CASE REPORTS

BRAIN DAMAGE REVERSAL ON TREATMENT IN MAPLE SYRUP URINE DISEASE: A CASE REPORT

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Abstract
Maple syrup urine disease (MSUD) is a rare disorder of amino acid metabolism, transmitted in autosomal recessive manner. It usually presents as neonatal encephalopathy. A 40 day old infant presented to us with complaints of excessive cry and refusal to feed. After ruling out common causes of encephalopathy, MRI with DWI was done which showed classical changes of MSUD. Tandem mass spectrometry showed markedly increased levels of valine (364.5 mmol/L) and leucine (1475.8mmol/L) in blood. Urinary metabolic profile revealed increased levels of their keto-acids, suggestive of MSUD. Infant was started on modified formula feed containing reduced amounts of branched chain amino acids and thiamine supplements. Infant was followed up after 3 weeks, 8 weeks and 12 weeks. Remarkable clinical improvement was present. Repeat MRI after 8 weeks of treatment showed marked improvement.

Keywords : inborn error of metabolism, maple syrup urine disease, encephalopathy

Introduction

Maple syrup urine disease (MSUD) is an amino acid disorder transmitted in autosomal recessive manner with an incidence of 1 in 1,80,0000 infants. (1) MSUD is caused by deficiency of branched chain alpha-ketoacid dehydrogenase complex. This leads to accumulation of leucine, isoleucine and valine in blood, causing the symptoms. (2) Treatment in the acute phase includes parenteral nutrition alone or along with enteral nutrition containing BCAA free proteins. (3) We present a 40 days old infant with encephalopathy, who was initially suspected to have severe sepsis leading to hypoxic ischemic encephalopathy, but later turned out to be due to MSUD and showed remarkable improvement both clinically and radiologically on treatment

Case Report

A male child presented to us on day 40 of life with excessive cry and refusal to feed for last three days. The infant was born at full term by normal vaginal delivery to a mother with non-consanguineous marriage. Birth weight was 3.5kg. Baby cried immediately after birth and remained asymptomatic till day 7 of life following which he had refusal of feeds, excessive cry, tachypnea, seizures and bulging fontanelle for which he was hospitalised and diagnosed to have late onset sepsis with meningitis. Routine investigations done in that hospital stay were unremarkable except for increased CRP (1.5mg/dl) and homogenous opacity in right lung field involving upper lobe on Chest X-ray. Cerebrospinal fluid (CSF) report (5 cells/cumm, 100% lymphocytes, 30mg/dl protein) was normal and blood cultures were sterile. He was started on parenteral nutrition, IV antibiotics (Ampicillin, Gentamicin for 5 days followed by Vancomycin, Meropenem for 14 days) as well as received oxygen for respiratory distress. After a long hospital stay of 24 days, baby became asymptomatic and was discharged. There was history of seizure and unexplained death of a previous sibling at 3 years of age. During the current admission with us, the infant had multiple episodes of seizures during initial few days of hospital stay. Hypoglycemia (blood sugar 21 mg %) was documented at admission and again on day 44 of life. Seizures did not correspond to hypoglycemia. Sepsis screen was negative, blood culture was sterile, serum ammonia (34mmol/L), lactate (1.2mmol/L) were normal; urinary reducing sugar was negative. Arterial blood gas analysis (ABGA) showed mild metabolic acidosis (pH 7.34; HCO3- 19meq/L). MRI Brain was done on day 45 of life in which T2 weighted images showed hyperintensities in white matter of deep cerebral cortex (cortico-spinal tract), cerebellum, internal capsule, thalamus, cerebral peduncle and dorsal pons. Diffusion-weighted imaging (DWI) showed characteristic pattern of bilateral symmetrical restricted diffusion within the myelinated areas in 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 suggestive of a metabolic disorder (Figure

1). Tandem mass spectrometry showed markedly increased levels of valine (364.5 mmol/L) and leucine (1475.8mmol/L) in blood. Urinary metabolic profile revealed increased levels of their keto-acids, suggestive of MSUD. Enzymatic assay and genetic analysis were not possible due to financial issues. The infant was started on formula feeds containing restricted amounts of branched chain amino acids and thiamine. Gradually he became seizure free, oral intake and activity improved. Follow up after three weeks and eight weeks of treatment initiation revealed weight gain and improved activity which was reconfirmed after 12 weeks. Repeat MRI with DWI after 8 weeks of treatment showed remarkable improvement with altered signal intensities only in periventricular white matter (Figure2).

Figure 1: Diffusion-weighted imaging (DWI) shows bilateral symmetrical restricted diffusion within the myelinated areas in the internal capsule, centrum semiovale, corona radiata, corticospinal tract, thalami.

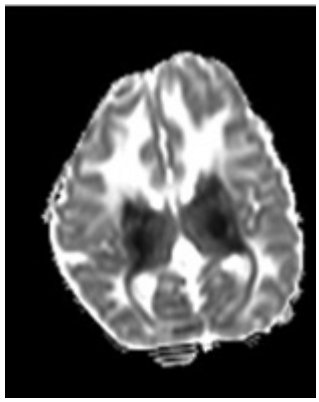
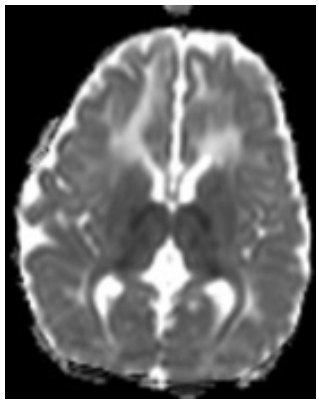


Figure 2: Diffusion-weighted imaging (DWI) shows altered signal intensity only in periventricular white matter.



Discussion

In developing countries, the most common causes of neonatal encephalopathy are perinatal asphyxia and infections. (4) Other causes include intracranial bleed, congenital malformation of brain and inborn errors of metabolism (IEMs). High index of suspicion is required among treating physicians for early diagnosis and treatment of IEMs. MSUD occurs in five forms: Classical, Intermediate, Intermittent, thiamine responsive, and MSUD caused due to E3 subunit deficiency. Classical form is the most common and severe type which presents early in neonatal life with encephalopathy. Neurotoxicity is mainly attributed to a combination of increased level of branched chain amino acid/ keto acid level, and decreased levels of other essential amino acids in brain, as well as neurotransmitter depletion. (5) Classical form of the disease presents within a few days of birth after an apparent asymptomatic period. Our patient presented with classical features of MSUD, but the diagnosis was delayed due to low index of suspicion among physicians as well as radiologists. MRI with DWI is a powerful tool for early diagnosis. MRI shows two types of edema in MSUD encephalopathy: intramyelinic edema and vasogenic edema. (6) Electro microscopic studies in animal models have shown that intramyelinic edema is due to accumulation of water between myelinic lamellae while vasogenic edema is due to alteration of blood brain barrier.(7) Myelin edema is visible as isotropically restricted water diffusion hence appearing hyperintense, while vasogenic edema is visible as isotropically increased water diffusion, appearing hypointense in DWI. This leads to beautiful demarcation of myelinated and unmyelinated areas in MRI with DWI; making it the most sensitive tool for early diagnosis. Similar picture may be seen in non-ketotic hyperglycinemia and Canavan disease. (8) The areas typically involved in acute stage of the disease are bilateral internal capsule, corona radiata, thalami, brain stem, cerebral peduncle, and cerebellar white matter (9) as was seen in our patient.

Treatment in the acute phase includes parenteral nutrition alone or along with enteral nutrition containing BCAA free proteins. Peritoneal or hemodialysis may be required to lower the levels of BCAA. Our patient survived the initial hospital stay before diagnosis as he received protein free parenteral nutrition. After stabilization, modified dietary regimen containing reduced amount of these amino acids has to be followed throughout life. The Genetic Metabolic Dieticians International (GMDI) and Southeast Regional Newborn Screening and Genetics Collaborative (SERC) have recently published a guideline on nutritional management of MSUD during acute illness as well as later. (3) Thiamine, a cofactor of BCKD complex, challenge is done for all patients with MSUD except those known to be homozygous for the 1312TNA mutation or other mutations resulting in less than 3% BCKD enzyme activity. (3) Liver transplantation has also been reported as successful therapeutic option in MSUD patients. (10) Follow up MRI may show reversal of findings in appropriately treated cases. (11) But loss of brain tissue has also been reported even after treatment. (9) Our patient showed remarkable improvement clinically as well as radiologically within few weeks of treatment.

Conclusion

MRI with DWI has emerged as a powerful tool for early diagnosis of MSUD, which can be put to use in

resource poor settings where newborn screening is still a goal to be achieved. With appropriate intensive care and nutritional management during acute illness followed by modified dietary adherence can lead to a reversal of brain damage and better clinical outcome.

Contributor Statement

S managed the patient and drafted the manuscript. SS did critical revision of manuscript. AC and SK were involved in drafting the manuscript.

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