Hereditary pancreatitis of 3 Chinese children
Case report and literature review

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Abstract

Background: Hereditary pancreatitis (HP) is quite rare and is distinguished by incomplete penetrance presentation as early-onset relapsing pancreatitis, usually beginning in childhood. HP is now known to be commonly relevant to mutations in the *PRSS1* (gene-encoding cationic trypsinogen), *SPINK1* (serine protease inhibitor, Kazal type 1), *CFTR* (cystic fibrosis), carboxypeptidase A1 (CPA1), and chymotrypsin C (*CTRC*) genes as reported in some Caucasian studies. HP has a variable spectrum of severity and may develop complications.

Methods & Results: We describe the clinical course of 3 preschool children, hospitalized with postprandial abdominal pain, whose laboratory tests showed high serum amylase. Similar episodes of abdominal pain led to readmission, and the patients recovered quickly after using symptomatic therapy. The condition of the first boy, who developed a pancreatic tail pseudocyst and splenic infarction, was especially complicated. The boy underwent 2 endoscopic retrograde cholangiopancreatographies and stenting, along with a surgical procedure that completely relieved his symptoms for 3 months. The 3 patients and their parents were given genetic testing. All of the patients carried 1 or more gene mutations inherited from their mothers, fathers, or both parents; however, none of the parents were affected.

Conclusion: For children with repeated pancreatitis, clinicians should consider HP in the differential diagnosis. It is reliable to perform gene sequencing on suspicious patients and their parents. Multidisciplinary and comprehensive treatment should be recommended to manage HP and its complications. Cholangiopancreatography and stenting is a relatively minimally invasive approach when compared with surgery and can be tried as an early intervention. Surgical procedures should be reserved for patients with complications.

Abbreviations: ERCP = endoscopic retrograde cholangiopancreatography, HP = hereditary pancreatitis.

Keywords: children, gene mutation, hereditary pancreatitis, treatment

1. Introduction

Hereditary pancreatitis (HP) is a rare, autosomal-dominant gene disorder that usually presents with recurrent episodes of acute pancreatitis during childhood. Since its clinical presentation is similar to other pancreatitis cases, the presence of HP in family history and the detection of a defective gene are both very important in differentiation. Causative mutations associated with HP, including mutations in the *PRSS1* (gene-encoding cationic trypsinogen), *SPINK1* (serine protease inhibitor, Kazal type 1), *CFTR* (cystic fibrosis), and chymotrypsin C (*CTRC*) genes,[1–3] have been discovered in recent decades. Carboxypeptidase A1 (CPA1) was identified as a novel pancreatitis susceptibility gene in 2013.[4] HP mainly starts in childhood; however, some individuals may not exhibit symptoms until adulthood,[5] and not all mutation carriers will have episodes of pancreatitis. It is reported that the penetrance is approximately 80% to 93%.[6,7] Complications of acute pancreatitis contain pseudocyst or abscess formation and extrapancreatic manifestations, such as pulmonary, renal, hepatic, endocrine, and coagulation abnormalities.

This study reports on 3 boys with early-onset HP. One of the boys had complications with pseudocyst formation, splenic vein thrombosis, and splenic infarction.

2. Case reports

2.1. Case A

A 5-year-old boy presented with a 2-week history of recurrent abdominal pain, which became intense postprandially, and was sent to a local hospital in September 2013. There was no history of trauma, and his physical examination was normal. His laboratory evaluation elevated at the followings: serum C
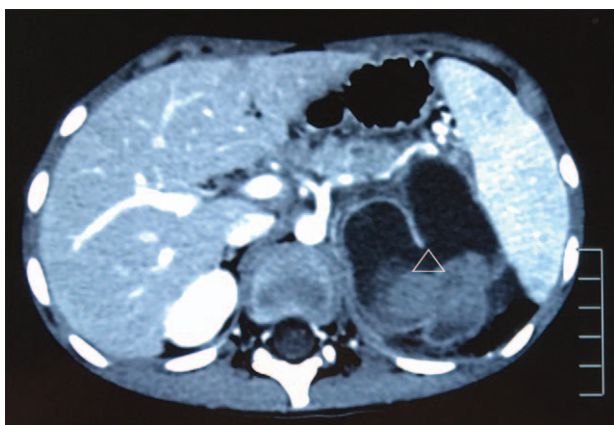
Figure 1. CECT reveals a large retroperitoneal cystic lesion of 61 × 90 mm in size (triangle). CECT = contrast-enhanced computed tomography.

reactive protein (CRP) 47 mg/L, white blood count (WBC) 12.18 × 10^9/L, serum amylase 143 U/L, urine amylase 1053 U/L, serum lipase 1025 U/L, serum alkaline phosphatase (ALP) 170 U/L, fasting blood-glucose 6.3 mmol/L, D-dimer 1.04 mg/L, fibrinogen degration products 10.80 mg/L; and serum calcium 1.48 mmol/L, serum creatinin (Scr) 30.8 µmol/L, serum γ glutamyltranspeptidase 10 U/L decreased; alanine aminotransferase and aspartate aminotransferase were normal. A diagnosis of pancreatitis and pancreatic pseudocysts were considered by using a contrast-enhanced computed tomography scan (Fig. 1). The patient was treated conservatively. Shortly after treatment, laboratory tests were normal and the abdominal pain had subsided, so the child was discharged with instructions to follow a hypolipidic diet. During the following 2 years, the boy's abdominal pain reoccurred; however, no dilatation of the main pancreatic duct and pancreatolith were found by magnetic resonance cholangio-pancreatography (MRCP). A CT scan showed splenomegaly and irregular hypodense regions consistent with infarction (Fig. 2). In addition, splenic vein thrombosis was visualized. The aggravation of the condition made the boy undergo 2 ERCPs and stenting in our hospital in July 2015; however, mild abdominal pain persisted after the procedure. Neither the father (33 years old) nor the mother (32 years old) had any history of pancreatitis. Given

Figure 2. CT scan shows the increscent spleen with irregular hypodense regions (white arrow). CT = computed tomography.

the unexplained episode of pancreatitis in the child, HP was suspected. Genetic testing identified a c.194+2T>C (IVS3) heterozygous mutation on the SPINK1 gene, a pancreatitis-related gene (Fig. 3A). The same mutation was absent in the patient's mother but present in his clinically healthy father. The patient was suffering and underwent a pancreatic pseudocyst excision on December 2, 2015.

2.2. Case B

In December 2014, a 4-year-old boy presented with the exact recurrent episodes of abdominal pain as the patient in Case A. The pain was nonradiating and dull. The patient's clinical examination was normal. His abdomen was mildly tender without any palpable lump. His laboratory tests showed that serum amylase, urine amylase, serum lipase, and ALP increased significantly; CRP, WBC, fasting blood-glucose, serum calcium, Scr, and blood coagulation function were all normal. The contrast-enhanced computed tomography scan showed acute pancreatitis. The clinical history revealed 6 similar episodes during the previous year, all requiring the boy to be hospitalized for 10 to 14 days for conservative treatment. The MRCP was normal. There was no history of injury. The father (35 years old) and the mother (34 years old) never had an episode of pancreatitis; therefore, he was transferred to our hospital for further diagnosis in December 2015. An ERCP was performed, and no abnormalities were found. Due to the presence of recurrent pancreatitis at a young age and the absence of anatomical abnormalities of the pancreaticobiliary duct system, HP was highly suspected, and genetic testing was performed after obtaining informed consent. In both the patient and his mother, testing identified a homozygous mutation in the CPA1 gene (Fig. 3B) and a heterozygous mutation on the SPINK1 (c.194+2: T>C) gene. In addition, the patient and his father had a heterozygous mutation in exons 4 and 5 of the PRSS1 gene, a pancreatitis-related gene (Fig. 3C). In other words, this patient had a homozygous mutation (CPA1) and heterozygous mutations for 2 genes (PRSS1 and SPINK1) associated with pancreatitis.

2.3. Case C

A 4-year-old boy was admitted to the hospital for his third episode of mild abdominal pain postprandially in January 2016. The previous 2 episodes lasted for 20 minutes and resolved at home without medical intervention. The patient experienced abdominal pain when eating and without nausea or emesis. The pain was characteristically dull and nonradiating in the upper belly. There was no trauma history. The abdomen was flat and soft with no palpable masses. No tenderness, rebound pain, or muscle guarding was evident. No skin rashes were apparent. Laboratory studies were as follows: serum CRP 23 mg/L, WBC 15.47 × 10^9/L, serum amylase 373 U/L, urine amylase 738 U/L, serum lipase 384 U/L, serum ALP 196 U/L, and γ glutamyl-transpeptidase 11 U/L with normal glycemia, creatinine, calcium, magnesium, and coagulation markers. No dilatation of the main pancreatic duct and calcification were found by MRCP. The child was diagnosed with either acute pancreatitis or an acute exacerbation of chronic pancreatitis. He was managed conservatively with bowel rest, parenteral nutrition, antibiotics, and subcutaneous Sandostatin. After 1 week of hospitalization, the laboratory tests were normal. Without any abdominal pain, the child was discharged on a hypolipidic diet. The results of genetic
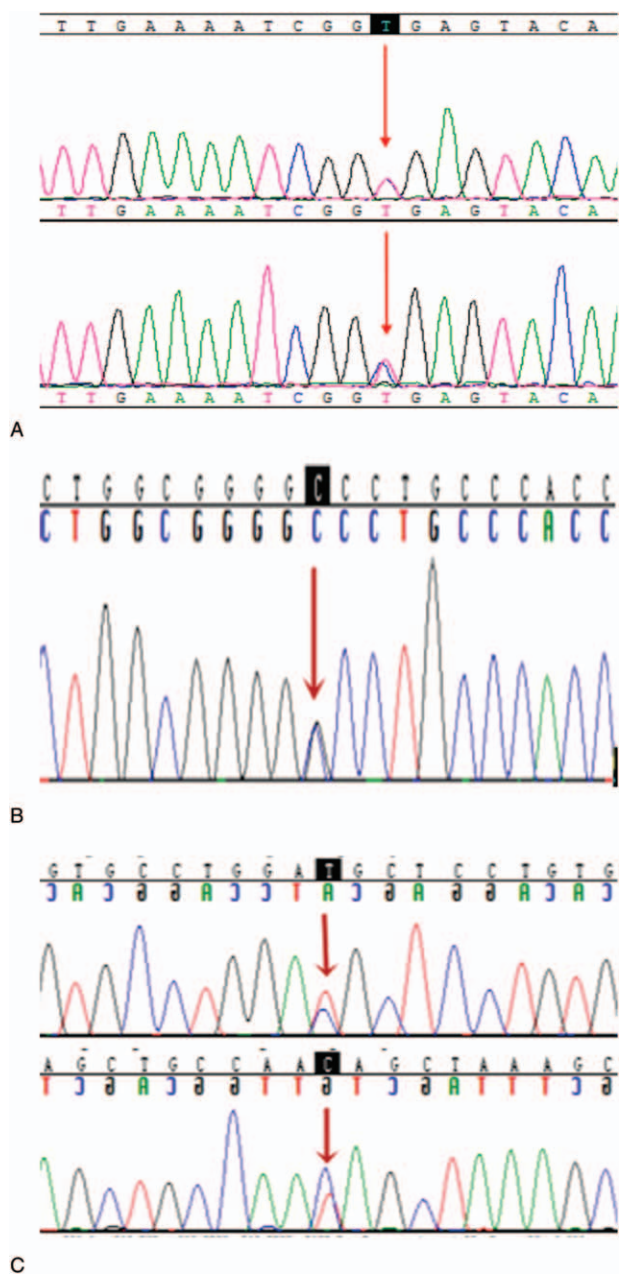
Figure 3. (A) Sequence chromatogram of the SPINK1 mutation c.194+2T>C. (B) DNA sequence electropherogram of a homozygous mutation in the CPA1 gene. (C) DNA sequence electropherogram of exons 4 and 5 of the *PRSS1* gene. *CPA1* = carboxypeptidase A1, *PRSS1* = gene-encoding cationic trypsinogen, *SPINK1* = serine protease inhibitor, Kazal type 1.

testing were as follows: the patient carried a heterozygous mutation in exons 4 and 5 of the *PRSS1* gene. Both of the parents carried heterozygous mutations for 3 genes (*CPA1*, *CFTR*, and *PRSS1*) but never had any onset of pancreatitis.

The patient in Case A had an uneventful postoperative course with his symptoms resolving; he was discharged on the 11th postoperative day. The boy remained completely asymptomatic for 3 months after the operation. In Case B, the patient reported no new episodes of pancreatitis at the 3-month follow-up. In Case C, the patient stayed healthy after discharge. These 3 patients remained free of recurrence and pancreatic pain at a mean 3-month follow-up.

3. Discussion

The diagnosis of HP should meet the requirements of 2 first-degree relatives or at least 3 second-degree relatives in 2 or more generations with chronic pancreatitis for which there is no other etiology.[5] The presence of a detected mutation in the *PRSS1* (with or without clinical or radiological manifestations) or *SPINK1* genes meets the genetic criterion and can be a cause for a diagnosis of HP, as reported in the literature.[8,9] In the current report, none of our patients had a familial history of HP. The diagnosis of HP is defined by the presence of detected gene mutations on the *PRSS1* or *SPINK1* or *PRSS1* with *SPINK1* and *CPA1* genes, respectively. The most frequent mutation gene is the *PRSS1* gene, and it has been identified to have more than 30 mutations. The *PRSS1* gene usually encodes cationic trypsinogen, which can prevent intrapancreatic autolysis of prematurely activated trypsin.[10] R122H, N29I, and A16 V are the most common *PRSS1* gene mutations. The former 2 mutations have been associated with increased autoactivation of cationic trypsinogen or reduced deactivation,[11] and the A16 V mutation may be linked to the multigenic inheritance of a predisposition to pancreatitis.[12] Recent research indicates that the A16 V mutation can promote trypsinogen activation by enhancing the function of chymotrypsin C. The SPINK1 gene encodes for the pancreatic secretory trypsin inhibitor, which protects the pancreas against premature intracellular of trypsinogen.[13] Some SPINK1 mutations will lower trypsin inhibitory function and facilitate the development of pancreatitis. These mutations may directly or indirectly relate to trypsin activation. It has been reported that the *SPINK1* and *CFTR* genes act more like modifier genes than pathogenic genes.[14] In addition, the underlying mechanism of the *CPA1* gene depends on the roles of endoplasmic reticulum stress in pancreatic acinar cells, resulting from the misfolding of mutated pancreatic enzymes rather than elevated trypsin activity.[4] So far, *PRSS1*, *SPINK1*, and *CFTR* genes are common mutations; therefore, patients should be routinely screened for these mutations and offered genetic counseling if necessary.[15]

In our series, no new mutation was detected: SPINK1 alone, PRSS1 alone, SPINK1 combined with CPA1, and PRSS1 mutations transmitted to these children either paternally or matrilineally, respectively, or parentally, and the boys all had repeated pancreatitis episodes, but their parents did not. The parents with pancreatitis-associated genetic mutations are all in their 30s but have never had any pancreatic symptoms or biochemical or ultrasound pancreatic alterations. It remains unclear why these 3 sets of heterozygous parents are still healthy. In some cases, the mode of inheritance of the *SPINK1* gene mutation follows a recessive inheritance pattern, which is associated with chronic pancreatitis.[16] This could well explain that the homozygous mutation of the *SPINK1* gene may trigger pancreatitis; however, that did not occur in the heterozygous case in our series. Perhaps, some functional unidentified modifier genes may be involved in this process.[6] The penetrance of mutant genes should not be overlooked. Dytz et al[17] suggested that the incomplete penetrance of the *PRSS1* gene mutation is the presence of mutations that protect against the development of proteolytic pancreatic injury. Some relevant environmental factors, such as viral infection and dietary habits, should also be emphasized because a low-fat diet seemed to be effective in preventing new episodes of pain in one of our patients. Based on genetic background, viral infection may induce acute pancreatitis of mutation carriers.[18] The function of new mutations, intricate

interactions between exons, and environmental factors are unknown yet.[19] We wonder if more HP-related genetic mutations in individuals will have any correlation with the frequency and severity of pancreatitis attacks. In Case A, the patient seemed to be the sickest one in the series, with only the heterozygous mutation of the *SPINK1* gene. In contrast, the patient in Case B, with more HP-related mutant genes (*CPA1* with *PRSS1* and *SPINK1*), seemed like the mildest case. In our opinion, the penetrance and nonpenetrance of HP-related mutant genes may, to some extent, contribute to the onset of disease. When it comes to the complex onset of HP, both genetic factors and environmental factors should be considered. In addition, the relationship between frequency, severity of pancreatitis, and gene mutation is highly variable. Possibly the disease is more relevant to key sites rather than the number of mutations.

Guidelines for treating chronic pancreatitis in childhood are still lacking.[20] Therapeutic management of HP is similar to that of other types of pancreatitis, which includes bowel rest, pain management, and monitoring of disease complications. Specific nutritional therapy, enteral and parenteral nutrition, are indispensable parts in the handling of acute conditions.[21] Data showed that early enteral nutrition can improve the outcomes of pediatric acute pancreatitis.[22] Endoscopic and surgical procedures can be considered if required. None of our patients developed exocrine and endocrine pancreatic insufficiency, diabetes mellitus, or pancreatic cancer. The clinical presentation and results of radiological diagnostic procedures were similar to those seen in other acute pancreatitis cases. Histologically, Singhi et al[23] found that PRSS1 HP is characterized by the progressive lipomatous atrophy of the pancreas. Pseudocysts occurring in HP are similar to those of other causes. In Case A, the patient presented with a large pseudocyst of the pancreatic tail and a diffuse splenic infarction. Splenic infarction secondary to acute pancreatitis is unusual and may be caused by splenic vein thrombosis. Plausible explanations are as follows: pancreatitis can induce the hypercoagulability stated and facilitate splenic vein thrombosis. Splenic vessels or splenic parenchyma might be compressed directly by the pseudocyst of the pancreatic tail due to the intimate anatomical relation between the two. Also, it has been mentioned that the density of the spleen is reduced by the high lipid concentration during hyperlipidemic acute pancreatitis.[24] However, the plasma lipid of the patient in Case A was normal. The integrated therapeutic strategy of HP includes pain control, prevention of recurrence, treatment of exocrine (maldigestion) and endocrine (diabetes) dysfunction, management of complications (pseudocysts, etc), and early detection of pancreatic ductal adenocarcinoma.[25] ERCP and stenting is believed to be an effective therapeutic approach to childhood HP.[26,27] Surgery has been suggested as a useful therapy, especially for cases with pancreatic anatomy and cancer risk[27] or with complication; however, experience is limited and the results are unpredictable.[28] Refractory abdominal pain and recurrent pancreatitis made us carry out pancreatic pseudocyst excision 6 months after 2 pancreatic duct stenting therapies were performed in the patient from Case A. Since then, the patient's postoperative course was uneventful.

3.1. Limitation

The limitation of the article was that the follow-up of our patients is fairly short, and a long-term follow-up will be required to evaluate the sustained relief of symptoms.

4. Conclusion

Young children presenting with recurrent acute pancreatitis without a history of risk factors and/or familial history should be highly suspected as having HP. The severity of pancreatitis is not parallel with mutations, and even the parents carrying the mutations can be asymptomatic. Thus, genetic testing should be performed to identify the etiology. Although ERCP and stenting is temporally effective in treating HP, long-term follow-up is necessary. An operation is only recommended for children with complications, such as pseudocysts, etc.

Acknowledgments

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