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Concise Communication

Beneficial screening of Fabry disease in patients with hypohidrosis

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Abstract

Fabry disease (FD), which is a lysosomal storage disease resulting from a deficiency of α-galactosidase A, leads to the accumulation of globotriaosylceramide in various tissues and multiorgan impairment. Early diagnosis is important to improve long-term prognosis. Early clinical manifestations of FD include neuropathic pain, vascular skin lesions, and sweating abnormalities. Hypohidorosis is one of the clinical findings in the early stage of FD. However, there have been no studies on prospective screening of FD in patients with definitive diagnosis of hypohidrosis. We examined α-galactosidase A activity in white blood cells in 17 (1 female and 16 male) patients with generalized hypohidorosis. Among 17 patients, 1 male patient (approximately 5.8%) had significantly reduced α-galactosidase A activity. He presented with a history of hypohidrosis with heat intolerance and neuropathic tingling pain in a warm environment from 6 years ago. He had a few angiokeratoma on the trunk and extremities. Ultrastructural examination of skin biopsy from the angiokeratoma revealed lamellar inclusions in endothelial cells. Kidney biopsy revealed swollen podocytes and Gb3 deposition in the glomerulus, and urinalysis revealed mulberry bodies. He was finally diagnosed with FD and started on enzyme replacement therapy with agalsidase alpha in the early stage. In addition, his family

screening led to find the patients of four additional FD. Screening for FD in patients with hypohidrosis may lead to efficient early detection of FD.

Keywords

Fabry disease, hypohidrosis, α-galactosidase A activity, screening, early diagnosis

INTRODUCTION

Fabry disease (FD, OMIM 301500) is an X-linked lysosomal storage disorder caused by mutations in *GLA* gene that encodes α-galactosidase A, resulting in reduced lysosomal α-galactosidase A activity [1]. Consecutively, globotriaosylceramide (Gb3) accumulates in various tissues, leading to multiorgan impairment. Because patients with FD often remain undiagnosed until severe complications involving cardiac, kidney, and cerebrovascular lesions develop, early diagnosis is important to improve long-term prognosis through suppressing multiorgan damage progression by several available therapies [1-3]. Early clinical manifestations of FD include neuropathic pain, vascular skin lesions, and sweating abnormalities [4]. However, to the best of our knowledge, there have been no studies on prospective screening of FD in patients with a definitive diagnosis of hypohidrosis on the thermoregulatory sweat test. To confirm the benefits of screening for FD in patients with hypohidrosis, we examined α-galactosidase A activity in white blood cells in patients with generalized hypohidorosis.

CASE REPORT

One female and sixteen male patients with generalized hypohidrosis confirmed by thermoregulatory sweat test at Kobe University (Kobe, Japan) were included.

Generalized hypohidrosis is defined as ≥25% of the entire body affected with anhidrosis or hypohidrosis according to diagnostic criteria for acquired idiopathic generalized anhidrosis (AIGA) [5]. The clinical characteristics of these patients are shown in Table 1. α-galactosidase A activity was abnormally low in two male patients (Table 1, Pt. No.12,17). Further examination for definitive diagnosis of FD was performed in these patients with low α-galactosidase A activity. Notably, one patient (Table 1, Pt. No. 12) was diagnosed with AIGA without any other symptoms or laboratory abnormalities of FD, and steroid pulse therapy was effective in improving sweating abnormalities in this patient. Another patient with markedly reduced α-galactosidase A activity (0.1 nmol/h/mg) (Table1, Pt. No.17 case report) was definitively diagnosed with classical FD. Of the other 15 patients, 1 patient had a hypothalamic pituitary tumor that caused hypohidrosis and 14 patients were diagnosed with AIGA. Detailed information on Pt. No.17 is described herein.

A 20-year-old man presented with a 6-year history of hypohidrosis with heat intolerance and neuropathic tingling pain in a warm environment. He had a past medical history of bronchial asthma and atopic dermatitis. Thermoregulatory sweat test using the iodine-starch method with sweating provoked by heat stimulation revealed anhidrosis of his entire body, including palms, soles, face, and axilla. Diseases that include hypohidrosis,

such as Sjögren's syndrome and hypothyroidism, were excluded by laboratory and physical examinations. As screening for FD, α-galactosidase A activity in white blood cells was examined, and it was significantly reduced (0.1 nmol/h/mg). The clinical examination revealed the presence of a few erythematous-purple papules on the trunk and extremities (Fig. 1a). This symptom was noticed about 4-5 years ago. Abnormal biochemical findings other than a decrease in α-galactosidase A activity were not detected. His enzymatic test showed low levels of plasma alpha-galactosidase A activity (0.1 nmol/h/mg), high levels of lyso-Gb3 (147.2ng/ml). Ultrastructural examination of skin biopsy specimen from the angiokeratoma of the left thigh revealed lamellar inclusions in endothelial cells (Fig. 1a, b). Kidney biopsy revealed swollen podocytes and Gb3 deposition in the glomerulus. Corneal opacity (cornea verticillata) was faintly observed, and urinalysis revealed mulberry bodies (Fig. 1c). Targeted sequencing by next-generation and sanger sequencing revealed a hemizygous mutation of c.928 C>T; p.(Leu310Phe) in exon 6, which has been reported previously as a pathogenic variant of *GLA* encoding α-galactosidase A [6]. The patient was started on enzyme replacement therapy (ERT) with agalsidase alpha 0.2 mg/kg body every 2 weeks. Furthermore, an interview with the patient about his familial history revealed that his mother and three brothers with neuropathic tingling pain and hypohidrosis from childhood. And his

mother was suffering from left ventricular hypertrophy of unknown origin. They were finally diagnosed with FD and started on ERT (Fig. 2). The patient and his two younger brothers noticed an improvement in sweating after ERT.

DISCUSSION

Early diagnosis is important to improve long-term prognosis of FD. Newborn screening and high-risk screening have been attempted for early diagnosis. A newborn screening study revealed that the frequency of FD was estimated to be 1:7683 in 599,711 newborns in Japan and 1:10,585 (2/21,170) in Washington, United States [7, 8]. High-risk screening studies have found 7 patients with FD among 230 males (approximately 3%) with left ventricular hypertrophy [9] and between 0.16 and 1.2 % have FD from dialysis patients [10]. The main causes of death for FD are renal failure, heart disease or stroke at around the age of 50 years for hemizygous men and 70 years for obligate carrier women[11,12]. Therefore, earlier screening before serious organ damage is important to improve the long-term prognosis of FD. In contrast, 1 patient with FD was found among 17 patients with hypohidrosis (approximately 5.8%) in our small study; this high rate indicates that screening by hypohidorosis might be more efficient, although further studies need.

Dermatologists play an important role in early diagnosis because the cutaneous findings like a neuropathic pain, angiokeratomas, and sweating abnormalities appear in early stage of FD. Orteu et al [13] have documented the dermatological features of this disease with reference to data from 714 patients (345 males, 369 females) registered on the Fabry Outcome Survey (FOS), a multicentre European database. They showed that 78% of males and 50% of females of FD had one or more dermatological abnormality, the commonest being angiokeratoma (66% males, 36% females), hypohidrosis (53% males, 28% females), and telangiectasia (23% males, 9% females)[13]. Although angiokeratoma is the most frequent manifestation, hypohidorosis is also an important sign that appears with a high probability, especially in men. It is widely assumed that the hypohidrosis of FD results principally from an autonomic peripheral neuropathy, although Gb3 deposition in sweat gland cells have also been reported[14], and the sweat gland dysfunction may play a role.

Collectively, screening for FD in patients with hypohidrosis may lead to efficient early detection of FD. Thus, the important role of dermatologists in the early detection of FD should be reaffirmed.

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187 **Figure legends**

188 **Figure 1** (a, b): Angiokeratoma of the left thigh. (a) Clinical image shows multiple,

189 raised, red-to-purple, hyperkeratotic papules on the thigh. (b) Electron microscopy

190 shows lamellar inclusions in endothelial cells on ultrastructural examination. (c):

191 Urinalysis revealed mulberry bodies.

192 **Figure 2:** Family pedigree: the index patient is marked with the arrowhead.

193

194 **Table 1.** α-galactosidase A activity in white blood cells of 17 patients diagnosed with

195 generalized hypohidrosis

Patient No.	Age	Sex	Medical history	α-galactosidase A activity in white blood cells (normal range: 49.6–116 nmol/h/mg)	Diagnosis
1	46	M	Chronic kidney disease, Hypertension, Atrial fibrillation	50.2	AIGA
2	41	M	Atopic dermatitis-	103.3	AIGA
3	31	M	Systemic lupus erythematosus, Lupus nephritis	89.1	AIGA
4	23	M	-	80.9	AIGA
5	29	M	-	72.7	Hypothalamic-pitutary tumor
6	50	M	-	62.5	AIGA
7	43	M	Central diabetes insipidus	83.2	AIGA
8	50	M	-	80.4	AIGA
9	25	M	-	52.5	AIGA
10	18	M	Asthma	69.1	AIGA
11	30	F	Gender dysphoria	66.3	AIGA
12	26	M	-	30.6	AIGA
13	39	M	-	51.2	AIGA-
14	17	M	-	79.6	AIGA
15	43	M	-	70.2	AIGA
16	38	M	-	72.7	AIGA
17	20	M	Atopic dermatitis, Asthma	0.1	FD

196 AIGA: Acquired idiopathic generalized anhidrosis, FD: Fabry disease

Figure 1

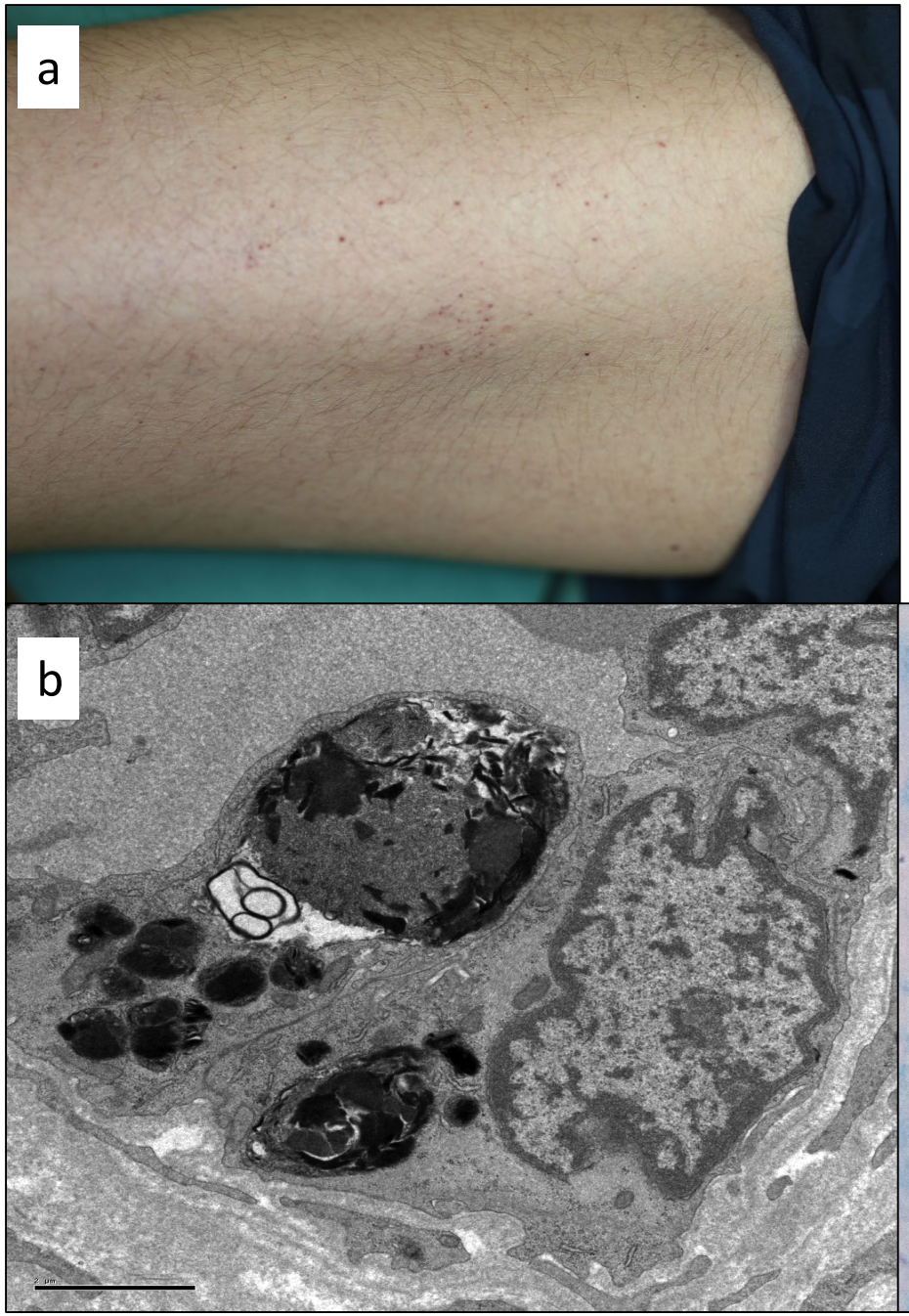
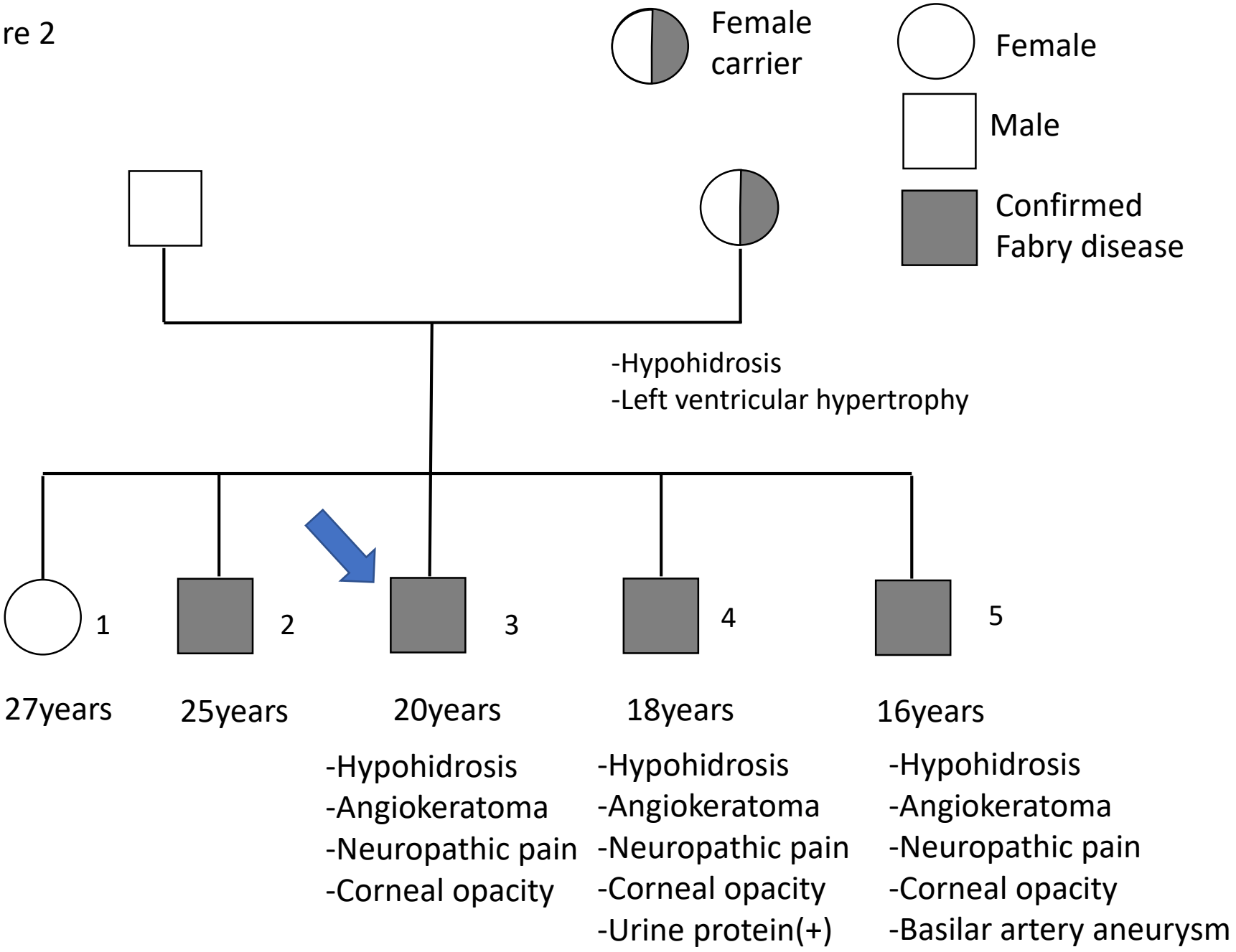


Figure 2


Female carrier
Female
Male
Confirmed Fabry disease
-Hypohidrosis
-Left ventricular hypertrophy
1
2
3
4
5
27years
25years
20years
18years
16years
-Hypohidrosis
-Angiokeratoma
-Neuropathic pain
-Corneal opacity
-Hypohidrosis
-Angiokeratoma
-Neuropathic pain
-Corneal opacity
-Urine protein(+)
-Hypohidrosis
-Angiokeratoma
-Neuropathic pain
-Corneal opacity
-Basilar artery aneurysm