Laronidase Replacement Therapy and Left Ventricular Function in Mucopolysaccharidosis I

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Abstract We assessed the effects of long-term laronidase replacement therapy (LRT) on the left ventricular (LV) function of a 52-year-old adult woman with mucopolysaccharidosis I (MPS I). The urinary uronic acid concentration significantly decreased by 78.7% (from 75 to 16 mg/g creatinine) after LRT; thereafter, estimated LV weight as assessed by two-dimensional (2D) echocardiography significantly decreased by 33.3% (from 189 to 126 g). Although systolic LV function of the ejection fraction as assessed by 2D echocardiogram did not change after LRT, the diastolic LV function parameters of the deceleration time (DcT) and the ratio of early (E) to late (A) ventricular filling velocities (E/A ratio) significantly improved. The DcT significantly decreased from 355 to 300 ms and the E/A ratio significantly decreased from 1.8 to 0.98. These diastolic parameters were normalized. In the contraction synchrony assessed by 2D speckle tracking imaging, the maximum time delay of contraction decreased from 148 to 14 ms. In addition, the LV weight significantly correlated with the E/A ratio ($p < 0.001$, $r = 0.63$), DcT ($p < 0.05$, $r = 0.48$), and contraction synchrony ($p < 0.001$, $r = 0.61$), respectively. This is the first study to report that LRT significantly improves diastolic LV function and contraction synchrony in a patient with MPS I.

Introduction

Mucopolysaccharidosis I (MPS I) is an autosomal recessive inherited disorder caused by mutations in the gene encoding α -L-iduronidase, located on chromosome 4p16.3 (Scott et al. 1992). The prevalence is approximately one in 100,000 live births; however, as with all MPS disorders international variation exists (Brown and Trivette 1998). α -L-iduronidase is a lysosomal enzyme that contributes to the degradation of glycosaminoglycans (GAG) (Neufeld and Muenzer 2001). The accumulation of GAG in cells and tissues results in a variety of organic dysfunctions, including joint disorders, hepatosplenomegaly, clouding of the cornea, degradation of the retina, cardiovascular disorders, mental retardation, umbilical herniation, and respiratory disorders (McKusick et al. 1965). The cardiovascular system is often affected; its prevalence is reported at 60–100% of MPS patients. Valvular disease, such as mitral valve or aortic valve regurgitation, is most commonly found in MPS I patients with valve and endocardium thickening caused by GAG accumulation, and valve replacement therapy is necessary for overcoming heart failure. Coronary artery disease, conduction abnormalities, and pulmonary hypertension are also often present. In left ventricular (LV) function, systolic LV function is preserved; however, diastolic LV dysfunction and LV hypertrophy are frequently found in patients with MPS (Braunlin et al. 2011).

Enzyme replacement therapy with recombinant human α -L-iduronidase (laronidase) provides an etiology-specific treatment by delivering enough α -L-iduronidase to prevent GAG accumulation in patients with MPS I (Wraith 2001). Laronidase replacement therapy (LRT) has been shown to be safe and effective in animal and human studies (Kakkis et al. 2001; Shull et al. 1994) and has been shown to improve respiratory function and physical capacity by reducing GAG

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retention in patients with MPS-I (Wraith et al. 2004). We previously reported that in an adult patient with MPS-I, short-term LRT was effective in improving myocardial function, including myocardial strain and torsion, as assessed by the two-dimensional (2D) speckle tracking imaging method (Harada et al. 2011). However, little is known about the effects of LRT on LV systolic and diastolic functioning long-term, as adult patients are rare and thus there is little opportunity for cardiologists to observe their outcomes. Therefore, we investigated whether long-term LRT improves LV function in an adult patient with MPS I.

Case Report

The patient is 52-year-old female with MPS I (Scheie) who was diagnosed at 35 years of age with deficient activity of the enzyme α -L-iduronidase. At 11 years of age, she started showing her first clinical symptoms, which included stiffness, joint deformity, hepatosplenomegaly, and umbilical herniation. At the age of 20, she developed clouding of the bilateral corneas. At 33, degradations in her retinal pigmentosa emerged, leading to amblyopia. She also had congestive heart failure (CHF) due to aortic and mitral valvular regurgitation, and underwent a double valvular replacement. After her procedure, a small amount of paravalvular leakage was found at the site of the aortic prosthetic valve, resulting in chronic heart failure. She was then placed on anti-heart failure medications, including candesartan, carvedilol, and amlodipine, as well as an antiarrhythmogenic agent (cibenzoline) and an anticoagulant (warfarin) for paroxysmal atrial fibrillation (PAF).

In 2006, LRT (Aldurazyme[®], Genzyme Corporation, Japan) was approved for use in Japan by the Ministry of Health, Labor and Welfare. The patient in this study was placed on LRT in November 2007; her dosage was 0.58 mg/kg administered once per week via a three-hour intravenous infusion, based on the manufacturer's recommendations.

Methods

Clinical assessment of the patient after LRT was performed over a 42-month follow-up period. This included a physical examination, measuring urinary uronic acid, estimating liver and spleen volumes via abdominal computed tomography, and monitoring LV function and weight through 2D echocardiography.

Conventional, Pulse Doppler, and Speckle Tracking Echocardiograms

The 2D echocardiography was performed using a Vivid 7 Dimension ultrasound machine with an M4S probe

(GE Medical Systems, Milwaukee, WI, USA). The LV ejection fraction and weight were measured using M-mode and area-length methods, respectively, and LV inflow velocity for early (E) wave deceleration time (DcT) and the ratio of early (E) to late (A) ventricular filling velocities (E/A ratio) by pulse Doppler. For speckle tracking echocardiography (D'hooge et al. 2000; Hurlburt et al. 2007; Notomi et al. 2005; Voigt and Flachskampf 2004), an offline speckle tracking analysis was performed on all digitally stored grayscale imaging using customized software (EchoPAC PC Dimension: GE Medical Systems, Milwaukee, WI, USA). The LV myocardium of the short or long axis in B-mode was divided into six segments. Ten to twelve speckles, which are a high echoic region of interest, are automatically determined in each segment of the myocardium and monitored during contraction.

For the assessment of contraction synchrony, the maximum time delay was measured. For the short axis view, the time for reaching the end-systolic phase was different in each of the six segments. The maximum time delay was obtained by measuring the difference between the maximum time and minimum time in each of the six segments. The maximum time delay became shorter in a well-synchronized contraction but was longer in a dys-synchronized contraction. The high reproducibility of speckle tracking echocardiography has previously been reported by us and others (Beaver et al. 2011; Harada et al. 2011).

Statistical Analysis

The time course values of the echocardiographic parameters were analyzed using one-way ANOVA. The correlations between LV weight and the echocardiographic parameters were analyzed through a single regression analysis using SPSS software (SPSS Inc. Chicago, IL, USA).

Results

Clinical Findings After LRT

The clinical findings in the patient on joint movements, vision, and distance by 6-minute walk test were not improved after LRT during the follow-up period. However, the concentration of urinary uronic acid and liver and spleen volumes were improved (Fig. 1). As we previously described in a six-month follow-up study of this patient (Harada et al. 2011), the concentration of urinary uronic acid decreased by 78.7% (from 75 to 16 mg/g creatinine after LRT). Thereafter, urinary uronic acid concentration was maintained during the follow-up period (Fig. 1a).

Hepatosplenomegaly also was improved after LRT. Estimated liver and spleen volumes decreased by 34.1% (from 1,746 to 1,150 mL) and 9.5% (from 400 to 362 mL), respectively (Fig. 1b). Most importantly, the disease state of the patient's CHF and PAF was stabilized following LRT.

Echocardiographic Findings After LRT

The cardiothoracic ratio as shown through chest X-ray imaging and LV ejection fraction (Fig. 1d) were unchanged after LRT. However, estimated LV weight decreased by 33.3% (from 189 to 126 g) during the follow-up period (Fig. 1c). LV diastolic function significantly improved after LRT (Fig. 1e–h). The E/A ratio significantly decreased from 1.8 to 0.98, with a normal range from 0.75 to 1.5 (Fig. 1e, g, h). The improved E/A ratio is attributable to decreased E wave velocity but not to an alteration in A wave velocity. The DcT significantly decreased from 355 to 300 ms, with a normal range from 150 to 250 ms (Fig. 1f–h). In the contraction synchrony, the maximum time delay decreased from 148 to 14 ms, with a normal range from 36 to 49 ms (Fig. 2a–c).

Relation of LV Weight to Urinary Uronic Acid Concentration, Diastolic Function, and Contraction Synchrony

LV weight correlated significantly with urinary uronic acid concentration ($n = 13$, $r = 0.73$, $p < 0.01$) (Fig. 3a). In the relationship between LV weight and diastolic function parameters, LV weight correlated significantly with E/A ratio ($n = 26$, $p < 0.001$, $r = 0.63$) and DcT ($n = 26$, $p < 0.05$, $r = 0.48$), respectively (Fig. 3b, c). Furthermore, LV weight correlated significantly with contraction synchrony ($n = 26$, $p < 0.001$, $r = 0.61$) (Fig. 3d).

Discussion

We previously reported on the improvement of LV myocardial longitudinal strain (shortening ratio), LV myocardial radial strain (thickening ratio), and LV myocardial

torsion using speckle tracking echocardiography for a six-month observation period (Harada et al. 2011). However, we could not recognize changes in systolic and diastolic function because of a short-term observation period. The effects of LRT on LV function during a long-term follow-up period remain unknown in patients with MPS I. This is the first report that long-term LRT has a beneficial effect on LV diastolic function but not on systolic function in an adult patient with MPS I.

In this report, the therapeutic effectiveness of LRT was confirmed by our clinical findings, which included a reduction of urinary uronic acid, LV weight, and hepatosplenomegaly. In fact, a good correlation was observed between LV weight and urinary uronic acid concentration. These findings are similar to the previous results of our studies and others (Arora et al. 2007; Harada et al. 2011; Kakkis et al. 2001). These findings suggest that decreased LV weight was due to GAG degradation in cardiac tissue, resembling volume reduction of the liver or spleen.

In MPS I, GAG accumulation in the heart affects the LV tissue and cytoplasmic structural changes. In an electromicroscopic examination, the interstitial fibroblast as a “clear cell” infiltrates the LV wall and the membranous cytoplasmic body is found in the interstitial fibroblast cytoplasm. However the sarcomeric structure of the cardiomyocyte is normally conserved (Braunlin et al. 2011; Dekaban et al. 1976; Nagashima et al. 1976; Shimamura et al. 1976). In the optical microscopic examination, GAG accumulation was predominantly found in the valves and endocardium and these tissues thickened (Braunlin et al. 2011; Dekaban et al. 1976; Nagashima et al. 1976; Shimamura et al. 1976).

These histological findings suggest that diastolic function is impaired by these thickened tissues. In the mouse MPS I model in which α -L-iduronidase was deleted, the structure of sarcomeres appeared normal; however, numerous empty vacuoles were observed in the cardiomyocyte, and endothelial cells of the mitral valve were also vacuolated on electromicroscopy. These empty vacuoles in the cardiomyocyte disappeared significantly and the endothelial cells in the mitral valve appeared normal, without vacuoles, when the MPS I mice were treated with gene

Fig. 1 Time courses of urinary uronic acid concentration, estimated liver and spleen volumes, LV weight, LV systolic and diastolic function after LRT. **(a)** Urinary uronic acid concentration. Dotted line: Normal range of urinary uronic acid is less than 20 mg/g creatinine. **(b)** Estimated liver and spleen volumes. **(c)** Estimated left ventricular weight. Significant decrease in LV weight was observed by LRT. LV weight in healthy women is about 66–110 g. **(d)** Ejection fraction did not change with LRT. **(e)** E/A ratio decreased significantly after LRT ($p < 0.05$). Normal range: 0.75–1.5, abnormal relaxation pattern: <0.75 , restriction (pseudo-normalization) pattern: ≥ 1.5 .

(f) DcT decreased significantly after LRT ($p < 0.01$). Normal range: 160–240 ms, abnormal relaxation pattern: >240 ms, restriction (pseudo-normalization) pattern: <160 ms. **(g)** LV in-flow velocity at 25 days after LRT. DcT was 406 ms and E/A was 1.7. The 1.87 m/s of E was in hyper in-flow velocity. The LV diastolic function status was within the range of impaired relaxation to pseudo-normalization. **(h)** LV in-flow velocity at 1,206 days after LRT. DcT was 299 ms and E/A was 0.98. The 1.06 m/s of E was at normal velocity. These findings suggest that LV diastolic function was within the normal range

Fig. 3 (a) Relationship between estimated left ventricular weight and urinary uronic acid concentration. A significant correlation ($n = 13$, $r = 0.73$, $p < 0.01$) was observed between urinary uronic acid concentration and LV weight. (b, c, and d) Relationship between

estimated LV weight and cardiac function. Significant correlations were observed between estimated LV weight and E/A ratio (b, $n = 26$, $r = 0.63$, $p < 0.001$), DcT (c, $n = 26$, $r = 0.48$, $p < 0.05$), and synchrony (d, $n = 26$, $r = 0.61$, $p < 0.001$), respectively

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Disclosure

All authors declare there is no conflict of interest associated with this study.

Synopsis

Long-term laronidase replacement therapy leads to improvements in left ventricular diastolic function and

contraction synchrony in an adult patient with mucopolysaccharidosis I.

Compliance with Ethics Guidelines

Conflict of Interest

Haruhito Harada, Hiroshi Niiyama, Atsushi Katoh, and Hisao Ikeda declare that they have no conflict of interest.

Informed Consent

All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation in Kurume University and with the Helsinki Declaration of 1975, as revised in 2005. The signed

informed consent form was obtained from the patient for their inclusion in the study.

Animal Rights

This article does not refer to any animal studies performed by the authors.

Author Contributions

Haruhito Harada contributed to data collection, data analysis, and preparation of the manuscript and figures.

Hiroshi Niiyama contributed in terms of clinical therapy.

Atsushi Katoh contributed in terms of clinical therapy and data interpretation.

Hisao Ikeda contributed to data interpretation, literature search, and preparation of the manuscript and figures.

Competing Interests

There are no competing interests.

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