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REVIEW

Controversies in the Etiologies of Acute Pancreatitis

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Introduction

Acute pancreatitis is a potentially life threatening acute inflammatory condition of the pancreas with an annual incidence in the United States estimated to be 40 cases per 100,000 adults [1] which is one of the highest in the world [2]. There is also a rising trend in the incidence of acute pancreatitis in the United States which has been observed over the past several decades [3]. Though most cases are mild with mortality below 1%, there is a subset classified as severe pancreatitis in which the mortality can reach as high as 30% [4]. The direct medical cost of hospitalization for acute pancreatitis is estimated to be $2.2 billion at a mean cost per hospital day of $1,670 [5] which is likely an underestimation. To determine the etiology of the acute pancreatitis is crucial to the management of this potentially fatal condition. Even though a wide variety of etiologies have been proposed, the exact role of the some of these still remains controversial and in some cases ill-defined. A cause is not clinically determined in up to 30% of cases which are labeled idiopathic pancreatitis [6]. This review attempts to re-visit some of the controversies surrounding these etiologies, discuss the current understanding of the mechanisms that underlie them and to identify areas requiring further research.

Hypertriglyceridemia

Mild to moderate elevations in triglycerides are seen in the early phase of acute pancreatitis of any etiology in up to 47% [7] of the cases which raises the question of whether the hypertriglyceridemia is an epiphenomenon or if it has a direct causal relationship with acute pancreatitis. Hypertriglyceridemia is thought to account for roughly 1-4% of cases (up to 7%) and it is interesting to note that the serum amylase may not be substantially elevated in these cases [8] in part due to the interference from the triglycerides with certain amylase assays. However, dilution of serum samples may reduce the interference. For unclear reasons, the clinical course in patients with pancreatitis with concomitant hypertriglyceridemia is often more severe with increased attendant complications (renal failure, shock, infections) [8, 9]. This may be due to the co-morbid conditions that go hand in hand with hypertriglyceridemia such as obesity, alcoholism, pregnancy and treatment with steroids. The bulk of literature indicates that serum triglyceride levels more than 1,000 mg/dL can precipitate an attack of acute pancreatitis [10] though some other studies have pointed to higher values [11]. Overall, it remains difficult to predict which patients with hyper-triglyceridemia will develop acute pancreatitis and the cutoff of 1,000 mg/dL appears arbitrary at best.

The contribution of hyperlipidemia in causing acute pancreatitis in alcoholics is also somewhat controversial [10]. Some studies have failed to show any relationship between alcoholic pancreatitis and hypertriglyceridemia, regardless of whether subjects were fasting, had had an ingestion of fat, or after ingesting a combination of fat and ethanol [12]. Other data however, point to a direct correlation between the amount of alcohol intake and the rise in the triglyceride levels [13].

The non-diabetic, non-alcoholic, non-obese patients with hypertriglyceridemia, which is diet or drug induced (e.g., estrogen [14] or beta blockers), appear to account for only about 15% of the acute pancreatitis associated with hypertriglyceridemia. The vast majority of these patients appear to be the poorly controlled diabetics with obesity which may corroborate the theory that hypertriglyceridemia may be an epiphenomenon in most cases seen in clinical practice.

Key words Biliary Tract; Celiac Disease; Cholelithiasis; Cystic Fibrosis; Cystic Fibrosis Transmembrane Conductance Regulator; Hypercalcemia; Hyperparathyroidism; Hypertriglyceridemia; Pancreatitis, Acute Necrotizing /etiology; Pancreatitis, Alcoholic; Pregnancy

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Reducing the triglyceride levels to below 1,000 mg/dL is thought to effectively prevent development of acute pancreatitis [15].

The mechanism of hypertriglyceridemia induced pancreatitis is unclear though some authors suggest stimulation of amylase release, and (at higher concentrations) cell damage from free fatty acids and chylomicrons in acinar cells [16, 17]. These free fatty acids, in high concentrations can overwhelm the binding capacity of albumin, self-aggregating into micellar structures with detergent properties which break down platelets and the vascular endothelium. This results in ischemic injury to the pancreatic parenchyma creating an acidic environment, which further enhances free fatty acid toxicity. It is also thought that the degree of hyperchylomicronemia itself causes sluggish flow in the capillaries in the pancreatic bed causing ischemia [18], though it is unclear whether other clinical stigmata of plasma hyperviscosity are present more often in patients with hyper-triglyceridemia induced acute pancreatitis. Recently, a mutation in the CFTR gene has been indicated as a possible contributor to the development of acute pancreatitis in patients with hypertriglyceridemia in a Chinese population. The CFTR gene mutation rates in hypertriglyceridemia with and without pancreatitis were 26.1% (12 of 46) and 1.3% (1 of 80), respectively [19].

Hyperparathyroidism

The actual incidence of acute pancreatitis secondary to hyperparathyroidism is somewhat debatable but considered to be very low. In fact the incidence reported by Bess *et al*. in a large series was approximately 1.5% (17 of 1,153 patients), which is about the same as the incidence for the general population [20]. It should be noted though that there appear to be difference even on the incidence, with some studies suggesting figures as low as 0.23% to 0.4% [21, 22] while others report much higher values (5.1% to 12% incidence from Shepard and Jacob and Jubbin, respectively [23, 24]).

Other mechanisms which may be concurrent with hyperparathyroidism are thought by some to play a role. In one study for example, acute hypercalcemia in 76 rats was seen to reproduce hyperamylasemia, early ectopic trypsinogen, intrapancreatic zymogen activation, and histological changes characteristic of acute pancreatitis [25].

However, even in the previous larger series by Bess, *et al*. [20], most of the acute pancreatitis patients (11 of 17) had alternative explanation for the pancreatitis, and treatment of the hypercalcemia did not alleviate the symptoms. Pancreatitis has been reported secondary to endogenous hypercalcemia (e.g. carcinoma) and after iatrogenic hypercalcemia, for example with total parenteral nutrition or Vitamin D poisoning. A prospective study of 300 patients receiving calcium infusions during cardiac surgery showed evidence of cellular injury in as many as 27% of the patients [26].

Overall it appears that chronic elevation of calcium may sensitize the patient to developing bouts of acute pancreatitis without directly initiating the onset, and that the acute elevation of calcium (secondary to any cause) appears to be more contributory. There is also some debate on whether genetic factors within this sub-population may predispose chronically hypercalcemic patients to develop acute pancreatitis (specifically, the SPINK1 and CFTR genes). Interestingly though mean serum calcium levels in pancreatitis patients did not differ significantly from the mean of the entire cohort, or from the primary hyperparathyroid patients without pancreatitis [27]. In chronic pancreatitis associated with hyperparathyroidism the corrected calcium and intact parathormone levels were significantly elevated, while levels of serum phosphate were significantly less when compared to chronic pancreatitis due to alcoholic or idiopathic pancreatitis patients [28]. Pancreatitis has also been described following parathyroid surgery because of an acute rise in calcium levels which may be due to the manipulation of the parathyroid glands during surgery, or perhaps due to a reduced response of calcitonin-producing cells from fatigue [29].

Celiac Disease

Celiac disease is most common in whites of Northern European ancestry. Epidemiological studies using serologic assays for IgA antibodies to gliadin and endomysium (with biopsy verification) have placed the prevalence from anywhere from 1:500 [30] to 1:250 [31] suggesting that celiac disease may still be under-diagnosed in the US population. The annual incidence of acute pancreatitis ranges from 4.9 to 35 per 100,000 population [32]. Given the very high prevalence of celiac disease it brings into question whether there is a causal relationship between celiac disease and acute pancreatitis at all. Ludvigsson *et al*. studied 14,239 individuals with celiac disease in the Swedish national registry and concluded that celiac disease was associated with an increased risk of subsequent pancreatitis of any type (HR: 3.3; $P<0.001$); on the basis of 95 positive events in these individuals, and even higher for chronic pancreatitis (HR: 19.8; $P<0.001$) [33]. Interestingly the risk increase for pancreatitis was only found among individuals with celiac disease diagnosed in adulthood [33] though it is unclear why this is the case. It is possible that earlier diagnosis of celiac disease may lead to better control though this needs further research into the exact mechanisms through which celiac disease is thought to contribute to pancreatitis. Some of the studies studying the possible association between celiac disease and pancreatitis are shown in Table 1.

The relationship of small bowel integrity and pancreatic morphology was first suggested by Novis *et al*. [34]. However, the exact mechanisms for pancreatic disease in patients with celiac disease have not been clearly defined. One study suggesting an autoimmune hypothesis compared total IgG levels in 20 patients with celiac disease and evidence of chronic pancreatitis

Table 1. Association between acute pancreatitis and celiac disease.

References	Year	Serological	Histological	No. of patients	Pancreatitis type	Median age (years)
Patel *et al*. [39]	1999	Yes	Yes	12	Acute (recurrent): 10; chronic: 2	61
Arya *et al*. [98]	2006	Yes	N/A	1	Acute	45
Sood *et al*. [99]	2007	Yes	N/A	1	Chronic (calcific)	36
Ludvigsson *et al*. [33]	2007	N/A	N/A	95	Acute and chronic	58

N/A: not available

with age/sex-matched controls with celiac disease and no evidence of pancreatitis. The mean IgG level in the former was 11.5 g/L compared with 9.8 g/L in controls (P=0.039). Patients with celiac disease and evidence of pancreatitis apparently also had significantly more autoimmune diseases compared with controls (11 *vs*. 3; Fisher exact test: P=0.019). Although the role of autoimmunity is not proven, this is an area requiring more work. Interestingly though, this same study did not find any evidence of acute pancreatitis in more than 700 patients with celiac disease despite active follow-up [35]. A more widely accepted etiology of pancreatitis in patients with celiac disease is believed to be related to malnutrition [36, 37]. Protein energy malnutrition even with causes unrelated to celiac disease (such as anorexia nervosa [37], Kwashiorkor [38]) have been described to be associated with increased levels of pro-inflammatory cytokines as well as pancreatic acinar cell damage and ductal disruption [37]. It is unclear however whether the malnutrition results primarily from the malabsorption from celiac disease or from the chronic pancreatitis which has been seen to be coexistent in patients with poorly controlled celiac disease. Also there is no clear evidence to show improvement of pancreatitis by episode, frequency or pain after correction of the malnutrition.

Papillary stenosis was discussed as another etiology for pancreatic disease in patients with celiac sprue by Patel *et al*. [39] concluding that pancreaticobiliary disorders in patients with celiac disease may be associated with papillary stenosis of the pancreatic orifice which in turn is related to chronic or chronic-active duodenitis. It remains unclear whether the improvement seen in this series was due to gluten restriction or due to the sphincterotomy. In patients with acute pancreatitis thought to be due to papillary stenosis, celiac disease should be considered in the differential diagnosis even in the absence of malnutrition. Another case of inflammatory papillary stenosis due to Giardia Lamblia causing pancreatitis in patients with immune deficiencies has been reported [40]. Finally, cytokine upregulation in celiac disease is considered to be a predisposing factor for acute pancreatitis. There is an increase in inflammatory cytokines of the T helper cell 1(TH1) class through polymorphisms in TNF alpha. However, it is unclear why celiac disease patients would have episodic acute pancreatitis if these cytokines are chronically up-regulated.

Microlithiasis

Some authors reserve the term microlithiasis for small concretions in gallbladder or biliary tree that are less than 3 mm and are not imaged on conventional ultrasonography or cholecystography [41, 42, 43]. In the bulk of literature, biliary sludge and microlithiasis are often used interchangeably. This condition was first described with the advent of ultrasonography in the 1970s and can be defined as a “mixture of particulate matter and bile that occurs when solutes in bile precipitate” [44]. The bile crystals can be composed of cholesterol monohydrates, calcium bilirubinate or as concretions of microspheroliths. Non-hydrated cholesterol crystals exist in variable forms (filaments or tubular structures) [44, 45].

Typically, sludge can be found in states of mechanical or functional delay in bile emptying, such as in distal bile obstruction, patients on total parenteral nutrition and in starvation or prolonged fasting states, or in patients with rapid weight loss (as in after gastric surgery). Certain drugs including octreotide and ceftriaxone can cause microlithiasis, as can solid or bone marrow transplantation [46]. There is some disagreement over the sequence leading to cholesterol microcrystal formation. Some studies indicate that cholesterol crystallization pathways are dependent on salt/lecithin ratio, total lipid concentration and salt hydrophobicity but as Abeysuriya *et al*. [47] point out, most of these studies are performed on synthesized bile rather than human bile, a fact that is often overlooked in the context of microlithiasis.

The exact mechanism for microlithiasis causing acute idiopathic pancreatitis remains somewhat unclear with most evidence pointing to biliary and pancreatic sphincter dysfunction by mechanical irritation by microcrystals and subsequent inflammation. This hyperinflammatory state may enhance gallstone formation and also contribute to papillitis and even sphincter of Oddi dysfunction [47, 48, 49]. Other investigators indicate that microlithiasis may indicate past formation of biliary stones with no direct contribution to acute pancreatitis by the sludge itself. In some studies, biliary crystals are present in 95% of patients with symptomatic gallstone disease and about 8% of individuals without gallstones harbor microliths [47, 50, 51]. Despite negative ultrasonography, bile duct crystals are found on microscopic exam of the aspirated bile from the common bile duct in up to 80% of patients early after suspected biliary pancreatitis [52, 53]. Though evidence supports a link among biliary sludge [53, 54, 55] and acute pancreatitis the exact relationship and the pathophysiology remains to be more clearly defined. The best method to diagnose biliary sludge and microlithiasis (duodenal sampling with bile microscopy, ERCP, EUS or some

combination thereof) is still controversial. There is some evidence to suggest that EUS may be superior for sludge when compared to duodenal aspiration for bile microscopy [56, 57] though according to Yusoff *et al*. [58] even if the EUS is negative, the yield for duodenal bile aspirate stood at 46%. Other authors indicate that nucleation times (indicating early aggregation of cholesterol molecules from supersaturated bile into submicroscopic foci), could be spuriously longer, likely due to contamination with pancreatic and duodenal secretions [47].

Also, role of cholecystokinin stimulation before duodenal aspirate or common bile duct sampling remains unclear as does the amount of bile required for diagnosis [53]. Medical therapy for microlithiasis is limited though for symptomatic patients cholecystectomy is recommended.

Pancreas Divisum

Pancreas divisum is the most common congenital pancreatic anomaly. It is thought to result from the failure of the embryologically derived dorsal and ventral pancreas fusion, resulting in separate pancreatic ductal systems. Pancreatic drainage occurs primarily through the minor papilla via the dorsal duct of Santorini, as opposed to the more common route, through the major papilla via the ventral duct of Wirsung. With increasing use of endoscopic retrograde cholangiopancreatography, pancreas divisum is being detected more frequently. In some autopsy series the frequency has been reported to be as high as 14% [59, 60, 61]. Its role in the development of acute pancreatitis is a matter of controversy. Some authors, such as Sugawa *et al*. [61], suggest that because of the very common nature of this condition it may even be considered a normal variant of pancreatic development with little or no role in pancreatic pathology. This is further supported by Delhaye *et al*. who suggest that pancreas divisum should not be regarded as an etiologic factor in pancreatitis but rather "a coincidental anatomic variant encountered in nearly 10% of the population" [62]. They also go on to suggest that there is not enough evidence to support the hypothesis that stenosis of the accessory papilla occurs any more frequently in pancreas divisum. Similar conclusions are reached by Burtin *et al*. as well [63].

Given how infrequently acute pancreatitis occurs in patients with pancreas divisum has raised controversy over the association between the two entities. Certainly, there appears to be a subgroup of patients with pancreas divisum that tend to develop pancreatic symptoms, approximately 5% or so [64]. Recent genetic studies that have suggested a link between CFTR dysfunction and recurrent acute pancreatitis in this subgroup [65] have further questioned the strength of the relationship of pancreas divisum with acute pancreatitis. Gelrud *et al*. [65] suggest that up to 20% of patients with pancreas divisum who have pancreatitis carry at least one allele of the cystic fibrosis gene product. Despite this possible genetic predisposition, there appears to be some indication that the minor papillary orifice in this subgroup of patients is significantly narrow giving rise to dorsal duct hypertension during active secretion and thus producing symptoms of acute recurrent pancreatitis [66, 67]. This has led some authors to call the condition "dominant dorsal duct syndrome" [68] to clarify the more central role of the minor papillary stenosis in leading to pancreatitis in the context of pancreas divisum. This appears to be corroborated in some series where accessory duct sphincteroplasty was successful in over 80% of patients in the long-term prevention of recurrent acute pancreatitis [69]. Traditionally, evaluation and correction of the minor papillary stenosis in pancreas divisum was undertaken surgically, requiring a laparotomy [70] with several studies showing benefit in the setting of acute recurrent pancreatitis, but with only limited response in "pancreatic pain" and chronic pancreatitis. Increasingly though endoscopic evaluation and therapy at specialized centers is fast replacing the need for an open duodenotomy. The measurement of minor papilla pressures is controversial given that a baseline for a normal pressure in the minor papilla is not established.

Pregnancy

Schmitt first described acute pancreatitis in pregnancy in 1818 [71] in a 30-year-old multigravida with a series of 53 patients being described two decades later. In the obstetrics literature, the incidence has varied anywhere from 1 in 3,799 cases to 1 in 11,467 cases [72]. The review from Parkland Hospital by Ramin found an incidence of about 1 in 3,333 patients [73]. Initially nulliparity was considered to be a specific risk factor in pancreatitis complicating pregnancy, though later literature did not support this theory, with some reviews placing multiparous women at 72% of the pregnant population being diagnosed with acute pancreatitis especially in the third trimester (as high as 53%) [73]. Coincidentally, the increase in triglycerides in pregnancy is also most pronounced in the third trimester. However whether this actually predisposes to bouts of acute pancreatitis is controversial since the level of hypertriglyceridemia rarely exceeds 300 mg/dL which is not considered high enough for precipitating acute pancreatitis.

In another large study by Jouppila *et al*., [74] the incidence of acute pancreatitis was seen to be about 8 in 16,000 patients. Of these 5 were considered to be due to gallstones and 3 were termed idiopathic. Other authors [75] have also shown this trend. Eddy and Gideonsen [76] found the majority (66%) of cases of acute pancreatitis to be biliary in origin, and suggested that these have a better outcome than non-biliary causes. Hypertriglyceridemia is thought to be a close second to biliary disease in being the likely cause of acute pancreatitis in pregnant patients. However, as noted above, there are usually pre-existing abnormalities in lipid metabolism [77] that would predispose the patient to acute pancreatitis given that

level of increase in triglycerides seen in pregnancies. Thus it is controversial whether simply having hypertriglyceridemia would put a woman at risk of pancreatitis during pregnancy. Pre-eclampsia is also reported in some literature to be a contributory to acute pancreatitis. The generalized microthrombi, vasculitis, and the intravascular coagulation associated with pre-eclampsia are thought to play a role [78]. However in an older review [79] 5 of the 9 cases thought to be due to pre-eclampsia had also received diuretics which could be a confounding factor in elucidating the role of pre-eclampsia in pregnancy associated pancreatitis. The exact role of pre-eclampsia thus is unclear at this point.

Genetic/Hereditary

Inherited forms of pancreatitis may present with recurrent symptoms. These hereditary forms can be divided into autosomal dominant, autosomal recessive, or a multigenic inheritance. In up to two-thirds of the cases of hereditary pancreatitis, the cationic trypsinogen gene (PRSS1) appears involved [80, 81]. The p.R122H and p.N29I (with particularly high penetrance up to 80% and 93% in two series) [82] can be found in approximately 90% of mutation-positive cases and are often implicated [83]. However up to 35 additional PRSS1 variants have been identified in patients with idiopathic chronic pancreatitis and many of these have been labeled pancreatitis-associated without sufficient functional or genetic evidence, often on the basis of proximity to other better known mutations. Szmola and Sahin-Tóth have commented on this controversial trend [83] and caution "that assignment of clinical relevance to rare PRSS1 variants should not be based on a perceived analogy with genuine disease causing PRSS1 mutations" [83].

The role of SPINK1 as a causative factor in pancreatitis is controversial [84, 85] and most authors consider it a disease modifying element which would in part explain its association with other etiological factors, some of which are discussed above. It is thought to lower the threshold for acute pancreatitis rather than being a direct causative agent [77]. However it should be noted that up to 2% of the general population carry the "high risk" SPINK 1 mutation [86] but only one percent of the carriers actually develop pancreatitis [86] identifying perhaps some unknown confounding factors affecting its phenotypic expression.

The roles of the cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations have been studied well over the years [82, 87, 88].The pathological impact of this gene continues to be debated. The large size of the gene involved (27 exons) and the very large number of the various polymorphisms (more than 1,600) makes clarifying its role in acute pancreatitis difficult [88]. Other candidates for genetic predictors of acute pancreatitis have had mixed results. The glutathione-S- transferases (GSTs) are a family of antioxidant enzymes which were implicated in one European study [89] where normal expression of the GSTtheta-1 gene appeared to result in an exaggerated inflammatory response to pancreatic injury possibly through depletion of glutathione stores. However the same results could not be reproduced in a North American study which concluded that functional GSTT-1 phenotypes did not correlate with susceptibility to acute pancreatitis or with its severity [90].

The role of genetic testing for some of the above genetic mutations remains controversial. Some authors [91, 92] have recommended using genetic testing for trypsinogen mutations (with relevant and appropriate genetic counseling) in predicting clinical and therapeutic implications for the patient and family members. They have also tried to define a framework of objective indications for testing, and counseling in these cases [91]. As more therapeutic options become available, specific, patient-tailored approaches could be adopted. However genetic testing for any disease, especially with implications on questions of heredity, coverage and insurance, should be approached with some forethought.

Alcohol

Given how commonly alcoholic pancreatitis is seen, some of the controversies in the pathophysiology of this particular entity are often overlooked. The exact mechanisms which underlie pancreatic injury, leading to acute or chronic pancreatitis and ultimately to pancreatic cancer, are being understood. Classically however alcoholic injury was considered mainly in the context of chronic pancreatitis, especially since even acute presentations ("first attack" pancreatitis) had significant evidence of chronicity on histological evaluation [93]. It has become clearer however that despite continued alcohol abuse, a significant subset of patients do not progress to chronic pancreatitis despite recurring bouts of acute pancreatitis associated with the alcohol intake [94]. It is quite possible then, that a subset of patients may have bouts of acute pancreatitis which may be non-progressive though the exact mechanism for this non-continuous spectrum is unclear. There is also new evidence implicating the increased gut permeability and resultant endotoxinemia which occurs in heavy alcohol use [95]. The activation of pancreatic stellate cells and transformation into myofibroblast-like cells [96] through some of these mechanisms may have a role to play in the patients that progress onto chronic pancreatitis and indeed pancreatic cancer. The origin of these pancreatic stellate cells (pancreatic parenchyma, *versus* the bone marrow) is also unresolved at this point [96]. The parallels between liver injury and pancreatic injury due to alcohol are also interesting especially in the light of the stellate cells and their role in fibrosis [97]. This may be particularly important in the subset of patients progressing to chronic injury and fibrosis, discussed earlier, though assumptions beyond what the current, limited evidence permits, should be guarded.

Conclusions

Acute pancreatitis continues to be a frequently encountered condition. Both in developed and developing countries it continues to be a significant financial strain on health systems, and appears to be increasing in frequency. The morbidity and mortality from acute pancreatitis can be significant. Though more commonly occurring etiologies are better understood, the mechanisms behind other, less common contributing factors are still a matter of some debate. These etiologies should also be the focus of further research and investigation, to achieve more focus in targeting therapies to prevent the potential sequelae. Some differences in demography, prognosis, clinical course and outcomes make these less common etiological factors more imperative to understand. The controversies surrounding factors behind acute pancreatitis discussed in this review continue on, improving our understanding of this dynamic organ and the role systemic conditions, genetics and environmental factors play in affecting its function.

Conflict of interest The authors have no potential conflict of interest

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