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Acute heart failure in an infant with methylmalonic acidemia: a diagnostic and therapeutic challenge

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ABSTRACT

Methylmalonic acidemia is characterized by the inability to convert L-methylmalonyl-CoA to succinyl-CoA, resulting in the accumulation of methylmalonic acid in the blood and/or urine. In its chronic form, it can cause cardiomyopathy with impaired cardiac function. Its management is based on several pillars; the most important is intramuscular hydroxycobalamin supplementation, which serves as a cofactor for methylmalonyl-CoA mutase.

We present the case of a 6-month-old girl who was admitted to the emergency department with signs of heart failure. A multidisciplinary evaluation was performed to determine the etiology, and methylmalonic acidemia was diagnosed. We also report a novel route of administration for hydroxycobalamin in this condition (subcutaneous).

We present the diagnostic approach and therapeutic challenges in this patient, given that the usual route of administration of hydroxycobalamin was contraindicated due to her comorbidities.

Keywords: *heart failure; metabolic diseases; hydroxycobalamin; methylmalonic acid, metabolism.*

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INTRODUCTION

Acute heart failure in pediatrics represents a diagnostic and therapeutic challenge due to its diverse etiology, low incidence, and potential severity, which can lead to death. Inborn errors of metabolism, such as organic acidemias, have been reported as rare etiologies.[1] Methylmalonic acidemia (MMA) is an organic acidemia characterized by a deficiency of the enzyme methylmalonyl-CoA mutase or defects in the biosynthesis of its cofactor, adenosylcobalamin, which prevents the conversion of L-methylmalonyl-CoA to succinyl-CoA, with accumulation of methylmalonic acid in physiological fluids.[2,3] The diagnosis is based on clinical suspicion, family history, and general and specific biochemical findings. Standard treatment focuses on parenteral hydroxycobalamin supplementation, usually intramuscular (IM), which acts as a cofactor for methylmalonyl-CoA mutase.[2-6]

We report the case of a 6-month-old girl who presented to the Emergency Department with acute heart failure. We highlight the diagnostic difficulties and the decision to implement a non-standard route of hydroxycobalamin administration, the subcutaneous (SC) route, due to the patient's comorbidities.

CLINICAL CASE

We present the case of a 6-month-old girl born at term with adequate weight and no relevant perinatal history. Her medical history was notable for outpatient follow-up by Pediatric Pulmonology due to multiple episodes of bronchial obstruction without prior hospitalization or other pathological history. There was no relevant family history. She was breastfed on demand, with complementary feeding initiated one week before admission. Her weight, height, and neurodevelopmental development were age-appropriate, according to pediatric checkups.

As part of the pulmonology study, a routine chest X-ray revealed cardiomegaly. The subsequent Doppler echocardiogram reported severe dilatation and systolic-diastolic dysfunction of the left ventricle, along with moderate-severe mitral regurgitation. Initially, ALCAPA syndrome (anomalous left coronary artery origin in the pulmonary artery) was suspected, and she was transferred to our institution for monitoring and treatment.

Upon admission to the hospital, she was in good general condition, with normal coloration, alert, responsive, and afebrile. Cardiovascular auscultation revealed normal phonetic cardiac sounds and palpable peripheral pulses. Respiratory examination showed regular bilateral air entry with superimposed rales. Her weight was 8725 g (93rd percentile; Z score = 1.44). At the time of admission, clinical checks showed a heart rate of 160 beats per minute, respiratory rate of 26 breaths per minute, blood pressure of 90-75 mmHg with an average of 79 mmHg, oxygen saturation of 97%, and temperature of 36.5° C.

A new echocardiogram was performed, confirming the previous findings, with a shortening fraction (SF) of 14% and an ejection fraction (EF) of 21%. A comprehensive multidisciplinary evaluation was initiated to determine the etiology of the dilated cardiomyopathy. Chest CT angiography ruled out ALCAPA syndrome and thrombosis. Anticoagulant prophylaxis with enoxaparin was initiated due to the high thrombotic risk associated with severe ventricular dysfunction. Viral serology was negative.

Consultation with the Genetics and Pediatric Neurology Departments led to the request for metabolic studies, which showed a markedly elevated urinary methylmalonic acid value. The Pediatric Metabolism Department confirmed the diagnosis of MMA based on elevated serum and urinary methylmalonic acid and homocysteine levels, with a normal vitamin B12 level.

Treatment with intravenous hydroxycobalamin at a dose of 1 mg/day (0.14 mg/kg/day) was initiated on day 17 of hospitalization. With this treatment, serum and urinary levels of methylmalonic acid and homocysteine normalized, but no significant improvement in cardiac function was observed.

During hospitalization, the need for chronic daily hydroxycobalamin administration was limited by two factors: the family's refusal to allow a central venous catheter and the inability to use the IM route due to anticoagulant prophylaxis. Faced with this dilemma, it was empirically agreed with the Metabolism and Hematology teams to administer hydroxycobalamin SC (as part of a B1-B6-B12 complex), which began on the 31st day of hospitalization. At the same time, carnitine (50 mg/kg/day) was initiated, and her diet was adjusted to the Nutrilón Profutura 2® formula, targeting 300 kcal/kg. The patient presented with a refractory *Clostridium difficile* infection and received multiple enteral antibiotic regimens (metronidazole and vancomycin). The evolution of the metabolic tests is presented in *Table 1*.

The patient was discharged with instructions for a daily hydroxycobalamin infusion SC to maintain normal homocysteine and methylmalonic acid levels. During periodic outpatient check-ups at the Clinic, Metabolism, and Pediatric Cardiology Departments, echocardiographic parameters remained stable, with no significant improvement in cardiac function (the last echocardiogram recorded an EF of 20% and no pericardial effusion). This follow-up confirmed that SC treatment was effective in stabilizing biochemical parameters, although it did not reverse the pre-existing myocardial injury.

DISCUSSION

In the case presented, acute heart failure was the warning sign that led to the etiological study of our patient. The initial differential diagnosis was broad: it included ALCAPA syndrome (ruled out by angiotomography) and undetected congenital heart disease. The absence of muscle weakness or neuromaturative delay allowed us to exclude muscular dystrophies and obvious genetic syndromes. Finally, the metabolic study revealed the underlying etiology: MMA.

MMA, with an autosomal recessive inheritance pattern and an incidence of 1/50,000 live births, is mainly due to a deficiency of methylmalonyl-CoA mutase, with accumulation of methylmalonyl-CoA and methylmalonic acid.[3,7] There are clinical forms with variable presentations; although neonatal presentation is the most common, chronic forms can manifest with organ involvement; cardiomyopathy and QTc prolongation are known complications, although their etiology is unclear.[3,8-10] The diagnosis is suspected in cases of unexplained metabolic acidosis, ketonemia, or hyperlactacidemia, and is confirmed by elevated urinary methylmalonic acid and molecular genetic testing.[3-5,8]

Treatment is based on a low-protein diet restrictive in amino acid precursors, the use

Table 1. Metabolic tests during hospitalization

Days of hospitalization	Normal values	4	15*	23	35
Total carnitine (nmol/mL)	46 - 64	78.1			
Free carnitine (nmol/mL)	37 - 58	53.0			
Phenylalanine (µmol/L)	26 - 98	49			53
Leucine (µmol/L)	30 - 246	104			87
Isoleucine (µmol/L)	6 - 122	74			52
Methionine (µmol/L)	3 - 43	12			17
Valine (µmol/L)	132 - 480	178			151
Tyrosine (µmol/L)	19 - 119	63			65
Proline (µmol/L)	40 - 332	154			169
Alanine (µmol/L)	120 - 600	188			235
Threonine (µmol/L)	40 - 204	194			138
Glutamic acid (µmol/L)	14 - 78	131			99
Glycine (µmol/L)	107 - 343	215			219
Aspartic acid (µmol/L)	1 - 17	15			18
Glutamine (µmol/L)	333 - 809	579			615
Serine (µmol/L)	70 - 194	176			152
Asparagine (µmol/L)	15 - 83	94			92
Citrulline (µmol/L)	8 - 47	20			23
Arginine (µmol/L)	12 - 112	72			82
Histidine (µmol/L)	47 - 135	47			61
Homocystine (µmol/L)	0 - 5	0			0
Lysine (µmol/L)	66 - 270	180			152
Ornithine (µmol/L)	20 - 136	95			76
Methylmalonic acid (serum) (ng/mL)	<0.4		5782	49.9	31
Vitamin B12 (pg/mL)	180 - 914		406		>1,500
Homocysteine (µmol/L)	4.44 - 13.56		21.4	5.4	4.5

nmol/mL: nanomoles/milliliter; µmol/L: micromoles/liter; ng/mL: nanograms/milliliter; pg/mL: picograms/milliliter.
**Based on these results, on day 17 of hospitalization, the patient began treatment with intravenous hydroxycobalamin.*
***On day 31 of hospitalization, treatment had been switched from intravenous hydroxycobalamin to subcutaneous hydroxycobalamin, and these were the results of monitoring this change.*

of enteral antibiotics to reduce propionic acid production by the intestinal flora, and parenteral supplementation with hydroxycobalamin and carnitine. The usual route of administration for hydroxycobalamin in MMA is IM, as intravenous administration is associated with a higher risk of adverse effects (cytopenias, headache, anaphylaxis).[3-5]

In our patient, the IM route was not a safe option due to the concomitant indication for anticoagulant prophylaxis, which increased the risk of hematoma and bleeding at the injection site. Therefore, the standard alternative would be central venous access for chronic infusion, which the family rejected. This situation led us to consider the SC route a practical and safe option for long-term, daily administration, despite the lack of clinical studies evaluating its efficacy in MMA.[3-5] Although the SC route is not the preferred route for MMA treatment, hydroxycobalamin is a small molecule that can be effectively absorbed via this route, as described in the context of vitamin B12 deficiency states.[11,12] Close monitoring of biochemical parameters (methylmalonic acid and homocysteine) confirmed that absorption and metabolic response were adequate and sustained with the chosen SC dose.

In the long term, although biochemical control was maintained within normal ranges, no significant improvement in cardiomyopathy was observed. This lack of reversal of cardiac injury underscores that, although optimal metabolic treatment is vital for neurological prognosis, it does not always reverse preexisting myocardial damage, whose pathogenesis is likely multifactorial (accumulation of metabolites, oxidative stress, and other concurrent factors).[3,9-10] This case highlights the need for further diagnostic evaluation to rule out other etiological factors that could aggravate myocardial injury.

This report emphasizes that acute heart failure in infants may be the first manifestation of organic acidemia, requiring a high index of suspicion in the differential diagnosis. Furthermore, it highlights the importance of considering the SC route of administration of hydroxycobalamin as a safe and effective alternative for metabolic control in patients with MMA who have contraindications for the IM route. However, the lack of formal pharmacokinetic and clinical evidence for MMA calls for studies evaluating the bioavailability and long-term efficacy of SC hydroxycobalamin to establish validated dosing guidelines and offer an alternative chronic treatment for these patients. ■

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