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LOOKING BEYOND SEVERE HYPERTRIGLYCERIDEMIA WHEN DIAGNOSING ADULT-ONSET CITRULLINEMIA TYPE II

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ABSTRACT

Background: Adult-onset citrullinemia type II (CTLN2) is a rare autosomal recessive urea cycle disorder caused by mutations in the solute carrier family 25 member 13 (*SLC25A13*) gene, which encodes citrin–a mitochondrial transporter involved in the malate–aspartate shuttle. In adults, CTLN2 may present atypically as isolated hypertriglyceridemia, often misattributed to secondary dyslipidaemia.

Case description: A 30-year-old Vietnamese male with longstanding severe hypertriglyceridemia, first identified at age 13, was referred after an episode of acute pancreatitis at age 28. At presentation, plasma triglyceride levels reached 34.61 mmol/l. Secondary causes were excluded. Genetic testing via next-generation sequencing revealed compound heterozygous *SLC25A13* mutations: c.2T>C and c.1638_1660dup, resulting in p.Met1Thr and p.Ala554GlyfsTer17, confirming the diagnosis of CTLN2. Initiation of a low-carbohydrate, high-protein, low-fat diet combined with fenofibrate (145 mg/day) led to a rapid reduction in triglyceride levels, normalizing within two weeks and remaining stable over three months. The treatment was well tolerated, with no reported adverse effects.

Conclusion: CTLN2 should be considered in young adults with persistent, unexplained, and severe hypertriglyceridemia. Dietary modification constitutes the cornerstone of management, with fibrates playing a supportive role.

KEYWORDS

Adult-onset citrullinemia type II, SLC25A13, hypertriglyceridemia, carbohydrate-restricted diet

LEARNING POINTS

- Persistent, unexplained, and severe hypertriglyceridemia in young adults should prompt consideration of inherited metabolic disorders, including adult-onset citrullinemia type II (CTLN2).
- Genetic testing to detect compound heterozygous or homozygous *SLC25A13* variants is essential for definitive diagnosis of CTLN2.
- In CTLN2, dietary management with a low-carbohydrate, high-protein, low-fat represents the cornerstone, with fibrates serving as adjunctive lipid-lowering therapy.

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INTRODUCTION

Adult-onset citrullinemia type II (CTLN2) is a rare autosomal recessive metabolic disorder, with an estimated prevalence of 1 in 100,000 to 230,000 individuals in East Asian populations. It results from pathogenic variants in the *SLC25A13* gene, which encodes citrin – a mitochondrial aspartate – glutamate carrier involved in the malate–aspartate shuttle. This pathway is essential for urea synthesis, gluconeogenesis, and lipid metabolism. Citrin deficiency disrupts hepatic energy homeostasis and contributes to a spectrum of clinical manifestations[1]. Unlike classical urea cycle disorders, adult-onset CTLN2 typically does not present with hyperammonaemia and may manifest with nonspecific or atypical metabolic abnormalities. In certain cases, severe hypertriglyceridemia may be the only biochemical abnormality, often leading to misdiagnosis as primary or secondary dyslipidaemia. If unrecognized, CTLN2 can progress to acute pancreatitis or hepatic dysfunction[2]. Definitive diagnosis requires the identification of biallelic *SLC25A13* pathogenic variants. Importantly, standard dietary regimens such as high-carbohydrate or low-protein intake may aggravate the underlying metabolic derangements. Early recognition and initiation of targeted dietary therapy—characterized by carbohydrate restriction, moderate protein intake, and low-fat content—are critical to restoring metabolic stability. Fibrates may be used as adjunctive therapy to manage hypertriglyceridemia[3]. Here, we report a case of CTLN2 in a young male presenting with refractory hypertriglyceridemia, underscoring the importance of considering inherited metabolic disorders in the differential diagnosis of severe dyslipidaemia and the pivotal role of genetic testing in guiding therapy.

CASE DESCRIPTION

A 30-year-old Vietnamese male was referred for evaluation of persistent, severe hypertriglyceridemia and a prior episode of acute pancreatitis. His 23-year-old brother also had early-onset hypertriglyceridemia, with plasma triglyceride levels reaching 37 mmol/l at age 16, partially responsive to fibrates and currently controlled at 3.26 mmol/l with combined fibrate–statin therapy. Both parents had normal triglyceride levels, consistent with autosomal recessive inheritance.

The patient was first diagnosed with hypertriglyceridemia at age 13 but did not receive regular lipid-lowering therapy during adolescence. At age 28, he was hospitalized for acute pancreatitis with a recorded triglyceride level of 23 mmol/l. Post-discharge, he was initiated on combined fibrate–statin therapy; however, triglyceride levels remained markedly elevated (23–34 mmol/l). He denied alcohol consumption. His medical history was otherwise unremarkable, except for chronic hepatitis B. There was no history of diabetes, thyroid disease, or other metabolic disorders.

At presentation, the patient was hemodynamically stable with a body mass index of 22.2 kg/m^2 (height: 163 cm, weight: 59 kg). He reported intermittent dizziness and headache but denied gastrointestinal or neurological symptoms. Abdominal examination was benign with no hepatomegaly. There were no xanthomas, lipemia retinalis, or other clinical stigmata of dyslipidaemia. Cardiopulmonary and neurological examinations were unremarkable.

Plasma biochemistry revealed severe hypertriglyceridemia (34.61 mmol/l) with mild hypercholesterolemia. Liver enzymes were mildly elevated; however, serum amylase and ammonia levels remained within normal limits *(Table 1)*. Abdominal ultrasound showed a mildly coarse hepatic echotexture, and transient elastography indicated stage F1 fibrosis (according to the METAVIR scoring system). Brain magnetic resonance imaging, carotid ultrasound, echocardiography, electrocardiogram, and chest radiography were normal.

The patient showed no clinical features suggestive of common causes of dyslipidaemia, secondary hypertriglyceridemia, or other syndromic or metabolic disorders associated with hypertriglyceridemia, including glycogen storage diseases, Alagille syndrome, Alström syndrome, lipodystrophic diabetes, sphingomyelinase deficiency, and Niemann–Pick disease type C. In the absence of clinical indicators of these conditions, genetic testing was pursued to clarify the underlying aetiology.

Next-generation sequencing was performed using whole-exome analysis of 4,503 genes, following previously described methods[4]. The analysis included genes associated with inherited primary hypertriglyceridemia, including those implicated in lipoprotein lipase deficiency, apolipoprotein A5 deficiency, apolipoprotein C2 deficiency, lipase maturation factor 1 deficiency, and glycosylphosphatidylinositol-anchored high-density lipoprotein–binding protein 1 deficiency.

Genetic analysis identified compound heterozygous pathogenic variants in *SLC25A13* (NM_014251.3; NP_055066.1), including a start-loss variant c.2T>C (p.Met1Thr) affecting the canonical translation initiation codon, and a frameshift duplication c.1638_1660dup (p.Ala554GlyfsTer17), predicted to result in premature protein truncation. Both variants were confirmed by Sanger sequencing. The presence of these biallelic pathogenic variants is consistent with autosomal recessive citrin deficiency and established the diagnosis of CTLN2.

Following molecular confirmation, the patient was initiated on fenofibrate at a dose of 145 mg once daily. Nutritional therapy was implemented with the goals of restoring metabolic homeostasis and minimizing the risk of hyperammonaemia. The prescribed diet emphasized restriction of simple carbohydrates, moderate protein enrichment, and limitation of total fat intake to <15% of total energy, primarily from unsaturated sources. Daily caloric intake was individualized to 1600–1800 kcal, with carbohydrates accounting for approximately 50–60% of total energy. Adequate micronutrient intake and

Category	Parameter	Result	Reference range/interpretation
Blood Chemistry	Urea (mmol/l)	5.8	2.8–7.2
	Creatinine (µmol/l)	100	74–110
	Sodium (mmol/l)	142	135–145
	Potassium (mmol/l)	3.9	3.4–4.5
	Chloride (mmol/l)	100	95–100
	AST (U/l)	62.5	<50
	ALT (U/l)	25.9	<50
	GGT (U/l)	165.7	< 55
	Total bilirubin (µmol/l)	8.8	<21
	Direct bilirubin (µmol/l)	3.6	<3.4
	Total cholesterol (mmol/l)	5.75	<5.2
	Triglyceride (mmol/l)	34.61	<1.6
	LDL-C (mmol/l)	0.05	<3.4
	HDL-C (mmol/l)	1.76	>1.03
	Uric acid (µmol/l)	211	208–428
	AFP (ng/ml)	2	<7
	Amylase (U/l)	87	28–100
	Ammonia (µmol/l)	58.9	16–60
	Free T4 (pmol/l)	14.9	12–22
	TSH (µIU/ml)	1.09	0.27–4.2
	Glucose (mmol/l)	4.35	4.1–5.9
	HbA1c (%)	5.3	4.8–5.9
	Cortisol (nmol/l)	346	166–507
	ACTH (pg/ml)	16.6	7.2–63.3
Urinalysis	Leukocyte esterase	Negative	–
	Protein	Negative	–
	Specific gravity	1.007	1.003 – 1.030
	Glucose	Negative	–
	Nitrite	Negative	–
	pH	6.0	5.5 – 6.5
	Ketones	Negative	–
	Urobilinogen (µmol/l)	3.2	3.2–16
	Red blood cells	Negative	–
	Bilirubin	Negative	–
Complete blood count	Leukocytes ($\times 10^9$/l)	3.41	4–10
	Neutrophils (%)	53.7	45–75
	Eosinophils (%)	3.0	0–8
	Basophils (%)	0.3	0–1
	Monocytes (%)	8	0–8
	Lymphocytes (%)	35	25–45
	Erythrocytes ($\times 10^{12}$/l)	4.35	4.4–5.9
	Haemoglobin (g/l)	141	136–175
	Platelets ($\times 10^9$/l)	148	150–400
Hepatitis B serology and viral load	HBeAb (automated immunoassay)	Positive	Reactive = Immune response to HBeAg
	HBeAg (automated immunoassay)	Negative	Non-reactive = No active viral replication
	HBsAg (quantitative) (IU/ml)	295	<0.05
	HBV DNA (viral load) ($\times 10^3$ IU/ml)	1.49	≥10 (limit of detection)

Table 1. *Laboratory findings at the Time of CTLN2 diagnosis.*

Abbreviations: CTLN2, citrullinemia type II; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; AFP, alpha-fetoprotein; T4, thyroxine; TSH, thyroid-stimulating hormone; HbA1c, haemoglobin A1c; ACTH, adrenocorticotropic hormone; HBeAb, hepatitis B envelope antibody; HBeAg, hepatitis B envelope antigen; HbsAg, hepatitis B surface antigen; HBV, hepatitis B virus; DNA, deoxyribonucleic acid.

dietary fibre requirements were ensured. The patient was also advised to engage in regular aerobic exercise to enhance lipid metabolism. Following initiation of dietary modification and fenofibrate therapy, plasma triglyceride levels declined rapidly and were sustained within the normal range during follow-up. Plasma triglyceride levels decreased from 34.61 mmol/l at baseline to 13.69 mmol/L after one week, 1.78 mmol/l after two weeks, and 1.63 mmol/l at three months. No adverse effects related to pharmacological or dietary intervention were reported. This stepwise biochemical improvement resulted from the rapid metabolic response to targeted dietary intervention combined with fenofibrate in CTLN2.

DISCUSSION

This case represents the first documented instance of adult-onset CTLN2 in Vietnam, characterized by persistent, treatment-refractory hypertriglyceridemia in the absence of classical hepatic or neuropsychiatric manifestations. This clinical presentation contrasts with the infantile and neonatal forms of citrin deficiency previously described in regional case series[5]. In adults, CTLN2 may be misdiagnosed as familial combined hyperlipidaemia or secondary dyslipidaemia due to its non-specific features[1,3].

In this case, diagnosis was established only after identification of two known *SLC25A13* pathogenic variants (c.2T>C and c.1638_1660dup)—both previously reported in Asian populations and consistent with autosomal recessive inheritance[3]. Given that hypertriglyceridemia is a common finding in metabolic and cardiovascular clinics, its occurrence may obscure rarer genetic disorders unless molecular testing is pursued. This underscores the critical role of genetic testing in evaluating unexplained or atypical lipid abnormalities. Hypertriglyceridemia may be the sole biochemical marker of adult-onset CTLN2, even during asymptomatic periods. The pathophysiological basis involves impaired citrin-mediated transport of aspartate, resulting in cytosolic nicotinamide adenine dinucleotide + hydrogen accumulation. This disrupts hepatic redox balance, inhibits β-oxidation and gluconeogenesis, promotes de novo lipogenesis, and increases hepatic very-low-density lipoprotein secretion. Without appropriate recognition, such cases may be misclassified as secondary dyslipidaemia, delaying definitive diagnosis and proper management. Furthermore, severe hypertriglyceridemia (especially >1,000 mg/dl) poses a significant risk of acute pancreatitis through mechanisms involving chylomicronaemia, lipotoxicity, oxidative stress, and endothelial injury[6].

Carbohydrate restriction is a cornerstone of dietary therapy in CTLN2, as excess carbohydrate intake exacerbates the redox imbalance and enhances hepatic lipogenesis. In contrast, adequate protein intake supports the urea cycle, provides alternative energy substrates, and promotes metabolic stability[2]. Fenofibrate (145 mg/day) was added during the initial phase and may have facilitated triglyceride clearance; however, sustained triglyceride control was achieved predominantly through dietary intervention. Nutritional therapy remains the mainstay of treatment, reflecting the unique hepatic energy disturbance in CTLN2. High-carbohydrate diets suppress gluconeogenesis and aggravate lipogenesis, thereby worsening hypertriglyceridemia in affected individuals. This case highlights the importance of individualized, genotype-informed dietary management. In contrast to typical hyperlipidaemia, pharmacologic interventions alone are often insufficient in CTLN2, and dietary measures directly targeting the metabolic derangement are essential.

In conclusion, this case highlights the need to consider CTLN2 in young patients with unexplained, treatment-resistant hypertriglyceridemia, especially in Asian populations where citrin deficiency is more prevalent. Early genetic diagnosis is essential for accurate classification and initiation of targeted dietary therapy. Individualized nutritional intervention, rather than standard lipid-lowering agents, is the most effective approach for metabolic control and prevention of complications such as acute pancreatitis.

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