EDITORIAL

DOI: http://dx.doi.org/10.15403/jgld-5400

Early Chronic Pancreatitis – A Difficult to Diagnose Form of Chronic Pancreatitis

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Received: 12.12.2023
Accepted: 11.01.2024

INTRODUCTION

Epidemiological data on the incidence and prevalence of chronic pancreatitis are not very numerous. An international multicenter epidemiological study in 2014 showed an incidence rate, i.e., the number of new diagnoses per 100,000 population per calendar year, of 7.8/100,000 population/year [1]. The annual prevalence, i.e., how the disease is represented in a sample of 100,000 inhabitants of a given population, was 120–143. It is evident that chronic pancreatitis is not a rare disease affecting the long-term survival of people with this diagnosis. Moreover, it is not clear whether chronic pancreatitis is an under-diagnosed disease, which would necessarily increase the risk of how the disease develops and progresses, including the occurrence of complications that accompany the disease, especially in the terminal stage. For this reason, much attention is now being paid to the possibility of diagnosing the early stages of the disease, with the possibility of using the most effective treatment.

An important contribution to addressing this issue is the introduction of a new mechanistic definition of chronic pancreatitis in 2016 [2]. The previous definition described chronic pancreatitis as "... an ongoing inflammatory process characterized by irreversible morphological changes, typically accompanied by pain and/or permanent loss of pancreatic function" [3-5]. According to the mechanistic definition, chronic pancreatitis is defined as "a pathological fibro-inflammatory syndrome of the pancreas in persons with genetic, environmental, and other risk factors leading to the development of persistent pathological damage to the pancreatic parenchyma". Of particular importance is the definition of the conceptual model characterizing the development of chronic pancreatitis. A total of five developmental stages are defined, indicated by capital letters A to E. From the stage of risk of chronic pancreatitis, i.e. the presence of risk factors (A), through the stage of induction of changes in acute or acutely recurrent pancreatitis (B), to the stage of the early form (C) of chronic pancreatitis, the stage of full development of the disease and the changes accompanying it (D), to the terminal stage (E), with the presence of irreversible changes in the pancreatic parenchyma and pancreatic functions.

The term "early" form of chronic pancreatitis was first used by Ammann et al. in 1996 [6]. The definition was mainly aimed at describing the clinical stages of the alcoholic form of chronic pancreatitis. However, as the early stage of alcoholic chronic pancreatitis could not be accurately diagnosed using available clinical tests, it was suggested that the term "probable alcoholic chronic pancreatitis" should be used for the early stage of chronic pancreatitis [6].

In 2014, the American Pancreatology Association issued a recommendation [5] to classify the diagnosis of chronic pancreatitis into three grades, namely definite, probable, or insufficient, using imaging and histological examination. In 2016, the Japanese Society of Pancreatology published the revised criteria for the diagnosis of chronic pancreatitis, whereby the early form of chronic pancreatitis was defined as the form in which the criteria for a definite or probable diagnosis of chronic pancreatitis are not met [7]. In the case of a probable diagnosis of chronic pancreatitis, signs of functional impairment were found, and the clinical criteria were met, but not the diagnostic markers using imaging methods. However, this approach has not been generally accepted.

According to the European Society of Gastroenterology 2017 [8], the assessment of clinical symptoms, functional capacity of the gland and the use of imaging methods are recommended in the diagnosis of chronic pancreatitis. However, the problem is that this recommendation allows

the determination of mild, or moderately advanced stages of the disease, but does not reliably determine the early form of chronic pancreatitis. Currently the word "early" in early chronic pancreatitis is used to described disease state, not disease duration.

DIAGNOSTIC POSSIBILITIES OF EARLY CHRONIC PANCREATITIS

The criteria that diagnostically define the early form of chronic pancreatitis, according to the Japanese Association of Pancreatology, include the following:

a) clinical symptoms-recurrent abdominal pain, elevation of serum or urinary pancreatic enzymes, impaired pancreatic function, regular alcohol intake > 80g/day;

b) findings of the imaging methods as follows:

Endoscopic ultrasonography (EUS):

- lobularity of parenchyma without honeycombing;
- lobularity of parenchyma with honeycombing;
- hyperchogenic loci;
- stranding;
- cyst;
- dilatation of secondary branches of the pancreatic duct;
- hyperechogenic main pancreatic duct;

Endoscopic retrograde cholangiopancreatography (ERCP):

- irregular dilatation of > 3 secondary branches of the pancreatic duct.

A positive diagnosis in the endosonographic picture is indicated by the presence of two or more features, of which the first four features mentioned above are the most specific.

Positivity of > 2 clinical features and positive imaging criteria EUS and ERCP, suggest a diagnosis of chronic pancreatitis [9].

A Japanese study of 116 people using the USS ultrasound speed (USS) and EUS system compared findings in already established diagnoses such as chronic pancreatitis, early chronic pancreatitis versus normal findings. The USS correction method generates a B-mode image and by converting the image to USS the quality of the image is maximized. The authors concluded that this method could differentiate early form of chronic pancreatitis from normal findings [10]. Despite the promising results, the limitation of this study is the reliability and reproducibility of the diagnosis of early form of the disease. The limitation is also the subjective evaluation, when using the B-mode, when the region of interest (ROI) is evaluated subjectively.

An interesting way to determine the early form of chronic pancreatitis is to evaluate the factors that contribute to the development of chronic pancreatitis. The theory of a "necrosis-fibrosis" process is accepted, whereby fibrosis arising from pancreatic necrosis leads to changes in the pancreatic duct resulting in efflux of pancreatic secretions [11]. A study by Lankisch et al. [12] evaluating the development of chronic pancreatitis in people after acute alcoholic pancreatitis, found that the development of chronic pancreatitis occurs in 13% within 10 years of acute pancreatitis and in 16% within 20 years [12]. An international multicenter study evaluating people enrolled in a registry of patients with acute pancreatitis found that three or more episodes of acute pancreatitis were an etiological risk factor for the development of chronic pancreatitis [13].

The alcoholic form of chronic pancreatitis is associated with an intake of 80–150 g of alcohol per day when drinking alcohol for 6–12 years [14, 15]. In a meta-analytic study of alcoholics, Corrao et al. [16] estimated the relative risk of developing chronic pancreatitis with an alcohol intake of 25 g/day-was 1.34, with an alcohol intake of 50 g/day was 1.78, and at a daily alcohol intake of 100 g/day was 3.19. Typical features on EUS examination of alcohol drinkers are the presence of hyperechogenic gland parenchyma regions with findings of dilated pancreatic ductal patency [17]. According to this study, asymptomatic alcoholics may have pre-existing pancreatic abnormalities, in the sense of changes in the early form of chronic pancreatitis.

Other risk factors leading to chronic pancreatitis are smoking and age. Old-age pancreatitis, which clinically manifests initially after the age of 60 and may have a painless course, has some features of chronic pancreatitis on EUS examination. When pancreatic elasticity is examined by semiquantitative EUS-elastography, the pancreatic tissue is stiffer in the elderly, yet the parenchymal stiffness is less than in chronic pancreatitis [18]. The features of chronic pancreatitis in the EUS picture, and their frequency, decrease with age, with a peak in those over 60 years of age [19].

Smoking is an established risk factor for chronic pancreatitis, and a meta-analysis evaluating a total of 8,498 patients in 14 studies found that alcohol and smoking were significant risk factors, with a prevalence of 65% in alcohol drinkers and 56% in smokers [20]. A high correlation between smoking intensity and the development of chronic pancreatitis has been demonstrated [21]. Heavy smoking is one of the major and independent predictors of the finding of significant abnormalities in EUS imaging [22]. Thus, smoking is associated with a considerable risk of inducing chronic pancreatitis and with the demonstration of hyperechogenic regions in the pancreatic parenchyma on EUS imaging [17].

Imaging methods are an undoubted positive, thanks to technical advances, in the diagnosis of pancreatic diseases. However, as a stand-alone test, they are not able to diagnose early forms of chronic pancreatitis. Endoscopic ultrasound examination together with elastography is an effective test in the diagnosis of fibrosis, including the assessment of the severity of parenchymatous changes [23]. The sensitivity of EUS examination with elastography is reported to be 76.4%, and the specificity 91.7% [24]. Current devices using ultrasound examination in the diagnosis of chronic pancreatitis report a method sensitivity of 0.69 (95% CI: 0.54–0.80) and specificity of 0.97 (95%:CI 0.90–1.00) [25]. Noninvasive computed tomography is not a method that identifies changes in early-onset chronic pancreatitis, and a definite limitation is the high rate of false-negative findings [26].

Confocal laser endomicroscopy allows the combination of real-time optical biopsy and subcellular imaging. The method is reported to allow very subtle changes in early chronic pancreatitis, especially in terms of distinguishing the presence of malignancy [27].

Until the development of imaging methods, most diagnoses of chronic pancreatitis were made by assessing the functional capacity of the gland. Currently, exocrine gland capacity tests are recommended for use in patients with

nonspecific symptoms or uncharacteristic features using imaging methods [28]. In terms of early diagnosis of chronic pancreatitis, the indirect functional tests, in clinical practice the determination of elastase-1 in stool, are inappropriate. Direct tests with stimulation of the gland with enteral hormones and determination of bicarbonate in duodenal aspirate confirm the correlation between the finding of low bicarbonate secretion and the early phase of pancreatic fibrosis [29].

Nevertheless, this examination is not sufficient in the diagnosis of the early form of chronic pancreatitis. Therefore, a combination of sophisticated imaging methods with assessment of the functional status of the gland, the presence of pain, or the general clinical condition is required.

A pioneering German multicenter study evaluating a total of 670 patients and controls from three cohorts identified 8 metabolic biomarkers from 620 serum metabolites that have significant potential to distinguish, with adequate accuracy, individuals with chronic pancreatitis from controls with no evidence of pancreatic disease [31]. Using a statistical analysis of metabolite findings /chronic pancreatitis vs. controls/, the positivity of serum beta-carotene was assigned the most significant position in the used biomarker algorithm, followed by cryptoxanthin and mannose findings. An undoubted potential effect of metabolomics determination is the identification of persons with early chronic pancreatitis, i.e., patients with initially unclear abdominal symptoms, or in cases where there is reasonable suspicion of the presence of chronic pancreatitis, which is particularly true in persons with a form of recurrent acute pancreatitis [32]. From the practical point of view, current diagnostic elements consist of typical early imaging markers (EUS, magnetic resonance colangiopancreatography, ERCP), histological findings and five evaluation elements: 1) repeated upper abdominal or back pain; 2) abnormal serum or urine pancreatic enzyme levels; 3) abnormal pancreatic exocrine function; 4) continued heavy alcohol consumption > 60 g/day; 5) history of acute pancreatitis [33]. Positivity of more than 3 of 1-5 findings is considered early chronic pancreatitis.

CONCLUSIONS

Establishing a consensus definition and, above all, diagnostic criteria for the diagnosis of early chronic pancreatitis is an essential requirement. Apparently, there is still no diagnostic method in clinical practice that can establish the diagnosis of the early form of chronic pancreatitis with adequate accuracy and reproducibility. The diagnosis is thus to some extent a "jigsaw" of individual test results, i.e. an indication of the etiology of suspected chronic pancreatitis, the presence of risk factors or the manifestation of complications in patients with suspected chronic pancreatitis.

Conflicts of interest: None to declare.

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