Pediatrics and Neonatology (2014) xx, 1–5

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journal homepage: http://www.pediatr-neonatol.com

CASE REPORT

Maple Syrup Urine Disease Complicated with Kyphoscoliosis and Myelopathy

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Received May 15, 2013; received in revised form Oct 1, 2013; accepted Oct 22, 2013

Key Words
acrodermatitis enteropathica;
DBT gene;
maple syrup urine disease;
myelopathy;
zinc deficiency

Maple syrup urine disease (MSUD) is an autosomal recessive aminoacidopathy secondary to an enzyme defect in the catabolic pathway of the branched-chain amino acids (BCAAs: leucine, isoleucine, and valine). Accumulation of their corresponding keto-acids leads to encephalopathy if not treated in time. A newborn male patient was suspected to have MSUD after tandem mass study when he presented symptoms and signs suggestive neonatal sepsis, anemia, and diarrhea. Food restriction of BCAAs was started; however, acrodermatitis enteropathica-like skin eruptions occurred at age 2 months. The skin rashes resolved after adding BCAAs and adjusting the infant formula. At age 7 months, he suffered from recurrent skin lesions, zinc deficiency, osteoporosis, and kyphosis of the thoracic spine with acute angulation over the T11-T12 level associated with spinal compression and myelopathy. After supplementation of zinc products and pamidronate, skin lesions and osteopenia improved gradually. Direct sequencing of the *DBT* gene showed a compound heterozygous mutation [4.7 kb deletion and c.650-651insT (L217F or L217fsX223)]. It is unusual that neurodegeneration still developed in this patient despite diet restriction. Additionally, brain and spinal magnetic resonance imaging, bone mineral density study, and monitoring of zinc status are suggested in MSUD patients.

1. Introduction

Maple syrup urine disease (MSUD, OMIM 248600) derives its name from the odor of the patient's urine, which resembles that of maple syrup (burned sugar). MSUD has been described in all ethnic groups and occurs in about 1/185,000 and 1/101,624 newborns in the USA and Taiwan, respectively.[1,2] MSUD is caused by the deficiency of a branched-chain α-keto acid dehydrogenase (BCKD) complex, which catalyzes the oxidative decarboxylation of the α-keto acids of branched-chain amino acids (BCAAs: leucine, isoleucine, and valine).[1,2] Accumulation of the pathogenic compounds including BCAAs and their corresponding α-keto acids contribute to the phenotype of

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1875-9572/$36
http://dx.doi.org/10.1016/j.pedneo.2013.10.013

Please cite this article in press as: Hou J-W, Maple Syrup Urine Disease Complicated with Kyphoscoliosis and Myelopathy, Pediatrics and Neonatology (2014), http://dx.doi.org/10.1016/j.pedneo.2013.10.013

MSUD.[1–4] Mutations in any one of the three different genes encoding for the BCKD components [*BCKDHA* (accession number: HS11695), *BCKDHB* (HS11696), and *DBT* (HS11697)] may be responsible for this disease.[1,2] All patients with MSUD are at an increased risk of developing decompensating status of metabolism during periods of increased protein catabolism (e.g., concomitant illness, trauma, and surgery).[1] With early diagnosis, as well as appropriate treatment at the time of diagnosis and during episodes of potential metabolic decompensation, the deterioration and comorbidity can almost always be prevented.[1–4] The reported male infant suffered from early onset of acrodermatitis enteropathica (AE)-like skin lesions secondary to isoleucine deficiency. However, recurrent skin lesions, zinc deficiency, significant osteoporosis, kyphoscoliosis with spinal compression, and myelopathy developed at age 7 months despite adequate diet control for BCAAs. DNA studies on the *BCKDHA*, *BCKDHB*, and *DBT* genes were performed.

2. Case report

This male patient is the second child of young, healthy, and nonconsanguineous parents of the Amis Tribe (Aborigines in Taiwan). He was born full-term with birth weight of 3275 g, birth length of 51 cm, head circumference of 33.5 cm, after a smooth pregnancy course and vaginal delivery. Decreased appetite and activity with easy choking developed since the 7th day after birth, accompanied by dry lips, hypothermia, and constipation. He was treated as neonatal sepsis, but subsequent features including bulging fontanelle, twitching of limbs, and apparent body odor were noted. Anemia with hemoglobin 1.36 mM [reference range (rr), 1.40–2.17mM] and thrombocytosis (613×10^9 platelets/L; rr, $150–400 \times 10^9$ platelets/L), slightly elevated liver enzymes, and hypoglycemia (glucose: 2.16 mM; rr, 3.3–5.5 mM) were found. A diagnosis of MSUD was made based on the clinical features, and findings of tandem mass metabolic screening in dried blood spots: high levels of valine (1026μM; rr, 84.07–354μM) and leucine/isoleucine (829.41μM; rr, 56.82–287μM). Later plasma BCAAs concentrations detected by an amino acid analyzer showed valine 1350 μM (rr, 86–190μM), leucine 3105 μM (rr, 48–160μM), isoleucine 543 μM (rr, 26–91μM), and urine gas chromatography/mass spectrometry studies revealed elevated α-hydroxyisovalerate, 2-hydroxyisovaleric, 3-hydroxyvaleric, 2-hydroxy-3-methylvaterate, lactate, pyruvate, and α-ketoglutarate. Seven days after initiating therapy with a particular diet (14% MJ MSUD Diet Powder, from Mead Johnson & Company, Evansville, IN, US; total protein: 2.4 g/kg/day, along with 62.5 mg/kg/day leucine), the plasma leucine/isoleucine and valine concentrations were reduced to about 1.25–1.5 times the upper normal limits. In addition, administering thiamine (10–20 mg/day) for 3 weeks excluded the possibility of thiamine-responsive MSUD. At age 1.5 months, hypertonicity of the lower extremities developed. Brain ultrasound showed abnormal faint echogenicity over the bilateral hemispheres, favoring edema or infarction. The result of echocardiography, thyroid, kidney, and liver function tests were all normal. At age 2 months, progressive scaling over the face, trunk, limbs, perineum, scalp, and digits appeared together with anemia and diarrhea. His periorificial and acral dermatitis was resistant to topical corticosteroid therapy. Plasma BCAAs concentrations at the time were as follows: valine 71 μM, leucine 50 μM, and isoleucine 15.7 μM. Serum zinc concentration was slightly decreased (zinc: 128.8 μM; rr, 144–227 μM). AE-like syndrome secondary to isoleucine and valine deficiency was suspected, possibly due to over-restriction of protein intake. Subsequent supplementation of BCAAs (115 mg/kg/day of leucine, 90 mg/kg/day of isoleucine, and 100 mg/kg/day of valine, combined with other amino acids) resulted in a rapid amelioration of his skin eruption. Later plasma concentrations of BCAAs (measured every 2–3 months) were kept at about twice (1.2–2.9) of mean levels of normal ranges by adjusting the milk formula.

At age 5 months, electroencephalography showed diffuse cortical dysfunction and focal epileptiform discharge. Motor development was markedly retarded. Recurrent skin rashes as AE and scoliosis were noted at age 7 months. Plasma zinc concentration was markedly decreased (92.6 μM). Imaging studies showed kyphoscoliosis of the thoraco-lumbar spine with acute angulation at the T11-12 level (Figure 1). Wedging deformity of the T11 and T12 vertebrae with retropulsion of the posterior bony margins compressing the lower spinal cord and conus medullaries resulted in hyperintensity and swelling on

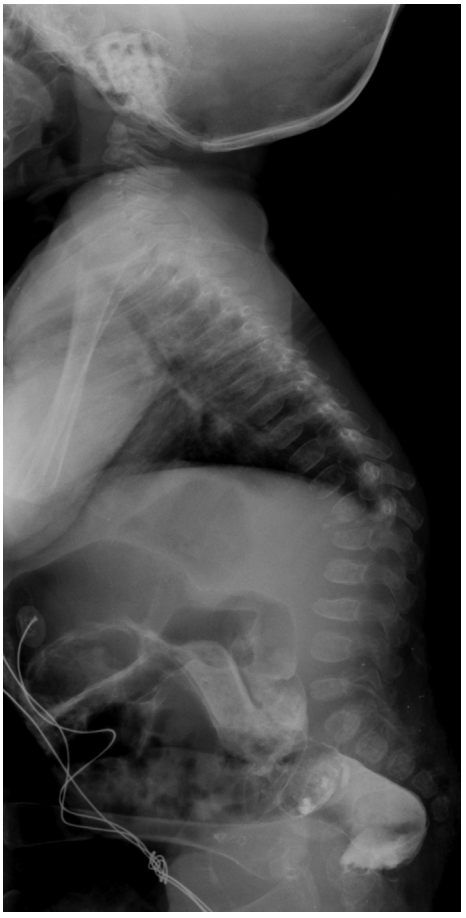

Figure 1 Spinal X-ray study showing kyphosis of the T-L spine with acute angulation at T11-12 level.

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