Research Paper

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Fabry's disease, X-linked α-galactosidase deficiency, features a variety of autonomic abnormalities including anhidrosis. In this study, we measured the skin sympathetic nerve activity (SSNA), skin potential and sweat rate in a symptomatic female carrier to investigate the underlying pathophysiology of anhidrosis. The basal activity and responsiveness of SSNA were both fairly well preserved, although slightly reduced compared with the control levels. However, sweating was completely absent, despite the normal skin potential change in response to SSNA bursts. These results suggest that anhidrosis in Fabry's disease is a result of sweat gland dysfunction as well as abnormal SSNA.

Keywords: Fabry's disease; symptomatic female carrier; anhidrosis; skin sympathetic nerve activity; sympathetic skin response

Possible mechanism of anhidrosis in a symptomatic female carrier of Fabry's disease: an assessment by skin sympathetic nerve activity and sympathetic skin response

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Introduction

Fabry's disease is an X-linked recessive disorder, in which the accumulation of ceramide trihexoside occurs as a result of a deficiency of α-galactosidase.[1,2] Autonomic abnormalities, such as anhidrosis, orthostatic hypotension, hypertension and bowel dysfunction, are common, but anhidrosis is the principal symptom in most patients.[3,4] In hemizygous males, who develop severe autonomic involvement in early childhood, the anhidrosis is so profound that adequate physiological analysis of sweating is impossible. In contrast, heterozygous female carriers have milder symptoms and could provide important information on the pathophysiological mechanisms of some manifestations of this disease. In our previous study, we found that skin sympathetic nerve activity (SSNA)[5–7] was enhanced in a patient with acquired idiopathic generalized anhidrosis[1,4] due to primary sweat gland dysfunction. To investigate how SSNA is altered in Fabry's disease and to clarify the underlying pathophysiology of anhidrosis, we recorded SSNA and the sympathetic skin response (SSR) in a symptomatic female carrier with Fabry's disease who displayed a variety of autonomic symptoms.

Case report

A 30-year-old woman was found to have corneal opacification and retinal vessel tortuosity at 8 years of age. At the age of 13 years, she noticed pain in the extremities, particularly when subjected to heat (e.g. while bathing). Heat retention began to occur frequently in high-temperature environments. Subsequently, she also developed dizziness on standing as well as alternating constipation and diarrhea associated with vomiting. There were a number of patients with Fabry's disease in her family (Figure 1).

On ophthalmological examination, corneal opacification and retinal vessel tortuosity were noted. She was alert and well oriented. Neurological examination revealed no abnormalities of the cranial nerves, and she had normal muscle strength and tonus without any atrophy. Deep tendon reflexes were all normal and there were no pathological reflexes. There was no sensory impairment, but pain was induced in the distal extremities on exposure to heat. Orthostatic hypotension (106/62 mmHg in the supine position and 76/48 mmHg on standing) was present, but urination and defecation were not impaired. The pupillary responses to 0.125% pilocarpine and 0.01% epinephrine were

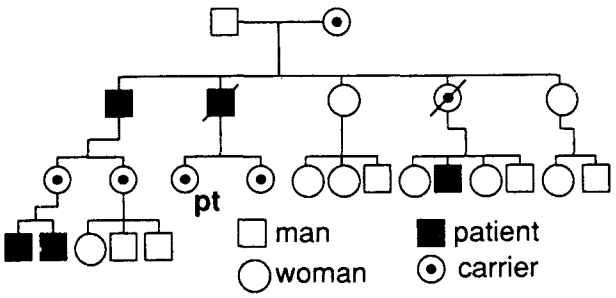

Figure 1. Family tree of our patient. Many of her relatives had Fabry's disease

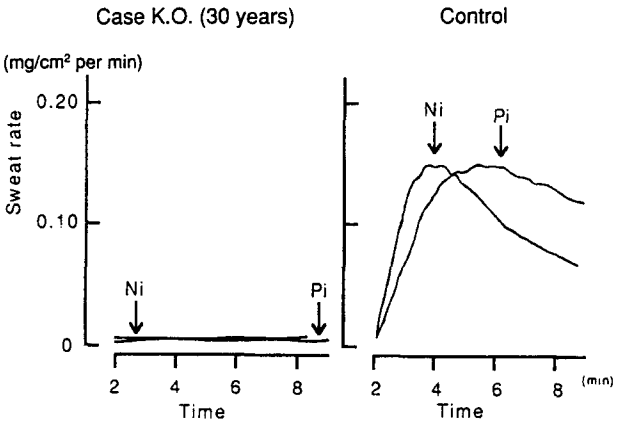

Figure 2. Recording of the sweat response to intradermal administration of cholinergic agents. At an ambient temperature of 25°C and 40% relative humidity, the sweat rate was recorded continuously by the capacitance hygrometry technique. There was no sweat response to intradermal injection of 0.1 ml nicotine (Ni; 0.1 mg/ml) or 0.1 ml pilocarpine (Pi; 0.1 mg/ml)

normal. Thermal sweating was examined in a climate chamber at 40°C and 40% relative humidity by the iodine-starch (Minor) method, and generalized hypohidrosis was found. A reduced sweat response was also detected after the intradermal administration of nicotine (0.1 mg/ml) and pilocarpine (0.1 mg/ml; Figure 2).

Electron microscopy of a skin biopsy specimen from the medial aspect of the forearm revealed sweat gland atrophy and granular deposits of glycolipids in the sweat gland stroma (Figure 3). Leukocyte α-galactosidase activity was 14.3 nmol/mg protein per h (normal: 25.1–55.4), showing an approximately 50% decrease. Routine hematology and biochemical tests, and urinalysis revealed no abnormalities. No mulberry cells were seen in the urine. Chest X-ray films, endoscopy of the upper gastrointestinal tract, electrocardiography (ECG), Holter ECG, computed tomography scanning and magnetic resonance imaging of the head also failed to show any abnormalities.

Methods

Skin sympathetic nerve activity (SSNA)[5–7] was recorded after resting in the supine position for at least 30 min. The purpose and possible benefits of the study were explained in detail to the patient, and informed consent was obtained beforehand. A tungsten microelectrode, with an impedance of approximately 3–5 MW and a

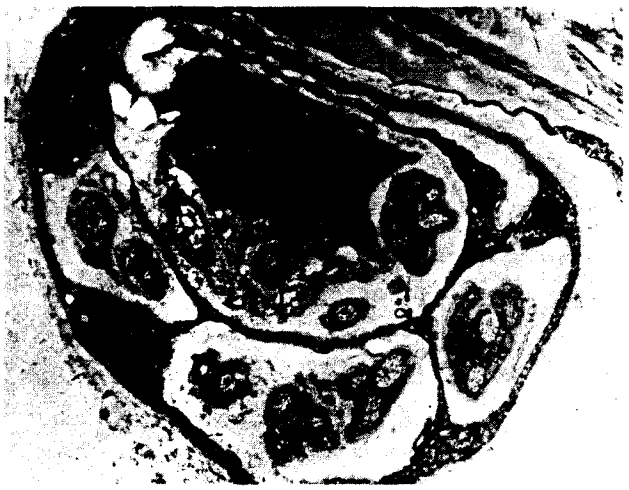

Figure 3. Electron micrograph of a skin biopsy. Electron microscopy examination of a skin biopsy specimen taken from the medial aspect of the forearm showed sweat gland atrophy and granular deposits of glycolipids in the sweat gland stroma × 7600

tip diameter of 1 mm, was inserted into the cutaneous portion of the tibial nerve at the popliteal fossa without anesthesia. Then SSNA was recorded as an indicator of the neuronal activity of sympathetic postganglionic fibers from the plantar skin. SSNA was identified using the reported criteria:[5,6] (1) pulse-asynchronous irregular burst activity with a duration of 300–500 ms; (2) increased burst activity in response to arousal stimuli or to psychological or physical stress (e.g. auditory or electrical stimulation); (3) firing of reflex bursts with a latency of approximately 0.81–1.1 s in response to auditory or electrical stimulation; (4) association with a reduction of the skin blood flow or an increase in sweating (or sweat expulsion); and (5) dependence on the ambient temperature.

SSNA signals were amplified with a pre-amplifier (WP Instruments DAM-6A, Hamden, CT, USA), and filtered through bandpass filters (500–5000 Hz; NF Circuit Block Design, E-3201 ×2, 24 dB/oct; Yokahama) to improve the signal-to-noise ratio. Then the SSNA was observed visually on a cathode ray oscilloscope (Tektronix 5113, Beaverton, OR, USA; gain ×200) with auditory monitoring[8] and stored in an FM magnetic data recorder (KS-616U, Sony Magnescale, Tokyo) for off-line processing. The SSNA neurogram was full-wave rectified and integrated, with a time constant of 0.1 s using an analog integrator for recording on a thermal pen recorder (Recki-Horiz-8K, NEC-San-ei, Tokyo, Japan).

Skin blood flow was measured with a laser Doppler flow meter (ALF21, Advance Co., Tokyo, Japan), and the sweat rate was determined by the ventilated capsule method (Fourtion, AMU-2, Nagoya, Japan). Both of these parameters were monitored continuously with the recording of SSNA. Skin potential changes were monitored with a bio-amplifier (AI-601G, Nihon Kohden, Tokyo, Japan) placed between surface electrodes on the sole and the dorsum of the

foot. The time constant was 2 s and the high cut-off frequency was 30 Hz. The response of skin potential changes to arousal stimuli was defined as the SSR.[9]

This study was performed according to the routine described elsewhere.[10] The patient rested supine on a bed in a soundproof room with the ambient temperature set at 25°C for at least 30 min, after which resting activity of SSNA was recorded for 10 min. Then the following maneuvers were performed in sequence at 5-min intervals: (1) mental arithmetic including serial subtraction of 7 from 100, addition and subtraction of two-digit numbers, etc.; (2) auditory stimulation by a sudden shot from a starting pistol; (3) supramaximal electrical stimulation to the median nerve at the wrist; and (4) hand immersion in ice water at 4°C for 2 min (cold pressor test).[10,11]

SSNA was quantified using two methods. For the resting activity and the SSNA response to continuous mental stimulation, the number of bursts per minute was counted and designated as the burst rate. For assessment of the magnitude of the response to physical stimulation, the amplitude of each integrated burst occurring after stimulation was summated, averaged by the mean amplitude of resting activity and then converted into values for 1-min intervals. These arbitrary values (reported in arbitrary units) were used to indicate the responsiveness to stimulation.

As controls, 16 healthy adult volunteers (aged 28–72 years, including 14 men and two women) were examined by the same protocol to determine their resting SSNA and responsiveness to mental and physical stress. The temporal relationships between SSNA and the skin blood flow, sweat rate and SSR were also examined.

Results

Skin sympathetic nerve activity

The resting SSNA burst rate in our patient was 8.0 bursts/min, which was lower than the mean – 2SD for the control group (16.0 ± 3.0 bursts/min). The SSNA was 8.0 bursts/min during the performance of mental arithmetic and 17.0 bursts/min during the cold pressor test in our patient, values which were lower than in the control group (28.1 ± 3.0 and 31.0 ± 3.0 bursts/min respectively; Figure 4A). The SSNA amplitude after arousal stimulation was 54.20 ± 7.50 arbitrary units for the pistol sound and 45.80 ± 7.09 arbitrary units for electrical stimulation in our patient. These values were also lower than those in the control group (79.41 ± 5.79 and 53.27 ± 4.64 arbitrary units, respectively; Figure 4B).

Sweat expulsion and the sympathetic skin response to changes of skin sympathetic nerve activity

There was a one-to-one correspondence between the SSR and the preceding SSNA burst elicited by electrical stimulation. The appearance of the SSR in our patient was almost the same as in the normal controls.

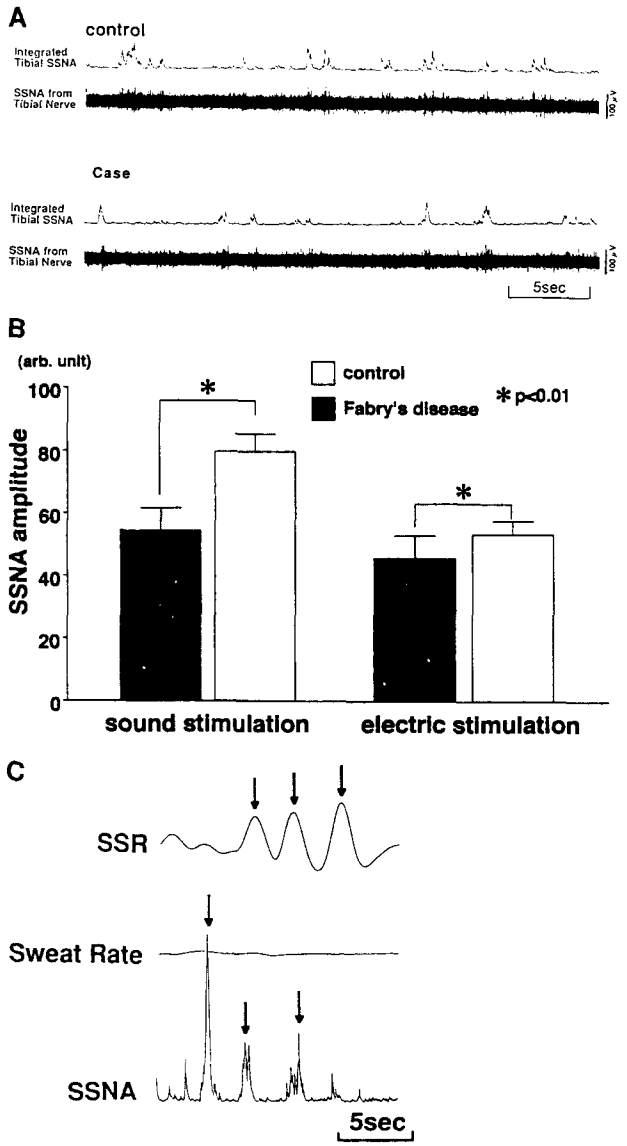

Figure 4. (A) Skin sympathetic nerve activity (SSNA) and response to arousal stimuli. The SSNA burst rate of our patient at rest and in response to stimulation was lower than in the controls. (B) SSNA amplitude responses to pistol shot sound and electrical stimulation. The SSNA burst amplitude of our patient at rest and in response to stimulation was lower than that of the controls. (C) Sweat expulsion and sympathetic skin response (SSR) elicited by SSNA in our patient. There is one-to-one correspondence between SSR and SSNA, but no sweat expulsion in response to SSNA bursts

However, there was no sweat expulsion corresponding to the preceding SSNA burst, even when both SSNA and SSR were clearly induced by electrical stimulation (Figure 4C).

Discussion

Impaired sweating is one of the principal manifestations of Fabry's disease,[1,2] but the pathology and the underlying mechanisms are not well understood. One reason for this is that anhidrosis is very severe, even in early childhood in hemizygous males, making adequate pathophysiological analysis of sweating impossible.

In the present study, we recorded SSNA, sweat expulsion[12] and changes of skin potential in a sympto-

matic heterozygous female carrier with relatively mild impairment of sweating, thus demonstrating some aspects of the pathophysiology of anhidrosis in this disease. Although both resting SSNA and its responsiveness were only slightly reduced, sweat expulsion was completely absent, even when a definite change in skin potential was obtained. The SSR, i.e. the change of skin potential in response to supramaximal electrical stimulation, appears to reflect the production and migration of sweat towards the lumen of the excretory duct.[13,14] Sweat expulsion, on the other hand, seems to reflect the actual process of excretion of sweat from the skin.[15]

Our present findings suggested that sweat is not effectively excreted in this disease, resulting in anhidrosis. However, sympathetic nerve function and sweat production by the sweat glands are relatively well preserved in the early stages of Fabry's disease. Laminar granular deposits corresponding to glycolipids in the ducts and stroma of the sweat glands were seen on electron micrographs obtained in our patient, supporting the view that impairment of the sweat glands and ducts also contributes to anhidrosis in this disease.

Since SSNA was somewhat reduced, sympathetic nerve dysfunction provides an additional contribution to anhidrosis. If only the sweat glands were involved, SSNA should be enhanced both at rest and in response to mental and physical stimulation, possibly as a result of a negative feedback mechanism. The sweat glands were impaired in our patient, but there was no corresponding increase of SSNA, suggesting that it was also abnormal to some extent.

It is still uncertain which factor has the more important role in anhidrosis, dysfunction of neural elements or abnormal sweat glands. However, the present study suggested that sweat gland and duct involvement may contribute to anhidrosis at least in the early phase. To obtain more data, it will be necessary to perform pharmacological studies on sweat gland activity in hemizygotic males with very early Fabry's disease.

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