International Journal of Contemporary Pediatrics
Raut D et al. Int J Contemp Pediatr. 2025 Apr;12(4):677-680
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291
DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20250780

Case Report

Thinking beyond sepsis to unmask a metabolic mystery: a rare case of neonatal maple syrup urine disease

Dinkar Raut[1]*, Sagar Yamnaji Walhekar[1], Anjini Misra[2], Rachna Singh[3]

[1]Neonatal and Pediatric Intensivist, Yogita Pediatric Critical Care Hospital and Nursing Home, Beed, Maharashtra, India
[2]Department of Pediatrics, Government Medical College, Nagpur, Maharashtra, India
[3]Punjabrao Deshmukh Medical College and Hospital, Amravati, Maharashtra, India

Received: 26 January 2025
Revised: 04 March 2025
Accepted: 10 March 2025

***Correspondence:**
Dr. Dinkar Raut,
E-mail: dr.dinkarrraut@gmail.com

ABSTRACT

Maple syrup urine disease (MSUD) was first reported by paediatrician Menkes in 1954, as the α-ketoacid excreted in urine smells like maple syrup. MSUD is a rare genetic disorder which manifested as impaired branched-chain amino acid (BCAA) metabolism caused by branched-chain α-ketoacid dehydrogenase (BCKD) complex deficiency. Early diagnosis and treatment of MSUD is important for better outcomes. Feed intolerance, history of consanguinity between parents and that peculiar odour of maple syrup in urine should raise suspicion of the above. Timely referral, especially by clinicians practising in rural areas, is essential for early diagnosis and treatment. We present a case of MSUD with poor prognosis probably due to advanced disease at the time of presentation. The case highlights the importance of suspicion and early diagnosis of MSUD, as well as thinking beyond sepsis as the root of all problems.

Keywords: Maple syrup urine disease, Consanguineous marriage, Prognosis, Feeding difficulty

INTRODUCTION

Maple syrup urine disease (MSUD) is a rare metabolic disorder due to deficiency of BCKDH enzyme complex leading to impaired catabolism of branched chain amino acids.[2] Valine, leucine and isoleucine accumulate in blood and urine, ultimately leading to the unique burnt sugar smell of urine, very characteristic of the said condition. Among the four types, classical neonatal form is commonest, yet the most severe.[3] Worldwide incidence of disease is 1 in 1,85,000 infants. It has an autosomal recessive inheritance.[4]

Classically, affected neonates present with feeding problems, vomiting, lethargy, and irritability, leading to seizures, coma, and death if left untreated.[5] We present a case of a neonate with MSUD who, unfortunately, succumbed to the disease.

CASE REPORT

An eight-day old male neonate was brought by parents with history of irritability over four days, followed by reduced acceptance of feeds and lethargy since 3-4 hours (Figure 1). The baby had been referred from a private setup in view of cyanosis, hypoglycemia and seizures.

On careful history, it was noted that the parents had a second-degree consanguineous marriage. They had previously (two years ago) lost a newborn on day ten of life in view of similar complaints. One history of abortion was also noted. For this baby, parents underwent infertility treatment. The baby was born full term, vaginally delivered with a birth weight of 2.7 kg.

The newborn did not require intensive care admission immediately after birth and was apparently alright for the

first six days of life. From the seventh day, the neonate gradually became irritable, started regurgitating feeds and showed reduced feed tolerance. Irritability progressed further and he was admitted on eighth day of life with history of bluish discolouration of skin, persistent staring look and non-response to audio-visual cues.

Figure 1: Presentation of the baby.

On admission, the baby had ongoing seizures, cyanosis, hypothermia, grunting and delayed capillary refill time (CRT).

Non-invasive ventilation (positive pressure ventilation with FiO_2 30%/flow 5 L/Min) was started. The baby received 5 ml of 10% dextrose bolus in view of low blood sugar levels (BSL). Calculated intravenous fluids were started. Active convulsions were managed with antiepileptics (levetiracetam and fosphenytoin).

After initial stabilization, the general appearance of newborn improved. Signs and symptoms of respiratory distress settled. CRT was normalized, BSL maintained. The baby passed dark coloured urine with strong abnormal smell (Figure 2).

Figure 2: Dark coloured urine with peculiar odour.

Urine routine examination showed presence of ketones (3+ by dipstick method). Septic screen was negative. Cerebrospinal fluid (CSF) analysis was normal. Cranial ultrasound did not show any significant abnormality. Magnetic resonance imaging (MRI) was not possible due to poor clinical status of the newborn. Despite given treatment, sensorium did not show substantial improvement.

Arterial blood gas report was suggestive of mild metabolic acidosis. Serum ammonia level was normal. CSF adenosine deaminase (ADA) level was 4.70 U/L (Normal level <9 U/L).

CSF microscopy report showed 2/cmm nucleated cells. No red blood cells were seen in CSF. Field's stain against clear background showed 100% lymphocytes. Ziehl-Neelsen and gram stain reports were negative. CSF protein and CSF sugar was 49 mg/dl and 36 mg/dl respectively.

With progressive deterioration in sensorium and odd scent of urine, an inborn error of metabolism (IEM) was suspected. Tandem mass spectrometry (TMS) screening was performed and parents were counselled regarding possibility of an IEM. TMS report showed high levels of valine, leucine and isoleucine (branched chained amino acids)-suggestive of MSUD (Table 1). The baby deteriorated further due to progressive encephalopathy and passed away on day thirteen since birth.

Table 1: TMS report of the patient.

Investigation	Observed value	Unit	Biological reference interval
Alanine	234.07	µM	132.00-826.51
Aspartic acid	224.72	µM	<420
Arginine	13.4	µM	5.40-53.9
Citrulline	23.16	µM	8.64-42.7
Glutamic acid	730.93	µM	207.00-1577.75
Glycine	362.62	µM	187-767
Leucine + isoleucine	3037.62	µM	64.0-235

Continued.

Investigation	Observed value	Unit	Biological reference interval
Lysine	170.44	µM	98.66-416.44
Methionine	18.86	µM	3-44
Ornithine	195.61	µM	28.33-392.50
Phenylalanine	76.43	µM	33-97
Proline	220.65	µM	107.18-233
Serine	286.23	µM	24.85-966.70
Tyrosine	79.34	µM	34-207
Valine	534.89	µM	57-212
Free carnitine (C0)	11.87	µM	11-59
Acetylcarnitine (C2)	4.91	µM	3-52
Propionylcarnitine (C3)	0.49	µM	0.39-4.50
Malonylcarnitine (C3DC) C4OH	0.11	µM	0.04-0.33
Butyrylcarnitine (C4)	0.15	µM	0.08-0.75
Isovalerylcarnitine (C5)	0.05	µM	0.05-0.39
Tiglylcarnitine (C5:1)	0.03	µM	0.00-0.08
Glutaryl carnitine (C5DC) C6OH	0.2	µM	0.00-0.21
OH-isovalerylcarnitine (C5OH) C4DC	0.08	µM	<0.40
Hexanoylcarnitine (C6)	0.04	µM	0.02-0.18
3-Methylglutarylcarnitine (C6DC)	0.02	µM	0.02-0.17
Octanoyl carnitine (C8)	0.04	µM	0.02-0.21
Decanoylcarnitine (C10)	0.05	µM	0.02-0.26
Dodecanoylcarnitine (C12)	0.04	µM	0.04-0.41

Parents were counselled afresh regarding the type of disease, inheritance pattern and future prospects of having another issue with the same disorder. The importance of antenatal screening was reiterated.

DISCUSSION

Considering the predominance of neurological symptoms, signs of encephalopathy, feed intolerance and characteristic maple syrup like smell of urine, a provisional diagnosis of MSUD was made.[2] Patients with MSUD show presence of elevated branch chain ketoacids in urine and blood.[2] In our case scenario, the results of TMS screening showed significantly elevated levels of valine, leucine and isoleucine, further strengthening our suspicion. MSUD has also been reported as an infrequent cause of febrile seizures in neonates.[6] In this case, the baby had seizures, not associated with high grade fever spikes, and kept under control with liberal use of anticonvulsants.

Inborn errors of metabolism (IEM) usually present as altered sensorium, seizures, encephalopathy, tachypnea, abnormal odour of skin and urine, metabolic acidosis (usually without anion gap), ketonuria, non-ketotic or ketotic hypoglycemia and distinct skin and ocular findings.

Usually after ruling out routine causes such as sepsis, CNS infections, metabolic derangement like hypoglycemia, hypocalcemia, hypo/hypernatremia, structural brain abnormalities, intraventricular or parenchymal hemorrhages, et ectera, IEM should be suspected in all such sick neonates.

If a neonate has Reyes-like symptoms, hyperammonemia (urea cycle defect) should be suspected. In case the neonate has a clinical profile suggestive of sepsis, disorders like organic acidemia, ketonuria and MSUD should be considered. Early presentation (since day one of life) with opsoclonus and hiccough (singultus) should raise a suspicion of non-ketotic hyperglycinemia (NKH). Molybdenum co-factor deficiency may be associated with persistent elevated uric acid levels.

Patients with lactic acidosis and organic acidemia, laboratory parameters may resemble those seen in gram negative sepsis (leukopenia and thrombocytopenia). Some IEM may present with liver disease, for example, unconjugated hyperbilirubinemia seen in Criglar Najar syndrome; cholestasis may be affiliated with conditions like galactosemia, tyrosemia or haemachromatosis. Refractory seizures are often seen with pyridoxine or magnesium deficiency. Certain characteristic odour are pointers to IEM-burnt sugar like smell may be correlated with MSUD, cabbage like smell seen in tyrosemia, musty odour is characteristic of phenylkentonuria and acid-like pungent smell is suggestive of methylmalonic acidemia. Fatty acid oxidation defects and mitochondriopathy are associated with cardiomyopathy and arrhythmias.

As the eye sees only what the mind is prepared to comprehend, it is of utmost importance to understand IEM and suspect the same, especially with unconventional presentations.

The prevalence of MSUD is more in parents with consanguineous marriage.[7] as also seen with our case. Antenatal amniotic fluid examination or chorionic villus

sampling before sixteen weeks can provide a confirmatory diagnosis of MSUD. New born screening and initiation of treatment early can help improve survival and long-term outcomes. However, severity of disease is an important prognostic factor.[8] In our case, the newborn succumbed perhaps due to severe disease at the outset.

MSUD is an autosomal recessive disorder, hence both parents must be carriers. There is a 25% chance of having an affected newborn in future pregnancy while 50% off-springs will be unaffected carriers.

Especially in rural areas, clinicians should refer the cases with unconventional presentation like ours i.e. irritability, feeding difficulty, peculiar odour of urine, deterioration of neurological symptoms despite best possible treatment and no improvement in symptomatology even after correction of common metabolic and electrolyte imbalances, early to the experts for further investigation and management. This ensures early diagnosis and prompt treatment/referral. Our case highlights and underscores the importance of early speculation and diagnosis of MSUD.

CONCLUSION

Neonates with declining neurological signs and symptoms, despite correction of common metabolic and electrolyte abnormalities and after ruling out possible CNS infections or structural abnormalities, including intracranial hemorrhages and presenting with feeding difficulty, history of consanguinity between parents and characteristic odour to urine, should be evaluated for IEM. Such children should be referred early to higher centers for confirmation of diagnosis and further management, albeit supportive care. Parents with history of newborns with MSUD should be counselled regarding the disease and its inheritance pattern and encouraged for prenatal screening in order to avoid loss of another child to the same disorder. Early treatment is preventive against the development of neurological side effects, and such patients usually perform well. Most patients survive and do not develop neurological effects if treated within a few days. However, once neurological symptoms appear, the damage is usually permanent and irreversible. It is important to diagnose the disease as soon as possible and initiate treatment. MSUD in neonates is rare. Our case report aimed to describe the clinical and imaging characteristics of it, and highlight the fact that physicians must be aware of this entity in newborns so as to reduce misdiagnosis due to unfamiliarity.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Strauss KA, Puffenberger EG, Morton DH. Maple syrup urine disease. Develop Med Child Neurol. 1959;1:104-5.
2. Blackburn PR, Gass JM, Vairo FPE, Farnham KM, Atwal HK, Macklin S, et al. Maple syrup urine disease: mechanisms and management. Appl Clin Genet. 2017;10:57-66.
3. Hassan SA, Gupta V. Maple syrup urine disease. StatPearls. StatPearls Publishing. 2025.
4. Fingerhut R. Recall rate and positive predictive value of MSUD screening is not influenced by hydroxyproline. Eur J Pediatr. 2009;168(5):599-604.
5. 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(4):903-18.
6. Ajmera P, Agarwal A, Dahiya A, Parripati VK. Maple Syrup Urine Disease: An uncommon cause of neonatal febrile seizures. Cureus. 2023;15(6):e40826.
7. Tabbouche O, Saker A, Mountain H. Identification of three novel mutations by studying the molecular genetics of Maple Syrup Urine Disease (MSUD) in the Lebanese population. Mol Genet Metab Rep. 20141:273-9.
8. Mengler K, Garbade SF, Gleich F, Thimm E, May P, Lindner M, et al. Treatment Outcomes for Maple Syrup Urine Disease Detected by Newborn Screening. Pediatrics. 2024;154(2):e2023064370.
9. Harshyenee KK, Ajmera P, Agarwal A, Dahiya A, Parripati VK. Maple syrup urine disease: an uncommon cause of neonatal febrile seizures. Cureus. 2023;15(6):e40826.
10. Liu Q, Li F, Zhou J, Liu X, Peng J, Gong L. Neonatal maple syrup urine disease case report and literature review. Medicine. 2022;101(50):e32174.

Cite this article as: Raut D, Walhekar SY, Misra A, Singh R. Thinking beyond sepsis to unmask a metabolic mystery: a rare case of neonatal Maple syrup urine disease. Int J Contemp Pediatr 2025;12:677-80.