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Rare Presentation: Maple Syrup Urine Disease as Severe Neonatal Metabolic Encephalopathy

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Abstract: ***Wereport 8 day old neonate who developed a progressive encephalopathy, after an apparent period of normalcy. Dried blood spots for tandem mass spectrometry confirmed elevation and excretion of branched chain amino acids. 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

1. 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]. 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[2]. Neurological symptoms like lethargy, irritability, poor feeding, apnea, opisthotonous and bicycling movements. As neurological symptoms are non - specific, these infants can often missed in the early neonatal period and later present with worsening obtundation, coma and respiratory failure. Our report highlights the importance of early neonatal screenings for inborn errors of metabolism in order to optimize outcomes.

2. Case Brief

A second order five days old neonate born out of second degree consanguineous parents presented with dull activity, lethargy and poor feeding for 3 days, one episode of convulsions in the form of excessive cry followed by cyclical movements of both upper limbs. Baby was born through normal vaginal delivery with birth weight of 2.5 kgs and cried immediately after birth. The baby was then initiated on direct breast feed and apparently remained asymptomatic till day five of life. Baby was presented to the emergency on day eight with severe encephalopathy and poor respiratory efforts and was ventilated for the same. On examination baby weighed 2.59kgs and had generalised hypotonia minimal spontaneous activity and poor reflexes including sluggish pupillary reaction and absent suck. No clinical seizures were noted at presentation. Blood workup showed mild metabolic acidosis (pH 7.21 and HCO_3 19.4), negative septic screen, normal blood sugar normal electrolytes and renal function, lactate within the normal range, urine ketone bodies positive. Baby was kept nil orally and was started on IV fluids and antibiotics. In view of non - improving neurological status over the next eight hours, lumbar puncture was done which shown normal. So suspecting inborn errors of metabolism, Tandem mass spectrometry was done using dry blood spots and showed elevated branched chain amino acids suggestive of MSUD.

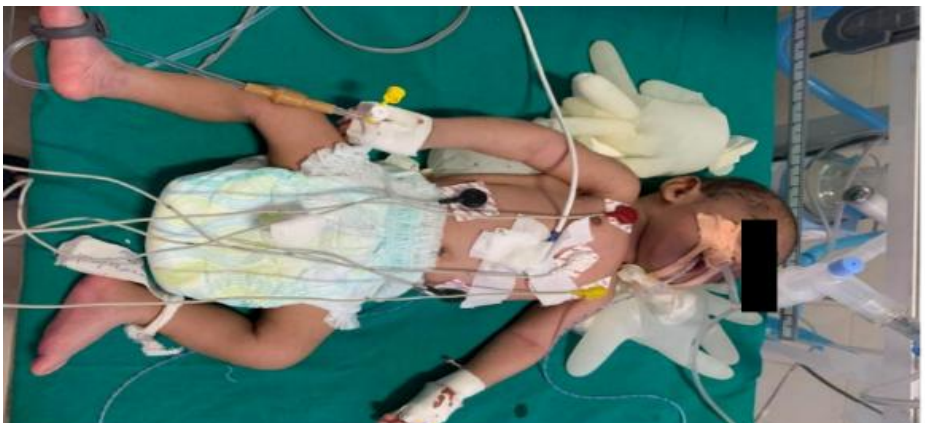


Figure 1: Baby with MSUD in a pithed frog like hypotonic posture

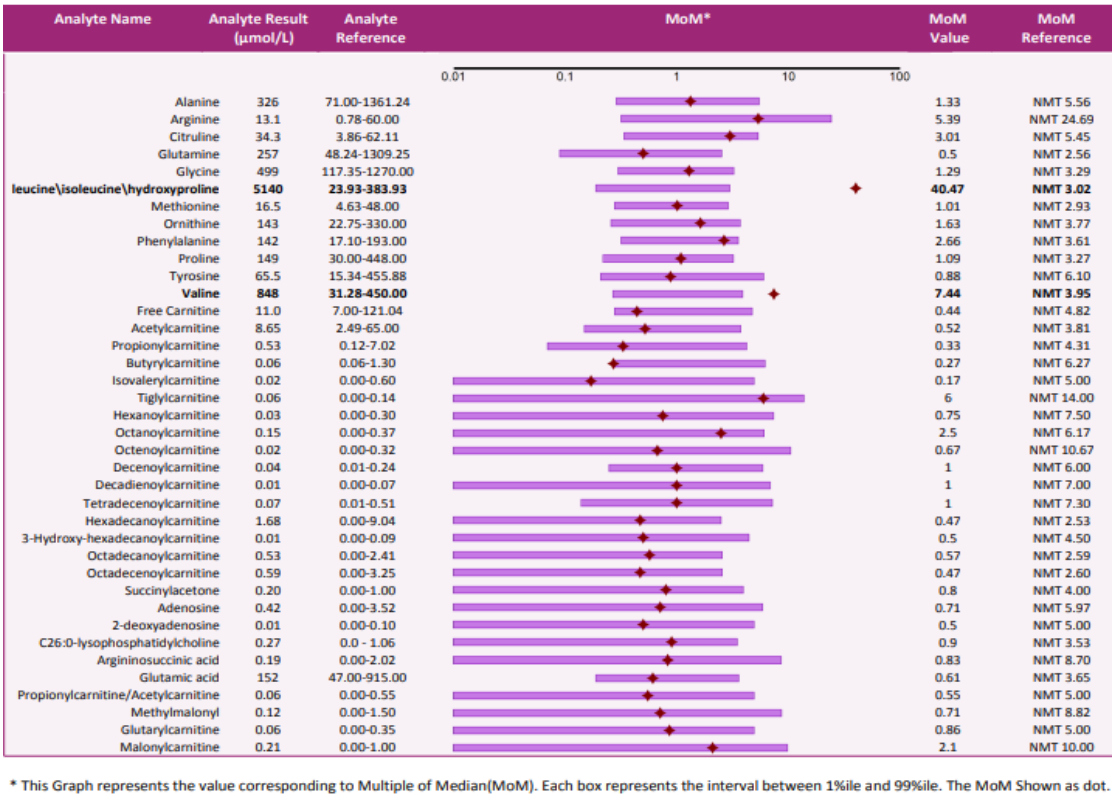
3. Discussion

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 theseand their ketoacids in the body. This results in severe neurodegeneration, if prolonged and untreated[3]. 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[4]. 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[5]. 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.

In our case, the neurological manifestations of MSUD are related to high levels of high leucine levels (plasma leucine 5140). Early diagnosis and dietary interventions place an important role in long term neurological outcomes. Tandem mass spectrometry is now the universal newborn screening tool for inborn errors of metabolism and MSUD can be easily confirmed using this tool. As newborn screening is not mandatory in India this was not done in our case. Thereby resulting with severe encephalopathy presentation in this neonate

Prevalence of MSUD in Indian population is not well known. It is likely to be high because of autosomal recessive inheritance and more levels of consanguinity in the Indian population[6].



Analyte Name	Analyte Result (µmol/L)	Analyte Reference	MoM*	MoM Value	MoM Reference
			0.01 0.1 1 10 100		
Alanine	326	71.00-1361.24		1.33	NMT 5.56
Arginine	13.1	0.78-60.00		5.39	NMT 24.69
Citruline	34.3	3.86-62.11		3.01	NMT 5.45
Glutamine	257	48.24-1309.25		0.5	NMT 2.56
Glycine	499	117.35-1270.00		1.29	NMT 3.29
leucine\isoleucine\hydroxyproline	**5140**	**23.93-383.93**		**40.47**	**NMT 3.02**
Methionine	16.5	4.63-48.00		1.01	NMT 2.93
Ornithine	143	22.75-330.00		1.63	NMT 3.77
Phenylalanine	142	17.10-193.00		2.66	NMT 3.61
Proline	149	30.00-448.00		1.09	NMT 3.27
Tyrosine	65.5	15.34-455.88		0.88	NMT 6.10
Valine	**848**	**31.28-450.00**		**7.44**	**NMT 3.95**
Free Carnitine	11.0	7.00-121.04		0.44	NMT 4.82
Acetylcarnitine	8.65	2.49-65.00		0.52	NMT 3.81
Propionylcarnitine	0.53	0.12-7.02		0.33	NMT 4.31
Butyrylcarnitine	0.06	0.06-1.30		0.27	NMT 6.27
Isovalerylcarnitine	0.02	0.00-0.60		0.17	NMT 5.00
Tiglylcarnitine	0.06	0.00-0.14		6	NMT 14.00
Hexanoylcarnitine	0.03	0.00-0.30		0.75	NMT 7.50
Octanoylcarnitine	0.15	0.00-0.37		2.5	NMT 6.17
Octenoylcarnitine	0.02	0.00-0.32		0.67	NMT 10.67
Decenoylcarnitine	0.04	0.01-0.24		1	NMT 6.00
Decadienoylcarnitine	0.01	0.00-0.07		1	NMT 7.00
Tetradecenoylcarnitine	0.07	0.01-0.51		1	NMT 7.30
Hexadecanoylcarnitine	1.68	0.00-9.04		0.47	NMT 2.53
3-Hydroxy-hexadecanoylcarnitine	0.01	0.00-0.09		0.5	NMT 4.50
Octadecanoylcarnitine	0.53	0.00-2.41		0.57	NMT 2.59
Octadecenoylcarnitine	0.59	0.00-3.25		0.47	NMT 2.60
Succinylacetone	0.20	0.00-1.00		0.8	NMT 4.00
Adenosine	0.42	0.00-3.52		0.71	NMT 5.97
2-deoxyadenosine	0.01	0.00-0.10		0.5	NMT 5.00
C26:0-lysophosphatidylcholine	0.27	0.0 - 1.06		0.9	NMT 3.53
Argininosuccinic acid	0.19	0.00-2.02		0.83	NMT 8.70
Glutamic acid	152	47.00-915.00		0.61	NMT 3.65
Propionylcarnitine/Acetylcarnitine	0.06	0.00-0.55		0.55	NMT 5.00
Methylmalonyl	0.12	0.00-1.50		0.71	NMT 8.82
Glutarylcarnitine	0.06	0.00-0.35		0.86	NMT 5.00
Malonylcarnitine	0.21	0.00-1.00		2.1	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 2: Tandem mass spectroscopy showing increased branched chain amino acids

4. Conclusion

MSUD is a rare inborn error of branched chain amino acid metabolism commonly resulting in metabolic encephalopathy. 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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