

Maple syrup urine disease: Role of diffusion-weighted magnetic resonance imaging

Ramakrishna Narra¹, P Bhimeswara Rao², B Johny Prasad³, Anusha Putcha⁴

From ¹Additional Professor, ²Professor, ³Assistant Professor, ⁴Junior Resident, Department Radio Diagnosis, Katuri Medical College, Guntur, Andhra Pradesh, India

Correspondence to: Dr. Ramakrishna Narra, Flat No: 30, 5 Floor, Venkatesh Estate Apartment ½ Chandramouli Nagar, Guntur - 522 006, Andhra Pradesh, India. E-mail: narra.ramki29@gmail.com

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ABSTRACT

Maple syrup urine disease (MSUD)/leucine encephalopathy is an inborn error of amino acid metabolism resulting in neurotransmitter depletion, disrupted brain growth and development. Magnetic resonance (MR) with diffusion-weighted imaging is the best imaging tool during hyperacute and acute phases. We report a case of a child who was presented with global developmental delay and foul smelling of urine and diagnosed as MSUD with typical MR imaging findings and laboratory findings.

Key words: *Branched-chain amino acids, Diffusion-weighted magnetic resonance imaging, Maple syrup urine disease*

Maple syrup urine disease (MSUD) is a rare autosomal recessive condition. It is a disorder of branched-chain amino acids (leucine, isoleucine, and valine) metabolism, which occurs due to the deficiency of branched-chain alpha-ketoacid decarboxylase complex. Accumulation of branched-chain ketoacid causes disruption of Krebs cycle, displaces other essential amino acids, causing neurotransmitter depletion, and resulting in disrupted brain growth and development [1]. The estimated worldwide incidence of MSUD is 1 in 185,000 infants [2]. Diffuse, bilateral symmetrical edema involving the cerebellum, brainstem, globus pallidus, thalami, cerebral peduncles, and corticospinal tracts with marked diffusion restriction on diffusion-weighted magnetic resonance imaging (DWI) and reduced apparent diffusion coefficient (ADC) values are the most common findings on magnetic resonance imaging (MRI) in MSUD.

CASE REPORT

A 1-year, 2-month-old male child, born to non-consanguineous parents, presented with complaints of unable to hold the neck of child and foul smelling of urine since birth. The child was unable to recognize his mother and there were feeding difficulties, especially to solid, semi-solid food, and pooling of secretions were also present. The antenatal period was uneventful with normal vaginal delivery in a hospital at term gestation. History of neonatal seizures was present at day 4 of life since then; the child was on sodium valproate therapy. The child was on bottle feeding from day 4 to day 25 of life. The child also had breath holding spells from 4 months of age and he has not attained the following milestones: Social

smile, stable head control, sitting without support, standing, and speech milestones. The global developmental delay was present, and in his family history, sibling of the child's mother had similar complaints.

On physical examination, general condition of the patient was good and vitals were stable: Respiratory rate=24/min (normal=20–30/min), pulse rate=92/min (normal=80–130/min), and blood pressure=90/60 mmHg (normal=86–106/42–63 mmHg). On systemic examination, hypotonia was present in all four limbs; power was 2/5 and gait was absent.

MRI of the brain revealed the following: Hyperintense signal on DWI and a hypointense signal on ADC indicating diffusion restriction on DWI and reduced ADC values were noted in bilateral perirolandic white matter (Fig. 1), thalami, internal capsules (Fig. 2), brainstem, and cerebellar dentate nuclei (Fig. 3). Diffuse T2W (Fig. 4) and fluid-attenuated inversion recovery (Fig. 5) hyperintense signal noted in bilateral fronto-parieto-occipital white matter, thalami, internal capsules, brainstem, and cerebellar dentate nuclei. Hence, based on the clinical and imaging findings, the possible differentials considered were MSUD and hypoxic-ischemic encephalopathy.

Laboratory investigations revealed elevated plasma levels of leucine=185.53 mmol/L (normal=47–155 mmol/L), isoleucine=127.52 mmol/L (normal=31–86 mmol/L), and valine=357.78 mmol/L (normal=62–294 mmol/L) and positive dinitrophenylhydrazine screening test of urine, thus confirming the diagnosis of MSUD. Treatment was initiated in the form of protein-restricted diet and intravenous glucose on follow-up, there was a symptomatic improvement.

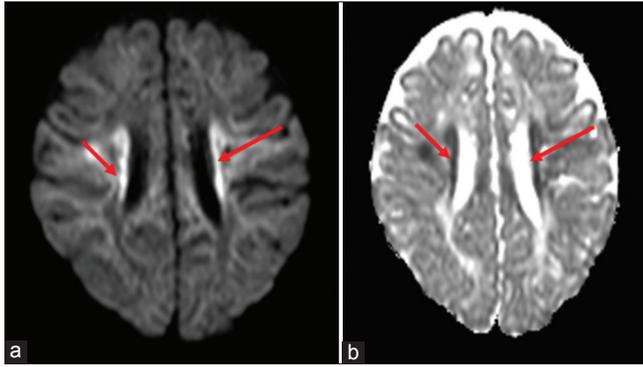


Figure 1: (a) Diffusion-weighted imaging (DWI) image showing restriction in bilateral periorlandic white matter (arrows), (b) Apparent diffusion coefficient (ADC) map showing reduced ADC values in bilateral periorlandic white matter (arrows)

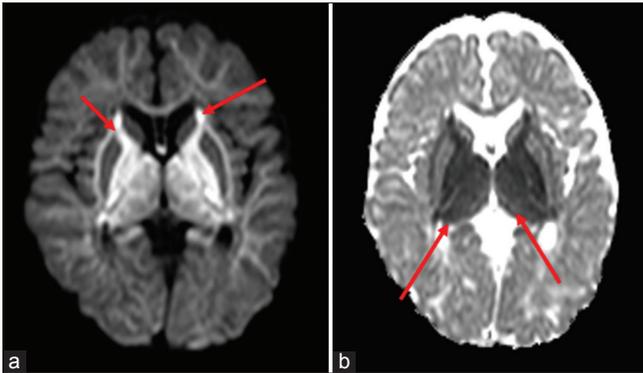


Figure 2: (a) Diffusion-weighted imaging image showing restriction in bilateral internal capsules (arrows) and thalami, (b) apparent diffusion coefficient (ADC) map showing reduced ADC values in bilateral internal capsules and thalami (arrows)

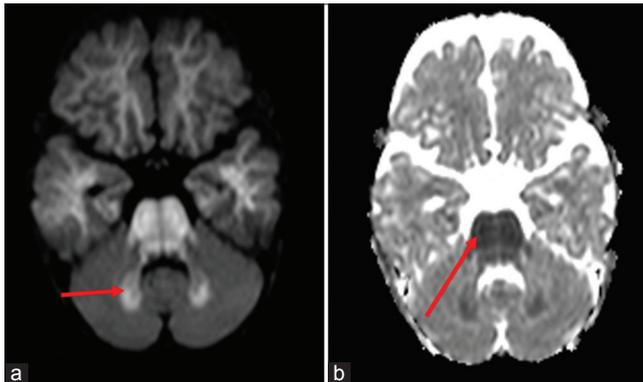


Figure 3: (a) Diffusion-weighted imaging image showing restriction in brainstem and cerebellar dentate nuclei (arrow), (b) apparent diffusion coefficient (ADC) map showing reduced ADC values in brainstem (arrow) and cerebellar dentate nuclei

DISCUSSION

In MSUD, intracellular (cytotoxic) edema affects the myelinated white matter involving cerebellar white matter, brainstem, globus pallidus, thalami, cerebral peduncles, and corticospinal tracts in the brain. MSUD is divided into four major categories: Classic, intermediate, intermittent, and thiamine responsive [3].

In a study by Cheng *et al.*, 10 MSUD patients had the classic form of MSUD with DCKBHB mutation is more common

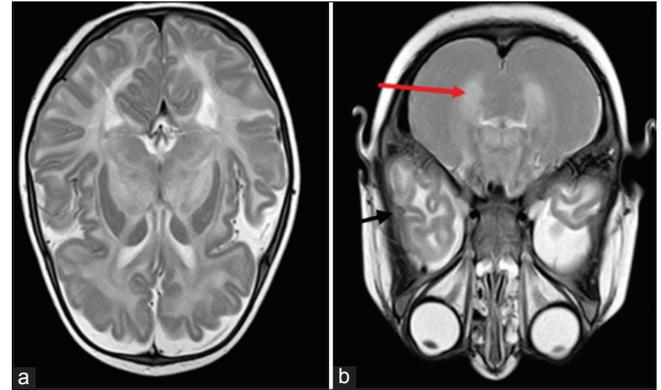


Figure 4: (a) T2W magnetic resonance (MR) image showing hyperintense signal in bilateral fronto-parieto-occipital white matter, thalami, internal capsules, (b) T2W MR image showing hyperintense signal in brainstem and cerebellar dentate nuclei (arrow)

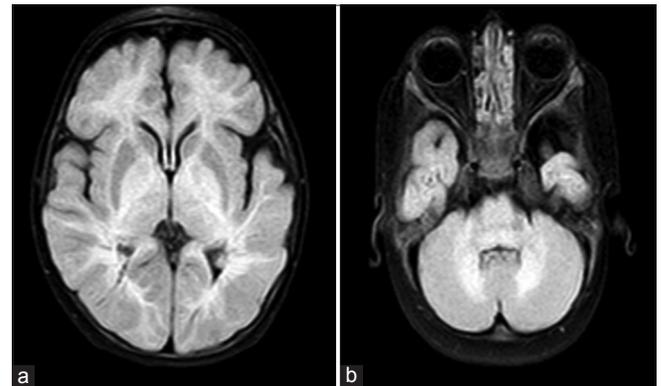


Figure 5: (a) Fluid-attenuated inversion recovery (FLAIR) magnetic resonance (MR) image showing hyperintense signal in bilateral fronto-parieto-occipital white matter, thalami, internal capsules, (b) FLAIR MR image showing hyperintense signal in brainstem and cerebellar dentate nuclei

with significant brain injury on MRI [4]. Age, at presentation, was 2–3 days of life with feeding difficulty, poor weight gain, lethargy, and irritability [5]. Classic form has a lifelong risk of metabolic decompensation and has little or no residual enzymatic activity, whereas the intermediate form has greater enzymatic activity. Age at presentation, in an intermediate form, ranges from 5 months to 7 years with symptoms such as seizures, neurological dysfunction, and global developmental delay. An intermittent form of MSUD is characterized by maple syrup or burnt sugar smell of urine and sweat, ataxia, and lethargy. Patients with intermittent form have normal growth and intellectual development. Thiamine-responsive form of MSUD has symptoms similar to the intermediate form and these patients respond to treatment with thiamine (Vitamin B1) [6].

Acute encephalopathy and coma are the rare presenting features. Neurological symptoms in MSUD are due to the rapid accumulation of leucine in particular. Increased plasma levels of isoleucine are associated with maple syrup odor of urine.

Non-contrast CT of the brain shows diffuse bilaterally symmetrical edema not sparing brainstem and cerebellum [7]. On T1W MRI, MSUD edema shows hypointense signal with sharp margins. On T2W MRI, edema shows hyperintense signal,

which disappears in late stages. DWI shows a marked restriction with reduced ADC values, which indicates MSUD edema is an intracellular edema. DWI is the most sensitive imaging tool in detecting MSUD brain alterations, for early diagnosis and follow-up of metabolic diseases in neonates [8]. DWI is particularly useful in the unmyelinated brain where T2W imaging findings may be masked.

In a study done by Jan *et al.*, they observed that in case of metabolic decompensation in MSUD the restriction of diffusion on DWI due to intramyelinic edema and elevated lactate, branched-chain amino acids on MR spectroscopy are reversible after metabolic correction [9].

On MR spectroscopy, abnormal branched-chain alpha-ketoacid peak was obtained at 0.9 ppm and elevated lactate was the finding obtained in MSUD. In metabolic decompensated MSUD, the changes in cell osmolarity and metabolism can reverse completely after metabolic correction with clinical neurological improvement [10,11]. Apart from neuroimaging, other diagnostic methods include tandem mass spectroscopy which is a screening method in newborns for amino acids in blood [12]. Urine analysis for the detection of elevated levels of the branched-chain amino acids is done. Molecular diagnosis was done for the detection of mutations in BCKDHA, BCKDHB, and DBT genes for confirmation of the diagnosis. Enzymatic analysis of white blood cells and DNA testing is other rarely used diagnostic modalities.

Imaging differential diagnosis of MSUD is hypoxic-ischemic encephalopathy. However, restriction of diffusion on DWI is more intense in MSUD compared to hypoxic-ischemic encephalopathy. Management of MSUD includes protein-restricted diet, thiamine therapy as a trial to determine the form of MSUD. In case of metabolic crisis, hemodialysis/hemofiltration and intravenous glucose administration are done.

CONCLUSION

MR with DWI is the best imaging tool during hyperacute and acute phases of MSUD, for early diagnosis and follow-up, particularly

in the unmyelinated brain where T2W imaging findings may be masked.

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