Imaging in Classic Form of Maple Syrup Urine Disease: A Rare Metabolic Central Nervous System

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ABSTRACT

Maple syrup urine disease (MSUD) is a rare autosomal recessive disorder of branched-chain amino acid metabolism. The condition gets its name from the distinctive sweet odour of affected infants' urine. MSUD is caused by a deficiency of the branched-chain α-ketoacid dehydrogenase enzyme complex, leading to accumulation of the branched-chain amino acids (leucine, isoleucine, and valine) and their toxic by-products (ketoacids) in the blood and urine. Imaging is characterestized by MSUD oedema affecting the myelinated white matter. We present a neonate with classic type of MSUD and its imaging features on computed tomography, conventional magnetic resonance imaging, diffusion-weighted imaging, and magnetic resonance spectroscopy.

Key words:
Brain, branched-chain amino acids, diffusion-weighted magnetic resonance imaging, maple syrup urine disease

CASE REPORT

Maple syrup urine disease (MSUD) is a rare inherited autosomal recessive disorder of branched-chain amino acid (BCAA) metabolism presenting with life-threatening cerebral edema and dysmyelination in affected individuals. MSUD affects approximately 1 out of 180,000 infants[1] and has a much higher prevalence in children of Amish, Mennonite, and Jewish descent.[1,2] We present a case report of a baby boy born to consanguineous married parents, who presented on the 8th postnatal day with history of poor feeding, lethargy, and tonic-clonic seizures, since 2 days. The child was born at term (39 weeks) after an uneventful pregnancy and normal vaginal delivery.

The baby was apparently normal in the first week of postnatal life. On 8th day, clinical systemic examination showed hypotonia and poor neonatal reflexes. Routine biochemical evaluation including serum electrolytes: Sodium 138 (133-145 mEq/L), potassium 4.2 (3.5-5.3 mEq/L), chloride 102 (98-106 mEq/L), calcium 8.6 (7.6-10.4 mg/dL), and magnesium levels 1.6 (1.40-2.55 mg/dL) were within normal limits.

Non-enhanced computed tomography (NECT) scan of the brain showed bilateral symmetrical white matter hypodensities in the posterior limb of internal capsule, thalami, midbrain, and cerebellar white matter [Figure 1].

Conventional magnetic resonance imaging (MRI) showed bilateral symmetric white matter hyperintensites in the posterior limb of internal capsule, thalami, midbrain, corticospinal tracts, and cerebellar white matter on T2-weighted magnetic resonance (MR) sequence [Figure 2a and b]. Turbo inversion recovery magnitude sequence showed similar findings as T2-weighted images. No abnormalities were detected on T1-weighted images.

Diffusion-weighted imaging (DWI) showed characteristic pattern of bilateral symmetrical restricted diffusion within the myelinated areas in the posterior limb of the internal capsule, centrum semiovale, corona radiata, corticospinal tract, thalami, posterior aspect of the mid brain, pons, middle cerebellar peduncle, medulla, and cerebellar white matter, attributed to intramyelinic edema[3] [Figure 3a and b].

MR spectroscopy

Multivoxel proton MR spectroscopy showed the presence of BCAAs and branched-chain α-keto acids resonating at 0.9-1.0 ppm, which are seen especially during a metabolic crisis[4,5] [Figures 4 and 5].

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Three days later tandem mass spectroscopy revealed increased levels of BCAAs (valine, leucine, and isoleucine), confirming the diagnosis of MSUD.

DISCUSSION

MSUD

It is a rare autosomal recessive disorder, associated with defects in the branched- chain α ketoacid dehydrogenase complex. It is divided into four major categories: (1) Classic, (2) intermediate, (3) intermittent, and (4) thiamine responsive, which carry differing symptoms and prognostic factors.[7] The exact cause for brain injury is not clearly understood. According to a study by Zinnanti *et al.*,[8] they suggest two converging mechanisms of brain injury in MSUD including: (i) Neurotransmitter deficiencies and growth restriction associated with BCAA accumulation and (ii) energy deprivation through Krebs cycle disruption associated with branched-chain ketoacid accumulation.

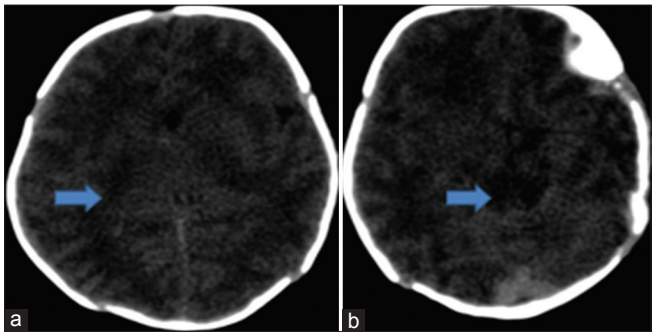

Figure 1: Seven-day-old newborn. NECT of the brain, axial images shows bilaterally symmetrical hypodensities in the posterior limb of internal capsule (blue arrow in Figure 1a) and in the midbrain (blue arrow in Figure 1b) with compressed ventricles and gyral swelling

This disease leads to accumulation of BCAA and metabolites (neurotoxic). The rapid accumulation of leucine in particular causes neurological symptoms. Increased plasma isoleucine is associated with maple syrup odour.

Neonates will be normal at birth, presents after disease-free interval, usually within the 4-7 days of life with poor feeding, vomiting, poor weight gain, and increasing lethargy. In crisis, patient's urine smells like maple syrup, secondary to the large accumulation of isoleucine. Maple syrup odour may be difficult to identify in first few days of life.

Imaging features are diagnostic in the early weeks of life. Classic appearing MSUD edema involving: Cerebellar white matter, brain stem, globus pallidus, thalamus, cerebral peduncles, and corticospinal tracts.

NECT of brain shows diffuse bilaterally symmetrical edema not sparing brainstem and cerebellum.[6]

DWI shows marked restriction and decreased apparent diffusion coefficient (ADC) which indicates MSUD edema is an intracellular oedema (cytotoxic oedema). DWI is more sensitive than conventional MRI in detecting MSUD brain alterations and it can become a useful tool for early diagnosis and follow-up of metabolic diseases in neonates.[9] Kilicarlsan *et al.*,[3] reported six cases with DWI in which the changes in all patients were reversed with treatment without evidence of volume loss or persistent tissue damage.

Acute "metabolic rescue" to reverse cerebral edema may require hemodialysis during acute crisis to limit neurotoxicity/

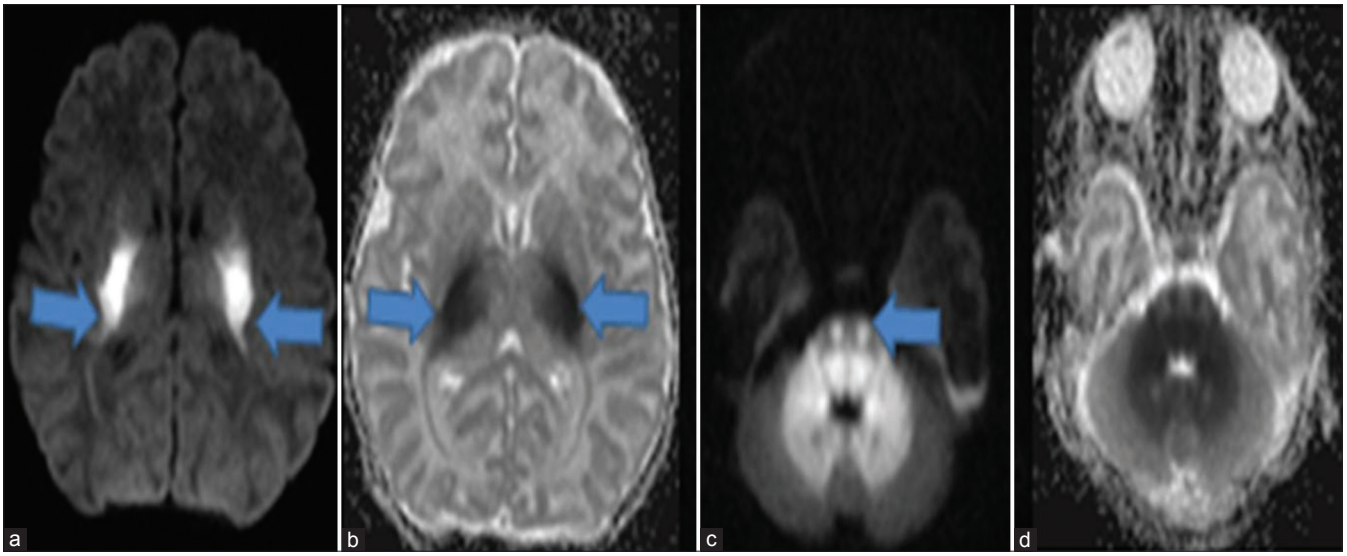

Figure 2: Seven-day-old newborn. DWIs with corresponding ADC maps demonstrate restricted diffusion in the posterior limbs of the internal capsules (blue arrows in Figure 2a and 2b), pons, corticospinal tracts (blue arrow in Figure 2c), and cerebellar white matter (Figures 2c and 2d)

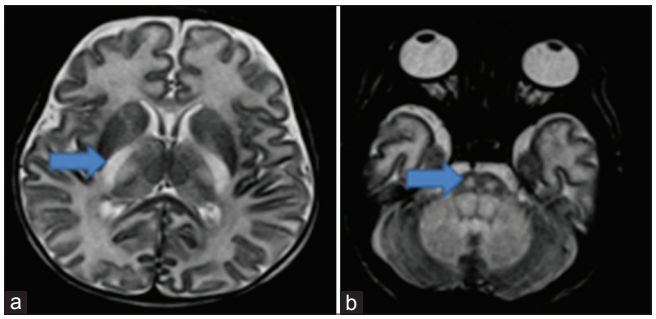

Figure 3: Seven-day-old newborn. Axial T2-weighted MR images shows bilateral symmetrical hyperintensities in posterior limb of internal capsule (blue arrow in Figure 3a), central cerebellar white matter, and in the corticospinal tracts (blue arrow in Figure 3b)

Tandem mass spectroscopy report

Amino acid	Observed value	Normal value
Leucine + Isoleucine	3613 – 3682 micrometer	25 – 350 micrometer
Valine	403.07 micrometer	20 - 300 micrometer
Leucine/ Phenylalanine	128.50	0.5- 2.25
Leucine / Alanine	20.17	0.22 – 0.55
Valine / Phenylalanine	14.34	0.34 -1.55

Figure 4: Spectroscopy chart

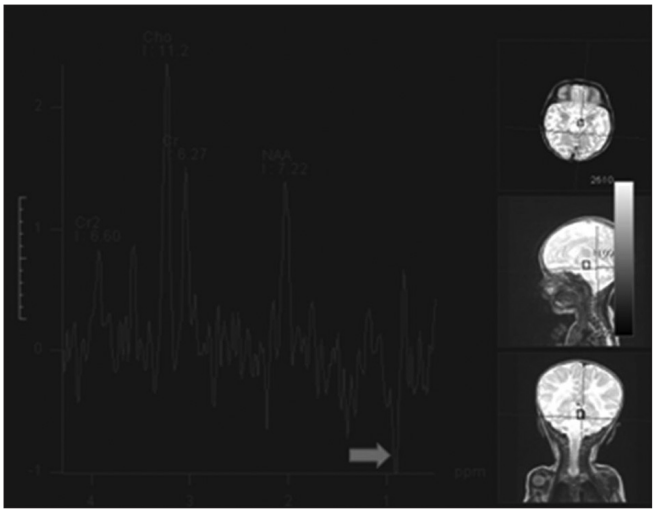

Figure 5: Image spectroscopy

damage. Metabolically appropriate diet (protein-modified) minimizes severity and prevent deficiencies of essential amino acids. Dietary therapy must be lifelong. If treated with low-BCAA diet and peritoneal dialysis within a few days from the onset of the symptoms, most patients survive and develop only minimal or no neurological deficits.

The changes in cell osmolarity and metabolism can reverse completely after metabolic correction in metabolic decompensated MSUD with clinical neurological improvement.[10,11]

CONCLUSION

MSUD is a rare autosomal recessive disorder of BCAA metabolism. Early imaging diagnosis of this condition can prevent the progress of neurological deficits and help in appropriate management of the disease.

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