Acute pancreatitis: Etiology and common pathogenesis

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Abstract

Acute pancreatitis is an inflammatory disease of the pancreas. The etiology and pathogenesis of acute pancreatitis have been intensively investigated for centuries worldwide. Many causes of acute pancreatitis have been discovered, but the pathogenetic theories are controversial. The most common cause of acute pancreatitis is gallstone impacting the distal common bile-pancreatic duct. The majority of investigators accept that the main factors for acute biliary pancreatitis are pancreatic hyperstimulation and bile-pancreatic duct obstruction which increase pancreatic duct pressure and active trypsin reflux. Acute pancreatitis occurs when intracellular protective mechanisms to prevent trypsinogen activation or reduce trypsin activity are overwhelmed. However, little is known about the other acute pancreatitis. We hypothesize that acute biliary pancreatitis and other causes of acute pancreatitis possess a common pathogenesis. Pancreatic hyperstimulation and pancreatic duct obstruction increase pancreatic duct pressure, active trypsin reflex, and subsequent unregulated activation of trypsin within pancreatic acinar cells. Enzyme activation within the pancreas leads to auto-digestion of the gland and local inflammation. Once the hypothesis is confirmed, traditional therapeutic strategies against acute pancreatitis may be improved. Decompression of pancreatic duct pressure should be advocated in the treatment of acute pancreatitis which may greatly improve its outcome.

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Key words: Acute pancreatitis; Pathogenesis; Pancreatic duct obstruction; Pancreatic duct pressure

INTRODUCTION

Acute pancreatitis, an inflammatory disease of the pancreas, is mild and resolves itself without serious complications in 80% of patients, but it has complications and a substantial mortality in up to 20% of patients[1]. Its etiology and pathogenesis have been intensively investigated for centuries worldwide[2]. In 1856, Claude Bernard suggested that bile reflux into the common pancreatic duct could trigger acute pancreatitis[3]. Several subsequent studies led to theories fuelling the debate until 1901[4], when Eugene Opie proposed that gallstone migration into the common bile duct is the main cause of acute pancreatitis[5]. Since then, many other causes of pancreatitis have been discovered[6]. However, the pathogenesis of acute pancreatitis is still controversial to date. Several theories attempt to explain the pathogenesis of acute pancreatitis. In terms of disease pathogenesis, whether acute pancreatitis is really one entity or it comprises a group of distinct pathogenic entities remains unclear. From a pathogenic perspective, acute pancreatitis is an identity crisis[7].

CAUSES OF ACUTE PANCREATITIS

There are many causes of acute pancreatitis, which can be easily identified in 75%-85% of patients. In developed countries, obstruction of the common bile duct by stones (38%) and alcohol abuse (36%) are the most frequent causes of acute pancreatitis[8]. Gallstone-induced pancreatitis is caused by duct obstruction by gallstone migration. Obstruction is localized in the bile duct and pancreatic duct, or both. Duct obstruction promotes pancreatitis by increasing duct pressure and subsequent unregulated activation of digestive
enzymes[9]. Alcohol abuse is the second most frequent cause of acute pancreatitis, but the correlation between alcohol and pancreatitis is not completely understood[10]. In experimental models, Gorelick showed that ethanol directly sensitizes acinar cells to cholecystokinin stimulation. As the development of pancreatitis might be affected by both genetic and environmental factors, failure to inhibit trypsin activity or to wash active trypsin into pancreatic ducts might promote alcoholic pancreatitis[11]. In fact, the exact mechanism underlying alcoholic acute pancreatitis has not been extensively elucidated.

Pancreas divisum, a common congenital anatomical variant of the pancreatic duct in about 7% of autopsies, results from the absence of fusion between the dorsal and ventral ductal systems. The possible consequence of pancreas divisum is a stenosed or inadequately patent minor papilla, preventing normal drainage of pancreatic secretions and leading to increased intraductal pressure. However, whether pancreas divisum is related to pancreatitis is highly controversial[12]. Whether dysfunction of sphincter of Oddi can trigger acute pancreatitis by increasing intrapancreatic duct pressure is also controversial[13]. Biliary sludge refers to a viscous bile suspension that contains cholesterol crystals and calcium bilirubinate granules embedded in strands of gallbladder mucus. Sludge is associated with bile stasis, long-lasting fast, distal bile duct obstruction, and total parenteral feeding. Most patients with biliary sludge are asymptomatic. Biliary sludge is commonly seen in patients with recurrent acute pancreatitis of unknown origin, and cholecystectomy might prevent the recurrence of pancreatic disease[14].

Intraduct papillary mucinous tumor might be another cause of acute pancreatitis. Tumor or mucus produced by it obstructs the main pancreatic duct and its side branch, or both. Logically, the consequence is increased pancreatic duct pressure caused by pancreatic hyperstimulation and pancreatic duct obstruction. Thus, these tumors might trigger acute pancreatitis through the same mechanisms underlying acute biliary pancreatitis[15].

Endoscopic retrograde cholangiopancreatography (ERCP) is a potential cause of acute pancreatitis. Asymptomatic hyperamylasaemia occurs in 35%-70% of patients after the procedure. ERCP has a higher risk of inducing acute pancreatitis when it is performed to treat Oddi sphincter dysfunction than to remove gallstones in the bile duct. Other risk factors for post-ERCP pancreatitis include young age, female sex, number of attempts to cannulate papilla, and poor emptying of pancreatic duct after opacification. Prevention of post-ERCP pancreatitis in high-risk patients might be achieved by placing a temporary pancreatic stent[16].

Hypercalcaemia is another rare and inconsistent cause of acute pancreatitis. Because the incidence of pancreatitis is low in patients with chronic hypercalcaemia, additional factors are probably needed to induce pancreatitis[17]. Drugs rarely induce acute pancreatitis. Cases of drug-induced pancreatitis have been reported[18]. Many infectious agents are associated with acute pancreatitis, but no microorganism has ever been identified within the pancreas. However, it was reported that acute pancreatitis is associated with viral or bacterial infections, and infestation with parasites[19]. Although a few researchers speculated that unexplained recurrent acute pancreatitis might be associated with some known genetic mutations, no decisive and persuasive evidence supports the notion[20].

In summary, many causes of acute pancreatitis have been discovered. The main causes are gallstone migration and alcohol abuse. Other causes are uncommon, situational, or controversial. Although there are many theories about the pathogenesis of acute pancreatitis, they are still controversial. These causes have not yet been completely elucidated.

**MULTIPLE AND CONTROVERSIAL PATHOGENETIC THEORIES**

For centuries, the pathogenesis of acute pancreatitis has been intensively investigated worldwide[21]. Many theories have been proposed attempting to explain the pathogenetic mechanisms underlying acute pancreatitis[22]. The important theories about the pathogenesis of acute pancreatitis include bile-pancreatic duct common pathway theory, pancreatic autodigestion theory, gallstone migration theory, enzyme activation theory, kinin and complement system activation theory, microcirculation disturbance theory, leukocyte excessive activation theory, pancreatic acinar cell apoptosis and necrosis theory, all of which are still controversial[23]. They can only explain the pathogenesis of some specific pancreatitis cases, or specific aspects of pathogenetic process of some forms of acute pancreatitis. In fact, no ideal theories on the pathogenesis of acute pancreatitis are available at present.

Although 70%-80% of acute pancreatitis cases are due to alcohol abuse and gallstones, the exact mechanisms by which they initiate acute pancreatitis are unknown. In addition, because of its rapid course and the relative inaccessibility of pancreatic tissue for examination during pancreatitis, investigations of the mechanisms underlying these pathobiologic processes have been hampered. Considering these obstacles, investigators have turned to animal models of acute pancreatitis to reveal the molecular steps initiating these pathobiologic responses to identify potential targets for therapeutic intervention[24-25]. Although the exact mechanisms underlying acute pancreatitis caused by alcohol and gallstones in humans have not been established, key steps in mediating the pathobiologic processes that define acute pancreatitis can be identified from animal models, and used to develop therapies that can be ultimately tested in human pancreatitis[20].

Since early in the twentieth century, a good many of experimental studies based on animal models have been carried out[26]. Many research results support that bile reflux and pancreatic auto-digestion by trypsin are central to the pathogenesis of gallstone pancreatitis[28]. A century later, the following questions still remain to be
We hypothesize that there is a common pathogenic pathway that triggers various forms of acute pancreatitis: acute biliary pancreatitis and other forms of acute pancreatitis. In our hypothesis, there are various causes which may cause acute pancreatitis and lead to pancreatic duct obstruction and blockage of pancreatic juice outflow under certain circumstances. In the presence of exocrine pancreatic hyperstimulation, pancreatic duct pressure, active trypsin reflux, and unregulated activation of trypsin within pancreatic acinar cells would increase. When intracellular protective mechanisms to prevent trypsinogen activation or reduce trypsin activity are overwhelmed, acute pancreatitis occurs.

CONCLUSION

Acute pancreatitis has been intensively studied for centuries. Many causes of acute pancreatitis have been discovered, but its pathogenetic theories are multiple and controversial. The true nature of acute pancreatitis still remains to be elucidated. The causes of acute pancreatitis are various, and its mechanism is common. Once the hypothesis is confirmed, traditional therapeutic strategies against acute pancreatitis may be improved, and decompression of pancreatic duct pressure should be advocated in the treatment of acute pancreatitis which may greatly improve the outcome of acute pancreatitis[36,37].

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