

IMAGING AND BIOCHEMICAL FINDINGS IN MAPLE SYRUP URINE DISEASE-**A CASE REPORT****Gajera S.^{1*}, Bhanderi A.², Mishra S.³, Goyal M.M.⁴**

1. Department of Radiodiagnosis, SMS medical college, Jaipur, Rajasthan.

2. Associate professor, Department of Radiodiagnosis, SMS medical college, Jaipur, Rajasthan.

3. Professor, Department of Biochemistry, SMS Medical College, Jaipur, Rajasthan.

4. Mr. Madhur M. Goyal, Department of Biochemistry, SMS Medical College, Jaipur, Rajasthan.

Email id of corresponding author-** gajera.sumit@gmail.com*Received: 23/10/2015**Revised: 26/01/2016**Accepted: 13/02/2016ABSTRACT:**

Maple syrup urine disease (MSUD) is a rare autosomal recessive disorder. It 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 byproducts (ketoacids) in the blood and urine. Imaging is characterized by MSUD oedema affecting the myelinated white matter. We present a neonatal case with classic type of MSUD with radiological findings confirmed by biochemical investigations.

Keywords: maple syrup urine disease, radiological findings, Biochemical tests.

INTRODUCTION:

Maple syrup urine disease (MSUD) is a rare inherited autosomal recessive disorder of branched chain Amino acid (BCAA) metabolism showing with life threatening cerebral edema and dysmyelination in affected individuals. MSUD affects approximately 1 out of 180,000 infants. (1) A few reports are available from different parts of the India (14-21).

Case Report

A baby boy born to nonconsanguineous married parents, presented on the 30 post natal day with

history of complaints of excessive cry, refusal to feed and seizure. Baby was born as full term, weighing 3.5 kg. Baby cried immediately after birth and remained asymptomatic till day 7 of life; then he developed complaints of decreased oral acceptance, excessive cry, tachypnea, seizure like activity and bulging fontanelle for which baby was admitted as a case of late onset sepsis with meningitis. Routine investigations done in that hospital stay were unremarkable except for increased CRP and homogenous

opacity in right lung field involving upper lobe. Any chance of neonatal sepsis was ruled out. CSF and blood cultures were sterile; baby was started on parenteral nutrition, IV antibiotics as well as received CPAP for respiratory distress. After a long hospital stay of 24 days, baby became asymptomatic and was discharged. Baby remained well for about five days then again developed complaints of excessive cry, refusal to feed; and was readmitted on day 40 of life. Baby had multiple episodes of seizure 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, Lactate was normal;; urinary reducing sugar was negative. ABGA showed mild metabolic acidosis.

USG brain showed increased echogenicity in basal ganglion region for further evaluation MRI brain with DWI was advised.

MRI findings: T2 and FLAIR hyperintensity noted in perirolandic area, internal capsule, thalamus, cerebral peduncal, dorsal pons, deep cerebellar white matter, medulla oblongata, Diffusion restriction noted in a in perirolandic area, internal capsule, deep white matter of occipital lobe, thalamus, cerebral peduncal, mid brain, dorsal pons, deep cerebellar white matter, medulla oblongata

Biochemical investigations were conducted by outside reference laboratory for Aminoacidopathies, Organic Acidemias, TCA cycle/mitochondrial abnormality, Fatty acid metabolism, Peroxisomal, Purine & pyrimidine metabolism, sugar metabolism and non-IEM disorders. Increased level of Valine and Leucine were found in given blood sample. It was screen positive for MSUD.

Baby 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.

DISCUSSION

MSUD 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). Two converging mechanisms of brain injury were proposed 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. This disease leads to accumulation of BCAA and metabolites (neurotoxic). The rapid accumulation of leucine in particular causes neurological symptoms (8). Increased plasma isoleucine is associated with maple syrup odour.

The clinical manifestation of MSUD depends on the severity of BCKAD deficiency. Patients with classic MSUD typically have enzyme activity less than 2%. They present with poor feeding, lethargy, irritability, maple syrup-like or burnt sugar smell and ketonuria in first week of life. Without treatment, they develop progressive neurological deterioration due to cerebral edema, culminating in coma, central respiratory failure and death. In patients with non-classical MSUD, residual enzyme activity varies from 2% to 30%, resulting in delayed clinical presentation to infancy or childhood as feeding problems, poor growth, developmental delay and behavioural problems (13)

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 followup of metabolic diseases in neonates (9). Kilicarslan *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/damage. Metabolically appropriate diets (protein modified) minimize severity and prevent deficiencies of essential amino acids. Dietary therapy must be life-long. 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

We should aim towards earlier diagnosis through improving accessibility to diagnostic facilities, increasing awareness among physicians and establishing a newborn screening programme. Biochemical screening tests are useful for

confirmation of IEM and could provide useful information in remote medical facilities where advance radiology instruments are not available.

REFERENCES

1. Mary K. Maple syrup urine disease. Rare diseases June. 2004. [Last accessed on 2004]. Available from: <http://rarediseases.about.com/od/rarediseases1/a/062004.htm> .
2. Puffenberger EG. Genetic heritage of Old Order Mennonites of Southeastern Pennsylvania. *Am J Med Genet C Semin Med Genet.* 2003;121:18–31. [PubMed: 12888983]
3. Kilicarslan R, Alkan A, Demirkol D, Toprak H, Sharifov R. Maple syrup urine disease: Diffusionweighted MRI findings during acute metabolic encephalopathic crisis. *Jpn J Radiol.* 2012;30:522–5. [PubMed: 22476847]
4. Thomas B, Al Dossary N, Widjaja E. MRI of childhood epilepsy due to inborn errors of metabolism. *AJR Am J Roentgenol.* 2010;194:W367–74. [PubMed: 20410380]
5. Jan W, Zimmerman RA, Wang ZJ, Berry GT, Kaplan PB, Kaye EM. MR diffusion imaging and MR spectroscopy of maple syrup urine disease during acute metabolic decompensation. *Neuroradiology.* 2003;45:393–9. [PubMed: 12736767]
6. Taccone A, Schiaffino MC, Cerone R, Fondelli MP, Romano C. Computed tomography in maple syrup urine disease. *Eur J Radiol.* 1992;14:207–12. [PubMed: 1563430]
7. Chuang D, Shih V. Disorders of branched chain amino acid and keto acid metabolism. In: Scriver C, Beaudet A, Sly W, Valle D, editors. *The Metabolic and Molecular Basis of Inherited Disease.* 7th ed. New York: McGrawHill; 1995. pp. 1239–77.
8. Zinnanti WJ, Lazovic J, Griffin K, Skvorak KJ, Paul HS, Homanics GE, et al. Dual mechanism of brain injury and novel treatment

- strategy in maple syrup urine disease. *Brain*. 2009;132:903–18. [PMCID: PMC2668944] [PubMed: 19293241]
9. Cavalleri F, Berardi A, Burlina AB, Ferrari F, Mavilla L. Diffusionweighted MRI of maple syrup urine disease encephalopathy. *Neuroradiology*. 2002;44:499–502. [PubMed: 12070724]
10. Naughten ER, Jenkins J, Francis DE, Leonard JV. Outcome of maple syrup urine disease. *Arch Dis Child*. 1982;57:918–21. [PMCID: PMC1628082] [PubMed: 7181520]
11. Kaplan P, Mazur A, Field M, Berlin JA, Berry GT, Heidenreich R, et al. Intellectual outcome in children with maple syrup urine disease. *J Pediatr*. 1991;119:46–50. [PubMed: 2066858]
12. Aditi Jain, K. Jagdeesh, Ranoji Mane, and Saurabh Singla. imaging in classic form of maple syrup urine disease: a rare metabolic central nervous system. doi: 10.4103/22494847.116411 [PMCID: PMC3775146]
13. Z Md. Yunus, DP Abg Kamaludin, M Mamat, YS Choy and LH Ngu. Clinical and Biochemical Profiles of Maple Syrup Urine Disease in Malaysian Children. *JIMD Reports*. DOI 10.1007/8904_2011_105
14. Narendra Mangal, Rajaram Agarwal, N. Miglani, Pradeep Vyas. Maple Syrup Urine Disease-2-4 DPNH Test as a Routine in Highly Sick Newborns. *INDIAN PEDIATRICS*. VOLUME 31-NOVEMBER 1994
15. Jailkhani R, Patil VS., Laxman HB, Shivashankara AR, Kulkarni SP, Ravindra MS. Selective Screening For Inborn Errors Of Metabolism In Children: Single Centre Experience From Karnataka. *Journal of Clinical and Diagnostic Research* 2008; 2: 952-958.
16. Mahesh H. Hampe, Pramod Ingale, Shrimant N. Panaskar and Ashwini A. Yadav. Two tier analysis of organic acid disorders: a comprehensive approach for newborn screening *International Journal of Biomedical and Advance Research* 2015; 6(02): 84-90.
17. Moushumi Lodh And Joshi Anand Kerketta. Citrullinemia And Hyperglycinemia Presenting With Seizures- Case Report of A 4 Day Old Baby. *Asian Journal Of Medical Sciences* 3(2012) 17-20.
18. M. P. Narayanan, Vaidyanathan Kannan, K. P. Vinayan and D. M. Vasudevan. Diagnosis of Major Organic Acidurias in Children: Two Years Experience at a Tertiary Care Centre. *Ind J Clin Biochem (Oct-Dec 2011)* 26(4):347–353.
19. Aditi Jain, K. Jagdeesh, Ranoji Mane, and Saurabh Singla. Imaging in Classic Form of Maple Syrup Urine Disease: A Rare Metabolic Central Nervous System. *J Clin Neonatol*. 2013; 2(2): 98–100. doi: 10.4103/22494847.116411
20. Venkatraman Indiran and R. Emmanuel Gunaseelan. Neuroradiological findings in maple syrup urine disease. *J Pediatr Neurosci*. 2013; 8(1): 31–33. doi: 10.4103/18171745.111419
21. Vidya S. Patil, Rama Jailkhani, Dhiraj J. Trivedi, Shreerang.P. Kulkarni, Aparna A. Sagare, Rakesh Mudaraddi and Anil Bargale. Screening for aminoacidurias and organic acidurias in patients with metabolic or neurological manifestations. *Biomedical Research* 2012; 23(2): 253-258.

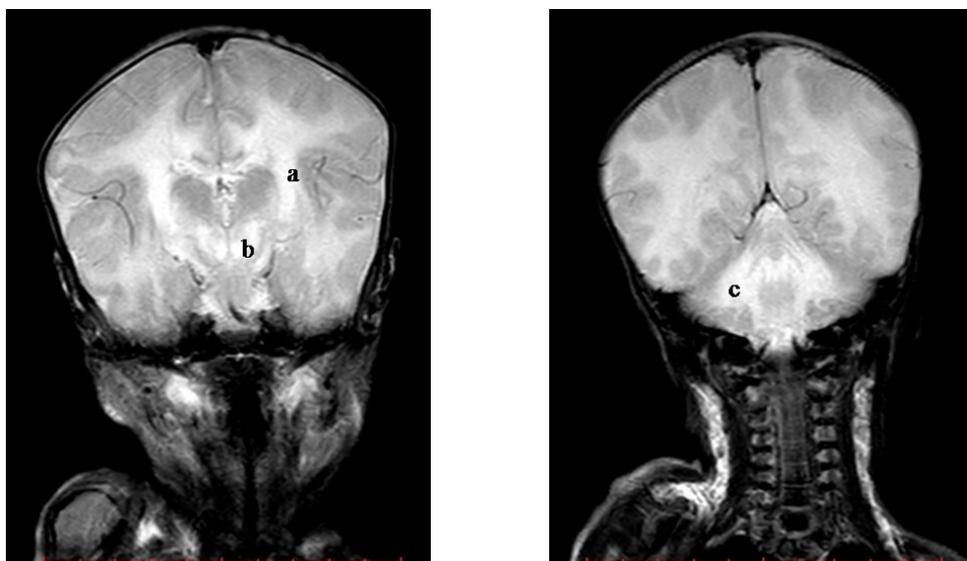


Figure 1. coronal T2 weighted MRI showing hyperintensity of white matter of deep cerebral cortex; cortico-spinal tract 'a', cerebellum 'c', thalamus 'b', dorsal pons

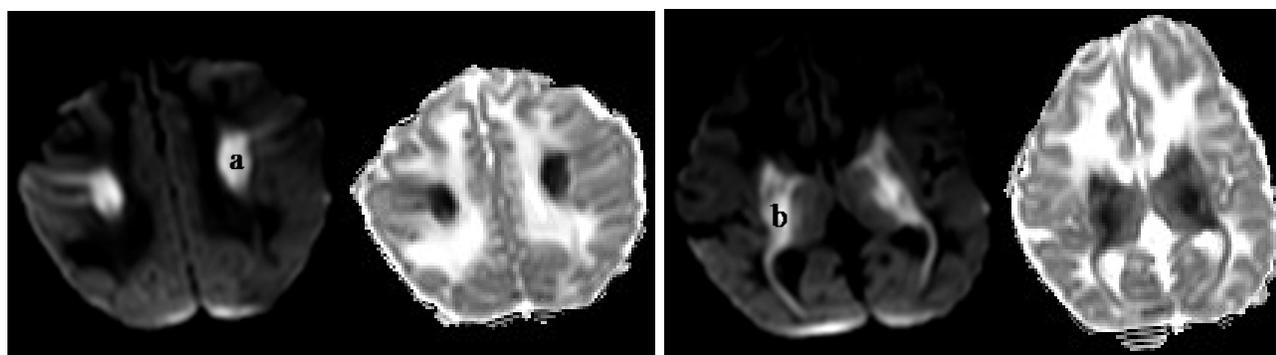


Figure 2. Bilateral symmetrical restricted diffusion within the myelinated areas in the centrum semiovale 'a', internal capsule 'b', corona radiata, corticospinal

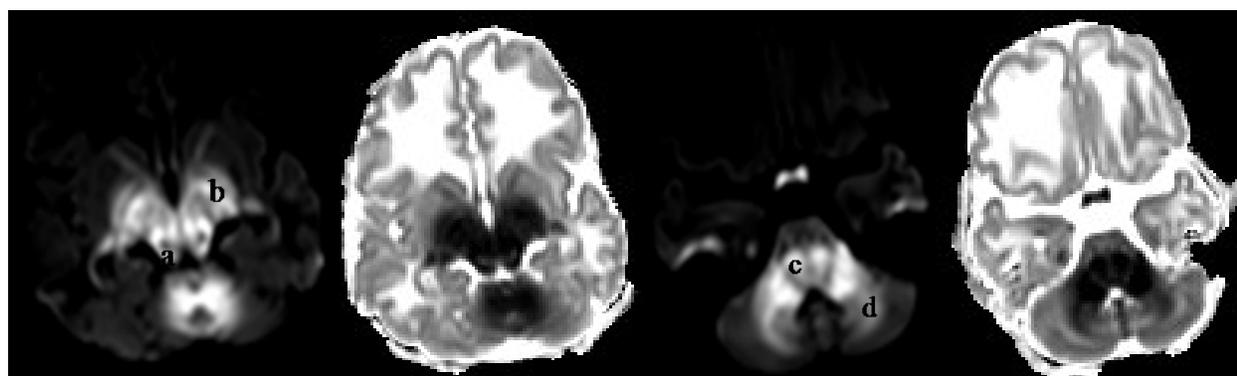


Figure 3. Bilateral symmetrical restricted diffusion within the mid brain 'a', cerebral peduncle 'b', dorsal pons 'c', , and cerebellar white matter 'd'.

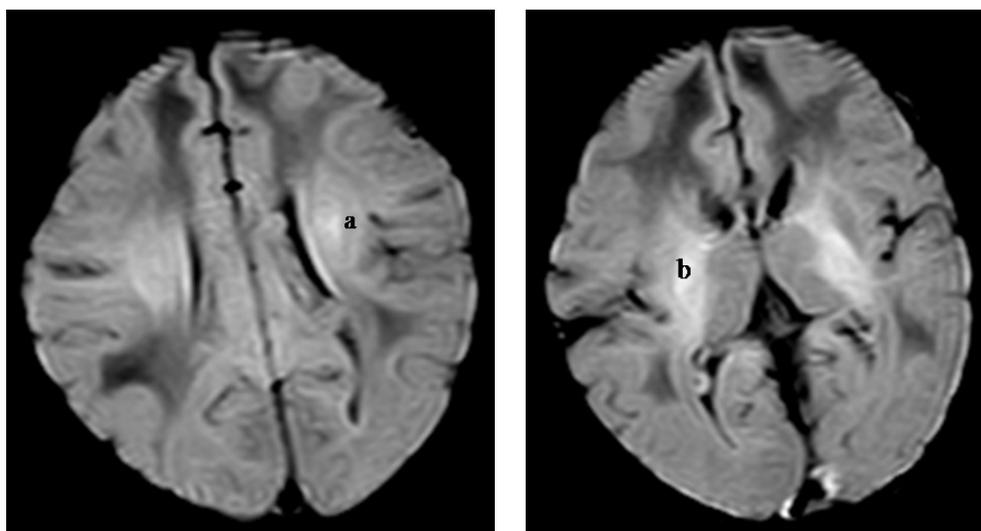


Figure 4. FLAIR AXIAL image shows hyperintensity in deep white matter of cerebral cortex 'a', internal capsule 'b', thalamus.

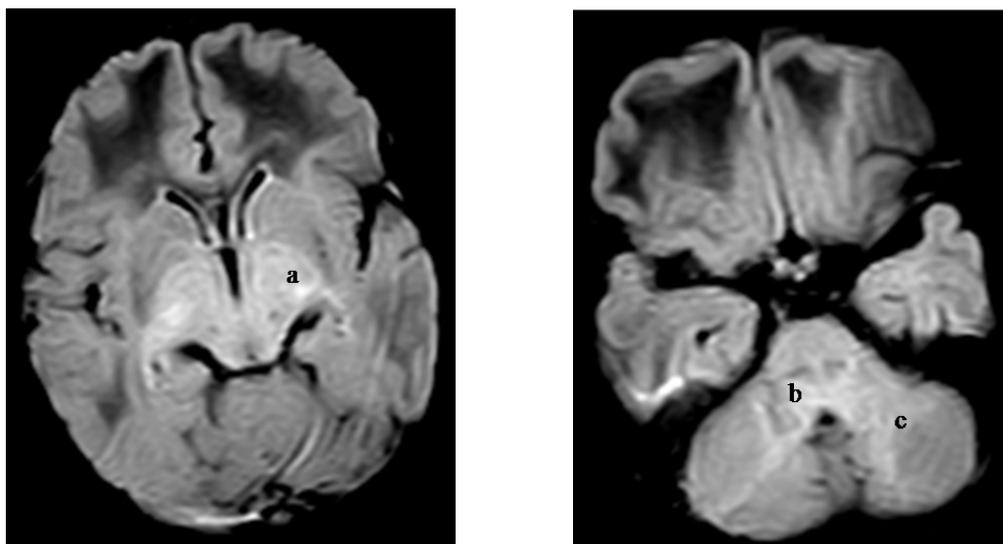


Figure 5. FLAIR AXIAL image shows hyperintensity cerebral peduncle 'a', mid brain, dorsal pons 'b' and white matter of cerebellum 'c'.