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CASE REPORT

Methylmalonic acidemia in Pediatrics: case report

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Abstract

Methylmalonic acidemia was first described in 1967 and represents an autosomal recessive disease originating from a disorder of propionate metabolism. Although rare, it is one of the most frequent inborn errors of organic acid metabolism. The disease can manifest itself in the first days of life or have late onset in childhood. The therapy is based on protein restriction and carnitine supplementation. The present study reports a case of an infant who was seen at the hospitals emergency room with vomiting, dehydration, fever, adynamia, hyporexia, hypotonia and hyporesponsiveness, and developmental delay. Started research for methylmalonic acidemia and confirmed diagnosis through laboratory tests. Therefore, it is important to have studies and research on rare genetic diseases so that medical professionals can update, diagnose and seek early treatment for such patients.

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INTRODUCTION

Methylmalonic acidemia (MA) was first described in 1967 and comes from an autosomal recessive disease. It represents a disturbance in propionate metabolism, in the conversion of methylmalonic acid to succinic acid^{1,2,3,4}. The disease incidence is estimated at 1:48,000 to 1:61,000 in the western population. In Brazil, the few available epidemiological data hinder the search for diagnosis in the pediatric population^{1,5}.

Although rare, MA corresponds to one of the most frequent innate errors in the metabolism of organic acids⁶. The disease can manifest itself in the first days of life or have a late onset in childhood, with chronic kidney disease as a late complication¹.

The purpose of this report is to describe a pediatric case of MA, highlighting the main milestones of its clinical progress until diagnosis.

CASE REPORT

Child of 3 years and 10 months old, female, born by cesarean section (41 weeks and 1 day), APGAR 6/9, weight 2550 g, 47 cm long - small for gestational age (SGA). There were no changes in the neonatal screening tests.

Without regular childcare follow-up, she first came to the health service at seven months of age, with symptoms of airway infection, associated with episodes of vomiting, dehydration, fever, dyspnea, hypotonia and excessive irritability.

During the seven days of admission to the Pediatric Intensive Care Unit (PICU), she received antibiotic therapy for airway infection and had hyperglycemia (capillary glycemia = 224-248 mg/dL) and metabolic acidosis (pH = 7.14; HCO₃ = 3.8 mmol/L; pCO₂ = 11.2 mmHg).

At nine months of age, she was admitted for treatment of cervical lymph node enlargement. In this hospitalization, there was a delay in psychomotor neurodevelopment; the child did not sit without support, being referred for follow-up with a neurologist and motor physiotherapy on an outpatient basis.

At 12 months, the infant was admitted to the PICU again with a new episode of vomiting, dehydration, fever, adynamia, hyporexia, hypotonia and hyporesponsiveness. Upon physical examination, she was in a Glasgow Coma Scale of 6; 93% oxygen saturation in ambient air, hypothermic and with slowed peripheral capillary perfusion. She received heated volume expansion with improved peripheral capillary perfusion, and she had mechanical ventilation for a period of five days.

We started investigating for innate metabolism error through the analysis of urinary organic acids and plasma amino acid chromatography. Table 1 shows the results.

In addition, magnetic resonance imaging was performed with skull spectroscopy, which showed adequate concentrations of N-acetyl aspartate, choline and creatinine, without myoinositol, lipid or lactate peaks; abdominal ultrasound, electrocardiogram and transthoracic echocardiogram with flow mapping, all normal.

Table 1. Results of exams ran to investigate inborn errors of metabolism.

EXAM	RESULT (mmol/mol of creatinine)	REFERENCE VALUE (mmol/mol of creatinine)
Methylmalonic acid	> 5000	< 3.6
Lactic acid	399	21-285
3-hydroxi-propionic acid	630	1-36
3-hydroxi-butyric acid	167	≤ 30
3-hydroxiisovaleric acid	782	10-67
Propionylcarnitine	25.58*	0.35-4.00*
Acetylcarnitine	25.08*	9-58*
Propionylcarnitine/ Acetylcarnitine	1.02	≤ 0.2

* mmol/L.

We diagnosed methylmalonic acidemia and prescribed carnitine, a vitamin B12 supplement, and a protein-restrictive diet. Faced with clinical and laboratory compensation, the patient remained hospitalized for 20 days and was discharged with instructions. After diagnosis, the child needed to be readmitted five more times, in the PICU, due to decompensation of the condition associated with uncontrolled diet and lack of medication.

Regarding neurological development, she presented with delays in the following milestones: "walking with support", at 1 year and 11 months, "duplicate syllables" and "imitating gestures" at 2 years. At 3 years of age, she had difficulties walking and speaking. She is still awaiting genetic testing to elucidate the mutation involved in the disease.

DISCUSSION

There are two forms of MA presentation, the classic, acute onset, with symptoms in the neonatal period, and a later post-neonatal form. In the neonatal period, clinical signs include symptoms such as vomiting, weight loss, dehydration, temperature instability, hypo or hypertonia, irritability, lethargy, seizures and coma¹. The differential diagnosis involves sepsis, drug intoxication and ischemic hypoxic encephalopathy⁷.

Post-neonatal crises are usually triggered by protein overload, catabolic events or use of certain medications, the same factors observed in the patient's history in the post-diagnosis period culminating in new hospitalizations^{1,6}. The symptoms can simulate other diseases, such as diabetic ketoacidosis¹, well-illustrated in the patient's first decompensation, when she presented hyperglycemia and metabolic acidosis, associated with systemic signs and symptoms of dehydration, vomiting and dyspnea. The most common clinical features include encephalopathy or unexplained coma, hypotonia, seizures, tachypnea, cardiomyopathy or prolonged QT interval and delayed neuropsychomotor development^{1,6}.

Some factors are capable of initiating acute decompensation of the disease, despite adequate treatment, such as viral infections, fever or surgical procedures^{7,8}. In this case,

the patient's first decompensation occurred after an infection of the airways, evolving with the need for intensive care. Chronic complications manifested during the disease include growth retardation, epilepsy, progressive kidney disease, cardiac dysfunction, loss of vision, osteoporosis or osteopenia, movement disorders and immunodeficiency^{7,8}.

Regarding laboratory findings, disease suspicion occurs in the presence of signs of metabolic acidosis, lactate increase, high concentrations of plasma ammonia, leukopenia, thrombocytopenia, anemia and presence of urinary ketone bodies, without other causes. In the presence of hyperammonemia, the patient requires additional tests, such as plasma amino acid chromatography, urinary organic acids and serum or plasma acylcarnitine. For diagnostic confirmation, one needs molecular genetic examinations and enzymatic studies¹. High levels of propionylcarnitine, alanine and glycine in the plasma, together with an increase in urinary methylmalonic, methylcitric acid and 3-hydroxy-propionic acid prove the diagnosis⁷. Likewise, the diagnosis of the patient under analysis was only possible after an increase in serum propionylcarnitine along with high urinary acids (methylmalonic and 3-hydroxy-propionic), which corroborated the diagnosis of MA, leading to better management of the clinical condition. Genetic tests have also been requested, however, they are still being carried out.

Treatment starts even before the exam results¹. Strict use of a specific diet is essential to improve the prognosis of patients until new therapeutic options appear⁸.

The initial treatment of the decompensation crisis included stabilizing the patient with supportive measures, suspending protein intake (for maintenance, protein intake up to 0.8 g/kg of protein daily) and prevention of prolonged fasting. One should also consider intravenous glucose infusion and parenteral nutrition therapy. Associated infections should be treated quickly. A specialized and multidisciplinary metabolic team should start the evaluation and the specific drug treatment. This should be guided from the level of plasma urea, with

L-carnitine, sodium benzoate and vitamin B12 supplementation, when there is a deficiency of the mitochondrial enzyme dependent on cobalamin and N-carbamylglutamate^{1,7,9}. In more severe patients, it may be necessary to use extracorporeal detoxification, as in those with ammonia levels higher than 400-500 $\mu\text{mol/L}$ ^{1,6}. In this case, the patient was stabilized and treated for the associated conditions that led to the decompensation, and once diagnosed as MA, drug treatment with vitamin B12 and L-carnitine was initiated, and we instructed the patient concerning the need for a low protein diet.

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