Serial MR Images and MRS Following Treatment in a Newborn with Maple Syrup Urine Disease

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ABSTRACT

Maple syrup urine disease (MSUD) is a rare autosomal recessive metabolic disorder affecting branched-chain amino acids. We report a newborn with MSUD established by neonatal metabolic screening at 2 days old which showed elevation of plasma level of leucine/isoleucine and valine. The magnetic resonance (MR) imaging at 16 days old revealed typical finding of high signal intensity lesions within the myelinated white matter areas on T2-weighted and diffusion-weighted images (DWI). Proton MR Spectroscopy (MRS) showed elevation of lactate (1.3 ppm) and BCAA/BCKA (0.9 ppm) peaks. The MRS findings in our case were well-corresponded to the change of serum levels of leucine, isoleucine, and valine by serial MR images and laboratory data following treatment. MR images and MRS provided specific diagnosis of MSUD and effective monitoring of the response following treatment and dietary restriction.

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Maple syrup urine disease (MSUD) is a rare inherited metabolic disorder due to decreased decarboxylation of branched-chain amino acids (BCAA), which include leucine, isoleucine and valine, leading to the accumulation of toxic levels of BCAA and branched-chain alpha-keto acid (BCKA) in the body resulting in severe metabolic acidosis and neurological deficits. The diagnosis of MSUD is made clinically based on the peculiar maple syrup or burnt sugar odor of the urine, encephalopathy, increased levels of branched-chain amino acids in the plasma and urine, and the presence of α-hydroxyacid and BCKA in urine. The presence of plasma L-alloisoleucine and urinary α-hydroxy isovalerate are pathognomonic for MSUD [1]. Although several previous reports had presented diffusion MRI and Proton MR Spectroscopy finding in maple syrup urine disease, correlation between MRI finding and serum level of BCAA was not mentioned. We report the initial and post-treatment findings of serial MR images and MR spectroscopy in a newborn with MSUD.

CASE REPORT

A full-term female infant was born by normal spontaneous delivery after an uneventful pregnancy. Her birth weight was 3,800 g and Apgar scores of 9/10 at 1 and 5 min respectively. Her mother did not receive any prenatal examination. The activity and respiratory condition was fair after birth. The plasma BCAA (leucine, isoleucine, and valine) levels were markedly elevated on chromatogram of neonatal
metabolic screening at 2 days old. Leucine level was 696 μmol/L (normal value < 300 μmol/L) and valine level was 471.4 μmol/L (normal value < 250 μmol/L). Classic type maple syrup urine disease was diagnosed. At 8 days, she was hospitalized because of poor feeding, irritable crying, and decreased urine output. Hyperammonemia and metabolic acidosis were disclosed clinically. Her chromatogram at 8 days showed high levels of leucine (3136.2 μmol/L), isoleucine (578.6 μmol/L), and valine (1226.9 μmol/L). MR images were performed at 16 days old and revealed bilateral symmetric high signal intensity lesions at the posterior periventricular white-matter, posterior limbs of internal capsules, globus pallidi, lateral thalami, midbrain, cerebral vermis, pons and brain stem. MRS showed elevation of lactate (1.3 ppm) and BCAA/BCKA (0.9 ppm) peaks (Fig. 2). She received treatments including peritoneal dialysis, total parental nutrition, sodium benzoate, and special diet.

Follow-up MR images were performed at 43 days and 68 days of age and revealed gradual improvement in the hyperintense lesions on T2-weighted and diffusion-weighted images (Fig. 3). MRS showed significant decrease in the concentration of lactate and BCAA/BCKA at 43 days of age; and obvious decrease of these abnormal metabolites at 68 days of age (Fig. 4). Following treatment, the serum levels of leucine, isoleucine, and valine returned to normal at 6 months of age (Table 1). We also observed decreased corresponding peaks of these metabolites on the MRS.
Figure 1

Figure 2. Proton MRS (TR=1600ms TE=288ms) showed elevation of lactate (1.3 ppm) and BCAA/BCKA (0.9 ppm) peaks with decline of NAA.
Figure 3. Follow-up MR images after treatment. a.-d. T2 FLAIR (TR=8627ms, TE=152ms, TI=2100ms). At 43 days old showed mild improvement of the hyperintense lesions in the involved regions as initial study. e.-h. At 68 days old, FLAIR T2WI (TR=7302ms, TE=121ms, TI=2000ms) revealed significantly diminished hyperintense lesions.
MSUD is a genetically heterogeneous aminoacidopathy, resulting in severe impairment or death if the disease is not recognized and treated. It is an inherited genetic disease with an autosomal recessive pattern affecting approximately 1 out of 120,000-500,000 infants worldwide [2-4]. It is caused by a deficiency of BCKA dehydrogenase, an enzyme complex catalyzing the oxidative decarboxylation of BCKA, which is produced after transamination of essential BCAA (isoleucine, leucine and valine). According to the literature, three (classic, intermediate, and intermittent) or five (classic, intermediate, intermittent, thiamine-responsive, and dihydrolipoyl dehydrogenase-deficient) forms have been described; these seem to correlate with the degree of residual enzyme activity [5]. The classic type is the most common form and has most severe clinical manifestation. Infants with MSUD are usually normal at birth. In the classic type, onset of clinical signs and symptoms occurs during first week of life with poor feeding, vomiting, lethargic sleep, alternating periods of hypertonia and hypotonia, irregular respiration and apnea. In the intermediate type, patient can usually tolerate a greater amount of leucine. However, when ill or fasting, the child with intermediate MSUD reacts just like a child with classic MSUD. The intermittent type is a milder form of the disease because of the greater enzyme activity present. The thiamine-responsive child will increase the enzyme activity which breaks down leucine, isoleucine and valine while giving large doses of thiamine. The dihydrolipoyl dehydrogenase-deficient type is similar to those of intermediate MSUD, but there is an accompanying severe lactic acidosis.
MUSD is diagnosed according to specific clinical findings and abnormal plasma L-alloisoleucine and urinary α-hydroxy isovalerate level. Specific MR findings also give a clue to make a diagnosis if lab data cannot be acquired initially. MR findings in acute phase are quite characteristic, usually revealing profound localized edema (hyperintense on T2WI) in the deep white matter, dorsal brainstem, cerebellar peduncles, and posterior limb of the internal capsule, perioralndic white matter, and globi pallidi [5-9]. Our case showed typical hyperintensity lesions in similar distributions. Jan et al. in the diffusion MR study of patients demonstrated marked restriction of diffusion (decreased ADC) compatible with cytotoxic or intramyelinic sheath edema in the involved [10]. The acute toxic effects of BCAA and BCKA might induce severe intramyelinic edema, which is associated with a reversible disturbance of the fluid retention mechanisms of the myelin sheath [11].

Proton MRS in our case demonstrated abnormal peaks of BCAA and BCKA at 0.9 ppm and lactate at 1.3 ppm with relative loss of NAA, which are consistent with the findings in previous reports [10, 12-14]. Heindel et al found that the use of a long TE is important to avoid contamination with the signal of lipids and macromolecules [13]. At TE=136 ms, the signal of BCAA/BCKA is inverted [13]. This also happened in our case when TE=144 ms was used. Lifelong dietary restriction of the BCAA may allow survival. MRS can be used to monitor response of treatment and diet restriction. The previous reports mention that abnormal peaks of BCAA and BCKA at 0.9 ppm disappear with clinical recovery [13, 14]. NAA is also shown to return to normal and lactate also disappears [15]. The abnormal peaks at 0.9 ppm were still visible after clinical recovery in few cases reported [14, 15]. In our patient, decline in the abnormally elevated lactate and BCAA/BCKA peaks was noted following treatment. The MRS presentations in our patient were parallel to the improvement of clinical symptoms. Furthermore, the MRS findings in our case were well-corresponded to the change of serum levels of leucine, isoleucine, and valine.

In conclusion, MR images and MRS provided specific diagnosis of MSUD and effective monitoring of the response following treatment and dietary restriction.

REFERENCES