



Case Report

Residual glycosaminoglycan accumulation in mitral and aortic valves of a patient with attenuated MPS I (Scheie syndrome) after 6 years of enzyme replacement therapy: Implications for early diagnosis and therapy

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ABSTRACT

Mucopolysaccharidosis (MPS) is an inherited metabolic disease caused by deficiency of the enzymes needed for glycosaminoglycan (GAG) degradation. MPS type I is caused by the deficiency of the lysosomal enzyme alpha-L-iduronidase and is classified into Hurler syndrome, Scheie syndrome, and Hurler–Scheie syndrome based on disease severity and onset. Cardiac complications such as left ventricular hypertrophy, cardiac valve disease, and coronary artery disease are often observed in MPS type I. Enzyme replacement therapy (ERT) has been available for MPS type I, but the efficacy of this treatment for cardiac valve disease is unknown. We report on a 56-year-old female patient with attenuated MPS I (Scheie syndrome) who developed aortic and mitral stenosis and coronary artery narrowing. The cardiac valve disease progressed despite ERT and she finally underwent double valve replacement and coronary artery bypass grafting. The pathology of the cardiac valves revealed GAG accumulation and lysosomal enlargement in both the mitral and aortic valves. Zebra body formation was also confirmed using electron microscopy. Our results suggest that ERT had limited efficacy in previously established cardiac valve disease. Early diagnosis and initiation of ERT is crucial to avoid further cardiac complications in MPS type I.

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1. Introduction

Mucopolysaccharidosis type I (MPS I) is caused by a deficiency of the enzyme alpha-L-iduronidase (IDUA), resulting in systemic glycosaminoglycan (GAG) accumulation [1]. The major organs and systems involved in MPS I are the joints, the skeletal system, the heart, and the nervous system [2]. Cardiac valve disease is a common symptom in MPS I [3]. Currently, the main therapeutic strategies for MPS I are enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation. Before the development of ERT, some cases of patients with MPS I who underwent cardiac valve replacement were reported [4]. ERT (Aldurazyme®) has been shown to be effective in the improvement of pulmonary function and walking capacity in patients with MPS I. It was therefore initiated as a therapy in 2003; however, the mechanism of its effect on the cardiac valve is unknown. Pathological improvement of cardiac valve disease after ERT implementation has not been

clearly observed because it is difficult to examine the affected cardiac valves.

We have previously reported on the pathology of cardiac valves in a patient with MPS II who successfully underwent aortic valve replacement (AVR) surgery while taking ERT [5]. It has been suggested that the efficacy of ERT might be limited in cardiac valve disease in patients with MPS II. Cardiac valve disease is commonly observed in MPS VI disease, and reports have shown that ERT might suspend the progression of cardiac valve disease if initiated in the early stages [6]. The efficacy of ERT on the cardiac complications of MPS I is still unknown.

Furthermore, coronary artery disease is another cardiac complication of MPS diseases. Braunlin et al. found GAG depositions in the coronary arteries [7]. In addition, coronary artery disease has been commonly seen in the postmortem coronary arteries of patients with MPS I. Reports have suggested that GAG deposition might cause secondary cellular damage.

Cardiac disease is one of the most significant complications of MPS because it is more common in patients with MPS than in healthy individuals and can harm patient's life. In addition, in milder phenotypes such as Hurler–Scheie and Scheie syndromes, cardiac complications such as left ventricular hypertrophy, cardiac valve disease, and coronary

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artery disease may be the first symptoms and hence, a diagnostic clue for MPS. In this study, we report on a patient with attenuated MPS I who underwent a double valve replacement (DVR) and coronary artery bypass graft (CABG) surgery after 6 years of ERT; we also discuss the pathological findings for the aortic and mitral valves.

2. Case report

The patient was diagnosed with aortic stenosis (NYHA II), glaucoma, and corneal clouding at the age of 42. MPS was suspected based on the cardiac and ophthalmologic complications. The urinary GAG level was elevated and an enzyme assay revealed a deficiency in IDUA at the age of 49. Thus, we diagnosed the patient with MPS I and started ERT at the age of 50. Antibody formation was detected 3 months after the initiation of ERT. Her antibody titer remained stable and was approximately 1:12,800. The urinary GAG level decreased to 60%–70% of baseline and stabilized. This observation indicated that the systemic efficacy of ERT had been maintained during the observation period. However, the aortic and mitral stenosis degenerated (NYHA III), and she was referred to our hospital for evaluation for potential valve replacement surgery.

Cardiac echography showed left ventricular hypertrophy as well as severe aortic and mitral stenosis; this had caused pulmonary hypertension, which was considered an operative indication for DVR (Fig. 1a). The electrocardiogram (EKG) also revealed right ventricular hypertrophy, which was a sign of pulmonary hypertension (Fig. 1b). In addition, she underwent cardiac catheterization to evaluate the cardiac valve and coronary disease; this catheterization revealed severe aortic and mitral

stenosis. Pulmonary hypertension (pulmonary artery pressure: 97/43 mm Hg) was also confirmed. Coronary angiography showed 75% narrowing of #3 and #6 which was an indication for CABG (Fig. 1c). The patient underwent DVR and CABG at the age of 56 (Fig. 1d). The perioperative period was uneventful except for a difficult intubation and delayed extubation caused by a tracheal deformity. Finally, she was discharged from the hospital and has been healthy since the surgery.

3. Pathology

The gross pathology of the cardiac valves is shown in Fig. 1. The mitral valve was remarkably thickened, and the aortic valve was thickened (Fig. 2a).

The hematoxylin and eosin stain of the mitral and aortic valve showed that numerous numbers of vacuolated cells were present in both valves (Fig. 2b). Alcian blue-positive material had also accumulated in the cells of the aortic and mitral valves (Fig. 2c). Periodic acid-Schiff stain-positive materials were observed in the aortic and mitral valves as well (Fig. 2d). These findings suggested that GAG continued to accumulate in both the aortic and mitral valves despite 6 years of ERT. The accumulated GAG may have led to the aortic and mitral stenosis and the cardiac valve degeneration.

Electron microscopy of the aortic and mitral valves is shown in Fig. 3. Cells containing Zebra body formations were seen in both the aortic and mitral valves (Fig. 3). Zebra body formation indicates GAG accumulation in lysosomes; this observation was consistent with the light microscopy

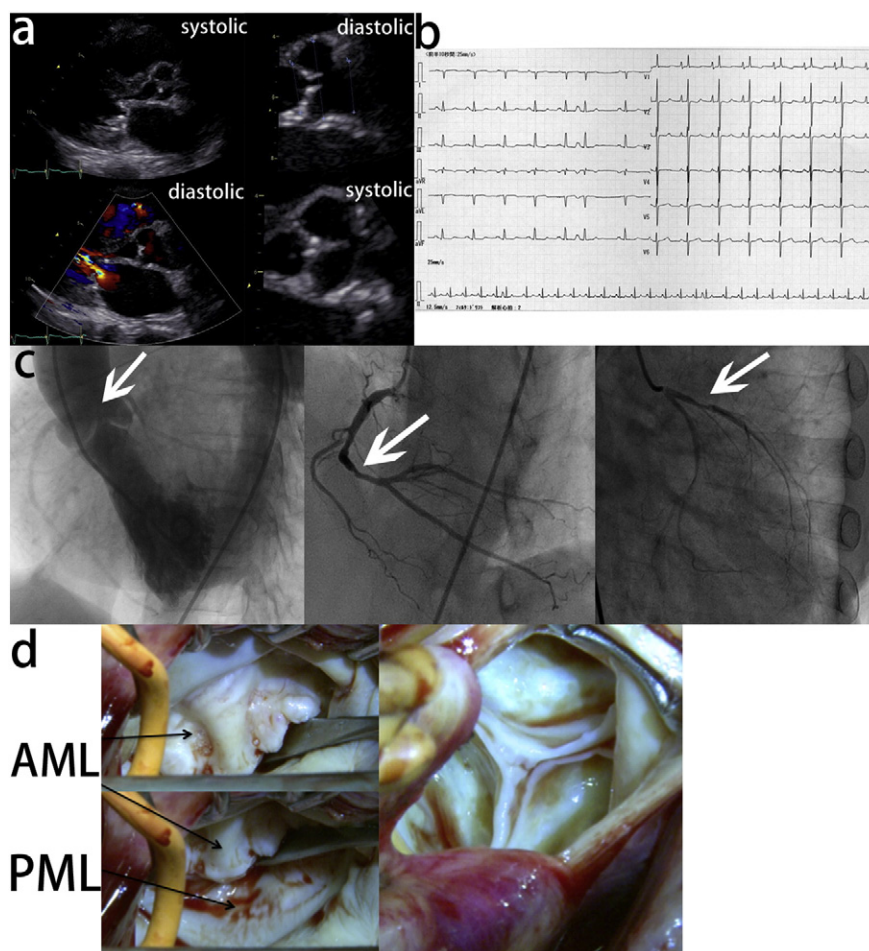


Fig. 1. Clinical findings of cardiac valve and coronary disease. (a) Cardiac ultrasound. Left panel shows mitral stenosis and right panel shows aortic stenosis. (b) Electrocardiogram of the patient shows right ventricular hypertrophy. (c) Left ventriculography shows aortic stenosis. Coronary angiography shows 75% narrowing of #3 (left) and #6 (right). (d) Intraoperative findings of double valve replacement. AML: anterior mitral leaflet. PML: posterior mitral leaflet.

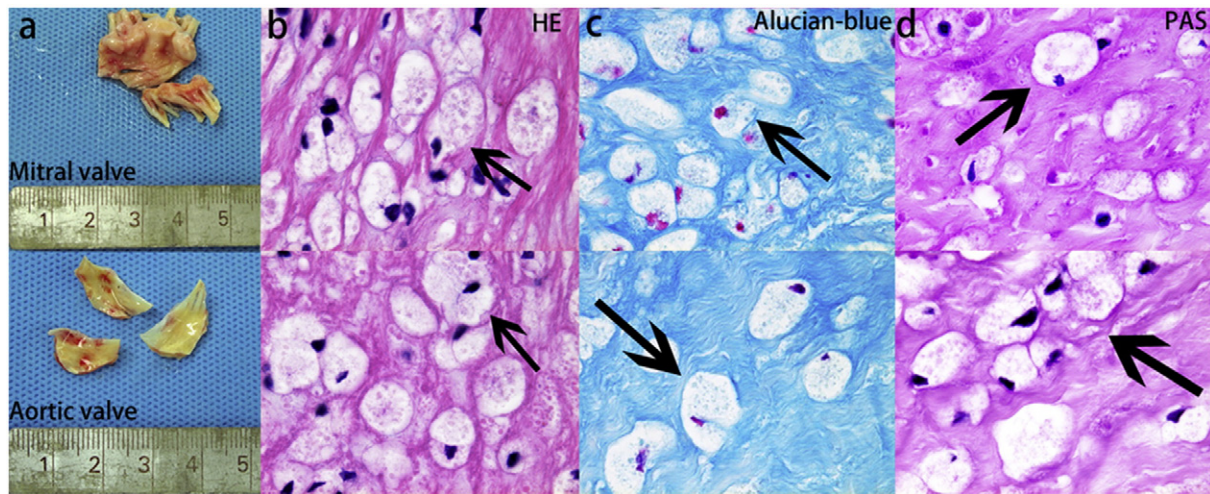


Fig. 2. Light microscopy of cardiac valves. (a) Gross pathology of cardiac valves. Upper column is the mitral valve and lower column is the aortic valve. (b) Hematoxylin and eosin stain of cardiac valves. Upper column is the mitral valve and lower column is the aortic valve. Arrow indicates lysosomal accumulation. (c) Alcian blue stain of cardiac valves. Upper column is the mitral valve and lower column is the aortic valve. Arrow indicates glycosaminoglycan accumulation. (d) Periodic acid–Schiff stain of cardiac valves. Upper column is the mitral valve and lower column is the aortic valve. Arrow indicates glycosaminoglycan accumulation.

findings. The light and electron microscopic findings of both valves were consistent for GAG accumulation.

4. Discussion

Since the development of ERT, >1000 patients with MPS I have been treated using ERT and have shown some clinical benefits such as improved pulmonary function and walking capacity [8]. However, the

enzyme cannot cross the blood brain barrier; therefore, ERT may be ineffective for central nervous system symptoms. It also has been shown that the efficacy of ERT has been limited in cardiac valve disease in MPS I. For example, Braunlin et al. showed that patients with MPS I receiving ERT showed improvements in cardiac hypertrophy; in contrast, the mitral and aortic valve disease clinically progressed despite ERT [9]. One of the explanations for the limited efficacy for cardiac valve changes may be associated with the structure of the valves. Cardiac valves are

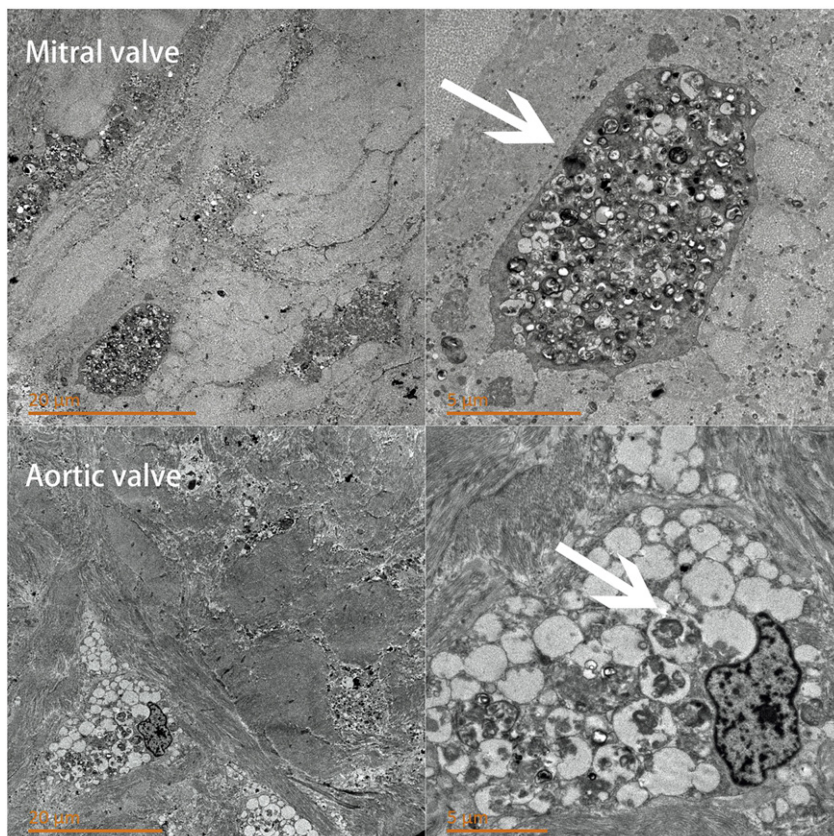


Fig. 3. Electron microscopy of cardiac valves. Upper column is the mitral valve and lower column is the aortic valve. Arrow indicates Zebra body formation. Scale bars: 20 µm and 5 µm.

avascular tissue similar to cartilage and tendons. The therapeutic enzyme is distributed by systemic perfusion and the amount of enzyme that reaches the avascular tissue may be small. Our patient had degenerative cardiac valve disease despite ERT. The urine GAG decreased to 60%–70% of baseline levels, which indicated that ERT lowered GAG levels throughout the body. However, the efficacy of ERT differs among organs. Our observation strongly suggests that it is difficult to achieve therapeutic efficacy for the cardiac valves.

The timing of ERT initiation should be another important factor related to efficacy. Early initiation of ERT has been effective. Baldo et al. showed that the cardiac valve pathology would almost normalize if ERT was initiated soon after birth [10]. Furthermore, Dierenfeld et al. showed that neonatal-initiated ERT ameliorated the pathology of the mitral valve in dogs with MPS I [11]. Some animal research has shown that early initiation was important and effective for cardiac valve pathology as well. However, Pasqualim et al. showed that the thickness of the aortic valve improved but did not normalize, even if when ERT was initiated at later stages of disease in murine models of MPS I [12]. Combining these results, early initiation could improve and possibly normalize cardiac valve disease associated with MPS I.

Coronary artery disease is another important manifestation of MPS. Braunlin et al. showed that coronary artery disease was often seen in some types of MPS [7]. In their study, significant pathological changes were observed in the coronary arteries of patients with severe MPS I. Our patient had significant narrowing of the coronary arteries, which might suggest that coronary artery disease could also be seen in patients with attenuated MPS I. However, we could not provide evidence that the coronary artery disease was mainly caused by the glycosaminoglycan accumulation in this patient.

Similar to a previous report, our patient had a difficult airway and multidisciplinary approach was critical during the perioperative period. The diagnosis of MPS before surgical procedure is extremely important. Arn et al. showed that the percentage of undiagnosed patients with MPS I who underwent surgery was increased in the Scheie syndrome compared to the Hurler syndrome [13].

Our study first showed that the efficacy of ERT was limited for aortic and mitral valve disease pathology in patients with MPS I. To overcome this obstacle in treatment, we should diagnose MPS I earlier and initiate ERT as soon as possible before the progression of the cardiac valve disease.

It is well known that the early initiation of ERT is key to the prevention of further complications from a sibling case which showed that early ERT appeared to be more effective in younger siblings who received earlier treatment [14]. Screening of newborns is one of the strategies to solve this problem and encourages early therapeutic intervention. Compared to typical Hurler disease, a severe form of MPS I, it is more difficult to diagnose Scheie syndrome, which is an attenuated form of MPS I, because of the late disease onset is late and less prominent clinical phenotypes. In fact, MPS I registry data have revealed that some patients have undergone valve replacement surgery before the diagnosis of MPS I [13]. Conversely, the risks during the perioperative period of MPS are high [15]. We would like to emphasize that cardiac valve disease is common in patients with MPS I and that ERT has limited efficacy for previously developed cardiac valve disease; therefore, early diagnosis and treatment is critical to avoid further complications of MPS.

Conflict of interest

H. Ida has active research support from Genzyme Japan Co., Ltd. and Shire Japan Co., Ltd. These activities have been fully disclosed and are managed under a Memorandum of Understanding with the Conflict of Interest Resolution Board of The Jikei University School of Medicine.

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