Case Study

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Sweet Smell, Sour Crisis: A Neurotoxic Neonatal Case of Classic Maple Syrup Urine Disease

Srikumar Chakravarthi[1]*, John Paul Judson[2], Barani Karikalan[3], Karthikesh Jayakumar[4], Prarthana Kalerammana Gopalakrishna[5], Mohammad Nazmul Hasan Maziz[6], Ranjith Karthekeyan[7] and Yong Lit Chen[8]

[1]Faculty of Medicine, Nursing and Health Sciences, SEGi University, Selangor, Malaysia

[2]Faculty of Medicine and Health Sciences, Universiti Tunku Abdul Rahman, Selangor, Malaysia

[3]Faculty of Medicine, MAHSA University, Selangor, Malaysia

[4]Department of General Pathology, KSR Institute of Dental Sciences and Research, Trichengode, Tamil Nadu, India

[5]Department of Human Biology, IMU University, Bukit Jalil, Kuala Lumpur, Malaysia

[6]Graduate School of Medicine, Perdana University, Kuala Lumpur, Malaysia

[7]Department of Cardiac Anaesthesia, Sri Ramachandra Medical College and Research Institute, Chennai, India

[8]Shanghai University of Traditional Chinese Medicine, Shanghai, China

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***Corresponding author:** Srikumar Chakravarthi, Faculty of Medicine, Nursing and Health Sciences, SEGi University, Selangor, Malaysia, E-mail: srikumarc@segi.edu.my

A B S T R A C T

Maple Syrup Urine Disease (MSUD) is a rare autosomal recessive disorder of Branched Chain Amino Acid (BCAA) metabolism caused by deficiency of the Branched Chain α Ketoacid Dehydrogenase (BCKAD) complex. This defect leads to accumulation of leucine, isoleucine, valine and their toxic metabolites, resulting in severe neurotoxicity. Classic MSUD, the most severe form, presents in the neonatal period with rapid neurological deterioration if untreated.

We report a 10-day old term male infant presenting with lethargy, poor feeding, hypotonia and a characteristic maple syrup like odour of urine and skin. Investigations revealed metabolic acidosis, mild hyperammonaemia, hypoglycaemia and cerebral oedema on neuroimaging, while sepsis was excluded. Plasma amino acid analysis showed markedly elevated BCAAs and urinary organic acid analysis confirmed branched chain α ketoacids. Genetic testing later identified biallelic pathogenic variants affecting the BCKAD complex.

The infant was managed as a metabolic emergency with high calorie intravenous support, correction of metabolic abnormalities and temporary protein restriction. A specialized MSUD formula was introduced after stabilization. Clinical and biochemical improvement was achieved.

This case highlights the importance of early recognition and prompt dietary management to prevent irreversible neurological damage, particularly in settings without newborn screening.

Keywords: Neurotoxic, Neonatal encephalopathy, Rare diseases, Metabolic disorders, Infant

Abbreviations: MSUD: Maple Syrup Urine Disease; OMIM: Online Mendelian Inheritance in Man; BCAA: Branched Chain Amino Acids; BCKAD: Branched Chain α Ketoacid Dehydrogenase; CoA: Coenzyme A; MS/MS: Tandem Mass Spectrometry; CSF: Cerebrospinal Fluid; CT: Computed Tomography; NICU: Neonatal Intensive Care Unit; IV: Intravenous; ABG: Arterial Blood Gas; kg: Kilogram; mmol/L: Millimoles per Liter; µmol/L: Micromoles per Liter; pH: Potential of Hydrogen (measure of acidity/alkalinity); BCKDHA: Branched-Chain Ketoacid Dehydrogenase E1 Subunit Alpha Gene; BCKDHB: Branched Chain Ketoacid Dehydrogenase E1 Subunit Beta Gene; DBT: Dihydrolipoamide Branched Chain Transacylase E2 Gene

1. Introduction

Maple Syrup Urine Disease (MSUD) is a rare autosomal recessive disorder of BranchedChain Amino Acid (BCAA) metabolism caused by deficiency of the Branched Chain α- Ketoacid Dehydrogenase Dehydrogenase (BCKAD) complex[1,2]. This enzyme complex is required for the oxidative decarboxylation of the αketo derivatives of leucine, isoleucine and valine into their respective acylCoA intermediates[3,4]. Deficiency leads to accumulation of these BCAAs and their corresponding αketo acids in blood, urine and cerebrospinal fluid, resulting in severe neurotoxicity and metabolic decompensation[5,6].

Classic MSUD is the most severe form, with onset in the first 7 to 10 days of life and rapid progression to encephalopathy, seizures and, if untreated, death. The disease is so named because affected infants characteristically develop a sweet, maple syrup like odour in urine and cerumen, a hallmark clinical clue[7,8]. With the advent of tandem mass spectrometrybased newborn screening, many cases are now detected presymptomatically, allowing early dietary intervention and markedly improved outcomes. However, in regions without routine newborn metabolic screening, the disease often presents as a fulminant metabolic emergency[9], as in the following hypothetical case.

This case report illustrates the clinical presentation, diagnostic work up, acute management and principles of longterm care in a term neonate with classic MSUD, emphasizing the importance of considering inborn errors of metabolism in any infant with unexplained encephalopathy or unusual body odour.

2. Clinical Study

A 10th day old male infant was brought to the emergency department of a tertiary care hospital with a 2nd day history of progressive lethargy, poor feeding and a high pitched, "fussy" cry. The parents reported that the baby had begun to "smell unusual," describing a sweet, burntsugar or maplesyruplike odour from his urine and skin, particularly around the head and neck. This odour had become more noticeable over the preceding 24 hours. The infant had been breastfed since birth and was initially feeding well, but over the last 48 hours his suck became weak, he fed less frequently and he appeared increasingly "floppy" and difficult to rouse.

The pregnancy was fullterm and uncomplicated and the delivery was spontaneous vaginal at 39 weeks' gestation with a birth weight of 3.2 kg. The Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. There was no history of consanguinity, no known metabolic disease in the family and no newborn metabolic screening result available at the time of presentation.

On examination, the infant was moderately dehydrated, with dry oral mucosa, reduced skin turgor and slightly sunken anterior fontanelles. Vital signs revealed sinus tachycardia (heart rate 148 beats per minute), tachypnoea (respiratory rate 44 breaths per minute) and a temperature of 37.2°C. The infant was semicomatose, reacting only faintly to painful stimuli, with minimal spontaneous movement. He was markedly hypotonic, with poor head control and a diminished or absent Moro reflex.

A distinctive sweet, maplesyruplike odour was easily detectable in the diapers and on the infant's skin, particularly around the axillae and neck, confirming the parents' description. There were no obvious dysmorphic features, rashes, hepatosplenomegaly or focal neurological signs at this stage.

Initial investigations in the emergency department showed:

- **Metabolic acidosis:** Arterial blood gas pH 7.28, bicarbonate 14 mmol/L, base deficit −12 mmol/L.
- **Mild hyperammonaemia:** Arterial ammonia 120 µmol/L (normal <60 µmol/L).
- **Hypoglycaemia:** Capillary blood glucose 2.8 mmol/L, necessitating intravenous dextrose infusion.
- Mild liver enzyme elevation and mildly increased bilirubin, but no overt hepatic failure.

A septic workup was performed to exclude infectionrelated encephalopathy. Blood culture, urine culture and lumbar puncture were carried out. Cerebrospinal fluid analysis was acellular with normal glucose and protein and cultures remained negative. Computed Tomography (CT) of the brain showed generalized cerebral oedema with effacement of sulci and mild ventricular compression, consistent with acute metabolic encephalopathy.

Given the clinical triad of early neonatal encephalopathy, poor feeding, lethargy and the characteristic maplesyrup odour, Tandem Mass Spectrometry (MS/MS) analysis of plasma amino acids was urgently ordered.

The results revealed striking elevations of the branchedchain amino acids:

- **Leucine:** 1,750 µmol/L (normal newborn reference range: 50–150 µmol/L).
- **Isoleucine:** 420 µmol/L (normal: 30–100 µmol/L).
- **Valine:** 580 µmol/L (normal: 150–350 µmol/L).

Urinary organic acid analysis showed large amounts of branchedchain α - keto acids, including α - ketoisocaproic acid (from leucine) and α - keto β - methylvaleric acid (from isoleucine), confirming a functional defect in the BCKAD complex. These findings, in the context of the clinical presentation and imaging, were consistent with Classic Maple Syrup Urine Disease.

Genetic testing subsequently revealed biallelic pathogenic

variants in one of the genes encoding the BCKAD complex (e.g., BCKDHA, BCKDHB or DBT), confirming the autosomal recessive inheritance pattern. The family was counselled regarding recurrence risk and the importance of cascade testing for future pregnancies.

3. Management

The infant was admitted to the Neonatal IntensiveCare Unit (NICU) and managed as an acute metabolic emergency. The primary goals of management were to halt catabolism, reduce the burden of toxic BCAAs, correct metabolic derangements and prevent further neurological injury.

Initial resuscitation and metabolic stabilization

- Intravenous highcalorie dextrose with added electrolytes and lipid emulsion was initiated to provide abundant energy and suppress catabolism. This helped reduce the rate of proteolysis and BCAA production.
- Natural protein (including breast milk and standard formulas) was temporarily withheld to minimize the intake of leucine, isoleucine and valine.
- Intravenous insulin and glucose were used cautiously to maintain euglycemia and promote anabolism, while avoiding hypoglycemia or hyperglycemia.
- Sodium bicarbonate was administered to correct significant metabolic acidosis and close monitoring of electrolytes and fluid balance was maintained.

3.1. Initiation of MSUD specific diet

Once the infant stabilized hemodynamically and feeding was tolerated, a specialized MSUD formula, low in leucine, isoleucine and valine but supplemented with other essential amino acids was introduced via nasogastric tube. The quantity of natural protein (expressed breast milk) was carefully titrated to meet growth requirements while keeping plasma leucine and isoleucine levels within prescribed target ranges.

Serial plasma amino acid analyses were performed to guide dietary adjustments. Over the next 48 hours, leucine and isoleucine levels began to decline, the maple syrup odour gradually diminished and the infant's level of consciousness improved. He started to feed more actively and his tone and responsiveness normalized.

Monitoring and supportive care

- Metabolic monitoring included repeated measurements of plasma amino acids, ammonia, blood gases, electrolytes and glucose.
- Neurological status was monitored continuously and the infant was observed for signs of seizures or recurrent encephalopathy.
- Brain imaging was not repeated in the acute phase, but the initial CT findings were compatible with reversible cerebral oedema in the context of metabolic decompensation.

Longterm management plans were discussed with the parents and the regional metabolic team. The infant was transitioned to a lifelong, proteinrestricted diet based on MSUD specific medical foods, with strict avoidance of prolonged fasting and illnessrelated protocols (e.g., increased caloric intake and temporary reduction of natural protein during febrile episodes). Regular follow up at the metabolic clinic was arranged to monitor growth, nutritional status, developmental milestones and plasma amino acid levels.

4. Discussion

Classic Maple Syrup Urine Disease (MSUD) is a severe inborn error of metabolism that typically presents in the first week of life with nonspecific but rapidly progressive symptoms. The hallmark clinical clue is the characteristic maple syrup or burnt sugar odour in urine and cerumen, arising from the accumulation of branched chain αketo acids[10,11]. In this hypothetical case, the presence of such odour, combined with early encephalopathy, metabolic acidosis and hyperammonaemia, strongly directed the differential diagnosis toward MSUD.

The biochemical defect lies in the BCKAD complex, which catalyses the oxidative decarboxylation of αketo derivatives of leucine, isoleucine and valine. Complete or nearcomplete loss of enzyme activity in classic MSUD results in marked elevations of these BCAAs and their corresponding keto acids, which are neurotoxic and cause mitochondrial dysfunction, oxidative stress and disruption of neurotransmitter metabolism. This leads to cerebral oedema, seizures and, if untreated, irreversible brain damage or death[12].

The clinical spectrum of MSUD includes classic, intermediate, intermittent and thiamineresponsive forms, with classic being the most severe and earliest onset phenotype. Classic MSUD is characterized by onset in the neonatal period, rapid neurological deterioration and marked biochemical abnormalities unless promptly treated. Intermediate and milder forms may present later in infancy or childhood with episodic neurological symptoms triggered by catabolic stress, whereas thiamine responsive variants may show partial clinical improvement with high dose thiamine supplementation[9,13].

Early diagnosis is critical. Tandem mass spectrometry of newborn blood spots allows detection of elevated leucine and isoleucine before clinical onset, enabling presymptomatic dietary intervention and preventing the first metabolic crisis[14]. However, in the absence of newborn screening, the disease often presents as a fulminant metabolic emergency, as in this case. Awareness of the characteristic odour and the possibility of an inborn error of metabolism is essential for timely referral and appropriate investigations.

Long term outcomes depend on the severity of the initial episode, the timing of diagnosis and adherence to a strict dietary regimen. Lifelong protein restriction, use of MSUD specific medical foods and careful metabolic monitoring can prevent recurrent crises and support normal growth and development. However, prior metabolic decompensations may still be associated with residual cognitive impairment, motor deficits or behavioural problems[15].

Gene therapy and enzyme replacement strategies are under investigation, but at present, dietary management remains the cornerstone of treatment[16]. This case underscores the importance of early recognition, rapid metabolic stabilization and multidisciplinary followup in improving both survival and quality of life for infants with classic Maple Syrup Urine Disease.

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