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Cardiac Characteristics of Fabry Disease in Japanese Children and Adolescents

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ABSTRACT

Fabry disease (FD) is a lysosomal storage disease caused by deficiency of α-galactosidase A. Although cardiac involvement is well documented in adult patients with FD, pediatric data is limited. The aim of the present study was to characterize cardiac changes in Japanese children and adolescents with FD. Data were collected from 25 patients (15 boys, 10 girls) ranging from 3 to 20 years of age. Median age at the first cardiac evaluation was 13.3 years in boys and 15.5 years in girls. Using the Sokolow-Lyon, Cornell, and Japanese left ventricular hypertrophy (LVH) criteria, LVH was found on ECG in 53%, 20%, and 0%, respectively, of male patients. The left ventricular mass index was normal in all patients. Thus, the Sokolow-Lyon and Cornell criteria might overestimate LVH in the ECG evaluation of pediatric FD. Although valvular regurgitation and prolapse were observed in 46% of male patients and 60% of female patients, the regurgitation was usually mild and subclinical. Some patients underwent enzyme replacement therapy during follow-up, and cardiac variables remained normal in all patients but 1 patient, who fulfilled the LVH criteria. In conclusion, cardiac involvement is minimal in Japanese children and adolescents with FD.

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Key words : Fabry disease, left ventricular hypertrophy, pediatrics, electrocardiography, echocardiography

INTRODUCTION

Fabry disease (FD) is a rare X-linked recessive disorder of lysosomal storage, caused by α-galactosidase A (GLA) deficiency. Absence or markedly reduced activity of GLA causes globotriaosylceramide (Gb-3) to accumulate in the heart, kidneys, dorsal root ganglia, and other tissues and organs throughout the body. FD is progressive and leads to premature death from cardiomyopathy, renal failure, or stroke[1,2]. The incidence of classic FD was previously estimated to be 1 in 40,000 to 60,000 live male births[3,4] but after the advent of neonatal screening the incidence is now thought to be 1 in 3,100 to 4,600 live male births[5]. The accumulation of Gb-3 starts in utero but symptoms do not appear until a few years after birth[6]. Common symptoms in the early stages of the disease are acute episodic pain in the extremities, acroparesthesia, hypohydrosis, heat and cold intolerance, angiokera-

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toma, and gastrointestinal symptoms[7,8]. Although these symptoms might not be life threatening, they strongly affect disease outcome and the quality of life of patients with FD. The mean age of disease onset is 10 years in boys[9] and 15 years in girls[10], but symptoms can appear as early as 3 years in boys and 6 years in girls[11]. Female heterozygotes with FD cannot be considered as simple carriers of the mutation because the majority of these patients will present with the same signs and symptoms of FD[12]. The difference in the age of onset and the severity of cardiac or renal dysfunction among female patients with FD was thought to be the effects of skewed X-chromosome inactivation. However, some studies have shown that the occurrence and severity of clinical manifestations are not correlated with X-chromosome inactivation[13].

The heart is a major organ affected by Gb-3 accumulation in FD. The main feature of cardiovascular involvement is left ventricular (LV) hypertrophy (LVH) with interstitial fibrosis and fibrotic replacement of the myocardium. Cardiovascular symptoms appear at around the age of 32 years in men and 40 years in women[14]. The accumulation of Gb-3 can be seen in all cardiac cell types. Myocardial accumulation can lead to hypertrophic cardiomyopathy[15]. Deposits of Gb-3 in coronary epithelial cells can lead to acute coronary syndrome[16], and endocardial involvement mainly causes thickening of the aortic and mitral valve leaflets[17]. Conduction cells are also prone to Gb-3 accumulation, which causes various types of arrhythmias and disturbances of the conduction system, including bradycardia, bundle-branch block, atrioventricular block, sick-sinus syndrome, atrial fibrillation, and PR interval shortening[18-20]. Arrhythmias may be accompanied by a disturbance in the autonomic control of heart rate, resulting in rate variability. Symptoms include dyspnea, palpitations, chest discomfort, shortness of breath, and reduced exercise intolerance[21].

Cardiovascular involvement increases with age and strongly affects the morbidity and mortality of patients with FD. However, little is known about the changes that occur during childhood. Structural changes are uncommon ; however, reduced heart rate variability (HRV) and arrhythmias are often seen[22,23]. Currently 2 types of enzyme treatments are available. One is agalsidase alfa (Replagal®, Shire Human Genetic Therapies Inc., Cambridge, MA, USA) and the other is agalsidase beta (Fabrazyme®, Genzyme Corporation, Cambridge, MA, USA). Substantial clinical data have demonstrated the effectiveness of both enzymes for slowing the progression of cardiac involvement in FD[24,25]. However, information on the effectiveness of enzyme replacement therapy (ERT) for reducing cardiac morbidity in pediatric patients is limited.

The main purpose of this study was to characterize the electrocardiographic (ECG) and echocardiographic findings of Japanese children and adolescents with FD and their responses to ERT.

METHODS

1. Study Population (Table 1)

We performed a chart review of 25 patients with FD, the diagnosis of which was confirmed by measuring GLA activity in peripheral white blood cells or analysis of the GLA gene (GLA) or both. All enrolled patients visited the Department of Pediatrics, The Jikei University School of Medicine, from 1997 through 2013. The patients were 15 male patients and 10 female patients. The age range at the time of the first cardiac evaluation was 3 to 20 years (mean, 13.3 years) for males and 14 to 20 years (mean, 15.5 years) for females. ERT was performed for 14 of 15 males and 4 of 10 females. ERT was started for male patients at the age of 5 to 26 years (mean, 16.1 years) for female patients at the age of 14 to 21 years (mean, 19.4 years). The mean duration of follow-up for patients who had received ERT was 7.7 years (range, 0.2 to 26 years) for males and 8.2 years (range, 4.5 to 15.9 years) for females. Patients had received either agalsidase alfa or agalsidase beta. Some patients had switched from agalsidase beta to agalsidase alfa because of the global shortage of agalsidase beta due to viral contamination during manufacturing. Patients 3 and 6 ; patients 4, 17, and 18 ; and patients 15 and 25 were from the same families. This study protocol was approved by the institutional ethics review board, and all subjects or their guardians or both gave written informed consent during the start of the annual visits.

All ECG and echocardiographic data obtained at the first cardiac evaluation were analyzed. From 6 of 14 male patients and 3 of 4 female patients who had received ERT, ECG, echocardiographic data, and brain natriuretic protein (BNP) values were obtained at different time points after ERT. Thus, the responses to ERT were able to be ana-

Table 1. Patient profiles

Patient number (n=25)	Sex	Age at first cardiac evaluation (years)	ERT during follow-up	Age at initiation of ERT (years)	Years of follow-up	Treatment (ERT)	Family
1	Male	3.0	–	–	–	–	
2	Male	4.9	Yes	5.1	7.0	beta	
3	Male	5.2	Yes	5.4	9.1	beta → alfa → beta	*
4	Male	8.5	Yes	19.8	18.3	alfa	**
5	Male	11.2	Yes	11.4	0.2	beta	
6	Male	12.0	Yes	12.3	9.8	beta → alfa → beta	*
7	Male	12.8	Yes	26.5	26.0	beta → alfa	
8	Male	14.5	Yes	14.6	4.4	alfa	
9	Male	15.5	Yes	15.9	8.5	beta	
10	Male	15.8	Yes	16	3.1	alfa	
11	Male	16.1	Yes	16.2	8.0	beta	
12	Male	18.7	Yes	19.8	1.5	beta	
13	Male	20.6	Yes	20.9	4.6	alfa	
14	Male	20.4	Yes	20.7	0.9	beta	
15	Male	20.6	Yes	20.8	6.6	alfa	***
		13.3 (mean)	14/15 (93%)	16.1 (mean)	7.7 (mean)		
16	Female	13.4	Yes	14.6	4.5	alfa	
17	Female	13.0	–	–	–	–	**
18	Female	13.0	Yes	20.4	15.9	beta	**
19	Female	13.4	–	–	–	–	
20	Female	14.2	–	–	–	–	
21	Female	16.1	–	–	–	–	
22	Female	17.9	Yes	20.8	6.8	beta → alfa	
23	Female	17.0	–	–	–	–	
24	Female	18.5	Yes	21.9	5.6	alfa	
25	Female	18.6	–	–	–	–	***
		15.5 (mean)	4/10 (40%)	19.4 (mean)	8.2 (mean)		

ERT : Enzyme replacement therapy
alfa : alfa agalsidase Replagal® 0.2 mg/kg biweekly
beta : beta agalsidase Fabrazyme® 1.0 mg/kg biweekly
* : Patient 3 and 6 are from the same family
** : Patient 4, 17 and 18 are from the same family
*** : Patient 15 and 17 are from the same family

lyzed. A value of "0" refers to data obtained just before the start of ERT. Other patients were transferred to another hospital after the start of ERT ; thus, the follow-up data were not available.

2. ECG

All ECGs were performed in a standard manner. They were recorded with a paper speed of 25 mm/second with an amplitude of 1 mV/cm. The following variables were assessed : QRS axis, heart rhythm, heart rate, PR interval, QRS duration, QTc (Bazett's formula and Fridericia's formula), and R wave and S wave amplitudes in leads V1, V5, and V6. Sokolow-Lyon voltage[26], Cornell voltage[27], and Japanese LVH criteria[28] were used to assess LVH. Sokolow-Lyon voltage was defined as the sum of the voltages of S in V1 and R in V5 or V6 (whichever was higher). To determine the Cornell voltage, the sum of S in V3 and R of aVL was used. The Japanese LVH criteria (Table 2) use a point-based scoring system based on sex and different age groups. The major components of the scoring systems are high R with a biphasic or inverted T wave in V5 or V6, voltage of RV5 or RV6, and sum of SV1 and RV5 or RV6. Bradycardia was defined as a heart rate less than 100 beats per minute (bpm) in patients aged 0 to 3 years, less than 60

Table 2. Japanese LVH criteria

score	Findings / Age	0–7 days	8–30 days	1 month–2 years	3–11 years	12 years and older	
						male	female
5 pts	Left hypertophic ST–T changes in V5 or V6	+	+	+	+	+	+
3 pts	(a) RV6	≧ 1.5 mV	≧ 2.0 mV	≧ 2.5 mV	≧ 3.0 mV	≧ 3.0 mV	≧ 2.5 mV
	(b) RV5	≧ 2.5 mV	≧ 2.5 mV	≧ 3.5 mV	≧ 4.0 mV	≧ 4.0 mV	≧ 3.5 mV
	(a) |SV1| + RV6	*	*	≧ 4.0 mV	≧ 5.0 mV	≧ 5.0 mV	≧ 4.0 mV
	(b) |SV1| + RV5	*	*	≧ 5.0 mV	≧ 6.5 mV	≧ 6.0 mV	≧ 5.0 mV
	(c) |SV1|	≧ 2.5 mV	≧ 2.0 mV	*	*	*	*
	|QV5| < |QV6| also |QV6|	*	*	*	≧ 0.5 mV	≧ 0.5 mV	≧ 0.5 mV
2 pts	(a) R II and R III	*	*	≧ 2.5 mV	≧ 2.5 mV	≧ 2.5 mV	≧ 2.5 mV
	(b) RaVF	*	*	≧ 2.5 mV	≧ 2.5 mV	≧ 2.5 mV	≧ 2.5 mV
	VATelongation on V5 or V6	*	*	≧ 0.04 s	≧ 0.05 s	≧ 0.06 s	≧ 0.06 s
1 pts	Left Axis Deviation	*	*	*	≧ 0°	≧ − 30°	≧ − 30°

1. Hypertrophic changes : Tall R wave on V5 or V6 and negative or biphasic T wave
   ST segment often presents as downsloping or horizontal
2. Distinguishing LVH may be difficult with Wolff–Parkinson–White syndrome or when LBBB is present
3. Only one match for subcriteria (a)–(c) is needed for each point

Result : 5 points or more : left ventricular hypertrophy
3–4 points : left ventricular hypertrophy suspected
1–2 points : no apparent left ventricular hypertrophy on ECG

bpm in subjects aged 3 to 9 years, and less than 50 bpm in those aged 9 to 16 years. The normal durations of the PR interval and QRS complex were defined as 120 to 240 milliseconds and 70 to 110 milliseconds, respectively. The PR interval was considered prolonged if the duration was greater than 240 ms. The QT interval was measured from the beginning of the QRS complex to the end of the T wave. The QT interval was corrected with Bazzet's formula and Fridericia's formula. A normal QTc was defined as 360 to 440 milliseconds. The ST segment elevation was defined as J point elevation of ≥2 mm in the precordial leads and ≥1 mm in the limb leads. Incomplete right bundle-branch block was defined as QRS <120 milliseconds with R´ wave > R wave in the precordial leads V1 and V2.

3. Echocardiography

Echocardiographic evaluation was performed with a digital ultrasound system with body size-matched transducers (2.5 MHz, 3.5 MHz, or 5.0 MHz). As recommended by the American Society of Echocardiography, measurements were made from M-mode tracings[29]. The LM mass was calculated with the modified Devereux formula. The LV mass was then indexed to body surface area to obtain the LV mass index (LVMI). LVH was defined as a LV mass greater than 103 g/m^2 in male patients and 84.2 g/m^2 in female patients[30]. The variables of systolic function were short axis LV ejection fraction (EF) and short axis fractional shortening. The variables of diastolic function included pulsed Doppler tracings of mitral valve inflow (including peak early [E] and late [A] diastolic transmitral velocities). A normal E/A ratio was defined as 2.4 ± 0.8 for ages 3 to 8 years, 2.2 ± 0.6 for ages 9 to 12 years, and 2.3 ± 0.6 for ages 13 to 17 years[31]. The normal value for adults was defined as 1.1 ± 0.3[32]. The diagnosis of mitral valve prolapse (MVP) was based on echocardiographic evidence of posterior displacement of one or both leaflets or coaptation of the left leaflet tips at or below the level of the annulus of the mitral valve. The severity of valvular regurgitation was graded as none, mild, moderate, or severe on the basis of previous transthoracic color flow criteria[33]. Regurgitation was considered clinically significant if the severity was greater than mild.

4. Statistical analysis

Statistical analysis was performed with the software package Graph Pad Prism® 6.03 (Graph Pad Inc., La Jolla, CA, USA) for Windows®. Data are expressed as mean ± standard error of the mean (SEM) when indicated. Differences among groups were analyzed with Student's *t*-test and Fisher's exact test. Differences were considered to be statically significant for $p<0.05$.

Results

1. ECG findings at the initial cardiac evaluation

The ECG findings revealed that LVH was present in 8 of 15 male patients (53%) on the basis of the Sokolow-Lyon criteria, in 3 male patients (20%) on the basis of the Cornell voltage criteria, and in no male patients on the basis of the Japanese LVH criteria (Table 3). One male patient (patient 14) had LVH on the basis of both the Sokolow-Lyon and Cornell voltage criteria. However, none of the female patients met the Sokolow-Lyon, Cornell, or Japanese LVH criteria for LVH.

Other ECG findings included sinus bradycardia, incomplete right bundle branch block, and right axis deviation. Heart rate, PR interval, QRS duration, and QTc time were within normal limits in all patients (data not shown). In addition, complete right bundle-branch block, atrioventricular block, and premature ventricular complex and ST-T change were not seen in any patient (Table 3).

2. Echocardiographic findings at the initial cardiac evaluation

The LVMI was within the normal range for 10 of 15 male patients and all 10 female patients (Table 4). None of the patients had systolic or diastolic dysfunction. Valvular insufficiency was present in the majority of patients (13 of 25 patients ; 52%). Among all patients, the most prevalent valvular disease was tricuspid regurgitation (40%) and was followed by MVP (16%) and mitral regurgitation (12%). Aortic valve regurgitation and valve thickening were not seen in any patient. Male and female patients did not differ significantly in mean LVMI, the prevalence of valvular insufficiency, or the prevalence of any type of valvular disease.

3. Cardiac response to ERT

Follow-up ECG and echocardiographic data after ERT were available for 6 male patients and 3 female patients. The ERT had been started in all patients before the age of 21 years (Table 1). The duration of ERT differed for each patient, and some data were missing. The HR and the PR and QRS intervals in all patients were stable during the study period (Fig. 1). EF and LVMI remained within normal range except for Patient 24. Patient 24 showed a continuous increase in LVMI, even while undergoing ERT (Fig. 2). Three years after the start of ERT, the LVMI in this patient was 84.6 g/m^2, which indicated LVH, although ECG findings did not meet Sokolow-Lyon criteria, Cornell, or Japanese criteria for LVH. The level of BNP also remained with the in normal range up to 3 years after the start of ERT. Other variables remained stable after ERT. The BNP levels remained within the normal range in all patients, except for patient 3. Although patient 3 had high BNP levels, the HR, EF, and other variables remained within the normal range (Fig. 3).

Discussion

Cardiac involvement strongly affects the overall disease outcome and decreases the quality of life of patients with FD. Previous studies focusing on FD in children and adolescents have shown that minute changes in HRV and ECG variables are early cardiac findings[22,23]. However, heart failure and cardiac remodeling are not seen at this stage. In the present study, some patients were found to have LVH on the basis of the Sokolow-Lyon criteria and Cornell voltage criteria, but none of the patients had LVH on the basis of the age-based Japanese LVH criteria. All patients had a normal LVMI value. Because our initial cardiac evaluation data were obtained from patients aged 3 to 20 years, the accuracy of Sokolow-Lyon and Cornell criteria for detecting LVH is questionable. Among numerous criteria, the only age- and sex-specific criteria available is the Japanese LVH criteria, which was created by the Japanese Society of Pediatric Cardiology and Cardiac Surgery for assessing LVH accurately on the basis of age and sex[28]. This criteria is widely used in Japan for screening for LVH, from newborns to adolescents.

To determine whether the ECG criteria of Sokolow-Lyon criteria and Cornell criteria for LVH are accurate for

Table 3. ECG findings at the first cardiac evaluation

	Patient number (n=25)	Positive for LVH criteria			others
		S-L	Cor	JA-LVH	
male	1	−	−	−	
	2	+	−	−	
	3	+	−	−	
	4	−	−	−	
	5	+	−	−	
	6	+	−	−	IRBBB
	7	−	−	−	
	8	−	−	−	IRBBB
	9	−	+	−	RAD, IRBBB
	10	+	−	−	
	11	+	−	−	
	12	−	+	−	
	13	+	−	−	
	14	+	+	−	
	15	−	−	−	
	frequency	8/15 (53%)	3/15 (20%)	0/15 (0%)	
female	16	−	−	−	
	17	−	−	−	
	18	−	−	−	bradycardia
	19	−	−	−	
	20	−	−	−	
	21	−	−	−	
	22	−	−	−	bradycardia
	23	−	−	−	
	24	−	−	−	
	25	−	−	−	
total (male and female)	frequency	8/25 (32%)	3/25 (12%)	0 (0%)	

S-L : Sokolow-Lyon voltage criteria
Cor : Cornell voltage criteria
JA-LVH : Japanese LVH criteria
RAD : right axis deviation
IRBBB : incomplete right bundle branch block

pediatric patients, we looked at ECG from all 15 individuals (8 male and 7 female), matched for age (2 to 20 years), who visited our department of pediatrics from July 2013 through November 2014 and had normal LVMI. LVH was present in 1 patient with the Sokolow-Lyon criteria and in 2 patients with the Cornell criteria (data not shown). All 3 patients did not have LVH according to the Japanese LVH criteria Therefore ; these results suggest that Sokolow-Lyon and Cornell criteria overestimate LVH in children, including those with FD. On the basis of these findings, we recommend the use of the Japanese LVH criterion for assessing LVH in pediatric patients, including those with FD.

In our study, various types of valvular dysfunction, including MVP, mitral regurgitation, and tricuspid regurgitation, were present in 7 male patients (46%) and 6 female patients (60%) at the initial cardiac evaluation. The aortic valves of all male and female patients were intact. Hopkin et al. have reported that valvular dysfunction was present in 22.6% of boys and 13.9% of girls with FD[7]. Sakuraba et al. have reported that MVP was present in 5 of 9 men (55%)

Table 4. Echo findings at the first cardiac evaluation and Statistical Analysis

	Patient number (n=25)	MVP	MR	TR	AR	Presence of Valvular insufficiency (+ or −)	Patient number (n=25)	LVMI (g/m^2)
male	1	−	−	−	−	−	1	44
	2	+	−	−	−	+	2	NA
	3	−	−	−	−	−	3	NA
	4	−	−	−	−	−	4	NA
	5	−	−	mild	−	+	5	66
	6	−	−	mild	−	+	6	76.1
	7	−	−	−	−	−	7	NA
	8	−	−	mod	−	+	8	85
	9	+	mild	mild	−	+	9	81
	10	−	mild	−	−	+	10	65
	11	+	−	−	−	+	11	NA
	12	−	−	−	−	−	12	40.1
	13	−	−	−	−	−	13	84
	14	−	−	−	−	−	14	64
	15	−	−	−	−	−	15	74
	frequency	3/15 (20%)	2/15 (13%)	4/15 (26%)	0/15 (0%)	7/15 (46%)	mean±SEM	67.92±4.943
female	16	−	mild	mild	−	+	16	65
	17	−	−	−	−	−	17	56
	18	−	−	−	−	−	18	60
	19	−	−	−	−	−	19	56
	20	−	−	mild	−	+	20	66
	21	−	−	mild	−	+	21	50
	22	−	−	mild	−	+	22	64.2
	23	−	−	−	−	−	23	66.9
	24	−	−	mild	−	+	24	64
	25	+	−	mild	−	+	25	60
	frequency	1/10 (10%)	1/10 (10%)	6/10 (60%)	0/10 (0%)	6/10 (60%)	mean±SEM	60.81±1.725
total (male and female)	frequency	4/25 (16%)	3/25 (12%)	10/25 (40%)	0/2 5(0%)	13/25 (52%)	comparison of male and female	p=0.1912
comparison of male and female		p=0.6265	p=1.00	p=0.1221	p=1.00	p=0.6882		

NA : not available
MVP : mitral valve prolapse
MR : mitral regurgitation
TR : tricuspid regurgitation
AR : aortic regurgitation
mod : moderate
LVMI : left ventricular mass index

and 5 of 13 women (38%) with FD[34]. The definitions of valvular dysfunction in previous studies are not clear ; thus, direct comparison of our data with previous data is difficult. The degree of regurgitation in most of our patients was mild and could be considered subclinical. On the other hand, the prevalence of MVP in our patients (16%) was higher than in the general population : the prevalence of MVP is 0.3%[35] from 0 to 19 years and 0.6% from 23 to 35 years[36]. This result suggests that FD should be considered in otherwise asymptomatic pediatric patients with sub-

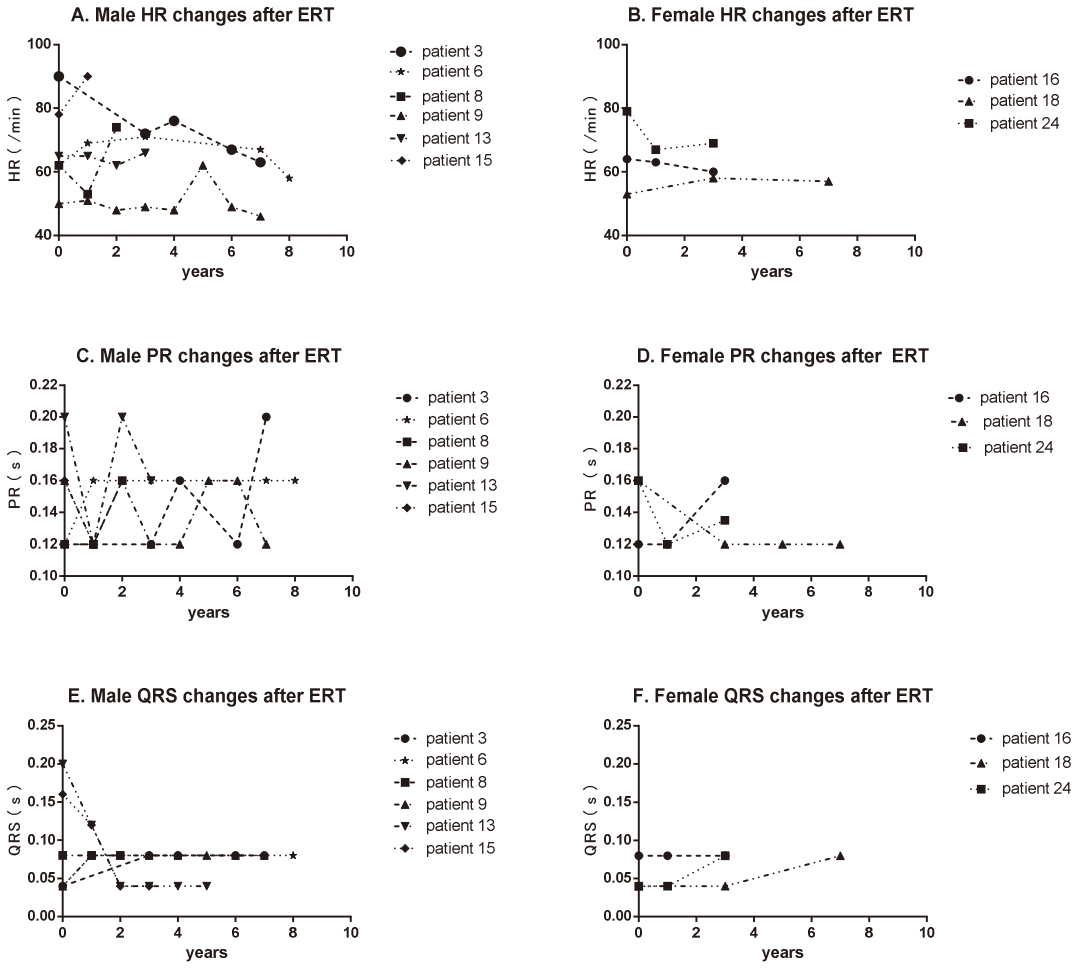

Fig. 1. Changes in ECG after ERT in male and female patients
Individual ECG data at various time points after the start of ERT are shown. All variables remained within their normal ranges.

clinical MVP or tricuspid regurgitation.

Patient 24 was the only patient in whom LVH developed during ERT. All cardiac variables were in their normal ranges at the initial evaluation and the evaluation just before ERT. We do not know why only this patient developed LVH. In other patients, most cardiac variables remained normal.

Our study had several limitations. Because this was a chart review study, some ECG and echocardiographic data from the first cardiac evaluation and from evaluations at various time points after ERT were not available. In addition, only conventional ECG and echocardiographic data regarding cardiac function were evaluated. Evaluation of HRV using Holter monitoring, tissue Doppler imaging[37], and speckle-tracking imaging indicating strain and strain rate[38] should be considered. In fact, tissue Doppler imaging is useful for the early detection of LVH, and strain and strain rate are used to analyze systolic and diastolic function. Cardiac magnetic resonance with late enhancement is used to detect fibrosis[39]. Combining these noninvasive methods should provide a better understanding of the progression of cardiac involvement. Also, it might be necessary to compare the cardiac effects of agalsidase alfa with agalsidase beta. However, the small sample size makes such a comparison difficult.

In conclusion, the present study is, to our knowledge, the first to characterize cardiac findings in Japanese children and adolescents with FD. Overall, the cardiac function of these patients was minimally affected. Regarding the timing of ERT, we cannot recommend an exact time on

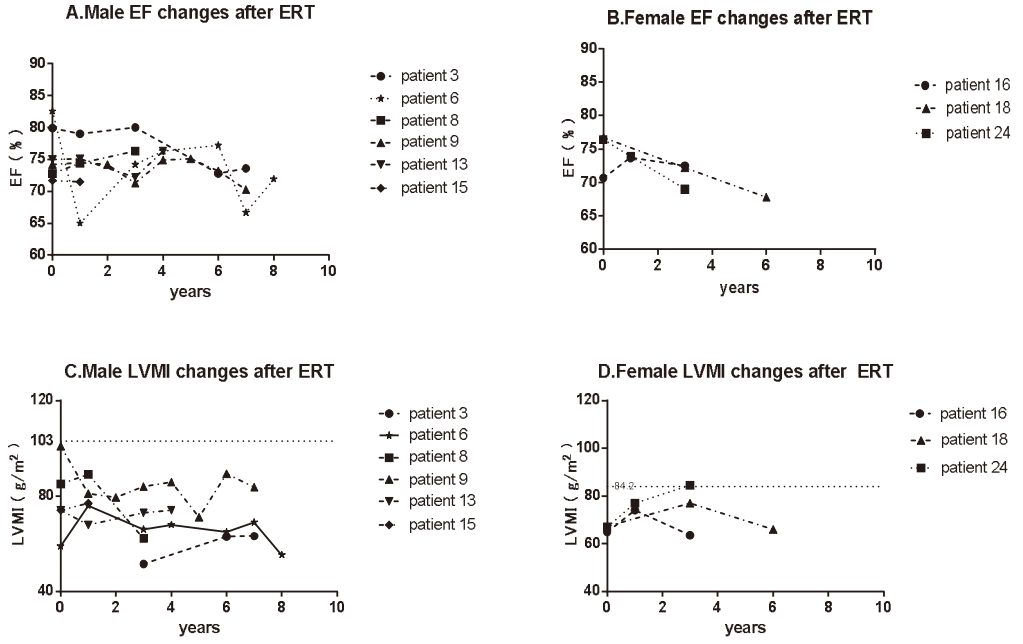

Fig. 2. Changes in echocardiographic data after ERT in male and female patients
Individual echocardiographic data at various time points are shown. All variables remained within their normal ranges after the start of ERT, except for LVMI in patient 24 at 3 years after ERT
EF : ejection fraction
LVMI : left ventricular mass index
ERT : enzyme replacement therapy
Dotted lines in C and D represent the value of LVH in each sex

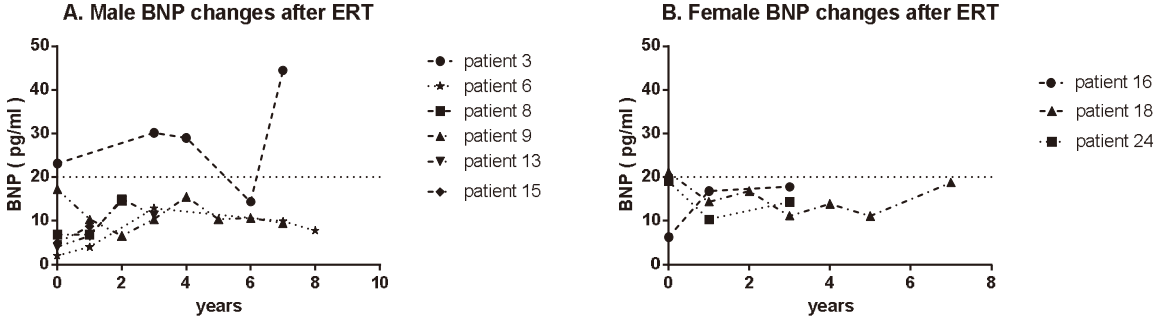

Fig. 3. Changes in BNP in male and female patients after ERT
Individual data of BNP at various time points are shown. The BNP levels remained within the normal range in all patients but patient 3.

the basis of our present data. However, MVP was present in some patients at the first cardiac evaluation, and LVH developed in 1 patient during the follow-up period. Therefore, an early start of ERT might be necessary in such patients. The progression of cardiac dysfunction differs greatly in individual patients. Therefore, to detect the early onset of cardiac dysfunction such biomarkers as atrial natriuretic peptide, BNP, and troponin T might be useful. These biomarkers and imaging studies described earlier should be considered to monitor FD in a prospective manner. A prospective study is needed to clarify the extent of cardiac involvement and the response to ERT in children and adolescents with FD.

CONFLICT of INTEREST STATEMENT

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