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Case Report

Fever of Unknown Origin in a Girl with Idiopathic Generalized Anhidrosis Diagnosed Based on a Discrepancy between Deep Body Temperature and Surface Body Temperature: A Case Report

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Patients with acquired idiopathic generalized anhidrosis (AIGA) present with reduced sweating and impaired thermoregulation, which causes body temperature to increase quickly during exercise or in a hot environment. A 14-year-old girl was admitted with a variety of symptoms and prolonged fever of unknown origin. AIGA was diagnosed because of a discrepancy between deep body temperature (tympanic membrane) and body surface temperature (axillary), and she was treated. Careful history taking and physical examination are essential for patients with fever of unknown origin.
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Introduction

Patients with acquired idiopathic generalized anhidrosis (AIGA) present with widespread anhidrosis/hypohidrosis (reduced sweating) of unknown cause but no other autonomic or neurological symptoms[1]. Because of impaired sweating, body temperature rises quickly during exercise or in a hot environment. The present patient was a 14-year-old girl admitted with prolonged fever of unknown origin and other symptoms. AIGA was diagnosed because of a discrepancy between deep body temperature (tympanic membrane) and body surface temperature (axillary), and she underwent treatment.

Case Presentation

A 14-year-old girl with prolonged fever was admitted to our hospital. She had cholinergic urticaria since age 9 years. At age 10 years, she was referred to our hospital for evaluation of numbness and muscle weakness of the right hand and double vision. Grip strength was almost unmeasurable, but there were no obvious abnormalities in other physical findings, including finger movement, and neurological findings. Brain magnetic resonance imaging (MRI), blood testing, and ophthalmological examination also showed no obvious abnormalities. There were also no obvious abnormalities on thoracic and lumbar MRI and cerebrospinal fluid examination. The symptoms persisted for 6 months after the referral. She experienced numbness and difficulty moving her legs and back pain, but brain MRI and thoracic and lumbar MRI again showed no abnormalities. She reported chronic abdominal pain and diarrhea, and weight loss of 4 kg was noted. Colonoscopy was performed, but no obvious abnormalities were found, and all symptoms improved spontaneously.

Because of the high prevalence of SARS-CoV-2 infection, her temperature had been measured daily since March 2020 (at age 13 years). Since November 2020 she had repeatedly experienced high fevers, as well as chronic insomnia, headache, and back pain. Her fever persisted during the period January through March 2021, and she was hospitalized for further examination. She had symptoms of photosensitivity and fever of unknown

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origin and a range of possible diagnoses was investigated, including collagen disease, malignant tumor, infection, and porphyria. Antinuclear antibodies were weakly positive (homo 80×) and autoantibodies were negative. There were no findings suggesting chronic inflammation, Ga scintigraphy showed no abnormal accumulation, and visible light examination showed no abnormalities. Blood counts, white blood cell differentials, CRP, and ferritin values were measured every time the patient had a fever, and all were within the normal ranges, confirming the absence of inflammation.

She reported fever while attending school. This fever subsided spontaneously during hospitalization but recurred repeatedly. At that time, her deep body temperature, measured by eardrum temperature, was 36.8°C, and body temperature at the armpit (body surface temperature) was 39.3°C. Her medical history was again taken, and it was found that she was sweating less than before 2020, even when exercising.

In July 2021, the patient was hospitalized for a sweat test. The results of blood and autoantibody testing are shown in **Table 1**. According to the revised diagnostic criteria for Sjögren's syndrome[2], the diagnosis is negative when there are no ophthalmological abnormalities and no abnormalities in serum tests (positive anti-SS-A antibodies, positive anti-SS-B antibodies). The IgE level was normal and did not change before or after treatment. IgE levels also remained within the normal range throughout the course of the disease. After admission, body surface temperature and deep body temperature were measured, and the body surface temperature (38.5°C) remained higher than the deep body temperature (36.5°C). There was no difference in tympanic membrane temperature between the left and right sides. Rectal temperature was slightly higher than tympanic membrane temperature but was within the normal range.

The findings at that time were weight 40 kg, body temperature 36.9°C, heart rate 72 beats/min, blood pressure 102/52 mm Hg, and respiratory rate 16 breaths/min. She was conscious and had no pharyngeal redness or cervical lymphadenopathy. Breath sounds were normal, and there was no heart murmur. No abnormalities in her skin condition were found before the fever began, and there was no obvious atopy. During a regular physical examination, dry skin would not have been noticed, and the patient herself did not realize that she was sweating less until she was asked about it again. With the approval of the Ethics Committee of Nippon Medical School Chiba Hokusoh Hospital (approval number 83), a sweat test using the starch iodine reaction was performed[3]. Sweating was absent in response to starch iodine on the lateral neck and forearm of the patient (**Figure 1a**), as compared with sweating at the same areas of a healthy control (**Fig-**

Table 1 Results of blood and autoantibody testing

Test	Result
Total protein, g/dL	6.2
Albumin, g/dL	3.9
UN, mg/dL	13
Creatinine, mg/dL	0.6
Na, mmol/L	139
K, mmol/L	4.2
Cl, mmol/L	105
Ca, mg/dL	9.4
Total bilirubin, mg/dL	0.8
AST, U/L	19
ALT, U/L	9
CK, U/L	74
CRP, mg/dL	<0.05
WBC, /μL	5,000
Band cells, %	0
Segmented nucleus cells, %	37
Lymphocyte, %	51
Monocyte, %	9
Eosinophil, %	2
Basophil, %	1
RBC, /μL	437×10^4
Hb, g/dL	12.4
Ht, %	37.4
Platelet, /μL	24.2×10^4
Vitamin B1, ng/mL	34.7
Vitamin B12, pg/mL	714
Folic acid, ng/mL	7.7
Zinc, μg/mL	70
Ferritin, ng/mL	8.7
IgG, mg/dL	1,004
IgA, mg/dL	83
IgM, mg/dL	170
IgE, IU/mL	203
Complement, U/mL	27
C4, mg/dL	9.9
C3, mg/dL	90
Soluble IL-2R, U/mL	336
Antinuclear antibody	80
Homogeneous	80
Speckled	80
Nucleolar	<40
Peripheral	<40
Acetylcholine receptor antibody, nmol/L	<0.3
MPO-ANCA, IU/mL	<0.5
PR3-ANCA, IU/mL	<0.5
Myelin basic protein, pg/mL	<31.2
Anti-muscarinic antibodies, nmol/L	<0.02
Anti-SSA antibody, U/mL	<0.5
Anti-SSB antibody, U/mL	<0.5

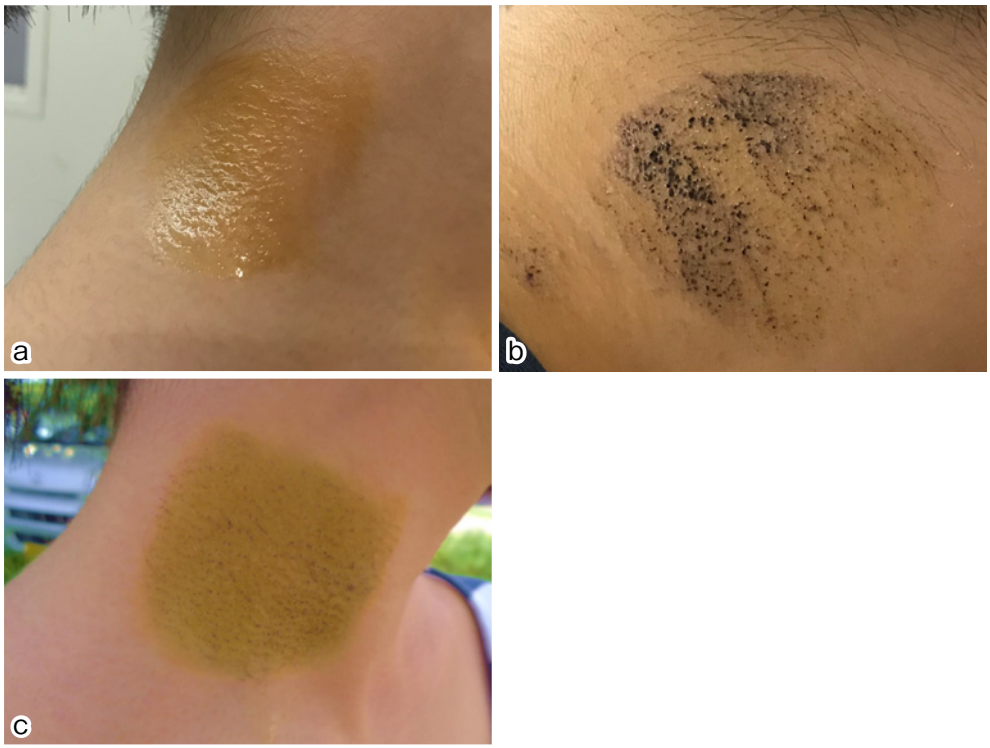

Figure 1 Sweat testing using the starch iodine reaction
(a) No positive reaction to starch iodine, indicating that sweating is absent in the lateral neck. (b) Positive reaction to starch iodine in a healthy control. (c) Positive reaction to starch iodine in the patient after dexamethasone treatment, indicating restoration of sweating.

ure 1b). The area of the anhidrosis/hypohydrosis affected was approximately 40% of the body surface area, which is classified as mild according to Ministry of Health Labour and Welfare, Labor and Welfare's severity rating[1]. However, because the area affected was greater than 25%, the diagnostic criteria were met.

The pathological findings of a skin biopsy showed a decrease in the number and size of eccrine glands and atrophy of the ducts (**Figure 2**). There was no significant change in the epidermis. Although there was fibrosis in the papillary dermis, there was no noticeable infiltration of inflammatory cells. The pathological findings were consistent with anhidrosis.

On the basis of these results she was diagnosed as having acquired anhidrosis and treated with methylprednisolone pulse therapy[4,5]. The fever subsided after 2 days, and there was no longer any discrepancy between the tympanic membrane temperature and body surface temperature. In addition, fatigue associated with the fever also improved. Sweating was observed on the 7th day of administration, and the sweat test using starch iodine was positive (**Figure 1c**).

The patient provided oral consent for publication of this case report.

Discussion

AIGA was first reported by Lutembacher in 1917[6]. It is a rare disease that is more prevalent in young men, and most cases have been reported in Asia, suggesting that racial factors may be involved[6]. AIGA is a disease in which sweating is reduced after birth, without an obvious cause. The condition is not accompanied by other autonomic or neurological abnormalities. Sweating, which is important for thermoregulation, is impaired, and body temperature rises easily during exercise or in a hot environment. Associated symptoms include cholinergic urticaria and pain. The diagnosis is made by confirming reduced sweating over 25% of the body with a sweat test using the starch iodine reaction and by ruling out secondary anhidrosis due to Sjögren's disease, neurological disorders, endocrine metabolic disorders, or drugs. Most cases of AIGA are treated with steroids, which usually results in improvement or cure[4,5].

In our patient, AIGA was diagnosed and treated because there was an abnormality in the dissipation of body heat: the core body temperature was almost normal despite an increase in skin temperature. No study has compared deep body temperature and superficial body temperature in patients with anhidrosis, and it is unclear

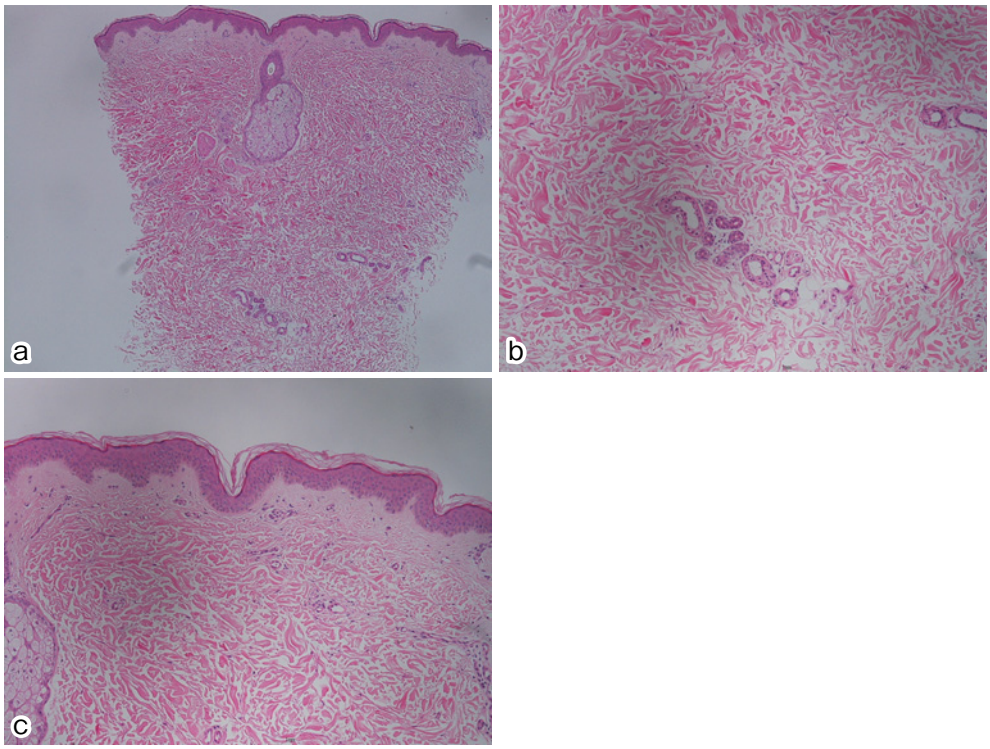

Figure 2 Pathological findings of the skin
(a) Image of the skin at low magnification showing a reduction in eccrine sweat glands and fibrosis of the papillary dermis. (b) Image showing a reduction in eccrine sweat glands. (c) Fibrosis of the papillary dermis is noted in the shallow dermis.

whether such a comparison is useful in diagnosing this condition. Although deep body temperature should normally be high, it is quite possible that body surface temperature will rise in a hot environment in the absence of sweating without initially affecting deep body temperature. Patients with anhidrosis have difficulty regulating their body temperature because they are unable to sweat, which increases their risk of heatstroke. If deep body temperature rises too much, it can have dangerous effects on the body, so appropriate measures are necessary.

In conclusion, a girl with fever of unknown origin was diagnosed as having anhidrosis by measuring eardrum temperature and body temperature at the armpit. Careful history taking and physical examinations are essential for evaluating fever of unknown origin.

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