Echocardiography in Mucopolysaccharidosis Iva: Evaluation of Enzyme Replacement Therapy

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Introduction

Mucopolysaccharidosis IVA (MPS IVA) or Morquio A syndrome is a rare autosomal recessive disease caused by a lysosomal enzyme deficiency that leads to the progressive accumulation of glycosaminoglycans (GAG) in many organs and systems, including the cardiovascular system.[1-3]

Signs and symptoms of cardiac involvement in MPS are generally subtle, which leads to an underestimation of the actual incidence of cardiovascular disease.[1]

Enzyme replacement therapy(ERT) with elosulfase alfa is a specific treatment for MPS IVA. It was only approved by the FDA (United States) and EMEA (Europe) in 2014, and later by Anvisa (Brazil), which explains the limited knowledge of its effect on the development of cardiovascular impairment. The frequency of MPS IVA in Paraíba is one of the highest ones in Brazil. Hospital Universitário da Universidade Federal de Campina Grande is a reference center in the state of Paraíba for diagnosis and treatment of mucopolysaccharidosis. Echocardiography was applied for the purposes of characterizing existing cardiovascular injuries and how they evolve in patients with MPS IVA.

Considering that the mortality of patients with MPS IVA occurs by cardiorespiratory disease, this study aims to contribute to a better understanding of cardiac involvement and the potential benefit of ERT.

Case Report

Prospective study involving 10 patients, 7/10 males and 3/10 females, aged 17 to 37, with clinical and laboratory diagnosis of MPS IVA. A single echocardiography specialist evaluated patients before ERT and after six months of weekly intravenous infusion of the enzyme elosulfase alfa at the recommended dose of 2 mg/kg/week. The sample was analyzed by sex and age group younger or equal to 30 years and older than 30 years.

The data were tabulated and analyzed using SPSS (version 19). Mean, standard deviation and median were the descriptive statistics used. Considering the small sample size, the Wilcoxon test was adopted to compare data before and after treatment. To determine statistical significance, $p < 0.05$ was considered.

The results of baseline echocardiography and after six months of ERT are show in Tables 1 and 2.

Discussion

This study was intended to observe baseline cardiovascular impairment in 10 patients with MPS IVA, aged 17-37 years and their evolution after six months of ERT, motivated by the lack of literature data on the topic.

Cardiovascular lesions were found in 90% of the patients in this study, confirming the findings of other studies.[1,4,5]

Valvular disease (regurgitation or thickening) was identified in 6/10 patients, in agreement with the literature.[5] Studies show that the most affected cardiac valves are the left valves. The mitral valve is more affected than the aortic valve.[6] However, the most affected valves were the tricuspid, aortic and mitral valve with equal impairment of each valve (30%). Regurgitation and thickening present 50% frequency as described in previous studies[6,7] (Figure 1).

In 5/10 patients, mild diastolic dysfunction was identified, which was also found by Gross et al.[8] in 24% of their patients; however, none of them presented systolic dysfunction, unlike the study by Mohan et al.,[9] which found moderate to severe systolic dysfunction in 13% of patients. Considering that diastolic dysfunction generally precedes systolic dysfunction and myocardial GAG deposits potentially affect ventricular filling.[7] It was not surprising to find 50% of patients with mild diastolic dysfunction, despite the absence of systolic dysfunction.

After six months of ERT, an improvement in tricuspid regurgitation was observed. However, the presence of tricuspid regurgitation was initially mild and minimal regurgitation can be physiological in most cases. When better investigated, the mild form of tricuspid valve regurgitation can be found in 80% to 90% of the normal population, as well as mitral valve regurgitation (70% - 80%) and pulmonary valve failure (70% - 80%). However, aortic regurgitation, even minimal, is found in less than 5% of the population younger than 40 and is usually pathological. This finding was observed in 1/10 patients both before and after six months of ERT. The improvement in the ejection fraction (EF) was

Keywords

Echocardiography; Mucopolysacharidoses/therapy; Enzyme Replacement Therapy.

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Table 1 – Description of the echocardiographic findings before and after ERT

Patient	SEX	Age	BASELINE ECHO	ECHO AFTER ERT
1	M	29 years and 10 months	Mild aortic regurgitation. Mild aortic thickening.	**Mild aortic regurgitation** **Mild aortic thickening.** Minimal tricuspid regurgitation. Impaired relaxation LV diastolic dysfunction.
2	M	30 years and 10 months	Impaired relaxation LV diastolic dysfunction **Mild hypertrophy of the LV walls.**	Impaired relaxation LV diastolic dysfunction
3	M	17 years	Impaired relaxation LV diastolic dysfunction	Impaired relaxation LV diastolic dysfunction
4	M	21 years and 11 months	Left ventricular cavity with reduced diameters. Impaired relaxation LV diastolic dysfunction. Mild tricuspid regurgitation. Mild mitral thickening. **PASP estimated at 35 mmHg.**	Ventricular cavity of reduced diameters. Impaired relaxation LV diastolic dysfunction. **IMPROVED tricuspid regurgitation.** Mild mitral thickening. **Mild aortic thickening.**
5	M	20 years and 5 months	Mild mitral thickening. Minimal tricuspid regurgitation **Minimal mitral regurgitation.**	Mild mitral thickening. Minimal tricuspid regurgitation.
6	M	36 years and 11 months	Impaired relaxation LV diastolic dysfunction.	Impaired relaxation LV diastolic dysfunction. **Minimal tricuspid regurgitation**
7	M	35 years and 8 months	Mild aortic thickening.	Normal
8	F	32 years and 2 months	No impairment	No impairment
9	F	17 years	Minimal tricuspid regurgitation.	Sharp interatrial septal movement, yet normal on examination. Minimal tricuspid regurgitation
10	F	29 years and 8 months	Mild aortic thickening. Mitral prolapse with minimal regurgitation. **Impaired relaxation** **LV diastolic dysfunction.** **Dilated abdominal aorta** **with spontaneous contrast**	Mild aortic thickening. Minimal mitral valve prolapse. **Mild mitral thickening.**

Source: Research data, 2016.

observed in 1/10 patients, rising from 58% to 75% after ERT. In 1/10 patient, there was a decrease in EF from 74% to 58% after six months of ERT, but still within the normal range. The fact that the measures have an intraobserver variation should be considered.

After ERT, there was an increase in the E/E' ratio, but still within the normal range, and left atrial enlargement, suggesting absence of change in the natural history of MPS IVA, which is a progressive disease. The presence of new findings after ERT, such as mild diastolic dysfunction in 1/10 patient — patient 1 also confirms the progression of cardiac involvement. Minimal tricuspid regurgitation was considered physiological. There are no studies specifying for how long ERT has positive effects on the evolution of these lesions. There is only reference to a decrease in interventricular septal hypertrophy that might have better results when ERT is started at early ages, before the consolidation of irreversible lesions.[10] The age for the onset of ERT in the sample of this study, 17 at least, may explain the unfavorable findings after therapy.

After six months of ERT, statistically significant left atrial enlargement was also observed, but only in males. This finding confirms the progressive course of the disease or insufficient ERT time for observing positive results. There is no analysis in the literature of the effect of ERT according to gender. Our results may have been influenced by the fact that the sample contains 7 males and only 3 females.

No statistical differences in the echocardiographic findings were found between groups divided into younger and older than 30, perhaps due to the lack of patients in the prepubescent age group, theoretically more responsive to treatment, as shown in the study by Lin et al.[10]

Baseline echocardiographic analysis and after six months of ERT suggests that this has not changed the natural history of progressive heart disease of MPS IVA. However, the number of patients, their age and ERT time indicate the need for further studies, in addition to the extension of this study, so ERT results on the evolution of cardiac lesions in patients with MPS IVA can be better evaluated.

Tabla 2 – Comparación de la media. desviación estándar y mediana de los parámetros numéricos ecocardiográficos antes y después del tratamiento

	Before			After			p
	Mean	Standard deviation	Median	Mean	Standard deviation	Median	(Wilcoxon)
SC (m²)	0.75	0.15	0.74	0.77	0.09	0.75	0.59
Aortic root diameter (mm)	26.00	4.16	24.50	26.40	3.92	25.00	0.33
Left atrium (mm)	24.90	2.84	***24.00***	26.10	2.37	***25.50***	**0.01**
Diastolic internal left ventricular diameter (mm)	36.50	5.38	37.00	36.10	5.23	36.50	0.57
Systolic internal left ventricular diameter (mm)	22.80	4.29	23.50	21.80	4.21	22.00	0.23
Diastolic septal thickness (mm)	6.50	0.52	6.50	6.20	0.63	6.00	0.18
Diastolic left ventricular posterior wall thickness (mm)	6.40	0.51	6.00	6.20	0.63	6.00	0.32
Ejection fraction	68.40	8.01	68.50	71.20	6.32	72.00	0.41
Left ventricular mass (g)	77.40	23.11	79.00	72.30	23.19	68.50	0.14
Body Mass/Surface Ratio (g/m²)	104.25	30.06	101.74	93.09	27.13	90.03	0.11
Cavity shortening percentage. (%)	38.00	6.56	38.00	40.10	4.90	40.50	0.44
Septum/left ventricular posterior wall ratio	1.01	0.05	1.00	1.00	0.08	1.00	0.99
End diastolic volume (mL)	57.80	18.87	58.00	56.30	17.48	56.00	0.72
Systolic volume (mL)	39.40	13.21	40.00	39.50	11.50	38.00	0.63
Volume/mass ratio (mL/g)	0.64	0.10	0.64	0.67	0.11	0.70	0.34
End systolic volume (mL)	18.60	7.02	19.00	16.80	7.25	16.00	0.23
Relative LV wall thickness	0.35	0.05	0.34	0.34	0.06	0.33	0.76
E/A ratio	0.98	0.32	0.82	1.01	0.36	0.92	0.48
E/E' ratio	9.30	4.67	***8.93***	12.70	6.77	***9.78***	**0.05**

Source: Research data. 2016.

Authors' Contributions

Research creation and design: Barbosa ICQ, Paula IS, Medeiros PFV, Eufrazino CSS; Data acquisition: Barbosa ICQ, Paula IS, Medeiros PFV; Data analysis and interpretation: Barbosa ICQ, Paula IS, Melo ICP, Nóbrega SMB, Medeiros PFV; Statistical analysis: Barbosa ICQ, Paula IS, Melo ICP, Nóbrega SMB, Medeiros PFV, Eufrazino CSS; Manuscript drafting: Barbosa ICQ, Paula IS, Melo ICP, Medeiros PFV; Critical revision of the manuscript as for important intellectual content: Barbosa ICQ, Paula IS, Melo ICP, Nóbrega SMB, Medeiros PFV.

Potential Conflicts of Interest

There are no relevant conflicts of interest.

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Academic Association

This study is not associated with any graduate programs.

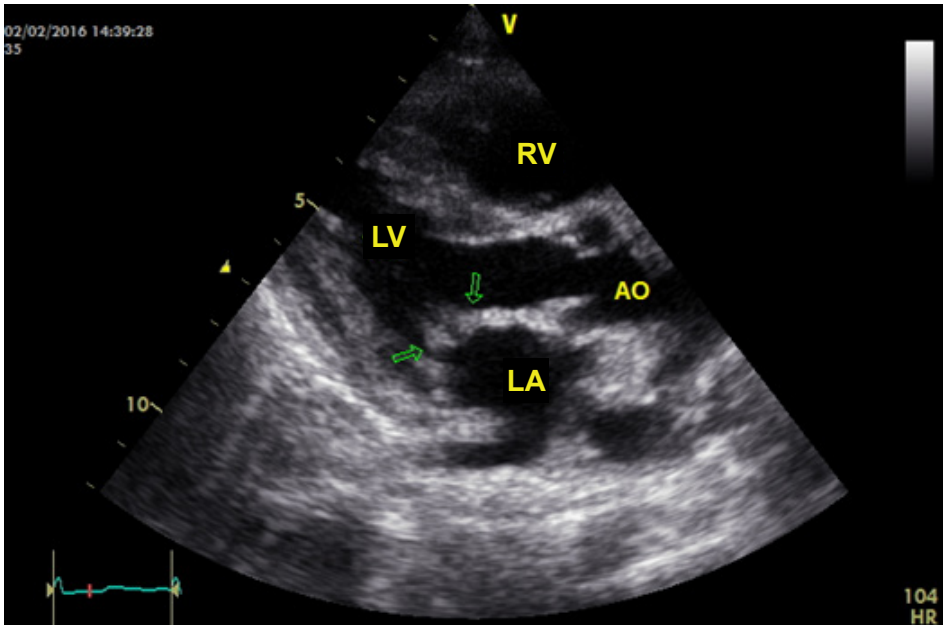

Figure 1 – *Mitral valve thickening in longitudinal parasternal section after six months of enzyme replacement therapy. RV: right ventricle; LV: left ventricle; AO: aorta; LA: left atrium..*

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