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■ Case report ■

# Two cases of Fabry disease identified in brothers

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= Abstract =

Fabry disease is a rare, X-linked inborn error of glycosphingolipid catabolism caused by a mutation in the gene encoding the α-galactosidase A (GLA) enzyme. We report two cases of Fabry disease in a 12-year-old boy who had acroparesthesia and in his elder brother with milder symptoms who were diagnosed by GLA activity assays and the presence of the GLA gene mutation. (Korean J Pediatr 2010;53:235-238)

Key Words : Fabry disease, Mutation, Enzyme replacement therapy

## Introduction

Fabry disease is a rare, X-linked inborn error of glycosphingolipid catabolism caused by a mutation in the gene encoding the alpha-galactosidase A (GLA) enzyme[1]. The rate of occurrence is estimated at 1/117,000 live births and at 1/40,000 or 1/60,000 in males[2, 3]. It is reported that females are equally affected in a large series[4].

Sphingolipids accumulate throughout the body and cause multisystem diseases such as renal, cardiovascular or cerebrovascular complications. In childhood, clinical manifestations such as pain, hypohidrosis, gastrointestinal disturbances, angiokeratomas, cornea verticillata and acroparaesthesiae may be common. Pain, which may also appear as acroparesthesia-chronic burning or tingling pain in the extremities, is the most striking feature of Fabry disease in young affected male patients[5].

We report two cases of Fabry disease diagnosed by GLA activity assays and the presence of the GLA gene mutation in a 12-year-old boy who has been suffering from acroparesthesia for 4 years and in his brother with milder symptoms.

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## Case report

### Case 1

A 12-year-old boy suffered from chronic pain, associated with walking, in the palms of his hands and soles of his feet for 4 years. He was given pes planus in the Physical Medicine & Rehabilitation (PMR) Department for 2 years but his symptoms did not improve. Seven months before being admitted to hospital, he visited the Department of Pediatrics and complained of pain on the palms of his hands and the soles of his feet, hypohidrosis and a heating sensation. During a follow-up examination, angiokeratomas of the penis and scrotum were found and Fabry disease was suspected (Fig. 1). The 24 hour creatinine clearance ratio (Ccr) was 115.5 ml/min (reference range: 75-125 ml/min) and the 24 hour urine protein was 9.4 mg/day (reference range: 0-100 mg/day). Ophthalmic examination showed no sign of corneal opacity and the auditory brainstem response test (ABR) and auditory evoked potential (AEP) showed no evidence of hearing loss. Electrocardiography (ECG) was normal and echocardiography showed mitral valve prolapse. Electromyography (EMG) and nerve conduction studies showed no abnormalities. Plasma and urine samples, which were taken after admission, showed a significant increase in globotriaosylceramide (GL3) level (plasma 9.1 μg/mL (reference range : 3.9-9.9 μg/mL), urine 5.11 μg/mgCr (reference range : 0.01-0.9 μg/mgCr) and a significant de-

crease in GLA level (3.5 AgalU (reference range in male : >15.0 AgaIU). Fabry disease was confirmed by the detection of the GLA mutation (c.270C>A cp.cys90x) in DNA analysis (Fig. 3). The patient has been treated with carbamazepine and gabapentin to control the pain, but pain still persists. The GLA enzyme treatment was started with aglasidase beta (Fabrazyme®, Genzyme Co., MA, USA) at the dose of 1 mg/kg every 2 week. After 3 months of treatment, the patient showed a significant decrease in GL3 level (plasma 6.54 μg/mL , urine 3.25 μg/mgCr).

### Case 2

A 15-year-old boy, the elder brother of case 1, complained of intermittent abdominal pain. Also, the patient suffered from pain in the palms of his hands and soles of his feet during walking 1 or 2 times per year. However, he did not complain of hypohidrosis or heating sensation and angiokeratoma was not found. The 24 hour Ccr was 109.4 ml/min and the 24 hour urine protein was 98.7 mg/day. Ophthalmic examination showed signs of corneal opacity (Fig. 2A) and ABR & AEP showed no evidence of hearing loss. ECG was normal and echocardiography showed myocardial infiltration on the mid to basal posterior wall. Plasma and urine samples showed a significant increase in GL3 level (plasma 14.3 μg/mL, urine 7.91 μg/mgCr) and a significant decrease in GLA level (5.7 AgalU). He was confirmed with Fabry disease by the detection of GLA mutation in DNA analysis, which is the same as the case of his younger brother. The GLA enzyme treatment was started at the same dose with his younger brother because of his age (15 years old) despite his slight symptoms. After 3 months of treatment, the patient showed a significant decrease in GL3 level (plasma 6.54 μg/mL, urine 2.54 μg/mgCr).

After confirming the diagnosis of Fabry disease, GLA activity assays and DNA analyses were performed on other family member. The patients' mother had no symptoms and was heterozygous. Ophthalmic examination showed signs of corneal opacity (Fig. 2B) but the 24hr urine analysis was normal. GLA level was 20.8 AgaIU (reference range in female: >20.0 AgaIU). The mutation was not any more found among their other family members (Fig. 4), suggesting a de novo mutation.

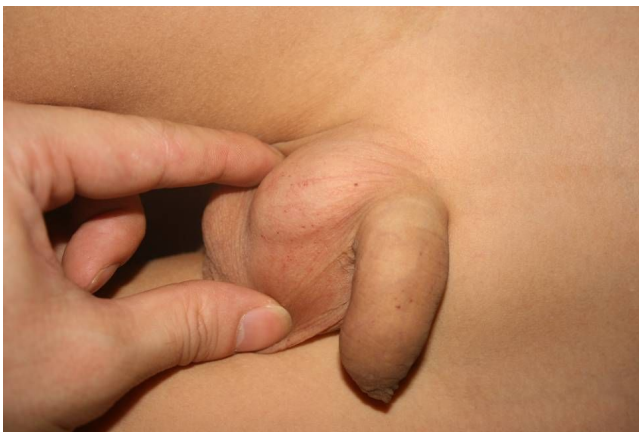

**Fig. 1.** Angiokeratomas on the penis and scrotum.

## Discussion

Fabry disease was identified in 1898[6]. This inborn error of metabolism is characterized by deficient activity of the lysosomal hydrolase, GLA[7]. The enzyme substrate, GL3, accumulates in cells of various tissues and organs and can lead to life threatening renal, cardiac, and cerebrovascular complications[8]. Mutations that cause Fabry disease are located in the seven-exon GLA gene on chromosome X, at Xq2[29]. Based on The Human Gene Mutation Database at the Institute of Medical Genetics in Cardiff (http://www.hgmd.cf.ac.uk/), there are currently 431 mutations for Fabry

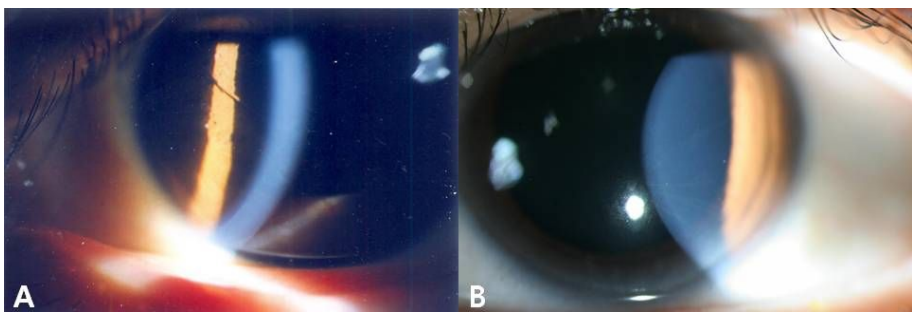


**Fig. 2.** Corneal opacity in the elder brother (A) and in the mother with a heterozygous genotype (B).

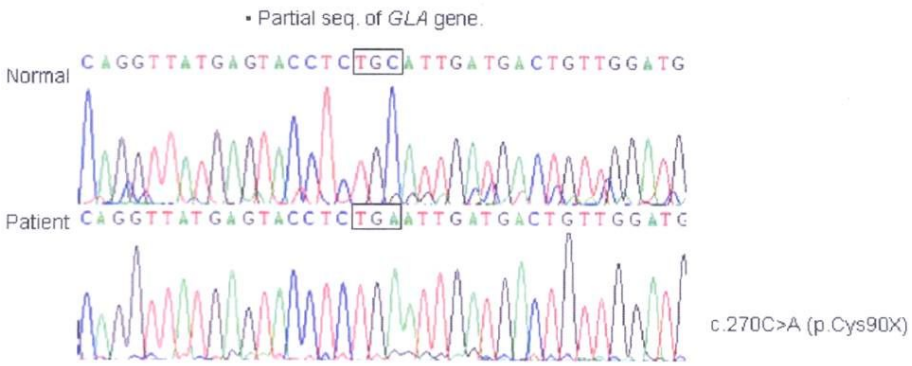


**Fig. 3.** Automated sequencing profiles of genomic DNA showing a α-galactosidase A (GLA) mutation (c.270C>A cp.cys90x) in the 2 brothers.

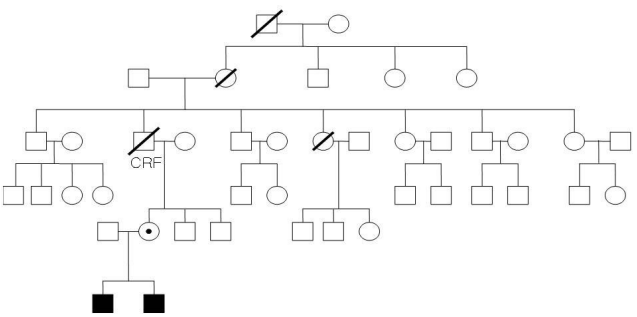


**Fig. 4.** The pedigree of the patients' family. The confirmed diagnosis of Fabry disease was made in the carrier mother and her 2 sons, while the other family members (arrowhead) and relatives were not affected.

disease described. Of those, 295 are missense/nonsense type mutations, followed by 66 small deletions, 21 splice defects, 12 large deletions, 3 complex rearrangements and 1 large insertion.

The first symptoms occur during childhood or adolescence and include episodes of pain in extremities, fever of unknown origin, hypohidrosis and gastrointestinal symptoms such as abdominal cramps and diarrhea[10]. Pain episodes can last from minutes to weeks and can be triggered by stress, heat, fatigue, or exercise. Despite their severity, acroparesthesias in children with undiagnosed Fabry disease is often dismissed as malingering or growing pains. In this case, electromyography and nerve conduction studies might easily fail to detect abnormalities because neuropathies involve small nerve fibers[11]. In our case, the diagnosis was delayed because it was misdiagnosed as pes planus induced pain. More specific disease manifestations that are usually present in late adolescence are angiokeratoma and asymptomatic corneal opacities. Neurological, cardiac and renal complications develop in the third or fourth decade. Sensorineural hearing loss of early onset Fabry disease is very common and its severity is correlated with both the cerebrovascular and the peripheral nerve manifestations of the disease[12]. Kidney disease is usually associated with progressive proteinuria following a decline in glomerular filtration rate, leading to end-stage renal disease over a number of years. Cardiac complications include conduction disturbances, valve disease, coronary artery stenosis and left heart failure. ECG and echocardiography combined with a doppler heart study are very helpful in characterizing the cardiac abnormalities. In our case, ECG was normal and echocardiography showed mitral valve prolapse (case 1) and myocardial infiltration (case 2). Other common symptoms of Fabry disease include skeletal and growth abnormalities[13]. The patient in case 1 seemed small for his age at height 147 cm (10-25 percentile) and weight 40 kg (3-10 percentile).

All family members suspected of having family history of Fabry disease should be tested, even if they have no symptoms. In affected males, GLA activity assays show severely diminished activity in the plasma and leukocytes. In case 2, the patient had slight symptoms but a significant decrease in GLA activity. As GLA activity in heterozygote female is nearly normal, detection of a gene mutation is needed for confirmation[14].

Enzyme replacement therapy (ERT) with aglasidase beta is the specific therapy for Fabry disease. In a clinical study of ERT in children, a reduction in plasma GL3 levels and in neuropathic pain were demonstrated[15]. ERT reduces lysosomal inclusions in kidney vascular endothelial cells and the urinary excretion of GL3[16]. In our cases, a significant decrease in plasma and urine GL3 level was seen. However, this therapy was not effective in progressed proteinuria,

damaged kidney tubular function or cardiac fibrosis[17]. ERT in young patients is expected to prevent progression of life-threatening symptoms[18]. For this reason, the elder brother who had only slight symptoms but was diagnosed by mutation analysis was started on ERT.

In summary, pain in the extremities of any young child needs careful evaluation, including the consideration of the possibility of the Fabry disease. Mutation analysis should be done on any family member with a family history of Fabry disease to detect the disease early and ERT should be administered as soon as possible to prevent end stage organ damage.

## 요 약

### 형제에서 발견된 파브리병 2례

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파브리병은 알파-갈락토시다아제(alpha galactosidase) A 효소에 위치하는 유전자 변이에 의한 글라이코스핑고리피드(glycospingolipid) 대사이상에 의한 질환으로 X-염색체와 연관된다. 말단 지각이상을 호소하던 12세 남자 환자와 증상이 미미한 그의 형에서 알파-갈락토시다아제 A 효소 활성도 측정과 유전자 변이 확인을 통하여 파브리병을 확진한 2례를 보고하고자 한다.

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