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'Gastroenterology in Pediatrics: Current knowledge about some common disorders'

Editor

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Chronic pancreatitis in children: Current knowledge in diagnosis and treatment

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REVIEW ARTICLE

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Abstract: Chronic pancreatitis (CP) is a progressive inflammatory disorder of the pancreas characterized by irreversible morphological changes and fibrosis, leading to exocrine and endocrine pancreatic insufficiency. The prevalence of chronic pancreatitis in childhood is unknown. Most likely, idiopathic causes comprise a large percentage of children with CP. CP should be considered in children presenting with recurrent abdominal pain. Pain may be disabling, exocrine pancreatic insufficiency and diabetes may develop over time. Diagnostic tests include abdominal ultrasound, contrast-enhanced CT, MRCP, ERCP, EUS. Genetic etiologies should be investigated in children with CP of unknown cause. Medical treatment includes control of the pain, replacement therapy with pancreatic enzymes, antioxidants, insulin. Endoscopic interventions (sphincterotomy/stent placement) can be used to decompress the pancreatic duct. Surgical approaches (lateral pancreaticojejunostomy, total pancreatectomy and islet autotransplantation) are rarely used in pediatrics. Although significant advances have been made in our understanding of CP in childhood within the last decade, challenge remains to develop better diagnostic techniques, treatment modalities and improved outcomes.

Key words: pediatric, chronic pancreatitis, etiology, diagnosis, therapy
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Chronic pancreatitis (CP) is a progressive inflammatory disorder of the pancreas characterized by irreversible structural changes and permanent loss of exocrine and endocrine function [1,2]. The prevalence of chronic pancreatitis in childhood is unknown, but the number of patients diagnosed with CP seems to be increasing in adults [3]. This article will summarize the recent advances in the diagnosis and treatment of children with CP.

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Etiology

The true prevalence of CP in childhood is unknown. In general, the TIGAR-O (Toxic-metabolic, Idiopathic, Genetic, Autoimmune, Recurrent and severe acute pancreatitis, Obstructive) classification described in adults [4] also applies to pediatrics (Table 1) [5]. Alcohol is the main cause of CP in adults in Western countries [6]; idiopathic causes most likely comprise a large percentage of pediatric patients with CP. Genetic causes (cationic trypsinogen or PRSS1 mutations; mutations in cystic fibrosis transmembrane conductance regulator (CFTR) and pancreatic secretory trypsin inhibitor (PSTI), also known as serine protease inhibitor, Kazal type I (SPINK1)) form another large group [7,8].

Table 1. Etiologies of Chronic Pancreatitis in Children
Idiopathic (most common)
Genetic • PRSS1 mutations • CFTR mutations • SPINK1 mutations
Drugs (L-asparaginase, valproate, metronidazole, azathioprine, tetracycline, pentamidine, etc.)
Metabolic disease • Hyperlipidemia • Hypercalcemia • Glycogen storage disease • Organic acidemias
Autoimmune • Isolated • Syndromic
Anatomic • Pancreas divisum • Anomalous junction of the biliary and pancreatic ducts • Annular pancreas • Ampullary obstruction • Crohn disease

Pathophysiology

Chronic pancreatitis is characterized by progressive inflammation that produces irreversible morphological changes in the pancreas including fibrosis, acinar and islet cell loss. Pancreas is not easily accessible for biopsy, therefore it is difficult to detect the earliest changes and identify the events that contribute to the pathophysiology of CP. The discovery of cationic trypsinogen gene mutations in patients with hereditary pancreatitis (HP) underscored the importance of trypsinogen activation within the acinar cells as an early event in pancreatitis [9]. Premature trypsinogen activation to trypsin causes an activation cascade, with additional trypsinogen and other digestive proenzymes converted to active enzymes, leading to pancreatic digestion and inflammation [7].

The current hypothesis is that chronic pancreatitis begins with an episode of acute pancreatitis (AP), followed by an ongoing chronic or recurrent inflammation that leads to fibrotic replacement of acini and islet cells [1]. The sentinel acute pancreatitis event (SAPE) hypothesis was proposed in 1999 and still remains the prevailing concept [10]. In this model, a metabolic or oxidative stress initiates the first episode of AP, the sentinel event. Activated lymphocytes, macrophages, and stellate cells increase in number within the pancreas. They produce cytokines and deposit small amounts of collagen. Most patients recover uneventfully and pancreas returns to normal. In some, due to continued presence of stress, inflammatory cells and stellate cells remain active and release cytokines and deposit collagen, eventually producing the fibrotic changes characteristic of CP. Although the process may be started and perpetuated by environmental factors, other factors must be present for CP to develop in some individuals and not others. Most recent studies have focused on the role of genetic predisposition to chronic pancreatitis.

Diagnosis

Clinical presentation (Table 2)

Initially, patients may represent with episodes of recurrent AP. Pain in the upper abdomen is the dominant clinical feature. The pain can be mild to severe, intermittent or persistent. Sometimes, pain is relieved by sitting upright or leaning forward. Older children describe the pain as deep and penetrating, radiating to the back and worse after meals. Younger

Table 2. Pertinent history and physical exam findings in chronic pancreatitis.

History

- Abdominal pain
- Nausea, vomiting
- Anorexia
- Frequent, bulky, foul-smelling, sometimes greasy stools
- Weight loss
- Bloating
- Flatulence
- Bleeding tendencies (if vitamin K is deficient)
- Bone fractures (if vitamin D is deficient)
- Night blindness (if vit A is deficient)
- Diabetes

Physical examination

- Abdominal tenderness
- Loss of subcutaneous fat
- Decreased muscle mass
- Jaundice
- Gastrointestinal bleeding (secondary to splenic vein thrombosis, rare)
- Acrodermatitis (if vit A is deficient)
- Neuropathy (if vit E is deficient)

children cannot verbalize the pain well, so clinicians must have a high index of suspicion in this age group. Early in the course, the pain often arises from the acute inflammation of pancreatitis. Later, pain may arise from pancreatic duct hypertension, increased pancreatic tissue pressure, tissue acidosis, or perineural inflammation. Pain may be accompanied with nausea and/or vomiting, anorexia.

Children with HP usually present with recurrent episodes of abdominal pain and symptom-free intervals [7]. The acute attacks may be triggered by fatty meal, stress, or environmental factors such as infection, smoking, and alcohol use. Median age of presentation for HP is 10 years of age and in 50% of patients CP develops 10 years after the first bout of AP [11]. Some patients may present with CP without a clear history of AP [12].

Patients with CP can present with symptoms of maldigestion/malabsorption, such as weight loss and steatorrhea. Fat-soluble vitamin deficiencies (A, D, E, K) can be seen. Patients with extrahepatic biliary obstruction from fibrosis in the head of the pancreas or from the pseudocyst can have jaundice. Gastrointestinal bleeding secondary to venous thrombosis (mainly splenic vein) is rarely seen. Subcutaneous or intramedullary fat necrosis can be the first sign of CP in children.

Diabetes mellitus usually develops late in the course of CP and rarely, if ever, patients can present initially with symptoms of diabetes mellitus. Because both insulin and glucagon producing cells are destroyed, the control of blood sugar in diabetic patient with CP is difficult, diabetes is “brittle”.

There is a lifetime risk for pancreatic adenocarcinoma in patients with CP (4%) [13], the risk is much higher in patients with HP (~40%) [14].

Differential diagnoses

The differential diagnosis of CP includes causes of recurrent and chronic abdominal pain in childhood: peptic ulcer disease, gastritis, gallbladder disease, intestinal obstruction, Crohn disease, functional

Table 3. Diagnostic tests in chronic pancreatitis
• **Laboratory tests** (serum amylase, lipase, Ca, lipid panel, total and direct bilirubin, alkaline phosphatase, GGT, AST, ALT, fasting serum glucose)
• **Fecal elastase**
• **72 h fecal fat**
• **Imaging studies** (US, CT, MRCP, ERCP)
• **Genetic testing** (PRSS1, CFTR, SPINK1)

abdominal pain, lactose intolerance are to name a few. If a patient presents with malabsorption, other causes of pancreatic insufficiency (PI) should be considered: developmental defects of the pancreas, severe enteropathies, cholestatic liver disease, celiac disease, cystic fibrosis (CF), rare isolated pancreatic enzyme deficiencies.

Diagnostic testing (Table 3)

The diagnosis of CP requires evidence of reversible structural change or a combination of structural and functional change. Structural changes include inflammatory cell infiltrates, fibrosis, acinar and islet cellular loss, pancreatic duct irregularities (strictures and dilations), intraductal calculi. The presence of PI alone is not sufficient for the diagnosis of CP, because PI can also be caused by other disorders, such as Shwachman-Diamond syndrome, CF. Figure 1 shows the algorithm for diagnosing CP in children [2].

Laboratory Testing

Laboratory tests that can be useful in determining the etiology of CP that are listed in Table 3. There are no specific laboratory tests for CP. In most cases, serum amylase and lipase are normal or only mildly elevated [15]. Liver enzymes, GGT, alkaline phosphatase and bilirubins are useful to rule out a biliary obstruction.

Radiology

Diagnostic imaging plays an important role in the initial diagnosis of CP and further planning for endoscopic and surgical interventions. Findings consistent with CP include (i) stricture/dilation/irregular contour of the pancreatic duct and/or its radicles; (ii) ductal stones; (iii) irregularities in gland margins; and (iv) calcifications. Below is the summary of the imaging modalities most commonly used in pediatric pancreatitis.

Ultrasonography (US). US is usually the first imaging modality when pancreatitis is suspected in children. Smaller size of patients, lack of fat and prominence of the left hepatic lobe make US of the pancreas more feasible in children than in adults [16]. US is 50–80% sensitive in diagnosing CP in adults; the diagnostic accuracy of US in pediatric CP has not been studied [17]. US is most helpful in assessing the pancreatic duct diameter in children with CP (normals are: <1.5 mm in children 1-6 years; <1.9 mm at ages 7–12 years; <2.2 mm at ages 13–18 years). Calcifications of the pancreas and intraductal stones can also be depicted with US in CP [16].

Endoscopic US (EUS)

EUS may detect early changes in CP and it is becoming the preferred imaging study for the diagnosis of CP in adults. EUS is also gaining popularity in the diagnostic imaging of pancreaticobiliary disorders in children. The high diagnostic accuracy and the low complication rate (1%) compared to ERCP are the driving forces for its use 16. In one study, EUS was technically feasible in

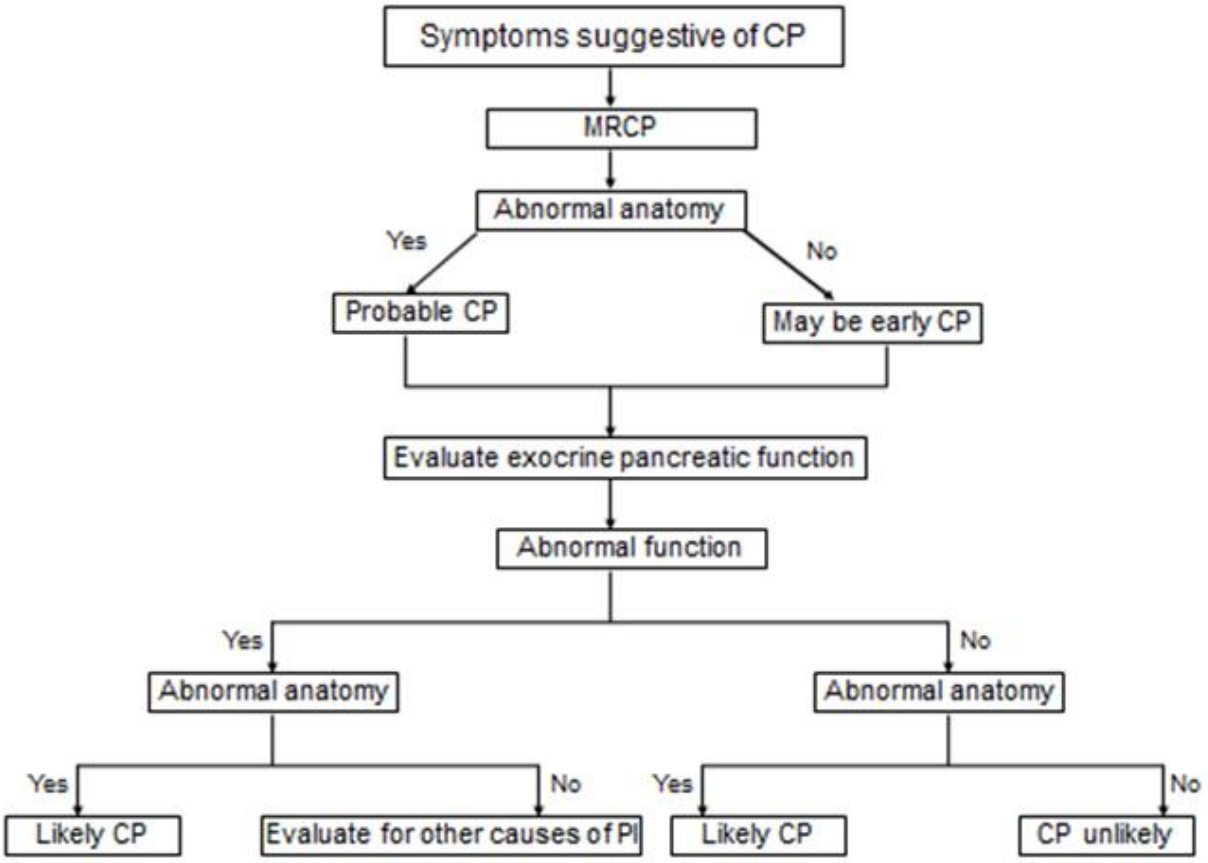

Figure 1. Algorithm for approach to children with chronic pancreatitis [2].

children as young as 5 years of age [16]. EUS is highly operator dependent and there is no consensus regarding the endosonographic definition of CP in adults. The role of EUS in the diagnosis of pediatric CP has not been thoroughly investigated.

Magnetic resonance cholangio pancreato-graphy (MRCP). MRCP can detect the dilatations in the pancreatic ducts, as well as irregularities in the duct diameter. Due to its non-invasive nature and lack of radiation, MRCP has become a diagnostic test of choice in children with CP [19,20]. Unlike ERCP that images ducts under pressure, MRCP visualizes the ducts in their normal physiologic state [16]. With MRCP, it is possible to visualize ducts as small as 1 mm [21]. However, MRCP in children is limited by small caliber non-dilated ducts, poor signal and patient motion. Secretin induces fluid secretion in the pancreatic duct and when administered with MRCP, it increases the diameter of pancreatic duct up to 3 mm in 3–5 min with progressive decline to baseline in 10 min. Secretin is probably more important in children than in adults as it increases the detectability of the normally smaller pancreatic ducts. In a pediatric study, secretin increased the number of main pancreatic duct segments visualized on MRCP from 53% to 93%; the visualization of the duct of Santorini increased from 7% -53% and the detection of side branches increased from 20% - 47% [22].

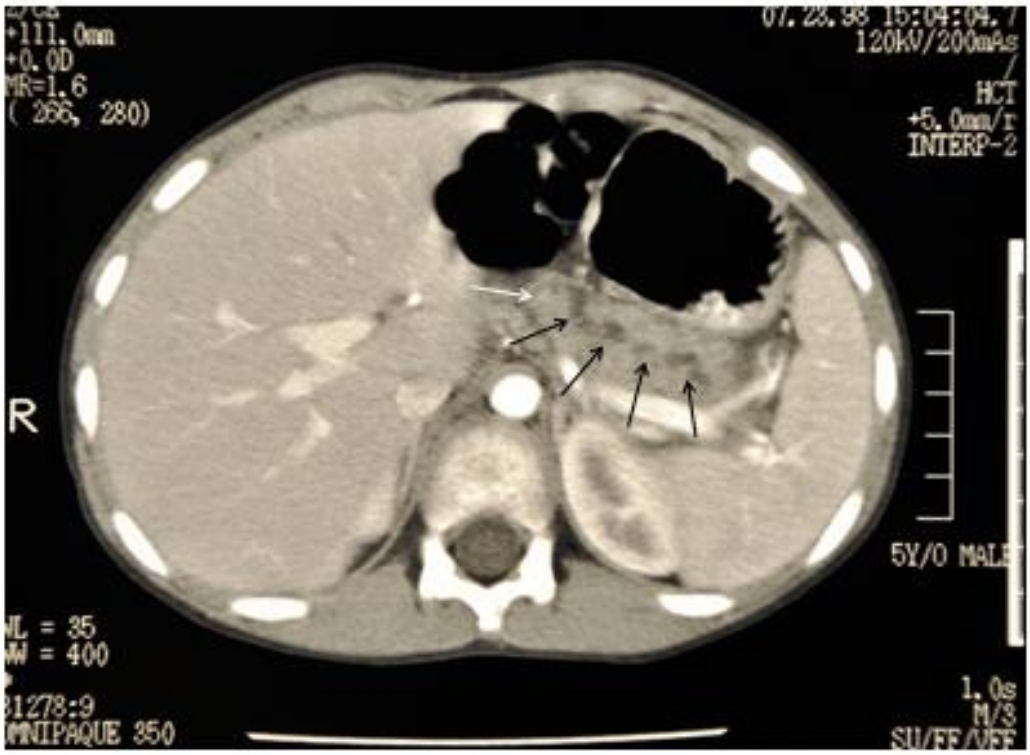

Figure 2. Computerized Tomography image from a child with chronic pancreatitis. The pancreatic duct is dilated and irregular (black arrows). A small calcification is noted on the pancreatic head (white arrow). There are multiple dense foci in the pancreatic parenchyma adjacent to the dilated duct, consistent with small stones. Photo is the courtesy of Dr. Yutaka Sato.

Secretin may also increase the number of false positive reports [23]. More studies with secretin-enhanced MRCP are needed to better understand its diagnostic accuracy in pediatric CP.

Endoscopic Retrograde Cholangio pancreateography (ERCP). With MRCP being widely available, ERCP is now mainly reserved for therapeutic interventions in pancreatico-biliary disorders. In CP, ERCP findings include main pancreatic duct dilatation, ductal stones, and changes in the main duct branches and small ducts (Figure 3). ERCP is generally safe with a complication rate that ranges from 0 to 11% (mainly pancreatitis); complications are more common with therapeutic intervention (17%) and particularly when manometry (11–22%) of biliary and pancreatic sphincters is performed [24]. ERCP can be done successfully in over 90% of children [25]. In about one-third of cases, the ERCP will be normal. Sphincterotomy with or without stone extraction are carried out in 45% of ERCPs in children. In a small pediatric study, children were evaluated with ERCP for recurrent acute and chronic pancreatitis; in 52% of patients ERCP altered the therapy [26]. ERCP is reserved for AP only if biliary pancreatitis is suspected and in selected patients with recurrent AP or pancreatic pseudocyst.

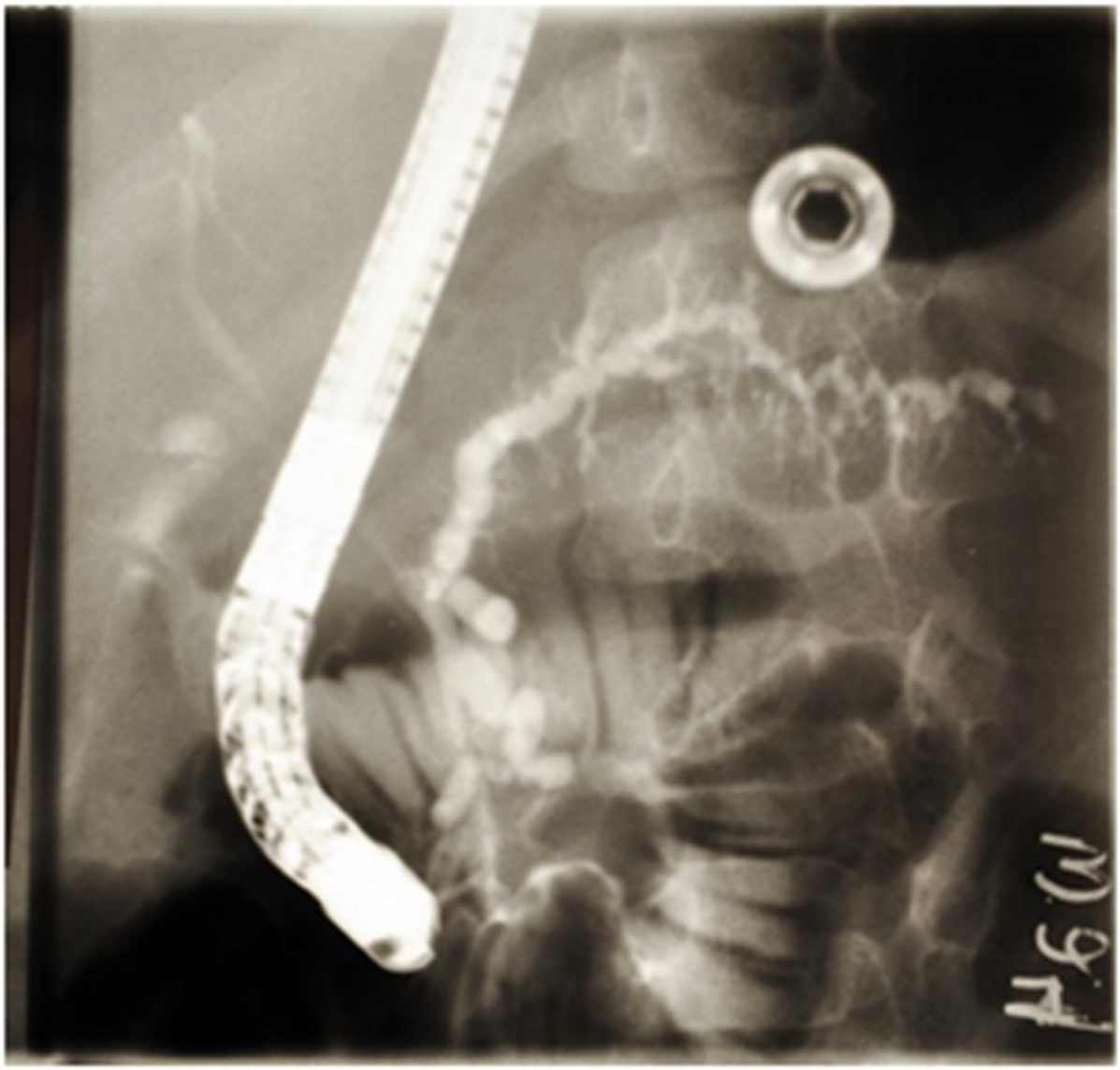

Figure 3. ERCP changes in chronic pancreatitis. The image shows a tortuous, irregular and dilated pancreatic duct. Contrast reached the small intestine in this child with hereditary pancreatitis who had Puestow. Photo is the courtesy of Dr. Yutaka Sato.

Computerized tomography (CT) with contrast. CT can detect advanced changes in CP, such as calcification, gland atrophy, fat replacement, and ductal dilatation (Figure 2). The advantage of CT is that it can evaluate pancreas for other pathology and detect other causes of chronic abdominal pain. CT has poor sensitivity to identify ductal abnormalities and subtle parenchymal changes; high radiation dose is another drawback [17,27].

Genetic testing

Genetic testing is indicated as a diagnostic test in children with CP to determine the underlying cause. Predictive testing is not

recommended in individuals without pancreatic disease and a positive family history of pancreatitis. The presence of PRSS1 mutation provides an adequate etiology for pancreatitis, but the presence of CFTR or SPINK1 mutations should not preclude a careful search for additional etiologies.

PRSS1

The mutations in the PRSS1 gene are associated with HP [7]. PRSS1 gene mutations increase the likelihood of trypsinogen activation within the acinar cell, thus predisposing patients to acute and chronic pancreatic inflammation. 80% to 90% of individuals with HP, an autosomal dominant disease with incomplete penetrance, carry R122H mutation [9,11]. This mutation is caused by the substitution of the amino acid histidine (H) for arginine (R) at position 122 (R122H) of the cationic trypsinogen gene.

N29I

This mutation is caused by substitution of isoleucine (I) for asparagine (N) at position 29. R122H and N29I are the most common mutations seen in patients with HP [28]. Genetic testing for PRSS1 mutations is recommended in patients with recurrent attacks of AP and CP of unknown etiology or a positive family history of pancreatitis in first-degree or second-degree relatives.

CFTR

Pancreatitis occurs in 2-4 % of all patients with CF and 15-20% of pancreatic sufficient patients with mild CFTR mutations during adolescence or later in life [29,30]. Pancreatitis is thought to result from thick secretions causing pancreatic ductular obstruction, ineffective clearing of secretions from the pancreatic duct, and autodigestion of the pancreas by activated proteolytic enzymes [7].

Patients with idiopathic chronic pancreatitis carry a higher frequency of CFTR mutations than the general population and a subset of these patients have CF [31,32]. CFTR mutations may also contribute to the development of chronic pancreatitis in patients who have additional risk factors for chronic pancreatitis [33]. Most commercially available genetic screening tests only identify the most severe CFTR mutations; therefore "milder" mutations may be missed in patients with CP. A complete sequencing of the CFTR gene is recommended since many patients have rare mutations in one or two alleles that are not included in the standard panels designed to diagnose patients with CF.

SPINK1. Synthesis of pancreatic secretory trypsin inhibitor (PSTI), which is coded by the SPINK1 gene protects against premature activation of trypsin within the pancreas before it is secreted into the duodenum [10]. Mutations in the SPINK1 gene (mainly N34S mutation, substitution of asparagine by serine at codon 34 in exon 3) increase the susceptibility to AP and predisposes to CP [34,35]. Interestingly, the risk of an asymptomatic SPINK1 carrier developing pancreatitis is thought to be only 1%. Therefore, SPINK1 mutations alone are not sufficient to cause pancreatitis, but may act as genetic modifiers in initiating the development of pancreatitis [35].

Exocrine pancreatic function testing

These tests can detect CP in its most advanced stage, when exocrine pancreatic insufficiency (PI) has developed. They are not specific for CP as they can be abnormal in patients with other causes of exocrine PI (CF, Shwachman-Diamond syndrome, etc).

Pancreatic stimulation test. This test involves the collection of pancreatic fluid secreted into

the duodenum and measurement of enzymes, fluid volume and electrolytes before and after stimulation with the pancreatic secretagogues (cholecystokinin and secretin) [36]. Although it is considered 'gold standard' to quantify the exocrine pancreatic function, stimulation test is not done because of its invasive nature. Only a few centers have the expertise to perform this test reliably. The collection of the duodenal fluid via the endoscope has been proposed as an alternative, but this approach may greatly underestimate the pancreatic secretary capacity and classify patients as pancreatic insufficient erroneously [36].

72-hour fecal fat collection. When pancreas loses greater than 95 percent of its enzyme secretory output, steatorrhea develops [37]. Steatorrhea can be measured by a 72-hour stool collection and calculation of coefficient of fat absorption [CFA: (grams of fat ingested-grams of fat excreted)/ (grams of fat ingested) x100]. In children younger than 6 months of age, a fecal fat greater than 15% of fat intake is considered abnormal; this value is 7% for children over 6 months of age. Main problems with this test are the lack of precision and reproducibility. It is not well-accepted by patients/parents; sample and data collection are not always accurate.

Fecal elastase-1 (FE1). Because it is easy to use and relatively inexpensive, this ELISA-based method is now the most preferred test to diagnose exocrine PI. A value of less than 100 μg/g is considered diagnostic of PI. Intermediate values of fecal elastase (100 to 200 μg/g) may be due to loss of pancreatic function, but not be severe enough to cause clinical PI. The sensitivity of FE1 to diagnose moderate and severe PI is close to 100%. In patients with mild loss of pancreatic function, the test sensitivity is ~ 25% with a specificity of 96% [38]. Therefore, the value of FE1 to determine patients with mild PI or borderline normal pancreatic function is limited. FE1 may be falsely low when the stool is diluted as a result of infectious diarrhea, severe enteropathies, short gut, or if it is collected from an ileostomy.

Endocrine pancreas function testing. Children with CP and significant exocrine pancreatic damage may develop diabetes as well, although this is rare in pediatric age group. 2006 WHO criteria for diabetes mellitus are: fasting glucose ≥ 7.0 mmol/L (126 mg/dL) or plasma glucose ≥ 11.1 mmol/L (200mg/dL) 2 h after 1.75 g/kg (max 75 g) of oral glucose load.

Treatment

Medical Treatment

If patients represent with recurrent episodes of AP, the management of acute attacks is the same as for AP. Most mild to moderate cases will respond to conservative management, withholding food and drink for a few days and offering pain control. In patients with advanced disease, the treatment is directed at the complications, including chronic pain, exocrine PI and diabetes mellitus.

Pain control

Analgesic medications are the mainstay of pain management. There are no prospective therapeutic trials of pain management in children, thus the practice is guided by common practice and expert opinion. Nonsteroidal anti-inflammatory drugs and acetaminophen are the first-line agents for pain control. Long-acting and short-acting narcotics can be used in a step-wise approach. The addictive profile of narcotics and their gastrointestinal side effects should be considered when initiating the therapy.

Pancreatic enzyme supplementation

Pancreatic enzymes are often prescribed theoretically to reduce the feedback loop of pancreatic exocrine activation. Current evidence on the effect of pancreatic enzymes on pain control are conflicting because of

methodological issues and types of preparation (enteric-coated versus nonenteric-coated tablets) [17]. Most physicians will do a therapeutic trial of pancreatic enzyme supplementation for 1-2 months. The dose is 1,000 lipase units/kg per meal and 500 lipase units/kg per snacks in children under 4 years of age; 500 lipase units/kg per meal and 250 lipase units/kg per snacks for children over 4 years of age.

Antioxidant therapy

Antioxidants (Table 4) have been evaluated for the treatment of chronic pain in CP. Results are not convincing and all studies have methodological issues. A recent randomized and placebo-controlled study showed that the antioxidant therapy was superior to placebo in treating pain in adults with CP [39]. A therapeutic trial is a reasonable approach in empirically treating pain as it is with pancreatic enzymes. Further studies are needed to evaluate the utility of antioxidants in pediatric CP.

Table 4. Antioxidant therapy in Chronic Pancreatitis.

Drug	Dose (based on adult data)
Organic selenium	600 µg
Ascorbic acid	540 mg
β-Carotene	9000 IU
α-Tocopherol	270 IU
Methionine	2 g

Endoscopic interventions

Therapeutic indications for ERCP include treatment of symptomatic stones and strictures. Ductal decompression by sphincterotomy and/or stent placement can be done in patients with CP and a dilated pancreatic duct. Endoscopic therapy may be useful if there is an identifiable stricture with evidence of pancreatic duct obstruction [40, 41]. There are no clinical trials in pediatrics that support the efficacy of endoscopic intervention.

Surgery

Surgical techniques have been employed for the management of patients with CP who do not respond to medical therapy. In general, surgical therapy is guided by the patient's individual anatomy. Patients with a dilated pancreatic duct are generally treated with operations that aim at drainage and decompression of the ducts. Pediatric data are sparse and the decision to operate is based on the experience in adult patients with CP. Even in large referral centers, less than 1 pediatric patient undergoes surgery for CP every year [42-44]. In general, decompressive operations are favored over resections in the pediatric age groups [45]. In the majority of cases, a Puestow-type procedure (longitudinal pancreatojejunostomy that involves opening the pancreatic duct throughout the body and tail of the gland) has been used. Ductal strictures can be excised and pancreatic stones can be removed during this operation. Frey and Whipple procedures are usually associated with high mortality and morbidity and rarely needed [17].

Patients who do not have a dilated main duct can be treated with pancreatic resection including total pancreatectomy with islet cell autotransplantation (TP+IAT). Interestingly, ~ 40% of children continue to have a significant amount of pain after the total removal of the inflamed pancreas [46]. A recent study suggest that TP+IAP may be more successful in preserving pancreatic beta cell mass if done early in the course of CP in children, and

prior drainage procedures are avoided to maximize the number of islets available, especially in HP [47].

Conclusion

Although we have made significant progress within the last decade in our understanding of pediatric pancreatic inflammatory disorders, we continue to have more questions than answers. Currently, our knowledge of pediatric CP is limited to the experience in adult data, local experience and expert opinions. With better understanding of the epidemiology, etiologies, natural history and outcome of CP in childhood, we can begin to develop novel therapies that can prevent the progression of disease process in CP.

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