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증 례

β-ureidopropionase 결핍증의 장기간의 임상경과 1례

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Long-term Clinical Course of a Korean Girl with β-ureidopropionase Deficiency

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β-ureidopropionase deficiency (*β*-UPD; OMIM # 613161) is a rare autosomal recessive inborn error of pyrimidine metabolism caused by mutations in the *UPB1* gene and approximately 30 cases have been reported in the world. The clinical features of patients with *β*-UPD have been reported to vary from asymptomatic to severe developmental delays. However, the long-term clinical courses of patients with *β*-UPD have not yet been reported. A Korean girl was diagnosed with *β*-UPD at the age of 8 years and 10 months by targeted next-generation sequencing which was subsequently confirmed by Sanger sequencing. She had many clinical features such as poor oral feeding, failure to thrive, global developmental delay, microcephaly, frequent infection, and intractable epilepsy. She died suddenly of an unknown cause at the age of 11 years and 5 months. Here we report the long-term (i.e. lifelong) clinical aspects of a Korean patient with *β*-UPD.

Key words: Clinical course, *β*-Ureidopropionase deficiency, Pyrimidine, Targeted next-generation sequencing

Introduction

β-ureidopropionase deficiency (β-UPD) is a rare autosomal recessive inborn error of pyrimidine metabolism caused by mutations in the *UPB1* gene and approximately 30 cases have been reported in the world[1)]. β-ureidopropionase is the last step enzyme involved in pyrimidine degradation pathway[1-3)]. The most common gene mutation in *UPB1* among Japanese and Chinese with β-UPD patients revealed a p.R326Q mutation. The clinical features of patients with β-UPD have been reported to vary from asymptomatic to severe developmental delays[3,4)]. Herein, we report a Korean case of ß-ureidopropionase deficiency with homozygous for p.R326Q (c.977G>A) and heterozygous for p.G31S (c.91G>A) mutations in the *UPB1* gene. Previous reports of patients with β-UPD have focused on their biochemical and genetic findings[5)]. To complement these reports, we aimed to describe the long-term clinical presentation and outcome of a Korean patient with β-UPD.

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Case Report

The patient was the first baby of nonconsanguineous Korean parents. Her birth history included a normal vaginal delivery at 41 weeks with a birth weight of 3,140 g (40th percentile), height of 51 cm (70th percentile), and head circumference of 32.5 cm (15th percentile). Her parents and two younger brothers had asymptomatic, although they were confirmed as β-UP deficiency carriers by Sanger sequencing analysis (Fig. 1). When she was 6 months old, her weight was 6.2 kg (below the 3rd percentile). Her body weight gradually increased as she turned 1 year of age (7.5 kg), 2 years of age (8.3 kg), 4 years of age (9.0 kg), 6 years of age (11.0 kg), and 8 years of age (13.0 kg). At age 9, her height (98.9 cm), weight (11.0 kg), and head circumference (44.5 cm) were all below the 3rd percentile for her age.

Regarding gross motor development, she could change position from supine to prone and sit with support at 7 months old. When she was 11 months old, she could sit alone. She walked with support for a period of time beginning when she was 3 years and 4 months old. However, after that time, her gross motor development did not progress. On the contrary, her development regressed and she could no longer sit unassisted for the rest of her life (Fig. 2). With respect to fine motor development, she could eat using her hands when she was 7 months old, could clap her hands at 9 months old, and moved things with the other hand at 11 months old. After the age of 11 months, her fine motor development regressed, and she could never catch things using her hands. With respect

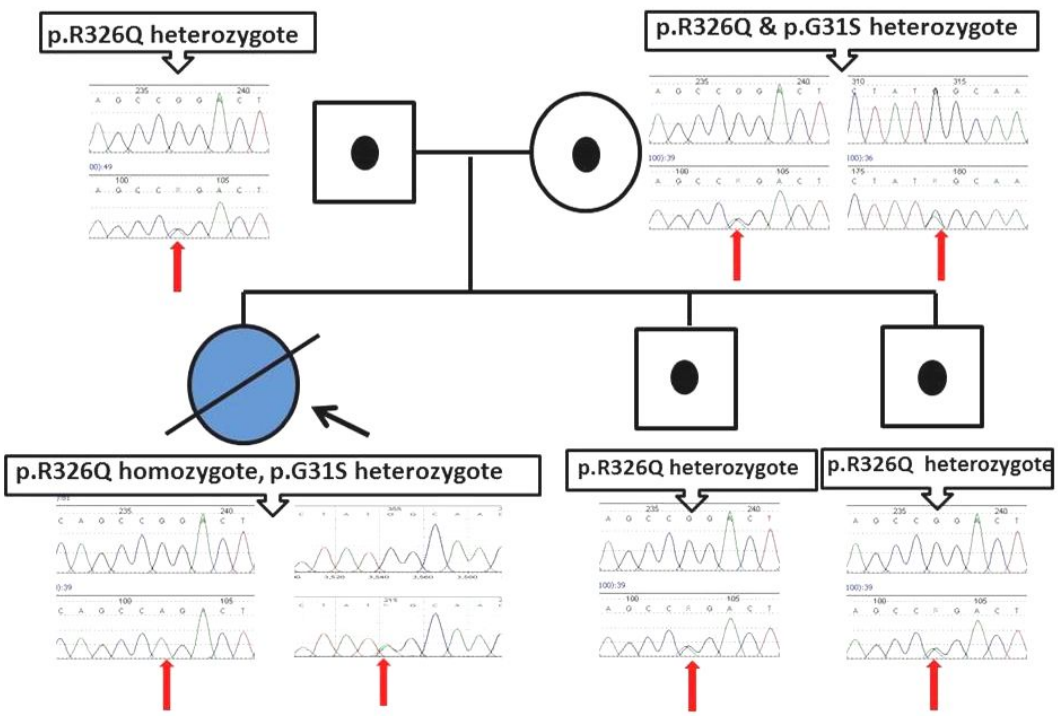

Fig. 1. Sanger sequencing analysis results for the *UPB1* gene in the patient family with β-ureidopropionase deficiency.

to speech development, she directly oriented to the sound of a bell at 11 months old. She could verbalize baby sounds such as cooing or babbling, but could not speak a word until death. With respect to cognitive–adaptive development, she looked closely at other people when she was 7 months old and responded to her name at 11 months old. However, she did not develop further; in fact, her cognitive–adaptive development regressed. Although she could not recognize her mother, she could only express positive and negative emotions throughout her life.

At the age of 27 months, her social quotient as measured by the social maturity scale test was below 35. She was also assessed for developmental delay using the Korean Bayley Scale of Infant Development–II (K–BSID–II). Using this scale, she was rated to have the fine motor skills of a 6–month–old infant, the gross motor skills of a 3–month–old infant, the communication skills of a 6–month–old infant, the social–emotional skills of a 4–month–old infant, the behavior of a 4–month–old infant, and the occupational skills of a 4–month–old infant. She was given special education consisting of verbal, social, and cognitive therapy; however, the therapy failed to yield significant improvements.

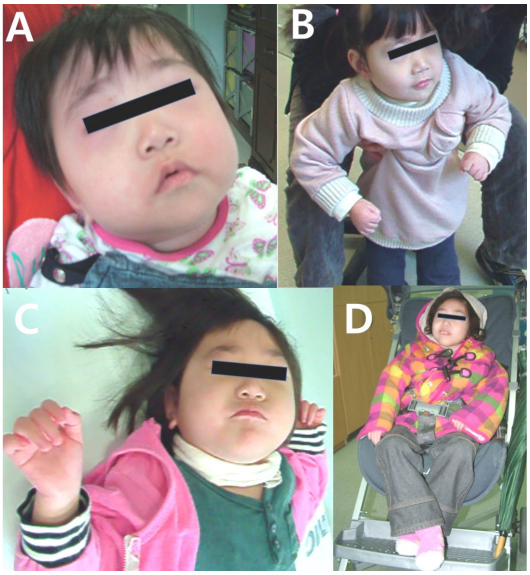

Fig. 2. Serial photographs of the patient. (A) Nearly normal development with seizure at 11 months old. (B) Walking with support for a period of time at 3 years and 4 months old. (C) During a generalized tonic–clonic seizure at 5 years and 7 months old. She could sit with support, but could not stand with support at 9 years and 2 months old (D).

Her seizure history is summarized as follows: Her first seizure occurred when she was 3 months old and was generalized tonic–clonic type without fever. We performed a full work–up for seizure including metabolic, electroencephalography (EEG), and brain magnetic resonance image (MRI) analyses; however, all work–up test results were nonspecific findings. She started a phenobarbital regimen and remained seizure–free until reaching 1 year of age. However, the sound of a car horn triggered multiple recurrent seizures beginning at 1 year of age. We added valproic acid (orfil syrup®), clobazam (sentil®), oxcarbazepine (Trileptal®), topiramate (Topamax®), and pyridoxine to her treatment, but these did not control her generalized tonic type seizures and all domains of her development deteriorated. She visited the emergency room because of generalized type status epilepticus at 3 years and 1 month of age. At this time we performed multiple tests, including serum amino acid and urine organic acid analyses, brain MRI and conventional EEG, the methyl CpG binding protein 2 (MeCP2) gene test for Rett syndrome, the methylation test for Prader–Willi/Angelman syndrome, and a muscle biopsy for mitochondrial disease. However, all results were all normal. As the next step, we performed targeted next–generation sequencing in the patient at age 8 that resulted in homozygous for p.R326Q (c.977G>A) and heterozygous for p.G31S (c.91G>A) mutation in the *UPB1* gene which was confirmed

by Sanger sequencing.

We introduced ketogenic diet therapy at 4 years of age and changed her antiepileptic drugs to lamotrigine (Lamictal®), levetiracetam (Keppra®), zonisamide (Exegran®), and rufinamide (Inovelon®) because of intractable seizure. However, these drugs did not control her seizures, which continued for the rest of her life. Her seizures changed from the generalized tonic-clonic type to the atonic, dialeptic, or head drop type. Her seizure frequency ranged from 4 to 5 times per day to once a day every few days and seemed to be activated by respiratory infection or the ingestion of lactose-containing products such as milk and yogurt. After she was diagnosed with β-UPD, she was placed on a purine-restricted diet because a pyrimidine-free diet was impossible. The frequencies of her seizures and severe seizures (e.g. status epilepticus) reduced slightly, but were still not well controlled. Valproic acid had some beneficial effects on reducing the frequency of generalized type seizures, but also led to decreased platelet count and frequent petechial rashes over the entire body. Rufinamide had some beneficial effects in preventing head drop type seizures. Her last medications before death were as follows: rufinamide (40 mg/kg/day), valproic acid (2.4 mg/kg/day), lamotrigine (5 mg/kg/day), clobazam (1 mg/kg/day), zonisamide (4 mg/kg/day), and L-carnitine (33 mg/kg/day).

She exhibited recurrent infections (10 times per year) such as acute pharyngotonsillitis, bronchitis, and pneumonia. No seasonal or monthly specificity was shown. Her generalized tonic clonic seizures were more difficult to control during infections. Upon reaching school age, her infection frequency reduced to 3 or 4 times per year. However, at this time her seizure pattern changed to atonic seizure and head drop. She also had chronic gastrointestinal problems, including gastroesophageal reflux disease and constipation. She had no behavior problems and was usually calm and shy.

At the age of 11 years and 5 months old, she expired suddenly during sleep the cause of which remains unknown.

Discussion

The purine nucleotides are adenine and guanine, whereas the pyrimidine nucleotides are thymine, cytosine, and uracil. These compounds play important roles in the human body in energy production, cellular signal transduction, protein modification, and also act as phospholipid sources for metabolism and catabolism[6]. Pyrimidine biosynthesis and catalysis also play pivotal roles in sustaining human biochemical metabolism. Specifically, in the central nerve system, pyrimidines participate in brain development and neurological function[7].

The catabolism of pyrimidine bases requires the sequential actions of three enzymes, dihydropyrimidine dehydrogenase, dihydropyrimidinase, and β-ureidopropionase (β-UP). β-UP acts to convert N-carbamyl-β-alanine to β-alanine and to degrade N-carbamyl-β-aminoisobutyric acid to β-aminoisobutyric acid[8]. These reactions begin with uracil and thymine, the products of which are important for neurologic function and structure. β-alanine acts as an inhibitory neurotransmitter in the central nervous system[9] and β-aminoisobutyric acid is a glycine receptor agonist[10].

As with the other pyrimidine catabolism enzymes dihydropyrimidine dehydrogenase and dihydropyrimidinase, defects in β-UP function have been associated with neurologic abnormalities[2]. Previous studies have revealed a range of diverse clinical phenotypes. Some patients with β-UP

deficiency have no clinical presentation[3]. The most predominant clinical features are neurological problems such as seizures; abnormal brain MRI scans; growth retardation; and verbal, social, cognitive, fine motor, and gross motor skill developmental delay (3, 4)[2,4]. The developmental domains of our patient were nearly normal, with only mild gross motor delay until the age of 12 months; however, her development deteriorated after she turned 1 year old and she later exhibited several symptoms such as intractable epilepsy, microcephaly, growth retardation, and feeding problems.

The p.R326Q mutation is known to be a common mutation in Japan and China. In Japan, 2 out of 7 patients with homozygous p.R326Q had seizure, mental retardation or autism, and 5 were asymptomatic. Two patients with Compound heterozygous p.R326Q and p.G31S were asymptomatic[3]. In China, of 3 patients with homozygous p.R326Q, 1 had symptoms of microcephaly and mental retardation and 2 had no symptoms. Our patient had homozygous for p.R326Q (c.977G>A) and heterozygous for p.G31S (c.91G>A) mutation with variable clinical symptoms such as intractable epilepsy, microcephaly, global developmental delay and feeding problems. In addition, the mother of the patient had one c.977G>A and one c.91G>A mutation in one allele. This is a very rare and characteristic finding (Fig. 1). The p.R326Q and p.G31S mutations have not yet been reported in other countries than east Asia[3,11].

Although the cause of the sudden and unexpected death of our patient is unknown, several possible causes can be considered. The first such possibility is epilepsy. She had been diagnosed with bronchiolitis three days before she died; moreover, she already had gastroesophageal reflux disease. Each of these factors is a potential risk factor for sudden unexpected death in epilepsy. In cohorts of patients with epilepsy, death is often related to diseases such as pneumonia, bronchitis, bronchiolitis, cerebrovascular disease, and cardiovascular disease[12]. Moreover, patients with epilepsy have a 24-fold higher risk of sudden unexpected death compared with the general population[13]. In epilepsy, sudden unexpected death is mainly a sleep-related and unwitnessed phenomenon[14,15]. Second, asphyxia due to vomiting or seizure was considered because digested food was found in her hair and face at the emergency room. Third, other unknown metabolic problems related to β-UPD were also considered. Though her death was not witnessed, we propose that β-UPD might be a risk factor for sudden unexpected death.

In conclusion, we think that if a patient with unidentified intractable epilepsy, global developmental delay or microcephaly is found, β-UPD should be considered as one of several diagnostic possibilities and targeted next-generation sequencing need to be performed if necessary.

요 약

β-ureidopropionase 결핍증(β-UPD)은 *UPB1* 유전자 변이에 의한 피리미딘 대사 이상에 의해 생기는 매우 드문 상염색체 열성 유전 질환으로 현재까지 전 세계에서 30여명 정도만 보고되었다. β-UPD는 무증상인 경우부터 심한 발달 지연, 소두증, 발작, 인지 저하의 증상을 보이는 경우까지 다양하다. 국내에서 진단된 유일한 β-UPD 여자 환자는 8세 10개월에 targeted next-generation sequencing 검사로 *UPB1* 유전자 변이를 확인 한 후, Sanger sequencing을 통해 확진하였다. 환자는 성장 장애, 발단 지연, 소두증, 반복되는 감염 및 난치성 뇌전증 증상을 보였으며, 11세 5개월에 원인 미상으로 갑자기 사망하였다. 이에 저자들은 β-UPD 환자의 장기간의 임상경과에 대해 보고하는 바이다.

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