

## Ecocardiographic Findings in Patients with Mucopolissacaridose II And VI: Report of Two Cases

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### Introduction

Mucopolysaccharidoses (MPS) are disorders of lysosomal storage characterized by functional deficiency caused by the genetic mutation of one of the lysosomal enzymes that act in the catabolism of Glycosaminoglycans (GAG), previously known as mucopolysaccharides.<sup>1</sup> It is a hereditary disease of an autosomal recessive form, or X-linked recessive, and with different phenotypes.<sup>2</sup> Cardiovascular involvement is common, occurring more frequently in types I, II and VI.<sup>1,3,4</sup> Two-dimensional transthoracic echocardiography is the method of choice for diagnosis and follow-up when there is cardiac involvement. It is extremely relevant for the echocardiographers to be familiar with this entity. We report the case of two patients diagnosed with MPS (types II and VI), with valvular heart impairment.

### Case report

#### Case 1

Male patient, 13 years old, with MPS type II (iduronate-sulfatase deficiency) diagnosed at 6 years of age. On physical examination, he presented a coarse face, light thoracic kyphosis, clawed hands especially caused by impairment of the distal interphalangeal joints and pes cavus. Normal heart sounds. Echocardiogram shows valve impairment, thickening of the aortic, mitral and tricuspid valves, and prolapse of the mitral valve cusps with mild to moderate regurgitation (Figures 1 and 2; Video 1). The patient is under Enzymatic Replacement Therapy (ERT) with elaprase, showing good evolution.

#### Case 2

Female patient, 14 years old, with MPS type VI (arylsulfatase B deficiency) diagnosed at 4 years of age. On physical examination, coarse face, continually hyper-extended head, noisy breathing, joint stiffness. Heart sounds with regular rhythm, normophonic sounds and grade III/VI systolic murmur in mitral focus irradiating to the left axillary region.

### Keywords

Mucopolysaccharidosis II; Mucopolysaccharidosis IV.

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Polysomnography compatible with severe obstructive sleep apnea. Electrocardiogram with biatrial overload. Echocardiogram with mild left ventricular (LV) concentric hypertrophy and preserved systolic function (77% ejection fraction), mitral valve thickening with significant stenosis and moderate regurgitation (valve area of 0.9 cm<sup>2</sup>); moderate biatrial increase (Figures 3 and 4; Videos 2 to 4); right ventricular (RV) dilatation with preserved systolic function; mild tricuspid regurgitation with high (60 mmHg) pulmonary artery systolic pressure (PSAP) and mild pericardial effusion. Patient under ERT with Naglazyme and multidisciplinary follow-up.

### Discussion

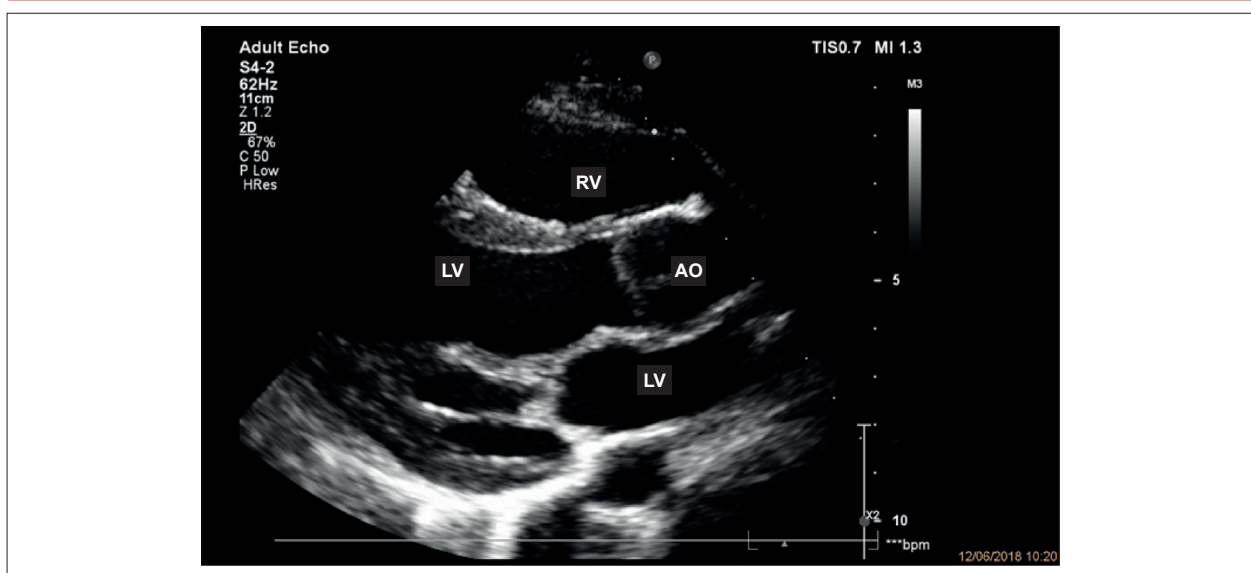
MPS were clinically described by Hunter in 1917<sup>5</sup> and were considered a group of lysosomal storage disorders resulting from lack of enzymes in GAG degradation. These accumulate in the cell lysosomes, leading to progressive tissue and organ dysfunction, which varies with the specific GAG deposited and enzymatic mutation. It is known that deficiency of 11 different enzymes causes seven MPS phenotypes that are hereditary, autosomal recessive (MPS I, III, IV, VI, VII and IX) or X-linked recessive (MPS II).<sup>1,2</sup>

Cardiac involvement was reported in all MPS syndromes, consisting of a common and early characteristic, particularly for those with MPS I, II and VI, which are the syndromes in which the dermatan sulfate catabolism is impaired.<sup>1</sup> Heart valve thickening, valvular dysfunctions and ventricular hypertrophies are commonly present; conduction disorders, coronary artery disorders and other vascular complications may also occur.<sup>1,6</sup> Cardiac signs and symptoms are underestimated because the disease affects other organs.<sup>1,4</sup>

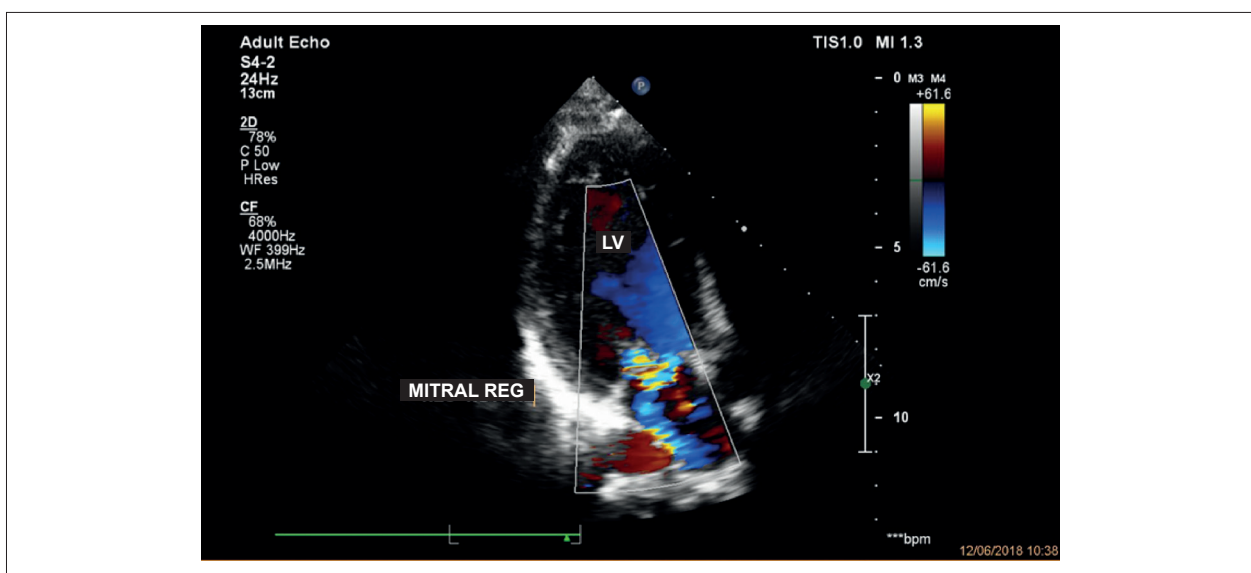
MPS II (or Hunter syndrome) has X-linked inheritance and is caused by the deficient activity of the enzyme iduronate-sulfatase (IDS), with consequent increase in the urinary concentration of GAG dermatan sulfate and heparan sulfate. The incidence of MPS II is estimated at 1:68,000 to 1:320,000 live births. In Brazil, MPS II seems to be one of the most frequent types.<sup>5,7</sup>

It is clinically characterized by coarse face, skeletal disorders, short stature, joint contractures, delayed neuropsychomotor development, recurrent infections of upper and lower airways, deafness and cardiopathy. MPS II is associated with major clinical heterogeneity and is usually classified according to the presence of developmental delays and/or mental retardation, in neuropathic or non-neuropathic forms.<sup>5,7</sup>

MPS VI (or Maroteaux-Lamy syndrome) is a rare autosomal recessive transcript with an incidence of 0.05 to 0.43 in 100,000 live births. It is caused by the deficient activity of



**Figure 1** – Parasternal longitudinal view evidencing mitral valve thickening and discrete aortic valve prolapse. RV: right ventricle; LV: left ventricle; AO: aorta; LV — left ventricle.



**Figure 2** – Longitudinal apical view evidencing mitral valve insufficiency with eccentric jet graduated as mild to moderate.

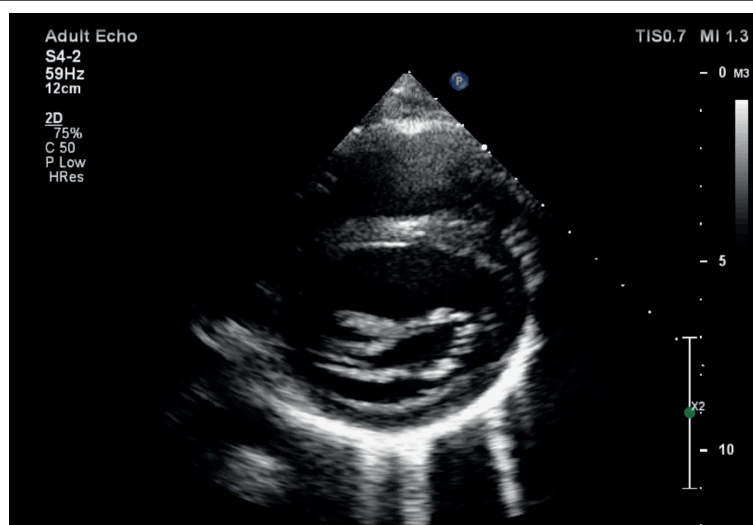
arylsulfatase B (N-acetylgalactosamine-4-sulfatase) resulting in intra- and extracellular accumulation of GAG, especially dermatan sulfate.<sup>3</sup>

The clinical manifestations of MPS VI and its severity are variable, but usually include facial dysmorphism, short stature, hepatosplenomegaly, multiple dysostosis, joint stiffness, corneal turbidity and craniocervical stenosis. However, irrespective of the rate of progression, all patients develop multiple debilitating and often life-threatening conditions. There is a small sample of studies and case reports available describing the cardiac conditions of this disease, but nearly all

of them describe substantial and progressive cardiovascular impairment, valvular impairment and ventricular hypertrophy.<sup>3</sup> Cardiorespiratory disease tends to progress with age and is the most common death cause.<sup>3</sup>

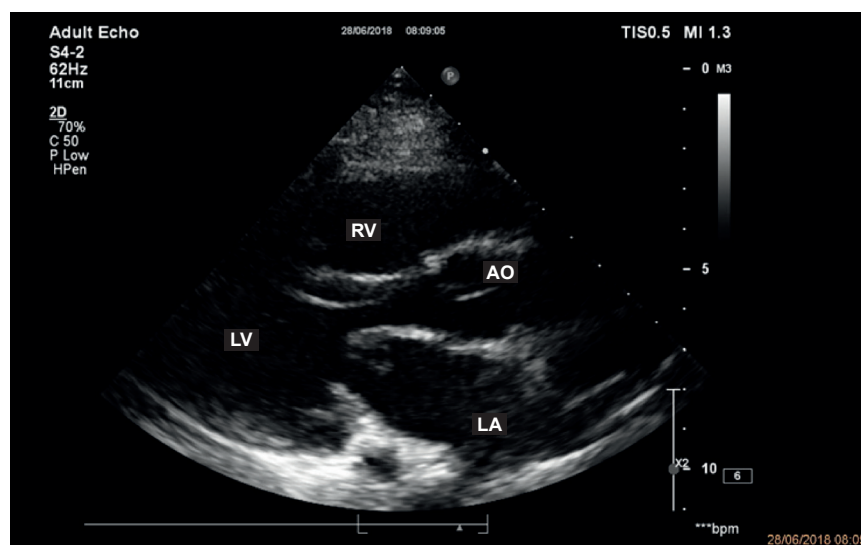
Regardless of the phenotype, all forms of MPS are associated with early morbidity and mortality.

Regarding diagnosis, transthoracic two-dimensional echocardiography is the imaging method of choice to evaluate anatomy and cardiac function in patients with MPS. Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) are advanced techniques, but not routinely used.<sup>1</sup>



**Video 1** – Parasternal short axis view showing mitral valve thickening.

Watch the video here: [http://departamentos.cardiol.br/dic/publicacoes/revistadic/2019/v32\\_2/video\\_v32\\_2\\_achados\\_ingles.asp](http://departamentos.cardiol.br/dic/publicacoes/revistadic/2019/v32_2/video_v32_2_achados_ingles.asp)



**Figure 3** – Parasternal longitudinal view evidencing mitral valve with thickening mainly at the tip of the cusps. RV: right ventricle; LV: left ventricle; AO: aorta; LA: left atrium.

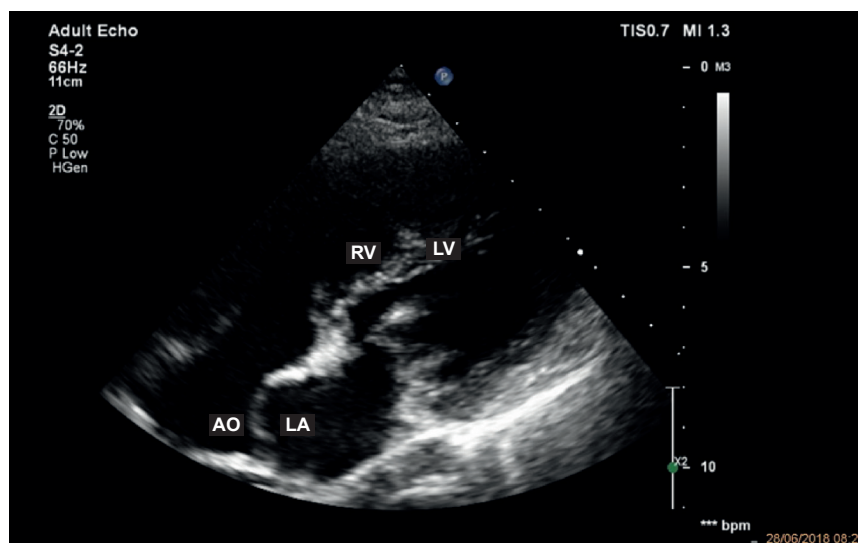
Progressive cardiac valve disease is the most prominent and uniform cardiac condition (60 and 90%) of patients with MPS. Cardiac valve thickening with associated dysfunction has been reported in more than 80% of patients with MPS I (including slowly evolving phenotypes), 57% of patients with MPS II, and in all individuals with MPS VI, except for the more slowly progressive ones.<sup>1</sup>

Most studies have reported that valve regurgitation is more common than stenosis, and the mitral valve is more commonly affected than the aortic valve. In general, the mitral and aortic valves are more severely affected than the

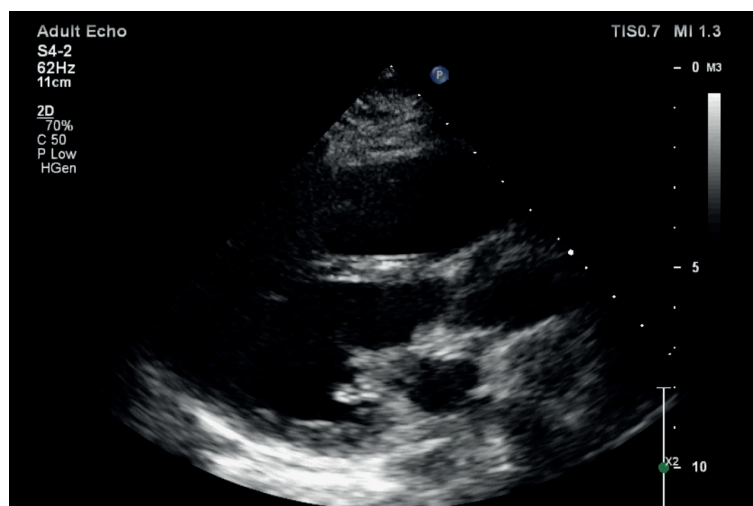
others. The mitral valve cusps are markedly thickened and similar to cartilage, with particularly thick edges. The subvalvular mitral valve apparatus may have shortened chordae tendineae and thick papillary muscles, resulting in dysmorphic and poorly movable leaflets.<sup>1</sup>

Moreover, concomitantly with valve impairment, Pulmonary Hypertension (HP) is a major cause of morbidity and mortality in these patients, especially in childhood.<sup>6,8</sup> Therefore, it is necessary to pay attention to its detection and early treatment in this population.<sup>6</sup>

Factors implicated in the genesis of pulmonary



**Figure 4** – 4-chamber apical window modified, evidencing significant mitral impairment with subvalvular thickening and impairment, as well as interatrial septum deviation to the right. RV: right ventricle; LV: left ventricle; AO: aorta; LA: left atrium.



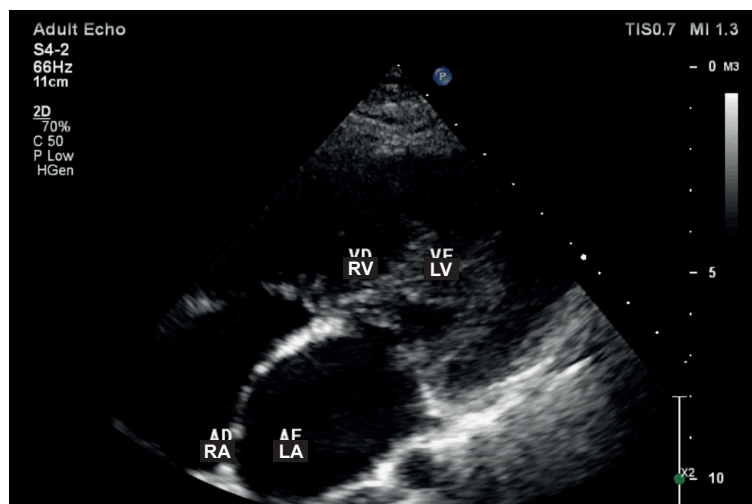
**Video 2** – Parasternal longitudinal window showing severe mitral valve thickening with restricted opening.  
 Watch the video here: [http://departamentos.cardiol.br/dic/publicacoes/revistadic/2019/v32\\_2/video\\_v32\\_2\\_achados\\_ingles.asp](http://departamentos.cardiol.br/dic/publicacoes/revistadic/2019/v32_2/video_v32_2_achados_ingles.asp)

hypertension are frequent in patients with MPS: left heart valve lesions, GAG deposits in the pulmonary and systemic vascular beds and lymphatic tissue, thoracic deformities, frequent upper and lower airway infections and obstructive apnea.<sup>6</sup>

Accumulation of GAG in the lymphatic tissue provides gum, tonsils and adenoid thickening, thereby causing obstruction of the airways. This progressive obstruction may result in sleep apnea, leading to severe hypoxemia. There is also a group of central apnea-prone

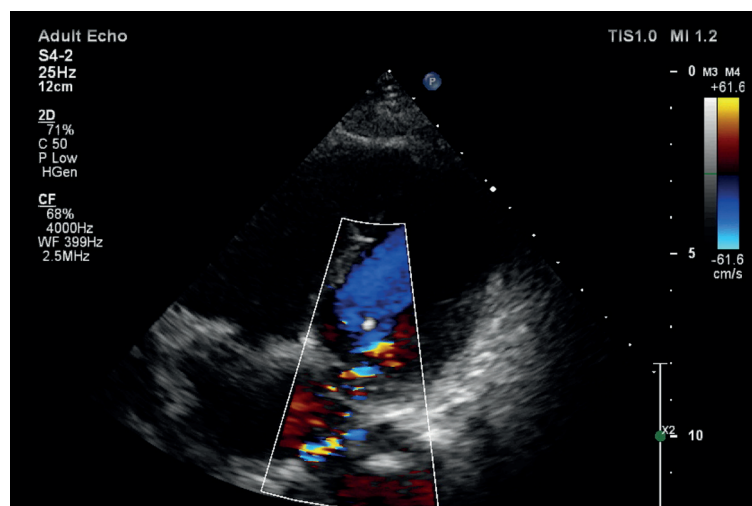
patients due to high medullary compression caused by atlantoaxial instability and odontoid dysplasia. Chronic hypoxemia due to airway obstruction and pulmonary disease may lead to pulmonary hypertension, which, in turn, may exacerbate right heart failure caused by the mitral disease.<sup>8</sup>

Treatment of MPS is done with enzyme replacement, which can be used in MPS I, II, IV and VI.<sup>4</sup> This therapy consists in infusion of recombinant enzyme to replace the absent or deficient activity of the involved enzyme.<sup>1,3</sup>



**Video 3** – 4-chamber apical window modified showing mitral valve thickening.

Watch the video here: [http://departamentos.cardiol.br/dic/publicacoes/revistadic/2019/v32\\_2/video\\_v32\\_2\\_achados\\_ingles.asp](http://departamentos.cardiol.br/dic/publicacoes/revistadic/2019/v32_2/video_v32_2_achados_ingles.asp)



**Video 4** – Apical 4-chamber view modified showing double mitral lesion.

Watch the video here: [http://departamentos.cardiol.br/dic/publicacoes/revistadic/2019/v32\\_2/video\\_v32\\_2\\_achados\\_ingles.asp](http://departamentos.cardiol.br/dic/publicacoes/revistadic/2019/v32_2/video_v32_2_achados_ingles.asp)

Transplantation of hematopoietic stem cells can also be performed. Both therapies may change the overall progression of the disease with regression of ventricular hypertrophy and maintenance of ventricular function. Cardiac valve disease does not generally respond or, at best, stabilizes, although ERT in the first months of life may prevent valvular involvement or serious cardiac damage, which emphasizes the importance of early diagnosis and treatment in MPS.<sup>1,9,10</sup>

## Authors' contributions

Acquisition of data: Carneiro SS, Vescovi EG, Costa PV; Analysis and interpretation of the data: Carneiro SS, Costa PV; Writing the manuscript: Carneiro SS; Critical revision of the manuscript for important intellectual content: Carneiro SS, Vescovi EG, Costa PV.

## Potential Conflicts of Interest

There are no relevant conflicts of interest.



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