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3-Hydroxy-3-methylglutaryl-CoA (HMG-CoA) Lyase Deficiency

CASE REPORT

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ABSTRACT

3-Hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency is an autosomal recessive disorder involving ketone body synthesis and leucine degradation. It is characterized by vomiting, hypotension, lethargy, metabolic acidosis, and non-ketotic hypoglycemia. A 3-month-old girl presented with clinical symptoms of vomiting and drowsiness. Her clinical findings included hypoglycemia, hyperammonemia, metabolic acidosis, and elevated alanine aminotransferase and aspartate aminotransferase levels. The level of C5OH acylcarnitine was elevated as determined by liquid chromatography–tandem mass spectrometry. The levels of 3-methylglutaric acid, 3-methylglutaconic acid, 3-OH isovaleric acid, glutaric acid, and 3-hydroxy-3-methylglutaric acid were found to be elevated in the analysis of urinary organic acids. According to these clinical and laboratory findings, she was diagnosed with HMG-CoA lyase deficiency. Carnitine treatment and protein- and fat-restricted and carbohydrate-rich diet were started. HMG-CoA lyase deficiency is one of the disorders that should be considered in the presence of non-ketotic hypoglycemia, metabolic acidosis, and hyperammonemia.

Keywords: HMG-CoA lyase deficiency, metabolic acidosis, non-ketotic hypoglycemia

INTRODUCTION

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) lyase deficiency is a rare autosomal recessive congenital defect of ketone body synthesis and leucine degradation. The HMG-CoA lyase enzyme is localized in the mitochondria and peroxisomes and converts HMG-CoA to acetyl CoA and acetoacetate at the last step of leucine catabolism (Figure 1) (1).

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) lyase deficiency leads to a reduced ability to synthesize ketones, which are the primary energy source of the brain when glucose is unavailable. In 1976, Faull et al. (2) first described the disorder in a 7-month-old boy with metabolic acidosis and hypoglycemia.

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) lyase deficiency is usually clinically evident during infancy and is characterized by vomiting, hypotonia, lethargy, metabolic acidosis, non-ketotic hypoglycemia, and Reye-like syndrome. Patients with this disorder are usually normal except for recurrent metabolic attacks that can be triggered by infection, starvation, and excessive physical exercise (1, 3). These attacks can cause deaths in 20% of cases and serious long-term morbidities such as psychomotor retardation, epilepsy, hepatic steatosis, pancreatitis, or dilated cardiomyopathy (3, 4).

Although the organic acid profile is essentially diagnostic, enzyme deficiency can be detected in cultured fibroblasts, or the diagnosis can be confirmed by molecular genetic analysis of the *HMGCL* gene (1). There are a few reports that demonstrate the clinical findings of this condition (2-6).

CASE REPORT

A 3-month-old girl presented with vomiting and drowsiness. She was born after an uneventful pregnancy by spontaneous vaginal delivery. She weighed 3000 g. Her prenatal, obstetric, and family histories were unremarkable.

She was hospitalized owing to hypoglycemia and elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels 1 month ago prior to the last hospital admission. She was discharged after her symptoms improved with supportive treatment.

Her body weight, height, and head circumference were 5.2 kg (10% to 25% percentile), 58 cm (10% to 25% percentile), and 40 cm (50% percentile), respectively. She was hypotonic, hypoactive, and lethargic, and she

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Table 1. Laboratory findings of the patient

Non-specific tests		Metabolic tests		Blood gas analysis	
Hb (g/dL)	9.5	Ammonia (mmol/L)	200	Blood pH	7.26
WBC (mm^3)	5930	3-Methylglutaric acid (mmol/mol creatinine)	536	Bicarbonate level	9.4
PLT (mm^3)	112,000	3-Methylglutaconic acid (mmol/mol creatinine)	3049	Base deficit	–9
Glucose (mmol/L)	1.1	3-OH isovaleric acid (mmol/mol creatinine)	4026		
ALT (IU/L)	534	Glutaric acid (mmol/mol creatinine)	494		
AST (IU/L)	788	3-Hydroxy-3-methylglutaric acid (mmol/mol creatinine)	4210		
Total/direct bilirubin (mg/dL)	1.6/1.3	C5OH acylcarnitine (µmol/L)	1.7		
Urinary ketone	(–)				

Hb: hemoglobin, WBC: white blood cell, PLT: platelet, ALT: alanine aminotransferase, AST: aspartate aminotransferase
ALT level (n:10-49), AST level (n:0-34), ammonia level (n:11.2–35.4), C5OH acylcarnitine level (n:0–0.9), 3-methylglutaric acid level (n:0-9), 3-methylglutaconic acid level (n:0-9), 3-OH isovaleric acid level (n:0-46), glutaric acid level (N<2), and 3-hydroxy-3-methylglutaric acid level (n:11-36)

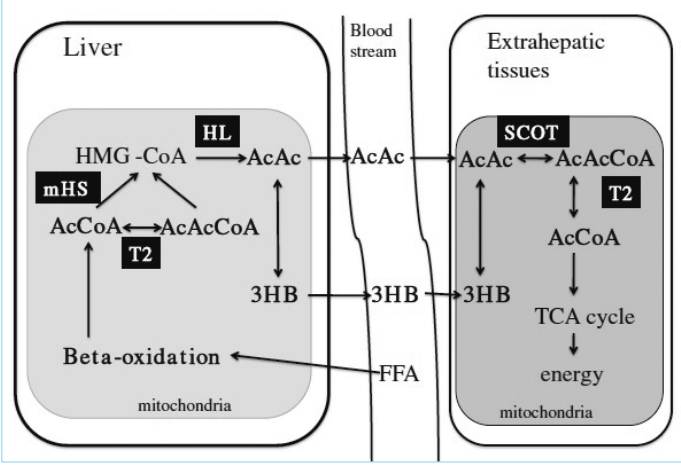

Figure 1. Summary of ketone body metabolism. The HMG-CoA pathway of the ketone body formation is much more active in the liver than elsewhere. The ketone bodies, 3HB and AcAc, diffuse from liver mitochondria into circulation and then to the extrahepatic tissues including the brain. In extrahepatic tissues, SCOT and T2 mediate the production of acetyl CoA for use in energy production or synthesis.

HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA, Ac-CoA: acetyl CoA, AcAc-CoA: acetoacetyl-CoA, TCA: tricarboxylic acid cycle, SCOT: succinyl-CoA-3-oxoacid CoA transferase, T2: beta-ketothiolase, 3HB: 3-hydroxybutyrate, FFA: free fatty acid, mHS: mitochondrial HMG-CoA synthase, HL: HMG-CoA lyase, AcAc: acetoacetate.

had hepatomegaly. Her liver edge was 5 cm below the right costal margin.

Metabolic tests were analyzed for inborn error of metabolism due to metabolic acidosis, hypoketotic hypoglycemia, hyperammonemia, and elevated liver enzymes. Plasma amino acid and blood acylcarnitine levels were quantified using liquid chromatography–tandem mass spectrometry, and urinary organic acid was analyzed using gas chromatography–mass spectrometry. Table 1 shows the laboratory findings of the patient.

The patient was diagnosed with HMG-CoA lyase deficiency according to the symptoms and laboratory findings. Sodium bicarbonate and fluid therapy with high dextrose were started for hypoglycemia and metabolic acidosis. Carnitine treatment (100 mg/kg/day) and carbohydrate-rich and protein- and fat-restricted diet were started. Liver function tests were normal on day 20 after hospitalization.

The patient was hospitalized due to infections three times after the diagnosis, but Reye-like syndrome did not develop. Molecular genetic analysis could not be performed due to familial reasons. The patient is 4 years old now, and her intelligence is normal.

DISCUSSION

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) lyase deficiency is a rare inborn error of leucine catabolism. The patient was admitted to the hospital with Reye-like syndrome and diagnosed with HMG-CoA lyase deficiency using organic acid analysis. Reye-like syndrome can be caused due to sepsis, intoxication, and various metabolic diseases. Inborn error of metabolism was considered in this patient because of lethargy, hepatomegaly, hypoglycemia, metabolic acidosis, elevated ALT and AST levels, and history of previous attack.

Patients with HMG-CoA lyase deficiency present with infection- or starvation-induced metabolic acidosis, hypoglycemia, vomiting, hyperammonemia, consciousness, hypotony, convulsions, hepatomegaly, and elevated ALT and AST levels (5, 6). Left ventricular cardiomyopathy and macrocephaly can be observed, but not frequently (4). Classical symptoms of the disorder were seen in our patient and were induced by infection.

Hyperinsulinism, endocrine deficiencies, and fatty acid oxidation defects can present along with hypoketotic hypoglycemia (7). Endocrine causes of hypoglycemia and fatty acid oxidation defects were ruled out in our patient.

White matter abnormalities, cerebral atrophy, mental retardation, and neurological disorders may occur due to prolonged hypoglycemia and convulsions (8). The neurological development of our patient was normal, and she did not have any convulsion.

Some treatment options for patients with HMG-CoA lyase deficiency include intravenous fluid, sodium bicarbonate therapy, diet, and carnitine supplementation. Leucine- and oil-restricted and valine-, isoleucine-, and carbohydrate-supplemented diet are recommended (9). The blood brain barrier is less selective during the early stages of development and can be more affected by neurotoxic metabolites. Ribas et al. (10) suggested that considering the ability of L-carnitine to easily cross the blood brain barrier, L-carnitine supplementation may also be beneficial in preventing neurological damage derived from oxidative injury. L-Carnitine with leucine-restricted diet appears to play an important role in preventing neurological damage.

Although HMG-CoA lyase deficiency is a defined disorder among the causes of hypoglycemia in the infancy period, it has been observed to manifest in very few patients and is rarely considered in the differential diagnosis of hypoglycemia.

Informed Consent: Written informed consent was obtained from the parents of the patient who participated in this study.

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