Maple syrup urine disease (MSUD) is a rare autosomal-recessive disorder that affects branched-chain amino acid (BCAA) metabolism. It is characterized by accumulation of BCAAs and corresponding branched-chain keto acids of leucine, isoleucine, and valine in plasma, urine, and cerebrospinal fluid. Leucine is toxic to brain cells, leading to cytotoxic edema affecting the myelinated white matter, and involving the corticospinal tracts, thalami, globus palladi, midbrain, dorsal brain stem, and cerebellum. We present a neonate with the classic subtype of MSUD and its imaging features on magnetic resonance imaging.

Keywords: Branched-chain amino acids, magnetic resonance imaging, maple syrup urine disease, myelinated white matter, restricted diffusion

INTRODUCTION

Maple syrup urine disease (MSUD) is a rare autosomal-recessive disorder of branched-chain amino acid (BCAA) metabolism. It has an annual incidence of 1 in 180,000 live births worldwide. Affected infants initially present with lethargy, irritability, feeding problems, and vomiting. If untreated, the disease progresses to cause seizures, coma, and eventually, death. The characteristic maple-syrup odor of the urine may occur late, and thus imaging provides a useful tool for early diagnosis. We present the case of an infant with the classic subtype of MSUD and characteristic findings on magnetic resonance imaging (MRI).

CASE HISTORY

A 2-week-old male infant was born at term after an uneventful pregnancy and a normal vaginal delivery. The patient presented with slight irritability and poor feeding in the second week of life. The patient’s newborn screenings were abnormal, showing elevated BCAAs. Confirmatory testing done with plasma amino acid levels collected at 8 days of life showed elevated levels of leucine. The patient was thereafter admitted to our hospital where he exhibited irritability, hypertonicity, high-pitched cry, and sleepiness. He did not have any evidence of overt obtundation or emesis. On physical examination, he was found to be normothermic, normotensive, and with stable vital signs. Laboratory testing revealed metabolic acidosis (serum HCO₃⁻ = 14 mmol/L), ketosis (urine ketones >80 mg/dL), and mild hyperammonemia (serum NH₄⁺ = 83 µmol/L). MRI was obtained and showed restricted diffusion involving the corticospinal tracts, thalami, globus palladi, midbrain, dorsal brain stem, and cerebellar white matter [Figure 1]. Extensive bilateral T2/Fluid-attenuated inversion recovery white matter hyperintensity was also noted [Figure 2].

DISCUSSION

MSUD, also known as branched-chain ketoaciduria, is a rare autosomal-recessive disorder of BCAA metabolism. It has an annual incidence of 1 in 180,000 live births, with a higher prevalence in Amish, Mennonite, and Jewish children. The condition gets its name from the characteristic maple-syrup odor of the affected infant’s urine. It is characterized by an enzymatic deficiency of branched-chain alpha-ketoacid dehydrogenase complex leading to accumulation of BCAAs (leucine, isoleucine, and valine), and their toxic by-products (keto acids) in blood and urine.

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Abnormal accumulation of these amino acids results in a variety of symptoms including lethargy, irritability, feeding problems, vomiting, and the characteristic maple-syrup odor of urine. If untreated, various neurological complications including seizures or coma may occur, as BCAAs, especially leucine, are cytotoxic to brain cells, leading to cytotoxic brain edema affecting the myelinated white matter as was seen in the diffusion-weighted imaging (DWI) of our patient. Increased plasma isoleucine is associated with the characteristic maple-syrup odor of the urine.

Four main subtypes of MSUDs have been identified and include (1) classic, (2) intermediate, (3) intermittent, and (4) thiamine responsive. Each of them can be distinguished from the other based on age of onset, severity of clinical symptoms, and response to thiamine. Classic MSUD is the most common as well as the most severe form. Newborns are typically normal at birth, develop ketonuria within the first 48 hours of life, and present with irritability, poor feeding, vomiting, lethargy, and dystonia secondarily. By 4–7 days of life, the neurological abnormalities include alternating lethargy and irritability, dystonia, apnea, seizures, and signs of cerebral edema such as obtundation or persistent emesis. Time of onset may vary depending on the amount of protein in the feeding regimen. Exclusive breast feeding may delay the onset to the second week of life. Maple-syrup odor usually occurs late, during the crisis stage, and may be difficult to identify in the first few days of life.

The most important diagnostic test for MSUD is the measurement of plasma amino acid concentrations to evaluate elevated levels of BCAAs (leucine, isoleucine, and valine) and alloisoleucine (a metabolite of leucine). However, elevation in plasma amino acid levels may not appear until after the first week of life.

Imaging features are useful for early diagnosis. MRI shows marked restricted diffusion, reflecting intracellular edema (cytotoxic edema), involving the corticospinal tracts (posterior limbs of the internal capsule), thalami, globus palladi, midbrain, dorsal brain stem, and cerebellar white matter [Figure 1]. In addition, diffuse white matter abnormalities may be seen on T2-weighted sequences [Figure 2]. These abnormalities resolve promptly after treatment. Noncontrast-enhanced computed tomography of the brain shows diffuse bilaterally symmetrical hypodensity within the aforementioned structures but lacks the specificity and sensitivity offered by MRI.

Management of MSUD involves two aspects: (1) metabolically appropriate diet (low in BCAAs) and (2) aggressive treatment of episodes of acute metabolic decompensation, via peritoneal dialysis to reduce cerebral edema and cytotoxic damage. Diet is, in most cases, sufficient to control clinical sequelae of MSUD. Most patients treated within a few days from the onset of symptoms survive and may not develop any residual neurological deficits. Liver transplantation remains the only definite cure for MSUD but is reserved for the few patients in which diet modification and other conservative management have failed to elicit a good response.

**CONCLUSION**

MSUD is a rare autosomal-recessive disorder of BCAA metabolism. Onset of clinical symptoms and protein levels in the blood and urine may vary depending on the amount of protein in the feeding regimen. Imaging
findings are a useful tool for early diagnosis and as a surrogate marker to evaluate for the response to treatment.

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Conflicts of interest
There are no conflicts of interest.

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