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EARLY CHRONIC PANCREATITIS: IS CLINICAL DIAGNOSIS POSSIBLE?

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ABSTRACT A "fatal chain" in pancreatology is discussed in the present article. Peculiar attention is paid to an early chronic pancreatitis (CP), being one of the little-studied "links" corresponding to the latent period of CP. Features of different stages of the pancreatic diseases' course are presented, substantiating a need for practical identification of the "early CP" diagnosis. Advantages and disadvantages of using the "early CP" diagnosis in practice are considered. The authors cite provisions of the International Consensus on Early CP, and list current diagnostic criteria for this disease elaborated by the Japanese Pancreas Society. Advantages and disadvantages of the instrumental and laboratory diagnostic techniques are analyzed, including probable early CP biomarkers (interleukin-8, prostaglandin E2). The most suitable therapeutic tactics for management of patients with early CP are presented, including correction of the exocrine and endocrine pancreatic function, as well as the use of antifibrotic drugs.

KEYWORDS : Chronic Pancreatitis, Early Pancreatitis, Diagnosis, Visualization, Functional State Of Pancreas, Biomarkers, Treatment

New knowledge of pancreatic pathology has been acquired over time; evolution of concepts on pathogenesis, diagnosis and treatment of this disease has occurred. One of the achievements of modern pancreatology is discovery of "fatal chain" not only in hepatology, but also in pancreatology [2, 4, 5]. What is the "fatal chain"? By recalling this term, academician E. M. Tareev meant "cirrhosis and the whole complex of its development: acute hepatitis, chronic hepatitis, cirrhosis and liver cancer" [13]. At the present stage of development of pancreatology, we can confidently say: "Yes, pancreatology also has "fatal chain": from acute pancreatitis (AP) to its recurrence and chronic pancreatitis (CP), progression of CP with development of pancreatic cirrhosis and adenocarcinoma". It should be noted that pancreatic cirrhosis is a pathologic term and is not a nosological unit. "Fatal chain" in pancreatology includes another link — early CP (Fig. 1). Does this link exist, and can/should it be diagnosed in practice?

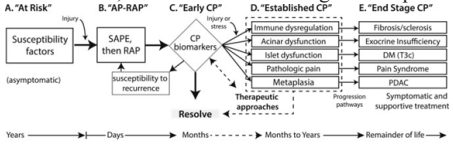

Fig. 1. Stages in the course of pancreatic pathology (D. C. Whitcomb et al., 2016 [18]).

Prof. D. Whitcomb (USA) formulated a new definition: "CP is a pathologic fibro-inflammatory syndrome in individuals with genetic, external and/or other risk factors that cause persistent pathologic response to damage to the parenchyma or stress".

Common signs in the established diagnosis of CP and its late stages include atrophy and fibrosis of parenchyma, abdominal pain, irregularity of the ducts and their stenosis, calcification, violation of exocrine and endocrine pancreatic functions, dysplasia.

Using the case of hereditary pancreatitis, Prof. D. Whitcomb shows that during CP there is a latent period before onset of clinical manifestations which can last 20 years.

Based on analysis of CP course and latent period without clinical manifestations, a hypothesis of "chain" of pancreatic pathology was developed, leading from AP to pancreatic adenocarcinoma (Fig. 1) [18]. In this chain, the term "early CP", corresponding to the latent period of CP, was first used. Features of each stage of the course of pancreatic pathology were also presented (Table 1) [18].

Table 1
Features of stages of the pancreatic pathologic process (D. C. Whitcomb et al., 2016 [18])

	Stage B	Stage C	Stage D	Stage E
	AP/recurrent AP	Early CP	Proven CP	Late CP
Other definitions	Single (completed) AP episode	Intermediate	Certain	Certain
	Recurrent AP			
Essence	Natural inflammatory response to acute damage of the pancreas	Persistence of inflammation with the presence of CP biomarkers that do not meet the diagnostic criteria of proven or late CP	Inflammation-associated pathology and/or dysfunction of two or more biological systems	Inflammation-associated pathology and insufficiency of two or more systems
Features	Characterized by acute abdominal pain, increased activity of enzymes 3 times or more, specific results of visualization	Persistence of post-AP: pain, hyperenzymemia, inflammation markers, visualization results	Visualization techniques confirming fibrosis, calcification, pancreatic atrophy; impaired glucose tolerance; pancreatic pain	Under research
Fibrosis	Revised Atlanta Classification criteria	Under research	Under research	Under research
Disease markers	Revised Atlanta Classification criteria	EUS CT MRI		

Biomarkers of disease activity	Revised Atlanta Classification criteria	Under research		
Exocrine pancreatic insufficiency	Not predictable	Functional test results reducing to 70% of normal	Functional test results reducing to 70–10% of normal	Functional test results reducing to less than 10% of normal
Disease markers		Under research		
Biomarkers of disease activity	C-reactive protein	Under research		
Pancreatogenic diabetes	First developed (in pancreatic necrosis)	Glycemia is corrected by diet	Sugar-reducing drugs, insulin	Dependence on insulin. Hypoglycemia
Disease markers		Under research		
Biomarkers of disease activity	C-reactive protein	Under research		
Notes: CT — computed tomography; MRI — magnetic resonance tomography; EUS — endoscopic ultrasound.				

Early CP rate is not precisely determined due to the complexity of its diagnosis. According to A. Masamune et al. [12], early CP prevalence in Japan is 1 case per 100,000 population, while prevalence of an established CP is 37–42 cases per 100,000 population.

There is a discussion about feasibility of allocation and possibility of diagnosis of early CP in practice. Prof. L. Frulloni cited the pros and cons of such a diagnosis. "Pros": explanation of pain syndrome; timely prognosis; selection of patients with an increased risk of pancreatic cancer; ability to compare data from different researchers. "Cons": absence of specific antifibrotic, anti-inflammatory therapy, i.e. early diagnosis of CP will not affect progression of the disease; it is difficult to diagnose, which would entail large financial expenses; later diagnosis does not affect clinical outcome; many patients have no symptoms at the stage of early CP, and the diagnosis is made at the stage of proven or late CP with clinical symptoms, which means that treatment will be prescribed when symptoms appear anyway [3]. We can agree with the arguments of Prof. L. Frulloni. In our opinion, diagnosis of early CP is impossible in clinical practice at the present stage. More widespread endosonography is needed, which will make it possible to diagnose early CP.

International Consensus on Early CP has been recently published [19]. The first question in the Consensus is: "What is an early CP"?

Statement: the term "early CP" describes the initial stage of a specific CP.

Quality assessment of the recommendation is low; conditional recommendation, conditional consent.

The consensus discusses issues related to the diagnosis of early CP; it is argued that this disease cannot be diagnosed only on the basis of one symptom/sign, in particular, pancreas imaging data. It is necessary to consider a combination of different manifestations.

In this regard, the question "Is it possible to diagnose early CP taking into account a combination of symptoms?" gets the following reply: "Yes, it is possible. Should be considered:
- presence of risk factors for CP;
- low risk of other diseases;
- clinical manifestations;
- biomarkers.

Quality assessment of the recommendation is low; strict recommendation, weak consent.

The Consensus provides diagnostic criteria for early CP meeting the modified criteria of the Japanese Pancreas Society [7]:

A. Clinical/functional criteria:
- recurrent abdominal pain in the upper abdomen (2 or more attacks);
- abnormal serum/urine enzyme levels;
- reduction of exocrine pancreatic function;
- prolonged alcohol abuse (more than 80 g/day).

B. Visualization — EUS (a or b):

a) more than 2 of the following characteristics, including one of the first four:
- lobulation with cellularity;
- lobulation without cellularity;
- hyperechoic foci without shadow;
- thickening;
- cysts;
- dilation of the lateral ducts;
- hyperechogenicity of the main duct walls.

b) uneven dilation of more than 3 branches of the main duct at ERCP.

Clinical symptoms are unreliable in the diagnosis of CP. Population study conducted by J. D. Machicado et al. included 89 patients with CP, and 21 (23.6%) did not experience pain [11]. In study by C. M. Wilcox et al. pain syndrome was absent in 81 (15.6%) of 521 patients with CP, despite the existing changes in the pancreas during imaging [20]. Nevertheless, visualization of the pancreas and, above all, endoscopic sonography, plays the leading role in the diagnosis of early CP, while CT and MRI are considered insufficiently informative [8].

It is important to evaluate the probability of progression of early CP to the established CP according to endosonography data. A. Sheel et al. [15] conducted a retrospective single-center cohort study, which included 40 patients with minimal pancreatic changes according to the results of endosonography. The observation lasted more than 3 years. 12 (30%) patients got CP; 8 (67%) of them abused alcohol, 10 (83%) were intensive smokers. These patients more often needed surgical treatment, they had exocrine pancreatic insufficiency (EPI), the mortality rate exceeded that in CP patients who did not abuse alcohol and did not smoke. The authors concluded that the cessation of alcohol abuse and smoking could reduce the risk of progression early to an established CP.

It should be noted that the fine-needle biopsy of the pancreas during endosonography was not informative [6].

It is important that minimal changes in the pancreas during endosonography and other imaging methods can be associated not only with early CP. In this regard, the results of study by B. H. Stamm [16] are indicative. Results of analysis of 112 randomly taken autopsies of adults who did not have a diagnosed pancreatic pathology are presented in Fig. 2.

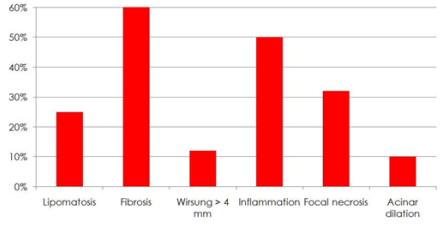

Fig. 2. Pancreatic changes identified in 112 autopsies in absence of known pancreatic pathology (B. H. Stamm, 1984 [16]).

Therefore, minimal changes in the pancreas are not necessarily caused by early CP. They can be associated with pancreatic steatosis, patient's age and other causes, such as smoking. It has been proven that smoking contributes to pancreatic fibrosis [17].

Functional tests for early CP are also not always informative. G. Ketwaroo et al. [9] conducted a retrospective single-center cohort study and examined 116 patients with suspected CP (there is clinical picture, but there are no changes in the pancreas during imaging). Patients underwent magnetic resonance cholangiopancreatography (MRCP) with secretin. EPI was diagnosed in 27 patients, and it was not possible to conduct the observation in 7 patients. CP developed in 9 of 27 patients with EPI over 4.8 years. In 89 patients, EPI was not detected, 19 of them were not observed. During longer observation

period (7 years), CP was diagnosed in 2 patients without EPI. Sensitivity of MRCP with secretin in the diagnosis of early CP was 82%, specificity — 86%, positive predictive level — 45%, negative predictive level — 97%.

According to the results of an endoscopic functional test with secretin, EPI was diagnosed in 8 of 27 patients with early CP and in 1 from control group. Test sensitivity in the diagnosis of early CP was 66%, specificity — 98%, positive predictive level — 95%, negative predictive level — 85% [10].

Literature data indicate the possibility of using biomarkers for the diagnosis of early CP. K.W. Noh et al. studied the concentration of cytokines in pancreatic juice, which was obtained from the duodenum after administration of secretin. Scientists examined 118 patients with pancreatic pain and control group. Only concentration of interleukin-8 was significantly different in healthy individuals and patients with CP (p=0.011), pancreatic cancer (p= 0.044), in healthy people and in presence of pancreatic pathology (p=0.007). Individual concentration of certain cytokines in CP was not significantly different from pancreatic cancer [14].

B. K. Abu Dayyeh et al. [1] studied concentration of prostaglandin E2 in pancreatic secretion in 10 patients with CP, 25 patients with minimal pancreatic changes (early CP) and 10 healthy volunteers. Prostaglandin E2 is a powerful mediator of inflammation which regulates profibrotic activity of pancreatic stellate cells. It has been proven that concentration of prostaglandin E2 in pancreatic secretion increases both with the established diagnosis of CP and with early CP, i.e. this indicator can serve as a marker for early CP.

Thus, diagnosis of early CP is difficult in practice. It is necessary to continue searching for available and informative diagnostic methods (pancreatic elastography, pancreatic blood flow assessment, other biomarkers, etc.). Modern approach to CP diagnosis, including early CP is presented in Fig. 3.

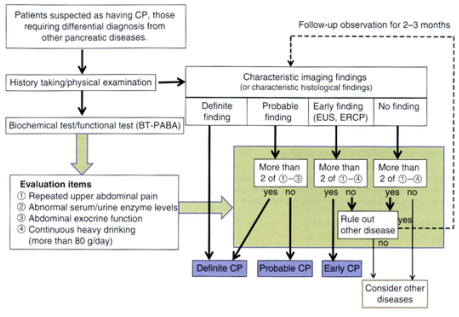

Fig. 3. "Roadmap" for CP diagnosis (H. G. Begeretal., 2018 [3]).

Alcohol abuse and smoking increase the risk of progression of pancreatic changes from early to the established CP. Therefore, it is important to recommend patients with early CP to stop smoking and drinking alcohol. Exocrine and endocrine pancreatic functions should be monitored for the timely appointment of replacement therapy. Prescription of anti fibrotic drugs would be the best option. Possibility of inhibition of pancreatic fibrosis by means presented in Table 2 is currently proved.

Table 2 Drugs inhibiting activity of pancreatic star cells (according to H. G. Begeretal., 2018 [3])

Antioxidants	Vitamin E, N-acetylcysteine, oxypurinol, L-cysteine, ellagic acid, salvianolic acid
Cytokine inhibitors	TGF-b: TGF-b antibodies, halofuginon, Saiko-keishi-to TNF-a: TNF-a antibodies, TNF-a soluble receptors, pentoxifylline
Anti-inflammatory agents	Protease inhibitors (camostat mesilate), IS-741
Modulation of signaling cells	Mitogen-activated protein kinase, phosphatidylinositol-3-kinase, protein kinase-C inhibitors, troglitazone (ligand of receptors activated by peroxisome proliferators–g)
Angiotensin inhibitors	Captopril (angiotensin-converting enzyme inhibitor), losartan (angiotensin II receptor antagonist)
Vitamin A	Retinol, retinol acid

We would like to conclude with Goethe quotation: "Human must believe that the incomprehensible can be understood; otherwise he/she wouldn't start thinking about it".

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