MAK HILL Publications Research Journal of Medical Sciences

Case Report
doi: 10.36478/makrjms.2024.10.334.339

Maple Syrup Urine Disease in a 9-Day-Old Term Male Infant: A Case Report and Diagnostic Approach

[1]Kanchi Lavanya, [2]Harshitha Bunga, [3]Sravya Sai Deepika Pandilla, [4]Katkam Shravani and [5]Vangapalli Gnana Deepika

[1,2]Department of Paediatrics, Osmania Medical College, 5-1-876, Turrebaz khan Rd, Troop Bazaar koti, Hyderabad, Telangana 500095, India

[3,4]Department of Paediatrics, Viswabharathi Medical College, PVVJ+Gfj, Kurnool Bellary Road, Penchikalapadu, Gudur, Andhrapradesh, 518467, India

[5]Department of Paediatrics, Siddhartha Medical College, GM8C+VHW, NH 16 Service Road, Beside Dr NTR University of Health Sciences, Gundala, Vijawada, Andhrapradesh 520008, India

ABSTRACT

Maple Syrup Urine Disease (MSUD) is a rare autosomal recessive disorder characterized by a deficiency in the branched-chain a-ketoacid dehydrogenase (BCKD) enzyme complex, leading to the accumulation of branched-chain amino acids (BCAAs) and their toxic metabolites. Early onset and rapid progression of neurological symptoms, including irritability, poor feeding, seizures and encephalopathy, are hallmark features. We present a case of a 9-day-old term male infant born to a G5A3L1 mother via normal vaginal delivery. The infant exhibited excessive crying from day 3 of life, followed by seizures on day 7 and respiratory failure on day 11, necessitating mechanical ventilation. Diagnostic tests revealed elevated serum lactate, positive urine ketones, and branched-chain ketoacids, confirming the diagnosis of MSUD. Acute management involved mechanical ventilation and aggressive metabolic control to reduce BCAA levels, including hemodialysis. Long-term management strategies focused on dietary restriction of BCAAs using specialized formulas, regular monitoring of BCAA levels and genetic counseling for the family. This case highlights the importance of early diagnosis and aggressive management in MSUD to prevent rapid neurological deterioration. Newborn screening and genetic testing are essential in families with a history of metabolic disorders to improve clinical outcomes.

OPEN ACCESS

Key Words
Maple syrup urine disease, neonatal metabolic disorder, branched-chain amino acids

Corresponding Author
Harshitha Bunga,
Department of Paediatrics, Osmania Medical College, 5-1-876, Turrebaz khan Rd, Troop Bazaar koti, Hyderabad, Telangana 500095, India
harshibunga30@gmail.com

Author Designation
[1,3,4,5]Medical Graduate
[2]Clinical Intern

Received: 20 August 2024
Accepted: 18 September 2024
Published: 21 September 2024

Citation: Kanchi Lavanya, Harshitha Bunga, Sravya Sai Deepika Pandilla, Katkam Shravani and Vangapalli Gnana Deepika, 2024. Maple Syrup Urine Disease in a 9-Day-Old Term Male Infant: A Case Report and Diagnostic Approach. Res. J. Med. Sci., 18: 334-339, doi: 10.36478/makrjms.2024.10.334.339

INTRODUCTION

Maple syrup urine disease (MSUD) is a rare autosomal recessive metabolic disorder caused by a deficiency in the branched-chain a-ketoacid dehydrogenase (BCKD) enzyme complex, which is responsible for the degradation of the branched-chain amino acids (BCAAs) leucine, isoleucine and valine. When this enzyme complex is defective or absent, it leads to the accumulation of BCAAs and their toxic metabolites, including their corresponding branched-chain a-ketoacids, in the blood, urine and tissues. This metabolic disruption is what gives rise to the hallmark symptoms of MSUD, which include a distinctive maple syrup odor in the urine, neurotoxicity and potentially life-threatening complications if not promptly treated[1].

Background on Branched-Chain Amino Acids and the BCKD Complex: The branched-chain amino acids-leucine, isoleucine and valine-are essential amino acids obtained from dietary protein. They play vital roles in protein synthesis and energy metabolism, especially in muscle tissues. The degradation of these BCAAs involves a two-step process. transamination to their respective a-ketoacids, followed by oxidative decarboxylation by the BCKD complex. In MSUD, the BCKD enzyme complex is either deficient or completely absent due to mutations in the genes encoding its subunits (such as BCKDHA, BCKDHB and DBT), leading to impaired catabolism of the BCAAs[2,3].

The accumulation of leucine is particularly neurotoxic and can cause significant brain damage if levels are not controlled. This neurotoxicity manifests early in life and is the primary driver of the severe clinical features seen in MSUD. Isoleucine is responsible for the maple syrup odor characteristic of the disease, while valine contributes to the overall metabolic imbalance.

Clinical Presentation of MSUD: MSUD typically presents in the neonatal period, usually within the first few days to weeks of life. The classic form of MSUD, which is the most severe, often becomes symptomatic within 48-72 hours after birth. Affected infants may appear healthy at birth but quickly deteriorate due to the accumulation of toxic metabolites. The early signs of MSUD are nonspecific and include poor feeding, vomiting, lethargy and irritability. If untreated, the condition can rapidly progress to severe encephalopathy, which is marked by a depressed level of consciousness, hypertonia, opisthotonos, seizures, and ultimately coma[4].

Neonatal encephalopathy in MSUD results from the toxic effects of elevated leucine and its metabolites on the developing brain, leading to cerebral edema, brainstem dysfunction and increased intracranial pressure. Feeding difficulties are common, often resulting from lethargy and poor suckling, and can further exacerbate the metabolic crisis due to catabolism of endogenous protein stores[5].

Case Presentation:

Patient Details: The patient is a 9-day-old term male infant, born to a gravida 5, abortus 3, living 1 (G5A3L1) mother via normal vaginal delivery. The infant presented with excessive crying starting on day 3 of life and seizure activity commencing on day 7. The seizures progressed and led to lethargy, poor feeding, and eventually respiratory failure by day 11. The patient required mechanical ventilation due to the severity of his condition.

Complaints at Presentation:

- **Excessive Crying:** The infant exhibited excessive crying from day 3 of life that was not relieved by feeding. This symptom raised concerns among the caregivers, but the initial evaluation did not yield a diagnosis.
- **Seizures:** Seizures began on day 7 of life, characterized by 5 episodes of generalized tonic-clonic movements lasting from 1-5 minutes. These were initially managed but recurred, resulting in lethargy and subsequent respiratory failure, necessitating mechanical ventilation by day 11.

History of Present Illness: The infant was asymptomatic during the first three days of life and breast-fed well. However, excessive crying began on day 3 and by day 7, the infant experienced multiple seizures that prompted a more thorough investigation. The seizures were initially controlled with medical intervention, but their recurrence contributed to increasing lethargy and feeding difficulties. By day 11, the baby developed respiratory failure, requiring ventilatory support. Throughout this period, there was no history of vomiting, fever, rash, respiratory distress, or bleeding, which might have otherwise pointed towards infection or other common neonatal pathologies.

Birth History: The infant was born at a community health center (CHC) via normal vaginal delivery with a birth weight of 3.2 kg, within the appropriate range for gestational age. The baby cried immediately after birth and no resuscitation was required. Breast-feeding was initiated promptly after delivery and the initial neonatal period was uneventful.

Past Obstetric History: The mother had a history of three prior abortions: one at 6 months and two at 5 months. She had one healthy living child from a previous pregnancy, with no history of complications

associated with that child. These prior adverse pregnancy outcomes raised the possibility of an underlying genetic or metabolic disorder that may have influenced the current pregnancy and the newborn's health.

Family History: The parents had a consanguineous marriage, which increased the risk of autosomal recessive disorders, such as MSUD. Additionally, there was a history of mental health challenges in the father's family, which could be suggestive of a genetic predisposition to metabolic or neurological disorders.

Physical Examination: On presentation, the following findings were noted during the infant's physical examination.

- **Vital Signs:** Temperature was 36.5°C (normal), heart rate was 136 beats per minute (within normal limits) and respiratory rate was 38 breaths per minute (normal range). The infant's skin was pink, indicating no overt signs of cyanosis or shock.
- **Anthropometry:** The infant's birth weight was 3.2 kg, with a head circumference of 35 cm and a length of 48.5 cm, all falling between the 10th and 50th percentiles, indicating appropriate growth for gestational age.
- **Neurological Examination:** The infant was in a deep stupor with markedly diminished reflexes and lack of spontaneous movements. Cranial nerve examination revealed sluggishly reactive pupils, pooling of oral secretions and an absent gag reflex, suggesting severe neurological impairment, possibly secondary to metabolic encephalopathy.

Investigations: Several investigations were carried out to assess the infant's metabolic status and potential causes of his clinical deterioration.

Complete Blood Count (CBC):

- **Hemoglobin:** 15.9 g/dL (within normal limits).
- **White Blood Cell Count:** 13,200 cells/µL (mild leukocytosis, potentially indicating a stress response rather than infection, given the absence of fever and negative CRP).
- **C-reactive protein (CRP):** Negative, ruling out an acute inflammatory or infectious process as the cause of the infant's symptoms.

Blood Gas Analysis:

- **pH:** 7.236 (indicating mild acidosis).
- **pCO2:** 54 mmHg (mild respiratory acidosis).
- **pO2:** 110 mmHg (adequate oxygenation).
- **Bicarbonate:** 3.5 mmol/L (severely decreased, indicating metabolic acidosis).
- **Base Excess:** -24 mmol/L (severe metabolic acidosis), consistent with a profound metabolic derangement such as that seen in inborn errors of metabolism like MSUD.

Serum Electrolytes:

- **Sodium (Na+):** 144 mEq/L (normal).
- **Potassium (K+):** 4.1 mEq/L (normal).
- **Blood Urea Nitrogen (BUN):** 18 mg/dL (normal).
- **Serum Creatinine:** 0.7 mg/dL (normal).

These values indicated normal renal function and electrolyte balance, ruling out primary renal pathology as the cause of the infant's metabolic crisis.

Serum Lactate: 32 mmol/L (normal <20 mmol/L). Elevated serum lactate is indicative of a significant metabolic crisis and suggests that anaerobic metabolism may be occurring due to the accumulation of toxic metabolites, such as the branched-chain ketoacids found in MSUD.

Serum Ammonia: 25 µmol/L (normal 11-40 µmol/L). Normal ammonia levels ruled out hyperammonemia, which is commonly seen in other metabolic disorders such as urea cycle defects.

Urine Analysis: Positive for ketones, which indicated ongoing catabolism and potential metabolic stress. Positive for 2,4-Dinitrophenylhydrazine (DNPH), a test used to detect abnormal ketoacids in the urine. This finding was consistent with MSUD, as the accumulation of branched-chain a-ketoacids is a hallmark of the disorder.

RESULTS AND DISCUSSION

Maple Syrup Urine Disease (MSUD) is a rare autosomal recessive metabolic disorder with an incidence of approximately 1:185,000 live births globally, although higher incidences are observed in certain populations due to founder effects or consanguinity. The disorder is caused by a deficiency in the branched-chain a-ketoacid dehydrogenase (BCKD) complex, which leads to the accumulation of branched-chain amino acids (BCAAs) and their corresponding ketoacids. These metabolites, particularly leucine, are neurotoxic and their buildup results in progressive neurological decline.

Clinical Presentation and Pathophysiology: In the classical form of MSUD, symptoms typically present within the first few days to weeks of life. Infants appear healthy at birth but quickly develop nonspecific signs such as irritability, poor feeding and lethargy. As the disease progresses, more severe neurological symptoms such as seizures, coma and encephalopathy emerge, as demonstrated in this case[6].

The underlying pathophysiology of MSUD is the impaired catabolism of BCAAs-leucine, isoleucine and valine-due to the deficiency of the BCKD enzyme complex. Leucine is the most neurotoxic of these amino acids and its accumulation leads to brain edema, encephalopathy and eventual respiratory failure. The neurological deterioration observed in MSUD is attributed to this toxic effect on the developing brain, particularly in the early neonatal period when the brain is highly vulnerable. This explains the rapid decline seen in this patient, who initially fed well and appeared normal before showing signs of excessive crying, seizures and lethargy[7].

Diagnostic Findings: The diagnosis of MSUD in this case was made based on a combination of clinical presentation and biochemical testing. Elevated serum lactate levels (32 mmol/L) indicated metabolic dysfunction, while the presence of ketones in the urine and a positive DNPH test confirmed the accumulation of branched-chain ketoacids. The DNPH test detects the presence of abnormal ketoacids in the urine, which is a hallmark of MSUD[8].

These findings are highly suggestive of a defect in the BCKD enzyme complex, but definitive diagnosis would require molecular genetic testing of the BCKDHA, BCKDHB, and DBT genes, which encode the subunits of the BCKD complex. Identifying mutations in these genes would confirm the diagnosis and provide valuable information for genetic counseling, especially in families with a history of consanguinity, as seen in this case[9].

Early Recognition and Prognosis: Early recognition of MSUD is critical for preventing severe neurological damage. Untreated neonates typically progress to coma and respiratory failure within the first week of life, as the toxic metabolites of BCAAs accumulate. In this case, the infant presented with excessive crying on day 3, followed by seizures on day 7 and respiratory failure by day 11, which required mechanical ventilation. This progression is typical of classical MSUD and underscores the importance of early intervention to prevent irreversible brain damage[10]. Newborn screening programs in many countries include testing for MSUD, allowing for early diagnosis and intervention. However, in settings where newborn screening is not routinely performed, the diagnosis may be delayed until symptoms manifest, as in this case. Given the consanguineous family history and the history of prior miscarriages, early genetic screening in future pregnancies would be warranted to identify affected infants before symptoms develop[11].

Management:

Acute Management: The primary goal in the acute management of MSUD is to rapidly reduce the levels of BCAAs in the bloodstream to prevent further neurological damage. In severe cases, such as this one, where respiratory failure occurred, aggressive interventions like mechanical ventilation and hemodialysis may be necessary to remove toxic metabolites. Hemodialysis is particularly effective in lowering plasma levels of leucine, which is the primary contributor to neurotoxicity in MSUD. In less severe cases, intravenous hydration, glucose and amino acid solutions (free of leucine, isoleucine and valine) can be used to manage the metabolic crisis[12].

Long-Term Management: The cornerstone of long-term management in MSUD is lifelong dietary restriction of BCAAs. Specialized medical formulas that are free of leucine, isoleucine and valine are used to provide adequate nutrition without allowing the accumulation of toxic metabolites. Regular monitoring of plasma BCAA levels is essential to ensure that levels remain within safe ranges and to adjust the diet as needed, especially during times of illness or stress, which can trigger metabolic crises[13,14].

Patients with MSUD require close follow-up with metabolic specialists, dietitians and pediatricians. Growth and development must be monitored, as even mild metabolic derangements can lead to long-term neurological impairment. For some patients, liver transplantation has been explored as a treatment option, as the liver provides a source of functional BCKD enzyme. Transplantation can allow for more normal metabolism of BCAAs, but it is generally reserved for patients who have frequent metabolic crises or poor dietary control[15].

Recommendations:

Aggressive Nutritional Management: Immediate dietary interventions with BCAA-free formulas are critical in preventing further metabolic crises. Frequent monitoring of plasma BCAA levels is necessary to guide dietary adjustments and ensure that levels remain within a safe range.

Monitoring and Early Intervention: Close monitoring for signs of metabolic decompensation is essential, particularly during periods of stress such as infections or surgeries, which can precipitate a crisis. Early interventions like hydration, intravenous glucose, or even dialysis may be required during acute episodes.

Newborn Screening and Genetic Testing: In countries where newborn screening is not routinely available,

molecular genetic testing should be considered, especially in families with a history of consanguinity or metabolic disorders. Early diagnosis through newborn screening can significantly improve outcomes by allowing early dietary interventions to prevent neurotoxicity.

Family Counseling and Genetic Education: Given the autosomal recessive inheritance pattern of MSUD, genetic counseling is recommended for the family to discuss the recurrence risk in future pregnancies and to explore prenatal diagnostic options.

CONCLUSION

This case serves as a critical example of the early onset and rapid progression characteristic of classical Maple Syrup Urine Disease (MSUD) in neonates. Despite being born full-term and initially appearing healthy, the infant rapidly developed severe neurological symptoms, including excessive crying, seizures and eventual respiratory failure within the first week of life. This case underscores several important aspects of MSUD and its management.

Early Onset and Clinical Progression: The infant in this case developed symptoms within the first few days of life, which is typical of the classical form of MSUD. This rapid onset of symptoms, including poor feeding, irritability and seizures, reflects the neurotoxic effects of elevated branched-chain amino acids (BCAAs) and their metabolites, particularly leucine, on the developing brain. The progression to encephalopathy and respiratory failure within days highlights the life-threatening nature of untreated MSUD. Early clinical recognition of these symptoms is vital to initiating appropriate diagnostic testing and preventing irreversible damage.

Importance of Early Diagnosis: Early and accurate diagnosis of MSUD is crucial in preventing the severe neurological and systemic complications that arise from the accumulation of toxic metabolites. In this case, biochemical testing-such as elevated serum lactate and positive urine ketones and DNPH testing-suggested a metabolic disorder, which was later confirmed to be MSUD. Early identification allows for prompt metabolic management, which can significantly reduce the risk of permanent neurological damage. Newborn screening programs, where available, have been instrumental in diagnosing MSUD before the onset of symptoms, allowing for preemptive dietary management. In regions without such screening programs, heightened clinical awareness and the availability of genetic testing play key roles in early diagnosis.

Metabolic Management: Effective management of MSUD requires a multidisciplinary approach that includes acute interventions during metabolic crises and long-term dietary control to maintain stable plasma BCAA levels. In this case, the patient required mechanical ventilation due to respiratory failure, a consequence of untreated metabolic derangement. Hemodialysis may be necessary in severe cases to rapidly reduce leucine levels, which are neurotoxic. Long-term, the cornerstone of MSUD management is a carefully controlled diet that restricts BCAAs, supplemented with specialized formulas free of leucine, isoleucine and valine. The infant will require lifelong monitoring of plasma BCAA levels to prevent further metabolic crises, especially during periods of stress, illness, or growth spurts.

Genetic Counseling and Family Planning: Given the autosomal recessive inheritance of MSUD, genetic counseling is essential for families with a history of metabolic disorders or consanguinity. This case involved a consanguineous marriage and a family history of mental health challenges, further increasing the risk of metabolic diseases like MSUD. Genetic counseling can provide valuable information on recurrence risks in future pregnancies and guide families on the availability of prenatal diagnostic options. For families with an affected child, this counseling offers insight into the condition and helps them prepare for the lifelong dietary and medical care their child will require.

The Role of Newborn Screening: Newborn screening programs that include MSUD can drastically improve outcomes by enabling early diagnosis before symptoms manifest. Early intervention with dietary restrictions and metabolic management can prevent the severe complications seen in this case. When newborn screening is unavailable, clinical vigilance and prompt testing based on early signs such as poor feeding, lethargy and seizures are critical. Introducing widespread newborn screening programs, especially in regions with higher incidences of MSUD, can significantly reduce morbidity and mortality associated with the disease.

Final Thoughts: This case of MSUD demonstrates the rapid and severe progression of symptoms in neonates when the disorder is not recognized and treated early. It emphasizes the need for healthcare providers to maintain a high index of suspicion for inborn errors of metabolism in neonates presenting with nonspecific but progressive symptoms like poor feeding, lethargy, and seizures. Early diagnosis, either through newborn screening or biochemical testing, combined with

aggressive metabolic management, can drastically improve the long-term outcomes for infants with MSUD. Genetic counseling and family planning are also essential components of managing MSUD, helping families understand the genetic basis of the disorder and explore options for future pregnancies.

REFERENCES

1. Scriver, C.R., A.L. Beaudet, W.S. Sly and D. Valle, 2001. The Metabolic and Molecular Bases of Inherited Disease. 8th Edn., McGraw-Hill, U.S.A., ISBN-13: 9780079130358, Pages: 4605.
2. Chuang, D.T. and V.E. Shih, 2001. Maple Syrup Urine Disease (Branched-Chain Ketoaciduria). In: The Metabolic and Molecular Bases of Inherited Disease., Scriver, C.R., W.S. Sly and D. Valle, (Eds.)., McGraw-Hill, U.S.A., ISBN-13: 9780079130358, pp: 1971-2006.
3. Saudubray, J.M., V.D.G. Berghe and J.H. Walter, 2016. Inborn Metabolic Diseases: Diagnosis and Treatment. 6th Edn., Springer, U.S.A., ISBN-13: 9783662631256, Pages: 689.
4. Strauss, K.A., E.G. Puffenberger and D.H. Morton, 2006. Maple syrup urine disease. GeneReviews. University of Washington, Seattle.
5. Nyhan, W.L., B.A. Barshop and P.T. Ozand, 2011. Atlas of Inherited Metabolic Diseases 3E. CRC Press, London, ISBN-13: 9780429100710, Pages: 888.
6. Fischer, S., A. Doolan and H.S.L. Ardern, 2015. Maple syrup urine disease: presentation and acute management. J Paediatr Child Health., 51: 275-280.
7. Blackburn, P., J. Gass, F.P. e Vairo, K. Farnham and H. Atwal et al., 2017. Maple syrup urine disease: Mechanisms and management. Appl. Clin. Genet., 10: 57-66.
8. Morton, D.H., 2011. Inborn Errors of Branched-Chain Amino Acid Metabolism: Maple Syrup Urine Disease. Vitam Horm., 85: 303-322.
9. Frazier, D.M., C. Allgeier and C. Homer,et al., 2014. The newborn screening and follow-up program in the diagnosis of MSUD. J Pediatr., 144: 131-135.
10. Chace, D.H., T.A. Kalas and E.W. Naylor, 2003. Use of tandem mass spectrometry for multianalyte screening of dried blood specimens from newborns. Clin. Chem., 49: 1797-1817.
11. Birk M.L., S. Tvedegaard and T.J. Corydon,et al., 2005. Mutations in the BCKDHA gene encoding E1a in MSUD. Hum Mutat., 25: 266-274.
12. Baumgartner, M.R., F. Hörster and V.C. Dionisi,et al., 2014. Proposed guidelines for the diagnosis and management of MSUD. Orph J Rare Dis., Vol. 9, No. 37.
13. Korman, S.H., 2006. Inborn errors of branched-chain amino acid metabolism: MSUD. Pediatr End Rev., 3: 399-407.
14. Simon, E., R. Fingerhut and M.R. Baumgartner, 2017. Newborn screening for branched-chain organic acidurias. Int J Neonatal Screen., Vol. 3, No. 1.
15. Grunert, S.C. and U. Wendel, 2012. Clinical presentation and management of MSUD. J Inherit Metab Dis., 35: 234-236.