Case Report

Beyond the Common Cause: Recurrent Pancreatitis Due to Carboxypeptidase A1 Mutation

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Abstract

Background: Acute pancreatitis is a condition characterised by inflammation that may affect the pancreas and adjacent tissues and distal organ systems, with an incidence of 5 to 50 per 100,000 populations. In India, the incidence of pancreatitis is 2.6-3.2 cases per 100,000 individuals.[1] The following case report is of a young female presenting with recurrent pancreatitis who was evaluated and found to have a Carboxypeptidase A1 mutation in a tertiary care hospital in Chennai.

Keywords: Recurrent pancreatitis, Hereditary pancreatitis, Carboxypeptidase A1.

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Introduction

The main function of the exocrine pancreas is to produce digestive enzymes that break down food in the small intestine.

The pancreas prevents its auto-digestion by four major mechanisms:

- Storage of its enzymes in precursor forms.
- Reduced intracellular calcium inactivates trypsin.
- Maintaining acid-base balance.
- Protective protease inhibitor enzymes that inactivate intracellular trypsin.

If any of these mechanisms are defective, premature enzyme activation and auto-digestion of the pancreas occur.

The very first step is the conversion of trypsinogen to trypsin in the acinar cells, which catalyzes the conversion of other proenzymes to active enzymes. This starts the dangerous cycle of releasing more active enzymes. The mechanisms that have been attributed to the pathogenesis of Acute pancreatitis are as follows: pathological calcium signaling, mitochondrial dysfunction, premature activation of trypsinogen in acinar cells and macrophages, endoplasmic reticulum stress (ERs), unfolded protein response (UPR), and impairment of autophagy.[2]

Recurrent acute pancreatitis episodes may result from chronic repetitive injury to the pancreas caused by alcohol, tobacco, or any other factor. This, in turn, activates pancreatic stellate cells (PSCs) and initiates fibrogenesis, ultimately leading to chronic fibrosing pancreatitis. These recurrent attacks may very often cause histopathological anomalies in the pancreas in a large number of people, some of whom may not exhibit any symptoms, without experiencing the clinical disease. The areas of pancreatic necrosis would be supplanted by fibrotic tissue after multiple attacks.[3]

Case Description

A 17-year-old female presented with complaints of abdominal pain for 3 days. She was apparently normal 3 days back when she had h/o abdominal pain for 3 days, insidious in onset, in the epigastric region radiating to the back. H/o vomiting for 2 days, 5-6 episodes /day, non-projectile, not blood or bile stained. She had no history of hospital admission or any other drug intake. She was born to non-consanguineous parents, and her birth history was uneventful. She had no significant family history of pancreatitis.

On examination, the patient was conscious, oriented, and of normal build. Her vitals were stable. Her abdominal examination showed epigastric tenderness radiating to the back.

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Her routine investigations showed:

HEMOGLOBIN	9.5 gm/dl
TOTAL COUNT	9400
PLATELET COUNT	102000
UREA/CREATININE	25/0.6 mg/dl
TOTAL/DIRECT BILIRUBIN	0.6/0.3 mg/dl
SGOT/SGPT	32/17
AMYLASE/LIPASE	770/530
SODIUM/POTASSIUM	129/4.4

CT ABDOMEN showed mild peripancreatic fluid collection, Abdominal lymphadenopathy, Mild hepatomegaly and features of acute pancreatitis.

CECT ABDOMEN showed features of acute necrotizing pancreatitis.

According to the Revised Atlanta Classification 2012 the patient was diagnosed as mild acute pancreatitis and was treated conservatively with Intravenous fluids and supportive care. After recovery Magnetic Resonance Cholangiopancreatography was done, and it showed features of acute pancreatitis with mild splenomegaly.

Oesophago-Gastro-Duodenoscopy was done which showed features of bulbar duodenitis. The patient recovered in the due course and was discharged.

The patient then had presented again after 1 year with the same clinical features. During the subsequent one year the patient had been admitted thrice with the same complaint and was diagnosed and treated as recurrent acute pancreatitis. We had ruled out the common causes of acute pancreatitis which are gall stones and alcohol. In order to rule out other causes further investigations were done.

In order to rule out autoimmune cause Anti nuclear antibodies was done which was negative C3, C4 was done which was normal.

After ruling out all the other possible causes of recurrent pancreatitis we proceeded with whole exome gene sequencing. Heterozygous variant of Carboxypeptidase A1 gene mutation was found.

A diagnosis of Recurrent pancreatitis due to Carboxypeptidase A1 mutation was made.

Discussion

Recurrent acute pancreatitis (RAP) is characterised by the lack of clear changes associated with chronic pancreatitis, at least two separate recorded bouts of pancreatitis, and a time of remission in between. The recurrence rate of acute pancreatitis is roughly twenty percent in the adult population and 23% in the paediatric population. The rate of progression into CP was 8% after AP and 24% after RAP.[4]

The causes of recurrent acute pancreatitis are

- Gall stones,
- Alcohol,
- Hypertriglyceridemia,
- Hypercalcemia,
- Anatomic variants like pancreatic divisum,annular pancreas.

Anatomical conditions connected to obstructive mechanisms, such as periampullary diverticula, benign and malignant tumours of the Vater's papilla or pancreatico-biliary junction, strictures of the main pancreatic duct, and cystic neoplasms like mucinous ductal ectasia, are also implicated. Less commonly associated conditions include choledochocele and ampullary choledochal cysts

- Idiopathic
- Genetic mutations.
- Autoimmune pancreatitis.

Hereditary Pancreatitis: A cross-sectional investigation of an international paediatric population was conducted recently, it was observed that 48% of patients with acute recurrent pancreatitis and 73% of chronic pancreatitis patients had at least one gene mutation associated with hereditary pancreatitis.[5]

The first significant pancreatitis related gene variant was mutation of the PRSS1 gene. Since then, numerous additional genes have been identified. Other noteworthy genes associated include, SPINK1, CFTR, CTRC, CPA1, calcium-sensing receptor (CASR) and claudin-2.

Hereditary pancreatitis seems to entangle an intricate interaction between environmental and genetic variables that result in pancreatic parenchymal injury by disrupting protease regulation.

CARBOXYPEPTIDASE A1-

Carboxypeptidases are enzymes that catalyze the cleavage of peptide bonds at the carboxyl end of proteins and peptides.

CPA1 (carboxypeptidase A1) mutations cause enzyme misfolding in vitro, resulting in reduced CPA1 secretion, intracellular retention and degradation, and associated Endoplasmic Reticulum stress with the development of chronic pancreatitis.[6]

Reduced secretion, intracellular retention, and disintegration were among the misfolding phenotypes that the CPA1-mutated animal in the Hegyi E. et al. research demonstrated. The cells also experienced significant Endoplasmic Reticulum stress as a result of it. Atrophy in the Cpa1 N256K strain was confirmed by pancreatic weight measurements, which corresponded to a 35–40% reduction at 6 months of age. Histological sections from CPA1 N256K mice demonstrated progressive pathological alterations, including a loosely organized tissue architecture resulting from acinar loss, infiltration of inflammatory cells, formation of pseudotubular complexes, and increased acinar cell vacuolization observed over time.[7]

PRSS1-PROTEASE SERINE 1

Pathogenic variations of PRSS1 have been identified in over 60% of large families affected by Hereditary pancreatitis, and they have been passed down through multiple generations. The penetrance of these mutations is as high as 93%, and they are inherited in an autosomal dominant manner.The R122H mutation is a gain of function mutation that suppresses trypsin autolysis, thereby increasing trypsin stability and facilitating improved enzyme activation and pancreatic digestion.In the same vein, the N29I mutation leads to an increase in the auto-activation of trypsin, which in turn enables the unimpeded auto-digestion of the pancreas.As a result, the clinic presentation of R122H and N29I mutations is generally comparable. Whereas the mechanism by which the A16V PRSS1 gene variant cause disease is not understood. The A16V mutation is believed to increase the secretion of the CTRC protein, which in turn results in a rise by four times in trypsin activation, according to certain data.

SPINK1 -serine peptidase inhibitor, Kazal type 1

In normal individuals, SPINK1 can inhibit a maximum upto 13% of trypsin potential. SPINK1 mutations are present in 6.4% to 43% of those diagnosed with idiopathic pancreatitis [8]. Since the incidence of heterozygous p.N34S mutation in the general population was estimated to be 1% to 2%, the existence of the SPINK1 p.N34S variation alone is inadequate to explain the development of chronic pancreatitis. Therefore, in the context of other risk factors for pancreatic inflammation, such as genetic or environmental/lifestyle variables, the SPINK1 p.N34S variation may be accounted as a disease modifier rather than an underlying cause of chronic pancreatitis.

Cystic fibrosis (CF)-Cystic fibrosis transmembrane conductance regulator: Cystic fibrosis is an autosomal recessive disorder caused by mutations in a gene encoding a chloride and bicarbonate channel located on the apical membrane of epithelial cells across multiple organ systems. These mutations lead to reduced chloride secretion and increased sodium reabsorption into the intracellular space. Enhanced sodium uptake promotes greater water reabsorption, resulting in thickened mucus along epithelial surfaces and dense secretions from exocrine tissues. The accumulation of viscous mucus in most affected organs causes mucous plugging and obstructive pathology. Commonly involved organs include the sinuses, lungs, pancreas, biliary and hepatic systems, intestines, and sweat glands.

The epidemiological analyses have demonstrated that even though one allele is sufficient to maintain the homeostasis, the carriers are at an elevated risk of developing 59 distinct medical conditions, with a fourfold increased risk of idiopathic chronic pancreatitis and recurrent sinopulmonary infections, infertility etc.[9]

CFTR modulators like Ivacaftor have been shown to be an effective drug therapy for reducing pancreatitis episodes and also improving the exocrine pancreatic function.

CASR-CALCIUM SENSING RECEPTOR GENE-

The calcium-sensing receptor is a transmembrane receptor that is coupled to G proteins and is expressed in the parathyroid glands and kidneys, where it plays a key role in maintaining calcium homeostasis. Elevated serum calcium levels activate this receptor, leading to intracellular signaling that suppresses parathyroid hormone (PTH) secretion and calcium reabsorption. Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant condition characterised by increased serum calcium and reduced urinary calcium excretion, the result of heterozygous inactivating mutations in CASR. In the pancreas, CASR regulates the calcium concentration of pancreatic juice by enhancing ductal fluid secretion, potentially through activation of CFTR. The most compelling evidence that CASR mutations may play a role in pancreatitis is the very high incidence of pancreatitis in FHH. Rather than the local consequences of inactivating CASR mutations in the pancreas, hypercalcemia is likely the aetiology of FHH-associated pancreatitis.[10] In persons with familial hypocalciuric hypercalcemia (FHH) due to heterozygous mutations that resulted in CASR inactivation and who also had a heterozygous SPINK1 p.N34S risk variation, the calcium-sensing receptor gene was shown to be a possible candidate for a chronic pancreatitis risk.[11] Additionally, compound heterozygosity for SPINK1 p.N34S and CASR mutations was confirmed in certain Indian patients with tropical pancreatitis.[12]

CLDN2

CLDN2 encodes claudin-2 (CLDN2), a paracellular cation-selective channel that is seen in the pancreas and other secretory organs and is localised at tight junctions. CLDN2 is essential for the secretion of fluids that are cAMP-driven and CFTR-dependent, as well as for the transport of water that is dependent on sodium. These results indicate the correlation between CLDN2 and CFTR, which is crucial for fluid transport in the pancreatic ductal epithelium. Additionally, it safeguards against pancreatitis by regulating pancreatic ductal secretion to prevent the deterioration of auto-digestion and inflammation. CLDN2 up-regulation during pancreatitis may serve as a protective mechanism by restricting the progression of the disease, while a reduction in CLDN2 function may exacerbate the severity of pancreatitis.[13]

Conclusion

Genetic or Hereditary causes of pancreatitis contributes as a major cause of pancreatitis classified as idiopathic. In the above said case in-spite of not having a clear family history further evaluation has uncovered a rare genetic mutation.

The patient is now under regular follow up with annual HbA1c, Fecal Elastase and Endoscopic ultrasound.

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Conflicts of interest

There are no conflicts of interest.

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