Case Report

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3-Hydroxy-3-methylglutaryl-coenzyme A lyase deficiency: case report of a child with rare HMGCL gene variants

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Abstract

Objectives: 3-Hydroxy-3-methylglutaryl-coenzyme A lyase deficiency (HMGCLD) is a rare autosomal recessive organic aciduria. Most patients present within the first year of life with metabolic decompensation, which can cause neurological damage or death if untreated.
Case presentation: A 20-month-old previously healthy boy was admitted to the hospital after a nocturnal seizure. Upon admission, the child was unconscious and laboratory analysis revealed severe hypoglycemia and metabolic acidosis without ketonuria. Hypoglycemia was corrected with a bolus of 10 % glucose followed by continuous glucose-electrolyte infusion. Status epilepticus was treated with midazolam and phenobarbital. Magnetic resonance imaging (MRI) performed on the second hospital day, revealed bilateral and symmetric T2 hyperintense lesions in the cortex, supratentorial white matter, basal ganglia and central pons, along with slight white matter volume reduction. Urinary organic acids indicated HMGCLD. HMG-CoA lyase activity in immortalized lymphocytes was significantly decreased. Sanger sequencing of the *HMGCL* gene identified a heterozygous sequence variant, c.796T>C, p.(Cys266Arg). MLPA analysis showed a reduced gene dosage for exons 3 and 4 of *HMGCL*, consistent with a heterozygous deletion. Upon diagnosis, a low-protein diet was recommended, as well as oral L-carnitine therapy with a high-calorie supplement drink at night. Initially, the child had slightly impaired psychomotor development, which normalized by age 3.5. He was without metabolic crises or seizures since diagnosis.
Conclusions: In any child presenting with hypoketotic hypoglycemia and metabolic acidosis of unknown etiology, HMGCLD should be considered. Given the rarity of HMGCLD and its sporadic cases across Europe, management should involve a well-experienced multidisciplinary team.

Keywords: inborn errors metabolism; HMG-CoA lyase; hypoglycemia; seizure; child

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Introduction

3-Hydroxy-3-methylglutaryl-coenzyme A lyase deficiency (HMGCLD) is a rare autosomal recessive organic aciduria. The HMGCL enzyme catalyzes the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A to acetoacetate and acetyl-coenzyme A, which are crucial in ketogenesis from fatty acids and leucine degradation. During catabolic states, ketone production from leucine and fatty acids is stimulated to provide an alternative energy source. In HMGCLD, impaired ketogenesis leads to the accumulation of leucine catabolism metabolites (3-hydroxy-isovaleric acid, 3-methylglutaconic acid, 3-methylglutaric acid, and 3-hydroxy-3-methylglutaric acid), potentially causing metabolic acidosis [1, 2]. Other common laboratory findings include hypoglycemia, elevated serum transaminases, and hyperammonemia [3].

Most patients present within the first year of life with metabolic decompensation, which can cause neurological damage or death if untreated. Diagnosis of HMGCLD is confirmed by enzyme activity testing in lymphocytes or fibroblasts and/or *HMGCL* gene analysis. The most common *HMGCL* variant is c.109G>T, p.(Glu37*) [3].

There is no specific therapy, but treatment focuses on avoiding fasting, a carbohydrate-rich diet, moderate protein (leucine) restriction, and L-carnitine administration [2].

Despite its early and life-threatening presentation, HMGCLD generally has a favorable long-term outcome [3].

Over 200 cases of HMGCLD have been reported, primarily from the Iberian Peninsula, Turkey, and Saudi Arabia [3].

Case presentation

A 20-month-old previously healthy boy, the third son of nonconsanguineous Serbian parents, was admitted to the hospital due to a nocturnal seizure. Apart from rhinorrhea for the previous 7 days, he had no other symptoms. Before bed, he had consumed milk and bread with margarine and jam. The seizure lasted 1 h despite rectal diazepam administration. Upon admission, the child was still unconscious. Laboratory analysis revealed severe hypoglycemia (blood glucose level 0.79 mmol/L; normal 2.8–4.5 mmol/L), severe metabolic acidosis (pH 7.17, base excess −14.3 mmol/L), mild hyperammonemia (82 µmol/L; normal 16–60 µmol/L), and elevated lactate (5.3 mmol/L; normal 0.5–2.2 mmol/L). Urea was elevated at 8.4 mmol/L (normal 1.8–6 mmol/L), as were uric acid (560 µmol/L; normal 124–330 µmol/L) and alanine aminotransferase (1.01 µkat/L; normal 0.27–0.95 µkat/L). Vitamin B12 level was low (110 pmol/L; normal 138–652 pmol/L). CRP and other biochemical analyses were normal. There was no ketonuria. Hypoglycemia was corrected with a bolus of 10 % glucose followed by continuous glucose-electrolyte infusion. Status epilepticus was treated with midazolam and phenobarbital, which was continued orally. Lumbar puncture showed normal results. The head CT scan showed no significant pathological findings. Magnetic resonance imaging (MRI) performed on the second hospital day, revealed bilateral and symmetric T2 hyperintense lesions in the cortex, supratentorial white matter, basal ganglia and central pons, along with slight white matter volume reduction. Electroencephalogram (EEG) on the third hospital day showed nonepileptic nonspecific electrocortical dysrhythmia, posterior delta theta hypersynchrony, and left temporal irritability without clear epileptiform discharges. Additional hormone (insulin, cortisol, growth hormone, thyroid hormones) and toxicological analyses were normal. Free serum L-carnitine was decreased (11.8 µmol/L; normal 22–66 µmol/L).

Urinary organic acids indicated HMG-CoA lyase deficiency. HMG-CoA lyase activity in immortalized lymphocytes was significantly decreased, confirming HMGCLD. Sanger sequencing of the *HMGCL* gene identified a heterozygous sequence variant, c.796T>C, p.(Cys266Arg). MLPA analysis showed a reduced gene dosage for exons 3 and 4 of *HMGCL*, consistent with a heterozygous deletion (Table 1). For both parents, the analysis of the *HMGCL* gene was performed. The mother was a carrier of the c.796T>C, p.(Cys266Arg) variant, and the father had a reduced gene dosage for exons 3 and 4 of *HMGCL*, as in the child.

Upon diagnosis, a low-protein diet was recommended. As the patient refused to eat uncooked cornstarch, he was given a high-calorie supplement drink at night to prevent nocturnal hypoglycemia. Oral L-carnitine therapy was started at 100 mg/kg/day. Vitamin B12 was supplemented initially parenterally, then orally. Due to persistently high uric acid, allopurinol was introduced. After discharge, the parents regularly monitored blood sugar levels with a glucometer, especially in the morning, which remained stable. Initially, the child had slightly impaired psychomotor development with speech delay, but after proper nutrition and L-carnitine supplementation, his development normalized by age 3.5. Follow-up MRI scans revealed significant resolution of the previously detected parenchymal lesions (Figure 1).

The child, now 6 years old, has normal development without metabolic crises or seizures since diagnosis. Follow-up EEGs were normal, and anticonvulsive treatment was discontinued at 2.5 years.

Organic acid analyses of his two older brothers showed normal results.

Discussion

HMGCLD is an autosomal recessive metabolic disorder caused by biallelic pathogenic variants in the *HMGCL* gene [1]. Although the worldwide incidence is unknown, it is

Table 1: Diagnostic test results that confirm HMGCLD in the patient.

Diagnostic test	Result
Urine organic acid analyses	3-ketoisovaleric acid, 3-methylglutaric acid, 3-methylglutaconic acid, 3-hydroxy-3-methylglutaric acid
HMG-CoA lyase activity in immortalized lymphocytes	Strongly decreased
Sanger sequencing of the *HMGCL* gene	Heterozygous missense variant, c.796T>C, p.(Cys266Arg)
MLPA analysis of the *HMGCL* gene	Reduced gene dosage for exons 3 and 4 of *HMGCL* indicating a heterozygous deletion

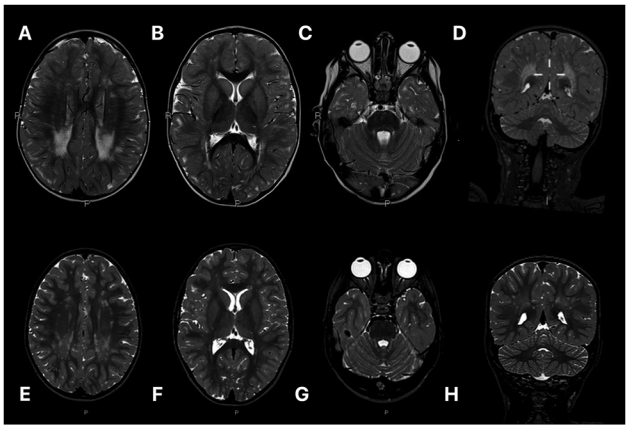

Figure 1: Initial MRI of a 20-month-old boy with HMGCLD (A–D) and follow-up MRI after 1 year of therapy and dietary restriction (E–H). The initial T2-weighted images show hyperintense cortical lesions, symmetrical confluent changes in the periventricular white matter, and patchy involvement of the "U" fibers (A). Symmetrical abnormalities are observed in the lentiform nuclei and caudate heads (B), with restricted diffusion on DWI (not shown). A small lesion is also seen in the central pons (C), with no cerebellar involvement (D). Follow-up images demonstrate complete resolution of the "U" fibers and pontine lesions (E, G). Smaller hyperintense areas persist in the periventricular white matter, along with mild atrophy of the basal ganglia (F), consistent with minor residual injury.

extremely rare, with fewer than 300 cases published so far. Higher incidences are noted in Saudi Arabia, Brazil, Portugal, and Spain, but still less than 1/100,000 live births [3]. To the best of our knowledge, this is the first reported case in Serbia. Most HMGCLD patients become symptomatic within the first year of life, with about half presenting in the neonatal period [3, 4]. Only around 8 % present symptoms in the second year of life [3]. Our patient showed first symptoms at 20 months. Acute metabolic decompensation is common, as was the case in our patient, often triggered by catabolism due to infections, prolonged fasting, or physical exercise [4]. The trigger in our patient is unclear, as he had no reduced energy intake and apart from a runny nose no other signs of infection. Common symptoms of acute decompensation include vomiting, lethargy/coma, tachypnea/apnea, seizures, and stroke-like symptoms. Our patient had status epilepticus during his first and only metabolic decompensation. Laboratory findings typically include hypoglycemia, metabolic acidosis, mildly elevated serum transaminases, and hyperammonemia [3]. Hypoglycemia with hypoketonemia is a medical emergency, as it deprives the brain of major energy sources, risking permanent neurological damage if not corrected rapidly [5]. Our patient had severe hypoglycemia, metabolic acidosis, and mildly elevated ammonium, urea, uric acid, and alanine aminotransferase levels. Apart from evident metabolic crisis, this disease can often lead to neurological long-term complications, and around one quarter of patients show severe mental impairment. Speech delay is frequent. Physical development is generally normal. Apart from CNS symptoms, involvement of other organs is rare [3]. Patients are usually asymptomatic between episodes of metabolic decompensation [1, 2, 4]. Our patient had impaired psychomotor development at diagnosis, which normalized later. Other organs were not affected. Brain MRI abnormalities in pediatric HMGCLD patients are common but do not correlate well with neurological symptoms. White matter abnormalities and cerebral atrophy are frequently seen on MRI [3, 4]. However, in our patient, these findings were associated with cortical, basal ganglia, and pontine lesions, on initial MRI. Seizures have been reported in 9 % of HMGCLD patients [3]. Our patient had status epilepticus but no further seizures, and anticonvulsive therapy was discontinued at 2.5 years. About one-third of patients experience repeated metabolic crises, especially in early childhood [4]. Our patient, now 6 years old, has not experienced another metabolic decompensation so far.

Diagnosis of HMGCLD is based on urine organic acid analysis, enzyme activity studies, and *HMGCL* gene analysis. Blood acylcarnitine patterns are usually abnormal, showing elevated acylcarnitines C5OH and C6DC. Urinary organic acid profiles in HMGCLD show characteristic patterns [2, 4]. Our patient's urinary organic acids were compatible with HMGCLD, with elevated 3-ketoisovaleric acid, 3-methylglutaric acid, 3-methylglutaconic acid, and 3-hydroxy-3-methylglutaric acid. HMGCL activity in immortalized lymphocytes was significantly decreased. Pathogenic *HMGCL* variants have been identified in all nine exons of the *HMGCL* gene and noncoding regions of the gene [3, 4]. An overview of cases published until 2020 showed 72.9 % of patients had homozygous variants, and 20.3 % were compound heterozygous for variants in the *HMGCL* gene. The most common *HMGCL* variant is c.109G>T, p.(Glu37*) [3, 4]. In our patient, sequence analysis identified only one heterozygous sequence variant c.796T>C, p.(Cys266Arg) in *HMGCL*. This missense variant had been previously identified in two patients with biochemically confirmed HMGCLD (urinary organic acids and enzyme testing) [6, 7]. In one of the two cases, cosegregation analysis confirmed compound heterozygosity for c.796T>C, p.(Cys266Arg) and a nonsense variant [6]. The cysteine at position 266 of HMG-CoA lyase is highly conserved, and several functional studies have shown that Cys266 is essential for the enzyme's catalytic function [8–10]. Computer-based predictions consistently indicate that the predicted amino acid change may affect protein function and be pathogenetically significant [11]. In the Genome Aggregation Database (gnomAD), c.796T>C, p.(Cys266Arg) is listed with only one allele among all

populations analyzed [12]. Based on these data, c.796T>C, p.(Cys266Arg) can be classified as pathogenic according to ACMG guidelines [13]. MLPA analysis in our patient showed a reduced gene dosage for exons 3 and 4 of *HMGCL*, suggesting a heterozygous deletion. Deletions encompassing this region of *HMGCL* have been reported as causative for HMG-CoA lyase deficiency in the literature [14–16]. In summary, genetic analyses revealed compound heterozygosity for two pathogenic variants in our patient, confirming the diagnosis of HMGCLD. Genotype–phenotype correlations are difficult to establish in HMGCLD, with extrinsic factors playing a major role [3]. Still, we can make some conclusions based on published cases to date. In two case reports by Roland et al. and Zafeiriou et al., the sequence variant c.796T>C, p.(Cys266Arg) in *HMGCL* with compound-heterozygosity was confirmed, however, combined with different variants than in our case. In these patients, the disease manifested at 3 days and 8 months of age, respectively. The first patient experienced a metabolic crisis without hypoglycemia and was followed up for a short period before the study was published, so the further course remains unknown. The second patient had a hypoglycemic crisis without metabolic acidosis, which presented with generalized tonic–clonic seizures, mild cortical atrophy, and extensive white matter changes on cranial magnetic resonance imaging, resembling the clinical picture of our patient [6, 7]. Additionally, Köksal et al. reported a patient with a homozygous deletion in exons 3 and 4 of *HMGCL*, who presented with hypoglycemic metabolic acidosis at the age of 8 months, leading to generalized tonic–clonic seizures. Cranial MRI demonstrated cortical atrophy, enlargement of the subarachnoid spaces, ventricular dilatation, and increased white matter hyperintensity. This patient experienced repeated metabolic crises and mild intellectual disability at 21 months of age [14]. These findings correlate with our patient, except for the repeated metabolic crises.

Treatment data for HMGCLD are sparse, and no controlled studies have been performed so far. However, there are some general recommendations [3, 5]. Treatment of acute decompensation includes correcting hypoglycemia with high-rate intravenous glucose infusion and treating metabolic acidosis with fluid therapy and bicarbonate in cases of severe acidosis (pH<7.1). The mainstay of therapy is the avoidance of fasting. Extremes of dietary fat intake should be avoided, and protein restriction may be beneficial. Most children are stable on a protein intake of about 1.5 g/kg/day, but this needs to be individualized. Some patients adopt a vegetarian diet [4, 5]. Our patient is on a low-protein diet with one high-calorie meal at night to prevent nocturnal hypoglycemia. After discharge from hospital, the parents monitored his blood sugar levels daily, especially in the morning, but these checkups were later discontinued. In patients with low carnitine levels, L-carnitine supplementation is recommended to avoid secondary L-carnitine deficiency and intracellular depletion of free coenzyme A [3, 5]. Our patient has been receiving L-carnitine at a dose of 100 mg/kg/day, a commonly applied dose [4].

The long-term outcome of patients with HMGCLD is generally favorable, with the majority showing normal cognitive development. Complications affecting other organs, such as the liver, pancreas, and heart, appear to be rare. Nevertheless, long-term follow-up remains a cornerstone of treatment to ensure adequate growth and development and to prevent complications [3, 4]. The physical and cognitive development of our patient, as well as laboratory findings, were regularly monitored through outpatient visits. Follow-up MRI scans were performed annually and showed significant improvement. At home, the blood glucose level was monitored using a glucometer. This approach resulted in a satisfactory outcome, and the patient has not experienced another metabolic crisis to date. As is standard in genetically confirmed disorders, genetic counseling was advised for the family and proved essential in guiding future reproductive decisions for both the parents and their children.

Learning points

- In any child presenting with hypoketotic hypoglycemia and metabolic acidosis of unknown etiology, with or without seizures and neurological abnormalities, HMGCLD should be considered as a differential diagnosis.
- Given the rarity of HMGCLD and its sporadic cases across Europe, management should involve a well-experienced multidisciplinary team. This case highlights the importance of international cooperation that resulted in the establishment of the definitive diagnosis and well-being of our patient.
- Long-term follow-up of patients with HMGCLD is essential to ensure adequate growth and development and to prevent complications.

What is new?

- We are presenting a rare manifestation of HMGCLD with hypoglycemic epileptic status as well as compound heterozygosity for c.796T>C, p.(Cys266Arg), and reduced gene dosage for exons 3 and 4 of *HMGCL*, which has not been published so far.

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