Clinical Features and One-year Experience with Enzyme Replacement Therapy in a Taiwanese Kindred with Fabry Disease

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Fabry disease is an X-linked recessive inheritance with defective activity of lysosomal enzyme, α-galactosidase A. Clinical diagnosis is sometimes difficult because of diverse manifestations. Confirmation of the disease is based on enzyme levels as well as on molecular biology. The prognosis is related to renal, cardiovascular and neurological complications. We report a family with Fabry disease, mother and her two sons (aged 25 and 22 years old, respectively). Both sons had numerous angiokeratomas on the lower trunk and thighs. In addition to cornea verticillata and acroparesthesia, the older one had left ventricular hypertrophy with severe mitral valve regurgitation, and the younger one had coarse liver surface on abdominal sonography, ST change on V2-4 leads and hypohidrosis. Furthermore, decreased α-galactosidase A activities (0.9 and 1.0 nmol/hr/ml, respectively, normal range: 7.6-16.5) were found. The mother, a Fabry carrier, had no abnormal findings except mild acroparesthesia, cornea verticillata and subnormal enzyme activity (2.6 nmol/hr/ml). A deletion mutation (c.1072_1074delGAG) in exon 7 of α-Gal A gene on Xq22 was detected. Both siblings are undergoing enzyme replacement therapy.

Compared with pretreatment, after one-year enzyme replacement therapy, the glomerular filtration rate (GFR) of the proband improved slightly (70.6 vs. 82.8 ml/min). There was also no tendency of progression in the younger brother after enzyme supplement. (Dermatol Sinica 22: 159-165, 2004)

Key words: Fabry disease, Angiokeratoma, α-Galactosidase A, Mutation, Enzyme replacement therapy

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INTRODUCTION

Anderson-Fabry disease (FD; OMIM 301500), now more frequently called Fabry disease, is an X-linked lysosomal storage disease associated with multisystem involvement resulting from the accumulation of neutral glycosphingolipids in various organs. It has an incidence of 1:117,000 live births and is the second most prevalent human metabolic storage disorder after Gaucher disease. Treatment was usually supportive, mainly focusing on symptomatic relief of acroparesthesia and episodes of excruciating pain and on complications of renal failure, cardiac, or cerebrovascular disease until 2001 when enzyme supplement was approved safe and effective.1-6

Fig. 1
Numerous asymptomatic punctate tiny dark-red papules over lower back, buttocks and thighs.

Fig. 2
Numerous dilated, thin-walled, congested capillaries underlie the variable acanthotic epidermis with hyperkeratosis (A); plumped endothelial cells with granular deposits (B) (H & E stain, A: X100, B: X400)
CASE REPORT

A 25-year-old Taiwanese male suffered from numerous asymptomatic punctate tiny dark-red papules over the lower back, which progressed and extended to the buttocks, thighs, pubic area, anterior trunk and upper limbs over time (Fig. 1). Histopathological examinations from one of the cutaneous papules revealed the characteristics of angiokeratoma (Fig. 2A). Plumped endothelial cells with granular deposits were also noted (Fig. 2B). Besides, he had complained of joint pain since the age of 10 years. Extremely intense generalized aching and burning pain, particularly in the hands and feet (known as acroparesthesia), was noted during febrile episodes and higher ambient temperature. Neurological examinations, including vibratory, pinprick, light touch, and position sensation modalities, were normal. Ophthalmologic examinations showed whorled deposition on the cornea (so-called cornea verticillata) and lens, and tortuous conjunctival vasculature (Fig. 3). Electrocardiogram and echocardiogram revealed left ventricular hypertrophy with severe mitral valve regurgitation and possible chordae tendinae rupture. Serum creatinine, blood urea nitrogen and 24-hour protein excretion in the urine were within normal limits. The glomerular filtration rate (GFR) by TC-99m-DTPA examination was 70.6 ml/min (the mean and lower normal limits for this age are 115 and 88, respectively). The enzyme activity of α-galactosidase A in plasma of the patient was 0.9 nmol/hr/ml (7.6-16.5).

The proband has one sibling aged 22 years (III-2), who has similar but milder dermatological manifestations. In addition, he has a generalized lack of sweating and heat intolerance. Investigations of the younger brother showed reduced α-galactosidase A activity (1.0 nmol/hr/ml). Whorled opacities on cornea and torturous conjunctival vessels were also noted under ophthalmologic examinations. Abdominal sonography showed coarse liver surface. Neither hepatitis B virus antigen, antibody nor hepatitis C virus antibody was identified. Electrocardiogram revealed ST change on V2-4 leads. Serum creatinine and blood urea nitrogen were within the reference range. Proteinuria amounted to 0.12 g in 24 hour (30-100 mg/24 h). The GFR was 89.9 ml/min (the mean and lower normal limits for this age were 118 and 90, respectively). His mother (II-5) had no abnormal findings except mild acroparesthesia, cornea verticillata and subnormal enzyme activity (2.6 nmol/hr/ml). Two of his aunts (II-8 and II-10) had burning pain on distal limbs while having fever. His maternal grandfather (I-6) died of a renal disease of unknown etiology. The second younger aunt's daughter (III-3), at

Fig. 3
Whorled radiation on the cornea (A); closer view (B); and tortuous conjunctival vessels (C) and (D).

Fig. 4
Clinical phenotypic pedigree of studied family with Fabry disease.

a Loss of contact with family since age of 20 years.
b Blood group.
the age of 7 years, did not like to wear socks because of heat intolerance. One of the index patient's maternal uncles (II-2) had been receiving hemodialysis since he was 40 years old. The older brother of his maternal grandfather (I-1) had dark-red papules on the trunk since adolescence but had been lost to contact with the family when he was about 20 years old. The clinical features and clinical phenotypic pedigree of this family are summarized in Table I and Fig. 4. The coding regions of the $\alpha$-galactosidase A of the proband, his sibling and mother were examined by PCR amplification and sequencing. A mutation c.1072_1074delGAG (deletion of Glu at codon 358) was found in exon 7.

We used pulsed dye laser and CO2 laser to treat the proband's skin lesions but the result was not satisfactory. Both siblings also received agalsidase beta (Fabrazyme®, Genzyme, Cambridge, Mass, USA) 70 mg infusion every two to four weeks for one year. Initially, rigors within one hour following the infusion ($<0.25$ mg/min) were often noted despite of prophylaxis with short-acting antihistamine and acetaminophen. Sometimes, the proband suffered from dyspnea and his younger brother had skeletal pain during the infusion. The above-mentioned discomfort could be relieved by slowing down the infusion rate plus intramuscular injection of ketoprofen. Moreover, febrile episodes eight to twelve hours after completing the infusion were noted several times and subsided after hydration. Adverse events were avoided when the infusion rate for the first hour was kept to less than 0.1 mg/min. Compared with pretreatment, the GFR of the proband improved slightly (70.6 vs. 82.8 ml/min). There was also no tendency of progression in the younger brother after enzyme supplement. However, the proband patient has suffered from frequent palpitation in recent months despite treatment.

**DISCUSSION**

Fabry disease is an X-linked sphingolipidosis caused by complete or partial deficiency...
of α-galactosidase A. The enzyme deficiency results in accumulation of globotriaosylceramide (abbreviated as GL3), digalactosylceramide and blood group B, B1, and P1 glycolipids in the lysosomes of vascular endothelial, smooth muscle, epithelial, and ganglion cells. This metabolic defect causes angiokeratomas, painful neuropathy, cardiac and cerebrovascular injury, and renal failure. Clinical presentations of Fabry disease are variable, depending on the organs affected. Classically, angiokeratomas develop on hips, back, thighs, buttocks, penis, and scrotum (termed angiokeratoma corporis diffusum). In addition, hypohidrosis due to GL3 deposits in the sweat glands were documented. Patients often have unique painful small fiber neuropathy that brings them to neurological attention before other serious manifestations appear. Intermittent bouts of burning, aching pain in the hands and feet, sometimes accompanied by elevated body temperature, can occur in patients as young as 5 years. Although the pain may be very severe, routine physical examination fails to detect any neurological abnormality. Moreover, in patients who have not yet developed renal insufficiency and therefore have not yet developed uremic neuropathy, results of electromyography and nerve conduction velocity studies are usually normal and may lead one to conclude that the pain has no organic basis. Most patients have proteinuria, and progressive renal insufficiency often occurs at the third, fourth, or fifth decade. Furthermore, cardiac hypertrophy is common, as are arrhythmia, valvular insufficiency, cardiac conduction abnormalities, and obstruction of coronary arteries leading to myocardial infarctions. Besides, small-vessel ischemic cerebral infarctions are usually present by the third and fourth decades. Dilative arteriopathy of the vertebrobasilar circulation with resultant hemorrhagic strokes has also been described. Cornea verticillata, which does not cause vision impairment, is seen in nearly all affected males and in 70 percent of carrier females. Other reported ophthalmologic abnormalities included posterior capsular cataract and excessively tortuous conjunctival or retinal blood vessels. In contrast to affected males, many carrier females experience little difficulty in adult life. Approximately 30 percent of carrier females have a few isolated skin lesions and acroparesthesia. Clinical diagnosis of male hemizygotes and female carriers is helped by the presence of characteristic angiokeratomas and the distinctive, but asymptomatic cornea verticillata.

Fabry disease is a rare disease with an incidence of 1 in 117,000 live births. Because of the X-linked inheritance, male patients are predominantly affected, while female carriers can be asymptomatic or affected to variable degree due to random inactivation of the X-chromosome. Variable genetic defects have been reported, which include partial gene duplication, partial gene deletion, small deletion and insertion, splice junction consensus site alterations and single-base substitutions. Single point mutation has been previously described in Chinese patients with Fabry disease. We have identified a mutation (c.1072_1074delGAG) causing classical Fabry disease in this Taiwanese family. Understanding the relationship between genotype and clinical phenotype will clearly aid in the prognosis, treatment and counseling of patients with lysosomal storage disease. The correlation of genotype and phenotype of Fabry disease was evaluated, but the results have so far been controversial. It is interesting to note that phenotypic variations can occur in the same family with identical genetic mutation. Whether the heterogeneous manifestations can be attributed in part to environmental factors has not been determined, but it has been suggested that such phenotypic variations may also be related to blood groups of affected individuals. Patients with blood group AB or B may have a more aggressive disease course due to a greater body substrate burden. In our studied family, the enzyme activities of both siblings are nearly the same and their blood group is both B, but the severities of dermatological and cardiac manifestations are different.

Treatments for Fabry disease are usually supportive, mainly focusing on symptomatic
relief of acroparesthesia and episodes of excruciating pain, and on the complications of renal failure, cardiac, or cerebrovascular disease. In 2001, enzyme replacement therapy (ERT) was approved to be safe and effective. For patients under ERT, clearance of plasma GL3 and microvascular deposits of GL3 was found by 14 weeks. Concerning angiokeratoma, current treatment is based mainly on the use of laser systems. The treatment result with pulsed dye laser and CO2 laser in our patients was not satisfactory. In the past, anticonvulsant drugs, such as carbamazepine, phenytoin or gabapentin, were used for partial reduction of neuropathic pain. For patients receiving ERT, the requirement of these medications was decreased in frequency and dosage. In addition to ERT, other therapies, including bone marrow transplantation, substrate-synthesis inhibitors, and gene therapy, have been investigated. However, their use is limited either by poor donor availability or by concerns for their safety.

In conclusion, Fabry disease is a rare but recognized disease in Chinese, which can present with dermatological, neurological, ophthalmologic, cardiovascular or renal manifestations. Physicians should be alert when facing patients with angiokeratoma corporis diffusum.

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