ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.

CARDIOLOGY JOURNAL

ISSN: 1897-5593

e-ISSN: 1898-018X

Heart valve disease in Hurler-Scheie syndrome

Authors: María del Carmen García del Rey, Javier Castrodeza, Ángel Pinto, Maria Ángeles Espinosa Castro, Cecilia Muñoz Delgado, Francisco Fernández-Avilés

DOI: 10.5603/CJ.a2022.0066

Article type: Research Letter

Submitted: 2022-04-13

Accepted: 2022-05-04

Published online: 2022-07-08

RESEARCH LETTER

Heart valve disease in Hurler-Scheie syndrome

María del Carmen García del Rey[1, 3], Javier Castrodeza[1, 3], Ángel Pinto[2, 3], María Ángeles Espinosa Castro[1, 3], Cecilia Muñoz Delgado[4], Francisco Fernández-Avilés[1, 3]

[1]Cardiology Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain

[2]Cardiac Surgery Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain

[3]Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain

[4]Internal Medicine Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Address for correspondence: Javier Castrodeza, MD, PhD, Cardiology Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain, tel: (+ 34) 915868290, e-mail: jcastrodeza5@gmail.com

Mucopolysaccharidosis (MPS) syndromes are classified by six subtypes [1]. Mucopolysaccharidosis type I (MPS I) is an autosomal recessive hereditary disease, characterized by the accumulation of glycosaminoglycans (GAGs) in any tissue as a consequence of a decrease in the enzymatic activity of alpha-L-iduronidase [2]. Traditionally, MPS I has been classified into three subtypes based on the severity of the disease and the age of onset: Hurler syndrome, Hurler-Scheie syndrome and Scheie syndrome; but a recent classification has been shortened to two subgroups: severe MPS I or Hurler syndrome, and attenuated MPS I or Hurler-Scheie syndrome [3]. The former has an earlier onset of symptoms, while in the attenuated form the clinical presentation occurs in patients between 3 and 10 years of age and the neurological structures are intact. The life expectancy is short, especially in the

severe form with a mean survival between 6 and 7 years, while in the attenuated form, patients can reach adulthood if they are treated with enzyme replacement therapy [4].

Cardiac involvement is common in MPS I [4, 5]. It is produced by the progressive infiltration of glycosaminoglycans not only in the valves, but also in the myocardium, coronary arteries, and conduction system [4]. Approximately, half of patients with severe MPS I die from cardiac causes, congestive heart failure, or sudden death [4]. The most affected structure is the mitral valve followed by the aortic valve. It mainly affects the mitral chords resulting in decreased leaflet mobility [5, 6]. In this regard, a transoesophageal echocardiogram usually shows a myxomatous mitral valve with leaflet restriction, resulting in a double mitral valve lesion, both mitral stenosis and insufficiency as seen in Figure 1A, B (**Suppl. Video 1 and 2**). Consequently, surgical repair is not commonly feasible and mitral valve replacement is the usual and most durable approach [5]. Usually, the left atrium is not dilated, as well as the sinus aorta, which make the surgical approach more challenging for the cardiac surgeon [7]. Furthermore, calcium deposits on the mitral annulus are common, and this fact can interfere with prosthesis sutures, sometimes requiring an annular reinforcement with a pericardial patch [7, 8]. Also, very shortened and thickened chords can be seen during surgery, accompanied by hypertrophic papillary muscles as seen in Figure 1C (**Suppl. Video 3**). All these features make it a very challenging scenario to propose mitral valve repair, leading to valve replacement in most cases.

As these patients have a small body size, small valves are required (generally the mean mitral size of the prostheses is 24 ± 2.2 mm, and aortic ones are19 ± 0.5 mm) [8]. Arrhythmias and conduction disorders are also common, especially in MPS II, III and VI [5].

Regarding respiratory involvement, patients can present with a restrictive respiratory pattern. The trachea and bronchi are often thickened and infiltrated by GAGs and tracheomalacia can be present [4]. A chest computed tomography is advisable to rule out tracheomalacia (Fig. 1D) in order to ensure the absence of difficult airway management.

A specific phenotype is usually present consisting in multiple dysostosis, upper and lower limb joint arthrogryposis, a sunken nasal bridge, corneal dystrophy, craniofacial abnormalities, short neck, prominent adenoids and tonsils, prominent macroglossia, glottis, and epiglottis [4]. As a result, patients usually develop obstructive sleep apnoea-hypopnea syndrome, recurrent upper airway infections, and recurrent rhinorrhea [4].

For all these reasons and due to the risk of spinal cord compression and atlas and axis vertebrae instability, anaesthetic induction and intubation are high-risk procedures [9].

The particular phenotypic feature can be a guide to establish a diagnostic suspicion. Some laboratory diagnostic methods such as the detection of heparan sulphate in urine testing can suggest the diagnosis and confirmation comes with a genetic test. There are known mutations associated with MPS, some of them are responsible for severe forms as pVal620Phe and p.Trp626Arg, while pArg619Gly and Ser633Leu are seen in attenuated forms. Nevertheless, if a histopathological analysis of the valve tissue is performed in cases of valve replacement, a marked GAG accumulation in the macrophage cytoplasm and valve stroma can be detected [10].

The course of the disease is chronic and progressive. There are two treatment options: bone marrow transplantation and enzyme replacement therapy.

Bone marrow transplantation is more effective at a younger age, however valvular involvement is usually resistant to it and often persists [4, 6]. Although the success of this therapy has increased during the recent years, the mortality rate is still quite high [9].

Enzyme replacement therapy with RL Aldurazyme® (laronidase) was approved in 2003 for exclusive use in MPS I and has emerged as a promising therapy [3]. Early treatment helps to stabilize lung disease, and slows down the tissue infiltration [3]. With regard to the heart involvement, it may decrease ventricular hypertrophy, but valve infiltration usually progresses despite treatment [3]. There is no identified interaction between the replacement therapy and vitamin K antagonist. Therefore, the combination of them can be done in patients with mechanical valve prostheses.

As a conclusion, valvular replacement in patients with MPS I remains a challenging scenario due to anatomical features and the multiorgan involvement of the disease, requiring a multidisciplinary coordination to achieve an optimal postoperative outcome. Enzyme replacement therapy slows down the tissue infiltration with a marginal effect on the valves. The mitral and the aortic valve are the most affected, requiring a valve replacement after the severity is established, oftentimes by a mechanical prosthesis due to the patients' young age.

Conflict of interest: None declared

References

1. Brazier A, Hasan R, Jenkins P, et al. Urgent resection of a giant left atrial appendage aneurysm and mitral valve replacement in a complex case of Hurler-Scheie syndrome. BMJ Case Rep. 2015; 2015, doi: 10.1136/bcr-2015-211551, indexed in Pubmed: 26546621.

2. Fischer TA, Lehr HA, Nixdorff U, et al. Combined aortic and mitral stenosis in mucopolysaccharidosis type I-S (Ullrich-Scheie syndrome). Heart. 1999; 81(1): 97–99, doi: 10.1136/hrt.81.1.97.

3. Pérez-López J, Morales-Conejo M, López-Rodríguez M, et al. Efficacy of laronidase therapy in patients with mucopolysaccharidosis type I who initiated enzyme replacement therapy in adult age. A systematic review and meta-analysis. Mol Genet Metab. 2017; 121(2): 138–149, doi: 10.1016/j.ymgme.2017.04.004, indexed in Pubmed: 28410878.

4. Martins AM, Dualibi AP, Norato D, et al. Guidelines for the management of mucopolysaccharidosis type I. J Pediatr. 2009; 155(4 Suppl): S32–S46, doi: 10.1016/j.jpeds.2009.07.005, indexed in Pubmed: 19765409.

5. Encarnacion CO, Hang D, Earing M, et al. Mucopolysaccharidoses causing valvular heart disease: report and review of surgical management. World J Pediatr Congenit Heart Surg. 2020; 11(4): NP22–NP24, doi: 10.1177/2150135117690105, indexed in Pubmed: 28421916.

6. Rocha RV, Alvarez RJ, Bermudez CA. Valve surgery in a mucopolysaccharidosis type I patient: early prosthetic valve endocarditis. Eur J Cardiothorac Surg. 2012; 41(2): 448–449, doi: 10.1016/j.ejcts.2011.06.013, indexed in Pubmed: 21820914.

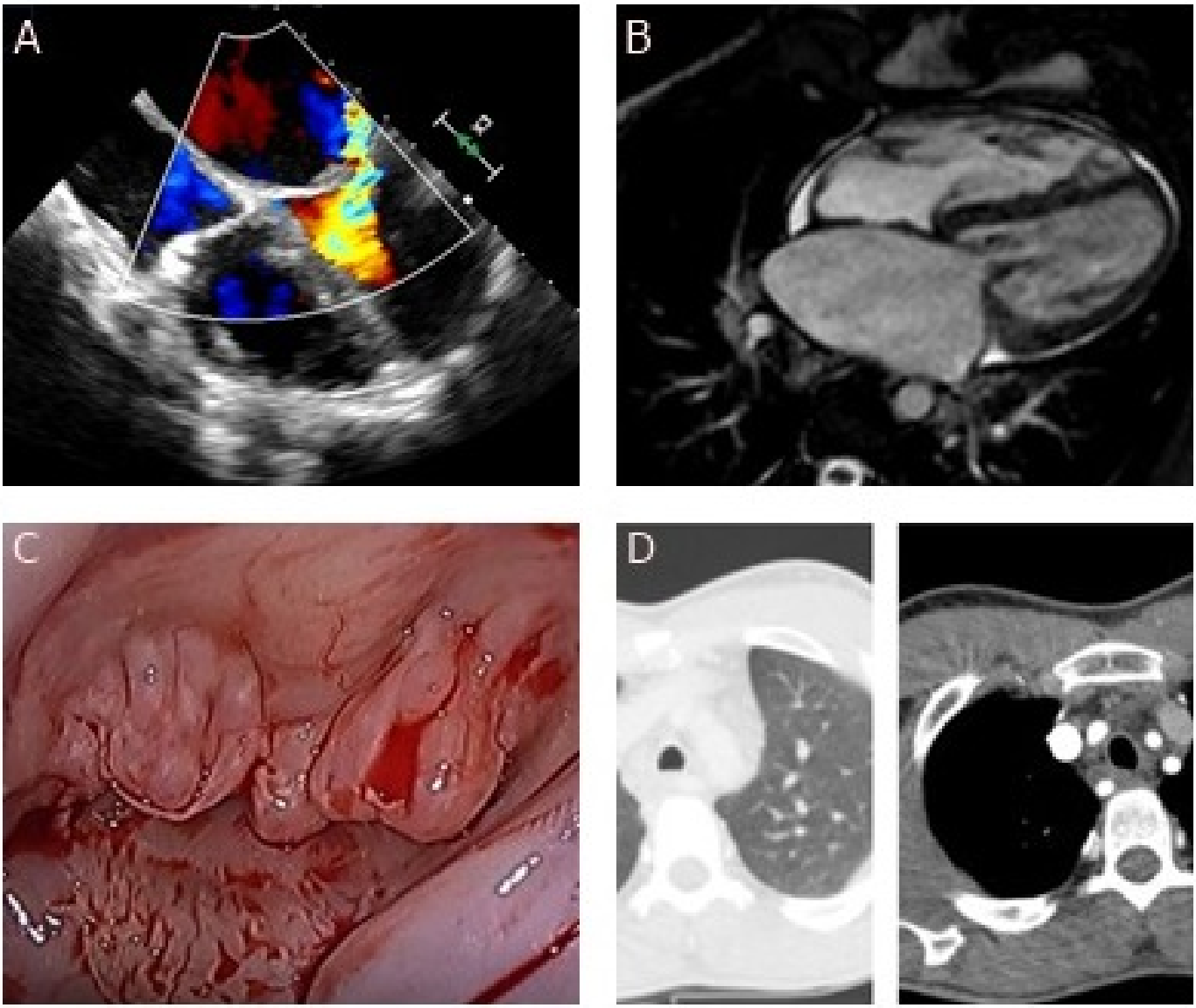
7. Robinson CR, Roberts WC. Outcome of combined mitral and aortic valve replacement in adults with mucopolysaccharidosis (the Hurler syndrome). Am J Cardiol. 2017; 120(11): 2113–2118, doi: 10.1016/j.amjcard.2017.08.001, indexed in Pubmed: 28964381.

8. Rocha RV, Alvarez RJ, Bermudez CA. Valve surgery in a mucopolysaccharidosis type I patient: early prosthetic valve endocarditis. Eur J Cardiothorac Surg. 2012; 41(2): 448–449, doi: 10.1016/j.ejcts.2011.06.013, indexed in Pubmed: 21820914.

9. Muenzer J, Wraith JE, Clarke LA. Mucopolysaccharidosis I: management and treatment guidelines. Pediatrics. 2009; 123(1): 19–29, doi: 10.1542/peds.2008-0416, indexed in Pubmed: 19117856.

10. Sherwood DJ, Adams MC, Mazzella AJ, et al. Mucopolysaccharidosis type i diagnosed by aortic and mitral valve replacement. JACC Case Rep. 2021; 3(18): 1891–1894, doi: 10.1016/j.jaccas.2021.10.013, indexed in Pubmed: 34984346.

Figure 1. A. Four-chamber transoesophageal 0^{o} view showing severe mitral regurgitation; **B.** Four-chamber magnetic resonance imaging view showing a dilated left atrium, a normal sized and not hypertrophic left ventricle, normal right chambers and a lateral jet of severe mitral regurgitation; **C.** Surgical view of a myxomatous mitral valve with shortened and thickened chords accompanied by hypertrophic papillary muscles; **D.** Chest computed tomography with no evidence of tracheomalacia in a patient with Hurler-Scheie syndrome.


A
B
C
D