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CASE REPORT

Marked increase in leucine as a sign of poor outcome in maple syrup urine disease

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Abstract

Introduction: Leucinoses or Maple Syrup Disease (MSD) is an innate metabolism error caused by a deficiency in the activity of the alpha-keto acid-dehydrogenase enzyme complex, which leads to the accumulation of essential branched-chain amino acids (leucine, valine, and isoleucine), leucine is particularly toxic to the central nervous system (CNS). **Objectives:** Report a case of maple syrup disease in a 10-day-old newborn (NB), born to consanguineous parents, with late diagnosis, with high levels of leucine, with an unfavorable prognosis. **Comments:** MSD is a rare condition, of autosomal recessive origin, which occurs due to the accumulation of essential branched-chain amino acids in tissues (leucine, valine, and isoleucine). The accumulation of amino acids mainly affects the CNS. Studies have shown that the elevated leucine concentration decreases the serum sodium concentration and increases intracellular water, causing cerebral edema. Neurological damage will depend on the degree and time of tissue exposure to metabolites. Despite the unfavorable outcome of the case presented, the prognosis of MSD can be modified with strict diet control and early and aggressive management of metabolic crisis.

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INTRODUCTION

Leucinosis or maple syrup urine disease (MSUD) is an inborn error of metabolism caused by a deficiency in the activity of the alpha-ketoacid dehydrogenase complex, which leads to the accumulation of essential branched-chain amino acids (leucine, valine, and isoleucine). Leucine is particularly toxic to the central nervous system (CNS)¹. First described in 1954 by Menks et al., its name derives from the characteristic odor present in the urine of patients, attributed to the high presence of amino acids in bodily fluids. MSUD is a rare autosomal recessive disease, with a worldwide prevalence of 1:185,000 live births. In areas with higher occurrence of consanguineous marriages, incidence may reach up to 1:200 newborns^{2,3}. In Brazil, prevalence is 1:100,000 live births, but literature on the subject is scarce⁴.

In the classic form of the disease, newborns develop symptoms within the first days of life. Protein catabolism that occurs during the transition from intrauterine to extrauterine life causes a progressive accumulation of leucine in tissues and plasma. Neurological symptoms appear within a matter of days, including irritability, lethargy, hypotonia, poor food acceptance, and intermittent apnea. By the time patients are diagnosed with MSUD, many may be comatose and require emergency interventions to prevent irreversible brain damage^{1,3}.

MSUD can be identified in neonatal screening with tandem mass spectrometry, a component of the expanded neonatal screening program, or by a quantitative analysis of the serum levels of the specific amino acids involved^{3,5}.

This article describes the case of a newborn aged ten days with consanguineous parents diagnosed with MSUD with high levels of leucine, which developed into an undesired outcome.

CASE REPORT

A full-term 10-day-old male infant born by cesarean delivery at a low complexity hospital in the inlands of the Pernambuco, a state in the northeastern region of Brazil, had an Apgar score of 9/9 and weighed 2400g after an uneventful delivery. He was admitted to the pediatric emergency department of a referral hospital in Pernambuco. The child had a history of hypoactivity observed since the fifth day of life, which gradually worsened. He was referred from another service near the town where he was born, at which he had stayed for one day suspected with neonatal sepsis. His 31-year-old mother was in her fourth pregnancy. Her first two pregnancies ended in miscarriages. She and her partner were first cousins.

The infant was in poor general condition, comatose, hypoactive, and with weak primitive reflexes on admission. Laboratory tests and cultures (cerebrospinal fluid, blood, and urine) showed no alterations. Transfontanellar ultrasound imaging showed diffuse alterations in brain echogenicity, while computed tomography (CT) scans of the head (Figure 1) showed diffuse white matter hypodensity and cerebral edema.

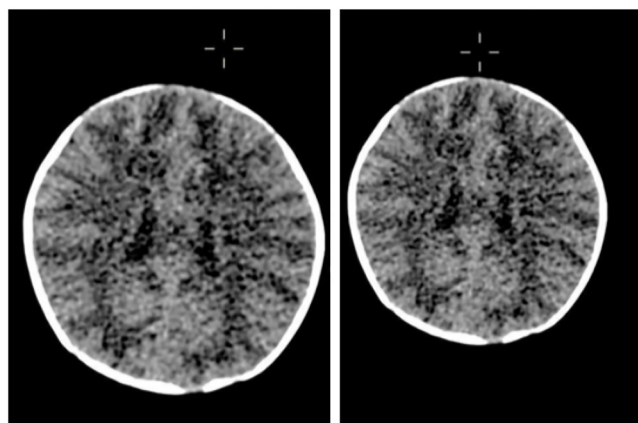


Figure 1. CT scans of the head showing diffuse white matter hypoattenuation, including the cerebellum and basal ganglia, in addition to absence of sulci and gyri, suggestive of cerebral edema.

The patient's overall condition worsened and he developed epileptic seizures, requiring assisted mechanical ventilation. Tests for inborn errors of metabolism (IMT) were performed and the patient was left unfed for 48 hours and on infusions with high concentrations of glucose to prevent catabolism.

Six days later, the test results showed valine levels of 713.7 $\mu\text{mol/L}$, isoleucine levels of 903.5 $\mu\text{mol/L}$, and leucine levels 5,123.3 $\mu\text{mol/L}$, thus confirming a diagnosis of leucinosis (Table 1).

Table 1. Dosagem sérica dos aminoácidos de cadeia ramificada. *VR: Valor de referencia.

Valine	713.7 $\mu\text{mol/L}$ (RV*: 86-190 $\mu\text{mol/L}$)
Isoleucine	903.5 $\mu\text{mol/L}$ (RV: 26-91 $\mu\text{mol/L}$)
Leucine	5,123.3 $\mu\text{mol/L}$ (RV 48-160 $\mu\text{mol/L}$)

While in intensive care, the patient was prescribed peritoneal dialysis and a diet with restriction of leucine, isoleucine, and valine. Fourteen days after admission, aged 24 days, the patient died due to worsening of neurological symptoms associated with a hospital-acquired infection.

DISCUSSION

MSUD is a rare autosomal recessive disease that occurs due to the accumulation of essential branched-chain amino acids in tissues, namely leucine, valine, and isoleucine. The accumulation of these amino acids affects primarily the CNS. Studies have shown that high leucine levels decrease serum sodium concentrations and increase intracellular fluid, causing cerebral edema. Neurological damage depends on the degree and time of tissue exposure to metabolites⁶.

Due to variations in enzyme activity and amino acid levels, the signs and symptoms of the disease vary widely, along with age of onset. In its classical, more aggressive form, less than 2% of the enzyme is active, and symptoms appear gradually between the fifth and seventh day of life^{1,7}.

In the case described, the patient had been hypoactive since the 5th day of life, and gradually lost his reflexes and had hypotonia and apnea. Although the degree of enzyme activity was not evaluated, the early appearance of symptoms and the rapid progression of the disease indicated that the patient developed the classic form of MSUD.

The disease is diagnosed based on the presence of branched-chain amino acids in blood or with the aid of tandem mass spectrometry via the extended neonatal screening protocol^{3,5}. In Brazil, the neonatal screening protocol reimbursed by the Unified Healthcare System (SUS) does not cover the identification of inborn errors of metabolism. Therefore, our patient was tested for the serum levels of the markers of interest. The literature stipulates that normal leucine levels reside in the 80-100 µmol/L range; the same range for isoleucine is 40-90 µmol; and 200-435 µmol for valine⁶. In 2014, a study conducted in Brazil by Hebbler et al. found that the mean level of leucine in individuals with MSUD over a period of nine years was 1,693 µmol/L. The study described as critical patients with levels greater than 1000 µmol/L, since they may suffer irreversible damage⁴. Our patient's leucine level was 5,123.3 µmol/L. However, there are few studies in the literature correlating amino acid levels to CNS damage or outcomes.

Neuroimaging exams such as computed tomography (CT) and especially magnetic resonance imaging (MRI) of the head are important in assessing CNS involvement and defining potential outcomes^{1,9}. A study conducted in Turkey in 2007 used MRI to monitor the response to MSUD treatment¹⁰. Brain MRI scans showed restricted diffusion in myelinated areas on diffusion-weighted imaging, a phenotype identified as an indicator of MSUD in newborns². Our patient's CT scans demonstrated diffuse involvement, with diffuse white matter hypoattenuation, including the cerebellum and the basal ganglia, and absence of sulci and gyri, suggesting cerebral edema. These findings are consistent with significant involvement and suggest poorer outcomes.

Despite the unfavorable outcome of the case presented, the outcomes of patients with MSUD can be modified with strict dietary control and early aggressive management of metabolic disorders¹¹. Defects in amino acid complex function may reduce the interactions between them and their cofactors, such as thiamine. Lower affinity for thiamine can be treated with the administration of thiamine in high concentrations¹². Some articles have reported patient improvement with L-carnitine supplementation, a potent antioxidant that crosses and blood-brain barrier and prevents neurological damage. We attempted to maintain normal circulating levels of branched-chain amino acids with the prescription of an amino acid-free medical formula and dietary protein restriction, but all measures failed since the patient had advanced brain damage.

Outcome depends on individual phenotype, time of diagnosis, and life-changing measures implemented. According to a case series published by Simon et al., adherence to amino acid-restricted diets may prevent developmental delays and

decrease the frequency of episodic metabolic decompensation, although symptoms such as hyperactivity and attention deficit have been reported in patients from other studies¹³. Results seem favorable for individuals undergoing liver transplantation, especially if measures are introduced before the onset of severe neurological damage, with fewer symptoms and flare-ups including encephalopathy¹⁴.

CONCLUSION

In Brazil, patients with MSUD are usually diagnosed in later stages of disease, with installed neurological involvement and poor survival, as in the case reported herein. The guidelines for comprehensive care of people with rare diseases of the Unified Healthcare System (SUS) stress the importance of providing care focused on the needs of individual patients¹⁵. The implementation of screening protocols can be decisive factor in improving the outcomes of patients who rely on early treatment to avoid severe brain damage.

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