Long-Term Effects of Enzyme Replacement Therapy for Anderson-Fabry Disease
Differences in Three Siblings with the Same Genotype

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Summary
Anderson-Fabry disease is a rare X-linked lysosomal storage disease caused by α-galactosidase A (α-GalA) gene variants and characterized by a large genotypic and phenotypic spectrum. Enzyme replacement therapy (ERT) using recombinant α-GalA has been approved for >10 years as a specific therapy for the disease. However, the long-term clinical efficacy for cardiac manifestations has been equivocal because it depends on several factors such as genotype, sex, age, and disease severity at the initiation of ERT. We report the differences in the clinical effects of ERT continued for >10 years in three patients with the same genotype. Left ventricular hypertrophy and myocardial dysfunction progressed in the heterozygote proband even under ERT, although disease progression was prevented in two sons of Case 1.

Key words: Left ventricular hypertrophy

Anderson-Fabry disease is a rare inherited X-linked genetic disease caused by a deficiency in α-galactosidase A (α-GalA) activity. Progressive accumulation of glycosphingolipids particularly occurs in lysosomes of the heart, kidneys, skin, and brain. Cardiac involvement is common, presenting various arrhythmias, valve dysfunction, and cardiomyopathy.1-4 Enzyme replacement therapy (ERT) with recombinant α-GalA has been available for >10 years. The short- and long-term efficacy of ERT mainly for cardiac and kidney lesions has been reported.5-7 However, the clinical course depends not only on genotype and sex but also on age and disease stage at the initiation of ERT.7,8 Additionally, the broad phenotypic spectrum among patients with missense mutations makes it difficult to evaluate the efficacy of ERT.9,10 We report here the clinical effects of long-term ERT in three patients with the same missense mutation.

Case Report
Case 1: In 1987, a 35-year-old female patient was first informed of an abnormal electrocardiogram (ECG) during her annual health checkup. At the age of 46, she was referred to a hospital for an ECG of short PR interval and left ventricular hypertrophy (Figure 1A). Transthoracic echocardiography showed diffuse left ventricular wall thickening (14-15 mm) with preserved wall motion. She had frequent paroxysmal supraventricular tachycardia (PSVT) in her late forties (Figure 1B) and was referred to our hospital, where she underwent ablation and cardiac biopsy. Marked vacuolar degeneration with a Periodic acid Schiff positive substance in a biopsy specimen and a family history of heart and kidney dysfunction of her father strongly suggested Anderson-Fabry disease. Her father died at the age of 42 (in his forties), and her grandparents also died at a young age, although the detailed cause of death was unknown (Figure 2). The diagnosis was confirmed by a low level of leukocyte α-GalA activity (44.75 nmol/hour/mg/protein; normal value: 49 ± 20 nmol/hour/mg/protein) and the missense mutation in exon 6 by α-galactosidase A (GLA) genetic analysis (c.924A>T). Enzyme analysis of her three children showed low levels of leukocyte α-GalA activity in the first and second sons.

Agalsidase-β (Fabrazyme) was started at a dose of 1 mg/kg 1q immediately after diagnosis. ERT had been continued until age 65 with the transient change to agalsidase-α (Replagal) at 0.2 mg/kg 1q from age 55 to 58 because of supply shortage.

From her late forties to early fifties, PSVT attacks completely disappeared, and atrioventricular AV junctional rhythm was often observed (Figure 1C). At age 57, she developed symptoms of heart failure with the onset of persistent atrial fibrillation (Figure 1D).
Even under ERT, the wall thickness continued to increase. In addition, wall thinning and increased echogenicity in the basal posterolateral areas appeared at the age of 59 (Figure 3A-C). Cardiac magnetic resonance imaging (MRI) at age 64 also showed left ventricular hypertrophy with wall thinning of the basal posterolateral area. Late gadolinium enhancement (LGE) was observed in the basal posterolateral and apical myocardial segments (Figure 4).

Symptoms of heart failure had been well controlled with standard therapies and cardiac rehabilitation. Temporary increases in antibody titers were observed during ERT, but no significant allergic reaction was recognized, and the plasma levels of GL3 remained normal (Figure 5).

Case 2: The patient in Case 2 was diagnosed as being homozygous of the same missense genotype as Case 1 at age 25. He had a history of chronic burning pain in the extremities, hypohidrosis in childhood, and lacunar-type brain infarction at age 24. The activity of leukocyte α-GalA was very low (2.27 nmol/hour/mg/protein; normal value: 10.72 nmol/hour/mg/protein). ERT was started at age 27, which continued for 11 years.

The patient had five episodes of lacunar cerebral infarction with transient minor neurological symptoms at ages 26, 27, 29, and 33. GLA antibodies became positive after early-phase ERT, but the plasma levels of GL3 remained low without signs of an allergic phenomenon (Figure 6). A 12-lead ECG at age 25 showed high voltage in V4-V6 (Figure 7A). Diffuse thickening of the left ventricular wall progressed until age 33 (Figure 8A), with T-wave changes on the ECG (Figure 7B). Because he also developed mild hypertension in his early thirties, pharmacological control by angiotensin II receptor blocker and counseling for life habits started at the same time. The left ventricular wall thickness decreased to normal range (Figure 8B), and the T-wave change also disappeared (Figure 7C) until age 37. Cardiac MRI at the same age showed normal wall thickness, and LGE was not observed (Figure 9).

Although mild proteinuria had been observed under ERT, the estimated glomular filtration rate (eGFR) was preserved for > 10 years (eGFR: 71 mL/minute/1.73 m² at age 37).

Case 3: The second son of the patient in Case 1 was diagnosed as being homozygous of the same missense genotype as Case 1 at age 23, with a low activity of leukocyte α-GalA (0.21 nmol/h/mL; normal value: 4.6 ± 1.6 nmol/h/mL) and mild proteinuria. Although he had no significant symptoms of Fabry disease, ERT was initiated...
Figure 2. Family tree of the cases. The presence of Fabry disease is suspected in Case 1’s father and grandmother.

Figure 3. Transthoracic echocardiography of Case 1 at the age of 59 years. The parasternal long (A)- and short (B)-axis view showed diffuse left ventricular hypertrophy with a maximal septal wall thickness of 20 mm. The basal inferolateral wall was thinner (11 mm) than the other areas and with increased echogenicity. Apical four-chamber view (C) showing apical hypertrophy and marked dilatation of the left atrium.

at age 25 and continued for 11 years. Both 12-lead ECG and echocardiographic findings remained normal, and cardiac MRI showed no LGE after 10 years. He had normal kidney function (eGFR: 85 mL/minute/1.73 m²) at age 35. The plasma GL3 level was low without significant elevation of antibody titer.

Discussion
There have been several reports about the short- and
mid-term efficacy of ERT for Fabry cardiomyopathy that have described the regression of Left Ventricular (LV) hypertrophy and improved myocardial function.\textsuperscript{5,8} Clearance of GL3 in various organs during ERT has also been demonstrated.\textsuperscript{8,11}

Recent studies on the long-term effects of ERT for >10 years have documented the benefits in younger, early-stage patients with less kidney involvement.\textsuperscript{6,11,12} However, the assessment of ERT efficacy is often difficult, especially in patients with a missense mutation that has a
Figure 6. Time course of wall thickness, plasma level of GL3, and antibody titers in Case 2. The increase in wall thickness continued until the age of 33 but decreased to normal range at the age of 35 years. Antibody titers continued to be significant in the early phase of ERT, although the plasma level of GL3 remained normal.

Figure 7. Time course of the 12-lead ECG in Case 2 at the age of 28 (A), 33 (B), and 36 (C) years. Significant T-wave inversion in V4-V6 leads appeared at the age of 33 years that could not be found at the age of 36.

The heterozygote proband of the family in Case 1 showed progressive increases in left ventricular wall thickness and lateral wall thinning during ERT. Advanced myocardial fibrosis was confirmed in the MRI images after prolongd ERT. In contrast to the proband, the patient’s two sons who started ERT at a younger age showed robust benefits of the therapy. The patient in Case 2 exhibited regression of Left Ventricular Hypertrophy (LVH) with preserved kidney function, even with symptoms of a broad spectrum of phenotypes.
classic Fabry disease in his childhood. MRI showed no signs of fibrosis after long-term ERT. Recurrence of lacunar cerebral infarction was also prevented during the late phase of ERT. The patient in Case 3 had no clinically significant symptoms and almost no signs of Fabry disease for 11 years. These observations absolutely confirmed the importance of earlier initiation of ERT at a younger age with less organ dysfunction. Preventing accumulation and/or clearance of GL3 leads to the preservation and recovery of cardiac and other organ functions.8)

A limitation of ERT in older patients in an advanced stage was demonstrated in a report,9) although the definite age and disease stage at which ERT should not be indicated or continued have not been decided yet.10) In addition, the appropriate age to start ERT for heterozygote patients is not clear. In female patients, myocardial fibrosis has been reported to progress earlier before significant thickening of the ventricular wall. An advanced technique, such as T1 mapping, to show the accumulation of sphingolipids might be preferable to decide the optimal timing to initiate ERT.14) There is a possibility that ERT somehow prevented the rapid worsening of cardiac dysfunction in Case 1. Standard therapies for heart failure, including cardiac rehabilitation, were also considered important to delay organ damage.

The progression and regression of left ventricular hypertrophy in Case 2 might be partially related to the appearance and disappearance of antibodies. The decrease in the efficacy of ERT among patients with high antibody titers has been documented in several reports.5,8,15) After the disappearance of the higher antibody titer, the clinical course of the patient in Case 2 improved. Although it is

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**Figure 8.** Two-dimensional echocardiography in Case 2 at the age of 33 (A) and 36 (B) years. The mid-ventricular short-axis view showed regression of LV hypertrophy within 3 years.

**Figure 9.** Cardiac MRI LGE images in Case 2 at the patient age of 35 years. No significant LGE was found in the left and right ventricles.
difficult to quantify the influence of antibodies on clinical outcomes because of the lack of biomarkers, there have been some reports about the negative effect of anti-αGal IgG antibodies.8,15) The monitoring of antibodies is an important consideration for the efficacy and safety of ERT.15) The regression of LVH is not only caused by ERT but also by the standard treatment of hypertension and cardiac rehabilitation. Another possible reason for the development of cerebral infarction in the earlier phase of ERT is the difficulty in crossing the blood-brain barrier.6) Stabilization of white matter lesion progression might result in a good clinical course at a later phase of ERT.16) Of course, diagnosis at a younger age and the earlier start of ERT in Case 3 could partially explain the better clinical course.

The lack of clinical symptoms in Case 3 also suggests the complex interrelationship between genotype and phenotype. Several different mutations have been reported with a poor genotype-phenotype correlation in Anderson-Fabry disease.13) There might be additional unknown intragenic abnormalities in the promoter or intron areas that affect the residual activity of enzymes. Interleukin 6 and factor V genes and other factors modifying lysosomal pH may influence the difference in phenotype.18,19) However, further studies are needed to clarify the complex relationship between the genotype and phenotype of the disease.

Disclosures

All three patients provided informed consent, and the case report was approved by the local ethical committee. Conflicts of interest: Mio Ebato (ME) received travel fee support from Sanofi K.K. to participate in the Fabry-related conference. ME also received honoraria from Sanofi K.K. for her contribution as a participant in round table discussions, adviser in educational meetings, and chairperson in local lecture meetings. The other authors have none to declare.

References