Novel α-Galactosidase A Mutation (K391E) in a Young Woman With Severe Cardiac and Renal Manifestations of Fabry Disease

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SUMMARY

Fabry disease, an X-linked lysosomal storage disorder due to α-galactosidase A deficiency, is associated with dysfunction of various cell types and results in a systemic vasculopathy. We describe a 29-year-old woman with Fabry disease presenting with severe cardiac and renal manifestations. Gene analysis demonstrated a novel mutation (K391E) in the GLA gene. Enzyme replacement therapy (ERT) was started with agalsidase-β after confirming the diagnosis of Fabry disease, resulting in normalization of LV systolic function and improvement of renal function. As early therapy is crucial for preventing life-threatening sequelae, clinicians should consider Fabry disease in young patients presenting with cardiac and renal disease without any likely causes. (Int Heart J 2016; 57: 637-639)

Key words: Acroparesthesia, Chronic renal failure, Congestive heart failure

Fabry disease, an X-linked sphingolipid storage disorder caused by mutations in the α-galactosidase A (GLA) gene, results in systemic intralysosomal accumulation of glycosphingolipids in various tissues, particularly skin, nervous system, eyes, kidneys, and heart. Women have an extremely variable phenotype due to random X-chromosome inactivation, with clinical manifestations ranging from asymptomatic disease to severe clinical dysfunction. Here, we describe a case of Fabry disease associated with a novel mutation in the GLA gene in a 29-year-old woman who presented with cardiac, renal, and neurological manifestations.

CASE REPORT

A 29-year-old Asian woman visited our outpatient clinic due to a 2-month history of poor vision in the right eye and acroparesthesia in the left upper extremity. She also complained of dyspnea on exertion with poor exercise tolerance, which she ascribed to obesity. She had no significant past history except for a uterine myoma detected at a routine gynecological visit. She took no medications and had never smoked. Her family history was negative for disease, including kidney failure, heart failure, stroke, or other manifestations suggestive of Fabry disease.

On examination, her temperature was 36.7°C; blood pressure was markedly elevated at 229/174 mmHg; heart rate was 94/minute and regular; and respiratory rate was 16/minute with an oxygen saturation of 98% on room air. She was 160.1 cm tall and weighed 82.6 kg, with a body-mass index of 32.2. Chest examination showed a pansystolic murmur (Levine II/VI) at the apex. Pitting edema was present in the lower legs. There were no angiokeratomas, cornea verticillata, hypohidrosis, or other typical features of Fabry disease.

Laboratory investigations revealed creatinine of 1.70 mg/dL, B type natriuretic peptide of 450.8 pg/mL, and marked proteinuria with normal urine sediment. Other laboratory tests, including complete blood count, electrolytes, and liver functions were normal. ECG demonstrated normal sinus rhythm and voltage criteria for LV hypertrophy; chest radiography revealed cardiomegaly (Figure 1A). Transthoracic echocardiography confirmed left ventricular hypertrophy with diffuse left ventricular systolic dysfunction (ejection fraction, 30%) (Figure 2A). Ophthalmological examination revealed bilateral retinal hemorrhage associated with hypertensive retinopathy. There was no evidence of renovascular hypertension, hyperaldosteronism, or other endocrine disorders that may cause hypertension.

Considering the early onset of chronic renal failure, diffuse LV systolic dysfunction with LV hypertrophy, and acroparesthesia in a young patient, we considered Fabry disease in the differential diagnosis. Screening for Fabry disease revealed reduced leukocyte α-galactosidase A activity (17.9 nmol/mg protein/hour, normal range 49.8-116.4). Subsequent gene survey revealed a novel mutation, c.1171A>G (K391E), in the 7th exon of the GLA gene (Figure 3), confirming the diagnosis of Fabry disease. Figure 4 shows the result of genetic counselling and evaluation of family members. The patient’s mother carried the same GLA mutation and her plasma α-galactosidase A activity was reduced to 1.6 nmol/hour/mL (normal range: 4.7-17.6 nmol/hour/mL). However, she did not have any cardiac, renal, neurological, or skin manifestations.

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The patient’s sister did not have the GLA mutation. We were unable to obtain informed consent for genetic analysis from the patient’s father and brother, because they had no apparent clinical problems.

The differential diagnosis of diffuse LV systolic dysfunction with LV hypertrophy in this case included hypertensive cardiomyopathy, dilated phase of hypertrophic cardiomyopathy, Fabry disease, and amyloidosis. The high blood pressure seen in this case was not consistent with the dilated phase of hypertrophic cardiomyopathy. Amyloidosis was less likely given that low voltage on ECG limb leads such as I and aVR, dysautonomia involving orthostatic hypotension, or distur-
bance of gastrointestinal function was not observed. It was reasonable to consider Fabry disease as most probable, despite the absence of classical features, considering the early onset of chronic renal failure and acroparesthesia.

Enzyme replacement therapy was started with agalsidase-β and administered at a dose of 70 mg every 2 weeks. Additional medications included azilsartan 10 mg/day, amlodipine 10 mg/day, carvedilol 10 mg/day, furosemide 10 mg/day, and spironolactone 12.5 mg/day.

After one year of therapy, her LV systolic function had normalized (ejection fraction, 77%) (Figure 2B) and the renal dysfunction had resolved. Chest radiography demonstrated improvement of the cardiomegaly (Figure 1B). There was no recurrence of the retinal hemorrhage after normalization of blood pressure.

**DISCUSSION**

Fabry disease, an X-linked lysosomal storage disorder caused by α-galactosidase A deficiency, is associated with dysfunction of many cell types and results in a systemic vasculopathy. To date, more than 600 mutations have been identified in the human GLA gene that are responsible for Fabry disease, including missense and nonsense mutations, and small and large deletions. Disease manifestations often start in childhood or adolescence, and include pain and parasthesias in the extremities that worsen with exercise or hot weather. Additional typical symptoms may include skin lesions (angiokeratomas), decreased sweating, corneal clouding, abdominal discomfort, and back pain. As lysosomal GL-3 progressively accumulates in the vascular endothelium, multiple organ involvement including chronic renal disease, cardiovascular and cerebrovascular disease, as well as death in the fourth and fifth decades of life, may be seen.

Clinical manifestations are more severe in homozygous male subjects than in heterozygous female subjects, who may be asymptomatic, consistent with the Lyon hypothesis of random X-chromosome inactivation. However, it is now widely accepted that even heterozygous female carriers remain at risk for developing severe renal, cardiac, and cerebrovascular manifestations. A presumed diagnosis of Fabry disease in males with classic or variant phenotypes can be reached by the demonstration of markedly deficient α-galactosidase A activity in plasma, isolated leukocytes, and/or cultured cells. As women often have normal or mildly reduced enzyme activity due to random X-chromosome inactivation, the finding of a mutated GLA gene is critical for confirmation of Fabry disease in women. Recent studies have shown that the mutation of specific exon codes, such as exons 5, 7, and 6 in the GLA gene are common areas for Fabry disease. Sugawara, et al reported a correlation between the 3-dimensional structural changes of mutant enzyme proteins and clinical phenotype in various mutations. It appears that there was no significant association between the domain of the mutation and clinical phenotype that may reflect α-galactosidase A activity.

In our patient, we identified a novel K391E mutation in the GLA gene associated with dysfunction in several organ systems. Representing an A to G transversion (codon 391) in the 7th exon resulting in low α-galactosidase activity, the mutation manifests as severe cardiac and renal disease with acroparesthesia, but lacks the angiokeratomas or hyphidrosis typical of classic Fabry disease.

In summary, we report the case of a heterozygous young woman with Fabry disease presenting with diffuse LV systolic dysfunction and hypertrophy, chronic renal failure, and acroparesthesia who was successfully treated with enzyme replacement. Molecular analysis of the GLA gene revealed a novel mutation, K391E, in the seventh exon. Fabry disease should be considered in young patients who show multi-organ disorders without obvious causes, because it is treatable with enzyme replacement.

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**DISCLOSURE**

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