

Rare cause of mitral stenosis: Clinically suspected Hurler-Scheie syndrome

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ABSTRACT

Mucopolysaccharidosis Type I is a rare inherited metabolic disorder with an autosomal recessive pattern of inheritance. The disease is characterized by the accumulation of glycosaminoglycans (GAGs) within lysosomes due to a deficiency of the enzyme α -L-iduronidase. Impaired degradation of GAGs results in their progressive accumulation in the lysosomes of various organs and tissues, including the eyes, central nervous system, cardiovascular system, gastrointestinal tract, skeletal system, and respiratory system. We present a case of clinically suspected Hurler-Scheie syndrome associated with severe mitral stenosis.

Key words: Hurler-Scheie syndrome, Mitral stenosis, Mucopolysaccharidosis

Mucopolysaccharidosis (MPS) is a group of lysosomal storage disorders characterized by the abnormal accumulation of glycosaminoglycans (GAGs) within lysosomes. MPS type I (MPS I) results from defective degradation of GAGs due to a deficiency of the lysosomal enzyme α -L-iduronidase, leading to their progressive accumulation in multiple tissues and organs [1]. The estimated incidence of MPS I is approximately 1 in 25,000 live births. Based on clinical severity, MPS I is classified into three phenotypes: Hurler syndrome (severe), Hurler-Scheie syndrome (intermediate), and Scheie syndrome (mild). The pathophysiology of MPS I involves progressive intracellular and extracellular deposition of GAGs in various organs, including the eyes, central nervous system, cardiovascular system, gastrointestinal tract, skeletal system, and respiratory system. The age at presentation varies according to disease severity. Patients with Hurler syndrome typically present during early childhood, whereas those with Hurler-Scheie and Scheie syndromes usually present later in childhood or adolescence. Systemic manifestations include short stature, developmental delay, cognitive impairment, skeletal abnormalities (dysostosis multiplex), valvular heart disease, coronary artery disease, hepatosplenomegaly, gastrointestinal involvement, umbilical hernia, recurrent respiratory tract infections, upper airway obstruction, dental

abnormalities, sensorineural hearing loss, and visual impairment [2]. The diagnosis of MPS I is suspected based on characteristic dysmorphic facies, developmental delay, skeletal abnormalities, and multisystem involvement, including cardiac and respiratory manifestations. Definitive diagnosis is established by demonstrating deficient α -L-iduronidase enzyme activity and confirmed by molecular genetic testing. Early diagnosis is essential, as disease-specific treatments, including hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT), can slow disease progression and improve clinical outcomes.

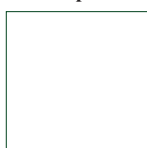
Cardiac involvement is a major cause of morbidity and mortality in MPS I and includes valvular heart disease, coronary artery disease, cardiomyopathy, and conduction abnormalities. Valvular involvement results from progressive deposition of GAGs within the extracellular matrix of the valve leaflets, leading to leaflet thickening, fibrosis, and valvular dysplasia, which may result in both stenosis and regurgitation. Left-sided cardiac valves are affected more frequently than right-sided valves. The mitral valve is the most commonly involved, followed by the aortic valve, with valvular stenosis occurring more frequently than regurgitation [3,4].

We present the case of a 17-year-old female with a history of developmental delay, intellectual disability, impaired speech, progressive difficulty walking, and recurrent lower respiratory tract infections who was bedridden at presentation.

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CASE REPORT

A 17-year-old female with a history of developmental delay, intellectual disability, impaired speech, progressive difficulty walking, and recurrent lower respiratory tract infections was bedridden and admitted with symptoms and signs of acute heart failure and Type 2 respiratory failure.

Physical examination revealed characteristic features of MPS, including coarse facial features, a short neck, hepatosplenomegaly, dysostosis multiplex, joint stiffness, shortened metacarpals, and kyphoscoliosis (Fig. 1).

Arterial blood gas analysis confirmed Type 2 respiratory failure. Chest radiography demonstrated severe kyphoscoliosis, while magnetic resonance imaging of the brain revealed hydrocephalus with cortical atrophy (Fig. 2). Transthoracic echocardiography demonstrated dysplastic mitral and aortic valves with severe mitral stenosis (mitral valve area by planimetry, 1.3 cm^2 ; mean gradient, 9 mmHg), mild aortic regurgitation, and severe pulmonary arterial hypertension (Figs. 3 and 4).

The patient was managed with intravenous diuretics, non-invasive ventilatory support, and other supportive measures, resulting in clinical improvement and resolution of acute heart failure. She was discharged on domiciliary bilevel positive airway pressure therapy and long-term oxygen therapy.

DISCUSSION

Cardiac involvement in MPS is well documented and is an important contributor to morbidity and mortality. Cardiovascular manifestations include progressive valvular disease, predominantly affecting the left-sided valves, myocardial hypertrophy, coronary artery involvement, and conduction abnormalities. Valvular disease is the most common cardiac manifestation, with mitral regurgitation being reported more frequently than mitral stenosis. However, progressive GAG deposition within the cardiac valves can cause leaflet thickening, fibrosis, dysplasia, and restricted leaflet mobility, resulting in either regurgitation or stenosis [4,5]. A recent international registry study of patients with MPS Type I confirmed that mitral regurgitation was the most common and earliest valvular abnormality in both severe and attenuated phenotypes [5].

Although mitral stenosis is less frequently reported, severe mitral stenosis has been described in patients with MPS I, including Hurler and Hurler-Scheie phenotypes [6,7]. In one reported patient with Hurler syndrome, severe mitral stenosis required mitral valve replacement, and histopathological examination demonstrated mucopolysaccharide deposition within the mitral valve [6]. Similarly, a case of Hurler-Scheie syndrome with severe mitral valve disease requiring valve replacement has been reported, highlighting



Figure 1: Clinical photograph of the patient demonstrating characteristic coarse facial features, including a prominent forehead, frontal bossing, depressed nasal bridge, widely spaced eyes (hypertelorism), an enlarged tongue (macroglossia), widely spaced teeth, and an open bite



Figure 2: Chest radiograph demonstrating kyphoscoliosis, cardiomegaly, an enlarged main pulmonary artery manifested by prominence of the pulmonary artery segment along the left cardiac border, peripheral vascular pruning, and oligemic lung fields. Right atrial and right ventricular enlargement were also noted

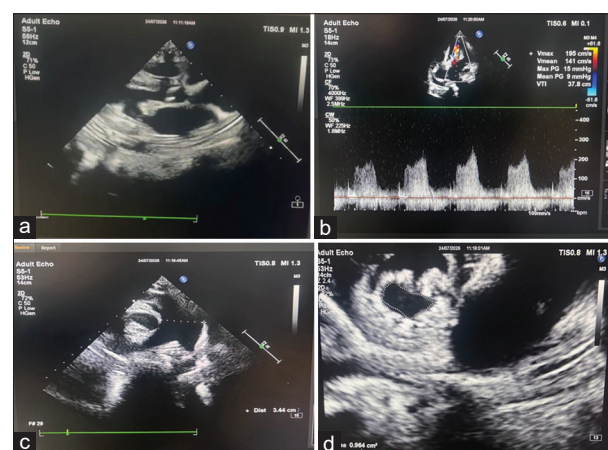


Figure 3: (a) Cardiac ultrasound, parasternal long-axis view, showing a dysplastic and thickened mitral valve with restricted opening; (b) Cardiac ultrasound, four-chamber view, with continuous Doppler interrogation across the mitral valve showing increased gradients across the valve, suggestive of severe mitral stenosis; (c) Cardiac ultrasound showing an enlarged pulmonary artery, suggestive of severe pulmonary arterial hypertension; (d) Mitral valve area by planimetry: 0.964 cm^2

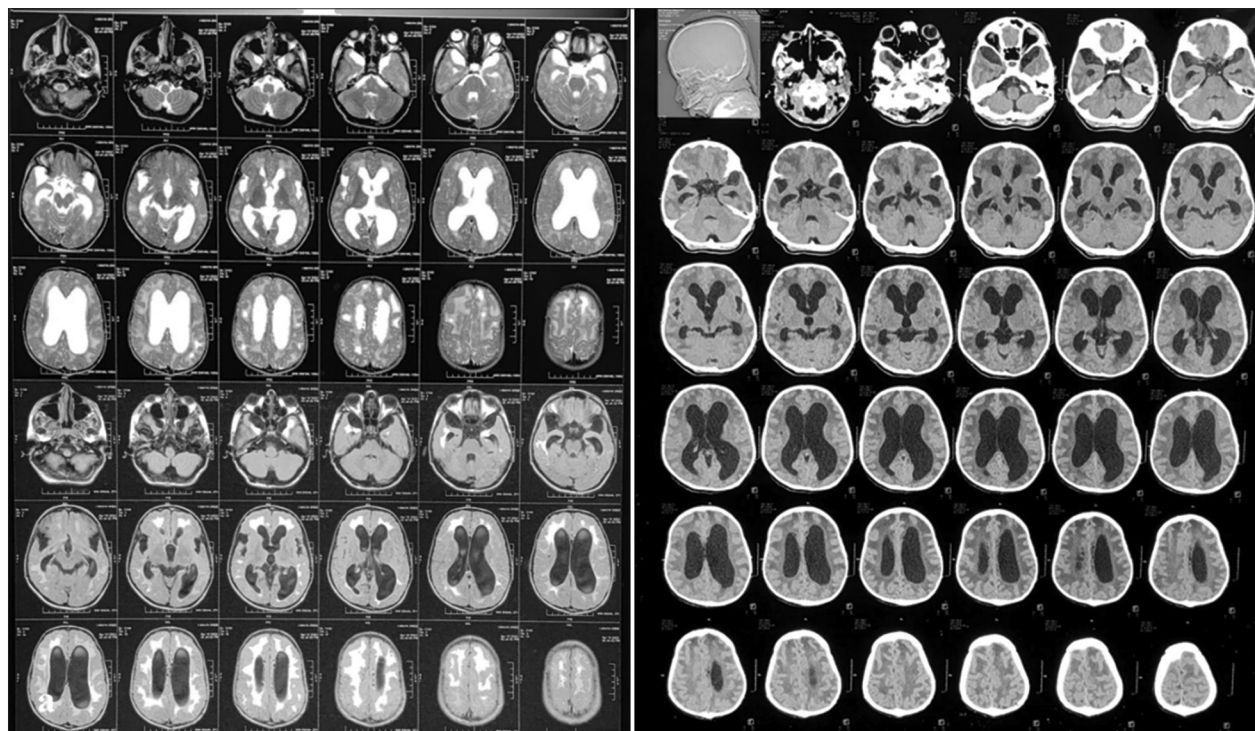


Figure 4: T1- and T2-weighted magnetic resonance imaging of the brain and non-contrast computed tomography of the brain showing enlarged ventricles with cortical atrophy

the potential for progressive and clinically significant valvular involvement in attenuated MPS I [7].

Mitral valve replacement in patients with MPS can be challenging because of the multisystem nature of the disease and the associated perioperative and anesthetic risks. Respiratory involvement, skeletal abnormalities, airway difficulties, pulmonary hypertension, and advanced cardiac disease may substantially increase surgical risk. Therefore, management requires careful multidisciplinary assessment and individualized decision-making [8,9]. In our patient, mitral valve replacement was considered but ultimately deferred by the cardiac surgical team because of advanced restrictive lung disease with Type 2 respiratory failure requiring long-term non-invasive ventilatory support and supplemental oxygen. Following multidisciplinary heart team discussion, conservative medical management was chosen in view of the high anticipated perioperative risk and the patient's advanced multisystem disease.

The pathophysiology of valvular disease is related primarily to the progressive accumulation of GAGs within the valve leaflets and supporting structures. Histopathological studies have demonstrated GAG accumulation and lysosomal enlargement within affected mitral and aortic valves. Importantly, established valvular disease may progress despite ERT, suggesting that early treatment may be particularly important before irreversible structural valve damage develops [10].

Early diagnosis and initiation of disease-modifying therapy are therefore important in MPS I. HSCT is the preferred disease-modifying treatment for appropriately selected children with severe MPS I, particularly when performed early, while ERT with laronidase is an important treatment for non-central nervous system manifestations

and is used in patients with attenuated disease [11]. These therapies can improve several systemic manifestations and may improve or stabilize myocardial involvement; however, their effects on established cardiac valvular disease are limited, and progressive valve disease may occur despite treatment [4,10,11].

CONCLUSION

Our case highlights the unusual occurrence of severe mitral stenosis in a patient with a clinically suspected Hurler-Scheie phenotype and advanced multisystem disease. It emphasizes the importance of comprehensive cardiovascular assessment, early recognition of valvular disease, and multidisciplinary decision-making when considering surgical intervention in patients with MPS.

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