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PEDIATRIC PANCREATITIS

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Abstract

Purpose of Review—The purpose of this review is to describe recent developments in pediatric pancreatitis and to discuss etiologies and current management.

Recent Findings—Although recent studies have estimated the annual incidence of pediatric acute pancreatitis approaching that of adults, there are no established guidelines about its diagnosis and treatment in children. Genetic and structural/congenital abnormalities are emerging as the primary risk factors for pediatric acute recurrent and chronic pancreatitis. Specifically, chronic pancreatitis is associated with a significant socioeconomic burden in children. Both medical and surgical therapies are proposed for pediatric chronic pancreatitis, but there is little evidence that they are beneficial.

Summary—Acute, acute recurrent and chronic pancreatitis create significant health issues in the pediatric population. Medical and surgical therapies exist to potentially treat these conditions, but the pediatric data is limited and the cohorts are small. A multidisciplinary and multicenter approach is necessary to better determine pancreatic disease processes and treatment options in children.

Keywords

abdominal pain; quality of life; pediatric gastroenterology; genetics

INTRODUCTION

In children, pancreatitis is categorized as acute pancreatitis (AP), acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP). We have significant gaps in our knowledge of pancreatitis in children. Here we summarize recent advances in the field of pediatric pancreatitis with focus on etiologies, diagnosis and therapy.

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ACUTE PANCREATITIS

Recent studies estimate the incidence of acute pancreatitis (AP) at ~1/10,000 children per year [1, 2], which approaches incidences reported in adults [3]. This incidence may represent a true rise in pediatric pancreatitis or improved awareness [1, 4, 5]. There are no evidence-based diagnostic guidelines for pancreatic disorders in children. A multicenter effort led by INSPPIRE (**IN**ternational **S**tudy Group of **P**ediatric **P**ancreatitis: **I**n Search for a Cu**RE**) defined AP as requiring 2 of: (1) abdominal pain compatible with AP, (2) serum amylase and/or lipase values ≥3 times upper limits of normal, (3) imaging findings consistent with AP [6, 7**]. Pediatric AP is associated with significant disease burden. Children with AP are hospitalized for 5–8 days, while infants and toddlers spend approximately 20 days in the hospital [5, 8–10]. An early study estimated the cost of pediatric AP in the US as $52 million per year [11]. The cost may be higher than reported due to increased incidence of pediatric AP in recent years, length of stay and higher charges in children hospitalized for AP [12].

Pathophysiology

The central event in the pathophysiology of AP is acinar cell injury and local tissue damage. The studies in animal models of AP suggest that cytosolic calcium changes, colocalization of zymogens and lysosomes, intraacinar activation of zymogens, nuclear factor-κb activation and inhibition of secretion play a significant role in the pathogenesis of AP. The animal models do not recapitulate the human disease and there is no consensus on a unifying theory. Although intra-acinar activation of trypsinogen has been considered as the main factor leading to cellular injury, it fails to explain all mechanistic events in AP [13].

Etiologies

In adults, gallstones and excessive alcohol use are the main risk factors of AP. Common causes of AP in children are markedly different compared to the adult population [4, 5, 8–10, 14–23] (Table 1). Biliary/obstructive factors, medications and systemic diseases are the main causes of AP in the pediatric age group. AP triggered by genetic mutations, metabolic factors, trauma or alcohol is not common in children. AP is idiopathic in 15–30% of cases.

Diagnosis of AP

The diagnosis of AP is based on clinical presentation, confirmed by laboratory and/or radiological studies. Abdominal pain and/or irritability are the most common findings of AP in children, followed by epigastric tenderness, nausea and vomiting [8, 10]. Clinical findings may be subtle in infants and toddlers, thus requiring a high level of suspicion.

Due to its safety profile, non-invasive nature and ability to detect biliary etiologies, the abdominal ultrasound (US) is the imaging modality of choice in children [5, 8]. It must be noted that US has lower sensitivity in visualizing the pancreas compared to computed tomography (CT) [24]. CT imaging of the abdomen can be most helpful in identifying complications of AP (i.e. fluid collections, necrosis, hemorrhage) when performed several days after the initial presentation [25].

In general, AP has a mild course in childhood and resolves without complications. Pancreatic pseudocysts may occur in ~15% of children with AP and in most cases resolve completely without intervention [2, 8, 9]. A subset of children with AP (6–25%) may develop severe pancreatic inflammation and necrosis, triggering systemic inflammatory response syndrome (SIRS) and multiorgan failure (shock, renal failure, pulmonary insufficiency). It is not easy to predict the severity of AP at the time of presentation because the scoring systems developed in adults do not typically apply to children [26]. A recent study suggests that serum lipase obtained within 24 hours of presentation may serve as a marker of AP severity in children, with levels over 7 times the upper limit of normal predicting a severe course [27].

Treatment of AP

Often, the treatment of AP is determined by the etiological factors. Pain control is at the center of AP management, followed by intravenous (IV) hydration and nutrition. In general, narcotic analgesics are preferred drugs for pain management in children [6]. Despite concerns of sphincter of Oddi spasm and further exacerbation of AP with morphine, there is no clinical evidence to support this theory [28].

Fluid resuscitation is critical in the management of AP. However, the volume, rate, timing and components of the IV fluid therapy are not well-established. Studies in adults suggest that early and aggressive fluid resuscitation and pH-buffering capacity of the IV fluid (i.e. lactated ringer) may decrease morbidity and mortality from AP [29–31]. Studies are needed to determine the adequate fluid management in pediatric cases.

Early nutrition (oral, nasogastric or nasojejunal) is safe and may promote more favorable outcomes in AP possibly via maintaining gut barrier function, preventing bacterial translocation and lowering the risk for SIRS [32–35].

Endoscopic or surgical approaches are rarely used in pediatric AP. Endoscopic intervention is indicated within 24 hours for adults with gallstone pancreatitis and cholangitis and within 72 hours if there is high suspicion of common bile duct stone [36, 37]. The optimal timing of cholecystectomy after hospital admission for gallstone pancreatitis may be within 48 hours for mild disease and after 2 weeks for more severe AP [38]. Conservative management is usually sufficient for pancreatic pseudocysts. If needed, pseudocysts may be treated by drainage via radiologic, endoscopic, or surgical techniques [39].

ACUTE RECURRENT AND CHRONIC PANCREATITIS

According to INSPPIRE, acute recurrent pancreatitis (ARP) is defined as: ≥ 2 distinct episodes of AP with intervening return to baseline [6]. CP is diagnosed in the presence of: (1) typical abdominal pain plus characteristic imaging findings or; (2) exocrine pancreatic insufficiency (EPI) plus imaging findings or; (3) diabetes plus imaging findings [6]. In children, ARP and CP are overwhelmingly associated with genetic risk factors [40**].

Overall ARP is reported in 15–35% of children following an initial occurrence of AP [9, 14, 15, 41] and CP is estimated as ~0.5 per 100,000 persons per year [42, 43]. Despite modest

incidence rates, ARP and CP are associated with significant disease burden. Children with CP experience frequent abdominal pain, emergency room visits and hospitalizations and they undergo numerous endoscopic and surgical procedures [40**].

Etiologies

The risk factors for ARP and CP are listed in Table 2. Although alcohol and smoking have long been recognized as major risk factors for CP in adults [44–46], they are uncommon in the pediatric age group. A few single center-studies with small cohorts suggest that children with ARP or CP often have mutations in the *cationic trypsinogen (PRSS1), cystic fibrosis transmembrane generator (CFTR), serine protease inhibitor Kazal type I (SPINK1), carboxypeptidase 1 (CPA1)* genes [15, 47–52], but it is not known whether genetic factors predict a more aggressive disease course in children. A strong association between CPA1 mutations and childhood-onset CP [52] suggests that genetic risk factors may determine early onset of CP. The genetic variants in the *claudin 2 (CLDN2)* [53], and *chymotrypsin C* (*CTRC)* genes [54], *carboxylesterlipase (CEL)* and *CEL-HYB* allele (originating from a crossover between *CEL* and its neighboring pseudogene, *CELP*) [55, 56] increase the risk for CP in adults with idiopathic CP or already have alcohol and smoking as risk factors. *CFTR* mutations associated with pancreatitis can occur in the heterozygous or homozygous state [57, 58]. Patients presenting with pancreatitis and homozygous *CFTR* mutations typically have mild lung manifestations of their cystic fibrosis [58]. Patients who carry >1 mild *CFTR* mutation are pancreatic sufficient and prone to recurrent attacks of pancreatitis [59].

Pancreas divisum is found in 7% of the general population, but almost half of patients with genetic mutations (primarily *CFTR* mutations) and pancreatitis [60]. This suggests that pancreas divisum synergizes with genetic mutations to cause ARP and CP.

Autoimmune pancreatitis (AIP) is a poorly defined entity in children and a rare cause of ARP and CP [61]. Possibly most cases of AIP in children are Type 2 [62].

Pathogenesis

In general ARP and CP are considered as disease continuum rather than two separate entities. In children with hereditary pancreatitis, mutations in *PRSS1* cause activation of trypsinogen as an early event [63]. Premature activation of trypsinogen to trypsin initiates an activation cascade, causing additional trypsinogen activation and conversion of other digestive proenzymes to active enzymes, leading to pancreatic digestion and inflammation [64]. As the ongoing insult to the pancreas continues (genetic mutations, obstructive factors, environmental exposures, etc.), activated inflammatory cells and stellate cells release cytokines and deposit collagen, eventually producing the fibrotic changes typically seen in CP [23]. The characteristic changes of CP are progressive fibrotic destruction of the pancreatic exocrine parenchyma leading to exocrine pancreatic insufficiency (EPI), glycemic abnormalities and eventually diabetes.

Diagnosis of CP

Chronic or recurrent abdominal pain and impaired quality of life are commonly seen in children with ARP or CP [40, 65**]. Nausea and/or vomiting, anorexia, weight loss may be present. In most cases, serum amylase and lipase are normal or only mildly elevated [66]. Serum transaminases, direct bilirubin, alkaline phosphatase, and gamma-glutamyl transferase levels may be elevated in the setting of a concomitant biliary obstruction [10].

Testing for pancreatitis-associated gene mutations is recommended for all children with ARP or CP (Table 2). Multiple gene mutations or combination of multiple risk factors may be present in the same patient. We recommend sweat chloride in children with ARP or CP if *CFTR* mutations are present to evaluate for cystic fibrosis.

Long-term consequences of pancreatic inflammation and fibrosis will invariably lead to EPI and diabetes in CP. If EPI has developed, children may have steatorrhea, weight loss and fat-soluble vitamin deficiencies (A, D, E, K). Exocrine pancreatic function can be measured by indirect testing (fecal fat analysis, fecal elastase-1 (FE-1), stool chymotrypsin, ^{13}C-mixed triglyceride breath test, serum immunoreactive trypsinogen (IRT), fat soluble vitamin levels) or direct testing (pancreatic stimulation test with Dreiling tube or endoscopic pancreatic function test (ePFT)). Dreiling tube testing is considered as the gold standard to measure the exocrine pancreatic function [67], but this test is not widely performed due to its invasive nature. Additionally, the collection of the duodenal fluid via the endoscope (ePFT) may underestimate pancreatic exocrine secretions and can lead to the diagnosis of EPI erroneously [67]. In recent years, FE-1 has proven to be a relatively easy and accurate method of detecting EPI. Although the sensitivity of FE1 to diagnose moderate and severe EPI is excellent, it cannot be used for the diagnosis of mild cases [68]. FE-1 may also be falsely low in patients with watery diarrhea. Pancreatic endocrine insufficiency (defined as “type 3c diabetes mellitus”) is a late complication of CP characterized as impaired beta cell function and relatively minor to no insulin resistance. Testing for Hemoglobin A1c and fasting blood glucose is recommended to screen for type 3c diabetes mellitus [69, 70]. Impairment in either fasting glucose or HbA1c should be further evaluated by a standard oral glucose tolerance test. There is a lifetime risk for pancreatic adenocarcinoma in patients with CP (4%) [71], and this risk is much higher in patients with HP (~40%) [72].

As pancreatic destruction progresses, lesions become easier to detect with imaging techniques including abdominal US, CT, magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasonography (EUS) and endoscopic retrograde cholangiopancreatography (ERCP). Ductal calculi, dilated side branches, parenchymal calcifications, irreversible ductal obstruction or stricture/dilatation/irregularities are common imaging findings of CP. MRCP is the test of choice in children because it is non-invasive, accurate, and does not have associated radiation exposure. Intravenous secretin may enhance the diagnostic accuracy of MRCP [73]. ERCP is mainly reserved for CP complications requiring interventions [74].

Treatment of CP

Pain control is the mainstay of CP management. We recommend avoiding long-term opioid therapy, but rather manage the neuropathic pain of CP with tricyclic antidepressants, gabapentin, or pregabalin [62, 75, 76].

Pancreatic enzymes are commonly prescribed in CP to reduce the feedback loop in the duodenum by reducing cholecystokinin release and inhibiting pancreatic exocrine activation, however their efficacy for pain control is debated [77]. Antioxidants are proposed for the treatment of chronic pain in CP, but their benefit is not established [78]. Studies are needed to evaluate the utility of these therapies in pediatric ARP or CP.

Endoscopic therapy may be useful if there is an identifiable stricture and pancreatic duct obstruction [79, 80]. Children with ARP or CP may experience significant benefit following therapeutic ERCP [81, 82*].

Surgery may be indicated for CP in the presence of debilitating chronic pain. Surgical techniques include drainage operations that aim to decompress dilated ducts or resections of strictures/removal of pancreatic stones. In general, decompressive operations (i.e. Puestow operation) are preferred in the pediatric age group [83]. Total pancreatectomy with islet cell autotransplantation (TP/IAT) is being proposed as a treatment for CP and recent studies report a more favorable outcome in children compared to adults [84–93**]. Even though single center experiences are encouraging, TP/IAT is an irreversible choice, which is associated with a significant risk of life-long diabetes after the procedure.

CONCLUSIONS

Pancreatitis is associated with significant disease burden in childhood. Although we are just beginning to understand the etiologies and socioeconomic burden of pancreatitis in children, many questions still remain. We have yet to determine the natural history of pediatric pancreatitis, identify risk factors for initiation and sequelae of CP and develop therapies to improve clinical outcomes. Because pancreatitis is not common in pediatrics, prospective multicenter longitudinal studies are crucial to address the fundamental gaps in knowledge.

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KEY POINTS

- There are significant gaps in our understanding of pediatric pancreatitis.
- Acute pancreatitis is an emerging disease in childhood with annual incidence similar to those found in adults.
- Children with acute recurrent and chronic pancreatitis have a high prevalence of genetic risk factors with few confounding environmental factors, thus distinguishing it from adult pancreatitis populations.
- Children with chronic pancreatitis have a significant burden of disease, including pain, school absences, and hospitalizations.
- Prospective multicenter studies are crucial to address the fundamental gaps in knowledge.

Table 1

Risk Factors for Pediatric Acute Pancreatitis [4, 5, 8–10, 14–23]

Biliary/obstructive factors (10–30%)
Gallstones
Biliary sludge
Pancreas divisum
Choledochal cyst
Sphincter of Oddi dysfunction
Annular pancreas
Medications (5–25%)
Valproic acid
6-mercaptopurine/azathioprine
L-asparaginase
Mesalamine
Trimethoprim/sulfamethoxazole
Furosemide
Tacrolimus
Steroids
Systemic diseases (10–50%)
Sepsis
Shock
Inflammatory bowel disease
Hemolytic-uremic syndrome
Trauma (10–20%)
Viral infection (8–10%)
Metabolic diseases (5–10%)
Diabetic ketoacidosis
Hypertriglyceridemia
Inborn errors of metabolism
Hypercalcemia
Idiopathic (15–30%)
Others (ERCP, genetic factors, alcohol <10%)

Table 2

Risk Factors for Pediatric Acute Recurrent and Chronic Pancreatitis [15, 40, 44–46, 47–62]

Genetic (most common)
PRSS1
CFTR
SPINK1
CTRC
CPA1
CEL
CEL-HYB
CLDN2
Obstructive
Pancreas divisum
Gallstones
Sphincter of Oddi dysfunction
Anomalous junction of the biliary and pancreatic ducts
Annular pancreas
Ampullary obstruction
Toxic-metabolic
Medications
Hypertriglyceridemia
Hypercalcemia
Metabolic diseases
Chronic renal failure
Autoimmune
Idiopathic