

Fabry's Disease

A Case Report and Review of Literatures Reported in Korea—

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Fabry's disease is a rare, X-linked disorder of the glycosphingolipid metabolism, in which a partial or total deficiency of a lysosomal alpha(α)-galactosidase results in the progressive accumulation of neutral glycosphingolipids with terminal alpha galactose moieties (i.e., cerebroside di- and trihexoside) in most body fluids and tissues. Accumulation of neutral glycosphingolipids occurs within the lysosomes of endothelial, perithelial, and smooth muscle cells of the myocardial and renal systems; to a lesser extent in reticuloendothelial and connective cells of the cornea; and in ganglion and perineural cells of the autonomic nervous system. In Korea, 7 cases of Fabry's disease have been reported. A 29-year-old man with fever and headache had typical skin findings and a family history of Fabry's disease, and it was confirmed through renal biopsy and enzyme assay for α -galactosidase. We report a case of Fabry's disease with a review of the literatures reported in Korea.

Key Words: Fabry's disease, α -galactosidase, glycosphingolipids

Fabry's disease was first described in 1898 as a disease of the skin(angiokeratoma corporis diffusum)(Anderson, 1898; Fabry, 1898). The clinical expression of the disease is usually fully manifested in hemizygous males who are severely affected. Heterozygous females may have an attenuated form, may be asymptomatic, or, rarely, may be affected as hemizygous males. Affected hemizygous males show various clinical symptoms, such as acroparesthesias, angiokeratoma, hypohidrosis, corneal and lenticular opacities, as well as progressive vascular disease of the kidney, heart, and brain, leading to

death (Desnick JR and Bishop DF, 1989). We report a case of Fabry's disease, established by renal biopsy for the evaluation of proteinuria and enzyme assay for α -galactosidase in a 29-year-old man with typical skin findings and a family history of the disease. We compared it to 7 cases previously reported in Korea.

CASE REPORT

A 29-year-old man was admitted to the hospital due to fever and headache lasting for the previous week. The patient had a history of multiple variable-sized erythematous maculopapules on his back, buttocks, and scrotum since the age of 8. He had experienced intermittent fever and burning pain on both hands and lower extremities, which spontaneously regressed after a few days, starting from the

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age of 10. Since age 13, he had gained heat intolerance. He left military service because he could not adapt to military training. He denied previous histories of hypertension, diabetes mellitus, pulmonary tuberculosis, and hepatitis. The patient was the oldest of 3 brothers, and his first younger brother had shown skin lesions similar to the patient on his buttocks starting from age 10. He had also experienced frequent swelling of the lower extremities since age 15 and had received an operation on both eyes due to retinal detachment. His mother had recurrent swelling of the lower extremities. His maternal uncle had skin lesions on his trunk and symptoms similar to the patient's. His maternal grandmother had died from renal disease. Physical examination revealed a well-developed male. On admission, blood pressure was 110/70 mmHg, heart rate was 68 beats/min, respiratory rate was 20/min, and the body temperature was 37.2°C. The conjunctivae were not pale. No lymphadenopathy was present. Lungs were clear and heart was normal. The abdomen was soft and flat without organomegaly. The extremities showed no edema, cyanosis or clubbing. There were multiple variable-sized erythematous-to-brownish colored macropapules on the patient's back, buttocks and scrotum (Fig. 1). The laboratory data showed the white blood cell count was 8,900/mm³ (72.3 % neutrophil, 17.3 % lymphocyte, 6.5 % monocyte, and 0.2 % eosinophil), hemoglobin 12.2 g/dl, hematocrit 36%, and platelet 289,000/mm³. Serum sodium was 137 mEq/l, potassium 3.9 mEq/l, chloride 103 mEq/l, blood urea nitrogen 5.6 mg/dl, serum creatinine 0.9 mg/dl, calcium 8.9 mg/dl, phosphorus 3.0 mg/dl, uric acid 3.3 mg/dl, total bilirubin 0.6 mg/dl, alkaline phosphatase 64 IU/L, lactate dehydrogenase 127 IU/L, aspartate aminotransferase 10 IU/L, alanine aminotransferase 7 IU/L, total protein 6.8 g/dl, and albumin 3.8 g/dl. Urinalysis showed pH 7.5, specific gravity 1.015, protein 3+, negative blood and leukocytes, and negative glucose, bilirubin and ketones. The 24-hour urine protein excretion was 1,376 mg. Liver and kidney ultrasonograms were normal, and the right kidney was 11.5 cm and the left kidney was 11.4 cm. Chest X-ray was normal. The erythrocyte sedimentation rate was 56 mm/hour. Tests for antinuclear antibodies and A.S.O. were negative, and positive for rheumatoid factor. Sero-

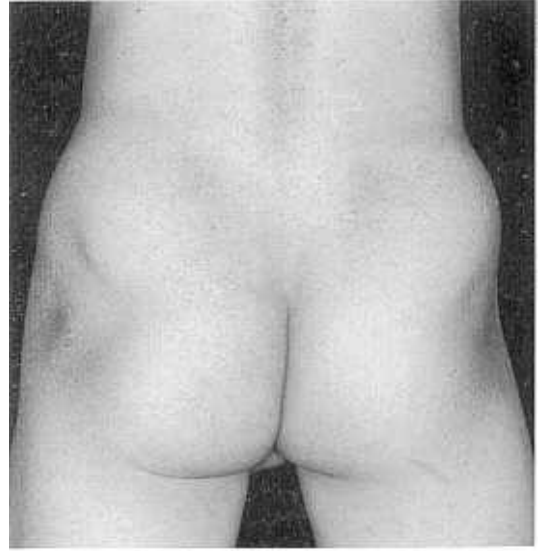


Fig. 1. Multiple variable-sized erythematous-to-brownish colored macropapules on the back and buttocks.

logic test for hepatitis B was HBs Ag(-), Anti-HBs(-) and Anti-HBc(-). Culture studies for blood, CSF, urine and stool were negative. In ocular examination, there was a fine whirl-like corneal opacity and conjunctival macroaneurysms in both eyes without decreased visual acuity. Nerve conduction velocities on all tested nerves of the right upper and lower extremities were normal. Skin biopsy on the back revealed angiokeratoma. Kidney biopsy showed a well-preserved renal cortex. Glomeruli were normocellular, but the cytoplasm of podocytes was vacuolated, which consisted of multiple, variable-sized, concentric electron-dense lamellated structures, by electron microscopy (Fig. 2, 3). The enzyme activity for α -galactosidase in serum was 11.71 nmol/hour/ng protein. This case was confirmed as a Fabry's disease through renal biopsy and enzyme assay for α -galactosidase.

DISCUSSION

Fabry's disease is an inborn error of the glycosphingolipid metabolism. The incidence is about 1 in 40,000 individuals in Western countries, but is very rare in Korea due to the traditional prohibition

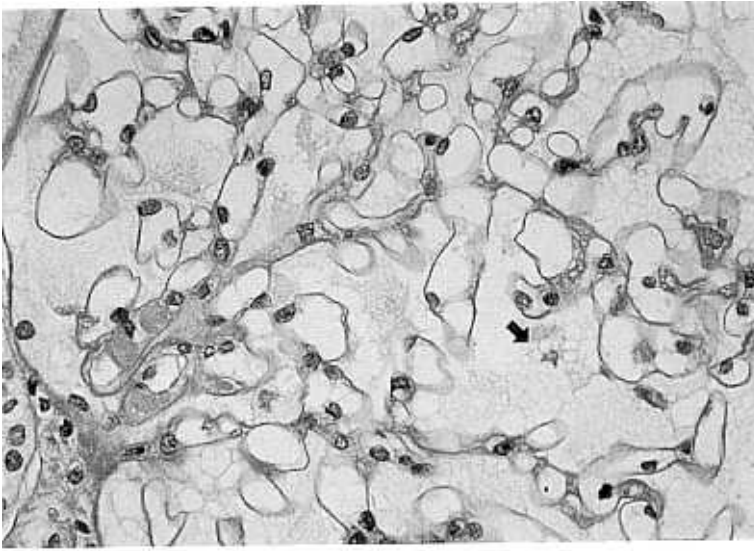


Fig. 2. The glomerular epithelial cytoplasm is stuffed with fine vacuoles (PAS, X400).

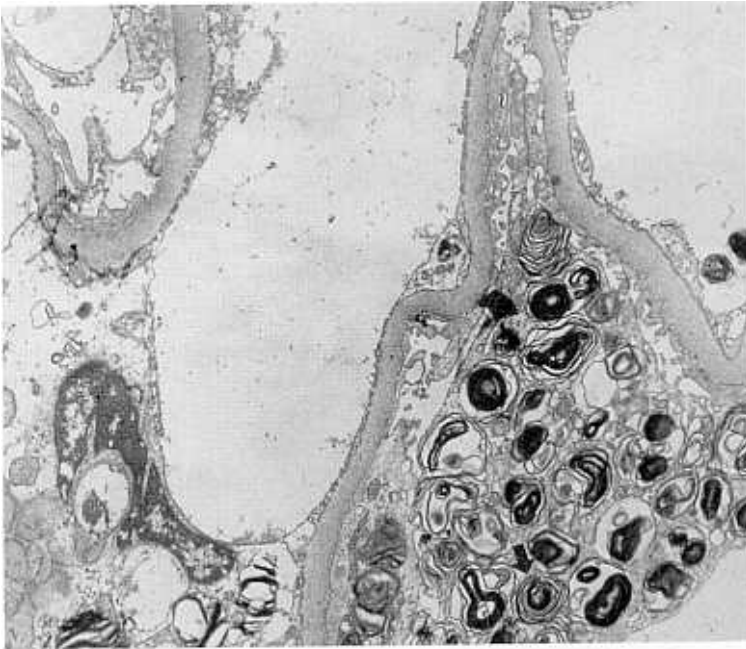


Fig. 3. Multiple variable-sized, concentric lamellated structures are seen, especially in the cytoplasm of podocytes(Uranyl acetate & lead citrate, X5,200).

of consanguineous marriage (Ko *et al.* 1996). Only 7 cases have been reported in Korea. Clinical manifestations of all the reported Fabry's diseases in Korea

including this case are shown in Table 1. All the cases were males, and the distribution of age ranged from 15 to 34. More than half of the patients at the

Table 1. Clinical manifestations of Fabry's disease reported in Korea

Author	Age	Sex	Skin	Eye	Fever	Neurologic Symptoms	Anemia	Heart	Kidney	Biopsy site
Choi <i>et al.</i> (1984) Im <i>et al.</i> (1984)	18	M	+	+	?	+	+	?	+	skin
Kang <i>et al.</i> (1987)	28	M	+	-	+	+	-	-	-	skin
Park <i>et al.</i> (1988) Kim <i>et al.</i> (1988)	21	M	+	+	+	+	-	-	+	skin
Kim <i>et al.</i> (1989)	16	M	-	-	+	+	+	-	-	nerve, muscle
Kim <i>et al.</i> (1989)	15	M	+	+	+	+	?	-	-	skin, kidney
	27	M	+	+	+	+	?	+*	+	kidney
Ko <i>et al.</i> (1996)	34	M	+	-	-	-	-	-	+	skin, kidney
Author <i>et al.</i> (1997)	29	M	+	+	+	+	+	-	+	skin, kidney

+: present, -: absent, ?: not described, *: Left ventricular hypertrophy

time of diagnosis had the disease involved in the skin, eye and kidney, and also had febrile episodes and neurologic manifestations such as painful crises on extremities, acroparesthesia and hypohydrosis or anhidrosis. Three cases out of 6 (50%) showed normocytic, normochromic anemia, and 1 out of 7 (14%) had cardiac manifestations. Tissue biopsies of 8 cases, including our case, on the skin, nerve, muscle and kidney provided typical histologic changes. In the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry, the most common symptoms were proteinuria (90%), angiokeratomas (71%) and painful paresthesiae (69%). And most patients were hypertensive, 74% had at least 1 cardiovascular problem, 26% had gastrointestinal complications, 19% had central nervous system complications, mainly headache, and 7% had aseptic bone necrosis and fractures (Tsakiris *et al.* 1996). Our case had most of the manifestations of Fabry's disease except heart involvement. Enzyme assay on α -galactosidase was performed in 6 of 8 cases, and all showed significantly decreased enzyme activity.

The alpha galactosidase gene is localized to the long arm of the X chromosome. The biochemical defect is from a lack of activity of the lysosomal enzyme and hydrolase alpha galactosidase A in tissues (El-Shahawy *et al.* 1996). Clinical manifestations of typical Fabry's disease are usually quite evident and often become severe during childhood and adolescence. Without dialysis or transplantation,

Table 2. α -Galactosidase activity* in leukocytes

Subject	Sex	Age(yr)	Activity (nmol/hr/ng protein)
Patient	M	29	11.71
Maternal uncle	M	45	11.34
Control 1	M	29	61.10
Control 2	M	27	63.00

*: The enzyme assay was performed according to methods described in Raghavan *et al.*

most affected males will succumb to renal failure by the age of 50. By contrast, most heterozygous females are clinically asymptomatic or have minimal symptomatology and live a normal life-span (Ko *et al.* 1996). The finding of typical histologic changes (i.e. zebra bodies) on appropriate tissue biopsy provides conclusive evidence. In this case, multiple, variable-sized, concentric lamellated structures were seen especially in the cytoplasm of podocytes. Further documentation requires the demonstration of decreased activity of alpha galactosidase A activity. This assay could be performed on serum, peripheral leukocytes, cultured skin fibroblasts, hair follicles, and biopsy specimens of the kidney or small intestine. In the patient and his maternal uncle, alpha galactosidase activity was significantly decreased (Table 2). DNA studies using the restriction fragment-length polymorphism technique may also help to confirm the diagnosis. The α -galactosidase gene

is about 12 kilobases long and contains 7 exons encoding a precursor protein of 429 amino acids. The basic molecular defects in Fabry's disease include partial deletion, duplication, and point mutation of the gene encoding α -galactosidase (Bernstein *et al.* 1989). The prenatal diagnosis of Fabry's disease can be established (as early as 14 weeks of gestation) either by XY karyotyping of cultured amniotic cells obtained by amniocentesis, or by DNA analysis of a chorionic villous biopsy sample (Kleisser *et al.* 1987).

No definite treatment of Fabry's disease is yet available. The debilitating pains of Fabry's disease may be considerably relieved by phenytoin or carbamazepine. The value of antiplatelet agents remains undetermined (Igarashi *et al.* 1986). Those with valvular heart disease should receive standard antibiotic prophylaxis for dental extractions, genitourinary, gastrointestinal, or upper respiratory tract procedures (Sakuraba *et al.* 1986).

An excess of glycosphingolipid can be removed by plasmapheresis (Pyeritz, 1980), with temporary symptomatic benefit. Enzyme replacement therapy using plasma or α -galactosidase purified from human spleen or placenta has been limited by the small amounts available. Even partial amelioration of the enzyme defect might result in considerable improvement in longevity and quality of life (Schrier and Gottschalk, 1997). When renal failure supervenes, both hemodialysis and peritoneal dialysis can be carried out with no specific problems (Nissenson and Port, 1989). Renal transplantation successfully reverses uremia, but the renal transplantation does not supply the defective enzyme to other organs. Therefore, the use of renal allograft as a means of altering the rate of progressive glycosphingolipid accumulation in patients with Fabry's disease remains unconvincing (El-Shahawy *et al.* 1996). Although survival was poor after transplantation in an early series (Maizel, 1981), later results have been more encouraging (Donati *et al.* 1987). Maizel (1981) reported 10 years of experience in renal transplantation for Fabry's disease. Six out of 8 patients died due to serious infection, liver failure and myocardial infarction (Maizel, 1981). Donati *et al.* reported that no lethal complication was found in 8 transplanted patients during a 241-month follow-up (Donati *et al.* 1987). Currently the most

practical approach for the early diagnosis and follow-up of patients with Fabry's disease includes screening, genetic counselling, and prenatal diagnosis.

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