A Case of Pure Autonomic Failure Initially Presenting with Hemihypohidrosis: Twelve-Year Follow-Up

Hiroshi Saito

Department of Neurology, Sendai Eastern Neurosurgical Hospital, Sendai, Japan

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Pure autonomic failure · Hemihypohidrosis · Thermoregulatory and pharmacological sweating · Mode of progression

Abstract
Although it is generally recognized that pure autonomic failure (PAF) is a progressive neurodegenerative disease selectively involving the autonomic nervous system, its mode of progression remains to be settled. A 57-year-old man presented with sweat reduction on the left side during previous 3 years. The thermoregulatory sweat test revealed left-sided multi-segmental hypohidrosis more markedly on the face. Pharmacological sweating was relatively preserved except for the face. During the subsequent 8 years, he developed erectile dysfunction and overt orthostatic hypotension. Plasma norepinephrine was markedly reduced without reactive increase during the tilt-table test. The heart to mediastinum ratio in 123I-metaiodobenzylguanidine cardiac scintigraphy was reduced. Over the following 3 years, he showed progressive and generalized postganglionic sudomotor impairment without cognitive impairment or somatic nervous dysfunctions. Present observations suggest that in some patients with PAF, pathological process might start mainly at the central level and later extends to the peripheral level.
**Introduction**

Pure autonomic failure (PAF) is a neurodegenerative disease, involving almost exclusively the various parts of the autonomic nervous system without somatic motor or sensory impairments [1, 2]. Patients with PAF usually present with progressive orthostatic hypotension (OH), sweating disturbance, constipation, or genitourinary impairment. While OH and syncope are known as the cardinal features of PAF, prevalence of other autonomic deficits and the chronological order of their occurrence have not been established.

According to the current literature, PAF predominantly involves pathological changes of postganglionic sympathetic and parasympathetic fibers with various degrees of preganglionic involvement [2, 3]. Specifically, recent studies have shown that α-synuclein deposits are found not only at the central level but also in the nerve fibers innervating the skin or gut [4, 5]. Thus, PAF is regarded as a type of α-synucleinopathy. Certain number of PAF patients however may convert to Parkinson’s disease, dementia with Lewy bodies, or multiple system atrophy, and nosological identity of PAF is questioned [6, 7].

The present report describes a case of PAF initially presented with thermoregulatory sweating (TS) deficit on one side of the body with relatively preserved acetylcholine-induced sweating (ACh-S). Long-term follow-up of the patient suggested that, at least in certain patients with PAF, the pathological process may extend from the central to the peripheral sympathetic system.

**Case Report**

A 57-year-old man who had undergone electrocauterization therapy for atrial fibrillation was referred to us because of a 3-year history of reduced sweating on the left side of the body. He reported an occasional orthostatic lightheadedness but unchanged sexual and voiding functions. On physical examination, his pupils were equal in size with normal reaction to light. Evaluation of motor and sensory systems revealed no abnormalities. Blood pressure (BP) and the heart rate in supine position were 129/90 mm Hg and 66 beats per min, respectively, compared with 120/100 mm Hg and 72 beats per min, respectively, in standing. Radiography and computerized tomography images of the chest as well as magnetic resonance imaging of the brain and the spinal cord revealed no abnormalities.

**Testing Sudomotor Functions**

After obtaining an informed consent from the patient, TS was assessed qualitatively using the modified Minor’s colorimetric method [8], and sweat rates on the forehead and extremities were continuously measured by capacitance hygrometers (Hidrograph-AMU-2, Kyokuto-Denshi, Nagoya, Japan, and Skinos-4000; SKINOS Company, Nagoya, Japan). Pharmacological focal sweat rates were assessed by an intradermal injection of 0.05 mL of 5% acetylcholine (ACh-S). The results were compared with a control group of age- and sex-matched subjects ($N = 15$) without diabetes mellitus, neurological or autonomic deficits, whose informed consents had been obtained.

On the TS test, there was no sweating before heating. Sixty minutes after heating, the right side of the body showed diffuse sweating, whereas the left side was hypohidrotic, especially in the upper half of the body. The left side of the forehead remained almost anhidrotic, while the right side displayed probable compensatory hyperhidrosis. The left side of the trunk at the T4/5 level displayed an area of relatively abundant sweating than adjacent segments (Fig. 1a). TS rates on the left side were unevenly reduced compared with the right side (Table 1), showing 2%, 2%, and 87% of the right-side values for the forehead, forearm, and leg, respectively. Less
A pronounced reduction of sweating was observed in ACh-S on the left side (Table 1), showing 36%, 56%, and 53% of the right-side values for the forehead, forearm, and leg, respectively. ACh-S values on the patient's forearm and leg were >65% of the control group.

**Table 1.** Changes of thermal sweat rates at a body temperature of 37.0°C and acetylcholine-induced sweat rates

| Age   | Duration, years | Type of sweating | Sweat rates, mg/cm²/min |
|-------|-----------------|-------------------|-------------------------|
|       |                 |                   | Forehead | Forearm | Leg |
|       |                 |                   | R | L | R | L | R | L |
| Present patient | | | | | | | | |
| 57    | 3               | TS                | 2.670 | 0.055 | 0.292* | 0.005* | 0.324 | 0.282 |
|       |                 | ACh-S             | 1.145 | 0.405 | 0.338 | 0.188 | 0.341 | 0.180 |
| 65    | 11              | TS                | 0.090 | 0.030 | 0.032 | 0.000 | 0.000 | 0.000 |
|       |                 | ACh-S             | NE   | NE    | 0.356 | 0.200 | 0.040 | 0.011 |
| 66    | 12              | TS                | 0.060 | 0.020 | 0.012 | 0.006 | 0.010 | 0.000 |
|       |                 | ACh-S             | 0.010 | 0.000 | 0.229 | 0.078 | 0.012 | 0.000 |
| 68    | 14              | TS                | 0.050 | 0.015 | 0.002 | 0.000 | 0.000 | 0.000 |
|       |                 | ACh-S             | NE   | NE    | 0.116 | 0.071 | 0.011 | 0.005 |
| Control** | | | | | | | | |
| 50 < 70 | (N = 15)      | TS                | 0.931±0.289 | 0.109±0.021 | 0.119±0.019 |
|        |                 | ACh-S             | ND   | 0.276±0.022 | 0.278±0.024 |

ACh-S, acetylcholine-induced sweating; ND, no data; NE, not examined; TS, thermoregulatory sweating.

*Sweat rates at body temperature of 36.8°C.

**Men without neurological and autonomic deficits.
Follow-Up

At the age of 65 years, the patient revisited the hospital because of orthostatic dizziness and occasional syncope. He reported that during previous 4 years, erectile dysfunction had occurred, whereas urination and defecation were still normal. On examination, cranial nerves and somatomotor and sensory systems showed no abnormalities. In supine position, BP and the heart rate were 112/80 mm Hg and 66 beats per minute, respectively, and 75/59 mm Hg and 81 beats per minute, respectively, in standing. The tilt-table test showed similar BP reduction and no reactive increase in plasma norepinephrine (0.04 ng/mL in supine position vs. 0.09 ng/mL after 60° tilting for 6 min). MRI of the brain was unremarkable. The heart-to-mediastinum ratio in 123I-meta-iodobenzylguanidine cardiac scintigraphy was reduced to 1.58 on the delayed image (institutional normal value: >2.20). The TS test showed patchy or blotchy sweating without apparent laterality, and TS rates were markedly reduced on all sites examined. ACh-S was preserved on the forearms but was markedly reduced on legs. During the following 3 years, sudomotor function was investigated twice (at the age of 66 and 68 years), and the results revealed progressive deterioration of the postganglionic sudomotor function (Fig. 1b; Table 1).

Treatments and Prognosis

The patient has been treated with daily doses of midodrine hydrochloride 6 mg, etilefrine hydrochloride 15 mg, and droxidopa 1,000 mg, which enabled him activities of daily living despite occasional orthostatic dizziness. The patient was also advised to prevent OH by drinking enough water and taking salty foods and to avoid the risk of heat retention during hot season. At the last visit (age 69 years), the patient was still free from the somatomotor and sensory symptoms and signs. His cognitive function remains normal.

Discussion

The present patient initially presented thermal hemihypohidrosis on the left side of the body with relatively preserved pharmacological sweating. Such a pattern suggested the impaired central (including the preganglionic level) sudomotor pathway [8]. While the TS test assesses the entire sudomotor function, pharmacological sweat tests evaluate only the postganglionic function [9–11].

Other autonomic functions as well as somatic nervous system appeared intact. During the following 9 years, however, he developed apparent OH and erectile dysfunction, with a reduced uptake ratio of the myocardium on 123I-meta-iodobenzylguanidine cardiac scintigraphy and a low level of the plasma norepinephrine level on the tilt-table test without somatic and cognitive decline for 15 years. Thus, clinical diagnosis of PAF is plausible.

Studies on sudomotor function in PAF are rather scarce. Abnormal sweating has been reported in approximately half of all patients with PAF [12, 13]. Cohen et al. [12] reported that among 10 PAF patients with anhidrosis on the TS test, six had a combined pre- and postganglionic anhidrosis, three had the preganglionic lesion, and one had the postganglionic lesion. Mabuchi et al. [14] reported that all 8 patients with PAF had experienced faintness and hypohidrosis on the first visit to the hospital, but the detail sudomotor features were not been described.

Recently, Triplett et al. [15] reported a case of PAF initially presenting as Harlequin syndrome. The patient displayed anhidrosis of the right face, neck, and upper limb, whereas pharmacological sweating was normal in all sites, suggesting segmental impairment of preganglionic sudomotor neurons innervating the anhidrotic skin area. In ensuing years, the patient developed progressive sudomotor function involving the postganglionic system as well as impairment of adrenergic and cardiovascular cardiovagal responses. Authors suggested that the early postural lightheadedness, which was seen also in the present case,
may have been a clue to evolving PAF rather than isolated Harlequin syndrome. The present patient may be a second case suggesting that in certain subjects with PAF, sudomotor deficits may be an initial symptom, and functional deterioration may start at a central level but progress to the peripheral part of the TS sudomotor pathway.

In the present patient, interval between the initial and second visits was as long as 8 years, and the tilt-table test and measurement of plasma catecholamines were not performed at the initial visit. To elucidate the chronological order of autonomic deficits in PAF and related disorders, the overall survey for autonomic functions are necessary for subjects with dyshidrosis or OH of unexplained etiology.

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Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local guidelines. Written informed consent was obtained from the patient for publication of the details of the medical case and any accompanying images.

Conflict of Interest Statement

The author has no conflicts of interest relevant to this article to disclosure.

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Author Contributions

Corresponding author: Saito H is the single author of the study and has all responsibilities for the study.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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