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Can a girl with 3-hydroxy-3-methylglutaryl-CoA lyase deficiency live a normal life?

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3-Hydroxy-3-methylglutaryl-CoA lyase (HMG-CoA lyase) deficiency (OMIM: 246450) is an extremely rare genetic metabolic autosomal recessive disorder. A higher incidence of the disorder is found in Saudi Arabia than in other countries. Fewer than 100 patients have been reported worldwide, with fewer than 10 in Taiwan. It is an enzymopathy of leucine metabolism that presents with metabolic decompensation because of accumulation of large amounts of organic acid metabolites in the serum and urine (Fig. 1). The clinical manifestations usually present before the first year of life. Patients may appear with episodic vomiting, diarrhea, poor activity, loss of consciousness, or a seizure disorder. Extreme tiredness, accompanied by hepatomegaly, liver dysfunction, or hyperammonemia, also occurs. These symptoms can be misdiagnosed as Reye syndrome. Metabolic decompensation, metabolic acidosis, ketoacidosis, and profound hypoglycemia are life-threatening situations and can lead to severe brain damage. Without appropriate management, the mortality rate is very high.

Our patient was an 11-year-old girl from the Bunun tribe (Taiwan) with no family history of consanguinity. She was referred from a local clinic when she was 4 years old because of a sudden onset of loss of consciousness and status epilepticus, hypoglycemia, and metabolic acidosis after an episode of bronchopneumonia. Urine gas chromatography with mass spectrometry revealed elevated levels of 3-methyl-glutaric acid, 3-hydroxy-3-methylglutaryl-CoA, and 3-hydroxy-isovaleric acid (Fig. 2A), which is the characteristic pattern of HMG-CoA lyase deficiency.

Acute management included treatment of pneumonia and seizures, correction of metabolic acidosis and electrolyte imbalance, and promotion of anabolism by intravenous infusion of large

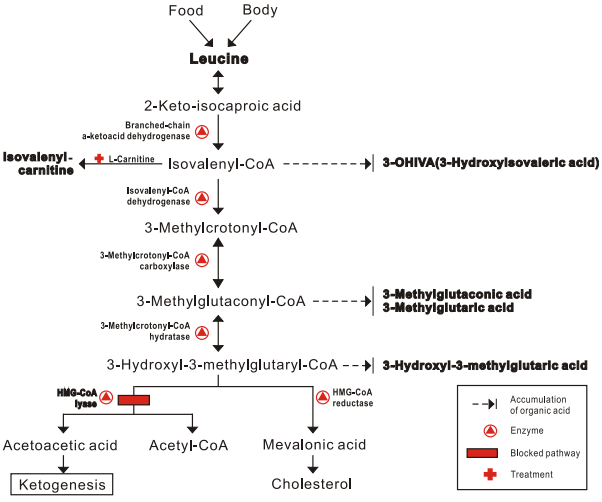

Fig. 1. The pathway of leucine catabolism. 3-Hydroxy-3-methylglutaryl-CoA lyase (HMG-CoA lyase) deficiency blocks the pathway of ketogenesis (▬). The disorder causes accumulation of precursor proteins, such as 3-hydroxyl-3-methylglutaric acid, 3-methylglutaconic acid and 3-OH isovaleric acid, which results in metabolic acidosis. L-carnitine (✚) can conjugate with isovalenyl-CoA and promote the excretion of accumulated organic acid in the urine.

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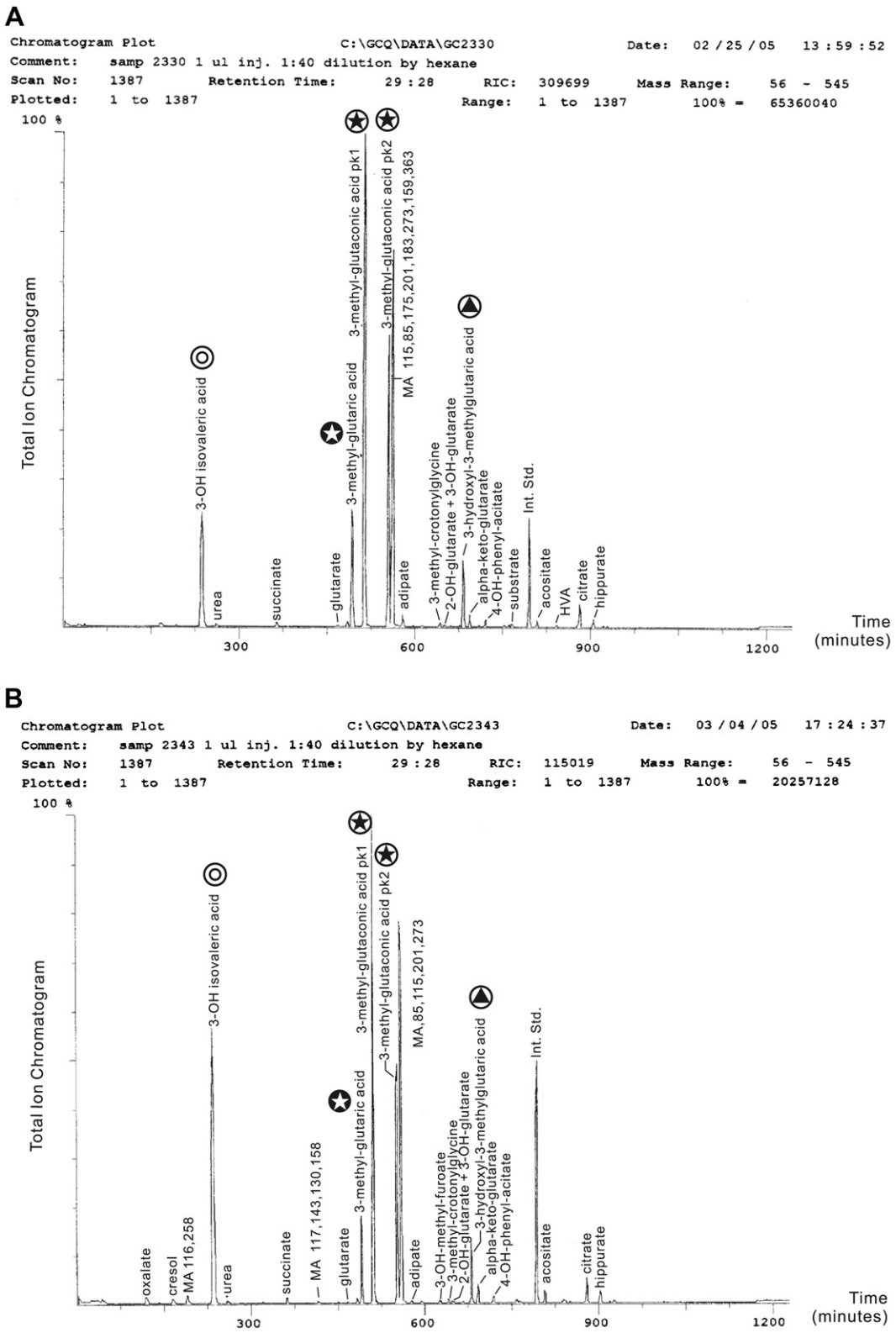

Fig. 2. Urinalysis by gas chromatography with mass spectrometry (GC/MS). (A) The GC/MS of the patient and (B) her sister reveals marked elevation of 3-OH isovaleric acid(◎), 3-methyl-glutaric acid(✪), 3-methyl-glutaconic acid(⊛), and 3-hydroxyl-3-methylglutaric acid(▲).

amounts of carbohydrates and lipids. Intravenous infusion of vitamin B was also attempted before the final diagnosis was reached. Chronic management of these patients included a special leucine-restricted formula (I-Valex-1) at the infant stage, supplementation of L-carnitine, multivitamins and minerals, and protein-restricted food additives later on throughout life. After comprehensive rehabilitation programs, our patient progressed from nasogastric tube feeding to independent feeding, and from being bedridden to

a wheelchair, and then to walking and running. A dietician was also consulted about school lunch preparation. To promote normal growth and development, the patient also underwent regular blood sampling to monitor levels of essential amino acids and nutritional status. To avoid hypoglycemia, her parents and local health care professionals were instructed to give her frequent meals at 3-hour intervals and intravenous glucose infusions during episodes of illness and metabolic decompensation. She had four episodes of bronchopneumonia during 7 years' follow-up, with no episodes of metabolic decompensation or hypoglycemia. Her full intelligence quotient (IQ) at the age of 10 years was 46. She received an individualized education program because of hyperactivity, short attention span, lack of self-expression and logical and abstract thinking, articulation defect, and poor socialization ability.

Because there is a 25% recurrence rate of this autosomal recessive disorder among siblings of affected patients, the patient's 15-month-old sister underwent urine gas chromatography with mass spectrometry screening and was found to have the same diagnosis (Fig. 2B). The younger sister received a leucine-restricted diet, L-carnitine, multivitamins and minerals, and the same health care supervision program as her older sister. The younger sister had a very good clinical outcome, with no episodes of metabolic decompensation or hypoglycemia during the past 7 years. Her growth and development were normal. Her IQ at the age of 8 years was 97. Her school performance was outstanding and she had very good peer relationships. Both girls are currently entering puberty.

With an early diagnosis and comprehensive interprofessional health care program, and collaboration with parents, public health nurses, school nurses, and teachers, patients with HMG-CoA lyase deficiency can live in a normal life, similar to the younger girl discussed in this report.

Further reading

[1] Wysocki SJ, Hahnel R. 3-Hydroxy-3-methylglutaryl-coenzyme a lyase deficiency: a review. J Inherit Metab Dis 1986;9:225–33.
[2] Dasouki M, Buchanan D, Mercer N, Gibson KM, Thoene J. 3-Hydroxy-3-methylglutaric aciduria: response to carnitine therapy and fat and leucine restriction. J Inherit Metab Dis 1987;10:142–6.
[3] Pié J, López-Viñas E, Puisac B, Menao S, Pie A, Casale C, et al. Molecular genetics of HMG-CoA lyase deficiency. Mol Genet Metab 2007;92:198–209.
[4] 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency. Genetics Home Reference. October 2008. Available at: http://ghr.nlm.nih.gov/condition=3hydroxy3methylglutarylcoenzymealyasedeficiency. [accessed 14.11.11].
[5] Seashore MR. The organic acidemias: an overview. Gene Reviews [Internet] 2009. http://www.ncbi.nlm.nih.gov/books/NBK1134/. [accessed 14.11.11].