Fabry's Disease

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A 20-year-old man presented with generalized acquired anhidrosis and heat intolerance which was confirmed by a sweat test. Other clinical features included severe pain of the extremities and cutaneous angiokeratomas. On electronmicroscopy, granules specific for Fabry's disease were observed in the endothelial cells. Biochemical examination revealed a decreased level of serum α -galactosidase A. These findings confirmed the diagnosis of Fabry's disease. (Internal Medicine 31: 682–685, 1992)

Key words: α -galactosidase A, ceramide trihexoside, angiokeratoma corporis diffusum

Introduction

Fabry's disease was first described by Fabry (1) and Anderson (2) in 1898. It is a rare, sex-linked recessive inborn error of lipid metabolism (3). The metabolic defect is a deficiency of α -galactosidase A (ceramide trihexosidase), which results in the accumulation of ceramide trihexoside (CTH) in various tissues, especially in endothelial cells (4, 5). Clinical features include painful attacks of extremities, skin lesions, anhidrosis and cardiac, cerebral, and renal vascular manifestations. The diagnosis is confirmed by a decreased activity of α -galactosidase A and histologic findings. In Japan, the first case was described by Taguchi in 1938 (6). In this report, we present a typical case of Fabry's disease and review the existing literature on Fabry's disease in Japan.

Case Report

A 20-year-old man was admitted to the hospital on July 9, 1990 because of generalized acquired anhidrosis and episodes of severe pain of the extremities. He first noticed dark red eruptions scattered on his back at 11 years of age. The lesions had gradually spread to the extremities and inguinal region. At 15 years of age he began to have attacks of severe pain in his extremities and noticed decreased sweating. At age 20, he began to have difficulty exercising due to rise in body temperature associated with generalized anhidrosis. These symptoms appeared often and required hospitalization occasionally.

Two years before he came to us, his mother died of renal dysfunction at the age of 55. His younger sister, who was 12 years old, sometimes had bouts of slight pains

in her extremities, which were similar to the patient's. Her attacks occurred during exercise or upon taking a bath. Hypohidrosis was not found.

On admission, the patient's stature and nutrition were within normal limits. The blood pressure was 120/80 mmHg, the pulse rate was 75 beats/min, and the body temperature was 37.2°C. The skin was extremely dry and rough, and clusters of dark red eruptions were seen on his back, lower abdomen, inguinal region, and in regions on his extremities (Fig. 1).

Laboratory data were as follows; Hb, 15.5 g/dl. WBC, 4,500/mm³ with normal differential and platelet count. The serum enzyme activities were GOT, 7 mU/ml; GPT, 7 mU/ml; and LDH, 136 mU/ml. The serum total protein was 7.3 g/dl and the creatinine, 0.8 mg/dl. The urinalysis was normal. The creatinine clearance was 58 ml/min. The electrocardiogram and chest radiograph were normal. An ophthalmic examination revealed no specific findings in the cornea, lens, or retina. For the evaluation of anhidrosis and heat intolerance, the patient was exposed to heat. During the test there was no visible sweating.

Two biopsy specimens were taken, one from the left forearm which was free of any skin eruption, and one from a dark red eruption on his back. Figure 2 shows the histologic findings of the former, with a normal number of eccrine glands. Figure 3 shows the histopathology of the eruption indicating angiokeratoma. The epidermis overlying dilated blood filled vessels in the upper dermis was hyperkeratotic.

Electron microscopic examination demonstrated numerous electron-dense granules in the endothelial cells. Higher magnification revealed periodic laminations

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Fig. 1. Clusters of dark red eruptions in the lower abdomen.

Fig. 2. Light microscopic examination of an eccrine gland (×200).

Fig. 3. Capillary dilatation in the papillary region of the dermis and hyperkeratotic epidermis (×200).

with approximately 60-A intervals (Fig. 4). These clinical manifestations and histologic findings were specific for Fabry's disease.

To confirm the diagnosis we measured the leukocyte α -galactosidase activity. The enzyme assay was performed

Fig. 4. Electron-dense granules in endothelial cells of a dermal blood vessel (×11,600).

Inset: Higher magnification of an electron-dense granule showing regular lamellar structure (×175,000).

Fig. 5. α -galactosidase A activity in leukocytes from the patient and his sister and brother (normal level is above the dotted line).

by means of 4-methylumbelliferyl- α -D-galactoside. While, the normal value is from 150 to 250 nmol/mg, the patient's enzyme activity was significantly lower than normal; his sister's enzyme activity was slightly decreased, and his brother's was normal (Fig. 5).

Discussion

Fabry's disease is a form of the glycosphingolipidosis and is characterized by the accumulation of ceramide trihexoside (CTH) secondary to a deficiency of α -galactosidase activity. CTH is deposited in all parts of body, predominantly in the lysosomes of vascular endothelial cells. The electron microscopic finding of characteristic intracytoplasmic lamellar granules in skin

Table 1. Cases of Fabry's Disease Described in Japan from 1983 to 1991

Date of publication	Author	Number of patient	
		Male	Female
1983	Ko et al (12)	9	9
	Kira et al (13)	1	
	Nunoda et al (14)		1
1984	Suzuki et al (15)	1	
1985	Kobayashi et al (16)	1	
	Ishii et al (17)	1	
1986	Sumi et al (18)	1	1
	Yamanaka et al (19)	1	
	Tamura et al (20)		2
	Aoyama et al (21)	3	3
1987	Hozumi (22)	4	3
1988	Narisawa et al (23)	1	
	Yamada et al (24)	1	
	Tanaka et al (25)	2	2
	Iwase et al (26)	1	
	Tsuda et al (27)		3
	Matsuyoshi et al (28)	1	
	Ujin et al (29)	1	
1989	Yoshida et al (30)	3	
	Nakanishi et al (31)	1	
	Yamamoto et al (32)	1	
1990	Yamada et al (33)	3	
	Matsubara et al (34)	4	
1991	Yamaguchi et al (35)	2	2

biopsy specimens is diagnostic of Fabry's disease (7, 8).

In this patient, Fabry's disease was suspected clinically due to the pain in his extremities, anhidrosis and characteristic skin lesions. This diagnosis was confirmed by the measurement of α -galactosidase A activity in leukocytes and typical histologic findings. As the patient's sister had a significantly decreased enzyme activity, she is likely heterozygous for Fabry's disease gene. Although most biochemically documented heterozygotes have few

symptoms, others have been reported to have severe cardiac or renal disease (9, 10). The patient's mother, who died of renal failure, may have been a heterozygote.

In Japan the first case of Fabry's disease was described in 1838. Sumida et al found that 96 patients comprising 39 family lines were present in Japan before 1982 (11). To our knowledge, 69 patients were reported from 1983 to 1991 (12–35) (Table 1). The clinical manifestations of these patients are shown in Table 2. Pain in the extremities, hypohidrosis, and skin lesions are common manifestations in the hemizygote. Ocular and cardiac involvement was found in less than 50% of male patients. Thus, it is interesting that cardiac involvement was frequent in heterozygotes. As some reports have suggested that deposits of CTH increase with age (36), the present patient may likely show additional symptoms. Therefore, it is necessary to follow these patients carefully.

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Table 2. Clinical Manifestations in Fabry's Disease Based on a Review of 53 Patients Described in Japan from 1983 to 1991

Symptom	Pain in extremities	Hypo- or anhidrosis	Skin lesions	Ocular features	Renal involvement	Cardiac involvement
Hemizygote n = 42 age in years (mean) = 6–52 (27.5)	79%	69%	60%	40%	57%	33%
Heterozygote n = 27 age in years (mean) = 8–80 (39.8)	45%	10%	5%	35%	35%	50%

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