Case Report

Dilated Cardimiopathy as Initial Presentation of Mucopolysacaridosis in Infant

Cardimiopatia Dilatada em Lactente como Apresentação Inicial de Mucopolissacaridose

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Introduction

Mucopolysaccharidoses are rare genetic diseases caused by decreased lysosomal enzymes that act in the catabolism of glycosaminoglycans, connective tissue extracellular matrix polymers. Glycosaminoglycans progressively accumulate in the airways, mucous membranes, lungs, bones, joints, heart, liver, eyes, ears, and central and peripheral nervous systems. The multiple affected organs characterize its multisystemic presentation with a wide spectrum of severity and clinical presentations. The most severe phenotype is Hurler syndrome (type I mucopolysaccharidosis), with an incidence of 0.61–1.30 per 100,000 live births.[1]

The heart is affected in more than 50% of mucopolysaccharidosis cases,[2] with both valvular and myocardial involvement in addition to a possible association with systemic arterial hypertension (SAH).[3]

Specific treatment consists of enzyme replacement therapy (ERT), which, along with hematopoietic stem cell transplantation (HSCT), prolong the child's life and improves their symptoms, especially if started early.[4–6]

Case report

Our patient was a male infant with a birthweight of 3,360 g and no perinatal complications. At eight months of age, he developed sweating during feedings, vomiting, and irritability. He was evaluated in the emergency room, where a chest X-ray showed remarkable cardiomegaly (Figure 1B). The patient had a previous history of a neuro-psychomotor developmental delay, recurrent respiratory infections, upper respiratory obstruction, hydrocephalus requiring ventriculoperitoneal shunt implantation, and recurrent bilateral inguinal hernia. The parents were young and non-consanguineous, and the couple's first child was stillborn without an identified cause.

At nine months of age, the patient was evaluated in a tertiary pediatric cardiology service and was already using captopril. He had persistent heart failure (HF) signs and symptoms in addition to a weight-height deficit, weighing 8,880 g (Z-score: -2.44). A general examination showed several dysmorphisms such as infiltrated facies (Figure 1A), a high and narrow palate, gingival hypertrophy, a saddle nose, pectus carinatum, inguinal hernias, an umbilical hernia, an extensive Mongolian spot, a lumbar hump, bilateral diffuse corneal opacification, and a claw hand. A cardiovascular examination showed a regular heart rhythm without murmurs, a heart rate of 130 bpm, O_2 saturation of 98%, a systolic blood pressure of 120 mmHg (p: 99.93), a diastolic blood pressure of 60 mmHg (p: 99.74), a palpable liver at 5 cm from the right costal margin, and a non-palpable spleen.

Echocardiography (Figure 1C) showed a significantly increased left ventricle (LV) with a diastolic diameter of 42 mm (Z-score: 4.4) and a systolic diameter of 34 mm (Z-score: 5.6) in addition to diffuse hypocontractility with an LV ejection fraction (LVEF) of 39% and 42% by the Teichholz and Simpson's methods, respectively, and global longitudinal strain (GLS) of 13.7%. His right ventricular systolic function was slightly compromised, with a tricuspid annular plane systolic excursion of 10 mm (Z-score: -2.84) and lateral tricuspid annulus S' of 6.0 cm/s (Z-score: -3.60). The mitral and aortic valves had mild leaflet thickening without associated dysfunction.

The patient underwent pharmacological treatment for the HF and was referred for a genetic evaluation, which confirmed the diagnosis of type I mucopolysaccharidosis. His urine glycosaminoglycan level was 880 mcg/mg (reference range [RR], 133–274 mcg/mg). Glycosaminoglycan electrophoresis showed the presence of dermatan and heparan sulfate. Alpha-iduronidase (IDUA) levels of the plasma and leukocytes were reduced at 0.10 nmoL/h/mg protein (RR, 6.6–34 nmol/h/mg protein) and 0.11 nmol/h/mg protein (RR, 27–71 nmoL/h/mg protein), respectively. A molecular genetic analysis detected the W402X/W402X variant in both alleles of the *IDUA* gene. A radiographic evaluation showed dysostosis multiplex, ovoid vertebrae, paddle-shaped ribs, convergence of the proximal region of the metacarpals, a shallow acetabulum, and small ilia — signs compatible with the diagnosis of mucopolysaccharidosis.

Electrocardiography revealed sinus rhythm, a heart rate of 136 bpm, QRS complex axis at +60º, a PR interval of 80 ms, a corrected QT interval of 366 ms, T-wave inversions in D2 and D3, a deep Q wave at V6, and signs of LV overload.

ERT was instituted at 11 months of age with reduced liver volume, weight gain, improved general condition, reduced upper respiratory obstruction, and greater diet acceptance. At 12 months, HSCT was indicated, but the family refused to

Keywords

Mucopolysaccharidosis I; Child; Cardiomyopathy, Dilated.

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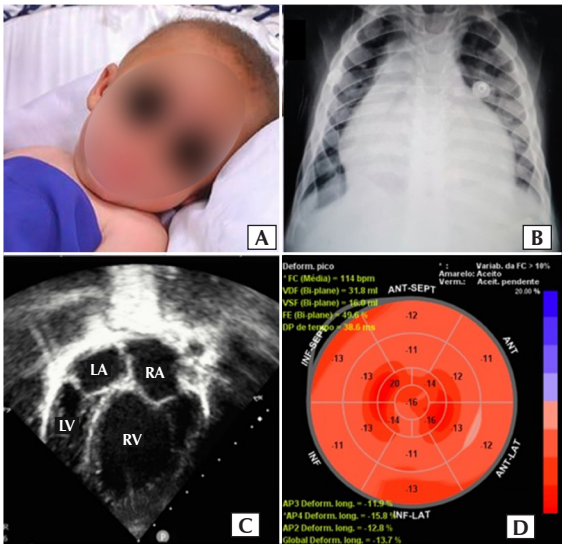

LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Figure 1 – *Infant with type 1 mucopolysaccharidosis and dilated cardiomyopathy. Infiltrated facies (A). Chest X-ray showing cardiomegaly and pulmonary congestion (B). Echocardiographic images showing enlarged left chambers (C) and global longitudinal strain (D).*

provide consent. At 16 months of age, the infant presented with an infectious respiratory intercurrence that resulted in acute decompensation of the treatment-refractory HF and culminated in death.

Discussion

Mucopolysaccharidosis is rare but associated with characteristic phenotypic findings that should arouse syndromic suspicion. A careful and detailed evaluation associated with knowledge of the disease presentation can lead to a suspected diagnosis that, once confirmed, is amenable to treatment that changes the natural course of the disease.[5,7]

The reported patient had phenotypic characteristics of mucopolysaccharidosis such as infiltrated facies, palate changes, gingival hypertrophy, saddle nose, pectus carinatum, Mongolian spots, a lumbar hump, restricted knee and elbow mobility, claw hands, corneal opacity, inguinal hernias, and an umbilical hernia.

The cardiovascular system involves glycosaminoglycan deposits in structures such as the valvular endocardium, subvalvular apparatus, myocardium, conduction system, and vessels, especially the coronary arteries.[3] This condition can cause conduction disorders, myocardial hypertrophy, valvular dysfunction, coronary heart disease, and sometimes SAH (Table 1).

The most common echocardiographic findings are mitral and aortic valve changes.[2] The leaflets are generally thickened, the mitral subvalvular apparatus involves shortened chordae tendineae, and the papillary muscles are thickened, possibly associated with valvular regurgitation or stenosis. Theodore *et al*. reported a case series that reiterated the findings of valvular changes in mucopolysaccharidosis.[9] Myocardial dysfunction, in turn, is uncommon, but types I, II, and VI are correlated with more severe cardiovascular involvement[3] and a worse prognosis. In the case reported here, the valvular changes were mild and lacked repercussion, but there was a significantly reduced LVEF and GLS.

The conduction system may present a broad spectrum abnormality ranging from frequent sinus tachycardia to severe arrhythmias with a risk of sudden death. In the case studied here, the electrocardiographic changes were attributed to chamber dilation.

Even with pronounced glycosaminoglycan deposits in the myocardium, ventricular function is impaired in only a minority of patients. Davison *et al*. evaluated 29 children with type I mucopolysaccharidosis, reporting that five of them had dilated cardiomyopathy at the initial presentation. Similarly, Wiseman *et al*.[4] studied a group of 44 children with type I mucopolysaccharidosis diagnosed in the first four months of life; of them, only six presented with severe dilated cardiomyopathy, with an LVEF of 15–40%. Hirth *et al*.[5] also corroborated the rare onset of HF as the main mucopolysaccharidosis presentation and detected several mutations in their patients, including *W402X/W402X*, which was identified in the reported case. The ventricular function of all patients recovered after ERT or HSCT. However, the present case was diagnosed late and the patient's ventricular function was unable to recover prior to death due to infectious complications.

The presence of myocardial dysfunction of undefined etiology associated with phenotypic characteristics of mucopolysaccharidosis in infants should raise early diagnostic suspicion of the disease. The introduction of specific treatments and the management of several associated morbidities greatly impacts patient quality of life.

Authors' contributions

Research creation and design: Romão LAT; Data acquisition: Romão LAT, Arantes RR; Manuscript writing:

Table 1 - Clinical, echocardiographic, and electrocardiographic findings in infants diagnosed with mucopolysaccharidosis.

	More frequent	Less frequent
personal history	- Recurrent respiratory infections - Weight-height deficit - Delayed neuro-psychomotor development	- Syncope and pre-syncope - Tiredness during feedings - Intolerance to physical exercise
Clinical characteristics	- Coarse facies - Macroglossia - Bone anomalies - thoracolumbar kyphosis, joint restriction, camptodactyly (claw hands), carpal tunnel syndrome - Inguinal and/or umbilical hernias - Corneal opacities	- Retinitis - Blindness - Extensive Mongolian spots
Cardiovascular physical examination	- Normal or functional heart murmurs	- Arterial hypertension - Heart failure signs (tachypnea, tachycardia, hepatomegaly, edema) - Heart murmurs related to mitral and/or aortic valve regurgitation and/or stenosis
Electrocardiography	- Atrioventricular blocks - Sinus tachycardia	- Signs of myocardial ischemia (inverted T-wave, ST segment change) - Extrasystoles - Ventricular tachycardia
Echocardiography	- Thickened, dysmorphic, and/or poorly mobile valve leaflets - Valve regurgitation (mitral and aortic) - Infiltrated myocardium aspect - Fibrotic and dense endocardium	- Valve stenosis (mitral and aortic) - Calcification of the subvalvular apparatus - Shortened chordae - Thick papillary muscles - Ventricular dysfunctions - Cardiac chamber dilation - Left ventricular apical aneurysm - Ventricular wall dyskinesia - Endocardial fibroelastosis - Ascending aorta dilation - Increased aorta thickness - Coronary dilation and thickening - Coarctation of the aorta

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Conflict of interest

The authors have declared that they have no conflict of interest.

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