

CASE REPORT

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Delayed diagnosis of chronic pancreatitis with Cystic Fibrosis and Pancreas Divisum**Burcu Volkan, Ali Islek, Dilara Fatma Kocacik Uygun, Erkan Parlak***Erzurum Regional Training and Research Hospital, Department of Pediatric Gastroenterology, Erzurum, Turkey**Ataturk University School of Medicine, Department of Pediatric Gastroenterology, Erzurum, Turkey**Ataturk University School of Medicine, Department of Pediatric Allergy and Immunology, Erzurum, Turkey**Sakarya University School of Medicine, Department of Gastroenterology, Sakarya, Turkey*

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Abstract

The incidence of pancreatitis in children and adolescents has increased in recent years. The etiology of pancreatitis is more diverse in children compared to adults. Pancreatitis may present as acute pancreatitis, recurrent acute pancreatitis or chronic relapsing pancreatitis. The majority of children with chronic pancreatitis had identifiable genetic risk factors associated with pancreatitis or congenital anomalies of the pancreaticobiliary system. Pancreatitis is a known complication of cystic fibrosis (CF) and may be the first manifestation of the disease in some cases. We report a case of late-diagnosed CF presenting with chronic pancreatitis and pancreas divisum.

Keywords: Cystic fibrosis, pancreatitis, pancreas divisum**Introduction**

Pancreatitis may present as acute pancreatitis (AP), recurrent acute pancreatitis (RAP) or chronic relapsing pancreatitis. AP presents with a reversible systemic inflammatory response characterized by the presence of interstitial edema, infiltration by acute inflammatory cells, and varying degrees of necrosis, apoptosis, and hemorrhage [1]. Tissue injury is a product of inappropriately activated and circulating pancreatic enzymes. In contrast, CP is an irreversible and progressive inflammatory disorder that results in histological changes such as fibrosis, infiltration of chronic inflammatory cells, and the decline or loss of exocrine and endocrine function [2].

The incidence of AP and CP in children appears to be increasing [1,3]. The etiology of pancreatitis is more diverse in children compared to adults. The most common etiologies are trauma, multisystem disease, drugs, viral infections, and congenital anomalies of the pancreaticobiliary system. However, 25–35% of cases of AP in children are idiopathic [4,5]. The majority of children with CP have either a genetic predisposition, such as in certain variants of the trypsinogen gene and cystic fibrosis transmembrane regulator (CFTR) gene, or obstructive lesions such as stricture or scarring of the pancreatic duct and pancreas divisum (PD), or both [3,6].

Pancreatitis is a known complication of cystic fibrosis (CF) and may be the first manifestation of the disease in

some cases. Pancreas divisum, the most common congenital variant of pancreatic ductal anatomy, is more common in individuals with RAP/CP, and specifically in those with pancreatitis-associated gene mutations [7]. We describe a case of late-diagnosed CF presenting with CP and PD, in order to emphasize the importance of early diagnosis of CF and CFTR-related pancreatitis. This can prevent the development of CF-related complications in other organs.

Case report

A 14-year-old boy was admitted to emergency department with vomiting and acute persistent epigastric pain. The patient was the second son of healthy, unrelated parents. His uncle had a history of AP. The patient had experienced an abdominal pain attack three months previously, but his serum amylase and lipase levels at that time were not known. There was no history of growth retardation, chronic diarrhea, recurrent pneumonia or bronchitis. Medical treatment was administered for recurrent cough. At physical examination, his weight was in the 3-10th percentile and height in the 25-50th percentile. His blood pressure was 106/74 mmHg, temperature 36.4° C and heart rate 82 beats/min. At abdomen examination, his abdomen was soft and he reported pain in the epigastric region. No rebound tenderness was observed. Blood analysis revealed hyperamylasemia (980 UI/L) and hyperlipasemia (913 UI/L). Abdominal ultrasound revealed pancreatic heterogeneity and peripancreatic fluid collection. Computed tomography scans of the abdomen revealed atrophy of the pancreas and dilatation of the Wirsung duct. He was given nothing per orem on admission. Intravenous fluid resuscitation and parenteral analgesia for pain control was administered. Three days

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after admission, he was started on a clear liquid diet. Magnetic resonance cholangiopancreatography (MRCP) revealed atrophic pancreatic gland, dilatation of the Wirsung duct with multiple intraductal calculi (Figure 1). CP was diagnosed, and the patient was started on pancreatic enzyme therapy. Serine protease inhibitor Kazal type 1 (SPINK1) and the CFTR gene were analyzed for the diagnosis of hereditary pancreatitis. Anti-nuclear antibody, anti-smooth muscle antibody and anti-mitochondrial antibody were negative, and IgG, IgM, IgG and IgG4 were normal. Endoscopic retrograde cholangiopancreatography (ERCP) revealed severely dilated, and narrowing main pancreatic duct in the head

region, incomplete PD and pancreatic duct stones (Figure 2). The main pancreatic duct was visualised through minor papillae. A 7 fr stent was inserted following minor papilla sphincterotomy. Three sweat chloride tests were performed. The first two values obtained were borderline, at 49 mmol/L and 55 mmol/L, while the final result confirmed a diagnosis of classic CF (110 mmol/L). Genetic examination revealed double heterozygosity for the D110H (p.Asp110His, c.328G>C), 2789+5G>A mutation in CFTR. Pulmonary computed tomography revealed bronchiectasis, and aerosolized recombinant human deoxyribonuclease therapy was initiated. The patient was treated using a multidisciplinary approach.

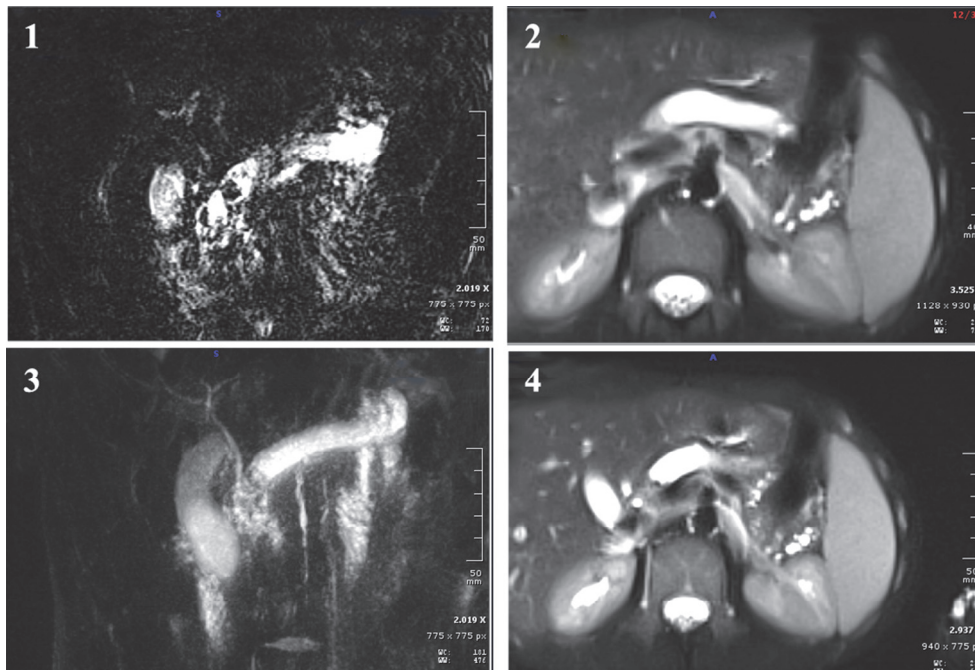


Figure 1. Image findings of MRCP show dilatation and stenosis of Wirsung duct, atrophy and cystic formation of the pancreas.

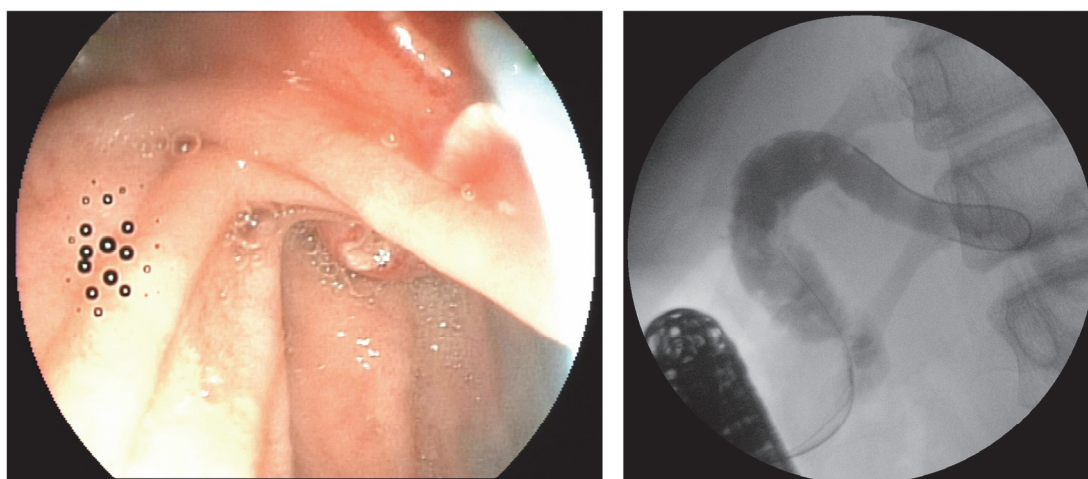


Figure 2. Image findings of ERCP

Discussion

The incidence of pancreatitis in children and adolescents has increased in recent years, as it has in adults. This may be related to multiple factors, including a change in the incidence of pancreatitis and increased clinical

awareness [8,9]. However, the condition may also be misdiagnosed due to the presence of mild and heterogeneous symptoms, such as abdominal pain, nausea and vomiting. These symptoms may lead pediatricians to incorrectly diagnose more common illnesses, such as viral gastroenteritis. Our patient had

experienced an abdominal pain attack three months before admission, but his pancreatic enzyme levels at that time were unknown. This might have represented a misdiagnosed attack of pancreatitis.

Approximately 15% to 35% of pediatric patients have recurrent episodes of AP [1]. It is more common in children with biliary anomalies, idiopathic and hereditary pancreatitis, metabolic disorders, particularly hypertriglyceridemia [10]. If the inflammation of the pancreas persists without full remission or if a patient have recurrent episodes pancreatitis, then CP is the appropriate term. Hereditary causes are seen in 5% to 8% of patients with CP [4,8]. Several genetic risk factors have been described in recent years, such as mutations of cationic trypsinogen (PRSS1), SPINK-1, and CFTR. Heterozygous SPINK1 as well as CFTR mutations are associated with a 20-40-fold increased risk of pancreatitis [11]. Most patients with genetic predisposition for pancreatitis present with AP in childhood and progress to CP over several years [11]. Sweat test, gene testing for CFTR and SPINK 1 mutations, imaging to exclude a structural (congenital or acquired) etiology and assessment for auto-immune causes should be performed for children with CP [2]. Our patient with CP was analyzed for these etiologies and diagnosed with CF and PD.

CF is caused by mutations in the CFTR gene, which is predominantly expressed in the apical plasma membrane of the pancreatic ductal cells and controls cAMP-mediated bicarbonate secretion into the duct lumen [12]. CFTR dysfunction leads to pancreatitis due to the presence of more viscous, acidic fluid (from reduced bicarbonate secretion) in the pancreatic ducts, the premature activation of zymogens (the lower pH promotes trypsinogen activation) as well as an excessive host inflammatory response, resulting in recurrent injury, progressive pancreatic fibrosis and ductal obstruction [6,12]. Pancreatic ductal dysfunction, particularly a low HCO₃ concentration in the pancreatic fluid, is one of the earliest defects observed in CP. It has been suggested that the mislocalization of CFTR is a cause of pancreatic ductal dysfunction and subsequent pancreatic stone formation in CP [13]. The viscous and acidic fluid in the pancreatic ducts can result in the precipitation of digestive enzymes in pancreatic fluid and protein plugs then form in the pancreatic ducts. Pancreatic stones are thought to develop initially as protein plugs in pancreatic ducts.

There are numerous reports of an association between CFTR gene mutations and RAP in patients with PD. This is the most common congenital variant of pancreatic ductal anatomy and is identified in 7.4% of children with pancreatitis and 19.2% of children with relapsing or chronic pancreatitis [6]. It occurs because the dorsal and ventral pancreatic buds fail to fuse during gestation. The majority of patients with PD are asymptomatic, but a subset of patients may present with RAP, CP or chronic abdominal pain. When the caliber of the minor papilla is

too small to drain pancreatic secretions, relative outflow obstruction of pancreatic fluid leads to high intraductal pressure, and pancreatic ductal distension progressing to pancreatitis. Diagnosis of PD is based on ERCP, endoscopic ultrasound or MR pancreatography. Treatment using endoscopic therapy involves minor papillotomy or dorsal duct stenting, or surgical drainage procedures [7].

Children with CP should be evaluated for hereditary pancreatitis and structural (congenital or acquired) etiologies. In this report, we described a patient with diagnosed at 14 years of age with marked reduction of pancreatic functions, signs of pancreatitis, and decreased respiratory functions due to bronchiectasis. We wish to emphasize the importance of early diagnosis of CF and CFTR-related pancreatitis, and that this may prevent CF-related complications in other organs.

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