Case Report

Maple Syrup Urine Disease Presenting as Neonatal Encephalopathy with Seizures

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ABSTRACT

Background: Maple syrup urine disease (MSUD) is a rare autosomal recessive disorder of branched-chain amino acid metabolism that may present in the neonatal period with non-specific symptoms, resulting in delayed diagnosis and significant neurological morbidity. Early recognition remains particularly challenging in resource-limited settings without newborn screening or readily available metabolic investigations.

Case Presentation: We report a day 7 of life neonate, who presented with poor feeding, lethargy, recurrent hypoglycemia, ketonuria, and progressive encephalopathy without evidence of infection. Initial investigations were non-specific, and metabolic testing was not immediately available locally. Magnetic resonance imaging (MRI) of the brain and magnetic resonance spectroscopy (MRS) demonstrated symmetrical diffusion restriction involving characteristic regions of the brain, raising suspicion of MSUD. Biochemical confirmation was obtained through plasma amino acid analysis (leucine 4259 µmol/L (reference range 150–300 µmol/L), valine 768 µmol/L (reference range 200–400 µmol/L), isoleucine 824 µmol/L (reference range 150–300 µmol/L), and alloisoleucine 438 µmol/L), which revealed markedly elevated branched-chain amino acids consistent with classic MSUD. Owing to severe neurological involvement, continuous veno-venous hemodiafiltration (CVVHDF) was initiated to achieve rapid leucine clearance, alongside dietary protein restriction and metabolic management. Clinical and biochemical improvement was observed following treatment.

Conclusion: This case highlights the importance of considering MSUD in neonates with unexplained neonatal encephalopathy, ketonuria, recurrent with negative septic parameters. Characteristic MRI and MR spectroscopy findings may facilitate early diagnosis when metabolic testing is unmailable. Prompt initiation of BCAA-free formula and CVVHDF in severe cases, is crucial to ensure good neurological outcome.

Keywords: Maple syrup urine disease; neonatal encephalopathy; branched-chain amino acids; leucine; continuous veno-venous hemodiafiltration; newborn screening

INTRODUCTION

Maple Syrup Urine Disease (MSUD) is a treatable metabolic disorder caused by decreased activity of the branched-chain alpha-ketoacid dehydrogenase complex (BCKD) responsible for the breakdown of branched-chain amino acids (BCAAs). Deficiency of the branched-chain α-ketoacid dehydrogenase (BCKD) complex results in accumulation of branched-chain amino acids and their corresponding ketoacids, particularly leucine, which is the principal neurotoxic metabolite responsible for acute neurological injury. Worldwide incidence of disease is 1 in 185,000 infants. It has an autosomal recessive inheritance.

The severe neonatal-onset form of maple syrup urine disease (MSUD) typically presents between the third and fifth days of life with progressive encephalopathy. Early clinical manifestations include irritability, poor feeding, lethargy, intermittent apnea, opisthotonus, and stereotyped movements such as "fencing" and "bicycling." Without prompt recognition and treatment, these symptoms may progress to coma and central respiratory failure[1].

Routine laboratory investigations are often unremarkable, with ketonuria being a notable finding. Hypoglycemia is uncommon. A characteristic maple syrup-like odor of the urine may be present and can provide an important diagnostic clue. Acute cerebral oedema is a well-recognized complication of severe MSUD and may progress to cerebral herniation if left untreated. However, cerebral oedema is potentially reversible with early diagnosis and appropriate treatment[1].

In East Malaysia, access to urgent metabolic investigations remains challenging, as specialized metabolic testing is primarily performed at the Institute for Medical Research (IMR) and Hospital Kuala Lumpur (HKL) in West Malaysia. Consequently, diagnostic samples often need to be transported across regions, which may delay the availability of results and the initiation of targeted treatment.

Current statistics recorded more than 100 patients diagnosed with MSUD in Malaysia, but none from East Malaysia[1]. Thus, this is one of the first few reported cases of neonatal MSUD from Sarawak, which characteristic MRI and MR spectroscopy findings prompted early metabolic intervention before biochemical confirmation. This case highlights the need for strengthened metabolic diagnostic pathways and consideration of expanded newborn screening programmed in East Malaysia.

Case description

A term Bidayuh male neonate was born via spontaneous vaginal delivery with a birth weight of 3.45 kg and Apgar scores of 8 and 9 at one and five minutes, respectively. He was discharged well after birth.

He initially presented to a primary healthcare clinic on day 5 of life with multiple daily episodes of abnormal posturing and stiffening of all four limbs, which interfered with breastfeeding. He was discharged with reassurance.

He re-presented to the emergency department at our center on day 7 of life with poor feeding, back arching, and cyclical movements. He was admitted to the general ward for further evaluation. On the following day, he developed recurrent generalized tonic-clonic seizures associated with apnea. He was electively intubated for airway protection, loaded with phenobarbital, commenced on an intravenous midazolam infusion, and empirically treated with intravenous cefotaxime for presumed meningitis before being transferred to the pediatric intensive care unit (PICU). He remained afebrile throughout. Blood cultures were sterile, and cerebrospinal fluid analysis was not suggestive of meningitis. Bedside ultrasound cranium did not show any significant abnormality.

Further history revealed very distant parental consanguinity, with a common ancestor approximately 8-9 generations earlier, both are of Bidayuh ethnic origin. He was the second child in the family. His elder sibling, an

8-year-old girl, was healthy. There was no family history of neonatal deaths, unexplained seizures, or metabolic disorders.

Despite being seizure-free and successfully weaned off sedation during his PICU stay, he remained profoundly encephalopathic. He exhibited no spontaneous breathing efforts or spontaneous movements. Electroencephalography (EEG) demonstrated a burst-suppression pattern. In addition, he developed ketonuria, recurrent hypoglycemia, and hepatomegaly. Serum ammonia and lactate levels were within normal limits.

Given the persistent encephalopathy and suspicion of an underlying metabolic disorder, an urgent MRI of the brain was performed on day 12 of life, and samples for inborn errors of metabolism (IEM) screening were sent to both the Institute for Medical Research (IMR) and a private laboratory. Three days later, a follow-up magnetic resonance spectroscopy (MRS) study was requested by the radiologist, as the initial MRI findings were suggestive of maple syrup urine disease (MSUD), demonstrating symmetrical abnormalities involving the centrum semiovale, posterior limbs of the internal capsules, thalami, dorsal brainstem, and cerebellum. MRS performed on day 16 of life demonstrated a characteristic doublet peak at 0.9 ppm, representing the accumulation of branched-chain amino acids and their corresponding ketoacids (Figures 1 and 2), further supporting the diagnosis of MSUD.

Based on the radiological findings, the metabolic team was urgently consulted, and the patient underwent immediate continuous venovenous hemodiafiltration (CVVHDF) on day 17 of life. A branched-chain amino acid (BCAA)-free formula was initiated, together with valine and isoleucine supplementation (Figure 3). On day 18 of life, IEM screening confirmed the diagnosis of MSUD, revealing markedly elevated amino acid levels: leucine 4259 μmol/L (reference range 150–300 μmol/L), valine 768 μmol/L (reference range 200–400 μmol/L), isoleucine 824 μmol/L (reference range 150–300 μmol/L), and alloisoleucine 438 μmol/L.

Following treatment, he demonstrated significant clinical improvement, with resolution of encephalopathy and recovery of spontaneous breathing and motor activity. He was successfully extubated on day 24 of life and discharged home at 8 weeks of age.

At follow-up at 10 months of age, he continued to have sucking-swallowing incoordination requiring nasogastric tube feeding. Nevertheless, he was thriving and maintained good metabolic control. Although he demonstrated global developmental delay, he continued to make developmental progress, including social smiling, maintaining eye contact, reaching for objects, babbling, and briefly maintaining a tripod sitting position, corresponding to the developmental age of 6 months old.

He remains follow-up by the visiting pediatric metabolic team from Hospital Kuala Lumpur. His whole exome sequencing (WES) showed homozygous deletion involving exon 1 of the BCKDHB gene. The parents were counselled regarding the nature of the disease, its inheritance pattern, and the 25% risk of recurrence in future pregnancies. The importance of genetic counselling and antenatal screening in subsequent pregnancies was emphasized.

Figure 1. Axial diffusion-weighted images (DWI) with corresponding apparent diffusion coefficient (ADC) maps demonstrate bilateral symmetrical hyperintense DWI and hypointense ADC map signal indicating restricted diffusion at centrum semiovale, posterior limb internal capsule, thalami, dorsal brainstem and cerebellum, attributed to intramyelinic oedema. These represent the typical myelinated areas in normal full-term neonates at birth.

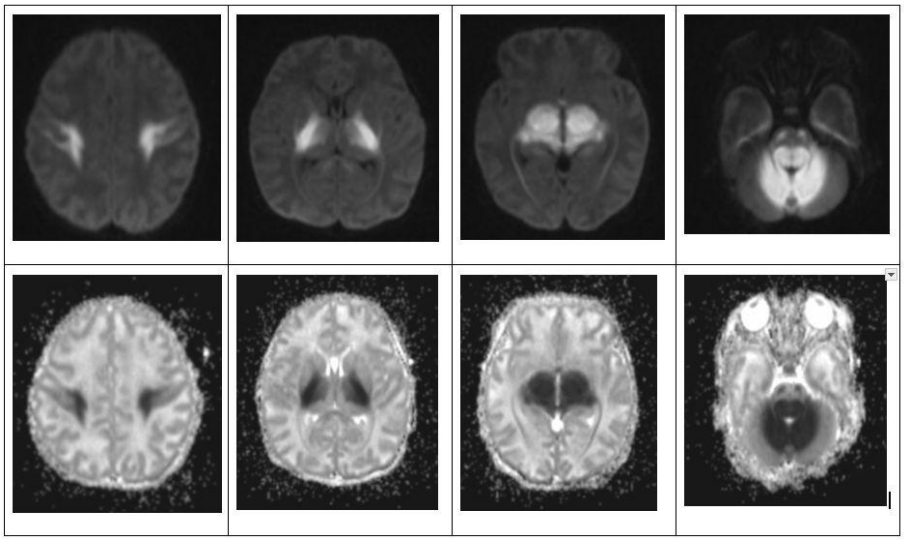


Figure 2. MR spectroscopy TE 30ms at left thalamus demonstrates doublet peak at 0.9ppm represent branched chain amino acids peaks.

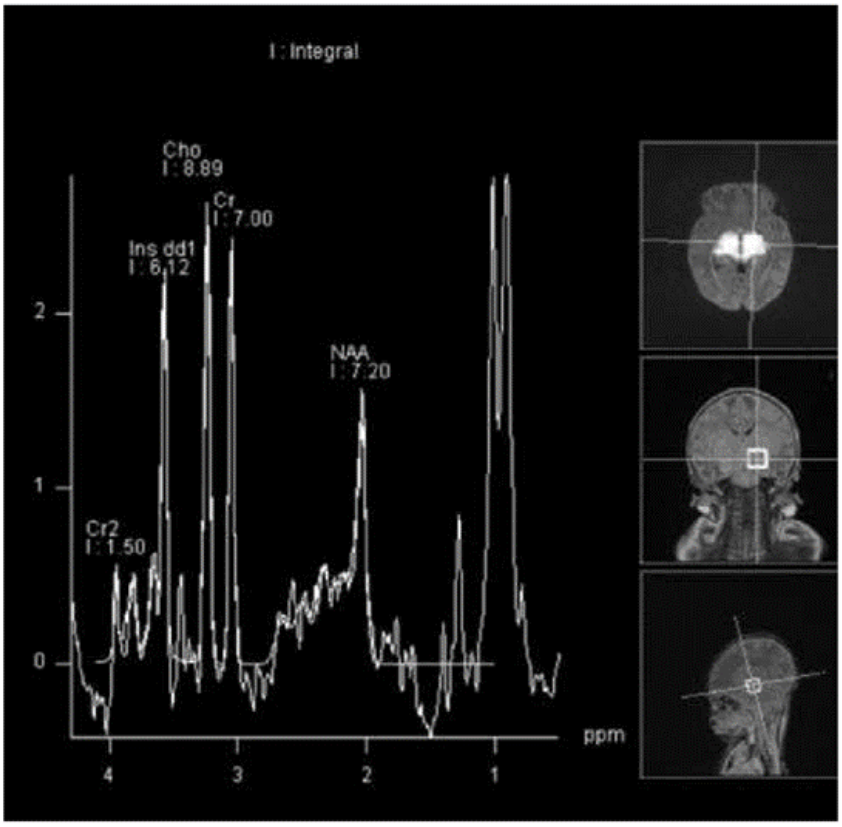
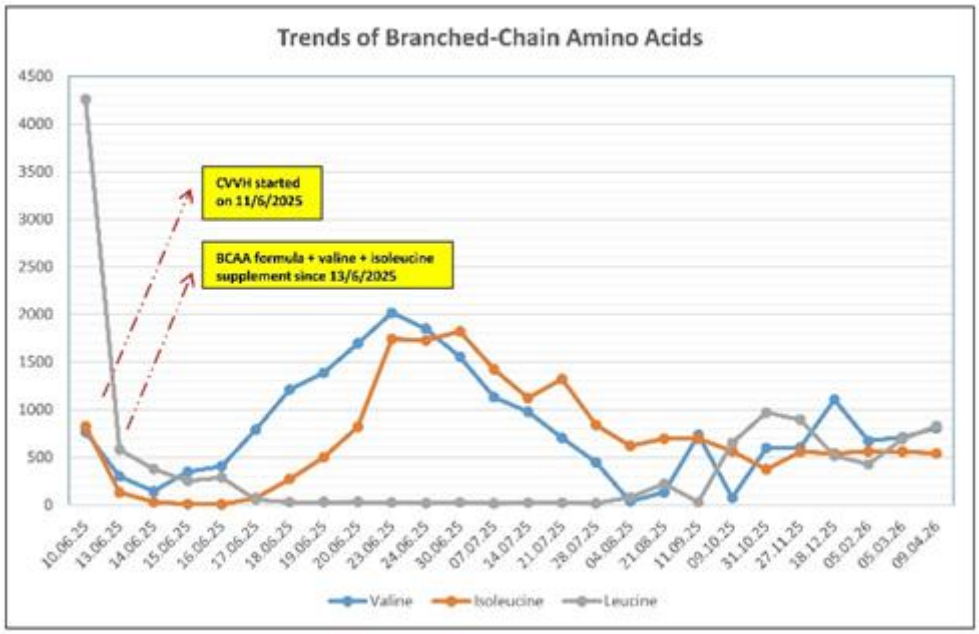


Figure 3. Trend of branched-chain amino acids after initiation of CVVHDF and BCCA-free formula



DISCUSSION

In a neonate presented with encephalopathy following seizures, after ruling out common causes such as sepsis, central nervous system infections, metabolic derangement like hypoglycemia, hypocalcemia, hypo/hypernatremia, structural brain abnormalities, intraventricular or parenchymal hemorrhages, inborn error of metabolism (IEM) should be suspected.

In this case, despite achieving seizure control and being successfully weaned off sedation, the child remained profoundly encephalopathic, without spontaneous breathing efforts and movements. Electroencephalography (EEG) demonstrated a burst-suppression pattern. Furthermore, the presence of hypoglycemia, ketonuria, and hepatomegaly raised suspicion of an underlying metabolic disorder. Consequently, inborn errors of metabolism (IEM) screening was performed, and an urgent MRI of the brain was requested.

It is also important to take note that normal ammonia and lactate do not rule out IEM. In fact, the presence of ketonuria on urine FEME further raised suspicion of an underlying metabolic disorder eg organic acidemia and MSUD.

This case underscores the importance of early recognition of neonatal seizures by primary care clinicians. Notably, this child had been presented to a primary healthcare clinic two days prior to admission with a history of abnormal movements but was discharged with reassurance. Neonatal seizures can present with subtle manifestations, including lip smacking, eye blinking, cycling movements, abnormal posturing, or limb stiffening, which may be mistaken for normal neonatal behaviors. Therefore, any abnormal or stereotyped movement in a neonate should raise clinical suspicion and prompt early referral to a pediatric center for further evaluation and management.

Although the patient was in the neonatal age group, he was admitted to the PICU rather than the NICU in accordance with our hospital's infection control policy. According to this policy, newborns who have been discharged home and subsequently require readmission are admitted to the PICU instead of the NICU to minimize the risk of transmission of community-acquired infections to neonates in the NICU.

Currently, in Malaysia, the Institute for Medical Research (IMR) and Hospital Kuala Lumpur (HKL) are the two main centers that perform specialized metabolic testing. In East Malaysia, access to urgent metabolic investigations is often limited by specimen transportation schedules and laboratory logistics. Therefore, in cases with a high suspicion of an underlying metabolic disorder, early referral to a metabolic specialist and prompt communication with the tertiary hospital laboratory can facilitate earlier processing and reporting of metabolic test results.

In centers with MRI facilities, urgent brain MRI can be helpful in identifying pattern-based groups of metabolic disorders. For example, organic acidemias and mitochondrial disorders commonly demonstrate predominant involvement of the basal ganglia, whereas maple syrup urine disease (MSUD) typically shows symmetrical diffusion restriction involving the cerebellar white matter, brainstem, and internal capsules, which correspond to regions of active or established myelination in full-term neonates at birth.

Magnetic resonance spectroscopy (MRS) may further aid diagnosis by detecting specific brain metabolites, including branched-chain amino acids, lactate, choline, and glutamate. This can facilitate earlier diagnosis, particularly when access to metabolic test results is not readily available. However, MRS should be regarded as a supportive diagnostic tool and does not replace definitive biochemical testing for MSUD.

In the management of this case, discussions were held with the metabolic team, and continuous veno-venous hemodiafiltration (CVVHDF) was initiated because the child was severely encephalopathic at the time of referral. The parents were informed that CVVHDF represented rescue therapy, with the primary aim of achieving rapid leucine clearance to reduce ongoing neurotoxicity.

CVVHDF combines both diffusion and convection, allowing for efficient and rapid clearance of small- to medium-sized molecules such as leucine. In contrast, peritoneal dialysis (PD) relies primarily on diffusion and is generally less effective at clearing branched-chain amino acids.[2] However, CVVHDF requires dedicated pediatric intensive care unit (PICU) resources, specialized continuous renal replacement therapy (CRRT) equipment, and central venous access. It may also be associated with complications such as filter clotting, thrombocytopenia, and transient hypotension, particularly in small neonates.

Peritoneal dialysis requires less complex equipment and can be performed in centers without specialized CRRT expertise. Potential complications of PD include catheter blockage, catheter dislodgement, and peritonitis.[5] However, a case report has suggested that PD may be used as an alternative when leucine levels are critically elevated and extracorporeal therapies are unavailable.[6]

Our patient presented at a similar age to the case reported by Raut et al., with both neonates developing symptoms and requiring hospital admission at approximately 7–8 days of life. He presented on day 8 of life with feeding intolerance, irritability, cyanosis, seizures, and respiratory distress requiring intubation. He was noted to have dark-colored urine with a peculiar odor, and urine FEME demonstrated ketonuria. Bedside cranial ultrasonography and cerebrospinal fluid (CSF) analysis were unremarkable. An inborn error of metabolism (IEM) workup was performed and confirmed MSUD, with a serum leucine level of 3037.62 µM. The patient subsequently deteriorated due to progressive encephalopathy and passed away on day 13 of life.

Our patient survived following prompt metabolic intervention, including continuous venovenous hemodiafiltration (CVVHDF) and initiation of a branched-chain amino acid-restricted formula milk on day 17 of life. This contrast highlights the importance of early recognition and aggressive management of acute metabolic decompensation in MSUD. Rapid extracorporeal leucine clearance through CVVHDF may be lifesaving in severely encephalopathic patients to rapidly bring down the leucine level and may improve neurological outcomes.

The reported mortality rate among children under five years with IEM is 1.4 per 10,000 population[3], with delayed diagnosis being a major contributing factor. The implementation of expanded newborn screening programs and improved metabolic diagnostic capacity in East Malaysia is essential for the early detection of treatable conditions such as maple syrup urine disease (MSUD), as there is potential for favorable neurological recovery with timely recognition and treatment.

Low disease prevalence and limited clinician exposure further reduce early diagnostic suspicion. Furthermore, challenges in accessing specialized metabolic formulas and metabolic services may delay the implementation of appropriate disease-specific management.

Collectively, these factors highlight a critical gap between clinical presentation and definitive diagnosis in East Malaysia. This case supports the need for heightened clinical awareness, streamlined diagnostic pathways, and consideration of expanded newborn screening to facilitate earlier identification and improve neurodevelopmental outcomes in affected infants.

Conclusion

Neonatal MSUD should be considered in any infant presenting with unexplained encephalopathy, seizures, ketonuria and negative sepsis investigations. In regions where metabolic testing is not readily available, characteristic MRI and MR spectroscopy findings may provide crucial diagnostic clues and enable early initiation of disease-specific therapy. Strengthening metabolic diagnostic pathways and newborn screening programmes may improve outcomes for affected infants in East Malaysia

Consent

Written informed consent was obtained from the patient's parents for the publication of this case report and any accompanying clinical information and radiological images.

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