Glutaric Aciduria Type 1 in Korea: Report of Two Novel Mutations

Glutaric aciduria type I (GA I) is an autosomal recessive disorder caused by a deficiency of glutaryl-CoA dehydrogenase. Although over 400 patients have been reported, reports from the Asian population have contributed to the minor proportion. We recently diagnosed two cases of GA I confirmed with mutational analysis. Here, we present their rather atypical clinical presentations with genetic characteristics for the first time in Korea. Profound developmental delay from birth, association of hearing loss, and neurological improvement after surgical intervention were considered to be different clinical features from most reported cases. One patient was a compound heterozygote for p.Ser139Leu and p.Asp220Tyr, and the other for p.Ser139Leu and Glu160X. The mutations of the two alleles (p.Asp220Tyr and p.Glu160X) were novel and reports of p.Ser139Leu were rare both in Western and other Asian populations. These might suggest different genetic spectrum of Korean GA I patients.

Key Words: Glutaric Aciduria Type I; Glutaryl-CoA Dehydrogenase; Mutation; Korea

INTRODUCTION

Glutaric aciduria or acidemia type I (OMIM # 231670, GA I) is an inborn error of metabolism caused by a deficiency of glutaryl-CoA dehydrogenase (GCDH) encoded by the GCDH gene. GCDH catalyzes the conversion of glutaryl-CoA (GA) to crotonyl-CoA in the metabolic pathway for lysine, hydroxylysine, and tryptophan (1). An accumulation of GA and 3-OH-GA is established as the biochemical hallmark of GA I, resulting in acute basal ganglia injury, movement disorders, and further neuropsychologic deterioration (2). Since the first description of the two index cases in 1975 (3), over 400 patients and 150 disease causing mutations have been reported (4). The estimated worldwide frequency of GA I is one in 100,000 newborns (5). However, this estimate was based on the tandem mass spectrometry newborn screening results conducted in several countries including the USA, Australia, and Germany. Since GA I is not included in the routine newborn screening program in Korea, exact frequency of this disorder could not be estimated. Only two cases had been reported in the Korean literature diagnosed on the basis of clinical features and results of urine organic acid analysis. Here, we report two Korean patients with GA I, proven by mutational analysis, which revealed two novel mutations, for the first time in Korea.

CASE REPORT

Patient 1

A 10-month-old female infant was referred to our hospital for developmental delay and large head size. She was born to unrelated healthy parents after a 41-week pregnancy. Although she could smile responsively and feed well, complete head control had not been achieved. She had never suffered from metabolic decompensation episodes, such as mental deterioration or seizures associated with infection or fever. Brain magnetic resonance imaging (MRI) revealed large amounts of bilateral subdural fluid collection, cerebral atrophy, and high signal intensity in both basal ganglia (Fig. 1A). After surgical drainage of subdural fluids, recurrent subdural bleeding, systemic infection, decreased mentality, and seizures occurred. These symptoms were not easily controlled in the immediate postoperative period. Under the suspicion of metabolic encephalopathies, urine organic acid analysis was conducted, which revealed high levels of GA (7,360.9 mM/M Cr, ref: <5.3) and 3-OH-GA (67.6 mM/M Cr ref: <4.2). We analyzed the GCDH gene and identified compound heterozygote mutations of p.Ser139Leu and p.Asp220Tyr (Fig. 1B). Her mother was a heterozygote carrier for p.Ser139Leu mutation.
and father was a heterozygote carrier for p.Asp220Tyr. Elder brother who was phenotypically normal did not harbor any of the two mutations.

After specific treatment for GA I, including a special protein restriction formula (Glutarex-1, Abbott) with supplementation of L-carnitine (100 mg/kg/day) and riboflavin (100 mg/day), the patient recovered from postoperative complications and her general condition improved. However, her swallowing remained impaired, requiring tube feeding, and her development remained delayed.

Patient 2

A 3-yr-old male, born from unrelated healthy parents after a 39-week pregnancy, was referred to our hospital for developmental delay. Large head size and hearing impairment were detected in the neonatal care unit soon after birth. His motor development was not delayed until six months of age when he could support weight on his forearms and roll over. Subsequently, he lost his motor skills gradually over 1 month without any intervening episodes such as infection or seizures. A brain MRI revealed asymmetric subdural fluid collection, suggesting hemorrhage with a mild mass effect (Fig. 1C). After surgical drainage, his motor skills improved to be able to creep at the age of 13 months. Metabolic screening tests, performed before a cochlear implantation procedure conducted at the age of 29 months, detected highly elevated GA (73.75 mM/M Cr, ref: <5.3) and 3-OH-GA (12.1 mM/M Cr, ref: <4.2) levels from urine organic acid analysis. We analyzed the GCDH gene and found compound heterozygote mutations of p.Glu160X (Fig. 1D) and p.Ser139Leu. The patient was treated with a special formula (Glutarex-1, Abbott), L-carnitine (100 mg/kg/day) and riboflavin (100 mg/day). He can now walk with assistance and did not show any features of movement disorder until his current age of three years.

Genetic analysis

Genomic DNA was extracted from peripheral blood leu-
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pressure (4). However, surgical intervention could play some circumstances including considerable mass effect or increased intervention for subdural hemorrhage should be decided cautiously and conducted in limited, acute, life threatening circumstances before deterioration. Recently published management guidelines of GA I recommended that neurosurgical decision making is important for confirming the diagnosis of GA I. We hope, from the present study, more GA I patients would be diagnosed in the early course of disease and the genetic and clinical characteristics of GA I in the Korean population would be further clarified.

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