A Case of Fabry's Disease

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A case of Fabry's disease in a 22-year-old male patient who had mild proteinuria and dark-red eruptions is reported. He had been treated as a case of a so-called "chronic glomerulonephritis" for one year. However, histopathological findings of the renal biopsy specimens showed the presence of numerous vacuolated cells in the glomeruli. These vacuolated cells contained numerous electron dense bodies observed by electron microscopy. Skin lesions of this patient were consistent with those of angiokeratoma corporis. The levels of serum alpha-galactosidase were significantly lower than those of healthy controls. The mother of this patient also showed decreased levels of serum alpha-galactosidase. The pedigree of this patient showed a familial history of various types of renal diseases. It was postulated that Fabry's disease occurring in older patients has a worse clinical course. It is concluded that early detection of this disease through biopsy and the assay of serum a-galactosidase levels is important in managing the future course of patients with Fabry's disease.

(Key Words: Fabry's disease, proteinuria, skin eruptions, alpha-galactosidase, vacuolated cells in glomeruli)

INTRODUCTION

Fabry's disease (1.3) is an inherited disorder of glycosphingolipid metabolism (8) characterized by the accumulation of ceramide trihexoside in plasma, cells and tissues due to a specific deficiency of alpha-galactosidase (2.5). Marked accumulation of glycosphingolipid is observed in the skin and kidneys as well as other visceral organs in patients with Fabry's disease (10). This is a case report of a patient with Fabry's disease mainly involving the skin and kidneys.

CASE REPORT

A 22-year-old male was admitted to Tokai University Hospital because of mild proteinuria. He was well until 21 years of age, when proteinuria was pointed out at Tokai University. There was no history of edema, arthralgia, fever, photosensitivity and polyserositis before admission. Although no

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family history of "collagen disease" was observed, a history of various types of renal diseases was observed in his pedigree (Fig. 1). The patient first noticed dark-red punctate eruptions on the back and hip at about 13 years of age. On March, 1982, he was admitted to the Tokai University Hospital for further examination of proteinuria.

![Pedigree Diagram]

Fig. 1 The pedigree of this patient.

On admission, his body temperature was 37.5°C, pulse 90/min and blood pressure 160/70mmHg. A large number of skin lesions was observed on the back (Fig. 2). The white blood cell count was 6,300/mm³ with 61% neutrophils, 1% band form, 29% lymphocytes, 8% monocytes, 1% eosinophils and 0% basophils. The red blood cell count was $4.34 \times 10^6$/mm³, hematocrit 39.3% and platelet count $3.46 \times 10^5$/mm³. Prothrombin time and partial thromboplastin time were within the normal ranges. Blood urea nitrogen was 12mg, serum creatinine 1.0mg, uric acid 5.6mg per 100ml, sodium 139mEq, potassium 4.1mEq, chloride 104mEq, glutamic oxalacetic transaminase (GOT) 23u, glutamic pyruvic transaminase (GPT) 21u, lactic dehydrogenase (LDH) 146u, and alkaline phosphatase (ALP) 79u per liter. Total cholesterol was 158mg and triglyceride 108mg per 100ml. Serum protein was 7.4g (albumin 4.4g), serum IgG 1396mg, IgA 167mg and IgM 170mg per 100ml. C3 was 68mg (normal values ranged from
Fig. 2  Macroscopical findings of skin eruptions on the back.
80 to 140mg) and C4 was 38mg (normal values ranged from 20 to 40 mg) per 100ml. CH50 was 37.9u per milliliter and C3 activator was 19.5mg per 100ml. Clq-binding immune complex was less than 1.5μg/ml (normal values: less than 3.0μg/ml). In urinalysis, the urine contained a small amount (0.3g/day) of protein and negative occult blood. The PSP test 15 minute value was 43%, total 100%. Creatinine clearance was 76ml per minute. A 24-hour specimen of urine contained 0.7g of protein. Culture of urine showed no growth of bacillus for 48 hours. Plasma renin activity was 6.1ng/ml/hr. Electrocardiogram and chest X-ray films were unremarkable. Slight hearing loss was noted, although the audiogram findings were normal. An analysis of amino acids showed elevation of taurine, aspartic acid, glutamine, glycine, phenylalanine and ornithine in peripheral blood, and of glycine and arginine in urine (Table 1). The levels of serum alpha-galactosidase were measured by the enzyme assay method using p-nitrophenyl alpha-galactoside as substrate as described by Kano and Yamakawa (4). In brief, 0.5ml of reaction mixture containing 15μ moles of citrate phosphate buffer (pH 4.6), 0.3μ moles of p-nitrophenyl alphagalactoside (Sigma chemical company, St. Louis M.O., USA. Lot No. 101F-5049) and 0.1ml of sera obtained from the patient, his mother, his younger brother and a healthy adult in 10mM phosphate buffer (pH 6.2) was incubated at 37°C for 1 hour. The reaction was stopped by the addition of 0.5ml of 0.4M glycine-NaOH buffer (pH 10.4) and then the absorbance at 400nm was measured using a spectrophotometer (HITACHI Model 100-40). The optimum temperature and duration for the incubation was determined by preliminary experiments. The levels of serum alphagalactosidase of this patient and his mother were significantly lower than those of his younger brother and the healthy adult (Fig. 3).

Open renal biopsy was performed without any complications on February 12th, 1982. Specimens which contained about 50 glomeruli per section were used for histological studies. Microscopically, numerous vacuolated cells with an eccentric nucleus were observed in the glomeruli and tubules (Fig. 4). These foamy cells were observed markedly among the epithelial cells of the glomerular capillary walls. Positive staining with PAS and luxol-fast blue stains in these foamy cells was seen. Negative staining of sudan III and oil red-0 stains in glomeruli was observed. Ultrastructurally, epithelial cells of the glomerular capillary walls contained electron dense bodies. The dense bodies showed lamellar and/or so-called "zebra-like" structures (Fig. 5). In immunofluorescent studies, trace amounts of IgM deposition were observed in the glomerular capillary walls. Negative staining of IgG, IgA, C3 activator, C3, C5 and C9 was observed in such glomeruli.

A skin biopsy of the back was also performed at the same time as the renal biopsy. Marked hyperkeratosis was observed beneath the papillomatous epidermis as well as in the dermis. These features were consistent with those of angiookeratoma corporis (Fig. 6).
Fig. 3 The levels of serum alpha-galactosidase in this patient, his younger brother, his mother and a healthy adult.

Fig. 4 Histopathological findings in glomeruli by light microscopy (PAS, × 400).
Fig. 5  Histopathological findings in glomeruli by electron microscopy.

Fig. 6  Histopathological findings of skin lesions on the back (H.E., × 400).
DISCUSSION

Fabry's disease (1.3) is considered to be a form of glycosphingolipidosis and is characterized by the accumulation of ceramide trihexoside in various organs due to a deficiency of alpha-galactosidase (5.7). Although renal functions were within the normal ranges, marked foamy cells were observed in the glomeruli by light microscopy and electron microscopy in this patient. These foamy cells showed positive staining with PAS and luxol-fast blue stains in the glomeruli. The skin eruption findings were consistent with those of angiookeratoma corporis. The levels of serum alpha-galactosidase activity were significantly lower than those of healthy adults. These histopathological and biochemical findings were consistent with those of Fabry's disease. Various clinical manifestations of this disease have been reported as follows: periodic episodes of excruciating pain, acral paresthesia, hypohidrosis, cutaneous vascular lesions, gastrointestinal tract involvements, and ocular, cardiovascular and renal disturbances (5.7). In Japan, 21 patients with Fabry's disease have been previously described by Okazaki et al (7). According to their report, onset of the cases was characterized by the following: hypohidrosis (95%), angiokeratoma (71%), acral pain (90%), proteinuria (81%), and impairment of renal functions (33%). However, only mild proteinuria and skin eruptions were observed in this patient and there was no impairment of renal functions. Since it is considered that patients with Fabry's disease with onset at an older age have worse clinical courses other than those occurring at a younger age (9), exacerbation of this patient in the future is anticipated. A family history of various types of renal diseases was shown in this patient's pedigree. Moreover, the levels of serum alpha-galactosidase of this patient and his mother were significantly lower than those of his younger brother and a healthy adult. These observations support the concept that Fabry's disease is an inherited disorder (8). Since there were five patients who received hemodialysis due to chronic renal failure in his pedigree, a careful follow-up is mandatory in this patient. Further examinations of other family members are warranted to determine the carriers of this disease. Recently, enzyme replacement therapy seems a promising approach to patients with Fabry's disease (6). It is concluded that early detection of this disease through biopsy and the assay of serum alpha-galactosidase levels is important in managing the future course of patients with Fabry's disease.

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REFERENCES
A Case of Fabry's Disease


