Chronic pancreatitis

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Abstract

Chronic pancreatitis is distinguished by structural and functional criteria. Alcohol is the major aetiological factor, but about 20% of patients have another cause such as hereditary pancreatitis. Abdominal pain is the usual presenting feature, often as recurrent attacks of acute pancreatitis but chronic pancreatitis may be clinically silent. The pathogenesis of chronic pancreatitis is incompletely understood. Diagnosis is usually made on imaging (CT, magnetic resonance cholangiopancreatography, endoscopic ultrasound). Complications include exocrine and endocrine insufficiency, obstructive jaundice, duodenal obstruction, left-sided portal hypertension, and the development of pancreatic cancer. Overall management is difficult and depends upon symptoms, morphological characteristics and complications. Treatment options include medical, endoscopic, and surgical strategies; the latter is reserved for patients with complications. Early involvement of a specialist centre in the care of patients with complicated chronic pancreatitis is important and should be encouraged.

Keywords Chronic pain; chronic pancreatitis; exocrine insufficiency; Frey procedure; pancreas

Chronic pancreatitis is characterized by a continuous, prolonged inflammatory process of the pancreas with irreversible morphological changes of fibrosis and stricture formation, resulting in pancreatic exocrine and endocrine insufficiency. It usually presents with abdominal pain but may be painless. The clinical course is also variable. The intensity of pain may range from low to severe even in patients with little evidence of parenchymal or ductal disease on imaging; complex morphological changes may give rise to minimal or extensive symptoms.

Pathophysiology

Most patients with chronic pancreatitis have had one or more attacks of acute pancreatitis resulting in inflammatory change and fibrosis, but some patients have a more insidious onset. The molecular and biochemical mechanisms causing the fibrosis and destruction of the pancreatic parenchyma are largely unknown, but four theories have attracted attention.

- Toxic-metabolic: a direct effect of alcohol combined with poor nutrition.
- Oxidative stress: over-activity in hepatic detoxification enzymes (mixed-function oxidases) that generates free-radical oxidant by-products that are secreted in bile and cause damage to the pancreatic parenchyma by reflux up the pancreatic duct.
- Ductal obstruction and stone formation: an increase in protein secretion with abnormal insoluble forms of protein, combined with an increase in ductal permeability to calcium, resulting in formation of 'protein plugs' and intraductal deposition of calcium.
- Necrosis–fibrosis: the characteristic fibrosis evolves from the recurrent cycles of inflammation and necrosis seen after repeated attacks of acute pancreatitis.

Each hypothesis is undermined by oversimplification; it is likely that a combination of factors is responsible because none accounts for the heterogeneity of clinical phenotypes. Within the pancreas, T-cell-activated cytotoxic cells and activated, pancreatic stellate cells are thought to have a key role. T-cells contribute to the chronic inflammatory process and the degree of lymphocytic infiltration correlates with pain severity. Stellate cells are stimulated by various factors (e.g. oxidative stress, transforming growth factor-β, platelet-derived growth factor). After stimulation, they transform into myofibroblasts and proceed to produce several components of the extracellular matrix, resulting in fibrosis.

Pathogenesis of the severe pain that is a major feature of chronic pancreatitis is incompletely understood, but three theories have emerged:

- increased pressure in the pancreatic ductal system
- parenchymal oedema causing a compartment syndrome
- the neuronal inflammatory mediator hypothesis, where inflammatory mediators (derived largely from infiltrating lymphocytes) are responsible for increased signals along the axons of pain-sensitive neurons.

Incidence

The annual incidence in western Europe is about five new cases per 100,000 population. The male:female ratio is 7:1 and the average age of onset is between 36 years and 55 years.

Aetiology

Alcohol

Alcohol is responsible for 70–80% of cases of chronic pancreatitis (Table 1). There is no uniform threshold for the toxic effects of alcohol on the pancreas, but the quantity and duration of alcohol consumption correlates with the development of chronic pancreatitis. There is little evidence that the type or pattern of consumption is important. It has been suggested that ingestion of 150–200 ml of more than 40% ethanol per volume daily for 10–15 years is needed for clinically significant chronic pancreatitis to develop, but one can assume a patient has alcohol-induced disease if they give a history of heavy use of alcohol. Emerging evidence suggests that the pancreas of one individual may be significantly more sensitive to alcohol than that of another, and that unidentified genetic factors may be responsible for this difference.

Idiopathic

In the UK, the next commonest cause is idiopathic, accounting for 20% of cases (Table 1). Epidemiological evidence suggests

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Causes of chronic pancreatitis

Main causes (90–95%)	Less common causes (5–10%)
• Alcohol 70–80%	• Tropical
• Idiopathic 15–20%	• Hypercalcaemia
	• Hyperlipidaemia
	• Hereditary pancreatitis
	• Autoimmune
	• Gallstones
	• Pancreatic tumours
	• Pancreatic divisum

Table 1

that idiopathic chronic pancreatitis is a distinct entity, and these patients resent the label of 'alcoholic'. Idiopathic chronic pancreatitis affects equal numbers of men and women, and delayed progression of endocrine and exocrine insufficiency is observed.

Other causes

Fewer than 10% of patients with chronic pancreatitis have one of these less common causes. Hereditary pancreatitis is being increasingly recognized and must be suspected in patients with a family history of pancreatitis or diabetes. It is inherited as an autosomal dominant condition with penetrance of 80%, with more than 80% of affected individuals developing clinical disease before the age of 20 years. The activation of trypsin appears to be an important step in the initiation of pancreatitis, therefore failure of mechanisms that prevent inappropriate activation of trypsin could lead to pancreatitis. Point mutations have been identified in the cationic trypsinogen gene (*PRSS1*) located on chromosome 7; example mutations are named R122H, N29I and A16V. The R122H mutation results in the elimination of a failsafe self-destruct, mechanism, which prevents the rapid accumulation of large concentrations of active trypsin in the pancreas. Mutations in the serine protease inhibitor, Kazal type-I (SPINK1), also known as 'pancreatic secretory trypsin inhibitor', have also been described. Patients with hereditary pancreatitis are usually more susceptible to acute attacks of pancreatitis secondary to alcohol and these patients and their relatives should avoid alcohol at all costs. Hereditary pancreatitis carries a substantially increased risk of pancreatic cancer (Figure 1).

Autoimmune pancreatitis is a rare but increasingly recognized cause of chronic pancreatitis. It is associated with autoimmune expression including elevated levels of immunoglobulin G4 (IgG4). Specialist management is required and treatment with corticosteroids will usually lead to resolution of complications including extrapancreatic manifestations.

Clinical features

History

Abdominal pain is the principal presenting feature of chronic pancreatitis. Usually, patients have had pain for months or years before seeking help. This pain, while typically deep, boring and radiating to the back, can be highly variable, ranging from mild to severe. Characteristically, it is eased by sitting upright or by drawing the knees up into the 'jackknife' position. Food consumption may exacerbate the pain, resulting in avoidance and consequential weight loss. Initially, abstinence from alcohol improves the episodic attacks but, as the disease progresses, the pain becomes more chronic, and the beneficial effects of abstinence from alcohol are reduced. Assessment of pain in alcoholic patients can be challenging because of their manipulative personalities and dependency; other surrogate markers may be more helpful including loss of sleep; interference with work or family responsibilities; and hospital admissions.

Pancreatic insufficiency characteristically develops 10–15 years after the onset of pancreatitis and is progressive. Exocrine insufficiency results in deficiency of protein and fat. Steatorrhoea with loose, grey, foul-smelling stools that are difficult to flush away is common. The nutritional status of alcoholic patients is frequently poor and awareness of thiamine deficiency (and Wernicke's encephalopathy) is important.

Endocrine insufficiency resulting in diabetes develops over time and is ultimately dependent on insulin. The medium- to long-term effects of diabetes (e.g. ischaemic heart disease, nephropathy, retinopathy, peripheral vascular disease) are less likely to be clinically significant than in other diabetic patients because of the shorter life expectancy associated with chronic pancreatitis.

Clinical examination

Physical examination may not reveal specific features. Weight loss and malnutrition may be clinically apparent and can be monitored with serial measurements. Erythema *ab igne* on the epigastrium or back represents attempts to relieve the pain by, the application of topical heat. Anaemia, jaundice, ascites and splenomegaly may be detected. Signs of liver failure should be looked for in alcoholic patients (although cirrhosis in patients with chronic pancreatitis is surprisingly rare).

Diagnosis and investigation

Diagnosis in the early stages of chronic pancreatitis can be difficult compared to an advanced stage where it is much more obvious. The principal differential diagnosis is pancreatic cancer, although other causes of pain (Table 2) should also be considered (particularly if presentation is early).

Laboratory tests

Blood tests are, in general, unhelpful; serum amylase, lipase and elastase are usually normal even during an acute painful exacerbation. Other blood tests that should be done are routine haematology, clotting screen and routine biochemistry (including bone and lipid profile) as a baseline.

Liver function tests may be deranged, indicating biliary obstruction; thrombocytopenia may suggest thrombosis of the splenic vein.

Assessment of glycaemic control by blood glucose and HbA_{1c} is essential.

Genetic sequencing with appropriate counselling is involved in the investigation of suspected hereditary pancreatitis.