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Acute Metabolic Crisis in Maple Syrup Urine Disease, a Rare but Life-Threatening Neurocritical Care Emergency: Case Report

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Case Report

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Abstract

Background

Maple syrup urine disease (MSUD) is a rare, autosomal recessive disorder characterized by a deficiency in the branched-chain alpha-keto acid dehydrogenase enzyme complex necessary for metabolizing the three branched-chain amino acids (BCAAs): leucine, isoleucine, and valine. Periods of stress and illness can cause patients to experience sudden metabolic crises. We present a rare but important case of an adult patient with MSUD in crisis who was admitted to our Neurologic Intensive Care Unit (NeuroICU) with encephalopathy, cerebral edema, and seizures triggered by sepsis.

Case presentation

A 49-year-old male with MSUD presented to the hospital with encephalopathy, which progressively worsened during his admission. The patient was diagnosed with sepsis, which thereafter triggered an MSUD crisis requiring transfer to the NeuroICU. Continuous EEG revealed focal seizures in the left frontal region, which were suppressed using a midazolam infusion. A head CT revealed cerebral edema, and an MRI demonstrated extensive DWI hyperintensity throughout the bilateral cerebral cortices and deep nuclei with ADC correlate. Despite dietary modifications, the patient continued to have elevated BCAA levels. Therefore, continuous renal replacement therapy (CRRT) was initiated and titrated to control BCAA levels. These BCAA levels were monitored daily while the underlying triggers were corrected. Over four weeks, the patient's condition improved to his neurological baseline, and he was subsequently discharged home.

Conclusion

Our case emphasizes the importance of understanding the neurological complications associated with an MSUD crisis--which include seizures, cerebral edema, and coma–as well as highlights CRRT as an effective method for correcting metabolic disturbances in adults with MSUD. Additionally, it highlights that extensive diffusion restriction (DWI hyperintensity) with an ADC correlate is not helpful in neurologic recovery prognostication. Intense multidisciplinary collaboration amongst nutrition, genetics, metabolic, nephrology, pharmacy, and NeuroICU teams aimed at developing effective strategies to reduce BCAA levels and prevent drug interactions was crucial to patient recovery.

Keywords

MSUD

Seizure

CRRT

Background

Maple syrup urine disease (MSUD) is a rare genetic autosomal recessive disorder characterized by a deficiency of an enzyme complex (branched-chain alpha-keto acid dehydrogenase) that is required to metabolize the three branched-chain amino acids (BCAAs) including leucine, isoleucine, and valine in the body [1]. During periods of illness, stress, or changes in diet, the body may be unable to process these branched amino acids properly, leading to dangerous spikes in both BCAAs and branched-chain amino keto acids (BCAKAs) that can cause severe systemic and central nervous system effects. Known CNS effects include impaired neurotransmitter synthesis, oxidative injury and mitochondrial dysfunction [1]. These effects result in an energy failure state that may lead to cerebral edema, seizure activity, and irreversible neurologic injury and cell death by both lysis and apoptosis [2]. Since MSUD is often a disease seen in neonates, the majority of data pertaining to acute management of MSUD crisis comes from this same infant population. Severe MSUD crisis in middle age is rare, and the management of MSUD crisis in adults is heterogeneous at best. To our knowledge, this is the first case involving hyperosmolar and chronic renal replacement therapy (CRRT) management of severe CNS MSUD crisis in an adult.

Case Presentation

A 49-year-old male with maple syrup urine disease (diagnosed through newborn screening), intellectual disability, diabetes, schizophrenia, hypertension, and asthma was admitted to the hospital for metabolic encephalopathy, agitation, and poor oral intake. Prior to admission, he was experiencing increased behavioral issues. Also prior to admission, he had begun seeing a new psychiatrist and was started on Lamictal 25mg a day with the plan to increase to two times a day. The patient's usual demeanor was calm, verbal, and he enjoyed going on outings. Following initiation of Lamictal, the patient would experience episodes of "freezing", become sleepy, and/or become catatonic whereby he would be able to hear but not move. His mother also also reported increased coughing and wheezing for 1-2 weeks, along with heightened sweating without clear documented fever.

Upon admission, the patient was tachycardic (normal sinus rhythm, 130s) with a blood pressure of 190/94. During the examination, the patient was alert and neurologically intact, though his mother noted that he appeared less talkative than usual. Initial workup revealed an elevated white blood cell count of 12, elevated beta-hydroxybutyrate and urinary ketones, and very high levels of leucine, isoleucine, and valine. The chest X-ray showed diffuse bronchitis.

Multidisciplinary teams including metabolic and nutritional specialists were consulted, and the patient was initiated on IV fluids and a BCAA restrictive high-protein diet supplemented with IV lipids. However, the diet was soon discontinued due to concerns about aspiration. On hospital day 6, the patient developed a fever to 102.2 degrees Fahrenheit with concerns for aspiration. The patient became progressively more altered with decreased arousal and inability to protect his airway. He was intubated, road-spectrum antibiotics were initiated, and an infectious workup revealed Staphylococcus epidermidis bacteremia.

In the NeuroICU, laboratory results demonstrated elevated BCAA levels and hyponatremia (Na=131). Continuous EEG revealed recurrent left frontal seizures (*Figure 1a*). Head computed tomography (CT) showed new cerebral edema, and brain magnetic resonance imaging (MRI) revealed extensive diffuse restricted diffusion throughout the bilateral cerebral cortices, caudate, putamen, and thalami with an ADC correlate (*Figure 1b*). This significant CNS involvement was concerning for a severe MSUD crisis with neurologic injury. Keppra and sedation with propofol were initiated, and the patient was placed on continuous renal replacement therapy (CRRT) to reduce BCAA levels refractory to initial diet-directed therapies. Hyperosmolar therapy was commenced to mitigate cerebral edema. The patient had a prolonged ICU stay of 25 days. During this time, daily multidisciplinary discussions among the intensivist, nutritionist, geneticist, metabolic team, and nephrologist were held to develop effective strategies to reduce amino acid intake and avoid drug interactions. The patient began receiving a blended metabolic formula via tube feeding to meet protein needs and was supplemented with valine and isoleucine. Urine cultures were positive for ESBL E. *coli* treated initially with linezolid, followed by Zosyn, daptomycin, and ertapenem. Sedation downtitration was complicated by autonomic storming. A tracheostomy was performed on the 16th day of intubation due to a persistently poor neurological exam and uncertain neurologic recovery. A PEG tube was placed on the 40th day of admission, and CRRT was discontinued. Over the next few days, the patient regained consciousness and exhibited bilateral upper and lower extremity movements in response to noxious stimuli. He began tracking and nodded appropriately. Once he was able to tolerate a tracheostomy collar, he was transferred to the floor, where he convalesced and made a strong recovery. The tracheostomy was decannulated, and the patient was discharged at his previous neurological baseline, such that he could walk into his own home despite the profound findings seen on his MRI brain.

Discussion and Conclusion:

Our case evidences a rare genetic disorder that falls within the spectrum of neurometabolic diseases. In maple syrup urine disease, periods of stress and illness can trigger a metabolic crisis. While metabolic crises are documented [2], such a severe case in a middle-aged adult is uncommon. Management of such cases can be challenging due to the limited experience of ICU physicians with adult MSUD crisis, lack of adult management guidelines, and sporadic heterogeneous management reports in the literature.

Controlling fluctuations in amino acid levels during the initial periods of instability, seizures, and cerebral edema was extremely challenging. This necessitated daily multidisciplinary discussions among specialists with differeing foci of expertise in order to develop effective strategies for reducing amino acids and avoiding drug interactions [3]. While many studies have discussed the role of CRRT in the pediatric population, its role among adults has not been addressed [4]. CRRT significantly contributed to our patient's recovery and effectively reduced leucine levels. It proved to be a safe and efficient method for correcting metabolic disturbances in this adult patient.

Malignant cerebral edema is the most common immediate cause of death from MSUD, which can be as high as 25% [5]. We used hypertonic 3% saline therapy to mitigate cerebral edema, which is similar to different studies that have used both hypertonic and mannitol therapy [6].

The MRI showed extensive diffuse restricted diffusion across the bilateral cerebral cortices, caudate, putamen, and thalami with an ADC correlate. This aligns with some of the MRI findings noted in the pediatric population [7]. However, caution should be exercised to avoid classifying this injury as anoxic. This case highlights that severe MRI findings are indeed compatible with excellent neurologic recovery.

Our case highlights the significance of understanding the neurological complications linked to an MSUD crisis, such as non-convulsive seizures, respiratory failure, coma, and cerebral edema. Continuous renal replacement therapy serves as an effective and safe approach to correcting metabolic disturbances in adults with MSUD. Regular multidisciplinary discussions among the nutritionist, geneticist, metabolic team, nephrologist, and neurointensivist were crucial to enhancing patient recovery, resulting in a positive outcome.

List of abbreviations
cEEG= Continuous Electroencephalography

MSUD= Maple syrup urine disease

CRRT= Continuous renal replacement therapy

CT
MRI
ICU

Availability of supporting data
All data supporting the findings of this study are included within the article. Additional de-identified clinical information is available from the corresponding author upon reasonable request.

Conflicts of Interest
The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Ethical Approval and Consent to Participate
Ethical approval was not required for a single case report, according to the policies of our institution.

Authors' Contributions
MME: Collected clinical data, contributed to the literature review, and drafted the initial manuscript.
BPL and JNL: Assisted in data collection, contributed to manuscript writing, editing, data interpretation, and provided critical feedback on the discussion.
All authors read and approved the final manuscript.

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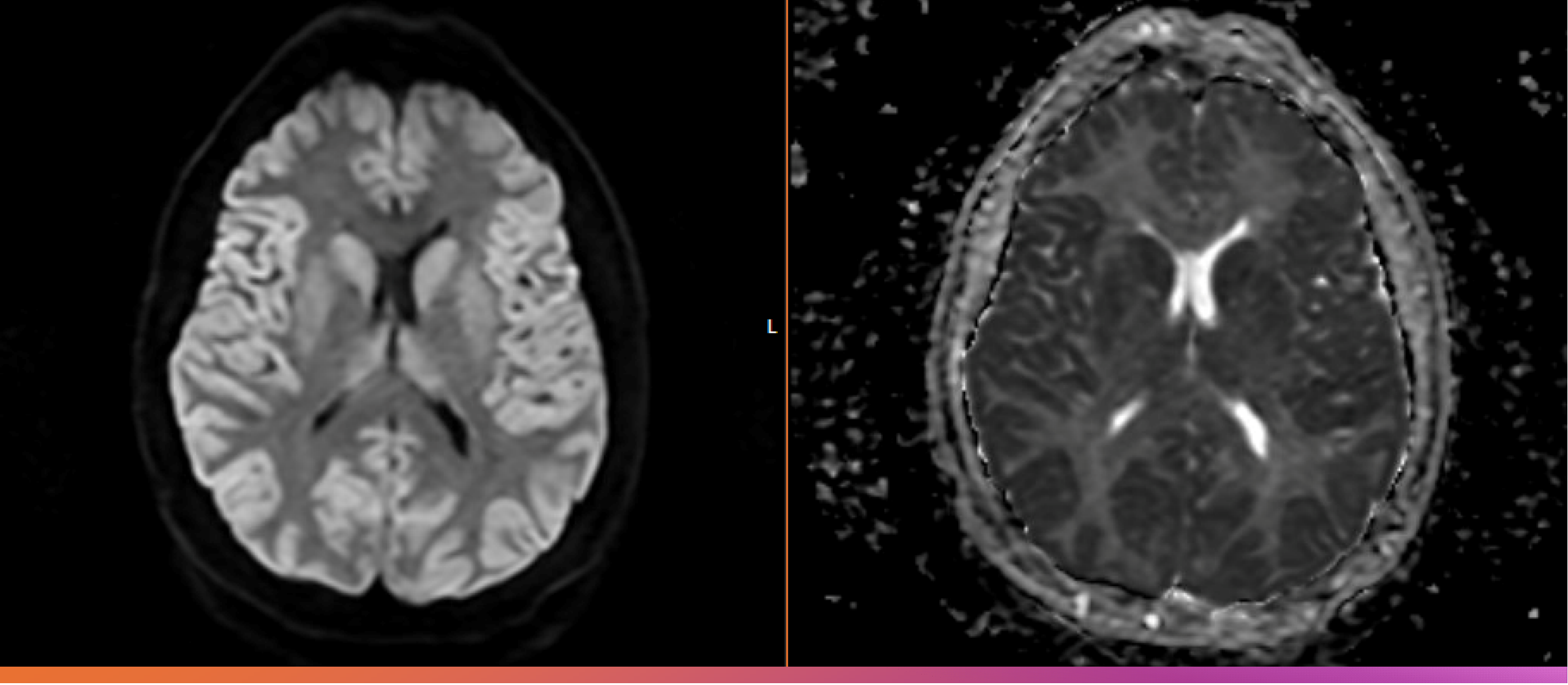
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Figure 1a: cEEG with a 10 sec epoch showing left frontal electroconvulsive seizure

Figure 1b: MRI revealed extensive diffuse restricted diffusion throughout the bilateral cerebral cortices, caudate, putamen, and thalami without an ADC correlate


Fp1-F7
F7-T3
T3-T5
T5-O1
Fp1-F3
F3-C3
C3-P3
P3-O1
Fz-Cz
Cz-Pz
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2


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