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Laronidase replacement therapy improves myocardial function in mucopolysaccharidosis I

Haruhito Harada [a], Hiroki Uchiwa [a], Mio Nakamura [a], Satoko Ohno [a], Hirohiko Morita [a], Atsushi Katoh [a], Makoto Yoshino [b], Hisao Ikeda [a,*]

[a] Division of Cardiology, Kurume University Medical Center, Japan
[b] Department of Pediatrics, Kurume University School of Medicine, Japan

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ABSTRACT

We assessed whether laronidase (recombinant human α-L-iduronidase) replacement therapy could improve left ventricular (LV) myocardial function in a 49-year-old woman with mucopolysaccharidosis I (MPS I) and valvular heart disease. After 6 months of laronidase treatment, the concentration of urinary uron acid decreased by 78.8%. Hepatosplenomegaly improved and LV weight decreased by 19.6%. LV ejection fraction assessed by two-dimensional echocardiogram did not change after laronidase treatment. However, in two-dimensional ultrasound speckle tracking imaging method, LV myocardial longitudinal strain (shortening ratio) increased from −13.2 to −17.4%. LV myocardial radial strain (thickening ratio) increased from 26.6 to 83.4%. LV myocardial torsion increased from +6 to +18°. These indexes of myocardial function were normalized after laronidase treatment. Thus, our findings were a first report that laronidase treatment had a beneficial effect on LV myocardial function in an adult patient with MPS I.

1. 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 [1]. The α-L-iduronidase is a lysosomal enzyme involved in the degradation of glycosaminoglycans (GAG) [2]. The GAGs accumulation in cells and tissues results in their organic dysfunction including joint disorder, hepatosplenomegaly, clouding of the cornea, degradation of retina, and cardiovascular disorders including valvular heart diseases, mental retardation, navel herniation, and respiratory disorder [3]. MPS I is phenotypically heterogeneous. Historically, MPS I is classified into three clinical syndromes including Hurler, Hurler–Scheie, and Scheie. Hurler disease shows a most severe phenotype expression. Hurler–Scheie disease is intermediate in phenotype expression. Scheie disease shows mild clinical manifestations with a sometimes normal life span. In these three MSP-1 phenotypes, the mental retardation is the most differentiating factor. Hurler disease shows the severest mental retardation. In contrast, Scheie disease is the lightest mental phenotype and frequently shows normal intelligence quotient (IQ). Hurler–Scheie type is an intermediate IQ phenotype.

Enzyme replacement therapy with recombinant human α-L-iduronidase, laronidase, has an etiology-specific treatment by delivering sufficient α-L-iduronidase for the prevention of GAG accumulation in patients with MPS I [4]. Laronidase treatment has shown safety and efficacy in animal and human studies [5,6], and is shown to improve respiratory function and physical capacity by reducing GAG storage in patients with MPS I [7]. However, the previous studies demonstrated that laronidase treatment did not affect the left ventricular (LV) ejection fraction in patients with MPS I [8,9]. In the past decade, two-dimensional (2D) ultrasound speckle tracking imaging method has enabled noninvasive measurements of LV myocardial function including myocardial strain and torsion [10–13]. Therefore, we assessed by 2D speckle tracking imaging method whether laronidase treatment improves LV myocardial function in a patient with MPS I and valvular heart disease.

2. Materials and methods

2.1. Case report

The patient is a 49-years-old woman with MPS I (Scheie) who was diagnosed at 35 years of age with the deficient activity of the enzyme α-L-iduronidase. At 11 years of age, she had initial clinical symptoms including stiffness and deformities of joints, hepatosplenomegaly and umbilical herniation. At 20 years of age, she had clouding of the bilateral corneas. At 33 years of age, degradations of retinal pigmentosa

* Corresponding author at: 155–1, Kokubu-machi, Kurume 839–0863, Japan. Fax: +81 942 22 6657.
E-mail address: ikeda_hisao@kurume-u.ac.jp (H. Ikeda).

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were emerged, leading to amblyopia. Moreover, since she had congestive heart failure due to aortic and mitral valvular regurgitations, she had surgical operation with double valvular replacement. After surgery, a small amount of paravalvular leakage was found at the site of aortic prosthetic valve, resulting in chronic heart failure. Until the present time, she has taken anti-heart failure drugs including candesartan, carvedilol and amlodipine. Also, she has taken an anti-arrhythmogenic agent, cibenzoline and an anti-coagulant, warfarin for paroxysmal atrial fibrillation.

In 2006, the laronidase treatment (Aldurazyme®, Genzyme Corporation, Japan) was approved by the Ministry of Health, Labor and Welfare in Japan. In this case, the laronidase treatment was started based on the manufacturer's recommendations at 0.58 mg/kg once weekly by a 3-hour intravenous infusion from November in 2007. Clinical assessment after laronidase treatment was completed including physical examination, urinary uron acid measurements, LV ejection fraction and weight by 2D echocardiogram, and myocardial function such as strains and torsion by 2D speckle tracking imaging method.

2.2. 2D speckle tracking imaging method

The speckle tracking echocardiography [10–13] was performed with Vivid 7 Dimension ultrasound machine with an M4S probe (GE Medical Systems, Milwaukee, Wisconsin). Offline speckle tracking analysis was performed on all digitally stored grayscale imaging with customized software (EchoPAC PC Dimension: GE Medical Systems, Milwaukee, Wisconsin). The LV myocardium of short or long axis in B-mode was divided into 6 segments. Ten to twelve speckles, which are high echoic region of interest, are automatically determined in the each segment of myocardium and chased during contraction. In the myocardial longitudinal strain measurement, the distance between the speckles becomes shorter toward the end-systole in the long axis view because the distance of long axis of LV is shortening by contraction. The LV radial strain (shortening ratio) was presented by the average value of 6 segmental shortening ratios. In the myocardial radial strain measurement, the distance between speckles becomes longer toward the end-systole in the radial axis view because the distance of thickness of LV wall is thickening by contraction. The LV radial strain (thickening ratio) was presented by the mean value of 6 segmental thickening ratios. In the myocardial torsional measurement, the apex rotates counterclockwise, whereas the base rotates clockwise. Counterclockwise LV rotation as viewed from apex was expressed as a positive value. The LV torsion is presented by the subtraction between positive degree of apical rotation and negative degree of basal rotation, as a following formula "Torsion (degree) = (counterclockwise rotation in apex) − (clockwise rotation in base)".

These indexes of myocardial function were obtained from 5 age-matched female healthy volunteers as a control group. In addition, to confirm the reproducibility of speckle-tracking echocardiograms which are longitudinal strain, radial strain, and torsion, we recruited 8 healthy volunteers and performed the speckle-tracking echocardiogram. Each volunteer was examined twice in a week interval by the same observer. The reproducibility was calculated with SPSS version 17.0 software (SPSS Inc. Chicago, Ili). The correlation coefficient values of longitudinal strain (shortening ratio), radial strain (thickening ratio), and torsion were 0.862, 0.985, and 0.933, respectively. And the intra-class correlation coefficient values of shortening ratio, thickening ratio, and torsion were 0.889 (95% CI, 0.446–0.978), 0.992 (95% CI, 0.961–0.998), and 0.964 (95% CI, 0.821–0.993), respectively. These data indicated the high reproducibility of

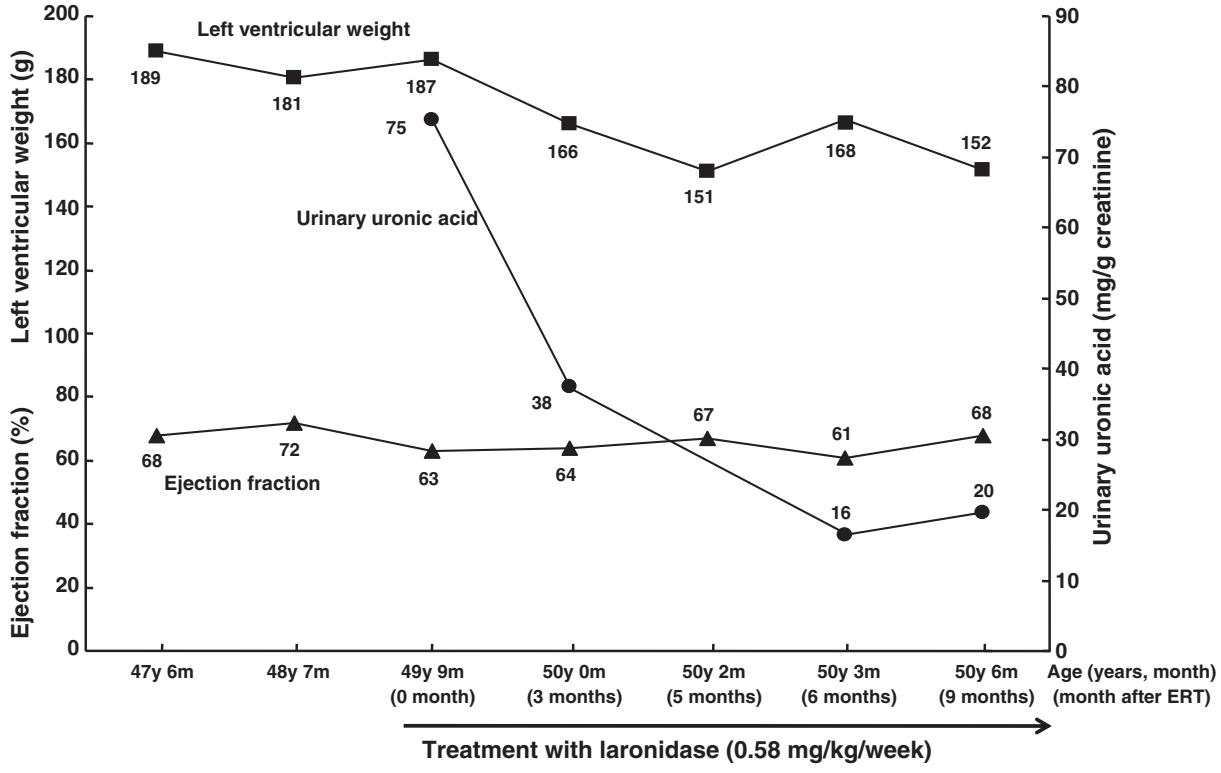

Fig. 1. Time course of urinary uronic acid concentration, left ventricular weight and ejection fraction during ERT. Urinary uronic acid concentration and left ventricular weight decreased after LRT. Note that laronidase treatment had beneficial effects on LV weight although the therapy did not affect left ventricular ejection fraction. Normal range of urinary uronic acid is less than 20 mg/g creatinine. Normal range of echocardiographic LV ejection fraction is 55 to 75%. Normal range of echocardiographic LV weight by area–length method is 66 to 110 g in female [18].