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Case Report Open Access

Alternating Hemiplegia as A Major Symptom of Maple Syrup Urine Disease: Case Report

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Abstract

The aim of the present study is to draw attention to the rare association of maple syrup urine disease and alternating hemiplegia.We present a case of a 3-year-old boy adopted 3 months before the onset of alternating hemiplegia events, with development delay, had investigation with MRI and Urinary organic acid suggestive of MSUD. Started the treatment restriction of leucine, isoleucine and valine intake and thiamine supplementation, with resolution of his neurology symptoms.

Keywords: Hemiplegia; Maple Syrup Urine Disease; Branched Chain Amino Acid; Leucinosis; Paroxysmal

Introduction

Maple syrup urine disease (MSUD; branched-chain keto aciduria; OMIM 248600) is an autosomal recessive disorder caused by deficient activity of the branched-chain alpha-ketoacid dehydrogenase complex (BCKAD). It consists of three catalytic components: thiamine pyrophosphate-dependent carboxylase (E1), transacylase (E2), dehydrogenase (E3) and two regulatory enzymes (a kinase and a phosphatase) [1]. Deficient activity of this complex leads to the accumulation of the branchedchain amino acids (BCAAs) leucine, isoleucine and valine and the corresponding branched-chain α-keto acids (BCKAs) α-ketoisocaproicacid, α-keto-β methylvaleric acid and α-ketoisovaleric acid (KIV) [1]. It has a worldwide incidence of 1: 185,000 live births and is not present in neonatal screening in our country, despite having treatment that alters the course of the disease [2].

Case Report

RFD, 3 years and 6 months, male, white, adopted 3 months before the beginning of, had abrupt, onset of paroxysmal motor events characterized by alternating hemiplegia, with a duration of 30 minutes, evolving with total and spontaneous recovery in up to 24 hours, totaling 28 events in 6 months .There were no information on prior development and symptoms of the child currentlypresenting language and fine motor delay.The physical exam showed dimorphisms: absence of lip groove, thin upper lip, large eyes, thick eyebrows, blond and fine hair, brachydactyly, hypotrophy, hypotonia, hyperreflexia and low weight. Complementary exams such as ECO, CPK, OFT, congenital adrenal hyperplasia, TORCH, HIV, lactate, laboratories were normal. Brain MRI was performed with spectroscopy showing hypersignal of globus pallidus, subthalamic nuclei, thalamus, mesencephalon and dentate nuclei; restriction areas in the cerebellar hemispheres and hypersignal in subcortical white matter; branched chain amino acid spike (Figure 1).

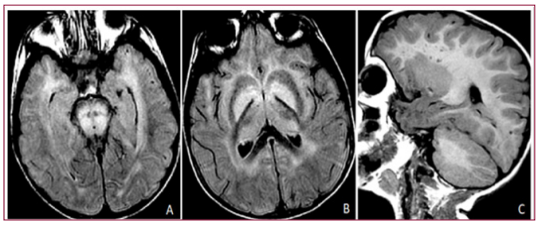

Figure 1: Brain MRI with Spectroscopy.
A. Axial plane: Hypersignal of mesencephalon
B. Axial plane: Hypersignal of globus pallidus, subthalamic nuclei, thalamus and dentate nuclei
C. Sagittal plane: Hypersignal in subcortical white matter

Urinary organic acids showed elevated levels of 3-hydroxybutyric acid, 2-hidroxisovaluric, 2-hidroxi-3-metilvaluric, 2-hidroxisocaproicand, 2-ketoisocapric acids. High ratios of leucine:phenylalanine, valine:phenylalanine. Serum aminoacid profile showed elevated leucine and isoleucine, low alanine, normal valine. All isoleucine was not available for testing. High levels of branched-chain, 2-hydroxyisocaproic acid, 2-hydroxyisovaleric. The patient was diagnosed with MSUD and started proper diet with restriction of leucine, isoleucine and valine intake and thiamine supplementation. During follow up with child neurology and nurology he showed resolution of neurological symptoms and milestones. New tandem profiles were normal during follow up. After two years of treatment, new MRI was performed showing complete resolution of previously reported lesions and normal signal of cerebral parenquima.

Discussion

There are five distinct clinical phenotypes of MSUD, according to the residual enzymatic activity, although there's not a good genotype–phenotype correlation: [3]. In the classic neonatal severe form patients symptoms begin between 4 and 7 days of age with lethargy, irritability, poor feeding, apnea, opisthotonus, "bicycling" movements, evolving to coma and death. The characteristic odor resembling maple syrup can be present in cerumen and urine since 12 hours after birth. Acute episodes of leucine intoxication can arise at any age, usually after triggers such as illness or any source of catabolic stress. Single patients have been reported with symptoms resembling Wernicke encephalopathy. These patients usually have less than 2% of BCKAD enzymatic activity [4]. Patients with intermittent form have an apparent normal development but present the classical features of MSUD during physiologic stress. They usually have up to 30% of BCKAD residual activity. Intermediate form individuals may appear normal during the neonatal period but have gradual neurological problems, eventually resulting in mental retardation.

Thiamine-responsive patients have residual BCKADH enzyme activity of up to 40 % normal and a clinical course similar to those with intermediate form [4]. The E3-deficient is a very rare condition, clinically similar to the intermediate form but with severe lactic acidosis; have a combined deficiency of BCKDA, pyruvate and alpha-ketoglutarate complexes, leading to more complex phenotype. The diagnosis relies upon biochemical signs of increased plasma concentration of leucine and the presence of allo-isoleucine, a distinctive metabolite present in all forms of MSUD. Isoleucine and valine are also typically elevated but may be normal or reduced [5,6]. Analysis of urinary organic acids reveal elevated excretion o branched-chain alpha-hydroxyacids and alpha-ketoacids. Newborn screening using Tandem mass spectrometry (MS/MS) can identify increased leucine isoleucine peak in blood spots after 24-36 hours. However, it is not included in our newborn screening program offered by the public system [7].

Neuroimage shows increased T2 signal in the brainstem reticular formation, dentate nucleus, red nucleus, globus pallidus, hypothalamus, septal nuclei, and amygdala. Proton spectroscopy demonstrate elevation of lactic acid, and presence of a peak at 0.9–1.0 ppm, belonging to methyl resonance of branched chain amino acids, decreased NAA/choline ratio, and elevated lactate [8]. It is postulated that leucine and its keto acid are the main neurotoxic metabolites involved in brain damage in MSUD. The increased plasma concentration of leucine correlates with neurological symptoms. It also interferes with the transport of other amino acids across the blood-brain barrier (such as tryptophan, methionine, tyrosine, phenylalanine, histidine, valine, and threonine), resulting in decreased synthesis of neurotransmitters, leading to additional dysfunction [5]. The main goal of MSUD management is to prevent neurological sequels associated with chronic hyperleucinemia and acute decompensation, which constitute a metabolic emergency. The treatment is based on dietary restriction by reducing BCAAs and providing adequate macronutrients to prevent catabolism and help maintain plasma BCAAs within targeted treatment ranges.

Thiamine supplementation is still controversial [9,10]. Although molecular diagnosis is important, not only to determine which subunit is deficient, which may be helpful in individualized therapies, but also to genetic counseling, it is not feasible in our current scenario of public health in Brazil. The majority of the population depends exclusively on the public health system SUS, which thus far does not provide adequate coverage for genetic medical procedures [7,11]. In the absence of newborn screening and molecular techniques, the majority of MSUD cases are still diagnosed clinically. In the presenting case gene sequencing was already requested for diagnostic confirmation, and still waiting for approval. In our case, lack of information of years previous to the adoption, associated with the rare atypical manifestation, lead to a difficulty in clinical suspicion and diagnosis.

Conclusion

Despite the compatible laboratory, radiological diagnosis and good response to therapy for MSUD (the resolution of symptoms and involution of disease signs in MRI with treatment), gene sequencing was already requested for diagnostic confirmation of the subtype of the disease.There are only a few reports of the association between MSUD and alternating hemiplegia, making effective recognition and treatment a challenge. Therefore, it is necessary to approach the subject in order to improve these patient's morbidity and mortality, preventing the progress of neurological deficits.

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