International Journal of Medical and Health Sciences

Journal Home Page: http://www.ijmhs.net ISSN:2277-4505

Case Report

Maple Syrup Urine Disease: Case Evolution From Birth To One Year

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ABSTRACT

Reports of Maple syrup urine disease from rural India are rare. A relatively normal neonate at birth, showed deterioration after 72 hours of life, which aroused suspicion of inborn errors of metabolism (IEM) particularly when septic workup was negative. In such situations, specific diet modification permits management of a range of severity of illness though with guarded prognosis. Confirmation of IEM by tandem mass spectrometry (TMS) of plasma sample by filter paper method should be done since facilities are now available.

KEYWORDS: Obnoxious body odour, Thiamine, Tonic Posturing.

INTRODUCTION

Maple Syrup Urine Disease (MSUD) is an autosomal recessive disorder of IEM due to defect in the branched chain α-ketoacid dehydrogenase (BCKD). This mitochondrial enzyme accomplishes decarboxylation of leucine, isoleucine and valine; defect of any of its subunits causes MSUD due to accumulation of the amino acids in plasma and excretion in urine. This results in cerebral dysfunction consequent to cerebral edema and is associated with an unusual urinary substance with an odour similar to that of Maple syrup from which the disease is named[1, 2]. The disease was first described in 1954 by Menkes, Hurst and Craig[3].

CASE REPORT

A five days male neonate 1st issue of 3rd degree consanguinity presented for admission with poor feeding and activity since the day before admission. Baby was extramural, delivered normally, at term with a birth weight of 3200g. There was no history suggestive of early onset sepsis such as premature rupture of membranes, maternal fever or meconium stained liquor. There was neither history of birth trauma nor any obvious congenital malformations. Baby had been put to breast within half hour of birth and had been passing meconium and urine with regular feeds for the days prior to admission.

Clinical examination revealed stable vital signs (temp 36.8°C, heart rate-140/min, resp. rate - 40/min, NIBP-60/40mm Hg, CRT <3sec.) Examination of head revealed bulging fontanel with bogginess. Clinical jaundice was evident at Kramers zone 3. Episodes of tonic decorticate posturing with neck retraction suggested possibility of meningitis **Fig. 1**.

Appropriate Lab investigations i.e. sepsis screen revealed no abnormality (CBC, CRP, LFT, RFT, BSL, Serum Calcium, Serum Magnesium and CSF was done). Baby was put on parenteral fluids following a dose of 10% Dextrose, 10% Calcium gluconate and pyridoxine. ABG revealed acidosis of pH-7.28 with bicarb of 10.2 mEq/L. Metabolic acidosis suggested an IEM. Smell of baby wrap and diapers drew our attention to inborn errors of amino acid metabolism associated with peculiar odour of urine. Despite frequent changes of the diapers and baby wraps, persistence of the unpleasant odour of the baby prompted us to suspect the diagnosis and send blood samples for TMS. Hence an evaluation was advised for metabolites in blood by Tandem mass spectrometry which revealed marked elevation of the branch chain amino acids leucine, isoleucine and valine, results of which are shown in Table 1.

Table 1: Tandem mass spectrometry findings of our case

Sr No.	Metabolites	Values Measured	Normal Range
1.	Leucine –Isoleucine	2918.69	25-250
2.	Valine	348.96	20-300

MRI Brain evaluation revealed hyperintensities in Thalamus, Internal capsule, mid brain, pons, medulla and cerebellum being suggestive of brain stem edema **Fig. 2.**

Treatment of acute state involved continuing parenteral fluids to maintain hydration and prevent and revert catabolic state with close monitoring of sugar, calcium and electrolytes. Furesemide was added for rapid removal of the branched chain amino acids and their metabolites. A dose of Mannitol was given along with Phenobarbitone which was continued till 10 DOL since seizures had ceased by day 7 of life. Child was subsequently continued on breast feeds and supplements as follows: Well day- T.Carnisure (500mg) ½ tds, T.Benalgis 75 mg (337.5mg/day), T. MCBM69 ½ tds. Sick day- T. Carnisure (500mg) 1-1/2-1, T.Benalgis 75 mg 2-2-2-2-1, T. MCBM69 1tab bd, InjOptineuron 0.5ml bd and oral high dose thiamine (Vit B1). On follow up at 6 months the child showed persistent Asymmetric Tonic Neck Reflex (ATNR)**Fig. 3**.

Though Mead Johnson provides BCKD Infant formula (free of leucine, isoleucine and valine) cost is well beyond the reach of commoners. Parents are advised diet low in BCKDs. Since such diet was not instituted, recurrent episodes of illness led to brain damage reflected in progressive retardation on follow up. Liver transplant offers a permanent cure. Risk of recurrence has been explained to the parents.

Figure 1: At birth showing head lag

Figure 2: MRI Brain evaluation revealed hyperintensities in thalamus, internal capsule, mid brain, pons, medulla and cerebellum being suggestive of brain stem edema

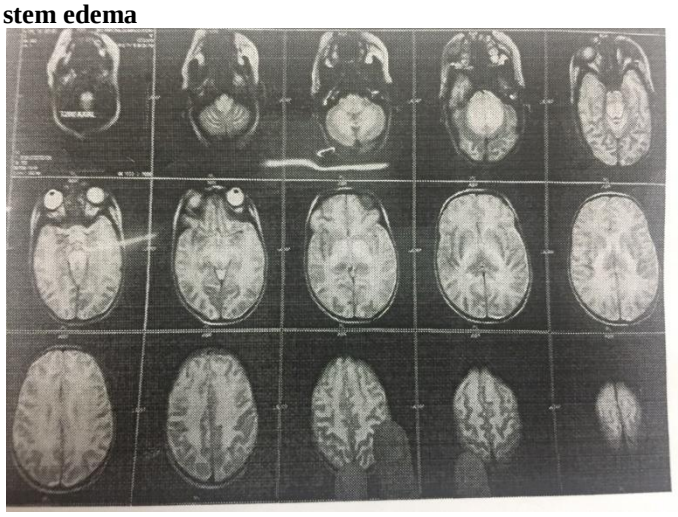


Figure 3: At 6 months showing ATNR

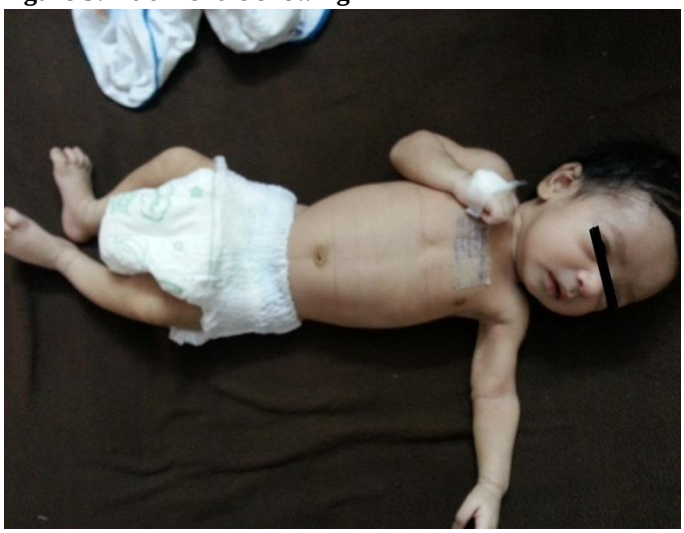
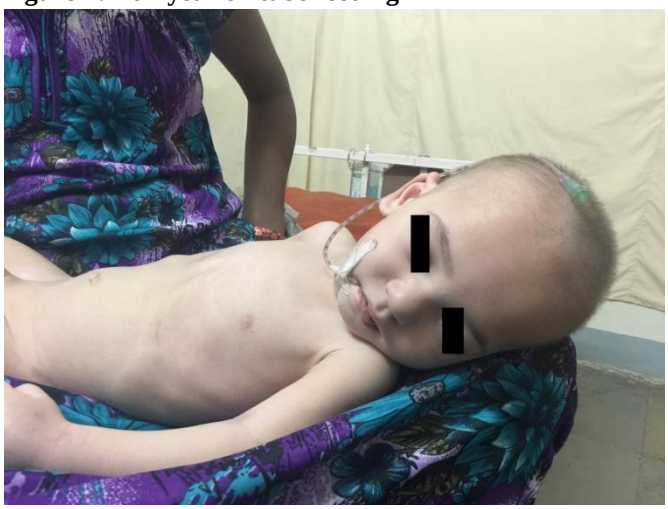


Figure 4: At 1 year on tube feeding



DISCUSSION

This AR disorder is seen throughout the world in all ethnic groups. It is common among the Mennonites of Pennsylvania, in whom the incidence is 1 in 760. In New England incidence of 1 in 290000 was encountered. Once a mutation is detected in a proband, molecular techniques may be used to establish the status. The enzyme activity can be measured in amniotic fluid cells for prenatal diagnosis. The enzyme is located on inner surface of the inner mitochondrial membrane. BCKD activity is widely distributed in mammalian tissues. Defective activity of BCKD leads to increased concentration of leucine isoleucine and valine [4].

The mitochondrial enzyme, branched chain α-ketoacid dehydrogenase using thiamine pyrophosphate (Vit.B1) as a coenzyme accomplishes decarboxylation of leucine, isoleucine and valine. Deficiency of any of the 4 subunits of this enzyme results in the types of MSUD designated as type 1A, 1B, 2 and 3. The clinical classification however, based on response to thiamine has 5 phenotypes of MSUD i.e. classic (most severe), intermediate (mild), intermittent, thiamine responsive and MSUD type 3 due to deficiency of E_3 subunit (rarest).

Affected infants, normal at birth but progress to poor feeding and vomiting in the first week of life associated with lethargy and coma are often mistakenly thought to be caused by sepsis and meningitis. Convulsions do occur in most infants and hypoglycemia is also often recorded, but does not respond even on correction of blood glucose.

Diagnosis is often suspected because of the peculiar odour similar to that of maple syrup found in urine, sweat and cerumen. Follow up MRI imaging[5] of brain, after recovery from acute stage and with advancing age shows hypomyelination and cerebral atrophy. Urine contains high levels of leucine, isoleucine andvaline and their respective ketoacids. These ketoacids may be detected qualitatively by adding a few drops of 2, 4-dinitro phenyl hydrazine reagent (0.1% in 0.1N HCL) to the urine. A yellow precipitate of 2, 4-dinitro phenyl hydrazine is formed in a positive test. The enzyme activity can be measured in leucocytes and cultured fibroblasts.

Milder variants manageable by restriction of protein intake to amounts required for normal growth. In thiamine responsive MSUD doses range from 10-300 mg/day [6].

Patients with MSUD should remain on the diet for the rest of their lives. Liver transplantation in patients with classic MSUD has promising results with these children being able to tolerate normal diet.

CONCLUSION

Long term prognosis of children with MSUD remains guarded. Severe ketoacidosis, cerebral edema, and death may occur following stresses such as surgery or infections especially in mid childhood. Cognitive and other neurological deficits are common as seen in our case with global developmental delay.

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