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Rare cause of recurrent acute pancreatitis in teenage man

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BACKGROUND

The patient, an 18-year-old Chinese male, has a medical history of eight episodes of recurrent acute pancreatitis occurring over the span of 17 months. For each episode of acute pancreatitis, clinical presentations were characterised by acute abdominal pain (Numeric Rating Scale ranging from 6 to 9), low back discomfort, fever (Tmax 38.5°C), nausea, oliguria, abdominal bloating and obstipation. Abdominal pain could be relieved by fetal position. The duration of symptoms ranged from 4 days to 2 weeks. The patient reported a weight loss of 20 kg over 17 months. Additionally, during hospitalisation, the patient exhibited a depressed mood and requested to discontinue treatment.

ESTABLISHING THE DIAGNOSIS OF RECURRENT ACUTE PANCREATITIS

Laboratory tests revealed elevated serum amylase (AMY ranged from 239 to 996 U/L; normal range, 36–143 U/L), alkaline phosphatase (ranged from 134 to 161 U/L; normal range, 35–100 U/L), gamma-glutamyl transferase (GGT ranged from 42.5 to 256 U/L; normal range, 7–45 U/L) and total bilirubin (Tbil ranged from 21.4 to 76.1 µmol/L; normal range, 5.1–22.2 µmol/L) levels. The abdominal CT scan revealed peripancreatic inflammation and effusion, hepatomegaly and decreased liver parenchymal density (figure 1). MRCP findings were consistent with acute pancreatitis. According to the Revised Atlanta Classification,[1] the diagnosis of acute pancreatitis was confirmed for each episode based on the patient (1) experiencing abdominal pain indicative of pancreatitis, (2) having serum AMY or lipase levels exceeding three times the upper normal limit and (3) exhibiting characteristic imaging findings, meeting all three diagnostic criteria. Recurrent acute pancreatitis (RAP) refers to repeated episodes of acute inflammation of the pancreas. Unlike chronic pancreatitis, where there is ongoing, irreversible damage and inflammation, RAP involves discrete episodes of inflammation separated by periods during which the pancreas returns to normal or near-normal function, which is seen in this patient. Based on meeting the criteria of experiencing two or more well-documented separate attacks of acute pancreatitis with complete resolution for more than 3 months between attacks, the diagnosis of recurrent acute pancreatitis is established.[2]

SCREENING FOR THE CAUSE OF RECURRENT ACUTE PANCREATITIS

Since the diagnosis of recurrent acute pancreatitis in this patient was undoubtedly established, the goal is to identify potential causes of recurrent acute pancreatitis to prevent the recurrence. In children of the same age group as this patient (11–20 years), known risk factors include but are not limited to biliary tract diseases, medication use, systemic disease, inborn errors of metabolism and metabolic disorders.[3] In the case of this patient, imaging findings did not support the presence of biliary tract diseases including gallstones, and there was no history of medication and alcohol use. Serum triglyceride levels were within the normal range, and there were no other metabolic diseases. Additionally, immunological screening was negative. Consequently, these common etiologies of acute pancreatitis were ruled out.

Genetic testing for susceptibility to acute pancreatitis is considered if a patient has a history of unexplained repetitive episodes of acute pancreatitis in childhood, particularly if the onset is before 30 years of age.[4 5] Given this guideline, the patient was advised to undergo whole exome sequencing, which did not reveal any known genetic predisposition associated with pancreatitis, including variants in Cystic Fibrosis Transmembrane Conductance Regulator, Serine Peptidase Inhibitor Kazal Type 1, Chymotrypsin C and PRSS1.[3]

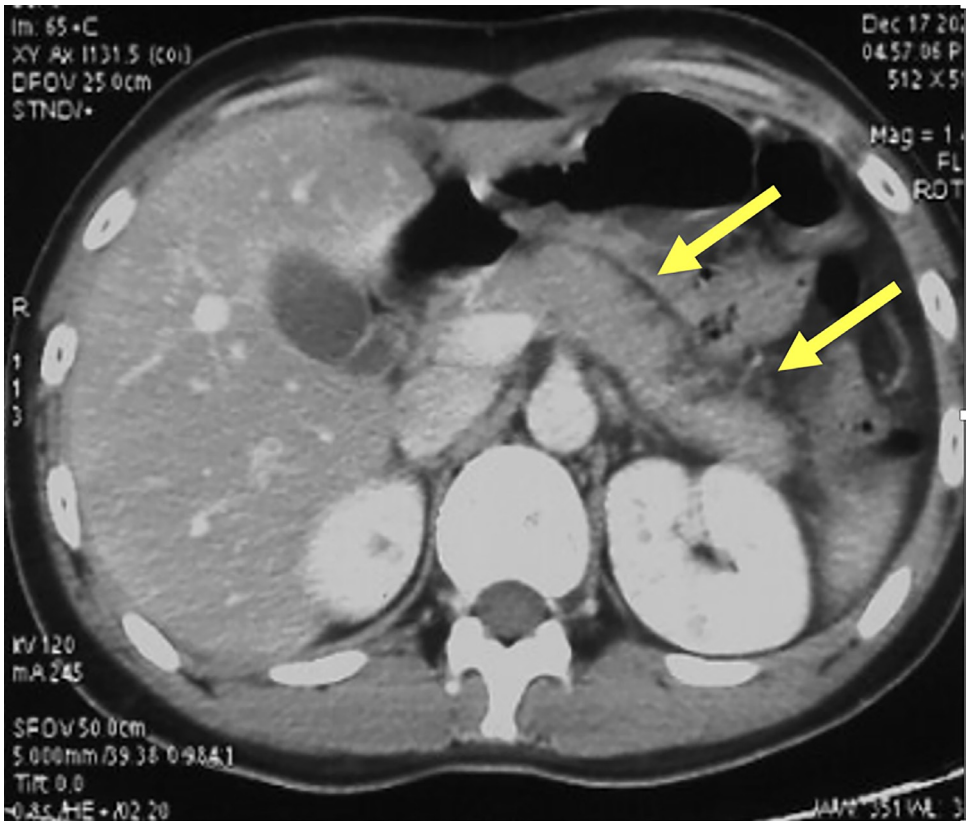

Figure 1 Image for contrast-enhanced abdominal CT scan. The CT scan was done on December 17 2021 during hospitalisation time of the second acute pancreatitis episode, showing pancreatic swelling and peripancreatic exudation. No apparent signs of parenchymal necrosis.

The result indicated a mutation in the SLC25A13 gene, which encodes a member of the mitochondrial carrier subfamily of solute carrier proteins. This mutation aligns with citrin deficiency, which is associated with neonatal intrahepatic cholestasis (NICCD) and adult-onset type II citrullinemia (CTLN2). Citrin deficiency is inherited in an autosomal recessive manner. Both parents are heterozygous carriers of pathogenic mutations in the SL25A13 gene, each carrying a different mutation. The patient happens to carry both mutated copies (figure 2).

OVERVIEW OF ADULT-ONSET CTLN2

Citrin deficiency, associated with mutations in the SLC25A13 gene, is a rare autosomal recessive disorder

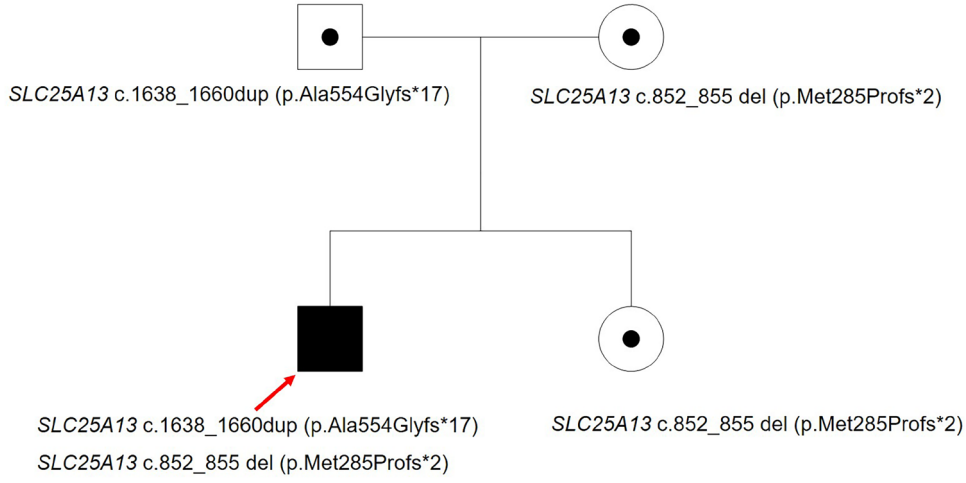

Figure 2 Pedigree of the family. Both parents of the patients harbour a pathogenic mutation in the SLC25A13 gene, leading to the condition observed in the offspring (patient indicated with red arrow). The sister of the patient inherited the pathogenic mutation of the SLC25A13 gene from their mother. As this disease follows an autosomal recessive pattern of inheritance, the sister did not exhibit any symptoms despite carrying the mutation.

primarily affecting liver function.[6] This disorder encompasses a spectrum of clinical manifestations, ranging from NICCD to CTLN2. NICCD typically presents in infancy with cholestasis, while CTLN2 manifests later in life with neuropsychiatric symptoms, hyperammonaemia and liver dysfunction. The pathogenesis involves impaired transport of aspartate from mitochondria to the cytosol, disrupting urea, protein and nucleotide synthesis pathways. While general incidence rates remain elusive, in the Japanese population, CTLN2 has a reported low prevalence of 1/100 000, while the carrier rate stands at approximately 1 in 65 or 1 in 42 based on analysis of the citrin-deficient gene.[7 8] The trigger of CTLN2 remains unclear, but factors such as alcohol consumption and excessive carbohydrate intake are suggested to contribute to its progression alongside citrin gene deficiency.[9] CTLN2 is primarily characterised by hyperammonemia and neuropsychiatric symptoms including abnormal behaviour, nocturnal delirium and seizures, the link between pancreatitis or pancreatic dysfunction and citrin deficiency is rare.[10] Ikeda *et al* have suggested that pancreatitis and type II citrullinemia cosegregate and a citrin deficiency plays an important role in causing chronic pancreatitis.[11] We also speculated adult-onset type II citrullinemia is the most likely cause for RAP in this patient. Serum amino acids and acylcarnitine profile analysis were performed considering this genetic metabolic disease in this patient. The citrulline level was elevated at 175.58 µmol/L, well above the normal range of 5.5–45 µmol/L. The ratios of citrulline/phenylalanine (Cit/Phe) were elevated, whereas the ratios of ornithine/citrulline (Orn/Cit) and glutamic acid/citrulline (Glu/Cit) were decreased (table 1). Laboratory analyses revealed increased plasma ammonia levels, along with elevated transaminases (AST and ALT) and GGT. All the findings strongly support the diagnosis of CTLN2.

Table 1 Report for amino acid profile analysis*

Amino acids	Unit (µmol/L)	Reference range (µmol/L)	
Alanine (Ala)	147.34	50.00–450.00	
Aspartic acid (Asp)	18.27	8.00–70.00	
Glutamic acid (Glu)	44.48	45.00–280.00	
Methionine (Met)	21.85	8.00–50.00	
Phenylalanine (Phe)	28.48	20.00–120.00	
Tyrosine (Tyr)	20.99	20.00–120.00	
Leucine (Leu)	68.18	40.00–250.00	
Tryptophan (Trp)	12.7	10.00–80.00	
Valine (Val)	104.06	50.00–280.00	
Arginine (Arg)	26.56	1.00–70.00	
Citrulline (Cit)	175.58	5.50–45.00	Elevated
Glycine (Gly)	156.35	65.00–450.00	
Ornithine (Orn)	54.45	7.00–120.00	
Glutamine (Gln)	16.23	1.00–55.00	
Histidine (His)	144.95	20.00–500.00	
Serine (Ser)	40.31	25.00–250.00	
Threonine (Thr)	100.02	10.00–150.00	
Proline (Pro)	655.28	250.00–2500.00	
Ratios of amino acids			
Arginine/ornithine (Arg/Orn)	0.49	0.05–2.80	
Citrulline/arginine (Cit/Arg)	6.61	0.25–16.50	
Ornithine/citrulline (Orn/Cit)	0.31	0.50–6.50	Decreased
Methionine/phenylalanine (Met/Phe)	0.77	0.12–1.50	
Leucine/phenylalanine (Leu/Phe)	2.39	0.75–5.50	
Phenylalanine/tyrosine (Phe/Tyr)	1.36	0.30–2.00	
Glycine/phenylalanine (Gly/Phe)	5.49	1.00–11.00	
Tyrosine/phenylalanine (Tyr/Phe)	0.74	0.30–3.50	
Glutamic acid/citrulline (Glu/Cit)	0.25	1.50–30.00	Decreased
Histidine/phenylalanine (His/Phe)	5.09	0.40–10.00	
Threonine/phenylalanine (Thr/Phe)	3.51	0.20–5.00	
Tryptophan/phenylalanine (Trp/Phe)	0.45	0.25–2.00	
Citrulline/phenylalanine (Cit/Phe)	6.17	0.10–1.20	Increased

Continued

TREATMENT OF ADULT-ONSET CTLN2

The primary therapeutic option for CTLN2 is liver transplantation. Management typically involves dietary protein restriction and arginine supplementation. Yet, recent findings suggest that the administration of medium-chain triglycerides (MCTs) along with a low-carbohydrate formula has demonstrated effectiveness in managing CTLN2.[12 13] Interestingly, Kakiuchi *et al* reported a case of patient with CTLN2 and chronic pancreatitis and pancreatic stones, who was treated with a high-fat diet and after 3 years of the treatment, this patient developed pancreatic pseudocyst and underwent endoscopic ultrasound-guided cyst drainage,[14] further highlighting that a more tailored nutritionally balanced diet would be helpful in CTLN2 patient with pancreatitis manifestations. Therefore, we decided to implement dietary restrictions, particularly limiting carbohydrate intake and incorporating MCTs in this patient.

Table 1 Continued

Amino acids	Unit (μmol/L)	Reference range (μmol/L)
Glutamic acid/ phenylalanine (Glu/ Phe)	1.56	0.70–8.00

Sample was collected on June 25, 2023 following consultation at the outpatient clinic and a multidisciplinary team (MDT) meeting on pancreas disorders. Sample was in the form of dried blood spots, and no visible abnormalities were presented.
*Reference ranges provided in this table may slightly vary across different clinical laboratories within a reasonable variation range.

MANAGEMENT OF THIS PATIENT AND PATIENT OUTCOME

Standard treatment of acute pancreatitis was given for this patient during each episode. That included fluid resuscitation, enteral feeding and analgesics. During the recovery phase of each acute pancreatitis episode, the focus involved limiting high-fat foods and a semi-liquid diet (low-fat, low-energy intake). Reduced exocrine pancreatic function might contribute to AP presentation.[15] Therefore, faecal elastase testing was performed to help confirm the presence of exocrine pancreatic insufficiency (EPI). The patient's low faecal elastase levels indicate impaired exocrine pancreatic function, prompting the administration of pancreatic enzyme replacement therapy (PERT) to aid digestion. However, recurrent episodes persisted, suggesting the ineffectiveness of the sole administration of PERT.

Therefore, dietary management was customised for this patient to prevent recurrence of AP. This patient was recommended to maintain the current carbohydrate intake (approximately 125–150 g/day) and protein intake (approximately 5–6 servings/day of protein-rich foods). MCTs, previously reported to be effective in CTLN2 management, were introduced at a dosage of 10–15 mL/day to substitute for conventional long-chain triglycerides, with the possibility of gradual escalation to 20–30 mL/day within a week. Long-term MCT intake was envisaged to exceed 50 mL/day. During the process of increasing fat intake, vigilance towards AP recurrence was advised. This involved close monitoring of gastrointestinal symptoms and periodical reassessment of bilirubin levels, liver function, blood ammonia levels and Sudan Ill staining of stools. Since the diagnosis of CTLN2, the patient has adhered strictly to the management regimen, and the current regimen of PERT was to be sustained at a dosage of 450 mg three times a day (150 mg preprandial, 300 mg intrameal, per os). Additionally, since vitamin D deficiency is present in this patient (25-hydroxy vitamin D level of 10.7 with the normal range of 20–40 ng/mL), as the result of EPI, vitamin D supplement (250 mg twice daily) was advised.

The combination of dietary management, PERT and vitamin D supplementation successfully prevented the recurrence of acute pancreatitis episodes since the start of this regimen in September, 2023. Additionally, it is known that patients with CTLN2 are prone to progressing into non-alcoholic fatty liver disease. Prolonged cholestasis carries the risk of irreversible liver failure, often resulting in the need for liver transplantation in CTLN2 patients.[13 16] Currently, the patient does not exhibit dyslipidaemia, such as high levels of low-density lipoprotein cholesterol and triglycerides, although ultrasound findings suggest potential fatty liver. Close monitoring of liver function and imaging is recommended to be repeated during each follow-up visit. Additionally, bone health is evaluated annually through bone density scans and serum vitamin D levels.

Contributors YL, DW, and LW planned the work. YL, JP and KP conducted the study and collected the data. JP, KP and LW drafted and revised the manuscript. LW is responsible for the overall content.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics Statement We received the verbal and written informed consent for this case report from the patient and his parents. The study was reviewed and approved by the Ethical Committee of Peking Union Medical College Hospital (I-24PJ1589).

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