Case Report

# Hereditary Chronic Pancreatitis in a Patient with Type 1 Diabetes Mellitus

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## Abstract

In this case report, we present a young patient with type 1 diabetes who had hereditary chronic pancreatitis. We evaluated him for the cause of pancreatitis, but it was inconclusive and finally the genetic testing was done for him, which revealed heterozygous missense mutation in exon 3 of the *PRSS1* gene (protease serine 1 gene) on chromosome 7. Hence, we were able to make the diagnosis of hereditary chronic pancreatitis. Chronic pancreatitis secondary to any cause can lead to permanent diabetes, which is typically difficult to control. However, in this case, the episodes of recurrent pancreatitis were present after the onset of type 1 diabetes as compared to the usual presentation of diabetes after the advancement of chronic pancreatitis.

**Keywords:** Abdominal pain, hereditary chronic pancreatitis, type 1 diabetes mellitus

## Introduction

Pancreatic disease is a rare cause of diabetes. Chronic pancreatitis leads to both exocrine and endocrine dysfunction. Chronic pancreatitis secondary to any cause can lead to permanent diabetes, which is typically difficult to control. Hereditary chronic pancreatitis is a rare entity, inherited in an autosomal dominant fashion. Mutations in a number of genes such as *PRSS1* (encoding cationic trypsinogen), serine protease inhibitor, Kazal type 1 (*SPINK1*) and cystic fibrosis transmembrane conductance regulator (*CFTR*) have been implicated as a cause of chronic pancreatitis. While diabetes can occur in a known case of chronic pancreatitis, ketoacidosis is rare.[1] In this case study, we report a patient with autoantibody-positive type 1 diabetes who was found to have hereditary chronic pancreatitis.

## Case Report

A 14-year-old boy studying in class IX with good scholastic performance was admitted to our hospital with chief complaints of upper abdominal pain associated with nausea and vomiting for 1 day. The vomitus was greenish-yellow in colour, and there were 3–4 episodes of vomiting. He was apparently normal until 3 months ago, when he started developing abdominal pain, which was mild initially. Gradually, it increased in intensity and severity. It was associated with 2–3 episodes of green-coloured vomitus. He was admitted to a private hospital for 6 days and was diagnosed to have acute pancreatitis. He had undergone MR cholangiopancreatogram, which was normal.

### Diabetic history

He was a known case of type 1 diabetes with glutamic acid decarboxylase autoantibody positivity (>150 IU/ml) and nearly absent C-peptide (fasting value was 0.2 pmol/L and stimulated value was 0.3 pmol/L) for the past 5 years. He was detected to have diabetes at the age of 9 years. There was a family history of type 1 diabetes mellitus (DM) (in one of the cousins on the paternal side, with onset at the age of 8 years). Pedigree chart is presented in Figure 1. He was originally diagnosed to have diabetes at our centre when he presented with diabetic ketoacidosis. He had been treated with basal-bolus insulin

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regimen (total 48 Units). He was on regular follow-up, and in view of recurrent hypoglycaemia, he had been counselled regarding initiation of continuous subcutaneous insulin infusion (CSII) pump.

## Birth history

He was a full-term baby and his mother had gestational DM during pregnancy. He was delivered by caesarean section and his birth weight was 5 kg. All vaccinations were given in his childhood as per schedule. All developmental milestones were attained at appropriate age.

## Physical examination

He was conscious, oriented, afebrile, dehydrated, not anaemic or jaundiced. Acanthosis nigricans was present in both armpits. His weight was 71.5 Kg, height was 170 cm and body mass index was 24.7 kg/m$^2$. Pulse rate was 108 beats/min and BP was 128/78 mmHg. On palpation of the abdomen, there was no tenderness, guarding, rigidity or organomegaly.

## Course in hospital

On the day of admission, random blood sugar was 416 mg/dl (23.1 mmol/L). Glycosylated haemoglobin was 8.9%. Serum beta-hydroxybutyrate level was significantly elevated (3.60 mmol/L [reference 0.03–0.30 mmol/L]). Serum amylase and serum lipase levels were markedly elevated: 762 IU/L (reference 28–100 IU/L) and 999 IU/L (reference 13–60 IU/L), respectively. Renal function test showed blood urea of 37 mg/dl and serum creatinine of 0.9 mg/dl. Lipid profile showed elevated serum cholesterol of 206 mg/dl (<200 mg/dl), serum triglyceride of 214 mg/dl (<150 mg/dl), high-density lipoprotein cholesterol of 48 mg/dl (>40 mg/dl) and LDL cholesterol of 115 mg/dl (<100 mg/dl). Serum calcium level was 9.9 mg/dl. Liver function test, thyroid function test, haemogram and serum electrolytes were within normal limits. Retinal examination showed no evidence of diabetic retinopathy.

Ultrasonography of whole abdomen revealed mild enlargement of body of the pancreas with hypoechotexture and minimal peripancreatic inflammatory changes, and minimal free fluid in the hepatorenal pouch and both iliac fossae. The features were suggestive of pancreatitis with no focal collection/necrosis.

He was admitted in the Intensive Care Unit and was treated with intravenous (IV) insulin infusion pump, IV fluids, IV antacids, IV antiemetics and other supportive measures. For fluctuating blood sugar levels, he was subsequently initiated on CSII pump with 2 basal infusion rates and 4 boluses (total daily dose = 50 Units), with which blood glucose levels were stabilised. After four days, his serum amylase and serum lipase decreased to 156 IU/L and 108 IU/L, respectively, and he felt symptomatically better.

He was readmitted twice in the 2 months following initial hospitalisation, with similar complaints. The levels of serum amylase and lipase during each hospitalisation are shown in Figure 2.

Tissue transglutaminase antibody was 3.3 U/mL (<4.0 U/mL – negative), Serum parathyroid hormone level was 14.09 pg/mL (reference 15–65 pg/mL). Serum IgG4 antibody level was 1.33 g/L (reference 0.049–1.985 g/L), thereby ruling out the possibility of autoimmune pancreatitis. MR cholangiopancreatogram was performed subsequently, showing mild relative loss of normal T1 hyperintensity in the pancreas, no evidence of pancreatic enlargement or restricted diffusion or peripancreatic inflammatory changes, pancreas divisum or calcification or common bile duct calculi. Hence, obstructive aetiology was ruled out.

Endoscopic ultrasound showed pancreatic parenchymal hyperechoic foci, strands and few lobulations along its entire length. The main pancreatic duct was normal in calibre in its entire length with hyperechoic wall. Parenchymal features were suggestive of chronic pancreatitis – small duct variant.

Genetic testing for hereditary pancreatitis genes showed a known heterozygous missense mutation in exon 3 of the PRSS1 gene (protease serine 1 gene) on chromosome 7 that results in substitution of lysine for glutamic acid at codon position 79. Mutation in this gene has been implicated in chronic pancreatitis. This mutation has been previously reported in a French cohort of patients with idiopathic chronic pancreatitis.

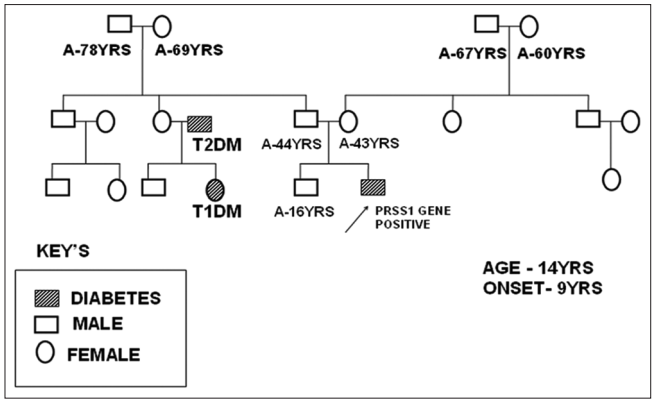


**Figure 1:** Pedigree chart

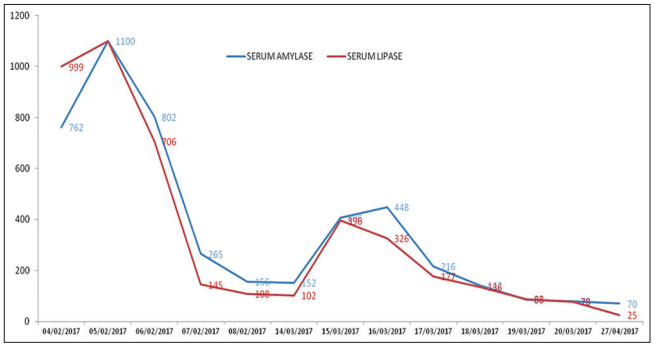


**Figure 2:** Trend of serum amylase and lipase levels during each hospitalisation

## Discussion

The most common cause of chronic pancreatitis in the Western world is alcohol abuse, and in India, it is non-alcoholic or tropical chronic pancreatitis.[2] In children cystic fibrosis is the most common cause.[3] When no underlying cause is identified, it is termed as idiopathic pancreatitis. Among these, approximately 15% of patients may have pancreatitis due to genetic defects.[3] Diabetes is common in chronic pancreatitis and occurs more frequently with the advancement of the disease.

Hereditary pancreatitis is a rare disease that is similar to chronic pancreatitis except for early age of onset and evidence of hereditary factors. It has an autosomal dominant inheritance with approximately 80% penetration.

In 1952, Comfort and Steinberg were first to recognise the condition in an American Caucasian.[4] Most reports have come from the United States and European countries.[5] Whitcomb *et al*. studied several large families with hereditary chronic pancreatitis and were able to identify a genetic defect that affects the gene encoding for cationic trypsinogen (PRSS1), the hereditary pancreatitis gene on chromosome 7.[6] The R122H and the N29I mutations are the most common PRSS1 mutation. Another variant of PRSS1, A16V mutation has been identified recently which have been associated with increased risk of pancreatitis.[5] The codon 122 plays an important role in the 'Fail-Safe Mechanism', that is, degradation of prematurely activated trypsin in the pancreas. This R122H mutation leads to a substitution of the corresponding arginine with another amino acid, usually histidine which eliminates the fail-safe mechanism and would increase intrapancreatic trypsin activity. The defect will also disturb the balance of proteases and their inhibitors within the pancreas and eventually provoke autodigestion of the organ, later on progressing to chronic pancreatitis.[3]

Additional genes have been associated with chronic pancreatitis (idiopathic and hereditary), such as the anionic trypsinogen (PRSS2), the SPINK 1 and the CFTR.[7] SPINK1, a 56-amino acid peptide, is a potent protease inhibitor and is considered to be a specific inactivation factor for intrapancreatic trypsin activity.[3]

The clinical characteristics of hereditary pancreatitis are that it initially presents as acute pancreatitis (sudden onset, <6 months duration), then progresses to recurrent pancreatitis (more than one episode of acute pancreatitis) and finally culminates in chronic pancreatitis (duration more than 6 months).[8] These features were typically present in our case as well. The cardinal symptom is abdominal pain, and it would be the usual reason for seeking medical care. Since the pain is variable in character and severity, it is often ignored. There is also associated nausea and vomiting during the acute stage.[1] In the absence of complications, the acute episodes remit gradually, and the patient will recover within 4–7 days. As age advances the frequency of acute episodes becomes less severe.[4] As the attacks of pancreatitis can lead to severe parenchymal destruction, the patients will also have symptoms of exocrine and endocrine pancreatic insufficiency.[7]

Other rare differential diagnoses are hyperlipidaemia type I, familial (hypocalciuric) hypercalcaemia, hereditary hyperparathyroidism and autoimmune pancreatitis which have been ruled out in this case.

Pain can be very difficult to manage in these cases. For alleviation of pain, analgesics (acetaminophen, non-steroidal anti-inflammatory drugs and narcotics) are widely used. Antioxidants can be utilised in pain reduction as they can reduce the oxidative stress to acinar cells. Surgical or endoscopic interventions are effective modalities in pain relief as well. It has been recently established in the United States that total pancreatectomy with islet autotransplantation appears to be effective in some patients.[5]

In case of malabsorption, low-fat diet and pancreatic enzyme supplementations have been tried. Histamine H2 blocker or proton-pump inhibitor can be introduced before meals to reduce gastric acid secretion.[9] Other management options include pancreatic enzyme supplementation.

Insulin is required for glycaemic control in about 80% of the patients, but the requirement is usually low, around 30–40 units/day. Frequent and severe hypoglycaemic episodes that occur due to inappropriate glucagon response make the diabetes control difficult to achieve in these patients.[9] In our case, he was already on CSII pump as he was diagnosed to have type 1 diabetes before the onset of the episodes of pancreatitis.

Based on the evidence from the previous literature, individuals with pancreatic diabetes have similar risk of microvascular complications such as retinopathy, nephropathy and neuropathy to those with type 2 DM. However, the risks of macrovascular complications are found to be comparatively lower.[9]

The individual prognosis of HCP is unpredictable due to pancreatic cancer risk. The occurrence of pancreatic carcinoma in patients with hereditary pancreatitis is >50-fold higher, the cumulative risk being 40 – <54% at the age of 70. Smoking, alcohol consumption and diabetes mellitus further increase the risk.[5] HCP patients with PRSS1 mutation tend to have higher risk to develop pancreatic cancer compared to other mutations.[7]

In our case, after ruling out other causes of pancreatitis, the genetic testing alone helped us to clinch the diagnosis of hereditary pancreatitis. The other family members (including the cousin who had diabetes) did not have any history of episodes of pancreatitis. The presence of type 1 diabetes before the onset of pancreatitis is quite unusual as well.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients

understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

## References

1. Dimango EP, Layer P, Clain JE. Chronic pancreatitis. In: Go VL, Lebenthal E, DiMagno EP, Reber HA, Gardner JD, Scheele GA, editors. The Pancreas – Biology, Pathobiology and Disease. 2nd ed. Ch. 35. New York: Raven Press; 1993. p. 668-85.
2. Naik D, Thomas N. Secondary diabetes. In: Chandalia HB, Sridhar GR, Das AK, Madhu SV, Mohan V, Rao PV, editors. RSSDI Textbook of Diabetes Mellitus. 3rd ed. Ch. 26. Jaypee Brothers Medical Publishers;2014. p. 392-426.
3. Conwell DL, Banks P, Greenberger NJ. Acute and chronic pancreatitis. In: Kasper DL, Hauser SL, Jameson JL, Fauci AS, Longo DL, Loscalzo J, editors. Harrison's Principle of Internal Medicine. 19th ed. Ch. 371. New York: Mc Graw Hill; 2015. p. 2090-102.
4. Garza JA, Hill ID, Lebenthal E. Hereditary pancreatitis. In: Go VL, Lebenthal E, DiMagno EP, Reber HA, Gardner JD, Scheele GA, editors. The Pancreas – Biology, Pathobiology and Disease. 2nd ed. Ch. 56. New York: Raven Press; 1993. p. 1095-101.
5. Shelton CA, Whitcomb DC. Hereditary Pancreatitis. American Pancreatic Association, Pancreapedia; 2016. p. 1-14.
6. Whitcomb DC, Preston RA, Aston CE, Sossenheimer MJ, Barua PS, Zhang Y, *et al.* A gene for hereditary pancreatitis maps to chromosome 7q35. Gastroenterology 1996;110:1975-80.
7. Rosendahl J, Bödeker H, Mössner J, Teich N. Hereditary chronic pancreatitis. Orphanet J Rare Dis 2007;4:1.
8. Solomon S, Whitcomb DC, LaRusch J. PRSS1-related hereditary pancreatitis. 01 March, 2012. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJ, *et al*., editors. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993-2017.
9. Unnikrishnan R, Mohan V. Pancreatic diseases and diabetes. In: Holt RI, Cockram CS, Flyvbjerg A, Goldstein BJ, editors. Textbook of Diabetes. 5th ed. Ch. 21. UK: John Wiley & Sons Ltd.; 2017. p. 291-305.