Acute Pancreatitis: Epidemiology and Etiology

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ABSTRACT

Acute pancreatitis is an acute in ammatory process of the pancreas. The in ammation can remain localized to the gland or can involve other regional tissues or distant organ systems. The diagnosis of acute pancreatitis requires two of the following three features: abdominal pain characteristic of acute pancreatitis; serum amylase and lipase levels three or more times the upper limit of normal; and characteristic findings of acute pancreatitis on cross-sectional imaging. Three degrees of severity were defined in the 2012 revision of the Atlanta Criteria: mild acute pancreatitis, moderately severe acute pancreatitis, and severe acute pancreatitis. The rate of mortality in severe acute pancreatitis is about 20–50% versus none in the mild acute pancreatitis group. The incidence of acute pancreatitis varies in Europe from 4.6 to 100/100 000. In most patients (75–85%) with acute pancreatitis, the etiology of their disease can be determined. In industrialized countries, gallstones and alcohol abuse are the most frequent reasons for acute pancreatitis. The peak incidence for alcoholic pancreatitis is around 35–44 years whereas the incidence of gallstone pancreatitis is commonest in the elderly.

WHAT IS ACUTE PANCREATITIS

Acute pancreatitis in an acute inflammatory process of the pancreas and has various causes. The in ammation can remain localized to the gland or can involve other regional tissues or distant organ systems. The initial step in the pathogenesis of acute pancreatitis is conversion of trypsinogen to trypsin within acinar cells in sufficient quantities to overwhelm normal mechanisms to remove active trypsin. The pathophysiology of acute pancreatitis starts with acinar injury that, if unchecked, leads to local inflammatory complications and systemic inflammatory response. Pathophysiologic mechanisms include microcirculatory injury, leukocyte chemoattraction, release of pro- and anti-inflammatory cytokines, oxidative stress, leakage of pancreatic fluid into the region of the pancreas, and bacterial translocation to the pancreas and systemic circulation. Pancreatic infection (infected necrosis and infected pseudocyst) can occur from the haematogenous route or translocation of bacteria from the colon into the lymphatic system. Under normal circumstances, bacterial translocation does not occur because there are complex immunologic and morphologic barriers to it. Howe-

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ver, during acute pancreatitis, these barriers break down, which can result in local and systemic infection.

Acute pancreatitis is divided into two pathological types: interstitial oedematous pancreatitis and necrotizing pancreatitis. In interstitial oedematous pancreatitis, the gland is di usely enlarged due to in ammatory edema. On macroscopic analysis scattered foci of fat necrosis are found. Haemorrhage and necrosis are absent, and changes resolve partially or completely over the course of one week. The key gross features of necrotizing pancreatitis are necrosis and haemorrhage. The lesion is often patchy in distribution, with con uent areas of varying extent and foci of relatively spared pancreatic tissue anking zones of necrosis and haemorrhage. This in ammatory process involves both peripancreatic tissue and peripheral pancreatic parenchyma, while a core of viable pancreas tissue remains in the center of the gland. Likewise, fat necrosis is not only present in and around the pancreas but also develops at distant sites. Necrosis is usually associated with haemorrhage and may extend into the surrounding tissues, for example, the mesentery and pararenal space, and from there to the subcutaneous tissues leading to discoloration of the ank (Grey Turner's sign) or periumbilical area (Cullen's sign). This destructive in ammation produces a large collection of peripancreatic uid, which is mostly occulent in appearance and fetid in odor. Because many of the constituent cells (acinar, ductal, and islet cells) and tissues (stroma, fat) of the pancreas are a ected, severe in ammation leads to significant organ loss with a reduction in both exocrine and endocrine function. Neutrophils dominate the in ammatory cell infiltrate and increase over time. Blood vessels can be involved in the necrotic process or can develop thrombosis within severely a ected areas of the pancreas (1).

EPIDEMIOLOGY

The incidence of acute pancreatitis in Europe varies from 4.6 to 100/100 000. One local Slovenian study estimated the incidence at 69/100.000 (2). The most common causes were alcohol abuse (39%) and gallstones (39%). Idiopathic or unexplained pancreatitis represented 11%, hyperlipaemic pancreatitis 3%, neoplasia 2% and after endoscopic retrograde cholangiopancreatography (ERCP) 3% of all cases. A review of etiologies of pancreatitis in Europe concluded that the highest ratios of gallstone to alcohol etiologies were identified in Southern Europe (Greece, Turkey, Italy and Croatia) with lowest ratios mainly in Eastern Europe (Latvia, Finland, Romania, Hungary, Russia and Lithuania) (3).

As the population is becoming increasingly overweight, the incidence of gallstones, the most common cause of acute pancreatitis, is rising. An increase in the annual incidence of acute pancreatitis has been observed in most recent studies. The overall mortality rate from acute pancreatitis appears to be decreasing gradually to less than 5%. The rate of mortality in severe acute pancreatitis is about 20–50% versus none in the mild acute pancreatitis group. In alcoholic acute pancreatitis the incidence peaks in the 35–44-year age group, and the highest incidence of acute biliary pancreatitis is among the eldest age groups (65+ years).

Approximately 75–80% of patients with acute pancreatitis, have a quick resolution of the disease process (interstitial pancreatitis) without long-term sequelae. However, in close to 20% of patients, a more protracted course develops, often related to the necrotizing process (necrotizing pancreatitis) lasting weeks to months. Mortality is related to a combination of factors, including organ failure secondary to sterile necrosis, infected necrosis, or complications from surgical intervention. There are two peaks for mortality in acute pancreatitis. Most studies in the United States and Europe reveal that about half the deaths occur within the first week or two, usually from multiple organ failure. Death can be very rapid. About one-quarter of all deaths in Scotland occurred within 24 hours of admission, and one third within 48 hours. After the second week of illness, patients succumb to pancreatic infection associated with multiple organ failure. Some studies in Europe report a very high late mortality rate from infection. It is unclear if high rate of late mortality from infection is related to endoge-

nous infection of the pancreatic necrosis or surgical interventions for infectious complications.

CLINICAL PICTURE

Most patients with acute pancreatitis experience abdominal pain, usually in the epigastrium, with radiation to the back in approximately half of cases. The onset may be swift, with pain reaching maximum intensity within 30 minutes, frequently unbearable, and characteristically persists without relief for more than 24 hours. The pain is often associated with nausea, vomiting, fever, tachycardia, leucocytosis, and elevated pancreatic enzyme levels in the blood and urine. Physical examination usually reveals moderate to severe upper abdominal tenderness often associated with guarding. These clinical findings parallel pathological changes with microscopic interstitial edema and fat necrosis of the pancreas. These alterations can extend to large areas of pancreatic and peripancreatic necrosis and haemorrhage.

The 2013 Atlanta Criteria define three grades of pancreatitis: mild acute pancreatitis, moderately severe acute pancreatitis, and severe acute pancreatitis (4). This classification includes criteria of transient organ failure, persistent organ failure, and local or systemic complications. Mild acute pancreatitis is characterized by the absence of organ failure and the absence of local or systemic complications. Patients with mild acute pancreatitis respond to appropriate uid administration with prompt normalization of physical signs and laboratory values. These patients can usually be discharged during the early phase. Moderately severe acute pancreatitis presents with transient organ failure or local or systemic complications in the absence of persistent organ failure. Peripancreatic uid collection defines a local complication, resulting in prolonged abdominal pain, leucocytosis and fever, and potentially preventing the implementation of enteral nutrition. This form of acute pancreatitis may resolve without intervention or may require a prolonged care. Mortality of moderately severe acute pancreatitis is far less than that of severe acute pancreatitis. Severe acute pancreatitis is defined by persistent organ failure and local complications, such as necrosis, abscess, or pseudocyst. The mortality rate in severe acute pancreatitis is about 20–50% versus none in the mild acute pancreatitis group.

DIAGNOSIS

The diagnosis of acute pancreatitis requires two of the following three features: abdominal pain characteristic of acute pancreatitis; serum amylase and/or lipase three or more times the upper limit of normal; and characteristic findings of acute pancreatitis on transabdominal US, contrast-enhanced CT scan or MRI. This definition allows for the possibility that an amylase and lipase might be less than three times the upper limit of normal in acute pancreatitis. In a patient with abdominal pain characteristic of acute pancreatitis and serum enzyme levels that are lower than three times the upper limit of normal, a CT scan must be performed to confirm a diagnosis of acute pancreatitis (1).

ETIOLOGY

Obstruction

The most common obstructive process leading to pancreatitis are gallstones, which cause approximately 40% of cases of acute pancreatitis. However, only 3–7% of patients with gallstones develop pancreatitis. Gallstone pancreatitis is more common in women than men because gallstones are more frequent in women. Acute pancreatitis occurs more frequently when stones are less than 5 mm in diameter because small stones are more likely than large stones to pass through the cystic duct and cause ampullary obstruction. Cholecystectomy and clearing the bile duct of stones prevents recurrence, confirming the cause-and-effect relationship. Biliary sludge is a viscous suspension in gallbladder bile that may contain small (< 3 mm) stones (i.e. microlithiasis). Because small stones can hide in biliary sludge, the two are commonly referred to together as biliary sludge and microlithiasis. Biliary sludge is asymptomatic in most patients. It is usually composed of cholesterol mono-

hydrate crystals or calcium bilirubinate granules. On US, sludge produces a mobile, low-amplitude echo that does not produce an acoustic shadow and that layers in the most dependent part of the gallbladder. Sludge may result from functional bile stasis, such as that associated with prolonged fasting or total parenteral nutrition, or from mechanical stasis such as occurs in distal bile duct obstruction. Commonly, biliary sludge is found in patients with idiopathic acute pancreatitis. Multiple studies have found that cholecystectomy reduces the recurrence of idiopathic pancreatitis by approximately half (5, 6).

The pathogenesis of gallstone-related pancreatitis is unknown. Factors that may initiate gallstone pancreatitis include reflux of the bile into the pancreatic duct or obstruction of the pancreatic duct at the ampulla from stone(s) or oedema resulting from the passage of a stone. Reflux of the bile into the pancreatic duct could occur when the distal bile and pancreatic ducts form a common channel, and a gallstone becomes impacted in the duodenal papilla. Alternatively, bile could reflux into the pancreatic duct from the duodenum through an incompetent sphincter of Oddi injured by recent passage of a gallstone.

Experimentally, reflux of the bile into the pancreatic duct, particularly if the bile is infected or mixed with pancreatic enzymes, causes pancreatic injury. The mixture of bile and pancreatic enzymes increase the permeability of the main pancreatic duct, which is associated with local parenchymal inflammation. The common channel theory is somewhat problematic because pancreatic duct pressure is invariably higher than bile duct pressure, making bile reflux into the pancreatic duct unlikely. Reflux of the bile from the duodenum is also unlikely because pancreatitis does not occur in conditions with easily demonstrable reflux, such as after surgical sphincteroplasty or endoscopic sphincterotomy (7).

A popular theory for the mechanism of gallstone pancreatitis is that an impacted gallstone in the distal bile duct obstructs the pancreatic duct, increasing pancreatic pressure, thereby damaging ductal and acinar cells. Experiments in the opossum supporting this theory are the observations that ligation of the pancreatic duct causes severe necrotizing pancreatitis and that decompression of the ductal system within three days prevents progression to acinar cell necrosis and severe inflammation.

Even small tumours in the pancreas can obstruct the duct and induce repetitive episodes of acute pancreatitis. Patients with pancreatic adenocarcinoma rarely develop acute pancreatitis even when the tumor obstructs the duct completely. Also, intraductal papillary mucinous neoplasm and adenomas of the major papilla can cause acute pancreatitis.

Alcohol

Alcohol causes at least 30% of cases of acute pancreatitis, and alcohol is the most common etiology of chronic pancreatitis in developed countries. Interestingly, only 10% of chronic alcoholic patients develop chronic pancreatitis. The classic teaching is that alcohol causes chronic pancreatitis and that alcoholic patients who present with clinically acute pancreatitis have underlying chronic disease. However, a small percentage of patients with alcohol-induced acute pancreatitis by clinical criteria do not have, or progress to, chronic pancreatitis, even with continued alcohol abuse. By contrast, a small percentage of chronic alcoholic patients develop attacks of acute pancreatitis that are indistinguishable from other forms of acute pancreatitis but eventually develop chronic pancreatitis after 10–20 years of alcohol abuse. Early in the course of the disease, when attacks occur, the diagnosis of underlying chronic pancreatitis is difficult without tissue specimens, because the diagnosis of chronic pancreatitis is usually made after definite signs of chronic pancreatitis appear (e.g. pancreatic calcification, exocrine and endocrine insufficiency, or typical duct changes by CT or ERCP). Most of the models described suggest possible mechanisms of alcohol-related injury, including perturbations in exocrine function, changes in cellular lipid metabolism, induction of oxidative stress, and activation of stellate cells. However, the exact mechanism of pancreatic damage

by ethyl alcohol remains unclear and may be related to other factors. Alcohol could be directly toxic to the acinar cell because it causes lipid accumulation, leading to cellular necrosis and eventual fibrosis. However, in contrast to what is seen in liver disease, a steatopancreatitis precursor to fibrosis has not been demonstrated. It is interesting that years of alcohol exposure are required for precipitation of alcoholic pancreatitis. Alcohol increases the mitogenicity of pancreatic fluid, leading to formation of protein plugs and stones. Ductal obstruction by stones can lead to stasis of pancreatic fluid and further stone formation, eventually leading to atrophy and fibrosis of the glad.

In contrast to the stone theory, which is based on the development of fibrosis without acute pancreatitis, the necrosis-fibrosis hypothesis entails the development of fibrosis from recurrent, perhaps subclinical, attacks of acute pancreatitis. Inflammation and necrosis from the initial episodes of acute pancreatitis produce scarring in the periductular areas, and scarring obstructs the ductules, leading to stasis within the duct and subsequent stone formation. Support for this theory comes from histopathologic studies that revealed mild perilobular fibrosis in resolving acute pancreatitis, with marked fibrosis with ductal distortion occurring later. It is thought that a stepwise progression occurs to fibrosis from recurrent episodes of acute pancreatitis. The correlation between the frequency and severity of acute attacks to the rate of progression to chronic pancreatitis supports this theory.

Drugs

Medications are an infrequent but important cause of acute pancreatitis. Although there are reports that drug-induced acute pancreatitis accounts for 1–4% of all cases, drug-induced acute pancreatitis probably accounts for less than 1% of cases. More than 120 drugs have been implicated, mostly from anecdotal case reports, however, clinicians must be careful not to blame a drug when a patient with acute pancreatitis does not have an obvious underlying cause. Many of the published case reports suffer from a combination of inadequate criteria for the diagnosis of acute pancreatitis, failure to rule out more common causes, or a lack of a rechallenge with the medication. Also, many case reports inappropriately implicate drugs when the latter have been administered for very long periods (> 6 months) before the onset of acute pancreatitis. Drug-induced pancreatitis tends to occur within 4–8 weeks of beginning a drug.

Lipids

Hypertriglyceridemia is the third most common identifiable cause of pancreatitis after gallstones and alcoholism, accounting for 2–5% of cases. Serum triglyceride concentrations above 11 mmol/L may precipitate attacks of acute pancreatitis. The pathogenesis of hypertriglyceridaemic pancreatitis is unclear, but the release of free fatty acids by lipase may damage pancreatic acinar cells or endothelial cells. Most people who abuse alcohol have moderate but transient elevations of the serum triglyceride levels because alcohol itself not only damages the pancreas but also increases serum triglyceride concentrations in a dose-dependent manner. In contrast with acute pancreatitis from other causes, the serum amylase and lipase level may not be substantially elevated at presentation.

Hyperkalaemia

Hyperkalaemia of any cause is rarely associated with acute pancreatitis. Proposed mechanisms include deposition of calcium salts in the pancreatic duct and calcium activation of trypsinogen within the pancreatic parenchyma

Trauma

Either penetrating trauma (gunshot or stab wounds) or blunt trauma can damage the pancreas. In most cases, there is also injury to adjacent viscera.

Post-endoscopic retrograde cholangiopancreatography pancreatitis

Acute pancreatitis is the most common and feared complication of ERCP, associated with substantial morbidity and occasional mortality. Around 2000 ERCPs are performed annually in Slovenia. Asymptomatic hyperamylasemia occurs commonly after ERCP, probably because of absorption of pancreatic enzymes through the papillotomy cut. Clinical acute pancreatitis occurs in 5% of diagnostic ERCPs, 7% of therapeutic ERCPs, and up to 25% in those with suspected sphincter of Oddi dysfunction or in those with a history of post-ERCP pancreatitis.

The mechanisms that lead to post-ERCP pancreatitis are complex and not fully understood. Rather than a single pathogenesis, post-ERCP pancreatitis is believed to be multifactorial, involving a combination of chemical, hydrostatic, enzymatic, mechanical, and thermal factors. Some risk factors have been identified as predictors of post-ERCP:

- Patient-related: young age, female gender, suspected sphincter of Oddi dysfunction, recurrent pancreatitis, history of post-ERCP pancreatitis, normal serum bilirubin level;
- Procedure-related: pancreatic duct injection, difficult cannulation, pancreatic sphincterotomy, precut access, balloon dilation;
- Operator- or technique-related: trainee participation, non-use of a guidewire for cannulation, failure to use a pancreatic duct stent in a high-risk procedure.

Pancreatitis may develop in up to 24 hours after ERCP. Studies have found serum pancreatic enzymes after ERCP as useful predictors of pancreatitis development. Serum amylase values above four-times the upper limit of normal or lipase levels above eight-times the upper limit of normal four hours after completing the procedure have a high specificity (> 90%) for predicting post-ERCP pancreatitis (8). Conversely, if the serum amylase was less than 1.5-times the upper limit of normal or lipase less than two-times the upper limit of normal, pancreatitis was unlikely. In the presence of abdominal pain, a normal serum amylase and/or lipase rules out acute pancreatitis at that moment.

A recent multicentre, double-blinded, randomized controlled trial of 602 patients undergoing a high-risk ERCP demonstrated a significant reduction of post-ERCP pancreatitis when given post-procedure rectal indomethacin (9). Other than rectal nonsteroidal anti-inflammatory drugs have failed to show any consistent benefit in multiple randomized studies evaluating several drugs.

Pancreatic stent placement decreases the risk of post-ERCP pancreatitis in high-risk patients and has become a standard practice for patients who are thought to be at high risk for pancreatitis after the procedure. It is effective presumably by preventing cannulation-induced oedema that can cause pancreatic duct obstruction. In all reported studies, which cumulatively include 1500 high-risk patients undergoing ERCP, only one patient developed severe pancreatitis after a pancreatic duct stent had been placed (10).

Guidewire cannulation, whereby the biliary or pancreatic duct is initially cannulated by a guidewire inserted through the catheter or sphincterotome, has been shown to decrease the risk of pancreatitis, However, the decrease in post-ERCP pancreatitis could to be related to a decreased need for precut sphincterotomy in patients undergoing guidewire cannulation.

Pancreas divisum

Pancreas divisum is the most common congenital malformation of the pancreas, occurring in 5–10% of the general healthy population, the vast majority of who never develop pancreatitis. Controversy continues to surround the issue as to whether pancreas divisum with otherwise normal ductal anatomy is a cause of acute recurrent pancreatitis.

Sphincter of Oddi dysfunction

Sphincter of Oddi dysfunction is also a controversial cause of acute pancreatitis. The main argument in favour of this entity as a cause of acute pancreatitis is the many observational series that report that endoscopic pancreatic sphincterotomy or surgical sphincteroplasty reduces recurrent attacks of pancreatitis. However, a recent prospective study found that despite endoscopic therapy, patients with pancreas divisum or Sphincter of Oddi dysfunction had recurrent attacks in 50% and 55%, respectively (11).

Genetic Factors

Genetic mutations in the trypsinogen gene or trypsin inhibitors have been well documented as a cause of chronic pancreatitis. Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene have also been implicated in acute and chronic pancreatitis. The CFTR anion channel allows for chloride and bicarbonate secretion into the pancreatic ducts and thus allows flushing of the liberated enzymes and proenzymes into the duodenum. There are more than 1200 mutations that have been described for the CFTR gene. Some of these are considered severe and some mild. Homozygous severe mutations produce a viscid, concentrated, acidic pancreatic juice leading to ductal obstruction and pancreatic insufficiency in infanthood. Heterozygotes of minor or major mutations may lead to acute recurrent or chronic pancreatitis by altering acinar or ductal cell function (e.g. alteration of bicarbonate conductance) (7). CFTR mutations associated with pancreas divisum could have a synergistic effect in the pathogenesis of acute pancreatitis. Although most patients with pancreas divisum (7–10% of the general population) never develop pancreatic disease, it may be that those persons who also harbour dysfunction in the CFTR transporter are at risk of developing pancreatitis when both are present in the same host (1).

Autoimmune pancreatitis

Autoimmune pancreatitis typically presents as a mass or fullness in the pancreas or with signs and symptoms of chronic pancreatitis. Acute pancreatitis resulting from autoimmune pancreatitis is rare.

Rare causes

Rare causes of pancreatitis are systemic or local ischemia as a result of vasculitis, emboli or intraoperative hypotension. Infection with viruses or parasites can cause pancreatitis. *Ascaris lumbricoides* is a frequent cause of pancreatitis in some countries. Anatomic developmental disorders such as annular pancreas, choledohocele or peripapillary diverticula can are have also been implicated as causes of acute pancreatitis.

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