Combined *SPINK1* mutations induce early-onset severe chronic pancreatitis in a child with severe obesity

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**Summary**

The most frequent causes of pancreatitis classically have been known to be gallstones or alcohol. However, genetics can also play a key role in predisposing patients to both chronic and acute pancreatitis. The serine protease inhibitor Kazal type 1 (*SPINK 1*) gene is known to be strongly associated with pancreatitis. Patients with these underlying genetic mutations can have severe diseases with a high morbidity rate and frequent hospitalization. We report an Arab girl who presented with acute pancreatitis at the age of 7 years progressing to recurrent chronic pancreatitis over a few years. She had severe obesity from the age of 4 years and developed type 2 diabetes at the age of 12. She had a normal biliary system anatomy. Genetic analysis showed that she had combined heterozygous mutations in the *SPINK1* gene (*SPINK1*, c.101A>G (p.(Asn34Ser)) and *SPINK1*, c.56-37T>C). Her parents were first-degree cousins, but neither had obesity. Mother was detected to have the same mutations. She had type 2 diabetes but never presented with pancreatitis. This case is the first to be reported from the Arab region with these combined mutations leading to recurrent chronic pancreatitis. It illustrates the importance of diagnosing the underlying genetic mutation in the absence of other known causes of pancreatitis. Considering the absence of pancreatitis history in the mother who did not have obesity but harboured the same mutations, we point out that severe obesity might be a triggering factor of pancreatitis in the presence of the mutations in *SPINK1* gene in this child. While this is not an assumption from a single patient, we show that not all carriers of this mutation develop the disease even within the same family. Triggering factors like severe obesity might have a role in developing the disease.

**Learning points:**

- Acute recurrent pancreatitis and chronic pancreatitis are uncommon in children but might be underdiagnosed.
- Biliary tract anomalies and dyslipidaemias are known causative factors for pancreatitis, but pancreatitis can be seen in children with intact biliary system.
- Genetic diagnosis should be sought in children with pancreatitis in the absence of known underlying predisposing factors.
- *SPINK1* mutations can predispose to an early-onset severe recurrent pancreatitis and acute pancreatitis.
Background

Acute pancreatitis is an inflammatory condition frequently caused by excessive alcohol intake or gallstones (1). In young patients, genetic mutations can predispose them to pancreatitis (1). These mutations can lead to chronic pancreatitis episodes resulting in an irreversible damage to endocrine and exocrine pancreatic function. Early diagnosis of the disease enables anticipation of complications and avoidance of triggering factors. It also allows genetic counselling. Multiple genetic causes that play an important role in the pathophysiology of chronic pancreatitis have been identified over the last few decades. These include the cystic fibrosis transmembrane conductance regulator (CFTR) gene, the cationic trypsinogen (PRSS1), anionic trypsinogen (PRSS2), serine protease inhibitor Kazal type 1 (SPINK1), and chymotrypsin-C (CTRC) genes (2). The SPINK1 protein secreted by the acinar cells of the pancreas prevents premature trypsinogen activity by inhibiting trypsin 1 and 2. Mutations in the SPINK1 gene lead to the lowering of trypsin inhibitory function and triggering of autodigestion of the pancreatic tissue. In 2000, it was identified that a mutation of its gene induces autodigestion of the pancreatic tissue and causes subsequent pancreatitis (3). In addition, knock-out mice models showed novel insights into the role of SPINK1 in pancreatic development and pancreatitis. SPINK1 is known to have a role in autocrine and/or paracrine factors involved in the development of primary tumours particularly pancreatic cancer, colorectal cancer, and metastatic spread of cancer (4). Considering its prominent role in cancer development, genetic diagnosis is critical for early diagnosis and regular surveillance of cancer. Diagnosis of the underlying genetic cause is also important to predict recurrence and educate patients on being vigilant of symptoms and start prompt hydration once feeling symptomatic and on the importance of restricting fat in the diet.

We report the first child from the Arab region presenting with acute recurrent pancreatitis progressing to chronic pancreatitis due to underlying combined heterozygous mutations in the SPINK1 gene at the early onset of 7 years of age. We hypothesize that severe obesity can be a possible triggering factor of pancreatitis, considering that the mother, who did not have obesity, carries the same mutations and never had pancreatitis.

![Figure 1](https://edm.bioscientifica.com/)

**Figure 1**
Growth chart showing BMI between the age of 4 and 14 years.

![Figure 2](https://edm.bioscientifica.com/)

**Figure 2**
Patient photo showing acanthosis nigricans on the neck.
Case presentation

We report the case of an Arab Emirati girl who presented with severe abdominal pain at the age of 7 years and was diagnosed with acute pancreatitis. Her presentation recurred at a frequency of three episodes per year. During the acute episodes, she complains of severe epigastric, right hypochondrial pain radiating to the back with nausea and vomiting. The pain was mostly severe enough to require hospital admission. She had no clear trigger for the acute episodes, but she reported having high-fat-containing meals in some of the episodes. On the latest admission at the age of 14 years, her weight was 117.2 kg and BMI was 49.4 kg/m².

Her parents were first-degree cousins. However, neither had obesity. The mother presented with type 2 diabetes at the age of 40 years. Her BMI was 27.3 kg/m². Mother is currently on 1000 mg of metformin daily with glycated hemoglobin (HbA1c) of 5.9% and a BMI of 26.9 kg/m². There is no family history of pancreatitis in the mother or any other family members. The patient had seven siblings who were all well except for a younger sister who had a global developmental delay with undiagnosed underlying aetiology. Our patient was noted by the parents to have obesity from the age of 2 years. Growth chart from her medical records showed that her BMI was above the 97th centile from the age of 4 years (Fig. 1). Her weight gain progressed steadily and was noted to have significant acanthosis nigricans (Fig. 2) and biochemical features of insulin resistance. She had tried lifestyle modification for years, but her obesity had progressed (Fig. 1). At the age of 12 years, she presented with polyuria and polydipsia. She was diagnosed with type 2 diabetes as her HbA1c was 6.5% with high fasting glucose readings ranging between 8.3 and 9.4 mmol. She experienced no symptoms suggestive of exocrine pancreatic function deficiency. The patient had no past history of trauma, recurrent infections, or any other systemic disease.

Investigation

Her investigations during the acute admissions showed very high amylase and lipase enzymes (Fig. 3). Her lipid profile showed mild elevation of triglycerides, but she had consistently normal total cholesterol, LDL, and HDL. C-peptide was low at 0.03 nmol/L with a normal range between 0.26 and 1.27. Her calcium, parathyroid hormone, and cortisol levels were normal. Anti-glutamic decarboxylase and insulin antibodies were negative.

Her abdominal CT scan showed an oedematous pancreas with peripancreatic oedema and fluid during the initial episode. The head of the pancreas showed a low attenuation suggesting possible necrosis with free fluid in the pelvis (Fig. 4A and B). Endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography showed no evidence of pseudocyst or bile duct abnormalities. At the age of 14, she had a whole-exome sequencing which showed two mutations at the SPINK1 gene. One is SPINK1,
M K Abbas and others

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Treatment

On the diagnosis of type 2 diabetes, she was started on metformin and is currently receiving 1 g daily. She is on no other medications. During her episodes of pancreatitis, she gets admitted to the hospital and receives conservative management with hydration and analgesics. Her metformin gets discontinued during her acute illness with glucose monitoring and strict diet control for glycemia management.

Outcome and follow-up

The patient was enrolled in an intensive follow-up for lifestyle changes under the supervision of a multidisciplinary team of specialist nurses, clinical dieticians, and psychologists. She remained on metformin with reasonable control of her glycemia. Pancreatitis episodes remained at a frequency of three times per year. Her weight was not significantly reduced on the lifestyle changes but remained stationary lately. She was kept under follow-up for the management of diabetes and other obesity comorbidities.

Discussion

Diagnosis of chronic pancreatitis at a young age in the absence of anatomical abnormalities of the pancreatic-biliary duct system or lipid abnormalities should prompt clinicians to the diagnosis of hereditary pancreatitis and requesting a genetic analysis. A cross-sectional study by Kumar et al. showed that pancreatitis-associated gene mutations like SPINK1 was the most common risk factor for acute recurrent pancreatitis in children under 19 years of age (5). SPINK1 mutation, in particular, is known to be associated with severe pancreatitis (1) and is significantly associated with faster progression to acute recurrent pancreatitis. In children, it is reported to cause acute recurrent pancreatitis progressing rapidly to chronic pancreatitis (6). This is in concordance with our patient, who presented with severe disease from the age of 7 and progressed to chronic pancreatitis within few years of presentation. Her episodes of disease presentation were severe enough to require hospitalization for hydration and parenteral administration of analgesics. In a study of chronic pancreatitis in children, the mean age of symptom onset was 5 years, with the most common symptoms being abdominal pain and vomiting. However, the mean age at symptom onset was 20.0 years with SPINK1 mutations in a Japanese nationwide survey which enrolled 271 hereditary pancreatitis patients from 100 families.

Figure 4
CT scan abdomen showing (A) oedematous pancreas with peripancreatic edema and fluid with low attenuation of head of pancreas suggesting necrosis and (B) coronal section showing oedematous pancreas and free pelvic fluid.

Figure 4

The patient was enrolled in an intensive follow-up for lifestyle changes under the supervision of a multidisciplinary team of specialist nurses, clinical dieticians, and psychologists. She remained on metformin with reasonable control of her glycemia. Pancreatitis episodes remained at a frequency of three times per year. Her weight was not significantly reduced on the lifestyle changes but remained stationary lately. She was kept under follow-up for the management of diabetes and other obesity comorbidities.

Discussions

Diagnosis of chronic pancreatitis at a young age in the absence of anatomical abnormalities of the pancreatic-biliary duct system or lipid abnormalities should prompt clinicians to the diagnosis of hereditary pancreatitis and requesting a genetic analysis. A cross-sectional study by Kumar et al. showed that pancreatitis-associated gene mutations like SPINK1 was the most common risk factor for acute recurrent pancreatitis in children under 19 years of age (5). SPINK1 mutation, in particular, is known to be associated with severe pancreatitis (1) and is significantly associated with faster progression to acute recurrent pancreatitis. In children, it is reported to cause acute recurrent pancreatitis progressing rapidly to chronic pancreatitis (6). This is in concordance with our patient, who presented with severe disease from the age of 7 and progressed to chronic pancreatitis within few years of presentation. Her episodes of disease presentation were severe enough to require hospitalization for hydration and parenteral administration of analgesics. In a study of chronic pancreatitis in children, the mean age of symptom onset was 5 years, with the most common symptoms being abdominal pain and vomiting. However, the mean age at symptom onset was 20.0 years with SPINK1 mutations in a Japanese nationwide survey which enrolled 271 hereditary pancreatitis patients from 100 families.

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Our patient is among the youngest presenting with pancreatitis induced by SPINK1 mutations. Her genetic testing showed two mutations in the SPINK1 gene; one is c.101A>G p.(Asn34Ser), causing an amino acid change from asparagine to serine at position 34, and the other is SPINK1, c.56-37T>C. While there are approximately 20 types of SPINK1 gene mutations, p.N34S mutation is the most common (8). The SPINK1 variant c.56-37T>C is reported to be associated with the most significant risk factor for chronic pancreatitis. Our patient harboured both of these mutations, which induced a severe form of chronic pancreatitis. Variations in the SPINK1 gene are frequently observed in fibrocalculous pancreatic diabetes who have evidence of chronic pancreatitis and ductal calcification (9). Our patient had no evidence of ductal calcification, and we diagnosed and treated her diabetes as type 2 diabetes secondary to severe obesity and insulin resistance. The impact of obesity on pancreatitis in children is not fully defined. In the INSPIRE cohort, children with obesity presented with pancreatitis later compared to normal-weight children (10). However, long-term studies in this regard are lacking. SPINK1 gene mutations have been postulated to act as a disease modifier requiring additional disease triggers or mutations in a more complex genetic model. These mutations have been identified in healthy people. Thus, the role of SPINK1 mutations in acute recurrent pancreatitis and chronic pancreatitis remains to be further defined. In this case report, we propose that SPINK1 mutations detected in our patient and her mother induced pancreatitis in the child with severe obesity, while the mother who did not have obesity was spared. In conclusion, we describe a rare case of combined SPINK1 gene mutations inducing an early-onset acute recurrent/chronic pancreatitis. She is the first patient to be reported with pancreatitis with an underlying SPINK1 mutation in the Arab region and, to the best of our knowledge, the youngest to present with SPINK1-induced pancreatitis in association with severe obesity reported in the literature.

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Patient consent
The mother of the patient gave written consent to publish the child’s case and to include the clinical photo and images.

Author contribution statement
M K Abbas wrote the initial draft of the manuscript and collected the data of the investigations. A Al Shamsi is the clinical geneticist who requested the genetic testing, counselled the patient and family, and revised the genetic part of the manuscript. I Jan is the pediatric surgeon who was involved in clinical care of the child during the hospital admission. He revised the final version of the manuscript. M S Masalawala revised the writing as per the journal requirement and submitted the manuscript. A Deeb is the primary physician for the patient who recognized the suitability of the case for publication, searched the literature, liaised between co-authors, and wrote the final manuscript.

References
1. Koziel D, Gluszek S, Kowalik A, Chlopek M & Pieciak L. Genetic mutations in SPINK1, CFTR, CTRC genes in acute pancreatitis. BMC Gastroenterology 2015 15 70. (https://doi.org/10.1186/s12877-015-0302-6)
2. Wang W, Sun XY, Weng XL, Zhou DZ, Sun C, Xia T, Hu LH, Lai XW, Ye B, Liu MY, et al. Comprehensive screening for PRSS1, SPINK1, CFTR, CTRC and CLDN2 gene mutations in Chinese paediatric patients with idiopathic chronic pancreatitis: a cohort study. BMJ Open 2013 3 e003150. (https://doi.org/10.1136/bmjopen-2013-003150)
3. Frossard JL & Morris MA. Two SPINK1 mutations induce early-onset severe chronic pancreatitis. Case Reports in Gastroenterology 2017 11 85–88. (https://doi.org/10.1159/000466564)
4. Cazacu IM, Farkas N, Garami A, Balaskó M, Mosdósi B, Alizadeh H, Gyongyi Z, Rakontzczay Jr Z, Vigh É, Habon T, et al. Pancreatitis-associated genes and pancreatic cancer risk: a systematic review and meta-analysis. Pancreas 2018 47 1078–1086. (https://doi.org/10.1097/MPA.0000000000001815)
5. Kumar S, Ooi CY, Werlin S, Abu El Hajja M, Barth B, Bellin MD, Durie PR, Fishman DS, Freedman SD, Gariepy C, et al. Risk factors associated with pediatric acute recurrent and chronic pancreatitis: lessons from INSPIRE. JAMA Pediatrics 2016 170 562–569. (https://doi.org/10.1001/jamapediatrics.2015.4955)
6. Liu QY, Abu-El-Hajja M, Husain SZ, Barth B, Bellin M, Fishman DS, Freedman SD, Gariepy CE, Giefer MJ, Gonska T, et al. Risk factors for rapid progression from acute recurrent to chronic pancreatitis in children: report from INSPIRE. Journal of Pediatric Gastroenterology and Nutrition 2019 69 206–211. (https://doi.org/10.1097/MPG.0000000000002405)
7. Masamune A, Kikuta K, Hamada S, Nakano E, Kume K, Inui A, Shimizu T, Takeyama Y, Nio M & Shimosogawa T. Nationwide survey of hereditary pancreatitis in Japan. Journal of Gastroenterology 2018 53 152–160. (https://doi.org/10.1007/s00535-017-1388-0)
8. Witt H, Luck W, Hennies HC, Claesen M, Kage A, Laß U, Landt O & Becker M. Mutations in the gene encoding the serine protease inhibitor, Kazal type 1 are associated with chronic pancreatitis. Nature Genetics 2000 25 213–216. (https://doi.org/10.1038/76088)
9 Kolly A, Shivaprasad C, Pulikkal AA, Atluri S, Sarathi V & Dwarakanath CS. High prevalence of serine protease inhibitor Kazal type 1 gene variations detected by whole gene sequencing in patients with fibrocalculous pancreatic diabetes. *Indian Journal of Endocrinology and Metabolism* 2017 **21** 510–514. (https://doi.org/10.4103/ijem.IJEM_116_17)

10 Uc A, Zimmerman MB, Wilschanski M, Werlin SL, Troendle D, Shah U, Schwarzenberg SJ, Rhee S, Pohl JF, Perito ER, et al. Impact of obesity on pediatric acute recurrent and chronic pancreatitis. *Pancreas* 2018 **47** 967–973. (https://doi.org/10.1097/MPA.0000000000001120)

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