The importance of medical interview with CKD patient in diagnoses of a family with Fabry disease

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Abstract A 47-year-old Japanese man was admitted to our hospital for evaluation of proteinuria, which was detected when he was 37 years of age. His creatinine clearance levels had fallen to 76.3 mL/min/1.73 m². A kidney biopsy was conducted, and the patient's low plasma α -galactosidase A levels suggested Fabry disease. After genetic counseling, *GLA* analysis revealed a novel mutation p.L387P. Interview with the patient revealed that both his younger brother and mother suffered from cardiomyopathy and were undergoing cardiological treatment. They also were positive for proteinuria. About 30 years ago, the patient's cousin (aged 25) was diagnosed with Fabry disease. He underwent hemodialysis for 9 years until his death at 42. At that time, the patient and his brother had not been investigated for Fabry disease so their cousin could not act

as a proband for the brothers. Eventually, the patient, his mother, and his brother were put on enzyme replacement therapy with agalsidase beta. As this series of cases shows, medical interviews to collate both medical and family history were essential for the discovery of Fabry disease in these patients. In addition, being a treatable genetic disorder, Fabry disease should be listed in the standard differential diagnoses of systemic and familial diseases, including unknown cause of nephropathy or cardiomyopathy, for early detection of the disorder.

Keywords Fabry disease · Familial study · Genetic counseling · Enzyme replacement therapy

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Introduction

Fabry disease is a progressive, hereditary disorder of glycosphingolipid metabolism due to full or partial deficiency of lysosomal α -galactosidase A (α -GAL) activity [1]. The *GLA* was localized to the X chromosome [2]. In Fabry disease, more than 600 disease-causing *GLA* mutations have been reported [3]. It is a systemic disease and manifests disease symptoms, which are sometimes non-specific, over the long term. As a result, patients with undiagnosed Fabry disease may be treated in multiple departments, such as pediatrics, dermatology, ophthalmology, cardiology, neurology, and nephrology, over the course of their illness. Cooperation among these departments in sharing medical data will have a positive impact on the diagnosis of Fabry disease.

To inhibit or delay the progression of organ dysfunction, it is desirable to initiate Enzyme replacement therapy (ERT) as early as possible. Here we describe an unusual Japanese family who were only diagnosed with Fabry

disease when the proband with chronic kidney disease (CKD) with proteinuria was diagnosed as such 10 years after his proteinuria was discovered, in spite of the presence of a cousin with Fabry disease.

Case reports

Clinical phenotypes of the patient and their relatives are shown in Fig. 1.

Proband (Case III/5)

This 47-year-old Japanese male patient has had CKD with long-standing proteinuria for 10 years. His records at initial diagnosis (aged 37) indicated proteinuria (1.0 g/24 h), and hyperfiltration (creatinine clearance levels of 162 mL/min/1.73 m²), and he was put on treatment with angiotensin-converting enzyme inhibitors. For over a decade, he was repeatedly recommended to undergo a kidney biopsy, but did not agree to it.

He had a past medical history of bronchial asthma but no history of skin eruption, anhidrosis, nor pain in the extremities.

On admission, the patient's physical examination revealed a blood pressure of 115/72 mmHg, while his electrocardiogram demonstrated saddle back ST segment elevation without any history of syncope. His laboratory report was as follows: total serum protein: 6.9 g/dL, albumin: 4.3 g/dL, serum creatinine: 0.89 mg/dL, sodium: 142 mEq/L, potassium: 4.6 mEq/L, chloride: 109 mEq/L, calcium: 9.6 mg/dL, daily urinary protein: 0.54 g (without hematuria). In addition, the patient's creatinine clearance had decreased to 76.3 mL/min/1.73 m². His serum lipid profile showed low-density lipoprotein cholesterol of

Fig. 1 The family tree. Black symbols indicate patients whose α -GAL levels were analyzed and diagnosed with Fabry disease. Diamond symbol and this internal numbers indicate the number of individuals with unknown gender. Numbers I, II, III, and IV indicate generation. Arabic numbers indicate members of each generation. The couple in Case III/5 and III/6 was an infertility case, and Case III/7 and Case III/8 was a divorced couple

Fig. 2 a Case III/5: light microscopic findings of kidney biopsy specimen. The foamy appearance of epithelial cells was observed. In focal mesangial area, some deposits were noted. (Periodic acid-Schiff stain $\times 200$). b Case III/7: electron microscopic findings of kidney biopsy specimen. Laminated myelin bodies such as zebra bodies on glomerular epithelial cells were observed

61.5 mg/dL, high-density lipoprotein cholesterol of 82.1 mg/dL, and triglyceride of 82 mg/dL.

An interview with the patient about his medical and familial history revealed two other patients with proteinuria in his family: his mother who was suffering from dilated cardiomyopathy (Case II/6), and his young brother who was suffering from hypertrophic cardiomyopathy after he received a pacemaker implant (Case III/7).

A kidney biopsy was performed on the patient. In light microscopy, focal and global glomerulosclerosis were observed in 10 of 24 glomeruli, and tubulointestinal atrophy with the foam cells was observed. In the remaining glomeruli, a foamy appearance of epithelial cells was noted (Fig. 2a). Immunofluorescence findings were essentially unremarkable. In electron microscopy, no glomeruli were found in the specimen. However, laminated myelin-like bodies were observed in the tubular epithelial cells.

Fig. 3 Nucleotide sequencing from the full-length α -GAL cDNA of Case III/5. A novel missense mutation in exon 7, a T–C transition at cDNA nucleotide number 1160 and a C–T transition at number 1161 (c.[T1160 > C; C1161 > T]) were identified, resulting in substitution from leucine to proline in codon 387 (p.L387P). Case II/6 and III/7 were also identified with the same mutation

Based on these findings, a lysosomal storage disease such as Fabry disease was the most likely suspect. The patient's plasma α -GAL level was also found to have fallen to 10.9 pmol/hr/mL. After genetic counseling and agreement to *GLA* analysis, a novel missense mutation in exon 7, p.L387P (c.[1160T > C; 1161C > T]), was identified (Fig. 3) (using previously reported method of *GLA* analysis [4]). Having collated the above-mentioned data, the patient was diagnosed as Fabry disease.

On ophthalmological examination, cornea verticillata was noted. The patient's chest X-ray did not reveal any cardiac enlargement. The results of his echocardiogram indicated that left ventricular septum and left posterior wall thickness were 13.0 and 14.0 mm, respectively, with an ejection fraction was 69.4 %. The only valvular abnormality present was trivial tricuspid regurgitation. He had no hearing abnormalities and brain magnetic resonance imaging did not reveal any other abnormalities. After the patient was evaluated, he was put on ERT, with agalsidase beta 1.0 mg/kg body every 2 weeks.

Familial study

Case II/6

Case III/5's mother, a 75-year-old female, was being treated for dilated cardiomyopathy, and also had proteinuria. Her medical records indicate that her right kidney was removed (etiology unknown) at the 20s, and that she had pregnancy-induced hypertension. Even though the patient did not have a medical history of coronary risk factors, such as diabetes mellitus or hypertension, she was admitted

to the hospital for congestive heart failure at 74. Her chest X-ray indicated a cardiothoracic ratio of 67 %, while a coronary angiography revealed no critical stenosis. She was treated with β -blockers and diuretics. A year later, at 75, she complained of visual impairment, and had an occipital stroke indicated by brain computing tomography. Her laboratory report was as follows: serum creatinine: 1.17 mg/dL, Japanese estimated glomerular filtration rate: 35.0 mL/min/1.73 m², brain natriuretic peptide: 1060 pg/mL, proteinuria is 1+ (without hematuria).

Her plasma α -GAL level was 62.7 pmol/h/mL. On ophthalmological examination, cornea verticillata was noted. Her electrocardiogram revealed a complete right bundle branch block, while her echocardiogram showed that left ventricular septum thickness was 12.0 mm and left posterior wall thickness was 12.0 mm. The ejection fraction had decreased to 33.0 %, and valvular abnormalities included mitral regurgitation of degree II, atrial regurgitation of degree I, and tricuspid regurgitation of degree I. After *GLA* analysis, she was identified with the same heterozygote missense mutation, and was diagnosed with Fabry disease. She started treatment with ERT, with agalsidase beta 1.0 mg/kg body every 2 weeks.

Case III/7

Case III/5's brother, a 45-year-old male was also diagnosed with the same disease. This patient has had angiokeratoma corporis diffusum on his trunk since childhood. Anhidrosis was noticed in summer, and he also had pain in the extremities. Five years prior to his diagnosis, he had been diagnosed with hypertrophic cardiomyopathy by electrocardiography and ultrasound cardiography. Furthermore, he had a fainting incident and was diagnosed with sick sinus syndrome 2 years before that. As a result, he received a permanent pacemaker implant. In spite of unknown etiology, myocardial biopsy was not performed. He had proteinuria.

After his brother's (Case III/5) and his mother's (Case II/6) diagnoses, this patient was strongly suspected to have this hereditary disease too. A kidney biopsy was performed. Light microscopy showed global glomerulosclerosis on half of the glomeruli. In the remaining glomeruli, histological findings that do not contradict Fabry disease, such as the foamy appearance of epithelial cells in light microscopy, and the laminated myelin bodies in electron microscopy (Fig. 2b), were observed. After genetic counseling and agreement to analysis, the same *GLA* mutation in exon 7 was identified.

This patient's laboratory report was as follows: urea nitrogen: 9.8 mg/dL, serum creatinine: 0.89 mg/dL, daily urinary protein: 1.9 g (without hematuria).

His creatinine clearance had fallen to 62.6 mL/min/1.73 m² and his plasma α -GAL level fell to 4.5 pmol/hr/mL. On ophthalmological examination cornea verticillata was noted. His echocardiogram indicated that the left ventricular septum thickness was 14.0 mm, the left posterior wall thickness was 17.0 mm, with ejection fraction of 69.6 %. Valvular abnormalities, such as degree I mitral regurgitation, and degree I pulmonary regurgitation, were found. He began treatment with ERT, with agalsidase beta 1.0 mg/kg body every 2 weeks.

Case III/4

Cases III/5 and III/7's male cousin (Case II/6's nephew) had been diagnosed with this hereditary disease 30 years before they were diagnosed. The critical information was discovered through the familial anamnesis, Case III/4's information from other hospitals, and his medical records in our hospital. He had mental retardation, pain in the extremities, and anhidrosis since young. At 25, he was diagnosed with Fabry disease based on his illness at that time, his proteinuria, and his low α -GAL level in white blood cells, as well as the familial history indicating that both his sister (Case III/3) and mother (Case II/4) had also been diagnosed with Fabry disease. At 33, he was diagnosed with end-stage renal disease, and started receiving maintenance hemodialysis at our hospital. At 42, he died due to abdominal infection and fatal hyperkalemia. In spite of this cousin being diagnosed with Fabry disease, the brothers (Case III/7 and Case III/6) were not investigated

for Fabry disease at that time. As a result, this cousin could not act as the proband for the above-mentioned family.

Discussion

We reported a missense mutation p.L387P in *GLA* in a Japanese family with Fabry disease, including two hemizygotes and a heterozygote. Phenotypic expression in hemizygotes with Fabry disease is highly variable, ranging from patients who present with less severe conditions with only cardiac and/or renal abnormalities, to patients who are the classic phenotype and present with angiokeratoma, acroparesthesia, hypohidrosis, corneal opacities, and progressive dysfunction of the kidney, and the heart [1, 5–7].

End-stage renal disease and cardiac disease are the most severe organ dysfunctions in Fabry disease that worsens a patient's prognosis. In the familial cases mentioned in this report, the clinical features of the three hemizygotes differ from each other (Table 1). Case III/4 had pains in the extremities and suffered from anhidrosis since young, and at 25 he had Fabry nephropathy, which consequently led to end-stage renal disease, and the patient was finally put on maintenance hemodialysis at 42. His clinical course was mostly consistent with the classical type of Fabry disease.

As for Case III/7, his clinical course was also similar to that of the classical type, although he did not reach end-stage renal disease at 45. In contrast, Case III/5, who was also the proband in this case report, did not manifest severe clinical symptoms for skin, nervous system, heart and kidney dysfunction, compared with the other two

Table 1 Summary of the familial cases in this report

Case	III/5	II/6	III/7	III/4
Gender	Male	Female	Male	Male
Age of onset (years)	37	20s	10	10
Age of diagnosis (years)	47	75	45	25
Clinical feature				
Anhidrosis	None	None	Yes	Yes
Pain in extremities	None	None	Yes	Yes
Heart	Abnormal ECG	Dilated cardiomyopathy	Hypertrophic cardiomyopathy	Unknown
Kidney	Fabry nephropathy	Proteinuria	Fabry nephropathy	Kidney failure
Central nerve system	None	Cerebral infarction	None	Mental retardation
Plasma α Gal-A (pmol/hr/mL)	10.9	62.7	4.5	(Activity of white blood cells; decreased)
Plasma GL-3 (ng/mL)	15.5	7.6	15.3	Not available
Urine GL-3 (μ g/mgCre)	Not available	0.83	19.21	Not available
Blood type	B	AB	B	B
ERT	Agalsidase β	Agalsidase β	Agalsidase β	None

hemizygotes, so he can be classified as not a typical clinical type. Although 10 years elapsed after his urine protein before he was diagnosed with Fabry disease, his variant-like phenotype needs to be considered when examining the reasons for this delay.

The incidence of Fabry disease has been estimated to be approximately 1 in 40,000 to 1 in 117,000 male births [8, 9]. However, it has also been reported that in Japan, the frequency of Fabry disease in high-risk groups, such as patients with kidney failure and patients with left ventricular hypertrophy, increases to 0.07–1.0 % [6, 10–13], and 3 %, respectively [5]. These reports suggested that screening high-risk groups is effective for the early diagnosis of patients, and families with Fabry disease. In the familial studies of the cases mentioned in this report, Case III/4, a classical phenotypic case, had been already diagnosed more than 20 years before his family members were diagnosed. If we had investigated the familial history in greater detail, particularly with Case III/4, the family members with Fabry disease could have been diagnosed earlier and treatment could have started sooner as well. In addition, because α -GAL activity analysis using plasma or white blood cells often fails to distinguish Fabry heterozygotes in normal females, familial study and subsequently, mutation analysis may be a valuable tool for diagnosis and genetic counseling for affected heterozygotes [14].

Furthermore, earlier diagnosis may inhibit or delay the progression of Fabry disease through ERT treatments, which have been in clinical use since 2001, and since 2004 in Europe and Japan. Based on current research, for adult males, ERT should be instituted from the outset when Fabry disease is diagnosed, and every hemizygotes should be offered ERT treatment, irrespective of what stage of CKD they are in. Heterozygotes should also be offered ERT treatment if they manifest significant symptoms, or show evidence of progressive end organ Fabry involvement [15]. In this family, when the two hemizygotes and the heterozygote had began receiving ERT treatment, organ dysfunctions of the three patients had either already progressed to CKD stage 3 or cardiac myopathy. The therapeutic effect of ERT treatment needs to be verified.

In conclusion, we reported a novel α -GAL missense mutation in a Japanese family with Fabry disease. For general physicians, particularly nephrologists, Fabry disease should be listed in the differential diagnoses of unknown etiology of systemic diseases, including those relating to the kidney or the heart. In order to make a definitive diagnosis for this treatable genetic disorder at as early a stage as possible, it is necessary to begin investigations at the basic medical interview, and gather data from patients' medical history and familial history.

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Conflict of interest The authors have declared that no conflict of interest exists.

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