

# 기면과 중추성 무호흡으로 나타난 단풍시럽뇨병 Type 1B 신생아 1례

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## A Newborn Case of Maple Syrup Urine Disease Type 1B Presenting with Lethargy and Central Apnea

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Maple syrup urine disease (MSUD, OMIM#248600) is a rare and autosomal recessively-inherited metabolic disorder that is caused by mutations in the branched-chain  $\alpha$ -ketoacid dehydrogenase (BCKDH) genes. It prevents the normal breakdown of branched-chain amino acids (BCAAs), such as leucine, isoleucine, and valine, and leads to poor feeding, lethargy, abnormal movements, seizure, and death if untreated. Here, we report the case of a Korean newborn of biochemically- and genetically-confirmed MSUD manifesting lethargy and central apnea, the acute state of which was successfully treated. The molecular genetic investigation revealed two novel heterozygous mutations (p.Ala32Phefs\*48 and p.Val130Phe) in *BCKDHB*, and both parents were confirmed as carriers. We emphasize the importance of early diagnosis and prompt introduction of specific treatment for MSUD in life saving and prognosis.

**Key words:** Maple syrup urine disease, Branched-chain  $\alpha$ -ketoacid dehydrogenase, Branched-chain amino acid, Central apnea

### Introduction

Maple syrup urine disease (MSUD, OMIM#248600) is a rare and autosomal recessively-inherited metabolic disorder caused by mutations in a complex enzyme system encoded by branched-chain  $\alpha$ -ketoacid dehydrogenase (BCKDH) genes. This mitochondrial enzyme complex consists of four subunits: E1 $\alpha$ , E1 $\beta$ , E2, and E3<sup>1)</sup>. The defects in E1 $\alpha$ , E1 $\beta$ , E2, and E3 are classified as MSUD

type 1A, type 1B, type 2, and type 3, respectively. Deficiencies in any of these subunits prevents the normal breakdown of branched-chain amino acids, such as leucine, isoleucine, and valine.

Based on the age of symptom-onset, severity of clinical symptoms or signs, and responsiveness to thiamine, MSUD can be classified as either classic, intermediate, intermittent, or thiamine-responsive<sup>2)</sup>. Classic MSUD is the most common and most severe form of MSUD. Patients with classic MSUD often present with poor feeding, vomiting, lethargy, and irritability within the first two days of life. Apnea, dystonia, and seizures

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may present by four to seven days of life<sup>3)</sup>. Intermittent and intermediate forms of MSUD show less severe metabolic and clinical manifestations than classic MSUD. MSUD is often initially suspected based on a maple syrup odor in bodily fluids, especially in urine. Diagnosis is typically confirmed through amino acid analysis showing markedly increased levels of leucine, isoleucine, alloisoleucine (a metabolite of leucine not normally found in blood), and valine. The worldwide prevalence of MSUD is 1 in 185,000 live births. However, it is much rarer in Korea, at a rate of 1 in 1,148,413 live births<sup>4)</sup>, which is related to the lack of a founder mutation cluster. In some populations such as Mennonite, the incidence is as high as 1 in 380 as a result of the representative founder variant (c.1312T>A) in *BCKDHA*<sup>5)</sup>.

Here, we report a case of a Korean newborn with biochemically- and genetically-confirmed classic MSUD (type 1B) manifesting with ketoacidosis, hyperammonemia, lethargy and central apnea.

### Case Report

A girl was born to a 24-year-old woman with para 0-0-0-0 as a singleton at the gestational age of 39+6 weeks, with a birth weight of 2.54 kg, via normal spontaneous vaginal delivery. She was the first baby of healthy and nonconsanguineous parents and did not have any perinatal problems or family history of inherited metabolic diseases. At 10 days of age, she visited the emergency room at the local hospital because of lethargy and poor-sucking. The initial laboratory data showed hypoglycemia (serum glucose 45 mg/dL) and ketoacidosis (VBGA pH 7.28, pCO<sub>2</sub> 40 mmHg, HCO<sub>3</sub><sup>-</sup> 20.1 mmHg, base excess -9.8 mEq/L, lactate 1.3 mmol/L), so she was admitted for in-

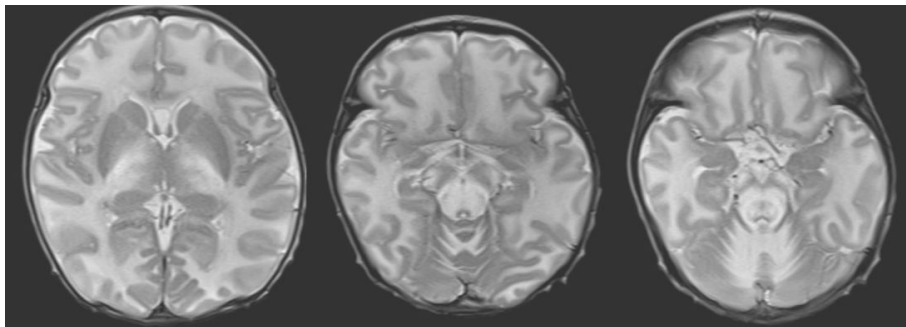
travenous hydration. Over the next day, the results of newborn screening performed at the age of three days showed a markedly increased level of leucine (41.1 mg/dL, reference range (ref.) < 4.1 mg/dL), and MSUD was suspected. She was transferred to Seoul National University Children's Hospital for further evaluation and management.

As for the findings of a physical examination upon admission to our hospital, she looked lethargic and her Glasgow Coma Scale (GCS) score was 7 of 15 (E2V1M4). Her length, body weight, and head circumference were 47.5 cm (3-10<sup>th</sup> percentile), 2,610 gm (<3<sup>rd</sup> percentile), and 33 cm (3-10<sup>th</sup> percentile), respectively, and her urine smelled like maple syrup. She had central apnea and repetitive desaturation down to SpO<sub>2</sub> 40% which appeared nearly every hour. Therefore, endotracheal intubation was performed and conventional ventilation was begun. Intravenous glucose (glucose infusion rate 9.7 mg/kg/min) and lipid without protein were administered and branched-chain amino acid (BCAA) low formula feeding was started via a gavage tube. Thiamine (10 mg/kg/d) was also tried for the evaluation of thiamine responsiveness. The biochemical analysis upon admission showed hyperuricemia (11.3 mg/dL, ref. 3.0-7.0 mg/dL) and hyperammonemia (236 μmol/L, ref. 15-51 μmol/L). Rasburicase and sodium benzoate were begun intravenously and the follow up laboratory findings showed decreased levels of uric acid (<3.0 md/dL) and ammonia (<150 μmol/L). The initial electroencephalography showed epileptiform discharge and phenobarbital was begun for seizure prevention. The brain sonography showed cerebral edema involving the deep gray matter (basal ganglia/thalami), brainstem, and cerebellum, while the brain MRI showed bilateral symmetrical hyperintensity with diffusion restriction, suggesting cytotoxic edema involving

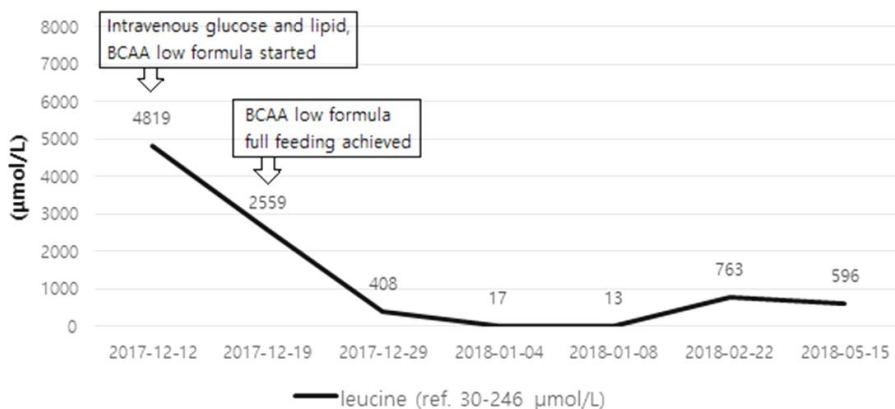
the optic chiasm, optic radiate, corticospinal tract, the anterior and posterior limb of internal capsule, thalami, posterior midbrain, pons, medulla, and the cerebellar white matter (Fig. 1). We started furosemide 1 mg/kg q 6 hrs and mannitol 0.5 g/kg q 6 hrs in order to manage the diffuse brain edema. The follow up brain sonography after seven days showed equivocal decreased diffuse edema. The initial serum amino acid analysis showed very high levels of isoleucine (979  $\mu\text{mol/L}$ , ref. 12–77  $\mu\text{mol/L}$ ), leucine (4,819  $\mu\text{mol/L}$ , ref. 46–147  $\mu\text{mol/L}$ ), alloisoleucine (726  $\mu\text{mol/L}$ , ref. <2  $\mu\text{mol/L}$ ), and valine (762  $\mu\text{mol/L}$ , ref. 79–217  $\mu\text{mol/L}$ ). The initial urine organic acid analysis showed increased

2-hydroxyisovaleric acid, 2-ketoisocaproic acid, 2-hydroxyisocaproic acid, and 2-hydroxy-3-methylvaleric acid. She could be diagnosed clinically as having the classic type of MSUD. We followed up serum amino acid analysis with specific treatment and a low-BCAA formula, and this was followed by decreased levels of the branched chain amino acids (Fig. 2).

After 29 days of NICU care, the GCS had increased to 15 and the respiration was stable without apnea in air, and a full oral feeding of low-BCAA formula was successfully achieved. She was transferred to the general ward and discharged at the age of 41 days. She has since vi-



**Fig. 1.** The brain MRI showed bilateral symmetrical hyperintensity with diffusion restriction, suggesting cytotoxic edema involving the optic chiasm, optic radiate, corticospinal tract, the anterior and posterior limb of internal capsule, thalami, posterior midbrain, pons, medulla, and the cerebellar white matter.



**Fig. 2.** The follow-up serum amino acid analyses showed decreased levels of leucine with specific treatment. The level has since been kept below 800  $\mu\text{mol/L}$  in the patient.

sited the outpatient clinic on a regular basis for growth and development check-ups and for monitoring of her BCAA levels. She is now five months old with a height of 60 cm (<3<sup>rd</sup> percentile), weight of 6.1 kg (3–10<sup>th</sup> percentile), and head circumference of 41.3 cm (25–50<sup>th</sup> percentile). She can babble and roll over toward both sides, although her head control is not perfect. Phenobarbital is being tapered and her levels of BCAA are kept stable below 800 μmol/L of leucine.

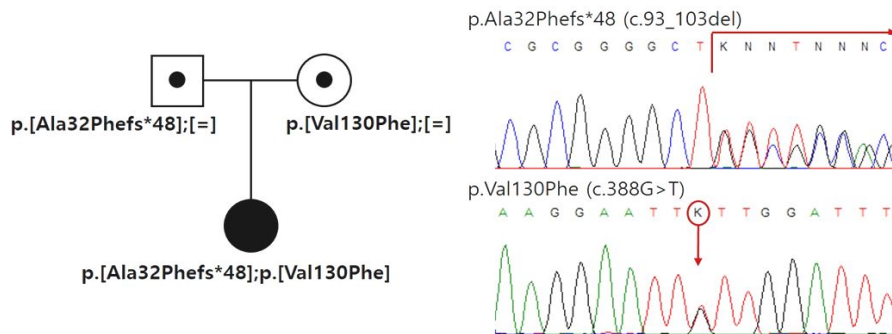
Under the clinical diagnosis of MSUD, the molecular genetic investigation for *BCKDHA*, *BCKDHB*, and *DBT* was performed, revealing two novel heterozygous mutations (p.Ala32Phefs\*48 and p.Val130Phe) in *BCKDHB*. Both parents harbored each of the two identified mutations and they were both confirmed as carriers (Fig. 3).

### Discussion

Maple syrup urine disease is caused by decreased activity of branched-chain α-ketoacid dehydrogenase (BCKAD), a multi-enzyme complex in the mitochondria. BCKAD has four subunits (E1α, E1β, E2, and E3). The gene of each subunit is located on different chromosomes: E1α (*BCKDHA*) on chromosome 19q13.1–q13.2, E1β (*BCKDHB*) on chromosome 6q14.1, E2 (Dihydrolipoamide

branched chain transacylase, *DBT*) on chromosome 1p21.2, and E3 (Dihydrolipoamide dehydrogenase, *DLD*) on chromosome 7q31.1<sup>6)</sup>.

MSUD type 1A, which is a deficiency of E1α, accounts for 45% of all cases, comprising approximately 1 in 411,000 newborns. There are about 70 reported sequence variants in E1α<sup>7,8)</sup>. Type 1B, a deficiency in E1β, accounts for 35%, or approximately 1 in 528,000 newborns. This type is much more commonly seen in Ashkenazi Jews. More than 70 sequence variants in E1β have been reported to date<sup>8,9)</sup>. It is known that most cases of MSUD involve compound heterozygotes for rare sequence variants<sup>10)</sup>. In Korea, less than 10 MSUD patients have been reported, and only three of them have been confirmed through molecular genetic testing<sup>11)</sup>. In this case, the molecular genetic study revealed two novel heterozygous mutations: c.93\_103del (p.Ala32Phefs\*48) from the father and c.388G>T (p.Val130Phe) from the mother, respectively. p.Ala32Phefs\*48 leads to premature truncation of protein synthesis, and p.Val130Phe is a missense mutation. The other variant at the same location, p.Val130Gly, has been previously reported as affecting cofactor binding<sup>12)</sup> so p.Val130Phe is thought to be pathological. As a result, the novel variants combined together are thought to be related to very low residual *BCKDHB* activity.



**Fig. 3.** The molecular genetic study revealed two novel heterozygous mutations (p.Ala32Phefs\*48 and p.Val130Phe) in *BCKDHB*, and both parents were confirmed as carriers.

A deficiency of E3 produces congenital lactic acidosis because the E3 subunit shares pyruvate dehydrogenase and  $\alpha$ -ketoglutarate dehydrogenase. It shows increased plasma levels of pyruvate and alanine and elevated urinary excretion of branched-chain ketoacids (BCKAs) and alpha-ketoglutarate. The clinical phenotype of E3 subunit deficiency differs from that of classic or intermediate MSUD. It ranges from early-onset neurologic symptoms to adult-onset liver complications. Affected infants usually do not survive their first few years of life but those who survive manifest intellectual ataxia, disability, spasticity and seizure. Adult-onset E3 deficiency has also been reported. If the onset is later in life, liver complications are usually the only symptom<sup>13</sup>.

Neonatal screening tests make it possible to detect MSUD early on; however, affected neonates might show clinical signs and symptoms before the results of the screening test are even returned, as seen in the present case. Now, if the pathogenic variants of *BCKDHA*, *BCKDHB*, or *DBT* have been found in a family, prenatal diagnosis for future pregnancy is possible through the genetic testing of DNA from amniocytes or chorionic villi<sup>14</sup>.

In the case of an acute MSUD crisis, sufficient nutrients and calories should be provided as soon as possible, because the patient is under a catabolic state. Rapid removal of BCAAs is also necessary. In this case, hydration and intake restriction of BCAAs without dialysis improved her metabolic state, although many publications have shown that hemodialysis or peritoneal dialysis can remove BCAAs and BCKAs rapidly during the acute phase of MSUD<sup>15</sup>. Dialysis should be considered in patients presenting with severely altered mental status and cerebral edema<sup>16</sup>.

BCAAs, especially leucine, are known to be

cytotoxic to brain cells, leading to cytotoxic cerebral edema affecting the myelinated white matter<sup>17</sup>. As a result, brain MRI during the acute state may show marked restricted diffusion, reflecting intracellular edema, involving the corticospinal tracts (the posterior limbs of the internal capsule), thalami, globus palladi, midbrain, dorsal brain stem, and cerebellar white matter<sup>18</sup>. In this case, the brain sonography and brain MRI showed diffusion restriction, suggesting cytotoxic edema involving the deep gray matter (basal ganglia/thalami), brainstem, and cerebellum. Although the definite effect of mannitol and furosemide on cytotoxic edema is not known, we successfully attempted to find the decreased cerebral edema on the follow-up brain sonographies.

Even following recovery from the acute state, patients should be kept on a diet low in BCAAs for the rest of their lives<sup>19</sup>. Dietary management should consider age-appropriate nutrition and tolerance of BCAAs. Patients also need frequent clinical and biochemical monitoring in order to maintain stable plasma BCAA levels. Severe ketoacidosis, cerebral edema, and even death can occur in the face of any stressful event, such as infection or injury, because infections and injuries mobilize a large endogenous muscle protein, causing a metabolic crisis<sup>3</sup>.

For patients in which diet modification and other conservative management have failed, liver transplantation might be considered. Only 10% of BCKDH is expressed in the liver and liver transplantation does not reverse the neurologic or psychiatric illness. However, it is known to decrease the frequency and the severity of life-threatening cerebral edema and to prevent the progression of neurocognitive impairment<sup>20</sup>.

The prognosis of MSUD is related to the age of the child at the time of diagnosis and to the

adequacy of metabolic control<sup>21</sup>). Although our patient had the classic infantile form of MSUD manifested by metabolic crisis on the day of her birth, she has since caught up with development without metabolic events through the application of immediate specific treatment. Here, we emphasize the importance of early diagnosis and prompt introduction of specific treatment for MSUD in life saving and prognosis.

## 요 약

단풍시럽뇨병은 드문 상염색체 열성 대사 질환으로 측쇄 알파 케토산 탈수소효소 돌연변이에 의해 발생되는 질환이다. 측쇄 아미노산인 류신, 이소류신, 발린의 분해가 되지 않아 몸에 축적이 되고 식욕 저하, 구토, 기면, 이상행동, 발작 및 심한 경우 죽음을 초래한다. 세계적으로 단풍시럽뇨병의 유병율은 185,000명당 한 명이지만 한국에서는 극히 드물어 1,148,413명당 한 명으로 보고된다.

이 증례의 여아는 만삭에 2.54 kg로 주산기 특이 병력 없이 출생한 첫째 아이로 특이 가족력 없었던 환자이다. 생후 10일경 식욕저하, 구토, 기면으로 타병원에서 대증치료 중에 선천성 대사이상 선별 검사 결과 상류신이 높아 전원 되었다. 환아는 기면, 혼수를 보였고 중추 수면무호흡으로 인공호흡기를 적용하였으며 소변에서 단풍시럽 냄새를 보였다. 뇌 초음파, 뇌 자기공명 영상에서 뇌부종 소견을 보였으며 혈중아미노산 검사상 류신, 이소류신, 발린의 수치가 정상치보다 매우 높았다. 측쇄 아미노산 없는 특수분유를 시작했고 뇌부종으로 만니톨과 이뇨제를 사용했으며 고암모니아혈증으로 벤조산을 투약하였다. 경련 예방을 위해 페노바비탈을 투약하였으며 측쇄 알파 케토산 탈수소효소의 조효소인 타이아민 보충을 시작하였다. 치료함에 따라 혈중 측쇄 아미노산 수치가 감소하였고 뇌부종의 감소가 확인되었다. 29일 간의 신생아중환자실 처치 후 환아는 호흡 및 구강 식이 진행이 안정적이었고 병동으로 전동 후 퇴원하였다. 환아는 현재 5개월로 페노바비탈을 점차 줄여가고 있으며 측쇄 아미노산 수치도 안정적으로

유지되고 있다. 고개 가누기는 완벽하지 않지만 용알이 및 뒤집기 가능하며 따라잡기 성장 및 발달을 보이고 있다. 유전학적 검사에서는 두 개의 *BCKDHB* 이형접합 돌연변이 p.Ala32Phefs\*48와 p.Val130Phe를 확인 하였으며, 가족 검사를 통하여 부모 모두 보인자임을 확인하였다. 이 두 변이는 모두 이전에 한국에서 보고되지 않은 변이이다. 단풍시럽뇨병의 빠른 진단과 즉각적이고 적절한 치료가 환자의 생명을 유지하고 예후를 호전시킴을 본 증례를 통하여 다시 한 번 확인할 수 있다.

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