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Homozygous SPINK1-Related Pancreatitis Complicated by Exocrine Pancreatic Insufficiency: A Case Report

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ABSTRACT

Background: Genetically mediated pancreatitis is a major cause of recurrent acute pancreatitis and chronic pancreatitis in children. While autosomal dominant hereditary pancreatitis is classically linked to *PRSS1* mutations, variants in *SPINK1* are increasingly recognized as important disease modifiers, particularly when present in a homozygous state. These variants may lead to early disease onset and rapid progression toward chronic pancreatitis and exocrine pancreatic insufficiency.

Case Presentation: We report the case of a 16-year-old girl with recurrent acute pancreatitis beginning in childhood, occurring three to four times per year, without identifiable secondary causes or a family history. Imaging revealed dilation of the main pancreatic duct and features suggestive of chronic pancreatitis. Endoscopic ultrasound demonstrated parenchymal atrophy, intraductal lithiasis, and mucous plugging, consistent with lithiasic chronic pancreatitis. Genetic testing identified homozygous *SPINK1* variants (c.101A>G [p.Asn34Ser] and c.56-37T>C), along with a homozygous intronic *CFTR* variant, supporting a diagnosis of genetically mediated pancreatitis

Conclusion: This case illustrates the aggressive clinical course of homozygous *SPINK1*-associated pancreatitis in pediatric patients, characterized by early progression to chronic pancreatitis and severe exocrine pancreatic insufficiency. It highlights the critical role of early genetic testing, detailed endosonographic evaluation, and comprehensive functional assessment in children with recurrent pancreatitis. Early diagnosis and individualized multidisciplinary management are essential to optimize nutritional status, preserve pancreatic function, and improve long-term outcomes.

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KEYWORDS:

Genetically mediated pancreatitis, SPINK1 mutations, Recurrent acute pancreatitis, Chronic pancreatitis, Exocrine pancreatic insufficiency, Endoscopic ultrasound

INTRODUCTION

Hereditary pancreatitis (HP) is a rare cause of chronic pancreatitis (CP), first described in 1952, and is characterized by recurrent episodes of acute pancreatitis beginning in childhood with progression to CP, exocrine pancreatic insufficiency (EPI), diabetes mellitus, and increased lifetime risk of pancreatic cancer [1,2]. Its estimated prevalence in Europe and North America ranges from 0.3 to 0.5 per 100,000 individuals, although pediatric cases are likely underrecognized due to heterogeneous clinical presentations [3].

Genetic advances have significantly refined the understanding of HP. While autosomal dominant forms are classically linked to PRSS1 mutations [4], variants in genes such as SPINK1 and CFTR are now considered contributors to genetically mediated pancreatitis rather than classical hereditary pancreatitis [5]. These variants may influence disease onset, severity, and progression.

EPI represents a frequent and early complication resulting from progressive acinar destruction and ductal alterations, leading to malabsorption and impaired growth in children [6]. Clinically, pediatric patients typically present with recurrent abdominal pain and elevated pancreatic enzymes. Imaging modalities such as magnetic resonance

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cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) facilitate early detection of structural changes, while functional testing, including fecal elastase measurement, allows assessment of exocrine reserve and guides enzyme replacement therapy [7–9].

We report the case of a 16-year-old girl with recurrent acute pancreatitis associated with a homozygous SPINK1 mutation, complicated by severe exocrine pancreatic insufficiency and chronic pancreatitis confirmed by EUS, highlighting the importance of early genetic and morphologic evaluation in pediatric genetically mediated pancreatitis.

CASE REPORT

A 16-year-old girl was referred to our department for evaluation of recurrent epigastric pain. She had been followed since 2019 for recurrent episodes of pancreatitis, occurring approximately three to four times per year. Each episode was characterized by severe, radiating epigastric pain, occasionally associated with nausea and vomiting, without fever. She denied alcohol or tobacco use, gallstone disease, abdominal trauma, or exposure to pancreatotoxic medications. There was no known family history of acute or chronic pancreatitis.

During acute episodes, physical examination revealed epigastric tenderness without guarding or peritoneal signs. Laboratory investigations consistently showed elevated pancreatic enzymes, with a peak serum lipase level of 3,000 U/L (five to eight times the upper limit of normal) and elevated serum amylase. Liver function tests, inflammatory markers, renal function, electrolytes, fasting glucose, and glycated hemoglobin (HbA1c) were within normal limits.

Contrast-enhanced computed tomography demonstrated features of acute pancreatitis (stage C) **(Figure 1)** , with diffuse pancreatic enlargement and dilation of the main pancreatic duct, raising suspicion of underlying chronic pancreatic disease. No pancreatic necrosis, peripancreatic collections, or biliary obstruction were observed.

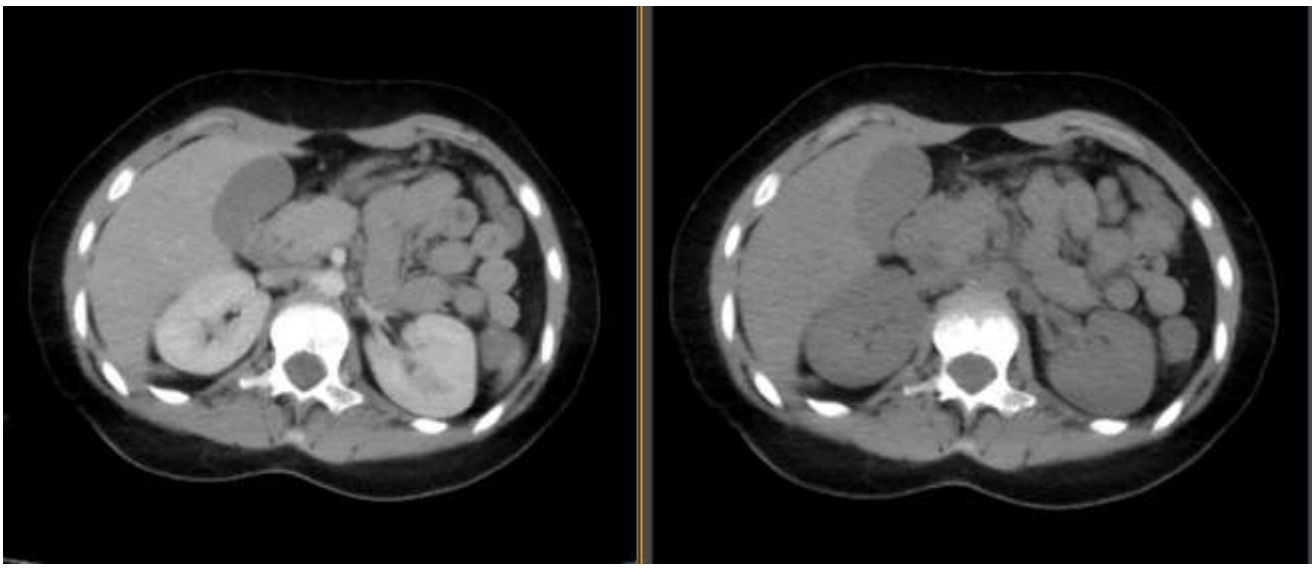

Figure 1 : CT scan showed grade C of acute pancreatitis

A comprehensive etiological workup excluded common secondary causes of pancreatitis. Infectious causes were ruled out with negative serologies for Epstein–Barr virus, cytomegalovirus, hepatitis B and C, and HIV. Metabolic causes were excluded by normal serum calcium, triglyceride levels, and glycemia. Autoimmune pancreatitis was considered unlikely given normal IgG4 levels and negative autoimmune testing (antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti–double-stranded DNA antibodies, and antiphospholipid antibodies), as well as normal complement levels.

Magnetic resonance imaging (MRI) of the pancreas (Figure 2**)** revealed dilation of the main pancreatic duct measuring up to 7 mm, associated with a proximal lacunar formation suggestive of ductal stenosis or a structural lesion.

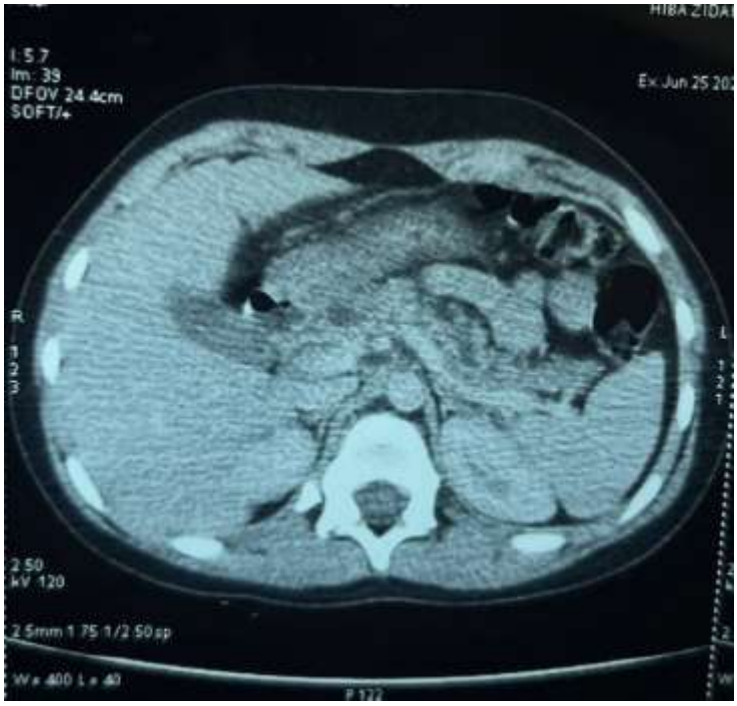

Figure 2 : MRI demonstrating significant dilation of the main pancreatic duct (Wirsung duct) upstream of a partially calcified lesion in the pancreatic head.

Subsequent endoscopic ultrasound (EUS), performed via transgastric and transbulbar approaches, demonstrated a heterogeneous and atrophic pancreatic parenchyma with increased echogenicity, consistent with chronic inflammatory changes. The main pancreatic duct was diffusely dilated, measuring up to 8 mm, with the presence of intraductal lithiasis, posterior acoustic shadowing, and mucin-containing formations compatible with mucous plugs. The gallbladder was unremarkable, without lithiasis, and the biliary tree and peripancreatic vascular structures were normal. No peripancreatic or periceliac lymphadenopathy was identified. Overall, the endosonographic findings were consistent with lithiasic chronic pancreatitis .

Given the early onset, recurrent disease course, and absence of identifiable secondary causes, genetic testing was performed using a next-generation sequencing panel for hereditary pancreatitis (CentoGene, Germany). This analysis identified two homozygous variants in the *SPINK1* gene (c.101A>G [p.Asn34Ser] and c.56-37T>C), as well as a homozygous intronic *CFTR* variant (c.1210-7_1210-6del, 5T). These findings supported a diagnosis of genetically mediated hereditary pancreatitis. No pathogenic variants were detected in *PRSS1*, *CPA1*, or *CTRC*.

Pancreatic functional assessment revealed severe exocrine pancreatic insufficiency, with fecal elastase levels of 7.9 µg/g (normal >200 µg/g). Endocrine pancreatic function remained preserved, with normal fasting glucose and HbA1c values.

At the most recent evaluation, the patient presented with another acute episode of pancreatitis but remained clinically stable, without jaundice or signs of cholestasis. Given the presence of significant ductal dilatation, intraductal lithiasis, and mucous plugging, endoscopic retrograde cholangiopancreatography (ERCP) was considered to further characterize the ductal lesion and potentially relieve obstruction. However, ERCP has not yet been performed. The patient is currently managed conservatively with a multidisciplinary approach, including pancreatic enzyme replacement therapy (25,000 IU with each meal), supplementation with fat-soluble vitamins (A, D, E, and K), nutritional counseling to support growth, and individualized pain management.

She is undergoing regular follow-up with clinical monitoring of abdominal pain, growth, and nutritional status; biochemical surveillance of pancreatic enzymes and vitamin levels; and periodic imaging with MRCP or EUS. Genetic counseling has been provided to the patient and her family to address prognosis, recurrence risk, and long-term follow-up. At follow-up, the patient reported intermittent abdominal discomfort between acute episodes, with improvement in nutritional status under enzyme therapy, and preserved endocrine pancreatic function. ERCP will be reconsidered if progressive ductal changes or persistent obstructive symptoms are confirmed.

This case emphasizes the importance of early diagnosis, detailed morphologic and genetic evaluation, and coordinated multidisciplinary management in pediatric hereditary pancreatitis, particularly in patients with homozygous *SPINK1* mutations complicated by severe exocrine pancreatic insufficiency.

DISCUSSION

Pancreatitis occurring in childhood is uncommon and differs substantially from adult pancreatitis in terms of etiology, disease course, and long-term outcomes [10] . In pediatric populations, classical adult risk factors such as alcohol consumption, gallstone disease, and abdominal trauma are rare, whereas genetic factors constitute a major underlying mechanism in recurrent acute pancreatitis and chronic pancreatitis . This has been consistently demonstrated in large international pediatric cohorts, including the INSPPIRE consortium [11].

Traditionally, the term *hereditary pancreatitis* has been reserved for autosomal dominant forms, most commonly associated with PRSS1 mutations, typically characterized by a positive family history and high penetrance [4] .

In contrast, variants in genes such as SPINK1 and CFTR are now regarded as predisposing or modifier factors, contributing to disease susceptibility rather than acting as fully penetrant Mendelian causes [12]. These entities are therefore more accurately classified as genetically mediated pancreatitis, particularly in patients without familial clustering, as observed in our case [12] . The SPINK1 gene, located on chromosome 5q, encodes a 56–amino acid pancreatic secretory trypsin inhibitor that plays a crucial protective role by preventing premature intrapancreatic activation of cationic trypsinogen through inhibition of its active site [13] .

Numerous SPINK1 variants have been described, with the p.Asn34Ser (N34S) mutation being the most frequently reported, identified in 6% to 21% of patients with idiopathic chronic pancreatitis, while its heterozygous prevalence in the general population is approximately 2%. The mode of inheritance is typically autosomal recessive [14].

At the molecular level, impaired *SPINK1* function lowers the threshold for intrapancreatic trypsin activation, predisposing acinar cells to recurrent injury and inflammation [13]. Repeated inflammatory episodes promote progressive parenchymal destruction, ductal abnormalities, and fibrotic remodeling, ultimately leading to chronic pancreatitis [13,14].

Unlike PRSS1 mutations, which directly enhance trypsinogen autoactivation, SPINK1 variants primarily act as disease modifiers, with a more pronounced clinical impact when present in a homozygous state [12,13]. This pathogenic mechanism explains why SPINK1-associated pancreatitis often presents early in life and progresses toward chronic pancreatitis, frequently complicated by exocrine pancreatic insufficiency (EPI) [14,15] . Progressive loss of acinar tissue leads to impaired digestive enzyme secretion, resulting in malabsorption, nutritional deficiencies, and growth impairment, particularly in pediatric patients [15]. A recent multicenter retrospective study by Müller et al., including 209 patients with SPINK1-related chronic pancreatitis, highlighted the marked heterogeneity in clinical expression and natural history, with wide variability in age at onset, disease progression, and functional impairment [16].

From a diagnostic perspective, early chronic pancreatic changes may be underestimated by cross-sectional imaging alone [11] . While magnetic resonance cholangiopancreatography provides valuable noninvasive assessment of ductal anatomy, endoscopic ultrasound offers superior sensitivity for detecting early parenchymal and ductal abnormalities, including ductal dilatation, intraductal lithiasis, and mucous plugging, as demonstrated in our patient [17].

Management of SPINK1-associated genetically mediated pancreatitis is primarily supportive and requires a multidisciplinary approach [11,15] .

Early initiation of pancreatic enzyme replacement therapy is essential to correct malabsorption, improve nutritional status, and support normal growth [15] . Long-term follow-up should include nutritional monitoring, pain management, and genetic counseling [12]. Endoscopic interventions such as ERCP may be considered in selected cases with obstructive ductal disease, although careful patient selection is required, particularly in pediatric populations [11,17].

Overall, this case underscores the importance of early recognition of genetically mediated pancreatitis, comprehensive genetic evaluation, and timely morphologic and functional assessment to prevent irreversible pancreatic damage and optimize long-term outcomes in children carrying homozygous SPINK1 variants complicated by severe exocrine pancreatic insufficiency [11,12,16] .

CONCLUSION

This case highlights the clinical and pathophysiological complexity of genetically mediated pancreatitis associated with homozygous SPINK1 variants in pediatric patients. It illustrates how early-onset recurrent pancreatitis, even in the absence of a family history, may rapidly progress to chronic pancreatitis complicated by severe exocrine pancreatic insufficiency.

Our findings underscore the importance of early genetic testing, comprehensive functional assessment, and advanced imaging—particularly endoscopic ultrasound—for timely diagnosis and disease characterization. Prompt initiation of pancreatic enzyme replacement therapy and multidisciplinary long-term follow-up are essential to optimize nutritional status, preserve growth, and limit irreversible pancreatic damage.

Overall, this case reinforces the need to consider SPINK1-related genetically mediated pancreatitis in children with recurrent acute pancreatitis and supports an individualized, genetics-driven approach to management .

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