

[CASE REPORT]

Fabry Disease with Pacemaker Implantation as the Initial Event

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Abstract:

Fabry disease (FD) is a rare X-linked hereditary disorder (Xq22) caused by a deficiency in alpha-galactosidase activity. A 34-year-old man was referred to our hospital because of renal dysfunction. He had previously undergone pacemaker implantation at 24 years of age. Investigations revealed undetectable alpha-galactosidase A activity levels. Renal biopsy results indicated vacuolization of podocytes. A genetic analysis revealed that the patient carried the W340X mutation. Enzyme replacement therapy with agalsidase beta was started. This case is novel because most cases of FD nephropathy precede cardiac disease. In our patient, the cardiac event was the initial event, and renal impairment followed.

Key words: Fabry disease, Lyso-Gb3, pacemaker implantation, chronic kidney disease, mulberry cell, W340X

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Introduction

Fabry disease (FD) is a rare X-linked hereditary disorder (Xq22) caused by mutations in the alpha-galactosidase gene (*GLA*) that lead to a deficiency in alpha-galactosidase (α -GAL) activity. This enzyme deficit results in a systemic accumulation of glycosphingolipids [globotriaosylceramide (Gb3)], leading to multi-organ failure affecting the heart, kidneys, and brain.

We herein report the case of a 34-year-old patient with renal insufficiency who had previously undergone pacemaker implantation (PMI) at 24 years of age. This case shows that a clinical diagnosis of FD may be complicated for patients with a cardiac history and highlights the importance of rethinking the natural history of FD.

Case Report

A 34-year-old Japanese man was referred to our hospital with an increasing serum creatinine (sCr) level (from 0.60 to 1.49 mg/dL within 1 year). We found subacute exacerbation

of the renal function. He had no history of renal toxic drug use, dehydration, body weight change, or contrast material use. Proteinuria had been noted at his annual health examination from 29 years of age, but no further examination had been recommended at that time.

He was referred to a nephrologist for further investigation and renal biopsy consideration. His medical history was significant because it included PMI for idiopathic sick sinus syndrome (SSS) at 24 years of age.

The results of a 12-lead electrocardiogram showed normal sinus rhythm and a PQ interval within the normal range at that time (Fig. 1). A Holter electrocardiogram showed sinus arrest for up to 4.11 seconds (Fig. 1). Sinus arrest with a maximum RR interval of 4.1 seconds on the Holter electrocardiogram and 13 sinus arrests for 2 seconds or more were recognized, and he was diagnosed with SSS type II (according to the Rubenstein classification). An electrophysiologic study (EPS) showed no sinus node recovery time extension of 1.4 seconds or more, thereby disproving SSS. The results of a cardiac ultrasound examination showed an ejection fraction of 71%, normokinesis and no left ventricular wall thickening. Coronary arteriography revealed no coronary artery

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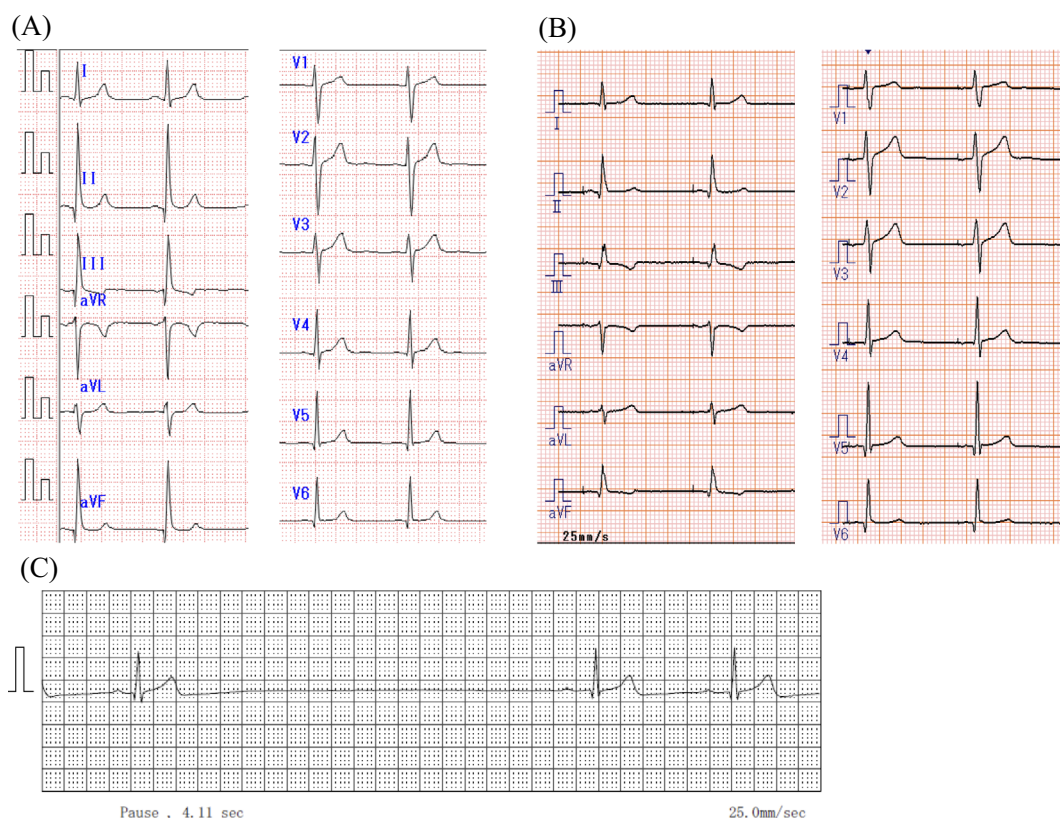


Figure 1. Results of 12-lead electrocardiograms (A) at 34 years old and (B) 24 years old, when a pacemaker was implanted. (C) The Holter electrocardiogram at the time when sick sinus syndrome was diagnosed.

stenosis or coronary artery spasm. A myocardial biopsy and magnetic resonance imaging (MRI) examination were not performed at that time.

On admission, his vital signs were as follows: blood pressure, 132/76 mmHg; heart rate, 66 beats per minute; height, 171 cm; weight, 103 kg; and body mass index (BMI), 35.2 kg/m². A physical examination revealed a dark red rash on his lower back, and biopsy results confirmed a diagnosis of angiokeratoma. The only abnormality that was found was obesity. Chest radiography showed the generator of the PMI in the left subclavian artery, with the tip of the lead in the right ventricular artery and no signs of congestion (cardiothoracic ratio, 46%). A paced rhythm was found with a 12-lead electrocardiogram (Fig. 1). The results of a complete blood count test and those of serum glucose, hemoglobin A1c, electrolyte, and liver function tests were all within the normal range. There was evidence of hypertriglyceridemia. Serum complement factor and immunoglobulin levels were within the normal range. Mulberry cells were detected in the urinary sediment (Table and Fig. 2). Cardiac ultrasound showed an interventricular septum thickness of 9.5 mm, left ventricular posterior wall thickness of 9.4 mm, ejection fraction of 62.7%, no left ventricular hypertrophy, and no patchy echo or layered echo, which are characteristic of FD.

The patient's family tree is shown in Fig. 3. The patient's father had a history of hypertension and gout; however, he had no characteristic symptoms of FD. The patient's mother

underwent PMI at age 56 years and had cardiomegaly. His older sister was obese (BMI, 35.6 kg/m²) but otherwise healthy. After FD was diagnosed, we re-interviewed his family members and found that his mother and older sister had experienced acroparesthesias (severe neuropathic or limb pain). His maternal grandfather died at 77 years of age due to laryngeal carcinoma and had a history of arrhythmia and heart murmur. His maternal grandmother had died at 70 years of age and had a history of angina pectoris in her 40s, as well as total uterine ablation, cataracts, and diabetes mellitus. There was no history of consanguineous marriage. The patient had a 7-year-old son and twin 5-year-old daughters. Following a further interview with the patient, it was revealed that he had also experienced acroparesthesias and had a history of reduced sweating during his youth that continued to the present.

We thought that the patient's history of cardiac and renal insufficiency was in keeping with the family history of cardiovascular events at a young age. Initial investigations revealed that the α -GAL activity was undetectable. Renal biopsy specimens included seven glomeruli with no evidence of glomerular hypertrophy. None of the glomeruli exhibited global sclerosis; however, one glomerulus exhibited segmental sclerosis. The podocyte vacuoles score (1) was 3. All glomeruli demonstrated foamy changes in the podocytes (Fig. 2).

An immunofluorescence study revealed negative immuno-

Table. Results of the Complete Blood Count, Biochemistry, Urinalysis, and Protein Fraction at Admission.

Compleat blood count data		Biochemistry data		Biochemistry data		Urinalysis	
WBC	5,500 / μ L	TP	7.6 g/dL	α -GAL activity	0.0 nmol/mg/protein	Specific gravity	1.005
Neut	69.6 %	T-bil	0.7 mg/dL	IgG	1,584 mg/dL	pH	5.5
Lymph	20.5 %	AST	20 IU	IgA	281 mg/dL	UP	0.5 g/gCre
Mono	6.1 %	ALT	29 IU	IgM	94 mg/dL	Glu	-
Eos	2.0 %	ALP	228 IU	C3	130 mg/dL	uOB	-
Baso	0.2 %	γ -GTP	28 IU	C4	26 mg/dL	Ketone	1+
RBC	463 $\times 10^4$ / μ L	LDH	170 IU	CH50	61.0 CH50/mL	WBC elastase	-
Hb	13.7 g/dL	CPK	85 IU	ANA	<40	Nitrate	-
Ht	41.9 %	Ferrrtin	136 ng/mL	MPO-ANCA	<1.0 U/mL		
Plt	16.2 $\times 10^4$ / μ L	BNP	7.3 pg/mL	PR3-ANCA	<1.0 U/mL	Urine sedimentation	
MCV	90.5 fL	Toroponin T	0.08 ng/mL	Anti-GBM	<2.0 U/mL	uRBC	<1 /HPF
MCH	29.7 pg	TChol	199 mg/dL			uWBC	<1 /HPF
MCHC	32.8 %	TG	233 mg/dL			Mulberry body	positive
ESR1h	16 mmh	HDL	39 mg/dL				
		BUN	17.3 mg/dL				
		Cr	1.43 mg/dL				
		UA	9.6 mg/dL				
		Na	142 mEq/L				
		K	4.3 mEq/L				
		Cl	107 mEq/L				
		Ca	9.0 mg/dL				
		P	3.2 mg/dL				
		Glu	97 mg/dL				
		HbA1c	5.6 %				
		CRP	0.21 mg/dL				

WBC: white blood cell, Neut: neutrophil, Lymph: lymphocyte, Mono: monocyte, Eos: eosinophil, Baso: basophil, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, Plt: platelet, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, ESR: erythrocyte sedimentation rate, TP: total protein, T-bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γ -GTP: gamma-glutamyltransferase, LDH: lactate dehydrogenase, CPK: creatine phosphokinase, BNP: brain natriuretic peptide, TChol: total cholesterol, TG: triglyceride, HDL: high-density lipoprotein, BUN: blood urea nitrogen, Cr: creatinine, UA: uric acid, Na: sodium, K: potassium, Cl: chloride, P: inorganic phosphorus, Glu: glucose, HbA1c: hemoglobin A1c, CRP: C-reactive protein, α -GAL: alpha-galactosidase, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, ANA: antinuclear antibody, MPO-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibody, PR3-ANCA: proteinase 3-antineutrophil cytoplasmic antibody, Anti-GBM: antiglomerular basement membrane antibody, UP: urine protein, uOB: urine occult blood, IU: international unit, HPF: high-power field

globulin (Ig)G, IgA, IgM, fibrinogen, C1q, and C3 levels. Electron microscopy showed no immune complex depositions. There were zebra bodies (myelin-like inclusions) in the podocytes as well as mesangial lesions (Fig. 2). These findings were compatible with Fabry nephropathy. A gene analysis revealed a W340X (TGG to TAG) mutation in the seventh exon of the *GLA*. An eye examination revealed cornea verticillata.

Based on these findings, enzyme replacement therapy (ERT) was initiated with the intravenous administration of agalsidase β at a dose of 1.0 mg/kg. After initiating ERT, the patient's condition remained stable without any complications. His sCr and proteinuria levels did not change, but the Gb3 level decreased by 30% (Fig. 4).

A further investigation revealed that the patient's mother, older sister, and twin daughters also carried the same *GLA* W340X mutation. His daughters are asymptomatic for FD to date; therefore, they have not undergone ERT, and we are observing them closely. However, the patient's mother also started ERT with agalsidase β at a dose of 1.0 mg/kg.

Discussion

FD is known to cause hypertrophic cardiomyopathy (HCM); in fact, FD is estimated to affect 1.1-3% of Japanese men with a clinical diagnosis of HCM (2, 3). A similar prevalence has been reported in other countries, including Great Britain, Italy, and Spain (4-6).

The accumulation of Gb3 in the myocardium begins early in life. Left ventricular hypertrophy can be found decades later, at an average age of 32 years for men and 40 years for women, when cardiac symptoms are reported (7). This suggests that left ventricular hypertrophy might not be the first cardiac event of FD. Arrhythmia, conduction abnormality requiring PMI, myocardial infarction, or heart failure can be the first cardiac event of FD (8, 9). Indeed, several cases of FD with SSS have been reported (9, 10).

PMI is an important consequence of FD cardiomyopathy. Schiffman et al. (11) reported that 10 out of 447 (2.2%) FD patients underwent PMI, whereas Lenders et al. (12) re-

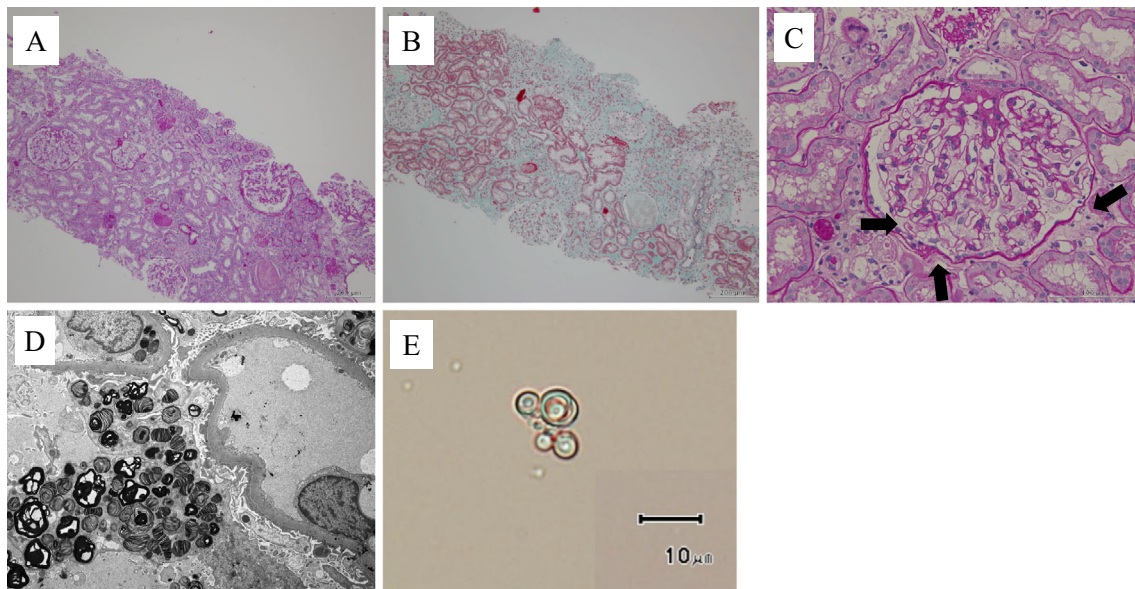


Figure 2. Results of the renal biopsy. (A) Periodic acid-Schiff staining on light microscopy in a low-power field (magnification $\times 100$). (B) Elastica-Masson staining on light microscopy in a low-power field to distinguish renal cells from surrounding connective tissue. (C) Periodic acid-Schiff staining on light microscopy in a high-power field (magnification $\times 400$). Foamy changes in podocytes are visible (arrow). (D) An electron micrograph of the renal biopsy. Zebra bodies (myelin-like inclusions) are visible in the podocytes and mesangial lesion. (E) A picture of Mulberry cells detected in the urinary sediment.

Family Tree

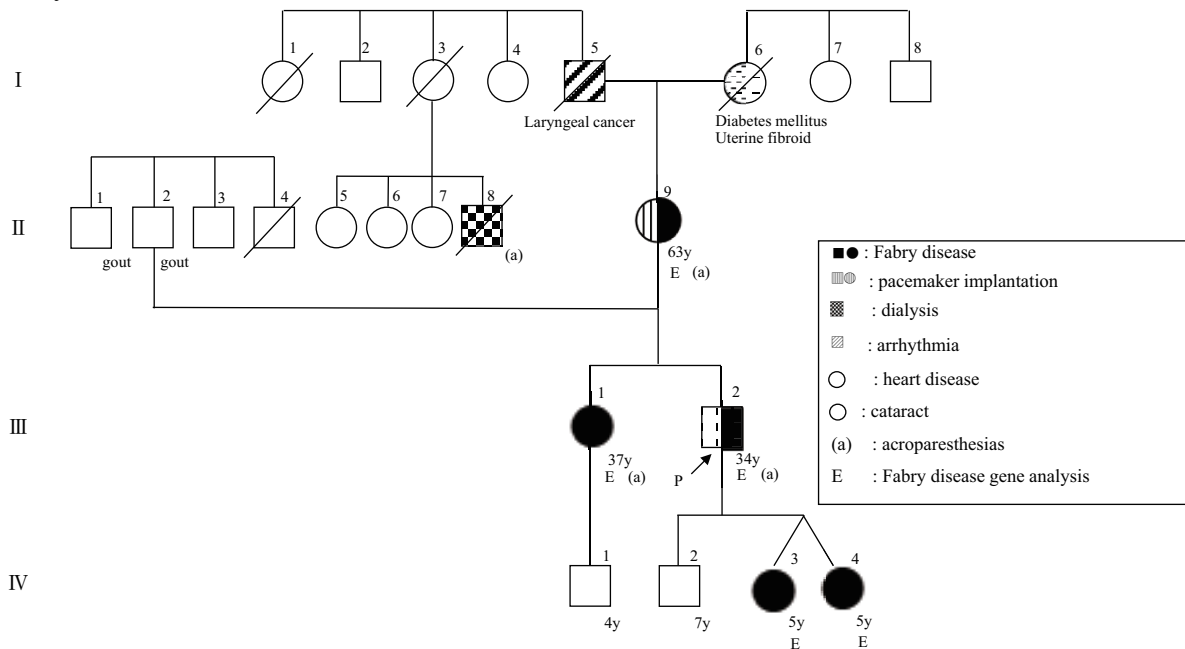
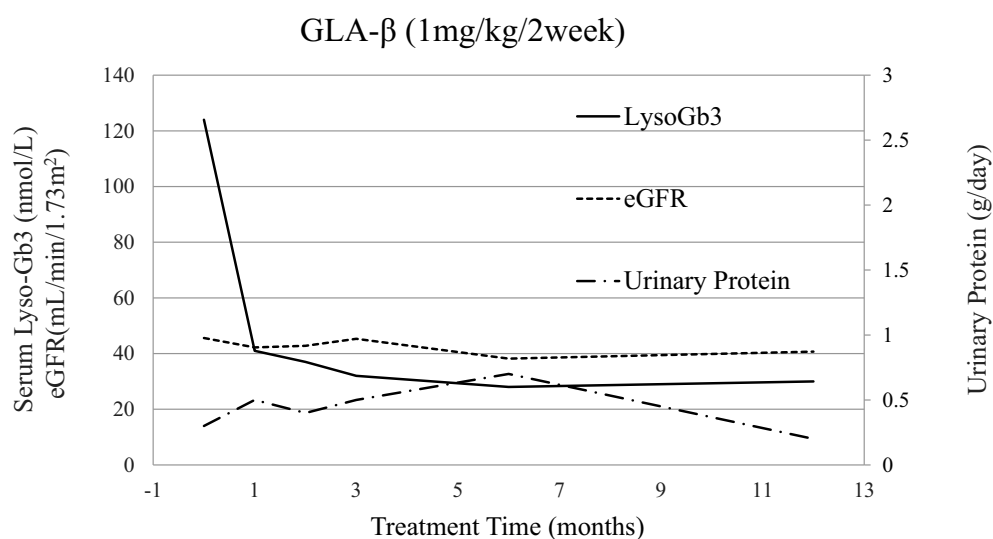


Figure 3. The patient's family tree. Squares denote men, circles denote women, and oblique lines denote deceased individuals.

ported that the prevalence of PMI for FD patients using ERT was 9.7%. Linhart et al. (7) reported that 22 out of 714 (3%) FD patients underwent PMI at the start of ERT, whereas Shah et al. (13) reported that 4 out of 78 (5%) FD patients received a pacemaker. Lidove et al. (14) reported that 37 out of 2,044 (1.8%) patients with FD underwent car-

diac PMI, transplantation, or defibrillator implantation. Sene et al. (9) reported that 8 out of 49 (16%) patients underwent PMI. One patient underwent PMI before an FD diagnosis. The median age at the time of cardiac device implantation was 57 years [interquartile range (IQR), 53-70 years; range, 26-57 years]. Furthermore, because FD is a progressive dis-



	0	4	8	12
BNP (pg/mL)	7.3	3.7	5.1	10.7
IVS (mm)	9.5	-	-	11.7
LVPW (mm)	9.4	-	-	12.5
BP (mmHg)	132/76	130/80	123/76	130/79
HR (bpm)	66	74	72	63

Figure 4. The effect of agalsidase- β on globotriaosylceramide (Gb3), eGFR, and proteinuria. BNP: brain natriuretic peptide, IVS: interventricular septum, LVPW: left ventricular posterior wall, BP: blood pressure, HR: heart rate, bpm: beats per minute

ease, the possibility of organ failure increases with age. Therefore, the frequencies of PMI, transplantation, and defibrillator implantation also increase with advancing age.

The above results suggest that PMI is not a rare occurrence for patients with FD. However, these reports did not mention the age at which patients underwent PMI. Indeed, as glycosphingolipid accumulation worsens during FD, there is an increased risk of conduction disorders due to the accumulation of glycosphingolipids affecting conduction tissues, thus contributing to prolonged refractoriness and electrical instability (15), which may explain the association between FD and PMI.

Frustaci et al. (15) evaluated endomyocardial biopsy sections of conduction tissues, finding that FD patients with ventricular arrhythmias demonstrated the prominent infiltration of conduction tissue compared to myocytes. They hypothesized that this pathological discrepancy might be caused by increased energy metabolism in conduction tissue cells with a reduced availability of the lysosomal enzyme α -GAL and degradation of the subcellular ultrastructure. Arrhythmia can precede left ventricular hypertrophy. The authors further suggested that the accumulation of Gb3 might shorten the PR time and HV interval, that the accumulated amount and magnitude of the potential of QRS were correlated, and that glycosphingolipid enhanced the conduction to the myocardium.

While the above findings may explain tachyarrhythmias, bradyarrhythmias such as atrioventricular block and SSS may occur through a different mechanism. In conduction tissues, Gb3 affects the degradation of myofilaments, energy metabolism, and creatinine-phosphate diffusion with consequent dysfunction of membrane pumps (16). In patients with amyloidosis and sick sinus syndrome, the degree of amyloid deposition in the sinoatrial node tends to be greater than in patients with amyloidosis without arrhythmia (17). In sarcoidosis, conduction abnormalities develop as a result of the formation of scar tissue and/or granulomas at the basal septum or near the nodal artery, causing ischemic damage to the conduction tissues (18). The mechanism by which arrhythmia occurs in FD has not yet been elucidated, and we speculate that these mechanisms cause SSS. To our knowledge, no study has yet reported on the frequency of GLA mutations in patients with SSS. This point should be investigated in a future study.

The presenting complication of FD in the present patient was SSS requiring PMI, highlighting an important question: Can PMI be the initial event of FD? In 1995, a Japanese research team studying idiopathic cardiomyopathy reported that 2 out of 155 (1.2%) PMI patients had an underlying diagnosis of FD (19). There are few case reports of FD patients undergoing PMI. In fact, we were only able to identify two Japanese articles (10, 20), and both were published

before ERT was used for FD. These case reports show that PMI can be the first event of FD.

One article pointed out that Fabry nephropathy can have early signs. Despite a normal renal function and urinalysis findings, renal biopsies show an abnormal structure with a marked accumulation of Gb3 in podocytes, partial effacement of foot processes, and irregularly reduced expression of nephrin in the slit diaphragm (21). In the present case, the cardiac event had occurred, but it was assumed that it had already changed the renal pathology at that time, and the patient's condition seemed to have progressed. Based on the available evidence, we recommend screening for FD among young patients undergoing PMI. For men, this can be performed by measuring the α -GAL activity. In women, however, screening is more difficult, as the α -GAL activity levels can vary; in these cases, a detailed interview to obtain a family history is essential, and the evaluation of urinary mulberry bodies may be helpful, as the detection of urinary mulberry bodies can confirm a diagnosis of FD (22-24). Lyso-Gb3 is another promising screening tool for women with FD (25, 26) and is also useful for evaluating the disease severity (27).

In general, it is difficult for FD patients to gain weight because of the associated digestive symptoms (28), but the present patient was obese. There has also been a case report of FD that may have included early progression of renal dysfunction due to obesity (29). There are cases of FD patients with obesity in which the progression of renal dysfunction may be early; however, it is necessary to accumulate more cases in order to confirm this. Kidney biopsy studies in morbidly obese subjects have demonstrated focal segmental glomerulosclerosis (FSGS) and glomerulomegaly (30). In the present case, no findings of glomerulomegaly were observed, and we did not make a diagnosis of typical obesity-related nephropathy. Although obesity may be an exacerbating factor of renal failure and heart disease, we believe that FD remains the underlying disease.

Classically, studies of the natural history of FD have led to the belief that renal insufficiency precedes cardiac dysfunction in FD (31). However, as highlighted in this case report, it is possible that disease trajectories differ among patients. In addition to the classic renal and cardiac features of FD, certain patients may present with FD with either a renal predilection or a cardiac predilection. These subtypes may affect the prognosis of FD and should be further investigated.

This case report highlighted important research questions that remain to be answered. For example, does genotype affect the phenotype of FD? This subject is controversial. Politei et al. (32) reported that patients with the same *GLA* mutation (L415P) exhibited different phenotypes. Yamamoto et al. (33) also reported clinical diversity in patients with FD with the R301Q mutation. In our case, both the patient and his mother had undergone PMI, but the patient's older sister, who also harbored the *GLA* W340X mutation, had not undergone this procedure. This discrepancy may be due to the

X-linked nature of the *GLA* mutation, which would be more severe in men and of unpredictable severity in women. In addition, because FD is a progressive disease, the sister may ultimately go on to exhibit both renal and cardiac phenotypes later in life. These observations seem to suggest that *GLA* W340X affects the cardiac conducting system.

A search for the *GLA* W340X mutation (fabry-database.org) yielded reports by Eng et al. (34), Lukas et al. (35), Garman et al. (36), and Whybra et al. (37). However, there was no mention of the course of the cases. Yano et al. (38) reported a case with the *GLA* W340X mutation, but its clinical course differed from our own patient's course. Therefore, accumulating cases with the *GLA* W340X mutation will help clarify the clinical disease type.

Differences in the phenotypes among women with FD are further complicated by random X-chromosomal inactivation (lyonization). Lyonization occurs in all tissues, resulting in a mix of normal and affected cells throughout the body (39), with differing ratios in each lesion. Therefore, the tissue function depends on the ratio of affected cells to normal cells. Tissues with a higher percentage of normal cells will function normally, but tissues with a higher percentage of affected cells could have aberrant functions.

To adequately answer the question of whether the genotype affects phenotype, we must accumulate more evidence through case reports and perform further studies of the influence of the degree of lyonization on disease pathogenesis in female patients. Based on the present case report, we recommend expanded newborn screening for all high-risk patients and screening for FD in young patients with unexplainable cardiac events (such as HCM and PMI), renal insufficiency, and a family history of FD. Screening for FD in patients with unexplainable cardiac events is already being performed clinically. Indeed, newborn screening for FD is performed in Taiwan and in parts of Japan (40, 41). We hope that these initiatives will become more widely performed.

We encountered a case of FD with a W340X mutation. The patient had received PMI before renal insufficiency occurred. This case highlights the fact that PMI at a young age may be an initiating event for FD.

The patients provided their informed consent. All procedures were performed in accordance with the Declaration of Helsinki.

The authors state that they have no Conflict of Interest (COI).

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