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Some Characteristics of Chronic Pancreatitis

Siniša Franjić
Independent Researcher

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***Corresponding author:** Siniša Franjić, Independent Researcher

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Abstract

Chronic pancreatic inflammation can result from chronic alcohol consumption, but the cause can be idiopathic. The first symptom is recurrent abdominal pain. In the later course of the disease, malabsorption and glucose intolerance may develop. The diagnosis is usually made by imaging tests such as ERCP, endoscopic ultrasound, or exocrine function tests. Most patients experience episodes of abdominal pain. About 10 to 15% of patients have no pain but have symptoms suggestive of malabsorption. The pains are epigastric, intense, and can last for hours or days. Attack pain typically declines after 6 to 10 years, which is caused by progressive damage to the pancreatic glandular cells that secrete digestive enzymes. Diagnosis can sometimes be difficult given that amylase and lipase values are often within reference values due to a significant decrease in pancreatic function. In patients who do not have a typical history, it is necessary to exclude malignancy as a cause of pain and to indicate CT of the abdomen.

Key words: Chronic Pancreatitis; Alcohol; CT, Patient; Health

Introduction

Benign disease characterized by permanent alteration of anatomy and function due to chronic inflammation [1]. Causes include alcohol (> 70% of cases); tropical pancreatitis (onset < 40 years in equatorial regions, and may be linked to protein–energy malnutrition); pancreatic duct obstruction (e.g., tumors, intraductal stones, traumatic strictures); hereditary pancreatitis; idiopathic chronic pancreatitis (20% of cases); intraductal papillary mucinous tumor (IPMT); cystic fibrosis; and autoimmune pancreatitis. Episodes of acute pancreatitis may occur during course of chronic disease.

Abdominal pain can be categorized as visceral, parietal or referred [2]. Visceral pain is dull and aching in character. It is poorly localized and is usually secondary to distention or spasm of a hollow viscus. Parietal pain is sharp and well localized and arises from irritation of the parietal peritoneum. Referred pain is the perception of pain at a site distant from the origin of the stimulus. One possible explanation for this is that the visceral and the somatic afferent nerve fibers share a common pathway at the level of the cord, which is the spinothalamic tract. The brain tends to associate the stimulation more with a somatic source rather than visceral. This type of pain is characteristically aching and perceived to be near the surface of the body. For example, referred pain from gallstones is sometimes perceived in the right shoulder because some of the afferent pain fibers run in the right phrenic nerve (C3–5).

Although chronic pancreatitis has a variety of clinical manifestations, most commonly patients present with intermittent chronic abdominal pain [3]. The pain originates from a myriad of protean manifestations, including inflammation and increased ductal and/or parenchymal pressure. In select patients, endoscopic or surgical decompression of the pancreatic duct has been shown to decrease pain.

Pancreatic duct disruption and/or increased pancreatic ductal pressure can lead to a pseudocyst formation. In patients with chronic pancreatitis, the pancreatic duct

becomes obstructed by fibrous scarring, inspissated protein, or stone(s), and the ongoing pancreatic secretion proximal to the obstruction leads to a saccular dilation of the duct, filled with pancreatic juice. These pseudocysts can cause symptoms of pain, early satiety, nausea, vomiting, weight loss, and can be complicated by obstruction (biliary and or enteric), hemorrhage, and infection. In the patient with chronic pancreatitis who develops a symptomatic pseudocyst(s), a multidisciplinary approach to drain these cysts, including endoscopic, surgical, and percutaneous methods, should be considered depending on local expertise and the character and location of the pseudocyst.

Chronic Pancreatitis

The term "chronic pancreatitis" (CP) implies an irreversible change in the acinar and ductal elements of the pancreas. This is based on the initial descriptions of the disease in the 1990s [4]. More recently an international mechanistic definition has emerged—"a persistent and often progressive fibro-inflammatory disease of the pancreas, most often seen in alcoholics, smokers and genetically predisposed individuals, which presents clinically with recurrent bouts of pancreatitis in its early stages and manifests with pain, ductal calcification, diabetes and steatorrhea in its later stages". However, this definition overlooks the fact that the condition in its preclinical early stages may neither be persistent nor progressive and not necessarily be irreversible. The pathophysiology of the disease is far from clear; many causes exist and each may affect the pancreas in its unique way. Thus chronic pancreatitis may represent a watershed pathomorphologic condition caused by various aetiologies.

Any description of the morphologic changes of chronic pancreatitis must take into account the gross morphology as well as the degree and type of histologic changes [5]. The changes may be isolated, segmental or diffuse. The lesion may manifest as areas of fibrosis, inflammatory infiltrates, calcifications or pseudocysts.

The classic histologic picture of chronic pancreatitis is one of progressive changes in the acinar and ductal tissues. In the early stages of the disease, the tissue damage is focal in character with involvement of the lobules and protein precipitation in the small pancreatic ducts. The ductal epithelium shows either hypertrophy, hyperplasia, metaplasia, or atrophy with associated periductal fibrosis. In addition, histologic examinations show inflammatory infiltrates with predominantly neutrophils in the tissue.

The endocrine compartment of the pancreas (the islets of Langerhans) is also eventually involved in the progressive fibrotic process involving the exocrine parenchyma. Light microscopy shows that the islets remain well preserved for a long time in areas traversed by scars, whereas using immunohistochemistry, there are decreases in the insulin-producing β cells and changes in the glucagon-forming A cells and the pancreatic polypeptide (PP) cells, even in less advanced stages. The degree of histomorphologic damage does not always correlate with the extent of the residual endocrine function.

In the stages of inflammatory recrudescence associated with a chronic inflammatory process, the pancreas frequently shows a macroscopically evident enlargement and should be distinguished from neoplasm, especially in the head of the pancreas. In a subgroup of patients with chronic pancreatitis, the inflammatory process takes place largely in the head of the pancreas, with involvement (compression) of adjacent organ structures. The chronically inflamed head of the pancreas acts as the 'pacemaker of the disease'. Later in the course of the disease, the gland is, if anything, reduced in size, with extensive loss of endocrine and/or exocrine function.

Chronic pancreatitis is a condition with inflammatory changes of the pancreas that results in permanent structural damage to the organ, leading to impairment of endocrine and exocrine function [6]. Chronic pancreatitis usually manifests as chronic abdominal pain with features similar to that of acute pancreatitis, as well as pancreatic insufficiency with steatorrhea and malabsorption of fat-soluble vitamins (Vitamins A, D, E, K) and vitamin B12. Severe cases of chronic pancreatitis can lead to glucose intolerance and diabetes mellitus. Biochemical testing is often less helpful in chronic pancreatitis, as serum amylase and lipase levels may be normal due to pancreatic fibrosis. Radiographic imaging may be useful, especially if pancreatic calcifications are noted in the organ with beading of the main pancreatic duct. Treatment for chronic pancreatitis usually involves supplementation with pancreatic enzymes, pain management, and avoidance of potential triggering factors, including alcohol and fatty meals.

Trauma to the abdomen or back may be clinically insignificant and still produce significant pancreatic injury, leading to chronic pancreatitis [7]. The pathogenesis may follow that of the obstructive type, but inflammation and pseudocysts frequently develop. Recognition of trauma as the cause for chronic pancreatitis is important because most cases are associated with severe ductal disruption, which responds poorly to medical treatment, but the results of surgical correction (particularly partial pancreatectomy) have been excellent.

Symptoms

The natural history of chronic pancreatitis (CP) is characterised by the appearance of clinical symptoms of acute pancreatitis, that recur and, later, develop towards the chronic more advanced phase, characterised by ductal dilatation, intraductal calcification, and clinical signs of exocrine and endocrine insufficiency [8].

Pain is characteristically recurrent and relapsing. The interval between the clinical onset of pancreatitis (1st painful episode) and diagnosis of chronic pancreatitis is quite variable. It appears to be shorter (1–2 years) in patients who have a high alcohol consumption rate compared to those who do not drink. The chronic pancreatitis onset-diagnosis interval is considerably longer in the case of pancreatitis associated with genetic mutation.

In the advanced stage, generally 5 years after the diagnosis of chronic pancreatitis, specific signs of exocrine function failure (malabsorption and steathorroea) and endocrine function failure (diabetes) begin to appear.

Other specific symptoms that can arise in CP may be: (1) nausea, vomiting and epigastric pain, secondary to duodenal obstruction by compression of the pancreatic head, (2) jaundice and cholestasis due to stenosis of the intra-pancreatic choledoch, (3) signs/symptoms secondary to portal hypertension, (4) signs/symptoms secondary to the formation of pseudocysts.

Complications [1]

- Portal vein thrombosis and portal hypertension in 1%.
- Jaundice due to low biliary stricture.
- Pancreatic pseudocyst formation.
- Pancreatic cancer develops in approximately 3% of patients (eightfold risk over general population).
- Life expectancy in patients with chronic pancreatitis is shortened by 10–20 years.

Forms

Patients with chronic pancreatitis seek medical attention predominantly because of two symptoms: abdominal pain or maldigestion [9]. The abdominal pain may be quite variable in location, severity, and frequency. The pain can be constant or intermittent with frequent pain-free intervals. Eating may exacerbate the pain,leading to a fear of eating with consequent weight loss. The spectrum of abdominal pain ranges from mild to quite severe with narcotic dependence as a frequent consequence. Maldigestion is manifested as chronic diarrhea, steatorrhea, weight loss, and fatigue. Patients with abdominal pain may or may not progress to maldigestion, and ~20% of patients will present with symptoms of maldigestion without a history of abdominal pain. Patients with chronic pancreatitis have significant morbidity and mortality and utilize appreciable amounts of societal resources. Despite the steatorrhea, clinically apparent deficiencies of fat-soluble vitamins are surprisingly uncommon. Physical findings in these patients are usually unimpressive so that there is a disparity between the severity of abdominal pain and the physical signs, which usually consist of some mild tenderness and mild temperature elevation.

It is helpful to differentiate chronic pancreatitis into its different forms. One obvious demarcation is whether the patient has small-duct or large-duct disease. The pathogenesis, diagnostic approach, clinical course, and treatment results vary greatly between these two forms of chronic pancreatitis. In contrast to acute pancreatitis, the serum amylase and lipase levels are usually not elevated in chronic pancreatitis. Elevation of serum bilirubin and alkaline phosphatase may indicate cholestasis secondary to chronic inflammation and/or stricture around the common bile duct. Many patients have impaired glucose tolerance with elevated fasting blood glucose levels. The diagnostic test with the best sensitivity and specificity is the hormone stimulation test utilizing secretin. It becomes abnormal when ≥60% of the pancreatic exocrine function has been lost. This usually correlates well with the onset of chronic abdominal pain.

Alcohol

Alcohol consumption is the major cause of chronic pancreatitis in Western societies [10]. The incidence of chronic pancreatitis at autopsy is 50 times higher in alcoholics than in nondrinkers, and there appears to be a direct relationship between daily alcohol consumption and the risk of chronic pancreatitis. Prolonged alcohol intake is usually required before chronic pancreatitis develops (eg, four pints of beer or 800 mL of wine per day for 6–12 years). Only 15% of alcoholics with this level of intake ultimately develop chronic pancreatitis, and this suggests that other factors such as diet (particularly one high in fat), genetic predisposition, or some other cofactor may also be important. In Western societies, 70% of cases of chronic pancreatitis are the result of alcohol consumption, with the remaining 30% due to other causes or idiopathic disease. The mechanism by which alcohol produces pancreatic injury and chronic pancreatitis is unknown. Alcohol appears to interfere with intracellular transport and secretion of digestive enzymes and augments the pancreatic response to cholecystokinin. In addition, alcohol promotes the formation of protein precipitates in the pancreatic duct. Whether these changes entirely explain the development of chronic pancreatitis remains to be elucidated.

Most patients with alcoholic chronic pancreatitis have an early phase of recurrent attacks of acute pancreatitis and later develop more chronic abdominal pain. Most patients (80%) who present with an acute attack of alcoholic chronic pancreatitis will ultimately progress to clear-cut chronic pancreatitis. Continued alcohol abuse after diagnosis hastens the pace of pancreatic damage, although, unfortunately, complete abstinence cannot prevent ongoing damage. The prognosis of alcoholic chronic pancreatitis is poor, with the frequent development of exocrine or endocrine insufficiency and increased mortality due to the consequence of continued alcohol abuse.

MRI

The diagnosis of CP on MRI (Magnetic Resonance Imaging) is based on signal intensity and enhancement changes as well as on morphologic abnormalities in the pancreatic parenchyma, pancreatic duct, and biliary tract [11]. The imaging features of CP can be divided into early and late findings. Early findings include low-signal-intensity pancreas on T1w FS (Fat-Suppression) images, decreased and delayed enhancement after IV contrast administration, and dilated side branches. Late findings include parenchymal atrophy or enlargement, pseudocysts, and dilatation and beading of the pancreatic duct often with intraductal calcifications.

MRI allows early recognition of CP based on changes in pancreatic signal intensity; these changes are best visualized on unenhanced and gadolinium-enhanced T1w FS images. Chronic inflammation and fibrosis diminish the proteinaceous fluid content of the pancreas, resulting in the loss of the usual high signal intensity on T1w FS images. The normal pancreas enhances uniformly and intensely on late arterial phase contrast-enhanced T1w FS images and exhibits rapid washout of gadolinium on subsequent images. In contrast, a pancreas with chronic fibrosis and glandular atrophy exhibits decreased and

heterogeneous enhancement on late arterial phase images and increased relative enhancement on delayed images.

Until recently, the role of MRCP (magnetic resonance cholangiopancreatography) in cases of CP was limited to diagnosis and follow-up of advanced cases. Owing to spatial resolution that is lower than that of ERP (Endoscopic Retrograde Pancreatography) , ductal abnormalities in cases of mild CP cannot be assessed at MRCP. Side branches usually are depicted only when dilated. Moreover, the condition in which the pancreatic ductal system is demonstrated at MRCP differs from that in which it is depicted during ERP. Indeed, in ERP, retrograde injection of contrast medium creates enlargement of the ducts, whereas in MRCP, the physiologic or physiopathologic ductal liquid content is demonstrated.

ERP by many is the standard of reference for imaging the pancreaticobiliary system because of its high image resolution and the advantage of allowing therapeutic intervention. ERP is useful especially for depicting side branch changes of early CP. Today, diagnostic ERP is challenged by MRCP, which is a noninvasive diagnostic alternative to ERP for the morphologic evaluation of normal and diseased pancreatic ducts. The administration of secretin during MRCP may help detect subtle side branch abnormalities and allows noninvasive assessment of exocrine pancreatic function. Duct abnormalities such as dilatation, irregularity, and stones and complications of CP such as pseudocysts are best depicted by thin-section T2w and thick-slab T2w MRCP images. MRCP is accurate in depicting strictures of the pancreatic duct or biliary tract. The beaded main pancreatic duct with its dilated side branches may have a chain-of-lakes appearance when more extensive.

Diagnosis

Over the past five decades, several classification schemes for chronic pancreatitis have been proposed, each of which has put a different focus on clinical, imaging, and morphological features [12]. Etiology has become an increasingly important criterion for the characterization of the disease, in particular as the genetics of pancreatitis are gradually elucidated. Whereas formerly, chronic pancreatitis was believed to be almost exclusively induced by environmental factors, the relationship between genetic predisposition and exposure to the environment has become a central concept in the understanding of the pathogenesis of this disease.

In all continents, alcohol overconsumption is the most frequent cause of chronic pancreatitis. About 70 % of pancreatitis cases are attributable to chronic heavy alcohol drinking.

Tobacco smoking contributes to the risk of chronic pancreatitis, and smoking and alcohol consumption are suspected to act synergistically with regard to the pancreatitis-associated risk for pancreatic cancer. Chronic obstruction is a further not uncommon cause of chronic pancreatitis, and the nature of the obstruction can be manifold. Hereditary chronic pancreatitis, that is, pancreatitis with a genetic pathogenesis. Tropical pancreatitis forms a small subgroup in which the exclusive geographical distribution is the main characteristic feature, while the underlying etiology is possibly a complex interaction between environmental and genetic factors. Autoimmune pancreatitis and groove pancreatitis have a distinct etiological basis. Other rare causes of chronic pancreatitis include radiation injury, metabolic diseases (many of which are hereditary) , and medication. In approximately 25 % of patients, a cause cannot be identified, and the disease is classified as idiopathic chronic pancreatitis.

Diagnosis of CP includes evaluation of the morphologic and functional (exocrine and endocrine) alterations [13]. Transabdominal ultrasonography (USG) can show pancreatic atrophy and a dilated pancreatic duct. Contrast enhanced computed tomography (CECT) scan of the abdomen provides reliable evidence of the pancreatic parenchymal volume, localization of pancreatic stones and calcifications, complications such as pseudocyst, and presence of a cancer. MRI/MRCP is helpful in identifying altered ductal anatomy such as dilatation, strictures, leaks, and communication between the pancreatic duct and pseudocysts. In addition, it has the advantage of avoidance of radiation exposure. The above tests are however, not sensitive enough to detect very early changes of CP, in which case endoscopic ultrasonography (EUS) plays an important role. EUS is an operator dependent procedure which requires expertise and experience. With increasing experience it is becoming apparent though that EUS has the tendency to over diagnose early CP. Endoscopic retrograde cholangiopancreatography (ERCP) is seldom used as a diagnostic tool.

Pancreatic function tests (direct and indirect) can be used to assess secretory function of the pancreas. The direct function tests are used to access pancreatic bicarbonate or exocrine enzyme secretion in response to secretin and cholecystokinin stimulation respectively.

Since 1963 several classifications of chronic pancreatitis have been introduced [14]. These classifications were mainly concerned with the distinction between acute and chronic pancreatitis. Moreover, they focused primarily on alcohol-induced chronic pancreatitis and only marginally considered the nonalcoholic types. Finally, none of the classifications correlated the etiology with the morphologic, functional, and clinical features. Hence there is still a need for a classification that includes all currently available criteria for characterizing the various types of chronic pancreatitis.

Management

The management of pain in chronic pancreatitis can be difficult [2]. Pain is the most common symptom that brings the patient to medical attention, and can range from mild and intermittent, to constant and disabling. Patients should be advised to abstain from alcohol. Small meals, low in fat, may also be helpful.

First-line therapy should always be with basic analgesics like acetominaphen (paracetamol), dihydrocodeine, NSAIDs (nonsteroidal anti-inflammatory drugs) etc. More often, narcotic analgesics are required to control pain. As narcotic dependence can become an important problem, a single practitioner should be identified as the designated prescriber. Before considering longterm narcotic analgesics, short-term hospitalization with the patient kept ‘nil by mouth’ to minimize pancreatic stimulation and simultaneous brief course of narcotics with low-dose amitriptyline and NSAIDs may break the pain cycle.

Pancreatic enzyme supplements seem to benefit patients with mild to moderate disease but the results of studies are variable because of a high placebo response rate (33%). The rationale for this therapy is based on the fact that oral administration of trypsin will suppress the feedback loop in the duodenum which regulates the release of cholecystokinin (CCK), the hormone which stimulates the exocrine pancreas.

The use of octreotide in chronic pancreatitis pain is still experimental but preliminary reports have shown promise. Patients with intractable pain in spite of aggressive noninvasive treatment should undergo CT (computed tomography) of the pancreas to look for complications (e.g. pseudocysts) and ERCP (endoscopic retrograde cholangiopancreatography) to assess the pancreatic and biliary tree. Stones in the pancreatic duct can be removed and strictures of the pancreatic duct may be considered for stenting. The studies on the use of plastic endoprostheses across strictures in the pancreatic duct were largely uncontrolled, but symptoms improved in a selected group of patients (50%).

Surgical drainage operations like pancreaticojejunostomy can successfully decompress pancreatic ducts which are larger than 8 mm. In patients with nondilated pancreatic ducts, the disease is largely parenchymal and partial or total pancreatectomy may be considered if symptoms are intractable. Celiac plexus block with alcohol or steroids is useful for unremitting pain.
The goal of surgical or interventional therapy is to improve the patient's quality of life [15]. This has lead to the steady increase of minimally invasive (e.g. endoscopic) therapies replacing "traditional" surgical treatments. The two approaches are complementary. Guidelines are continually being outlined to help the clinician towards an optimal therapeutic choice; however, endoscopic approaches will be favored over surgical when the outcome of treatment is equivalent. Nevertheless, there are few controlled short or long term clinical trials that have compared the results and impacts of the different therapeutic options. Not surprisingly, therapeutic choices are still based on local experience and expertise rather than on medical evidence. Moreover, the absence of a more precise definition of a "painful and disabling" symptom actually makes comparison of inter-institutional experiences considerably less reliable. Many scores and/or questionnaires have been proposed to attempt to make evaluation of pain in CP more "objective".

Patients

Patients with chronic pancreatitis seek medical attention primarily because of chronic or episodic abdominal pain and less frequently for consequences of maldigestion (eg, steatorrhea, weight loss, or malnutrition) or diabetes mellitus [10]. Although most patients develop pain, approximately 15% will develop steatorrhea or diabetes in the absence of pain, and a substantial number will suffer from pain alone and will never develop pancreatic exocrine or endocrine insufficiency. Chronic pancreatitis is defined histologically by irreversible damage to the pancreas with the development of inflammation, fibrosis, and eventually destruction of exocrine and endocrine tissue. The inability to obtain histologic confirmation of disease in most cases has made diagnosis and classification of chronic pancreatitis difficult. Although a series of international panels have attempted to draw up categories and definitions, these have often been based on histology and so have never become useful to clinicians. Other attempts to define and categorize chronic pancreatitis have focused on abnormalities of pancreatic morphology as visualized by computed tomography (CT), ultrasound (US), or endoscopic retrograde cholangiopancreatography (ERCP). Although more useful to clinicians, these are also inadequate as morphologic abnormalities (such as diffuse pancreatic calcifications or a dilated pancreatic duct) may take years to develop and may not even develop in some patients. More recent attempts to categorize chronic pancreatitis have focused more on etiology, but no single, widely accepted method for categorizing chronic pancreatitis exists. Given the rapid pace of our evolving knowledge of the genetic basis of pancreatic disease, it is likely this information will also need to be included in subsequent classification schemes.

Chronic pancreatitis is a progressive disease with variable tempo. Despite the fact that the damage due to the disease is usually irreversible, medical, endoscopic, and surgical therapy can often produce substantial improvement in the major complaints of abdominal pain, maldigestion, and diabetes mellitus.

Chronic pancreatitis is an irreversible and progressive disease, and its pathological hallmarks are inflammation, glandular atrophy, ductal changes, and fibrosis [16]. Although excess alcohol consumption is the most common cause of chronic pancreatitis in developed countries, several other etiologies are known and there are many cases whose etiologies remain unclarified. Also, the exact pathogenic mechanism of chronic pancreatitis has so far remained elusive, in spite of a great deal of cellular, genetic and molecular research. To recognize these histological characteristics is not only helpful in trying to elucidate the causes of pancreatic damage in cases whose etiologies remain clinically unknown, but also necessary to investigate the pathogenic mechanism of chronic pancreatitis. Consequently, patients with chronic pancreatitis exhibit variable degrees of pancreatic exocrine and endocrine dysfunction [17]. Chronic pancreatitis is a complex disease, afflicting heavy drinkers in the majority of cases, but it is also associated with several other causes. Although much is known about the etiological background of the disease, there is still a large group of patients, perhaps 20–25% of the total, in whom the exact cause of the disease is unknown.

Conclusion

Chronic pancreatitis is a consequence of alcoholism, hemochromatosis (accumulation of iron in the liver) and other unknown factors. Inflammation and fibrosis result in destruction of the functional glandular tissue of the pancreas. The result is a

lack of pancreatic enzymes and an inability to digest fat. Insulin production is also impaired. Seizures are becoming more common with the development of the disease. Chronic pancreatitis marks the spectrum of various inflammatory changes that progressively lead to the loss of all pancreatic functions, both the production of digestive juices and enzymes, and the synthesis of insulin. Pain relief, first of all pain, then slowing down the progression of chronic inflammatory changes and treating complications are the basic requirements that a physician sets.

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