgical treatment using minimally invasive techniques", 2008-2010 (VN.25.01.001.08, №0107U012136) and "To study the mechanisms of fibrotic processes in chronic pancreatitis and technology to improve their surgical correction", 2011-2013 (VN.25.01.001.11, №0111U001065), which examined the role of mediators of inflammation, fibrogenesis markers and pancreatic lithiasis, apoptosis with morphological forms of CP, determined predictors of progression of fibrosis, formation of calcifications and based on the factor and correlation analysis of the data developed diagnostic algorithm morphological forms of CP.

The aim of the study – is to study the role of immune-morphological factors of oxidative stress in the progression of fibrosis and pancreatic stone formation (pancreas) to identify the main pathogenetic links and develop a diagnostic algorithm different morphological variants of CP.

Material of the research. The observation included 210 patients with CP, which conducted a comprehensive survey followed a conservative choice, and in some cases — surgical treatment in the clinic SI "Institute of Gastroenterology of the NAMS of Ukraine" for the period from 2006 to 2012.

Among surveyed were 169 men and 41 women, age of the patients ranged from 26 to 72 years, the average age was (47,3 ± 0,7) years. Value for women and men — 1: 4.1.

According to the Marseille-Roman classification of 1998 patients (210 people) were divided into four clinical groups: I group consisted of 26 patients (12.4%) in the obstructive form of CP, II — 56 patients (26.7%) of calcificating, III — 78 patients (34.1%) of parenchymal fibrous form, and IV — 50 patients (23.8%) of CP complicated pseudocyst.

Research methods — general clinical, instrumental (endoscopy, ERCP, X-ray, CT, ultrasound), functional (sensing gastric and duodenal intubation), morphological (determination of degree of fibrosis pancreas apoptotic nucleases, morphometry), biochemical (determination of POL and AOP, molecules middle weight (IMS), products of collagen synthesis — OP_{pb} and CC), immunological (enzyme to determine blood levels of interleukins TNF-α, TGF-β1, REG-1α, lactoferrin, fecal elastase-1, methods of analysis of immune status and nonspecific resistance body), microbiological (determination of microbial contamination of gastric contents and ducts pancreas). We used the method of statistical analysis.

Research results. All patients were studied risk factors for the different morphological forms of CP and quality of life, conducted at prices were ca possibilities of modern methods of diagnostics of different morphological forms of CP; by morphological features of the pancreas, role of POL-AOP in the progression of morphological forms and features CP lipid spectrum of the blood of patients; studied the diagnostic possibilities of markers of inflammation, fibrosis, stone, apoptosis with morphological forms of CP; developed diagnostic and therapeutic algorithm CP considering factors of disease progression and assessed its

effectiveness in improving the clinical course of disease and quality of life of patients.

As a result of working it is stated that the activity of fibrotic processes (TGF-β1) higher in patients with a longer history of the disease against a background of reducing re receptor protein of apoptosis — CD95. The level of proinflammatory cytokines (TNF-α) is higher in patients with impaired outflow of pancreatic secretion and pseudocyst pancreas. Found that for patients with parenchymal fibrous CP pseudocyst complicated and characterized by dysfunction of cellular immunity (the formula of immune disorders — Friso), and for patients with CP calcificating — humoral.

In patients with different clinical and morphological forms of CP installed unidirectional changes in markers of stone — a significant increase in the content lithostatin (REG-1α) and lactoferrin. It was established that the probability of stone formation is high — at the value 0,5-1,0 calcification factor (REG-1α/lactoferrin), low — at 1.5 and above.

Defined possibilities of modern diagnostic methods morphological forms of CP and set the highest sensitivity in the diagnosis of structural change pancreas method CT. It is shown that for the diagnosis calcificating and complicated pseudocyst CP effective use of ultrasound, and to diagnose other forms of CP to be additionally used CT and at necessary ERCP. In assessing fibrosis CP pancreas installed at important indicators of compliance with this ultrasound morphological studies Pancreas: in terms of areas of fibrosis organ parenchyma (FS) and measure the density of the parenchyma (g).

It is shown that there are different mechanisms of apoptosis in exogenous endocrine parts and pancreas — proapoptotic protease DNA-ase I expressed in the cytoplasm of acinar cells, and endonuclease-G — in insular cells in the epithelium ducts. Early marker of apoptosis is the translocation of DNA I basics from the cytoplasm to the nucleus of acinar cells.

The identified markers of progression CP: value ratio calcium cation (REG 1α / lactoferrin) 0,5-1,0, translocation of DNA-ase I of the cytoplasm to the nucleus of

acinar cells, activation of collagen (reduced OP_{pb} ratio/CC 0.5 below) activators increase in fibrosis (TGF-β1, TNF-a), intensification of LPO (MDA).

As a result of factor analysis and correlation of the data and to develop a diagnostic algorithm formulated the main pathogens cal link different forms of CP (Fig. 1-4).Factor analysis allowed to investigate the relationship between the variables and interpret "nature" factors that are major contributors to explain the variability of the sample variables.

Patients and groups (obstructive pancreatitis) Four factors explain about 59% of the total variance.

The first factor correlates mainly with indicators that reflect violations of the biliary system, balance of POL-AOP processes and activation of humoral immunity. Thus, when the gall stone disease is defined bile reflux in pancreatic duct, along with an imbalance in the system of POL-AOP leads to inflammation and tissue damage pancreas.

Volume duodeno-pancreatic reflux affects the degree of oxidative damage. Prolonged exposure leads to fibrosis refluxate of the pancreas. There is a vicious "vicious circle", that is — the interplay of immune factors, indicators POL-AOP, disorders of the biliary tract in the development and progression of CP ($OP_{pb,}$ GA SML POL-AOP, cholestasis, Ca, r =0,63-0,95, p=0,0008-0,05).

The second most important factor — the toxic-metabolic, nutritional stress, pollutants and toxins directly affect the acinar cells break cellular metabolism, followed by lipid accumulation in the cytoplasm of acinar cells, which leads to fatty degeneration, necrosis cells and the spread of fibrosis. There is growing endogenous intoxication, the level of which (MSM r=0,78, p=0,01), metabolic changes x-LP (r=0,76, p=0,03), Ca (r=0,73, p=0,028) and violations AOP (SOD r=0,77, p=0,04) depended significant structural changes Software that are identified during ERCP, CT or ultrasound. Periductal fibrosis develops and accordingly duct dilatation. Software fibrosis tissue from scarring in periductal area leads to obstruction of the ducts. Full and continued obstruction leads to atrophy and fibrosis [5].

The third factor — immune: as a result of toxic effects of substances damaged acinar cells activate inflammation with increasing content of proinflammatory cytokines (TNF-α), anti-inflammatory (IL-10) and profibrotychnyh (TGF-β1), which in turn leads to the activation of acinar cells followed by their products with a predominance of extracellular matrix collagen, leading to the replacement of functional parenchyma to fibrous tissue cancer (r=0,79-0,82, p=0,001-0,03).

The fourth factor — oxidative stress: diverse xenobiotics (Ca r=0,73, p=0,028) in their metabolism cause oxidative stress in the tissue Software (MDA r=0,79, p=0,003), which leads to cell and body injury (r=0,56, p=0,007), with especially big t malnutrition (r=0,72, p=0,001). Increase of lipid peroxidation products (MDA r=0,62, p=0,04) blood ("oxidative stress") leads to inflammation and tissue damage pancreas and ultimately — to fibrosis pancreas.

In the development of different forms of CP matter the same factors: toxic-metabolic, biliary, immunity, oxidative stress, but there are differences.

In patients of II group (calcificating pancreatitis) found the largest number of factors — 5 (Fig. 2) confirming on the basis of complex clinical-laboratory and instrumental research data that the most unfavorable for the course and prognosis is calcificating form of CP. Five factors account for about 58.4% of the total variance.

In the first place in importance comes toxic-metabolic factor which further includes also a violation of humoral mechanisms of regulation of the pancreas. Together with the second factor (oxidative stress) and third (immune system disorders) and disorders in the biliary system (the fourth factor), these changes lead to activation of stone (total Ca, REG-1α). Against the background of the growth phenomena of cholestasis and metabolic disorders ever more fibrosis of parenchymal tissue of organ comes (fifth factor).

Patients of group III (parenchymal fibrous form CP), and a similar group found four factors that explain the variance of 50.8%, in the first place is determined by the toxic-metabolic factor, the second — violation of the immunity and humoral regulation of pancreas that causes oxidative stress (the third factor). All these changes, along with violations of the biliary system (the fourth factor) leading to

injury parenchymal pancreas. The high stone probability indicates REG-1α, which is part of the fourth factor.

The smallest number of factors found in the patients group IV — 3 factors: biliary, impaired immune system, stress oxide cess that explain 37.1% variance. This coincides with data on the short history of the disease in this group of patients and the development of pseudocyst after acute pancreatitis.

On the basis of these studies and factor analysis improved diagnostic algorithm for patients with CP (Fig. 5).

Introduced diagnostic algorithm with maximum information content of the data allowed to evaluate the pathophysiological features functional and organic disorders Software in patients with CP, shorten hospital stay and select a reasonable pathogenetic treatment.

Defined group of patients with a constant and intermittent pain due to obstruction of the ducts at different levels of the system pancreas, the development of complications that could not be removed by conservative methods and subjected to surgical treatment. In obstructive CP treatment aimed at removing the cause of obstruction, which is achieved only by surgical methods. Require treatment in the surgical department as patients with CP, complicated pseudocyst formation, which in the first stage of treatment carried gastro-/duodenotstomy or percutaneous puncture pseudocyst, and further surgery was performed. Surgical treatment of patients with CP is generally aimed at improving the outflow of pancreatic juice or duct resection of the affected organ.

The tactics of conservative treatment of patients with CP was a good use of basic waste treatment complex, which was designed compartments ing exacerbation, chronic pain, exocrine/endocrine insufficiency pancreas correction of metabolic disorders and complications. Used analgesics, nonsteroidal anti-inflammatory medications, enzymes, anticholinergic drugs, antacids, middle-chain triglycerides. To ensure analgesic action enzymes, "functional peace" and pancreas to reduce inactivation of the enzymes under the action of gastric juice administered H2-receptor blockers or proton pump. In patients with hyperenzymatic CP to create peace

functional pancreas correction enzyme-inhibition imbalance blockers prescribed pancreatic secretion (somatostatin, dalarhin). In patients with endocrine insufficiency pancreas displays restrict carbohydrate intake, insulin was administered (if necessary).

In addition to basic therapy treatment was applied, which was aimed at normalizing disorders of the immune system, the elimination of oxidative stress, inhibition fibrotic process.

For immune, increase adaptive capacity of the organism, reduction of proinflammatory cytokines and cytokine responsible for fibrosis of parenchymal pancreas for CP patients in addition to the basic treatment prescribed by autocytokine therapy scheme developed by us.

For the normalization of the system of POL-AOP, glutathione and ultimately as antifibrosis agent used glutargin, fat-soluble vitamins and minerals. In addition, for pain relief administered pulse magnetic field (WIMPs) with influence on projection of the pancreas and BAP 5-15 minute rate 10-15 sessions.

Analysis of the use of these principles in the remote period of treatment in 34 patients revealed its clinical efficacy, in particular, good and satisfactory results wasps er patients were 94.1% and were 1.2 times higher than the comparison group. In the medical exclusion complex patients with CP autocytokines, glutargin WIMPs and improves the efficiency of treatment by correcting the first cytokine profile (reduction of TGF-β1, $p<0.05$, REG-1α, $p<0.001$) liperoxidation indicators (reducing the concentration of substrates in the LPO α-phase, ($p<0.05$), endogenous intoxication (MCM, $p<0.001$), optimization of AOP, improving the general condition and quality of life ($p<0.05$). Developed technique for the treatment allowed to obtain a positive effect in the majority of patients with CP. Thus, treatment strategies should be integrated CP considering morphological changes and to influence the pathogenesis of major diseases in order to inhibit the development of fibrous structural changes and other pancreas.

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210 patients with various clinical and morphological forms of chronic pancreatitis were examined. We studied the role of immune-morphological factors of oxidative stress in the progression of fibrosis and pancreatic stone formation, defined the basic pathogenetic links of the disease and developed the diagnostic algorithm for different morphological variants of chronic pancreatitis. Therapy of patients, in addition to the basic treatment, included autocytokines, glutargin and vortex pulse magnetic field, thus improving the effectiveness of treatment by correcting the cytokine profile, indicators of peroxidation of endogenous intoxication, improving the overall condition and quality of life of patients.

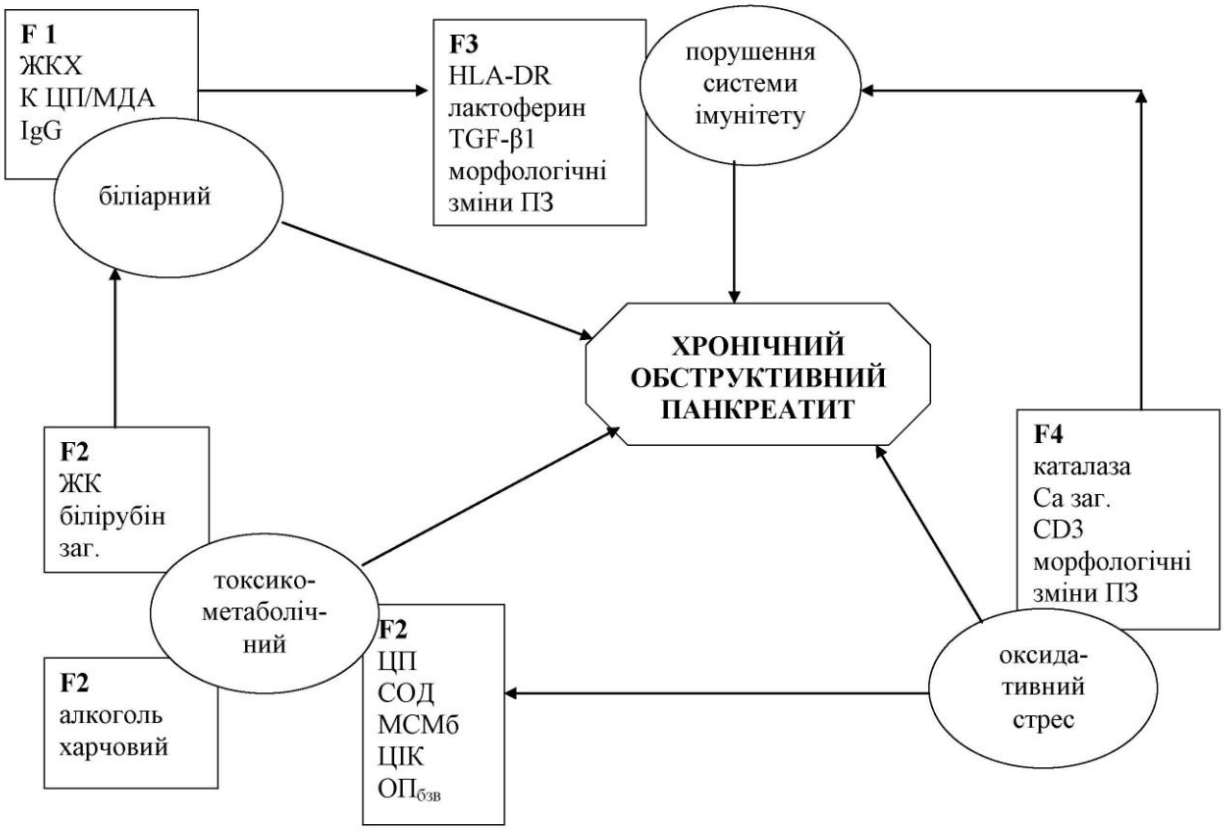

Fig. 1. Pathogenesis of obstructive chronic pancreatitis.

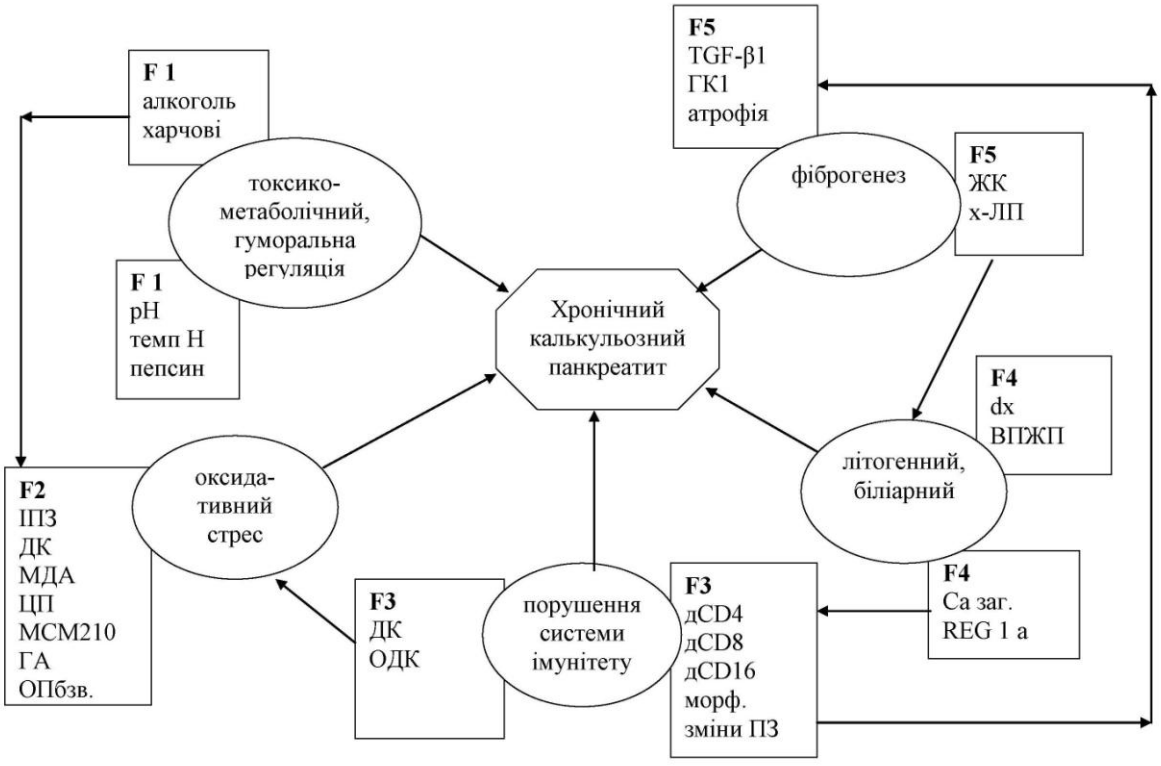

Fig. 2. Pathogenesis of calcificating chronic pancreatitis.

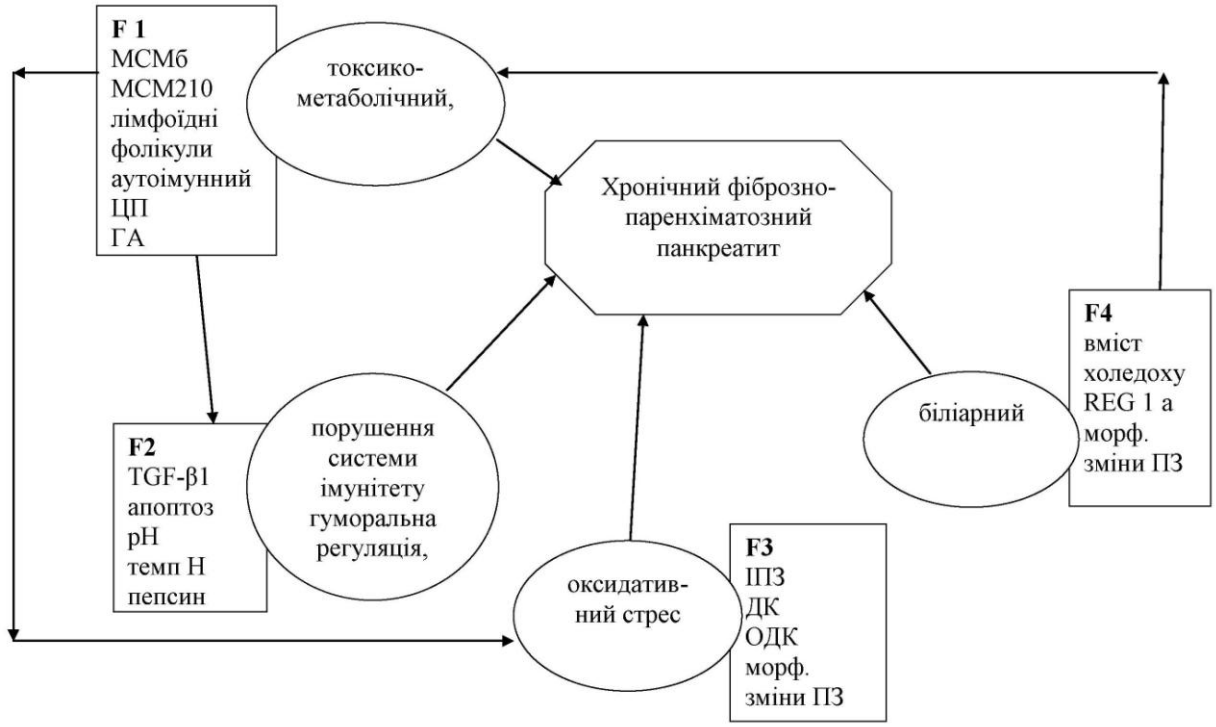

Fig. 3. Pathogenesis of fibrous-parenchymatous chronic pancreatitis.

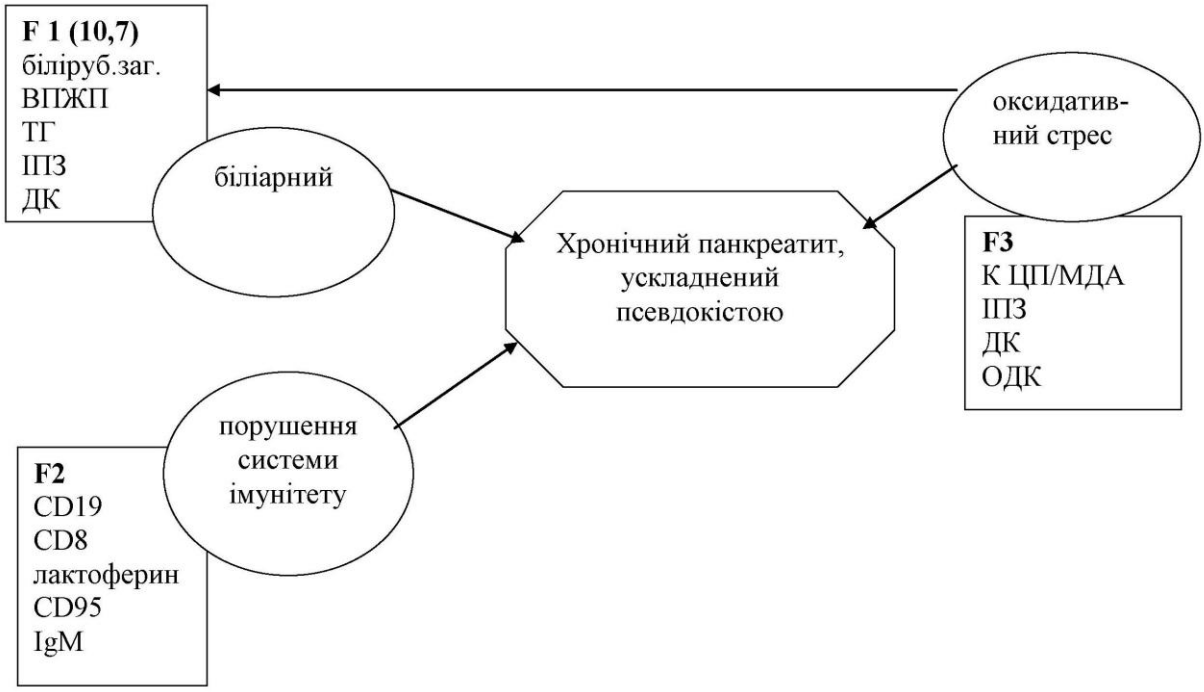

Fig. 4. Pathogenesis of chronic pancreatitis complicated by pseudocyst.

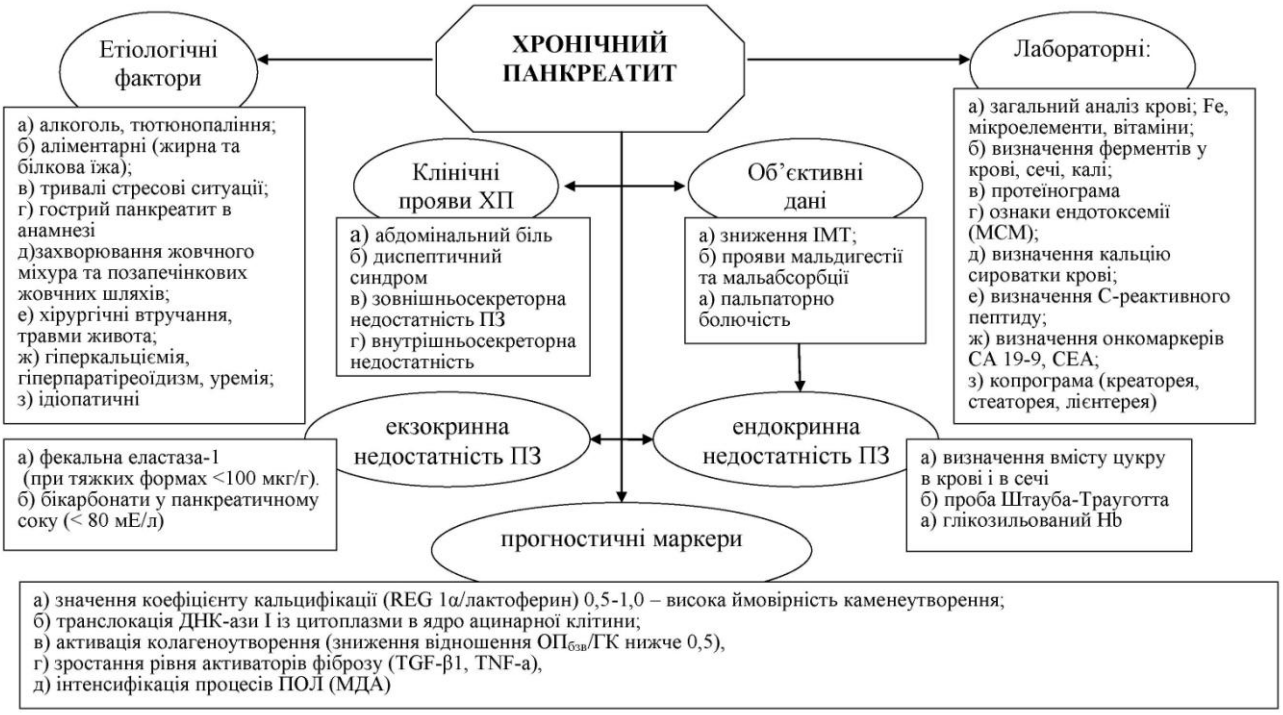

Fig. 5. Algorithm of diagnostics of the clinical and morphological forms of chronic pancreatitis.