MINIREVIEWS

Hereditary pancreatitis: An updated review in pediatrics

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Abstract

Hereditary Pancreatitis (HP) has emerged as a significant cause of acute, acute recurrent and chronic pancreatitis in the pediatric population. Given that it presents similarly to other causes of pancreatitis, a positive family history and/or isolation of a gene mutation are vital in its designation. Inheritance patterns remain complex, but mutations involving the PRSS1, SPINK1, CFTR and CTRC genes are commonly implicated. Since being first described in 1952, dozens of genetic alterations that modify the action of pancreatic enzymes have been identified. Among children, these variants have been isolated in more than 50% of patients with chronic pancreatitis. Recent research has noted that such mutations in PRSS1, SPINK1 and CFTR genes are also associated with a faster progression from acute pancreatitis to chronic pancreatitis. Patients with HP are at increased risk of developing diabetes mellitus, exocrine pancreatic insufficiency, and pancreatic adenocarcinoma. Management follows a multi-disciplinary approach with avoidance of triggers, surveillance of associated conditions, treatment of pancreatic insufficiency and use of endoscopic and surgical interventions for complications. With significant sequela, morbidity and a progressive nature, a thorough understanding of the etiology, pathophysiologic mechanisms, diagnostic evaluation, current management strategies and future research considerations for this evolving disease entity in pediatrics is warranted.

Key Words: Hereditary pancreatitis; Acute pancreatitis; Acute recurrent pancreatitis; Chronic pancreatitis; Pancreatitis; Pediatrics

Core Tip: Herediatry Pancreatitis is associated with the inheritance of pathologic genetic mutations. Recent work in pediatrics has isolated genetic variants responsible for early onset and rapidly progressive disease. Early identification of at risk patients and timely referral to appropriate tertiary centers has the ability to limit health care cost and substantial sequelae of this aggressive disease continuum. Further research is warranted to better define preventative management strategies.

INTRODUCTION

Acute pancreatitis (AP) in pediatrics is on the rise, with incidence rates now similar to that of the adult population[1]. In many children AP is self-limiting with a largely uncomplicated course[2]. However, single center reports have noted that as much as 35% of patients experience recurrent attacks with development of chronic pancreatitis (CP)[3]. Pediatric CP is associated with a high disease burden and complications, necessitating multiple hospitalizations, procedures, psychiatric comorbidities and days away from school, all impacting negatively on the quality of life (QOL) of affected patients[4].

In pediatrics, the rapid progression from the initial episode of AP to CP is striking, with a median time of 3.79 years[5]. Such an aggressive disease continuum calls for a closer analysis of the etiologies involved in childhood pancreatitis. Alcohol and cigarette smoking are well established risk factors for acute recurrent pancreatitis (ARP) and CP in adults, but these are uncommon among children. Risk factors in the pediatric setting are more varied and include; infections, systemic illness, trauma, pancreatic ductal anomalies, metabolic disease, biliary/obstructive causes and hereditary factors such as gene mutations[4,6]. With the implementation of more widespread genetic testing, mutations in pancreatitis related genes have now been demonstrated to be commonly implicated in both pediatric ARP and CP[4].

Historically, herediatry pancreatitis (HP) was grouped and defined as pancreatitis in association with highly penetrant germline mutations, with particular reference to *cationic trypsinogen (PRSS1)* gene defects. Pancreatitis associated with the inheritance of other genetic variants in a non-autosomal dominant manner were termed as familial pancreatitis[7]. However, these designations have changed as more pancreatitis related gene mutations have been discovered and complex inheritance patterns have been characterized. Some have adopted the definition that HP describes patients with pathologic genetic variants predisposing them to the development of pancreatitis. Such a definition would therefore, also encompass genetic mutations inherited in both an autosomal recessive or complex pattern, namely those of the serine *protease inhibitor Kazal type 1 (SPINK1)* and *cystic fibrosis transmembrane conductance regulator (CFTR)* genes[8].

Recent work in pediatrics has implicated particular gene mutations in early onset and rapidly advancing disease[5,9]. This together, with several unique features, and a significantly increased risk of pancreatic carcinoma, places HP as a disease process under intense debate and study. In this regard, we aim to review the historical perspectives, clinical features, genetics, diagnostic evaluation, current management strategies and future research considerations for this evolving disease entity in pediatrics.

HISTORICAL PERSPECTIVES

The emergence of HP as a unique entity was first noted in 1952, wherein, the authors reported the pedigree of six family members (four definite and two probable),

spanning three generations with repeated episodes of pancreatitis. Age of onset ranged from 5 to 23 years of age, with clinical features and complications seeming to occur in an autosomal dominant inheritance pattern[10]. Since, more than 100 families with HP have been reported. In 1996, an exceptional family genealogy was studied between 1800 and 1993, involving 249 members across eight generations. Such a series yielded 63 definite and 17 probable cases of HP. Importantly, this report confirmed an autosomal dominant pattern of inheritance with variable penetrance[11]. Later that year, Whitcomb and colleagues, discovered the first genetic mutation associated with the HP phenotype; an arginine to histidine substitution at codon 122 of the *PRSS1* gene, further designated as the *R122H* variant[12]. Since, dozens of mutations of the *PRSS1* and other genes associated with HP have been identified.

EPIDEMIOLOGY

True prevalence rates of HP may be difficult to determine given infrequent genetic testing outside of specialized centers[13]. The prevalence has been estimated to be 0.3 per 100,000 persons in France[14], but, this, along with worldwide estimates are likely under representations of actual figures.

Germline mutations are common in both pediatric ARP and CP. In a recent cross-sectional study of a multinational, pediatric cohort, 48% of patients with ARP and 73% of CP patients were noted to have at least one gene mutation implicated in HP. Having said that, not all patients in this study underwent testing for pancreatitis-associated gene mutations, and in those who did, the genetic panel was rarely comprehensive, making the true impact of childhood HP likely more significant than reported[4].

CLINICAL FEATURES

HP generally presents as an acute episode of pancreatitis, manifested by significant abdominal pain, nausea and vomiting, with amylase and/or lipase levels more than 3 times the upper limit of normal. If abdominal imaging is warranted features consistent with AP can be noted; typically acute interstitial pancreatic edema, peripancreatic inflammation, fluid collections or pancreatic/peripancreatic necrosis[15]. Given inherent genetic mutations, patients are predisposed to recurrent episodes of AP. In particular, pediatric patients experience a rapid progression from the initial episode of AP to CP, with a median time of 3.79 years being described. Children with pathogenic *PRSS1* mutations progress at a faster rate to CP, as compared to patients without *PRSS1* variants (median time to CP: 2.52 *vs* 4.48 years; *P* < 0.05)[5]. Such an aggressive disease process leads to chronic parenchymal and ductal changes (Figures 1 and 2). These include hyperechoic foci with and without shadowing, main pancreatic duct calculi, lobularity with honeycombing, cystic changes, duct dilation, hyperechoic duct margins, dilated side branches and hyperechoic stranding. The Rosemont Criteria can be used to categorize such imaging findings, however its use in pediatrics has not been validated[15,16].

All in all, the clinical spectrum of pancreatic disease noted with pediatric HP closely resembles other etiologies of ARP and CP, albeit, at a faster rate of progression with particular phenotypes. There are however, a few notable distinguishing features. HP tends to have an earlier presentation. Variants of the *PRSS1, chymotrypsin C (CTRC) and carboxypeptidase A1 (CPA1)* genes are associated with early disease onset, particularly before 10 years of age[9,14]. Additionally, there is some evidence to suggest that a maternal pattern of inheritance confers earlier disease onset as compared to a paternal pattern of inheritance[17]. At this time there is no compelling evidence to indicate that patients with HP develop exocrine or endocrine insufficiency at a faster rate[13]. However, given an earlier progression to CP in certain HP phenotypes, such a protracted disease course with ongoing pancreatic parenchymal damage and atrophy, may represent a contributory factor to the rapid development of exocrine pancreatic insufficiency and diabetes noted in children with ARP[5].

HP in the adult setting confers an increased risk of pancreatic cancer, with a lifetime risk of at least 40% for developing carcinoma of the pancreas among HP adults[17]. Of note environmental factors, namely tobacco smoking and alcohol consumption may act as confounders in this population. Further analysis controlling for smoking did reveal a relative risk of approximately 7% for the development of pancreatic cancer among adults with a *PRSS1* gene mutation[18]. To the best of our knowledge, the risk of pancreatic cancer in childhood CP, let alone pediatric HP, remains unknown[19].

Figure 1 Radial endoscopic ultrasound in a 13 year old male with SPINK1 and CTRC gene mutations demonstrating pancreatic duct dilatation (arrow) in addition to chronic parenchymal changes: Honeycombing with lobularity, non-shadowing hyperechoic foci, cystic changes and hyperechoic duct margins.
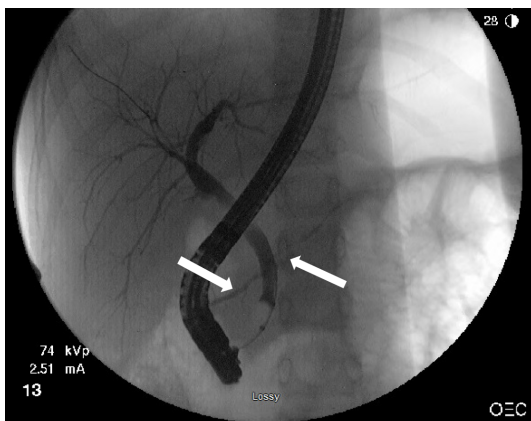
Figure 2 Endoscopic retrograde cholangiopancreatography in a 10 year old male with a CFTR gene mutation and pancreas divisum demonstrating contrast entering the dorsal pancreatic duct (arrows) from the common bile duct during a balloon occlusion cholangiogram. This occurred due to a fistula between the common bile duct and pancreatic duct secondary to repeated episodes of acute pancreatitis.

PANCREATITIS RELATED GENE MUTATIONS

It was not until 1996 that the first pancreatitis related gene variant, the *R122H* mutation of the *PRSS1* gene was discovered. Since then, numerous pathogenic mutations of the *PRSS1* and additional genes have been identified[12]. Other notable genes associated with HP include, *SPINK1, CFTR, CTRC, CPA1, calcium-sensing receptor (CASR)* and *claudin-2*. In many instances, HP seems to involve a complex interplay of genetic and environment factors that causes an imbalance in protease regulation leading to pancreatic parenchymal injury. From recent analyses, these genetic mutations have been grouped and classified into disease causing or modifiers of disease[7,20-22]. The following section describes the inheritance pattern and proposed mechanism of action of the major pancreatitis related variants implicated in HP. A summary of this information has also been provided (Table 1).

PRSS1

Pathogenic variants of *PRSS1* have been isolated in >60% of large families afflicted with HP, spanning numerous generations[7]. Although dozens of *PRSS1* mutations have been identified, *R112H, N29I and A16V* are the most common disease causing variants. These are all inherited in an autosomal dominant manner. *R122H* (80% penetrance, 78% of mutations) and *N29I* (93% penetrance, 12% of mutations) together are estimated to account for approximately 90% of *PRSS1* HP cases[14,23].

The *R122H* mutation has been classified as a gain of function mutation that prevents autolysis of trypsin, which increases trypsin stability, thereby allowing for enhanced enzyme activation and pancreatic digestion[24]. Similarly, *N29I* mutation results in

Table 1 Prominent pathogenic pancreatitis related gene variants

Pathogenic gene (Variant)	Inheritance pattern	Mechanism of action
PRSS1 (R122H)	Autosomal dominant	Impaired autolysis of trypsin
PRSS1 (N29I)	Autosomal dominant	Increased autoactivation of trypsin
PRSS1 (A16V)	Autosomal dominant	Possible increase in trypsin activation
CFTR (R75Q)	Autosomal recessive	Impaired zymogen secretion
Disease modifiers		
SPINK1 (N34S)	Autosomal recessive	Decreased trypsin inhibition
CTRC (A73T, V235I, R253W, K247_R254del)	Autosomal dominant or multigeneic	Impaired lysis of trypsin

increased autoactivation of trypsin, also allowing for unchecked pancreatic autodigestion[25]. As a result, *R122H and N29I* mutations generally follow a similar clinic presentation. On the other hand, the mechanism by which the *A16V PRSS1* gene variant cause disease remains incompletely understood. Some evidence suggest that the *A16V* mutation increases the secretion of the *CTRC* protein, ultimately leading to a fourfold increase in activation of trypsin[26].

SPINK1

The *SPINK1* gene encodes an acute phase reactant that functions as a trypsin inhibitor. Pathogenic *SPINK1* mutations are loss of function mutations leading to decreased trypsin inhibition, predisposing to pancreatitis[27]. The *N34S* variant is the most common haplotype reported globally. In the majority of cases *SPINK1* mutations are inherited in a heterozygous form and require other genetic and/or environmental factors to effect pancreatitis. As such, they are better considered as disease modifiers [28].

CFTR

Mutations in the *CFTR* gene are also associated with HP. One would readily associate the F508-delta variant with the typical multisystem cystic fibrosis syndrome. Such a variant is rarely associated with HP, but rather inheritance of a milder variant in an autosomal recessive manner, such as the *R75Q* mutation has been implicated with recurrent attacks of AP[29]. The presence of the *R75Q* mutation is associated with at least a 40 fold increased probability of developing pancreatitis when compared to the general population[30]. Bicarbonate secretion is essential for the release of pancreatic zymogens. A dysfunctional variant such as the *R75Q* mutation, leads to failure of acinar cell alkalization. As such, zymogens are not released, and once protease activation ensues, autodigestion of surrounding pancreatic tissue occurs leading to episodes of AP[22].

CTRC

The *CTRC* gene encodes for chymotrypsin C, a protease involved in trypsin regulation. Loss of function mutations in this gene, impair tyrpsin lysis and reduce the protective function against developing CP. Numerous CTRC gene variants, including *A73T, V235I, R253W*, and *K247_R254del* act by this mechanism. Such variants do not seem to be causative of HP when found in isolation, but are rather seen in concert with other genetic mutations (*SPINK1* or *CFTR*) or environmental factors[31,32].

Other genetic mutations

There are several less studied genetic variants that appear to contribute to HP. One example is the *CASR* gene, which encodes for a plasma membrane calcium sensing receptor involved in regulation of intracellular calcium levels and thereby, trypsin stability[33]. Another notable genetic variant involves the *CPA1* gene. This gene encodes for carboxypeptidase A1, which also functions as a pancreatic protease. Pathogenic defects of CPA1 are believed to confer a propensity towards developing HP through trypsin misfolding and aggregation, cumulating in increased endoplasmic reticulum stress[34]. The *CLND2* gene is located on the X chromosome and encodes claudin-2, which mediates sodium and water transport in the proximal pancreatic duct. From the results of a genome wide susceptibility study, mutations of the *CLND2* gene appear to mediate an atypical distribution of claudin-2, and consequently

increase the risk of alcohol induced pancreatitis, particularly in males[35,36].

DIAGNOSTIC EVALUATION

The investigation of HP typically begins with an extensive history to delineate previous episodes of acute pancreatitis, as well as an extended family history of clinical symptoms, aimed at identifying possible inheritance patterns. Diagnostic criteria for AP, ARP and CP in the pediatric population follow those outlined by the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) consortium. Once 2 of the following 3 are met AP is diagnosed; suggestive abdominal pain, serum amylase or lipase at least 3 times the upper limit of normal and/or characteristic imaging findings. If a patient has normalization of amylase and lipase levels and symptoms, or complete resolution of pain for at least 1 mo in between episodes of AP, this is termed ARP. CP is diagnosed when imaging findings of chronic pancreatic injury is noted along with at least one of; typical abdominal pain, endocrine or exocrine insufficiency[13,15].

Abdominal imaging studies may be required to assess for radiographic features of acute or chronic pancreatitis. In the pediatric setting such a radiologic workup generally begins with non-invasive cross-sectional imaging, mainly computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP). Endoscopic ultrasonography (EUS) can be considered if the aforementioned studies fail to establish a diagnosis, etiology or adequately outline the extent of disease. Use of endoscopic retrograde cholangiopancreatography (ERCP) solely for diagnostic purposes in pediatrics is discouraged, mainly due to procedure related risks and similar diagnostic capabilities of MRCP in children[37].

When HP is suspected genetic testing to identify pathogenic pancreatitis related gene variants may be warranted. Criteria have been proposed to assist in determining which patients should undergo genetic evaluation (Table 2). Once the patient satisfies at least one of these, testing is recommended[38,39]. The decision to test children, whether symptomatic or asymptomatic can have considerable psychosocial impact not only for patients, but also their families. Consequently, it is recommended, that such testing and interpretation of results is best done with the assistance of an experienced genetics provider[21,40].

MANAGEMENT

HP can present at any juncture of the pancreatitis continuum. Generally children are brought to specialist medical attention and subsequently diagnosed after experiencing repeated episodes of AP. As with AP resulting from other etiologies, management generally involves early aggressive fluid hydration with appropriate monitoring, adequate pain control and early enteral nutrition. Invariably patients experience repeated pancreatic insults and complications necessitating further medical care, endoscopic and surgical procedures[13]. Given the early and aggressive nature of disease associated with pancreatitis related gene variants[5,9,14] we aim to examine the role that preventative measures and other therapeutic modalities can have in the management of HP among children.

Preventative measures
Substantial alcohol consumption is a well described predisposing factor for AP and subsequent progression to eventual CP among adult studies[41,42]. Similarly, data from the adult population has demonstrated that tobacco use is associated with pancreatic disease progression and development of pancreatic calcifications in a dose-dependent manner[42,43]. Expert consensus strongly recommend that pediatric providers caution their patients against the use of tobacco and ethanol due to the negative short and long-term effects on pancreatic health [19].

Inflammatory processes that underlie the pathophysiology of CP involves antioxidant depletion and oxidative stress. Supplementation of antioxidants has been proposed as a mechanism to prevent CP progression and the development of exocrine pancreatic insufficiency (EPI). To date, insufficient data exists to recommend antioxidant supplementation in children with CP for such indications[19,44].

Studies from the adult population have also implicated truncal obesity as a risk factor for severe AP, mainly due to the pathogenic role that peripancreatic or intrapan-

Table 2 Criteria Necessary for Genetic Testing of Pancreatitis related Gene Variants

Criteria necessary
Documented pancreatitis in a child without a definite cause
Acute recurrent pancreatitis without an identifiable etiology
Idiopathic chronic pancreatitis in patients younger than 25 years old
Family history of idiopathic chronic pancreatitis or acute recurrent pancreatitis
Relatives with known pancreatitis related gene mutations
Patients eligible for participation in approved study protocols

creatic fat plays in the development of pancreatic necrosis [45]. Interestingly, overweight or obese children have been found to be less likely to develop CP compared to children with a normal BMI. Obese children generally also experience their first episode of AP later than their non-obese counterparts. However, research examining the effects of BMI on CP outcomes in pediatrics remains limited and the current expert consensus recommendation is for pediatricians to recommend a balanced, healthy diet and lifestyle for their patients afflicted with CP [19].

Unfortunately, aside from these lifestyle modifications, there remain no novel therapeutic agents available for preventing repeated episodes of AP and the eventual progression to CP in patients with HP. In this regard, present treatment strategies are focused on managing the natural history of HP as opposed to preventing or delaying disease progression. Further research is warranted to better define 'optimal' preventative management in this population.

Medical management

Pediatric patients with progressive pancreatic disease are at risk for a number of sequelae which are best managed with a multidisciplinary approach. Given the significant postprandial abdominal pain and discomfort associated with ARP and CP, many patients are at risk of macro- and micronutrient deficiencies. With the help of a clinical dietician, growth and nutritional status should be carefully evaluated at every clinic visit (at least every 6-12 mo). Dietary education should also be provided to prevent obesity and malnutrition[19,44].

In a recent report of data analyzed among pediatric patients with ARP, it was noted that 18% and 7.7% developed EPI and diabetes mellitus respectively within 6 years of the initial AP attack[5]. EPI can be subclinical or present with steatorrhea, poor growth and nutritional deficiencies, particularly of fat-soluble vitamins. These patients should be provided with pancreatic enzyme replacement therapy, along with monitoring of fat-soluble vitamin levels at least every 12-18 mo. Screening for endocrine pancreatic insufficiency should be done at least yearly with a HbA1c and fasting glucose level. Should these values be outside the reference range, referral to a pediatric endocrinologist is indicated[19].

Pediatric CP is associated with a considerable disease burden, impairing quality of life and significantly disrupting childhood educational activities. These children can require frequent emergency room visits, hospitalizations and absences from school, mainly for management and control of chronic, severe pain[46]. In this regard, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition pancreas committee has set forth a number of recommendations to address pain management in pediatric patients with CP. These recommendations stress the importance of working alongside physical therapists, psychologists and pain specialists to institute a multi-modal approach to pain management. Before immediately using a non-opioid to opioid analgesic 'step-up' approach, neuromodulators, cognitive behavioral therapy and physical therapy should be considered as adjunctive measures for pain management[19].

Endoscopic therapy

As the sequalae of HP progress, endoscopic interventions may become necessary. As previously noted, EUS can play a diagnostic role if conventional cross-sectional imaging modalities fail to establish an etiology or disease extent. Among adults, therapeutic EUS is increasingly being considered as a first therapy for pancreatic walled off necrosis, and psuedocysts[47]. Though conservative measures should always be considered for pediatric pancreatic fluid collections, expert consensus from

the pancreas committee of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) recommend EUS intervention when endoscopic drainage is indicated.

Given associated procedural risks, ERCP use solely for diagnostic purposes is discouraged. However, therapeutic benefits have been derived among children with pancreatic duct stenting and removal of pancreatic calculi. Such patients have experienced improvement in symptoms and reduction in pancreatitis episodes[48,49].

Special considerations apply when undertaking these advanced endoscopic procedures in pediatrics. Theapeutic EUS, and in particular ERCP should only be undertaken after all the potential risks and possible need for multiple procedures are thoroughly discussed with caregivers. In addition, patients under 10-15 kg, may require specialized equipment not available in most centers. Primary physicians should consider referral to an appropriate tertiary center if therapeutic endoscopic procedures are required, as these procedures should ideally be done by endoscopists with ample experience in the pediatric setting.

Surgical therapy

Pancreatic necrotic collections and psuedocysts not amendable to endoscopic intervention may require surgical drainage[13]. Incapacitating CP that has failed medical and endoscopic therapy may benefit from conventional surgical approaches. A longitudinal pancreaticojejunostomy (Puestow procedure) can be utilized as a drainage procedure for an obstructed main pancreatic duct, whereas with involvement of the pancreatic head, a pancreaticoduodenectomy has proven some (Whipple procedure) benefit among adult patients[50,51]. Such procedures compromise islet cell yield and if undertaken, the remaining pancreatic tissue would still be subject to repeated insults. In this regard, its applicability to pediatric HP remains questionable [50,52,53]. Ultimately, pediatric patients with unremitting constant pain and grossly impaired quality of life proceed to total pancreatectomy with islet autotransplantation (TPIAT). Unfortunately this procedure commits the patient to lifelong pancreatic enzyme replacement therapy and a high likelihood of becoming insulin dependent, however, it has demonstrated improved quality of life and substantial pain relief. No formal criteria exist for which pediatric patients should proceed to TPIAT, so this decision should ideally involve a multidisciplinary team of pediatric pain specialists, surgeons, endocrinologists, gastroenterologists and dietitians[50,53,54].

CONCLUSION

HP has emerged as a significant cause of AP, ARP and CP in the pediatric setting. Given that it presents similarly to other causes of pancreatitis, a positive family history and/or isolation of a pathogenic pancreatitis related gene mutation are vital in its designation. Since the discovery of the first genetic mutation associated with the HP phenotype in 1996, dozens of other genetic defects have been identified, with varying inheritance patterns. More recent work among pediatric patients has associated particular variants with early onset and rapid progression, potentially making pediatric HP an aggressive disease with significant sequelae and substantial burden. Primary care physicians can play a vital role in identifying at risk patients with careful screening, and providing timely referral to tertiary centers adept at genetic testing and managing the continuum of pediatric pancreatitis. This model has the ability to limit health care cost and reduce the negative psychosocial effects on patients and families. Further work should focus on analyzing the impact that genetic and other risk factors have on the natural history and progression of pediatric pancreatitis, so that preventative interventions can be implemented to limit debilitating disease.

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