Genetic Risk of Acute Pancreatitis

Subjects: Pathology

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Acute pancreatitis is a primarily noninfectious inflammatory disease of the pancreatic gland. With an annual incidence of 13–45/100.000 acute pancreatitis is one of the most common gastroenterological indications for emergency admittance and hospitalization in Europe and the USA. The presence of two of three criteria from the 2013 revised Atlanta classification system is required for the diagnosis of acute pancreatitis: (1) typical belt-like abdominal pain, (2) elevated serum lipase level three times above the normal threshold or (3) diagnostic imaging signs of pancreatitis. An interstitial oedematous subtype of acute pancreatitis prevails, but a necrotizing form of pancreatitis may develop in 5%-10% of cases. While milder oedematous pancreatitis has a high tendency to resolve spontaneously, necrotizing pancreatitis has a mortality of more than 20% and is accompanied by sometimes lifelong consequences such as diabetes mellitus or exocrine insufficiency. The new classification system distinguishes three degrees of severity—mild, moderate, and severe—based on the presence of local and systemic complications and the duration of organ failure. Gender predominance is only seen in specific etiologies: gallstones are more common in women, whereas alcohol abuse is more frequent in men. The peak incidence of alcoholic acute pancreatitis is between 25–34 years in women and ten years later in men. Overall, pancreatitis risk increases continuously with age. Typically, patients are affected in their sixth decade of life and African Americans have a two to three fold increased pancreatitis risk compared to the white population. Characteristically, 20%–30% of patients with acute pancreatitis experience recurrent pancreatitis attacks and of these 10% will develop chronic pancreatitis.

acute pancreatitis genetic risk diagnosis disease severity progression

1. Introduction

Pancreatitis, a primarily sterile inflammatory condition of the pancreas, is frequently triggered by gallstones, alcohol consumption or the presence of a variety of other initiating factors. Complex gene–environment interactions are involved in the pathogenesis of pancreatitis, giving rise to a diverse clinical appearance and a sometimes hard-to predict course of progression. While in past decades we discriminated between acute and chronic pancreatitis as different disease entities, the current understanding conceives them as intergradient stages of pancreatic injury. The underlying individual genetic susceptibility in combination with environmental stimuli like alcohol and tobacco smoke are believed to trigger either acute single lifetime events or recurrent episodes with an impact on fibrotic replacement processes that may progress to a chronic disorder.

2. Diagnostic Approach to Identify Pancreatitis Etiology

2.1. Anamnestic Investigation and Physical Examination

The clinical challenge in the management of pancreatitis is the identification and permanent elimination of pancreatitis inducing risk factors. A thorough medical record and family history can provide first evidence of the underlying etiology. General symptoms like abdominal pain (quality, frequency, intensity, need of analgesia), weight loss and stool behavior (quality, frequency, steatorrhea) should be recorded. The pathognomonic symptom for pancreatitis is belt-like abdominal pain. Alcohol abuse is the most common reason for acute and chronic pancreatitis in adults. Smoking is an independent risk factor for the progression of chronic pancreatitis. Therefore, the examination of drinking and smoking behavior is essential. To quantify the alcohol consumption useful questionnaires, like the Alcohol Use Disorders Identification Kit (AUDIT) or CAGE score, are available [1][2]. A comprehensive medical history including medications must also be gathered. Chronic kidney disease may indicate hyper-calcaemia via tertiary hyperparathyroidism, or drug induced pancreatitis by diuretics or immune suppressants. Depression, nephrolithiasis, and osteopenia can be caused by primary hyperparathyroidism. Heart attacks, especially in young adults or frequently occurring in families, could indicate a metabolic lipid disorder. There is an association between autoimmune pancreatitis and other autoimmune diseases, like Sjogren syndrome, primary sclerosing cholangitis and inflammatory bowel diseases. A genetic risk or even hereditary pancreatitis should be considered in case of first-degree relatives affected by pancreatic disorders.

Often the physical examination already provides relevant information about the stage or aetiology. Signs of malnutrition or growth retardation in infants can be found in advanced stages of chronic pancreatitis. Oedema and cachexia (loss of both adipose tissue and skeletal muscle mass), dry skin and mucosa (vitamin A deficiency), muscle weakness (low potassium), angular cheilitis, aphthous ulcer, koilonychie (hollow nails), nail brittleness, and hair loss (lack of iron, zinc, copper) are typical signs of malnutrition. Muscle atrophy with emphasis on calf muscles, telangiectasia, facial redness, spider nevi, increased sweating in cold acres and intention tremor are indicators for alcohol abuse. Xanthomatosis (yellow coloured, lipid containing deposits under the skin), and arcus lipoides corneae (white-yellowish or greyish turbidity on the edge of the cornea due to lipid deposits) are extremely rare but could be indicative of hypertriglyceridemia. In older patients, acute pancreatitis may frequently be caused by underlying pancreatic cancer. The physician should look for signs of pancreatic cancer, such as loss of appetite, weight loss, new diagnosis of diabetes or existing diabetes that is becoming more difficult to control. Physical examination may be able to identify a palpable intra-abdominal mass.

3. Genetic Predisposition in Different Etiologies of Acute Pancreatitis

Chronic alcohol consumption causes 17%–25% of acute pancreatitis cases worldwide. A literature review from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) suggested in 2008 that 40%–60% of the variance among people at risk of alcoholism has a genetic background [3]. Some specific genes that contribute to alcohol-use-disorder have been identified, and they correlate with the development of the reward centers in the brain. People who have a genetic predisposition to alcohol-use disorder may experience fewer or different warning signals from their brain or body when they need to stop drinking. People with a genetic condition to drink only

moderate amounts of alcohol may still have the genetic predisposition to lose control over their drinking behavior [4]. In contrast to the complex effects on the central nervous system, the metabolism of alcohol is much better understood. Variations in the genes of alcohol eliminating enzymes, such as aldehyde dehydrogenase (*ALDH*), alcohol dehydrogenase (*ADH*), cytochrome P450 (*CYP2E1*), and catalase have been identified as influencing alcohol consumption, alcohol-related tissue damage, and alcohol dependence. Variants of ADH and ALDH enzymes are believed to influence alcoholism risk by local elevation of acetaldehyde, a toxic substance whose accumulation leads to a highly aversive reaction that includes facial flushing, nausea, and rapid heartbeat (i.e., tachycardia). ALDH2 eliminates the majority of the acetaldehyde; however, the ALDH2*2 variant is enzymatically nearly inactive [5]. This variant is relatively common in people of Asian descent and the presence of even a single *ALDH2*2* allele triggers a highly aversive reaction to alcohol and therefore protects against alcohol dependence. There is no linear association between the consumed amount and the duration of abuse. Still, many case-control studies have shown a causal relation between alcohol abuse and chronic pancreatitis [6][7][8]. There is a logarithmic association between the relative risk of developing pancreatitis and daily alcohol consumed. It is estimated that 80 g of alcohol per day, consumed over 6–12 years, increases this risk. A safe lower threshold for alcohol consumption is not known. Women experience a higher risk for chronic pancreatitis at comparatively lower levels of alcohol intake compared with men [9].

Treatment of alcoholism by medication is so far of limited efficacy. Results from clinical trials showed moderate effects of Naltrexon, a μ-opiod receptor antagonist and one of three approved pharmacotherapies for the maintenance of abstinence in alcoholism. A functional polymorphism within *OPRM1*, the gene encoding the μ-opioid-receptor 1, was found to associate with a better response to Naltroxene in clinical trials [10]. A future perspective on improving the clinical management of these patients may involve a personalized treatment strategy following genotyping of genetic *OPRM1* variants.

Biliary acute pancreatitis accounts for 30%–50% of cases. The female sex predominates in the biliary etiology of acute pancreatitis and gall stones are found in 50% of women compared to 15% of men, a rate which is also seen in the healthy population [11][12]. The pathogenesis of biliary pancreatitis is described by the common duct theory. The papilla Vateri, which is the common aperture of the common bile duct and the pancreatic main duct, is obstructed by a migrating gall stone leading to congestion of pancreatic fluid with consecutive pancreatic injury [13]. The latter is based on pressure damage and autoactivation of trypsin, lipase and elastase leading to autodigestion of pancreatic tissue [14]. Stones in the biliary tract lead to pancreatic injury but cholecystolithiasis is in 75% of cases asymptomatic [15]. Less than 1% of patients with gallstones develop acute pancreatitis, and 15%–30% of these develop a severe necrotizing pancreatitis, needing intensive care medicine and multidisciplinary treatment strategies [16][17].

Metabolic causes, like moderate hypertriglyceridemia (2–10 mmol/L or 177–886 mg/dL) have been shown to increase the risk of acute pancreatitis and 10% of cases seem related to elevated triglyceride levels [18]. Hypertriglyceridemia and elevated levels of chylomicrons increase the blood viscosity leading to local tissue ischemia. A cell metabolism change to anaerobic glycolysis results in elevated intra- and extra-cellular levels of lactate and lowered local pH. Increased toxicity of free fatty acids and autoactivation of trypsinogen in a condition

of acidosis may follow. As lipoprotein lipase is known to degrade plasma triglycerides, Hansen et al. recently analyzed if variants in *LPL*, *APOA5*, *APOC3*, *ANGPTL3* and *ANGPTL4*, which regulate the lipoprotein lipase pathway, result in increased or reduced plasma triglyceride levels [19]. Their analysis of 15 genetic variants in DNA samples from Danish registries of 102,888 participants showed a correlation between the highest genetic allele score and a higher plasma level of triglycerides of 0.54 mmol/L (48 mg/dL). The odds ratio for acute pancreatitis among participants with the highest vs. the lowest genetic allele score was 1.55 (95% CI, 1.08–2.23). Mutations in the lipoprotein lipase gene and recurrent attacks of abdominal pain are independent risk factors in patients with hyper-lipidemic pancreatitis for the development of calcifications and steatorrhea as signs of chronic pancreatitis [20]. Chronic pancreatitis primarily based on elevated free fatty acids is more prevalent in children with hereditary metabolic disorders like familial chylomicronaemia syndrome (FCS), LPLD or apolipoprotein CII (Apo CII) deficiency [21]. In case of this type of primary hyper-lipidaemia the course of disease can be more severe and manifests itself at a younger age. Strategies to reduce plasma levels of triglycerides, by increasing lipoprotein lipase function, are being developed for preventing episodes of acute pancreatitis.

Hypertriglyceridemia alone usually does not cause abdominal or pancreas-specific symptoms. Often the combination with other risk factors like alcohol, tobacco or medical drugs is the local elicitor for acute pancreatitis [22]. Pregnancy and hormonal contraceptives are known to increase cholesterol and triglyceride levels and also cortisol and its derivatives, beta receptor blockers or isotretinoin, used for medication of acne, can affect hypertriglyceridemia induced AP [23].

Familial lipoprotein lipase deficiency (LPLD) is another hereditary condition leading to recurrent episodes of acute pancreatitis [24]. Often acute pancreatitis is the first symptom of LPLD in infancy. The age at onset of symptoms varies highly; especially in woman with unknown LPLD, the first use of hormonal contraceptives or the first pregnancy could trigger acute pancreatitis as the first symptom of LPLD.

Elevated triglycerides based on obesity, pregnancy, insufficiently controlled diabetes, medication or chronic and acute alcohol abuse is defined as secondary hypertriglyceridemia. Both primary and secondary hyperlipoproteinemia are associated with high plasma levels of triglycerides and can cause recurrent pancreatitis [25].

Other known metabolic causes include disorders of calcium homeostasis. Compared with pancreatitis caused by alcohol or hyperlipidaemia, hypercalcemia-induced pancreatitis is a rare event. On chief cells of the parathyroid gland, the calcium-sensing receptor CASR is involved in the regulation of parathyroid hormone (PTH) secretion in response to changing calcium concentrations. Inappropriate PTH secretion, the primary defect seen in primary hyperparathyroidism (PHPT), results in hypercalcemia and thus likely sensitizes patients with PHPT to pancreatitis. Prinz et al. found that hyperparathyroidism causes only 0.4% of cases of pancreatitis [26]. Nevertheless, patients with hyperparathyroidism have a 20-fold increased risk for acute or chronic pancreatitis compared with the general population [27]. Guidelines for PHPT patients recommend parathyroidectomy in nearly all affected patients. When patients with acute pancreatitis are found to have no obvious causes and elevated serum calcium is observed, PHPT-induced pancreatitis should be suspected.

Other causes of hypercalcemia-associated pancreatic injury are malignoma (bone metastasis, multiple myeloma), sarcoidosis, or familial hypocalciuric hypercalcemia. Mutations in the calcium-sensing receptor gene (*CASR*) were found to be associated with recurrent pancreatitis in families with familial hypocalciuric hypercalcemia (FHH) [28]. The mechanism of calcium-induced injury is not clearly defined and may involve additional genetic or environmental stressors. The acinar cell has been identified as the primary initiating site for pancreatitis and low acinar calcium concentrations constitute a fail-save mechanism against intra-acinar protease activation. Experimental evidence suggests that hypercalcemia promotes premature trypsinogen activation and may sensitize the pancreas to pancreatitis. In studies on experimental pancreatitis altered acinar calcium signals have also been observed [29][30][31]. Masamune et al. reported that patients with early onset CP not associated with alcohol consumption carry variants in the transient receptor potential cation channel subfamily V member 6 gene (*TRPV6*). TRPV6 regulates Ca^{2+} homeostasis and pancreatic inflammation and functional variants that affect the Ca^{2+} balance seem to increase the pancreatitis risk [32].

In a recent systematic search of the literature and meta-analysis, the association of *SPINK1*, *ALDH2*, *IL1B*, *IL6*, and *IL18* variants with disease risk for AP was identified [33]. This meta-analysis of nine studies (1493 patients, 2595 controls) identified an association of *SPINK1*-N34S in the allelic model with susceptibility for acute pancreatitis mainly in Caucasians (OR 2.49, 95% CI 1.55–3.98, p value 1.5×10^{-4}), but not in Asians. The N34S variant is a known genetic risk factor for chronic pancreatitis with a high prevalence of 1%–2% in the healthy population. Recent findings suggest linkage with a functional enhancer variant located ~4 kb upstream of the *SPINK1* promoter [34].

4. Genetic Factors That Influence Disease Severity of Acute Pancreatitis

A major challenge in the treatment of AP patients is the identification of patients who develop a severe course of AP. In 65% to 85% of cases, AP is self-limited, not requiring specific treatment other than parenteral intravenous fluid, analgesics, and supportive care [35]. In the remaining cases, a persistent generalized inflammation may entail an increased risk of organ failure and local complications, which is connected with a high morbidity and mortality. To prevent mortality in these patients an aggressive treatment must be started as early as possible. The disease progression may be related to the genetic polymorphic propensity to produce proinflammatory cytokines or may be related to cellular regulation mechanisms including the control of apoptosis and oxidative stress. Polymorphisms in the promoter regions of interleukin genes *IL-1b*, *IL-6*, *IL-8*, and *IL-10* were identified as affecting transcriptional activities and therefore were considered as potential risk factors for disease severity [36][37][38][39]. Epidemiological studies in different populations have investigated the associations of these interleukin gene polymorphisms with acute pancreatitis but with inconclusive results. A meta-analysis in 2013 by Yin et al. suggested a slightly increased AP risk for *IL-8* -251T>A polymorphism, but not for other variants in *IL-1b*, *IL-6*, or *IL-10* [40].

The recent meta-analysis by van den Berg et al. also systematically assessed the literature for reported associations with disease severity and complications. Their search included seventeen variants with data from two or more publications and identified variants in *TNF*, *GSTP1* and *CXCL8* as associating with disease severity,

however, at a rather low level of reliability. Several preliminary positive associations with disease severity (including *TLR3*, *TLR4*, *TLR6*, *CD14*, *NFKBIA* and *SERPINE1*) were not replicated in other studies. Still, other candidate variants for association with infectious complications (*TLR14*, *IL10*), systemic complications (*TNF*), pancreatic necrosis and mortality have been proposed and await further replication. In another study Martins et al. evaluated the role of 15 gene polymorphisms in *GSTM1*, *GSTT1*, *GSTP1*, *CASP7*, *CASP8*, *CASP9*, *CASP10*, *LTA*, *TNFRSF1B*, and *TP53* genes, all involved in oxidative stress and apoptosis [41]. This study provided more insight into the potential role of gene polymorphisms in AP susceptibility.

Currently no credible predictive genetic biomarker for disease severity has been identified. Not yet validated variants are mainly found in genes that are connected to the activation of the innate immunity pathways.

5. Genetic Risk Factors That Influence the Course of Pancreatitis

Risk sequence variants associated with recurrent and chronic form of pancreatitis were identified in *PRSS1*, *SPINK1*, *CTRC* and *CPA1* genes which are linked to the regulation of intra-pancreatic trypsin activity [42][43][44][45][46]. In addition, mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) disturb the transports of Cl^- and HCO^{3-} ions across the apical membrane of pancreatic duct cells and affect the pancreatic ductal secretory function [44][47]. CFTR mutations which associate with chronic pancreatitis (CP), but not with CF, were found to selectively modify the HCO^{3-} permeability of CFTR [48]. Other genetically determined disease mechanisms include mutations in lipase genes like the carboxyl ester lipase (*CEL*) or pancreatic lipase (*PNLIP*) [49][50]. As well as the induction of endoplasmic reticulum stress (ER-Stress) caused by mutation-induced protein misfolding and intracellular retention of digestive enzymes [51][52]. Current genetic diagnostic screening schemes are focused mainly on genes related to trypsin activity. In comparative studies of CP in children, the most common risk factors are genetic variants associated with CP, whereas in adults CP is more commonly related to environmental risk factors, particularly alcohol and smoking [53]. Genetic risk factors with high penetrance frequently associate with early onset CP, whereas alcohol and tobacco use normally starts in early adulthood and therefore are associated with a later onset of CP.

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