Case report

Chronic pancreatitis in children: treat like an adult?

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SUMMARY

A 15-year-old boy with a medical background of obesity, familial hyperlipidemia and acute recurrent pancreatitis, presented to emergency department reporting a 3-day course of periumbilical abdominal pain and nausea. Pain was noticed on epigastric palpation. Laboratory evaluation revealed leucocytosis, neutrophilia and pancreatic enzymes elevation more than three times the upper limit of normal. An acute recurrence of pancreatitis was diagnosed, was admitted to the hospital, being discharged after 5 days. Four days after, he was readmitted because of symptoms recurrence. Elevation of transaminases, GGT and direct bilirubin were noticed. Pancreatic enzymes still elevated but lower than in the previous episode. An endoscopic ultrasound revealed a Wirsung with a cephalic stricture and diffuse structural abnormalities suggestive of chronic pancreatitis. The patients was submitted to endotherapy with several sessions of endoscopic retrograde cholangiopancreatography including stenting and pancreatoscopy with marked clinical and imaging improvement. A genetic variant was identified.

BACKGROUND

Although chronic pancreatitis (CP) is a rare disease in children and adolescents, it has an important disease burden and a negative impact in quality of life. Given the rarity of the diagnosis, all cases of CP in paediatric age represent learning opportunities. This case shows the importance of a multidisciplinary team in the management of patients with CP to ensure optimal outcomes and reinforces the value of a genetic analyses when no other cause is found for the disease.

CASE PRESENTATION

A 15-year-old adolescent boy presented to a paediatric emergency department (ED) reporting a 3-day course of periumbilical abdominal pain, accompanied by general malaise and nausea, without vomiting. The patient was obese, with history of familial type IV hyperlipidemia (Fredrickson's) phenotype and acute recurrent pancreatitis (ARP) (five episodes beginning at age 11 years, having undergone multiple abdominal ultrasounds, an upper gastrointestinal endoscopy, an abdominal CT, a magnetic resonance cholangiopancreatography (MRCP), investigation of celiac disease, cystic fibrosis, autoimmune diseases and other etiological studies, without identification of the cause). Between the acute episodes, nutritional support was provided to the patient. Family history was positive for obesity (both parents), asthma and celiac disease (mother), and type II diabetes, dyslipidemia and early cardiovascular disease (maternal family). The patient has a healthy older sister.

On examination, the patient had skin pallor, tachycardia and pain was elicited on epigastric palpation. No fever, jaundice, hepatosplenomegaly or active bleeding was observed.

Blood tests were performed and revealed leucocytosis, neutrophilia and elevation of amylase 16 times the upper limit of normal (ULN) (1750 U/L) and lipase 53 times the ULN (11 550 U/L). The serum calcium, liver enzymes and bilirubin were normal. Total cholesterol (188 mg/dL), LDL cholesterol (119 mg/dL) and triglycerides (178 mg/dL) were slightly elevated. An abdominal ultrasound was performed but no clear image of the pancreas was obtained because of gas interference. An acute recurrence of pancreatitis was diagnosed, and he was admitted to the hospital with no oral intake and was kept on intravenous hydration and analgesia. By the fifth day from admission, clinical improvement and stability were noteworthy so he was discharged and scheduled a follow-up appointment with a gastroenterologist. Four days after discharge, he returned to the same paediatric ED due to recurrence of nausea and abdominal pain, associated with jaundice and coluria. Analytically, elevation of transaminases, GGT and direct bilirubin, with a clear decrease of pancreatic enzymes in relation to the previous episode. An abdominal ultrasound was performed, showing a gallbladder with a 5 mm parietal thickening, not distended, with thick bile, with no signs of lithiasis and a Wirsung channel with 3 mm calibre. The patient was admitted and started on intravenous analgesia and hydration. He clinically improved and was discharged after 6 days. A multidisciplinary meeting was held (paediatrics, paediatric and adult gastroenterology, surgery and radiology), and it was decided to perform an endoscopic ultrasound in the outpatient setting.

INVESTIGATIONS

An endoscopic ultrasound was performed 1 month after discharge and revealed diffuse structural abnormalities throughout the pancreas suggestive of CP, more evident in the cephalic region, with a lobular pattern, bands and hyperechogenic foci, and also a small parenchymal calcification in the head of the pancreas; the Wirsung showed an irregular calibre, with a stenosis in the cephalic region and marked echogenicity of the wall compatible with periductal fibrosis; a pseudocyst (17×14 mm) was found adjacent to the body–tail transition of the pancreas. Biopsies showed mild non-specific duodenitis, chronic atrophic gastritis with mild

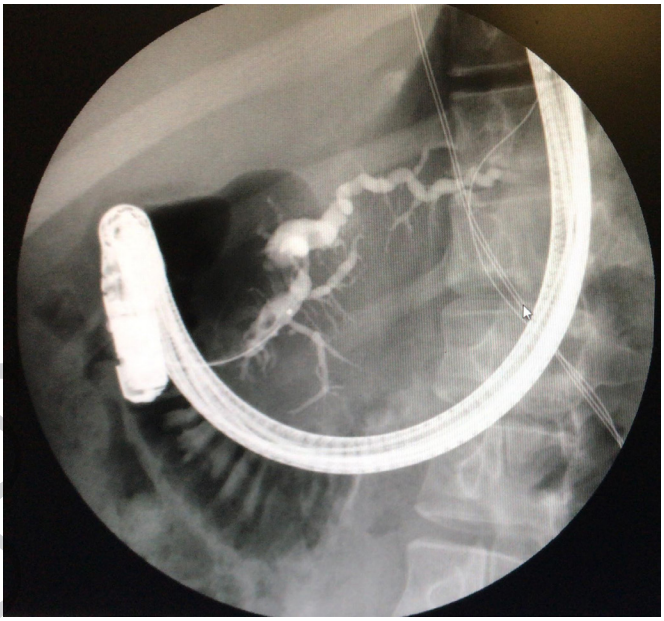

Figure 1 Pancreatogram showing distortion of the Wirsung with a major cephalic stricture, body dilatation and minor strictures of the tail. Intraductal lithiasis can be noted.

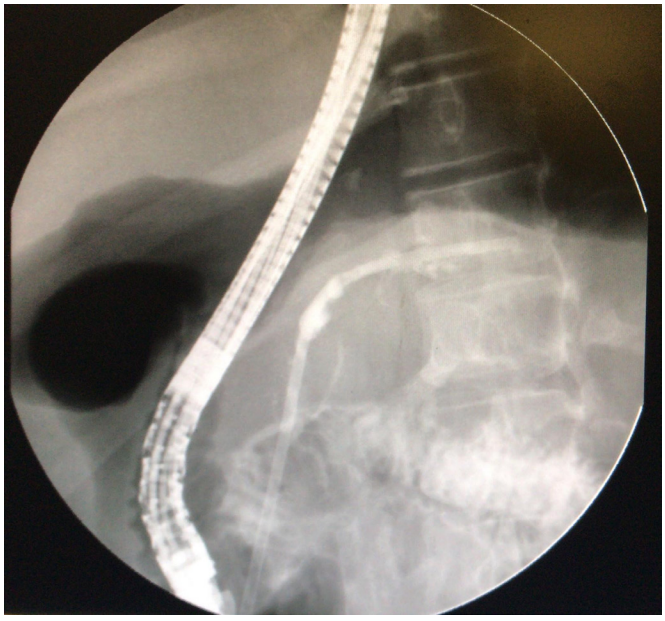

Figure 2 Fluoroscopic image of the Wirsung showing a 10Fr stent in place from the head to the tail of the pancreas.

activity and focal intestinal metaplasia and foveolar hyperplasia, consistent with reactive gastropathy.

An endoscopic retrograde cholangiopancreatography (ERCP) performed 3 months after discharge confirmed features suggestive of CP with multiple Wirsung stenoses, conditioning dilatation and eventual intraductal lithiasis (figure 1).

In the genetic study, no recognised pathogenic variants were identified in the genes analysed. A variant was identified in the CFTR gene c.2991G>C (p.Leu997Phe).

DIFFERENTIAL DIAGNOSIS

Following the INternational Study Group of Pediatric Pancreatitis: In search for a cuRE (INSPPIRE) criteria, this is a case of CP since the patient has pancreatic duct abnormalities together with some periods of consistent abdominal pain and lipase or amylase elevation.

Despite being a known risk factor for CP, the hypertriglyceridemia in this case does not seem to be the main reason since during the acute episodes, the patient usually has normal to slightly elevated triglycerides and LDL cholesterol levels. Accordingly to this hypothesis, a genetic study was run and identified a variant in one of the genes whose mutations are associated with a higher risk of CP.

Even though the interpretation of pathogenesis of this CFTR variant is still conflicting (clinical significance uncertain or probably pathogenic), bioinformatically it is predicted to be deleterious.

We hypothesised that the pancreatic duct stenoses were probably the result of a cicatricial process due to the various exacerbations of ARP, considering that such alterations were not noticed in previous ultrasounds and MRCP's. In this case, CP was the result of sequelae changes in the Wirsung duct resulting from recurrent acute pancreatitis (AP), which in this case has a multifactorial aetiology with a genetic predisposition associated with risk factors such as obesity and hypertriglyceridemia.

TREATMENT

The patient underwent five sessions of therapeutic ERCPs between May and November with placement of an increasing number of plastic stents after dilation with a balloon of the pancreatic stenosis. During the ERCP procedures, the patient was submitted to pancreatoscopy which helped to confirm the presence of small intraductal stones which were removed by a dormia basket. Furthemore, the pancreatoscope allowed successful placement of a guidewire across the tail strictures (figures 2–6).

The patient was also started on pancreatin 150 mg 2id (lunch and dinner), and nutritional support.

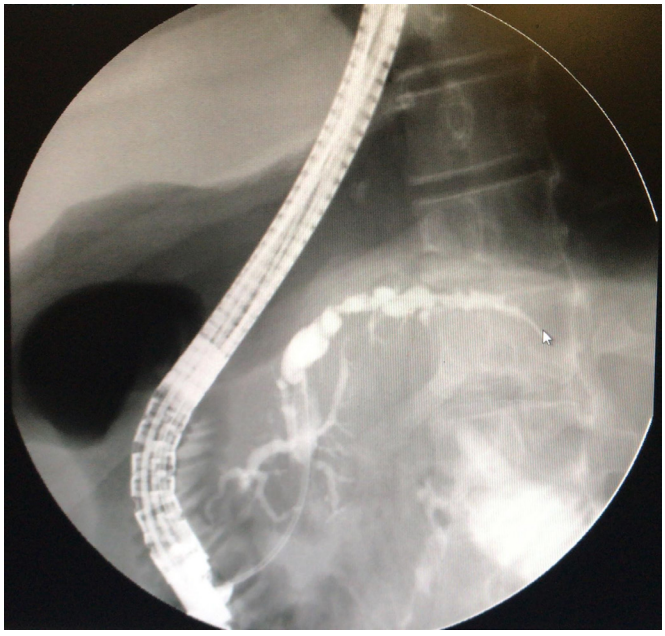

Figure 3 Wirsungography showing a marked radiological improvement after five sessions of endotherapy.

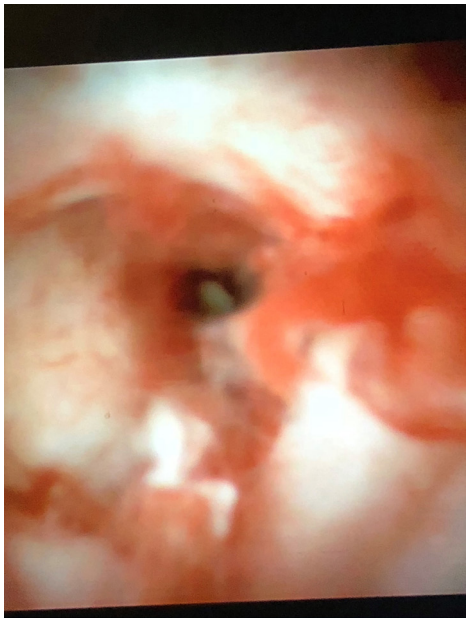

Figure 4 Image of pancreatoscopy of the pancreatic head where a stricture and new vascularisation due to chronic inflammation can be noted.

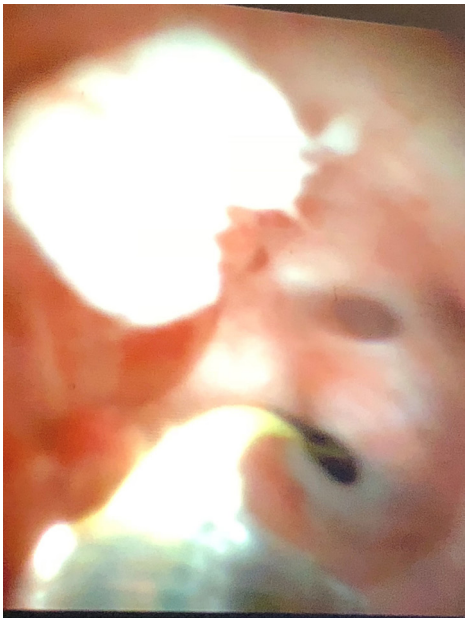

Figure 6 Image of pancreatoscopy of the tail, in which a stone and correct placement of the guidewire can be seen.

OUTCOME AND FOLLOW-UP

The patient improved clinically after the therapeutic interventions, being currently without nausea and without the general malaise that he felt for several years sometimes on a daily basis.

During the last procedure, there was a clear improvement of the cephalic stenoses, still with stenosis in the middle portion of the body and a closed stenosis in the body–tail transition, unconstrained by the wire. A new ERCP has been scheduled within 4 months and these interventions are planned to be stopped after 15 months of endoscopic treatment.

He maintains the usual follow-up with the general paediatrician and paediatric gastroenterology, and is expected to progressively transit to adult gastroenterology in the coming years, in order to ensure clinical stability in the future.

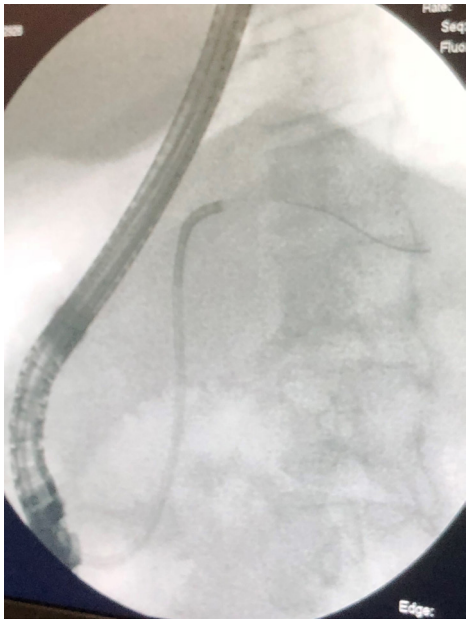

Figure 5 Fluoroscopic image of a pancreatoscope in the Wirsung allowing the placement of a guidewire under direct visualisation.

DISCUSSION

This patient had the first episode of AP at age 11 years. After multiple acute bouts, with symptom-free periods between them, the diagnosis of ARP was made. By the sixth episode, with Wirsung's duct irreversible changes on endoscopic ultrasound, the diagnosis of CP was presumed.

Despite the increasing incidence (or increased awareness) of AP in paediatric age,[1 2] there is still limited literature regarding ARP and CP in children.[3] CP remains an uncommon diagnosis in this age group, and there is no specific epidemiology available in paediatrics, despite two studies estimating low-incidence rates ranging from below 0.5/100 000 person-years in people younger than 20 years old to 0.5/100 000 person-years in children and young adults between 0 and 34 years old. In the second mentioned group, it has been estimated a prevalence of 10.3 per 100 000 people.[4 5] Major risk factors identified for adult ARP and CP are rare in children, so data on the factors that predispose to progression from AP to ARP and CP in children was missing.

The INSPPIRE Consortium defined the concepts of AP, ARP and CP. The diagnosis of ARP requires the occurrence of two episodes of AP, in the absence of irreversible pancreatic structural changes, with a diseased-free period between the episodes. AP is defined by the presence of at least two of the following: characteristic abdominal pain; imaging consistent with AP; or lipase or amylase levels greater than three times the ULN. The diagnosis of CP requires the presence of irreversible, structural changes in the pancreas such as diffuse or focal destruction, sclerosis, pancreatic duct abnormalities/obstruction with at least one of the following: some periods of consistent abdominal pain or lipase or amylase levels greater than three times the ULN; exocrine pancreatic insufficiency; or endocrine pancreatic insufficiency.[3]

During the episodes of AP, the patient went through multiple etiological studies, including blood analyses, MRCP, investigation

of celiac disease, cystic fibrosis, autoimmune diseases and other, all excluding non-genetic risk factors. After the sixth episode, he undergone an endoscopic ultrasound and an ERCP that revealed pancreatic structural changes, specifically encompassing the Wirsung duct and a genetic test was performed revealing a CFTR genetic variant.

The INSPPIRE group developed consensus relatively to the causal evaluation of ARP and CP. Accordingly, initial evaluation of ARP should include AST, ALT, GGT, total bilirubin, fasting lipids and total serum calcium. Patients with ARP also should have MRCP imaging of the pancreas. The search for a genetic cause of CP should include a sweat chloride test and mutation analysis of the genes mentioned above.[6] MRCP should be used as the imaging method of choice, but if the likelihood of therapeutic intervention is high, ERCP is the best option.[7]

Recently, using INSPPIRE Consortium database, several risk factors were identified. The most commonly identified for children with CP were pancreatitis-predisposing genetic mutations (PRSS1—present in more than a half; SPINK1; CFTR; CTRC; CPA1). Other risk factors, in descending order of importance, include obstructive, toxic/metabolic, autoimmune causes.[8 9]

CP has an important negative impact on physical and mental quality of life.[10] Children with severe abdominal pain, multiple ED visits, hospitalisations and consequently, missed days of school, experience an extreme disruption of normal childhood and education. Pain exacerbation and persistency also may lead to malnutrition, social deprivation, depression, analgesic dependence and other adverse effects.[8] Over time, children with CP can develop exocrine pancreatic insufficiency and pancreatogenic diabetes mellitus.[11]

In this case, once the diagnosis of CP was established, successive therapeutic ERCP were planned and executed by an experienced adult gastroenterologist. The patient was also started on pancreatic enzyme replacement therapy (PERT) with pancreatin and nutritional support. Throughout the acute episodes the treatment was supportive, comprising intravenous hydration and analgesia.

For treating painful uncomplicated CP, the European Society of Gastrointestinal Endoscopy recommends ERCP as the first-line interventional option.[12] In children, there is no single therapy that showed efficacy in stopping progression from ARP to CP.[9] The main goal of medical management is to treat the complications of disease and to alleviate pain (acetaminophen and hydrocodone). Therapeutic ERCP is frequently utilised in children with CP and may offer benefit in selected cases, specifically if ductal obstruction is present.[13] It proved to be a safe therapeutic option for pancreatic disorders in children when performed at centres with expertise.[14] When all medical and endoscopic therapies fail to alleviate the pain and burden of CP, surgical interventions like cholecystectomy and total pancreatectomy or islet cell autotransplantation are considered.[9 15] PERT is indicated to correct exocrine pancreatic insufficiency and malnutrition in CP. Nutritional support must be provided.[16]

Subjects with a CFTR variant have increased risk of recurrent AP and CP, which is associate with a significantly increased risk of pancreatic cancer but also male infertility and chronic sinusitis with minimal lung disease. The mortality rate compared with the general population is significantly increased in patients who develop pancreatic cancer, but does not appear to be increased in patients without pancreatic cancer.[17]

In the setting of a genetic mutation associated with hereditary pancreatitis, there are no clearly established methods of preventing development of disease, and so no family screening is indicated unless they develop symptoms. However, close relatives should be counselled to avoid environmental risk factors.[17]

Patient's perspective

Before the illness manifests itself, although it was some years ago, I remember feeling good and having a normal life. During hospitalisations and at the time of diagnosis, I remember suffering, of feeling exhausted and of not feeling well. Hospitalisations were always boring. After the ERCP's I feel much better, I still do not like being hospitalised to perform these procedures, but I hope not to suffer so much in the future.

Learning points

- The episodes of acute recurrent pancreatitis may be responsible for the development of chronic pancreatitis (CP), since successive sudden events contribute to the development of irreversible ductal lesions, particularly stenoses, in the pancreatic canals, which fit the definition of CP making it important to reassess the clinical situation after each recurrence.
- CP is a rare diagnosis in childhood, and so it is necessary to recognise the lack of experience that paediatric specialists have in this area and to recognise the benefits of bringing together a multidisciplinary team including adult physicians in order to approach the patient.
- In addition to reducing the risk of life-threatening exacerbations, successful treatment of CP allows the patient to have a significant improvement in life quality, alleviating the daily symptoms that may have been present for years.

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