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Case Report

Maple syrup urine disease presenting as severe neonatal metabolic encephalopathy: a case report

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ABSTRACT

We report a 17 day old boy, who developed progressive encephalopathy, after an apparent period of normalcy. Magnetic resonance imaging showed diffusion restriction in myelinated areas like, a pattern suggestive of maple syrup urine disease. Dried blood spots for tandem mass spectrometry and urine for gas chromatography mass spectrometry confirmed elevation and excretion of branched chain amino acids respectively. After peritoneal dialysis, baby improved but continued to have residual neurological deficit, in spite of MSUD-specialized diet. Molecular studies confirmed the diagnosis. This report highlights the need for early identification of these infants to optimize neurological outcomes.

Keywords: Inborn error of metabolism, Maple syrup urine disease**,** Neonatal metabolic encephalopathy

INTRODUCTION

Maple syrup urine disease (MSUD) is a rare inborn error of amino acid metabolism and has an autosomal recessive inheritance with a reported incidence of 1 in 1,85,000 infants.[1]

A study done by Dindagur N et al, found that among 3550 symptomatic Indian children, 113 cases (3.2%) were identified with a metabolic disorder. Results showed that IEM (inborn error of metabolism) is overrepresented in 70 (62%) babies born to consanguineous parents. They also found a high frequency 62 (54.8%), of positive history of IEM or of unexplained death among these families. In their study, amino acid disorders accounted for 54% of total cases of which phenylketonuria (PKU) was the most common. The second most common disease was maple syrup urine disease (MSUD).[2]

MSUD is caused by deficiency of branched chain alpha-ketoacid dehydrogenase complex. This leads to accumulation of leucine, valine and isoleucine in blood causing CNS symptoms.[3]

Neurological symptoms are commonly reported and include lethargy, irritability, poor feeding, apnea, opisthotonus, and "bicycling" movements. Yang Nan et al in their report on 33 cases of MSUD, showed that 28 cases (84.8%) had neurological symptoms of feeding difficulties, lethargy, convulsions, etc.[4] As neurological symptoms are often subtle and non-specific, these infants can often be missed in the early neonatal period and later present with worsening obtundation, coma and respiratory failure. This presentation is more common in low middle-income countries, where adoption of neonatal direct blood spot screening for inborn errors of metabolism, is not widespread. We, therefore, report a 17 days neonate, who presented with severe encephalopathy, requiring respiratory support, and was later diagnosed as MSUD. Our report highlights the importance of neonatal screening, in the pre-symptomatic period, in order to optimize outcomes, in these rare disorders.

CASE REPORT

A 17-day-old boy, first born of non-consanguineous parents, presented to the out-patient department of our institution, with history of fever, poor feed intake and lethargy for 2 days. He was born to 26 years old primigravida, who conceived after intra-uterine insemination. During pregnancy, the initial serial ultrasonograms were normal; but at 36 weeks of gestation, oligohydramnios was diagnosed with no other associated anomaly. She delivered at 39 weeks by emergency LSCS in view of severe oligohydramnios. The baby cried immediately after birth and weighed 3.26 kg. The baby was then initiated on direct breast feeds and apparently remained asymptomatic till day 14 of life when he developed poor suck, fever, lethargy and abnormal breathing. He presented to the emergency on day 17, with severe encephalopathy and poor respiratory efforts and was ventilated for the same (Figure 1).

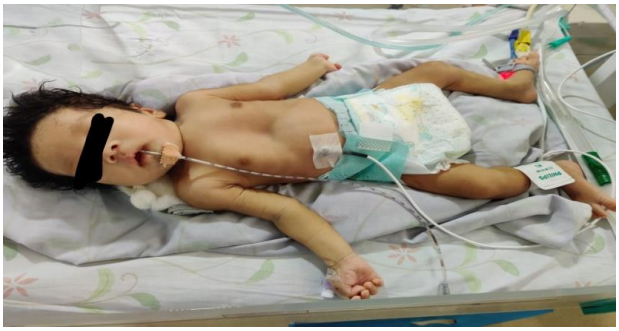


Figure 1: A 17 day old boy with MSUD, in a pithed frog-like hypotonic posture.

On examination he weighed 2.5 kg and had generalized hypotonia, minimal spontaneous activity, and poor reflexes including sluggish pupillary reaction and absent suck. No clinical seizures were noted at presentation. Blood work up showed respiratory acidosis (pH 7.021, PCO_2 80 mmHg), negative septic screen, normal blood sugar (73 mg/dl), normal electrolytes (sodium 140 mmol/L, potassium 5.3 mmol/L, chloride 107 mmol/L, bicarbonate 20 mmol/L, calcium 11.0 mg/dl, magnesium 1.5mg/dl) and renal function (blood urea 35 mg/dl, serum creatinine 1.0 mg/dl), lactate 0.39 mmol/L (normal range 0.22-2.98 mmol/L) and liver function. Ammonia was mildly elevated 130 µmol/L (normal range 11 to 32 µmol/L). He was kept nil oral and was started on IV fluids-1/2DNS and antibiotics. In view of non-improving neurological status over the next 8 hours, magnetic resonance imaging of brain was done (Figure 2, Figure 3 and Figure 4), which showed bilateral symmetrical T2 and flair hyperintensities with T1 hypo intensity in peri-rolandic white matter, corticospinal tracts, centrum semi ovale, corona radiata, posterior limb of internal capsule, thalami, brain stem and deep cerebellar white matter. Involved areas show restriction on diffusion weighted imaging with low apparent diffusion coefficient values suggestive of cytotoxic edema. MR Spectroscopy shows prominent peak at 1ppm for branched chain amino-acids and branched-chain alpha-keto acids with reduced n-acetyl aspartate. These imaging findings were consistent with MSUD.

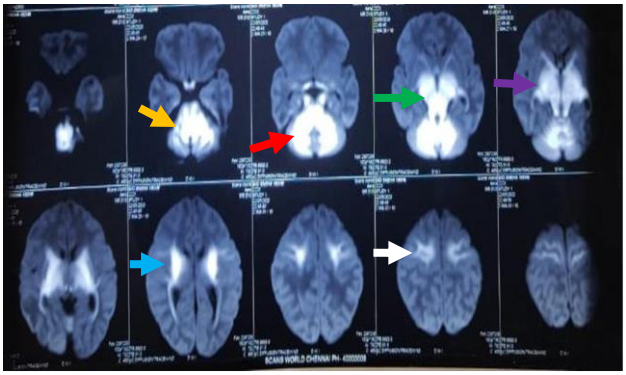


Figure 2: DWI axial images, diffusion restriction in bilateral perirolandic white matter (white arrow), corticospinal tracts (green arrow), corona radiata (blue arrow), thalamo-ganglionic region (purple arrow), brain stem (yellow arrow) and deep cerebellar white matter (red arrow).

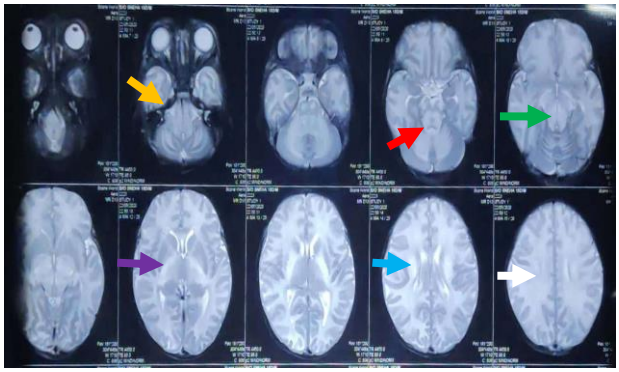


Figure 3: MRI brain T2 axial, T2 hyperintensities in bilateral perirolandic white matter (white arrow), corticospinal tracts (green arrow), corona radiata (blue arrow), thalamo-ganglionic region (purple arrow), brain stem (yellow arrow) and deep cerebellar white matter (red arrow).

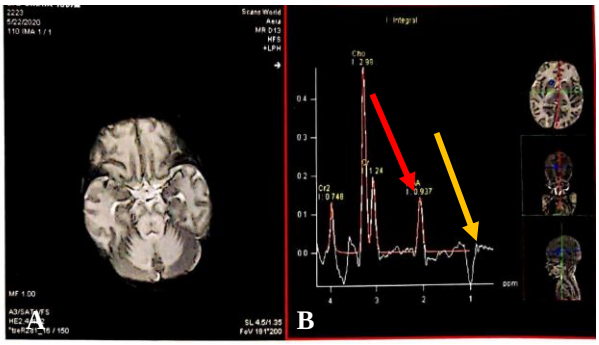
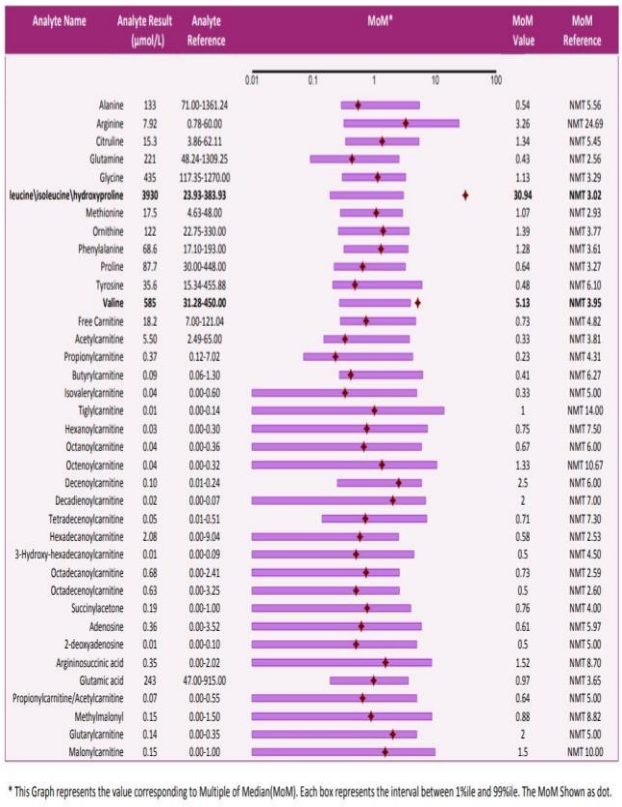


Figure 4: MRI brain, T2 axial, A) bilateral symmetrical hyperintensities seen in brain stem & bilateral cerebellar lobes, B) MRS, prominent peak at 1ppm BCAAs and branched-chain alpha-ketoacids (yellow arrow) with reduced NAA (red arrow).

Tandem mass spectrometry was done using dried blood spots and showed elevated branched chain amino acids (BCAA) leucine/isoleucine/hydroxyproline, 3930 (normal 23.93-383.93), valine 585 (normal 31.28-450.00), suggestive of MSUD (Figure 5) .



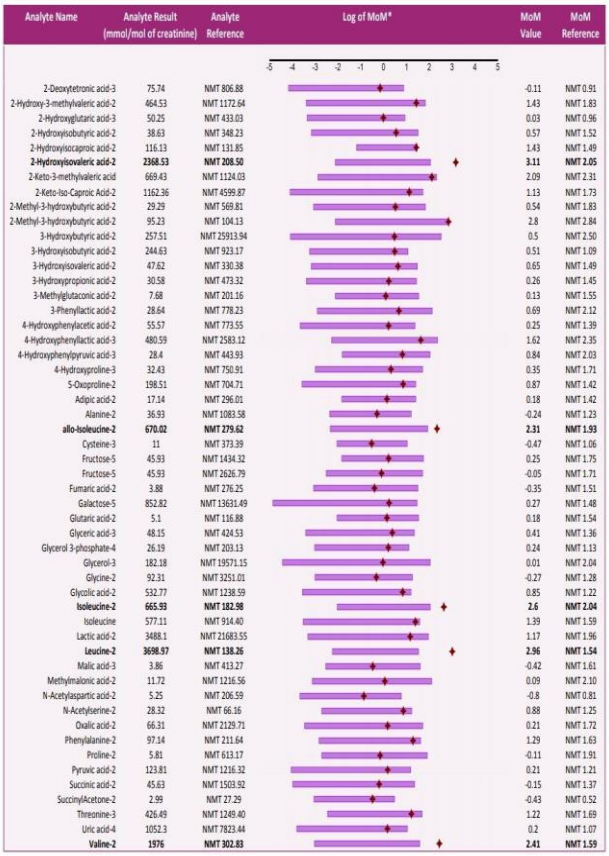
Analyte Name	Analyte Result (µmol/L)	Analyte Reference	MoM*	MoM Value	MoM Reference
			0.01 0.1 1 10 100		
Alanine	133	71.00-1361.24		0.54	NMT 5.56
Arginine	7.92	0.78-60.00		3.26	NMT 24.69
Citruline	15.3	3.86-62.11		1.34	NMT 5.45
Glutamine	221	48.24-1309.25		0.43	NMT 2.56
Glycine	435	117.35-1270.00		1.13	NMT 3.29
leucine\isoleucine\hydroxyproline	**3930**	**23.93-383.93**		**30.94**	**NMT 3.02**
Methionine	17.5	4.63-48.00		1.07	NMT 2.93
Ornithine	122	22.75-330.00		1.39	NMT 3.77
Phenylalanine	68.6	17.10-193.00		1.28	NMT 3.61
Proline	87.7	30.00-448.00		0.64	NMT 3.27
Tyrosine	35.6	15.34-455.88		0.48	NMT 6.10
Valine	**585**	**31.28-450.00**		**5.13**	**NMT 3.95**
Free Carnitine	18.2	7.00-121.04		0.73	NMT 4.82
Acetylcarnitine	5.50	2.49-65.00		0.33	NMT 3.81
Propionylcarnitine	0.37	0.12-7.02		0.23	NMT 4.31
Butyrylcarnitine	0.09	0.06-1.30		0.41	NMT 6.27
Isovalerylcarnitine	0.04	0.00-0.60		0.33	NMT 5.00
Tiglylcarnitine	0.01	0.00-0.14		1	NMT 14.00
Hexanoylcarnitine	0.03	0.00-0.30		0.75	NMT 7.50
Octanoylcarnitine	0.04	0.00-0.36		0.67	NMT 6.00
Octenoylcarnitine	0.04	0.00-0.32		1.33	NMT 10.67
Decenoylcarnitine	0.10	0.01-0.24		2.5	NMT 6.00
Decadienoylcarnitine	0.02	0.00-0.07		2	NMT 7.00
Tetradecenoylcarnitine	0.05	0.01-0.51		0.71	NMT 7.30
Hexadecanoylcarnitine	2.08	0.00-9.04		0.58	NMT 2.53
3-Hydroxy-hexadecanoylcarnitine	0.01	0.00-0.09		0.5	NMT 4.50
Octadecanoylcarnitine	0.68	0.00-2.41		0.73	NMT 2.59
Octadecenoylcarnitine	0.63	0.00-3.25		0.5	NMT 2.60
Succinylacetone	0.19	0.00-1.00		0.76	NMT 4.00
Adenosine	0.36	0.00-3.52		0.61	NMT 5.97
2-deoxyadenosine	0.01	0.00-0.10		0.5	NMT 5.00
Argininosuccinic acid	0.35	0.00-2.02		1.52	NMT 8.70
Glutamic acid	243	47.00-915.00		0.97	NMT 3.65
Propionylcarnitine/Acetylcarnitine	0.07	0.00-0.55		0.64	NMT 5.00
Methylmalonyl	0.15	0.00-1.50		0.88	NMT 8.82
Glutarylcarnitine	0.14	0.00-0.35		2	NMT 5.00
Malonylcarnitine	0.15	0.00-1.00		1.5	NMT 10.00

* This Graph represents the value corresponding to Multiple of Median(MoM). Each box represents the interval between 1%ile and 99%ile. The MoM Shown as dot.

Figure 5: Tandem mass spectrometry was done using dried blood sample - highlighted areas show the abnormal values.

Urine Gas chromatography mass spectrometry (GCMS) in multiples of median showed increased excretion of 2-hydroxy isovaleric acid, 2368.53 (not more than 208.5), allo-isoleucine-2, 670.02 (not more than 279.62), isoleucine-2, 665.93 (not more than 182.98), leucine-2, 3698.97 (not more than 138.26), valine-2, 1976 (not more than 302.83), an organic acid excretion profile consistent with MSUD (Figure 6).

The baby developed worsening neurological symptoms in the form of coma, sluggish pupillary reaction, absent gag reflex and pooling of secretions. After biochemical confirmation of MSUD, peritoneal dialysis was initiated for the next 48 hours. Thereafter, the baby improved clinically in the form of return of spontaneous activity and breathing, and was hence extubated to nasal continuous positive air way pressure. Peritoneal dialysis was discontinued and baby was started on specialized formula feeds (leucine, valine and isoleucine free diet, metanutrition, Pristine organics private limited, Bengaluru, India) along with carnitine and thiamine supplementation (Figure 7). Genetic analysis of peripheral blood showed a homozygous mutation of the E1 alpha sub-unit in the BCKDHA gene on 19q13.



Analyte Name	Analyte Result (mmol/mol of creatinine)	Analyte Reference	Log of MoM*	MoM Value	MoM Reference
			-5 -4 -3 -2 -1 0 1 2 3 4 5		
2-Deoxytetronic acid-3	75.74	NMT 806.88		-0.11	NMT 0.91
2-Hydroxy-3-methylvaleric acid-2	464.53	NMT 1172.64		1.43	NMT 1.83
2-Hydroxyglutaric acid-3	50.25	NMT 433.03		0.03	NMT 0.96
2-Hydroxyisobutyric acid-2	38.63	NMT 348.23		0.57	NMT 1.52
2-Hydroxyisocaproic acid-2	116.13	NMT 131.85		1.43	NMT 1.49
2-Hydroxyisovaleric acid-2	**2368.53**	**NMT 208.50**		**3.11**	**NMT 2.05**
2-Keto-3-methylvaleric acid	669.43	NMT 1124.03		2.09	NMT 2.31
2-Keto-Iso-Caproic Acid-2	1162.36	NMT 4599.87		1.13	NMT 1.73
2-Methyl-3-hydroxybutyric acid-2	29.29	NMT 569.81		0.54	NMT 1.83
2-Methyl-3-hydroxybutyric acid-2	95.23	NMT 104.13		2.8	NMT 2.84
3-Hydroxybutyric acid-2	257.51	NMT 25913.94		0.5	NMT 2.50
3-Hydroxyisobutyric acid-2	244.63	NMT 923.17		0.51	NMT 1.09
3-Hydroxyisovaleric acid-2	47.62	NMT 330.38		0.65	NMT 1.49
3-Hydroxypropionic acid-2	30.58	NMT 473.32		0.26	NMT 1.45
3-Methylglutaconic acid-2	7.68	NMT 201.16		0.13	NMT 1.55
3-Phenyllactic acid-2	28.64	NMT 778.23		0.69	NMT 2.12
4-Hydroxyphenylacetic acid-2	55.57	NMT 773.55		0.25	NMT 1.39
4-Hydroxyphenyllactic acid-3	480.59	NMT 2583.12		1.62	NMT 2.35
4-Hydroxyphenylpyruvic acid-3	28.4	NMT 443.93		0.84	NMT 2.03
4-Hydroxyproline-3	32.43	NMT 750.91		0.35	NMT 1.71
5-Oxoproline-2	198.51	NMT 704.71		0.87	NMT 1.42
Adipic acid-2	17.14	NMT 296.01		0.18	NMT 1.42
Alanine-2	36.93	NMT 1083.58		-0.24	NMT 1.23
allo-Isoleucine-2	**670.02**	**NMT 279.62**		**2.31**	**NMT 1.93**
Cysteine-3	11	NMT 373.39		-0.47	NMT 1.06
Fructose-5	45.93	NMT 1434.32		0.25	NMT 1.75
Fructose-5	45.93	NMT 2626.79		-0.05	NMT 1.71
Fumaric acid-2	3.88	NMT 276.25		-0.35	NMT 1.51
Galactose-5	852.82	NMT 13631.49		0.27	NMT 1.48
Glutaric acid-2	5.1	NMT 116.88		0.18	NMT 1.54
Glyceric acid-3	48.15	NMT 424.53		0.41	NMT 1.36
Glycerol 3-phosphate-4	26.19	NMT 203.13		0.24	NMT 1.13
Glycerol-3	182.18	NMT 19571.15		0.01	NMT 2.04
Glycine-2	92.31	NMT 3251.01		-0.27	NMT 1.28
Glycolic acid-2	532.77	NMT 1238.59		0.85	NMT 1.22
Isoleucine-2	**665.93**	**NMT 182.98**		**2.6**	**NMT 2.04**
Isoleucine	577.11	NMT 914.40		1.39	NMT 1.59
Lactic acid-2	3488.1	NMT 21683.55		1.17	NMT 1.96
Leucine-2	**3698.97**	**NMT 138.26**		**2.96**	**NMT 1.54**
Malic acid-3	3.86	NMT 413.27		-0.42	NMT 1.61
Methylmalonic acid-2	11.72	NMT 1216.56		0.09	NMT 2.10
N-Acetylaspartic acid-2	5.25	NMT 206.59		-0.8	NMT 0.81
N-Acetylserine-2	28.32	NMT 66.16		0.88	NMT 1.25
Oxalic acid-2	66.31	NMT 2129.71		0.21	NMT 1.72
Phenylalanine-2	97.14	NMT 211.64		1.29	NMT 1.63
Proline-2	5.81	NMT 613.17		-0.11	NMT 1.91
Pyruvic acid-2	123.81	NMT 1216.32		0.21	NMT 1.21
Succinic acid-2	45.63	NMT 1503.92		-0.15	NMT 1.37
SuccinylAcetone-2	2.99	NMT 27.29		-0.43	NMT 0.52
Threonine-3	426.49	NMT 1249.40		1.22	NMT 1.69
Uric acid-4	1052.3	NMT 7823.44		0.2	NMT 1.07
Valine-2	**1976**	**NMT 302.83**		**2.41**	**NMT 1.59**

* This Graph represents the metabolites which are found above the detection limit. Each box represents the reference interval between 1%ile and 99%ile Multiple of Median(MoM) in Logarithmic scale. The Log of MoM of the analyzed sample is shown as dot.

Figure 6: Gas chromatography mass spectrometry screening was done using blood sample highlighted areas show the abnormal values.

Figure 7: MSUD, specialized formula feeds (leucine, valine and isoleucine free diet, metanutrition, Pristine organics private limited, Bengaluru, India).

Initially, baby had feed intolerance but then gradually tolerated feeds. Baby continued to have abnormal neurological signs in the form of pooling of secretions and weak suck. Baby also developed dystonia and tremors necessitating addition of anti-cholinergic trihexyphenidyl. Baby was also started on oro-motor training for paladai feeds. By 2 months of age, baby started tolerating paladai feeds and hence baby was discharged on day 75 of life on paladai feeds (MSUD specialized formula feeds, leucine, valine and isoleucine free diet-metanutrition). At discharge he had dystonia and occasional tremors but significant improvement in brainstem reflexes. Genetic counselling was provided for parents and a carrier screening was planned on follow up.

DISCUSSION

MSUD is a rare inborn error of branched-chain amino acid metabolism. Due to the defective decarboxylation of branched chain amino acids (leucine, isoleucine and valine), there is accumulation of these and their ketoacids in the body. This results in severe neurodegeneration, if prolonged and untreated.[5] There are five phenotypes in MSUD: Classic, intermittent, intermediate, thiamine responsive, and dihydrolipoyl dehydrogenase deficient forms. Among them, classic MSUD is characterized by a neonatal onset of encephalopathy and is the most common and most severe form.[6]

The prevalence of MSUD in Indian population is not well studied but is likely to be high, considering the autosomal recessive inheritance pattern and high levels of consanguinity in the Indian population.[2]

The neurological manifestation of MSUD is related to the high leucine levels as seen in our case (plasma leucine 3930). The neurological manifestations start as lethargy, feeding difficulty, tone alterations and abnormal cry and in the absence of early recognition and treatment, evolve into abnormal movements together with increasing hypertonia and spasticity progressing to seizures and coma.[7] Finally severe manifestations such as central respiratory failure, brain stem dysfunction and death occur. Intercurrent illnesses like infection and starvation worsen the neurological signs resulting in temporary episodes of extreme hypotonia. The disease gets its name from the distinctive maple syrup odour of the urine (burnt sugar odour), which is often difficult to recognize for the uninitiated clinician.

The acute neurological presentation often mandates an MR imaging of the brain. Diffusion weighted imaging (DWI) has uncovered early alterations in the white and grey matter of newborns with MSUD and can identify cytotoxic or intramyelinic edema. The cerebral edema can be diffuse or localized with particular predilection for cerebellar white matter, brainstem, globus pallidus, internal capsule, and thalamus.[8] Edema typically occur in areas that are myelinated in normal full-term neonates.[9] Both brain alterations and MRI findings in MSUD are reversible with early treatment and normal neurologic development can be achieved with successful treatment.[10] Early diagnosis and dietary intervention is thus vital in optimizing long term neurological outcomes.

Acute neurological crisis in MSUD often necessitates rapid measures to lower to abnormal BCAA's in the blood. In neonates, peritoneal dialysis is easier and is the preferred method for rapid metabolic clearance, as BCAA free enteral diet generally takes time to work. Also oral intake is often impossible in sick presentations, necessitating renal replacement therapy. Other renal replacement methods like continuous veno-venous hemofiltration, though more efficacious, are often difficult to perform in small infants and requires considerable expertise, which might not be available in resource poor settings.[11] In our case, peritoneal dialysis was initiated in view of worsening neurological status and high metabolite levels, and it resulted in clinical improvement. We did not perform follow up BCAA levels due to cost constraints, but in view of the improving course, the levels were likely to have declined. Nevertheless, peritoneal dialysis was not able to totally reverse the neurological insult and the baby continued to have weak suck and pooling of secretions. The residual neurological signs at discharge could be because of the late presentation resulting in late treatment initiation and irreversible neurological damage, despite of normalization of BCAA levels.

Molecular genetic tests in the index case revealed the mutations in the E1 alpha sub-unit in BCKDHA gene on 19q13. These tests not only help in establishing the diagnosis but are also useful for prognostication in future pregnancies. This genetic variation has previously been reported in many infants with classic Maple syrup urine disease.[12]

As early diagnosis improves outcomes, neonatal screening plays a pivotal role in identification of these infants. Tandem mass spectrometry using dried blood spots is now the universally preferred newborn screening tool for inborn errors of metabolism and MUSD can be easily suspected based on the typical abnormal analyte pattern. As newborn screening is not mandatory in India, this was not done in our case, resulting in a late presentation with severe encephalopathy. In MSUD, appropriate immediate treatment not only improves survival but also reduces chances of neuro-developmental sequelae.[13]

CONCLUSION

MSUD is a rare inborn error of branched chain amino acid metabolism commonly resulting in metabolic encephalopathy. Knowledge about the classic MRI with DWI findings will enable us to suspect MSUD as a cause of encephalopathy. Blood TMS, urine GCMS and molecular testing help us in confirming the disease. Late presentations with severe encephalopathy require renal

replacement therapy for metabolic clearance, followed by specialized diets. Residual neurological deficits are common in case of late initiation of treatment. Long term neurological, nutritional, growth and development assessment is mandatory. With the ease of availability of neonatal screening tests, infants with MSUD should be identified in the pre-symptomatic phase, so that prompt therapy can be started and outcomes optimized.

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Ethical approval: Not required

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