Acute pancreatitis

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Abstract

Acute pancreatitis is a common diagnosis and its incidence may be rising. The most common aetiological agents remain gallstones and alcohol misuse. Eighty per cent of patients will have a mild attack which resolves within a few days without specific treatment. Severe disease is characterized by a significant systemic inflammatory response which may be associated with varying degrees of organ dysfunction. The mortality in patients with multi-organ failure may be as high as 50%. This article reviews the definition, aetiology, pathophysiology, therapeutic strategies and outcomes in light of recent evidence.

Keywords Acute pancreatitis; multi-organ failure; necrosectomy; pancreatic necrosis; severity scoring

General considerations

Epidemiology

The incidence of acute pancreatitis (AP) varies between populations, (4.9 to 35 per 100,000 population), being reportedly higher in the USA and other European countries than in the UK.[1] Overall incidence is rising with a 100% increase in the hospitalization rate in the USA over the last 20 years, a 75% increase in admissions in the Netherlands and a 3.1% yearly rise in incidence in the UK.[2] The mean age at presentation is 53 years with a roughly equal gender distribution, although the largest increase in incidence has been among women under 35 years. Socioeconomic deprivation confers a twofold increase in incidence. The overall mean hospital stay is around 7 days, suggesting that most cases are mild and settle spontaneously. One in five cases, however, will develop organ failure with or without local complications − defined as severe AP. In the first week after admission organ failure persisting for more than 2 days of supportive care has profound prognostic implications.[3] Half of the deaths attributable to AP occur within the first 7 days of admission, with the majority in the first 3 days. Patients with severe AP who survive this first phase of illness are at risk of developing secondary infection of pancreatic necrosis. Mortality in patients with infected necrosis and organ failure may reach 30−40% and an increased mortality is seen with increasing age.

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Aetiology

Some 40% of cases of AP are linked to gallstones. Gallstones are common in the general population and European studies estimate prevalence rates in excess of 20% in females and 11−15% in males over the age of 60 years. Population studies have suggested that 3−7% of patients with gallstones will develop AP. The mechanism by which gallstones induce AP is not certain but increased pressure in the pancreatic duct due to transient mechanical obstruction at the ampulla is thought to be the likely initiating event. This is believed to lead to the activation of pancreatic enzymes and development of a local inflammatory response. Smaller stones pass through the cystic duct more easily and are at increased risk of precipitating AP. Endoscopic ultrasound is more sensitive than transabdominal ultrasound at identifying biliary microlithiasis and should be considered in the diagnostic algorithm prior to labelling patients with idiopathic recurrent AP.

Alcohol is the other major cause of AP, depending on the level of consumption and misuse prevailing in the population. It appears that the incidence in Northern Europe is rising. The exact mechanism whereby alcohol causes AP is still unclear and several theories have been proposed. As in gallstone AP, despite a high prevalence of alcohol misuse, only 10% of chronic alcohol abusers eventually present with AP. The risk is highest in young males who drink in excess of 80 g of alcohol per day. Many patients with a significant alcohol history may also have gallstones and these should be excluded. Smoking has been considered a significant cofactor in the development of alcohol-related pancreatitis, but large population-based studies have established it as an independent risk factor for acute and chronic pancreatitis, with dose-dependant and time-dependent increases in hazard ratios observed.[4]

Endoscopic retrograde pancreatography (ERCP) is the most common cause of iatrogenic AP. Post-ERCP hyperamylasaemia is not uncommon and should not be equated with pancreatitis. Post-ERCP pancreatitis refers to a condition where the patient develops abdominal pain associated with hyperamylasaemia requiring hospitalization after ERCP. Six out of fifteen fatal ERCP lawsuits in the United States were due to pancreatitis and it is therefore advised that patients should be counselled appropriately prior to the procedure. Conversely, the clinician should always be aware that pain and hyperamylasaemia following ERCP may be caused by duodenal perforation, especially when a sphincterotomy has been performed. In this setting we have a low threshold for investigating patients with urgent computerized tomography (CT). The incidence of post-ERCP AP ranges from 0 to 10%. Risk factors are a normal pancreas, therapeutic procedures (including balloon sphincteroplasty), low operator case-load, female gender, young age, sphincter of Oddi dysfunction (30% of such patients may develop AP), pancreatic duct injection (especially high pressure) and previous post-ERCP AP. Several drugs have been tested for their prophylactic potential. A recent multicentre, double-blind, randomized placebo controlled trial of 602 patients undergoing high-risk ERCP (the majority with sphincter of Oddi dysfunction) revealed a significant reduction in the incidence of pancreatitis in those who received rectal indomethacin following the procedure compared

to a placebo (9.2% versus 16.9%).[5] In an era when CT and magnetic resonance imaging (MRI) are readily available, there is no place for early diagnostic ERCP in the non-septic jaundiced patient. More often than not the risks outweigh the benefits in this setting.

Other iatrogenic causes of AP include pharmaceutical agents (amongst them: furosemide, corticosteroids, thiazides, sulindac, azathioprine, various antibiotics and pentamidine) as well as biliary, pancreatic and gastric surgery. However, attributing AP to a specific drug should be avoided unless viral titres and adequate biliary investigations (i.e. EUS) have been undertaken. Repeat exposure resulting in a further episode of AP is the strongest evidence of a direct causal association. Specific viral infections associated with AP include mumps, Coxsackie B, viral hepatitis and increasingly HIV infection.[6]

Hypertriglyceridaemia in excess of 11 mmol/litre is known to precipitate AP and has been reported as the cause of AP in up to 4% of patients. However, no correlation between triglyceride levels and severity has been observed. Hypercholesterolaemia is not associated with pancreatitis.

Hypercalcaemia (of any cause) may cause pancreatitis, possibly by calcium crystal deposition in the pancreatic ducts or by calcium mediated activation of pancreatic enzymes. It should be noted, however, that in a large population of patients with hyperparathyroidism only 1.5% developed acute pancreatitis.

Any **benign or malignant mass** that obstructs the main pancreatic duct can result in AP. It has been estimated that between 5 and 14% of patients with benign or malignant pancreaticobiliary tumours present with pancreatitis. The entity should be considered in any patient >40 years of age presenting with no clear cause for AP. A dilated distal pancreatic duct may be the sole sign of malignancy on CT and should prompt further investigation, such as EUS.

Autoimmune pancreatitis (AIP) is a rare presentation and is considered as a manifestation of the IgG4-related disease spectrum that is associated with other autoimmune diseases (polyarteritis nodosa, systemic lupus erythematosus, other vasculitides) and inflammatory bowel disease. It usually presents with chronic symptoms of pain, weight loss and jaundice but acute presentations are recognized. The distinguishing features are a sausage-shaped pancreas with ductal strictures, inflammatory infiltrates and high serum titres of immunoglobulin G(4).[7] A key feature in diagnosis is the response to steroid therapy. In some cases focal autoimmune pancreatitis may be difficult to differentiate from malignancy.

Trauma-related hyperamylasaemia usually results from a crush injury to the body of the pancreas against the vertebral column. Clinicians should have a high index of suspicion for associated injury to neighbouring organs. The majority of cases can be managed by simple drainage but transection of the pancreatic duct may necessitate endoscopic (transpapillary stenting) or operative (distal pancreatectomy) interventions.

A genetic predisposition to AP has long been suspected and over recent years the influence of mutations in the PRSS1 (cationic trypsinogen), CFTR (cystic fibrosis) and SPINK1 genes have been recognized.[8] The EUROPAC (European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer) study has observed multiple families and patients who usually have a long history of recurrent abdominal pain from childhood or adolescence, and changes of chronic pancreatitis are often present by the age of 20–40 years.[8] They have a significantly increased lifetime risk of pancreatic cancer. Recurrent idiopathic attacks, especially if also experienced by relatives should alert the clinician to seek genetic advice. The development of AP is a complex interplay of environmental and, as yet incompletely characterized genetic factors.

Congenital or acquired anatomical abnormalities can occasionally present with AP. Examples including choledochal cysts, duodenal duplication and secondary fibrosis of the pancreatic duct causing ductal obstruction. The association between AP and pancreas divisum remains controversial and is probably overstated.

The UK guidelines for the management of acute pancreatitis issued by the British Society of Gastroenterology (BSG) in 2005 are now largely out of date.[9] However, these guidelines stipulate that no more than 20–25% of cases of AP should be termed idiopathic. No equivalent figures are provided in more recent guidelines issued by the International Association of Pancreatology/American Pancreatic Association (IAP/APA) (2012) and the American College of Gastroenterology (2013).[10,11] Idiopathic AP requires a thorough investigative strategy with exclusion of all of the causes described above. It should be noted that hyperamylasaemia with no evidence of pancreatitis is not uncommon and patients with multiple other pathologies may be misdiagnosed as suffering from AP.

Pathophysiology

The mechanisms giving rise to AP and its complications are complex and still incompletely understood. Whatever the aetiology, AP commences as a sterile inflammatory process. Premature activation of zymogens appears to be crucial in the initiation of pancreatic injury. The trigger is still elusive but circumstantial evidence implicates cathepsin B which is a lysosomal serine protease. Zymogen activation results in the release of active enzymes such as trypsin (from trypsinogen) which in turn activates other proteases leading to acinar cell injury by unchecked autodigestion. Alcohol may generate aldehydes and esters which are directly toxic to the pancreatic acinar cells. Moreover it may sensitize acinar cells to the effect of cholecystokinin, potentiating the latter's effect on zymogen synthesis and activation. Both acute alcohol intake and chronic alcohol exposure result in a highly charged monocyte response to inflammatory signals and may contribute to increased inflammation in pancreatitis.

The first phase of AP is characterized by calcium-mediated enzymatic activation and cellular injury giving rise to abdominal pain and other early symptoms. The systemic inflammatory response (SIRS) emerges as the second phase in AP. This variable systemic process depends on the circulatory interplay of pro-inflammatory cytokines (such as Il-1, Il-2, Il-6, TNF-α and nitric oxide) and anti-inflammatory mediators. SIRS, as well as organ dysfunction, may therefore develop early in the absence of established necrosis and infection. Necrosis is itself a potent monocyte activator which results in TNF-α production. The