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Review Article

Chronic Pancreatitis in Children

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ABSTRACT

Chronic pancreatitis (CP) in children is a rare condition and its etiology varies; it is mainly associated with genetic abnormalities, autoimmune pancreatitis, and obstruction. Most cases of CP have a history of acute pancreatitis. The magnetic resonance cholangiopancreatography is a diagnostic technique that allows noninvasive multiplanar visualization of the biliary and pancreatic ducts, and does not require contrast administration. In children with CP, the step-up management includes a limited trial of endoscopic interventions, such as endoscopic retrograde cholangiopancreatography, followed by surgery.

Keywords: children; chronic pancreatitis; pancreatitis

INTRODUCTION

Chronic pancreatitis (CP) is a pancreatic fibro-inflammatory syndrome disease in which progressive inflammation progressively demolishes dually the pancreatic parenchyma and ductal systems, resulting in irreversible structural changes[1,2]. The incidence is 0.5 per 100,000 in people younger than 20 years[3]. The common causes of pediatric pancreatitis are anomalies of the pancreaticobiliary duct[4,5], systemic infection, trauma, drugs, metabolic abnormalities, liver transplantation, nutrition, familial pancreatitis and idiopathy[3,6-8] (Table 1).

Chowdhury et al. investigated 3,887 cases in a gastroenterology department: 99 (2.5%) had CP. Ninety-five out of the 99 (95.9%) children were without a definite diagnosis, but were tagged as "idiopathic CP"[9]. Current studies show their situation with idiopathic CP may also involve a genetic disorder[10-12].

Acute recurrent pancreatitis (ARP) and CP in children occur infrequently and are not well-known illnesses. The International Study Group of Pediatric Pancreatitis: In search for a cure (INSPPIRE) is a consortium that was created in order to gather more thorough knowledge using a cohort of ARP and CP in children[13]. Pediatric CP is the appearance of "permanent pancreatic structural changes, for instance, scatter or focal destruction, sclerosis, and/or pancreatic duct malformations/occlusions"[14], while acute recurrent pancreatitis is defined as two separate episodes of acute[15].

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Table 1 Etiological category of chronic pancreatitis

Factor group[16]	Examples
Toxic/metabolic: 11.0–16.0%[11,16,21]	medications (ie, azathioprine sodium, 6-mercaptopurine, mesalamine[17]), passive smoking exposure, hypertriglyceridemia, chronic kidney disease, alcohol use, active smoking, propionic acidemia[11], organotin compounds
Idiopathic: 15.0%[21]	tropical, early onset, late onset The INSPPIRE group: age at onset less than 6, 6–11, and 12 years to older[17]
Genetic: 15.0%[21], 67.0%[11], 73.0%[16]	*CFTR* 14.0–28.0%[11,22], *SPINK1*[23] 19.0–20.0%[11,22], *PRSS1* 33.0–43.0%[11,22], *CTRC* 3.0–7.0%[11,22]
Autoimmune/Immunologic factors	Autoimmune pancreatitis (AIP); 4.0–14.0%[11,16,21,22] Inflammatory bowel disease[17]
Miscellaneous	Acute recurrent pancreatitis, post-necrotic severe acute pancreatitis, vascular disease/ischemia, post-irradiation
Obstruction: 33.0–45.0%[11,21,22]	Pancreas divisum 16.0–35.0%[11,16,21], annular pancreas, choledochal cysts or biliary cyst, pancreaticobiliary malunion[23] 3.0–19.0%[11,16,24], gallstones 4.0%[11,16], sphincter of Oddi dysfunction, duct occlusion (e.g., tumor), duodenal diverticulum[17], posttraumatic pancreatic duct scars

CFTR=cystic fibrosis trans membrane conductance regulator gene; *SPINK-1*=serine protease inhibitor kazal type 1; *PRSS1*=protease, serine 1; *CTRC*=trypsinogen-degrading enzyme chymotrypsin C (Chymotrypsin C gene); CP=chronic pancreatitis

Etiology

Pediatric CP is related to genetic mutations in 67.0–73.0% of cases and obstructive risk factors in 33.0%[11,16,17]. Pancreaticobiliary maljunction or malunion (PBM) and pancreas divisum (PD)[11,18,19] are the common congenital anomaly risk factors of CP. The TIGAR-O version 1 category for CP was presented by Etemed in 2001[20] and revised to version 2 by Whitcomb in 2019[17] (Table 1).

Genetics and pancreatitis

In normal children, minimal trypsinogen is activated to trypsin in the pancreas, with defense mechanisms such as trypsin inactivation by proteolytic enzymes such as *SPINK1*, protecting itself against pancreatic autodigestion. *PRSS1* mutations cause increased autoactivation, leading to a high trypsin concentration. *SPINK1*, together with the protease inhibitor α1-antitrypsin, bind to activated trypsin and inhibit its activity[15]. Current research has identified various genes which have been recognized as being related to hereditary and idiopathic CP, such as *PRSS1*, *CFTR* and *SPINK1*[10,16,19,23,25]. Witt, H. reported 164 unrelated and 238 related CP cases, 43 cases (26.0%) with a family history in which there were 15 cases of *PRSS1* mutation, and 34 cases of *SPINK1* mutation[10]. *SPINK1* mutations in patients without a family history were mainly recognized (29/121; 24.0%)[10]. Liu, Xia et al. reported c.194+2T>C mutations in 41 (56.0%) of 73 juvenile idiopathic CP cases, and 42 (42.0%) of 100 in adult patients. A comparison of CP children with or without *SPINK1* c.194+2T>C mutations found that among all 41 cases carrying the *SPINK1* intronic mutation, 29 (71.0%) showed ARP. Whereas, among the 32 cases without the *SPINK1* c.194+2T>C mutation, 10 (31.0%) showed ARP[12]. A Kaneko, Ito et al. showed in a report on genomewide data on changed gene expressions in the biliary tract of choledochal cyst/PBM children[26] that there were various deregulated genes in the gallbladders of PBM children. The Bcl2 modifying factor (BMF) protein has a single Bcl2 homology domain, and belongs to the BH3-only proteins, which work as apoptotic activators[26]. The BMF was remarkably expressed at both the mRNA and

protein levels in gallstone patients, and significantly higher in both the cytoplasm and nucleus of the PBM children than in the controls.

Congenital anomalies

PD is an inborn fusion malformation in which the abortion of the ventral and dorsal pancreas fuse through the fifth to eighth week of gestation[27,28]. PD is categorized as either complete or incomplete fusion. Complete PD is complete separation of the ventral and dorsal ductal systems, whereas incomplete PD has a tiny communicating ductal system linking the ventral and dorsal pancreas[11]. In incomplete PD, the dorsal pancreas or the entire body and tail secrete most of the exocrine pancreatic juice sent to the main duct of Wirsung, that drains across the small minor duct of Santorini. Consequently, the following relative partial obstruction may induce recurring episodes of pancreatitis[29]. PD develops in 7.0–10.0%[29,30] of the population and in ~20% of CP children[11], but in about half of the genetic mutation and pancreatitis patients[11,30]. PD synergizes with genetic anomalies, and thus is feasibly a cofactor in the progress of ARP and CP[11,30]. The median time interval from the onset of symptoms for abdominal pain to the detection of PD has been reported as 2.6 (range 0–34) years[29].

PBM is a congenital duct malformation in which the pancreatic and bile ducts connect anatomically to the surface of the duodenal wall[31]. Therefore, the work of the sphincter of Oddi does not functionally change the connection. Occlusion of a long common channel by stones simply causes bile to pass into the pancreas. A PBM can lead to pancreatitis by biliopancreatic reflux[32]. The inborn PBM identification is proven by visualization of the biliary and pancreatic ductal systems on the ERCP[23,33]. One study reported that 72.0% of PBM cases could be detected on the MRCP[34].

Diagnosis of CP

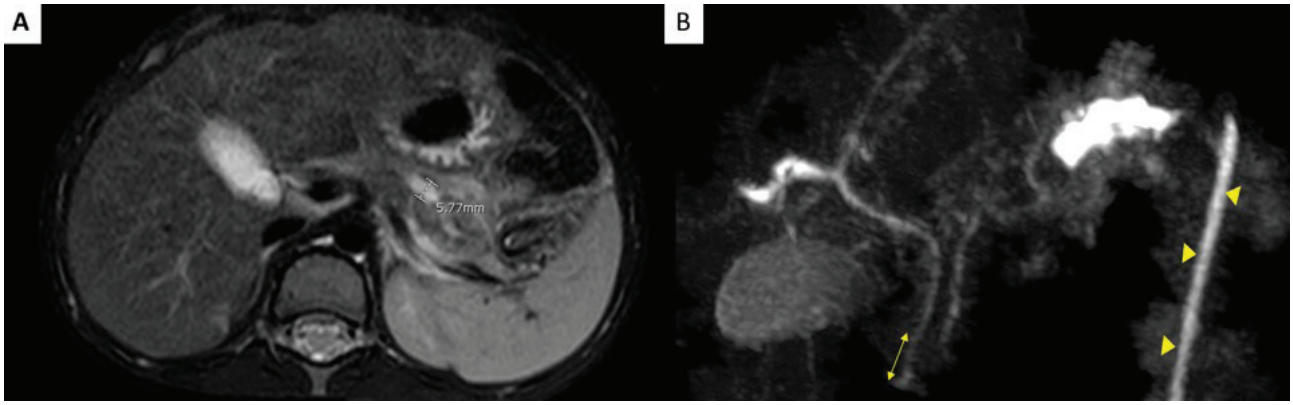
The INSPPIRE agreement clarification of pediatric CP requires one of the following: (1) abdominal pain reliable with pancreatic source and imaging findings indicative of CP destruction; (2) manifestation of exocrine pancreatic insufficiency and imaging findings indicative of pancreatic degeneration; (3) manifestation of endocrine pancreatic insufficiency and imaging findings indicative of pancreatic degeneration; or (4) a surgical or pancreatic biopsy showing histopathological characteristics consistent with CP[35].

The diagnosis of CP or ARP is based on clinical findings, biochemical test, and imaging studies. The pancreatic endocrine function test is an important element in the diagnosis of CP[15]. Most cases of CP have a history of acute pancreatitis. Symptoms raising suspicion for CP include presenting with abdominal pain[23], 74.0–100.0%[9,11,16], recurrent acute pancreatitis, 83.0%[11], steatorrhea, 10.0%[11], and diabetes, 1.0–9.0%[9,11]. The median age at the first attack of acute pancreatitis and diagnosis of CP are 6.8 (IQ 4.5, 12.1) and 9.9 (IQ 6.1, 14.0) years[11], respectively.

Besides the pancreatic endocrine insufficiency, the exocrine function and serum biochemical test also help to diagnose CP. Testing includes the direct pancreatic function test, which is the gold standard but more invasive and not widely available, and the indirect test that estimates the consequences of exocrine insufficiency. Indirect tests are frequently used: the fat digestion and absorption test, stool fat staining, 72-hour fecal fat assessment, and the oral fat loading test are all used to evaluate exocrine pancreatic function. Among the indirect tests, Fecal elastase-1 (FE-1) is more sensitive and widely used for screening exocrine insufficiency. An FE-1 level of <200 μg/g of collected stool is a cutoff for exocrine insufficiency; a value of 100–200 μg/g indicates mild exocrine insufficiency, and <100 μg/g shows a severe exocrine insufficiency[15,36].

MRCP is a noninvasive diagnostic method without contrast application that shows multiplanar visualization of the biliary and pancreatic ducts[34,37]. Standard MRCP is helpful and noninvasive in providing diagnostic figures similar to ERCP in a great proportion of pediatric CP[23] (Figure 1), and thus MRCP should be the primary imaging tool used, particularly if the chance of therapeutic

intervention is low[33]. One study reported that the sensitivity, specificity, positive predictive value, and negative predictive value of MRCP for diagnosing CP were 77.1%, 50.0%, 90.0%, and 27.3%, respectively[33].



A: Pancreatic duct dilatation (5.7 mm)
B: A long common channel (7 mm, two-way arrow) with residual tiny ascites at the perisplenic space, paracolic gutter, and percutaneous drainage (triangle).

Figure 1 The magnetic resonance cholangiopancreatography (MRCP)[23]

Complications

Acute peripancreatic fluid collections are clarified as an accumulation of liquid in or close to the pancreas, without a wall of granulation or fibrous tissue and no related peripancreatic necrosis[38,39]. This term is used only regarding the regions of peripancreatic fluid seen within the first 4 weeks after the beginning of interstitial edematous pancreatitis and without the characteristics of a pseudocyst. Contrast-enhanced computed tomography detections show a homogeneous collection with fluid density, restricted by the regular peripancreatic fascial planes, indefinable wall encapsulating the collection, and close to the pancreas without intrapancreatic addition[38]. The treatment of infected necrotizing pancreatitis patients should be performed using percutaneous catheter drainage (PCD) or endoscopic transmural drainage as the first step (GRADE 1A, strong agreement)[40-42]. Antibiotics should not be used in the management of AP, except in the presence of infected necrosis, or necrotizing pancreatitis. For necrotizing pancreatitis, antibiotics with the ability to penetrate the necrotic tissue are recommended, such as carbapenems, quinolones, and metronidazole, as antibiotic use in this setting has been documented to delay surgical interventions and decrease morbidity and mortality[43].

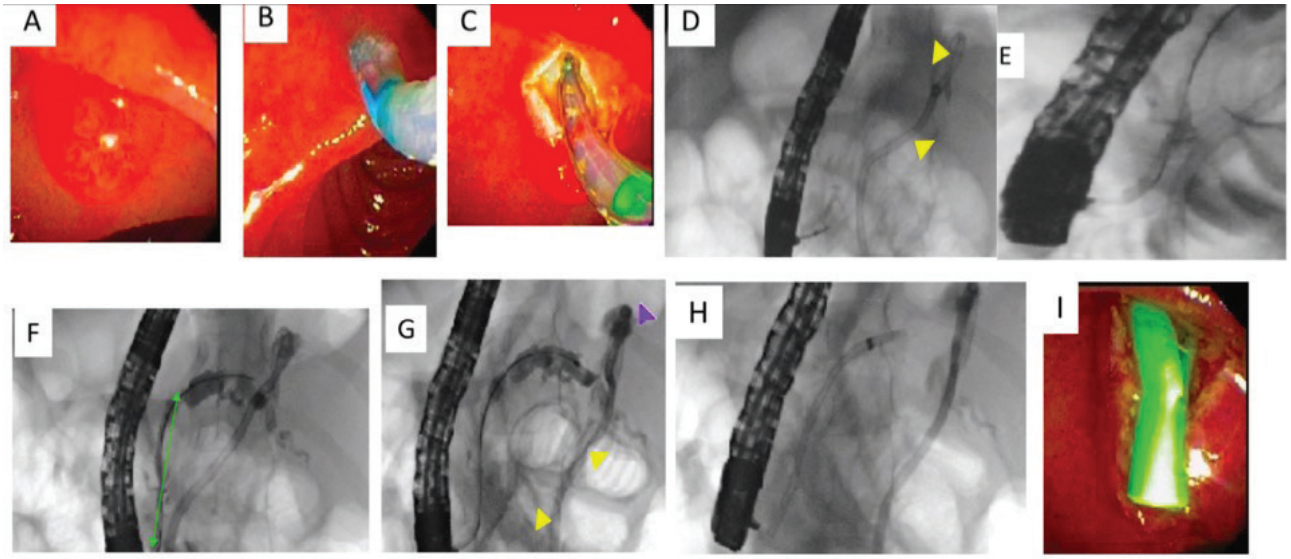
Complications from CP with ARP and infected peripancreatic fluid collections were also found in some patients[23] (Figure 1) in which PCD was undertaken as the primary option in the treatment, due to clinical sepsis. A fluid profile found active pancreatic enzyme leakage even though octreotide was used to decrease pancreatic secretions[44,45].

Exocrine pancreatic insufficiency (EPI) symptoms included steatorrhea, diarrhea, bloating, and weight loss[46]. Exocrine pancreatic function should be evaluated[15]. Diabetes secondary to pancreatic disease is commonly referred to as pancreatogenic diabetes or type 3c diabetes mellitus (DM). An oral glucose tolerance test is recommended to determine the impaired glucose tolerance in patients with CP[15,36]. The American Diabetes Association defines the

criteria for abnormal glucose for pre-diabetes mellitus (DM) patients as: fasting blood glucose [FBG] ≥100 mg/dL, Hemoglobin A1c (HbA1c) ≥5.7%, or 2-hour glucose testing of ≥140 mg/dL; the DM patient criteria: FBG ≥126 mg/dL, HbA1c ≥6.5%, or 2-hour or random glucose testing of ≥200 mg/dL)[47]. Abnormal glucose results were found in 38.0% (5/13) of the patients after diagnosis of CP[47].

Steatorrhea diagnosis requires one of the following: (1) malodor, fatty chronic diarrhea; (2) positive results in the quantification of fecal fat determination within three days and stool fat excretion over 14 g/day[48]. After the onset of CP, the steatorrhea in children and adults were reported as 15.8% (46/291) and 24.0% (447/1862), respectively[48]. Severe acute pancreatitis before the diagnosis of children was a significant risk of developing steatorrhea with a hazard ratio [HR] of and 95%. CI were14.0 and 1.4–134.9, respectively[48]. Deficiency of fat-soluble vitamins (A, D, E, and K), osteopathy, and malnutrition should be evaluated in the CP patients[46,49,50], using the Malnutrition Universal Screening Test (MUST), qualitative fecal fat assays, fat-soluble vitamin levels, albumin levels, and dual-energy x-ray absorptiometry (DEXA) scan T-scores[46].

Pancreaticopleural fistula (PPF) is a very rare complication of pancreatitis, which may occur secondary to AP or CP, pancreatic trauma, and leads to a fistula connecting to the pancreas and pleural cavity, or could be caused by direct extension of a pseudocyst, which occurs when a pancreatic duct ruptures or there is a pseudocyst formation. It should be considered when a child presents with recurrent massive pleural effusion. Endoscopic treatment is minimally invasive, and an effective method for the treatment of PPF in children[51,52].



A-D: Sphincterotomy
E-G: Pancreaticogram shows dilated pancreatic duct at tail 6.7 mm, pancreatic stricture (two-way arrow) at head and body 49.9 mm long. Leakage (purple arrow head) was seen when the contrast was injected at the tail to PCD (yellow triangle) area.
H-I: After sphincterotomy, pancreatic stent insertion 7 Fr 5 cm

Figure 2 Endoscopic retrograde cholangiopancreatography (ERCP)[23]

Management

In children with CP, the step-up strategic management should be applied[15], and include a restricted trial of endoscopic interventions, such as therapeutic endoscopy 85.0%[21-23] (Figure 2), endoscopy alone 84.9%[48], and any ERCP 72%[11]. After which, proceed with surgery adjusted to the anatomical deformities and gene mutation status, which is constructive in establishing long-term pain reduction and conserving pancreatic function[21].

Endoscopic intervention or therapeutic ERCP have traditionally been used for the management of CP complications, such as pancreatic ductal stones and narrowing pancreatic duct[15], and before more invasive surgical interventions are introduced[22,53]. The choice of intervention includes biliary sphincterotomy with or without pancreatic sphincterotomy to prevent AP episodes. On the other hand, post-ERCP pancreatitis is the most common complication and should be considered in all patients who have undergone ERCP[22,53].

One study reported that in the ERCP with intervention, 22/33 cases recovered with pain as a consequence of the intervention[11]. Other studies have reported that a lateral pancreaticojejunostomy resulted in recovery or resolution of abdominal pain symptoms in almost 60.0%[18]-73.0%[11] of CP patients.

Various studies have reported that surgical procedures alone were performed in 3.4%[48] and 39% of cases[11]: sphincteroplasty in 10%[21,22], pseudocyst drainage in 15%[21,22], lateral pancreaticojejunostomy in 14%[11], longitudinal pancreaticojejunostomy in 20%[21,22], partial pancreatectomy in 1-45%[11,21,22], and total pancreatectomy with islet autotransplantation in 10-28% of cases[11,21,22].

CONCLUSION

In children with abdominal pain, pancreatitis should be in the differential diagnosis. Anatomical obstruction, PBM, pancreatic diverticula, and genetic disorders should be considered as a cause of childhood pancreatitis. Genetic disorders such as a *SPINK1* mutation, should also be considered, especially in idiopathic pancreatitis.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest. Authorship: All authors (Piyawan Chiengkriwate, Kulpreeya Sirichamratsakul) attest that they meet the current ICMJE criteria for authorship.

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