JDA Japanese Dermatological Association
THE JOURNAL OF DERMATOLOGY
doi: 10.1111/1346-8138.13649
Journal of Dermatology 2017; **44**: 394–400

GUIDELINE

Revised guideline for the diagnosis and treatment of acquired idiopathic generalized anhidrosis in Japan

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ABSTRACT

Acquired idiopathic generalized anhidrosis (AIGA) is characterized by an acquired impairment in total body sweating despite exposure to heat or exercise. Severe cases may result in heatstroke. Most cases of AIGA have been reported in Asia, especially in Japan. However, there is limited information on the epidemiology of this condition, and no diagnostic criteria or appropriate treatment options have been established. This guideline was developed to fill this gap. It contains information on the etiology, diagnosis, evaluation of disease severity and evidence-based recommendations for the treatment of AIGA. Appropriate treatment according to disease severity may relieve the clinical manifestations and emotional distress experienced by patients with AIGA.

Key words: **acquired idiopathic generalized anhidrosis, anhidrosis, disease severity, guideline, hypohidrosis.**

BACKGROUND TO THE DEVELOPMENT OF THE GUIDELINES

At present, there is no specified definition, diagnostic criteria or appropriate treatment protocol for acquired idiopathic generalized anhidrosis (AIGA). In addition, the epidemiology of AIGA in Japan is as yet undetermined. Developing guidelines for diagnosing and treating AIGA can help determine the incidence in Japan as well as enable appropriate treatment to be instituted according to disease severity. This can relieve the emotional distress experienced by active young and middle-aged AIGA sufferers and improve their quality of life.

POSITION OF THE GUIDELINES

This committee, which comprised members commissioned by the Japanese Dermatological Association, the Japan Society of Neurovegetative Research and the Japanese Society for Perspiration Research, commenced its meetings and deliberations on written documents in August 2014 and revised the guideline. This guideline provides a summary of the treatment modalities currently used for AIGA in Japan.

DISCLAIMER

The guideline was prepared by integrating the opinions of the committee members based on the data available at the time of writing. However, depending on the results of future studies, the conclusions and recommendations described in this report may be revised.

Deviation from this guideline is acceptable in certain patients and under certain circumstances. There will even be some cases in which deviation is preferable. Thus, physicians providing treatment cannot evade liability for negligence simply by complying with the guideline. Similarly, physicians providing treatment that deviates from the guideline are not necessarily negligent.

EVIDENCE LEVELS AND RECOMMENDATION GRADES

The evidence levels and recommendation grades used in the guidelines were based on the Criteria for Determining Evidence Levels and Recommendation Grades document prepared by the Malignant Skin Tumor Group (Table 1).[1]

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Received 24 March 2016; accepted 7 September 2016.

Table 1. Criteria for determining evidence levels and recommendation grades

A. Evidence levels	
I	Systematic review/meta-analysis
II	Based on at least one randomized controlled trial
III	Based on non-randomized controlled trials
IV	Analytical immunological studies (based on cohort or case–control studies)
V	Descriptive studies (based on case reports or case series)
VI	Opinions of the expert committee or individual experts[†]
B. Recommendation grades[‡]	
A	Application is strongly recommended (at least one piece of level 1 evidence or level II evidence of high quality indicating efficacy)
B	Application is recommended (at least one piece of level II evidence of low quality, level III evidence of high quality, or level IV evidence of extremely high quality indicating efficacy)
CI	Although application can be considered, sufficient evidence is lacking[§] (level III–IV evidence of low quality, several pieces of level V evidence of high quality or level VI evidence accepted by the committee)
C2	Presence of evidence indicating ineffectiveness)[‡]
D	It is recommended not to apply (evidence of high quality indicating ineffectiveness or harmfulness)

This table was cited from Saida *et al.*[1] with modification. [†]The evidence levels for data from basic experiments and theories derived from the data are set at this level. [‡]Evidence refers to findings of clinical or epidemiological studies. [§]Some recommendation grades described in the text do not correspond to the above criteria. This is attributed to the fact that the committee determined recommendation grades on the basis of consensus (while indicating evidence levels) while considering the lack of evidence for the treatment of malignant skin tumor worldwide and the actual situation in which overseas evidence is not directly applicable to Japan, as well as the usefulness of the evidence.

EPIDEMIOLOGY, ETIOLOGY, AND PATHOPHYSIOLOGY

Epidemiology

No epidemiological data on AIGA has been published thus far, and so its prevalence and morbidity remain unknown. AIGA is assumed to be rare, as only approximately 100 cases have been reported. However, it is plausible that without exposure to heat or vigorous exercise, the presence of AIGA may go unnoticed. Alternatively, patients may be misdiagnosed as having other conditions, such as cholinergic urticaria associated with anhidrosis or atopic dermatitis associated with anhidrosis. Thus, AIGA may only be diagnosed in a small proportion of actual cases.

The majority of known AIGA cases were reported in Japan. As such, it is unknown whether its prevalence varies with race and geography. AIGA is markedly commoner in men, who account for more than 80% of known cases. Although the age of onset typically ranges from the second to fourth decade of life, AIGA can occur at any age from infancy to the eighth decade.[2]

According to the results of an epidemiological survey conducted by this study group, the incidence of AIGA at 94 departments of neurology or dermatology at Japanese university hospitals from 2010 through 2015 was 145 cases. The incidence was significantly higher in men (126 men and 19 women). The age at onset ranged broadly from 1 to 69 years, while the peak age at onset was between the second and fourth decades of life. The mean age at onset was 30.3 years (31.0 years in men and 22.7 years in women).[3]

Etiology and pathophysiology

Acetylcholine is the main neurotransmitter transmitted by sudomotor nerves to sweat glands. This sudomotor nerve activity is expressed in bursts, and is to some extent synchronized with respiratory movement. The sweat glands secrete pulses of sweat droplets in synchronization with the sudomotor nerve activity, which is referred to as "sweat expulsion".

Acquired idiopathic generalized anhidrosis is assumed to be associated with the following three pathological conditions:[2]

1 Sudomotor neuropathy
2 Idiopathic pure sudomotor failure (IPSF)
3 Sweat gland failure

Skin sympathetic nerve activity controlled by sweat glands, which can be recorded with microneurography, is decreased in (1) sudomotor neuropathy. However, it is normal or enhanced in (2) IPSF and the early stage of (3) sweat gland failure.[4] Thus, (2) IPSF and (3) sweat gland failure can be regarded as conditions in which sweat glands do not respond to normal or enhanced nerve signals that induce sweating. In the case of (3) sweat gland failure, sweating does not occur because of abnormalities in the sweat glands, while (2) IPSF may be attributed to a lack of response by the cholinergic receptors in sweat glands to the acetylcholine released from sudomotor nerve terminals. Decreased expression of the muscarinic acetylcholine M3 receptor has been observed in sweat glands.[5] These pathological conditions are common in young men and are likely to be complicated by pain, paresthesia and cholinergic urticaria; however, psychogenic sweating is preserved. This may be attributed to excessive acetylcholine that cannot interact with cholinergic receptors. In addition, serum levels of immunoglobulin (Ig)E are elevated in many cases, and early steroid pulse therapy can often achieve a complete response. This lends credence to the theory that an autoimmune mechanism is involved.[6] The involvement of autoantibodies to the muscarinic acetylcholine M3 receptor in sweat glands has been proposed as the underlying mechanism.[7]

Sudomotor neuropathy is believed to affect only sudomotor function without causing any other types of neuropathy. In sudomotor neuropathy, the following have been proposed as possible sites of dysfunction: (i) the hypothalamus;[8] (ii) the medulla oblongata and spinal cord; and (iii) the preganglionic and postganglionic sympathetic efferent fibers. None of these affect the induction of skin sympathetic nerve activity regardless of changes in ambient temperature. Notably, hypothalamic dysfunction is associated with a decreased

threshold for sweating. Dysfunction of the medulla oblongata and spinal cord is generally associated with neurological symptoms other than anhidrosis. Dysfunction of the preganglionic and postganglionic sympathetic efferent fibers results in segmental spinal dysfunction and is often simultaneously complicated by vasoconstrictor dysfunction. When peripheral skin blood flow is measured with laser Doppler skin blood flowmetry, it may be observed that blood flow normally decreases in response to bursts of skin sympathetic nerve activity; however, there is no such decrease in sudomotor neuropathy. On the other hand, a decrease in skin blood flow is normally observed in IPSF and sweat gland failure.

Idiopathic pure sudomotor failure and sweat gland failure have different clinical courses. Sweat gland failure has a more prolonged clinical course. This suggests the presence of two conditions: in one, anhidrosis due to autonomic neuropathy, sudomotor neuropathy or IPSF results in histological degeneration; in the other, primary immunological destruction of sweat glands results in anhidrosis. However, these conditions cannot be differentiated at present. Thus, sweat gland failure may comprise many heterogeneous pathological conditions. In contrast, IPSF can be considered a well-established homogeneous disorder. As IPSF accounts for a large proportion of AIGA cases, it can be regarded as a narrowly defined subtype of AIGA.

DIAGNOSIS AND DIFFERENTIATION

Classification of anhidrosis

Anhidrosis is characterized by a lack of sweating or reduced sweating (hypohidrosis) in conditions that would normally promote sweating, such as exercise, high temperature or excessive humidity. This disorder includes congenital or hereditary anhidrosis, as well as acquired anhidrosis.[9] Acquired anhidrosis can be further classified into secondary anhidrosis (e.g. anhidrosis due to neuropathy, endocrinopathy and metabolic disorders, and drug-induced anhidrosis)[10] and idiopathic anhidrosis, in which the pathology, etiology and mechanism of the condition remain unknown.[11]

Acquired idiopathic generalized anhidrosis is a type of idiopathic anhidrosis. It affects nearly the entire body, and can be differentiated from anhidrosis with segmental spinal or segmental distribution of anhidrotic areas, such as idiopathic segmental anhidrosis[12] and Ross syndrome (Fig. 1). It is defined as "an acquired disorder that reduces the amount of sweat without any clear cause and is not associated with either dysautonomia or neurological abnormality except sudomotor dysfunction".[13] Sweating, which is essential for regulating body temperature, is inhibited. This results in patients experiencing body temperatures easily raised by exercise or heat.

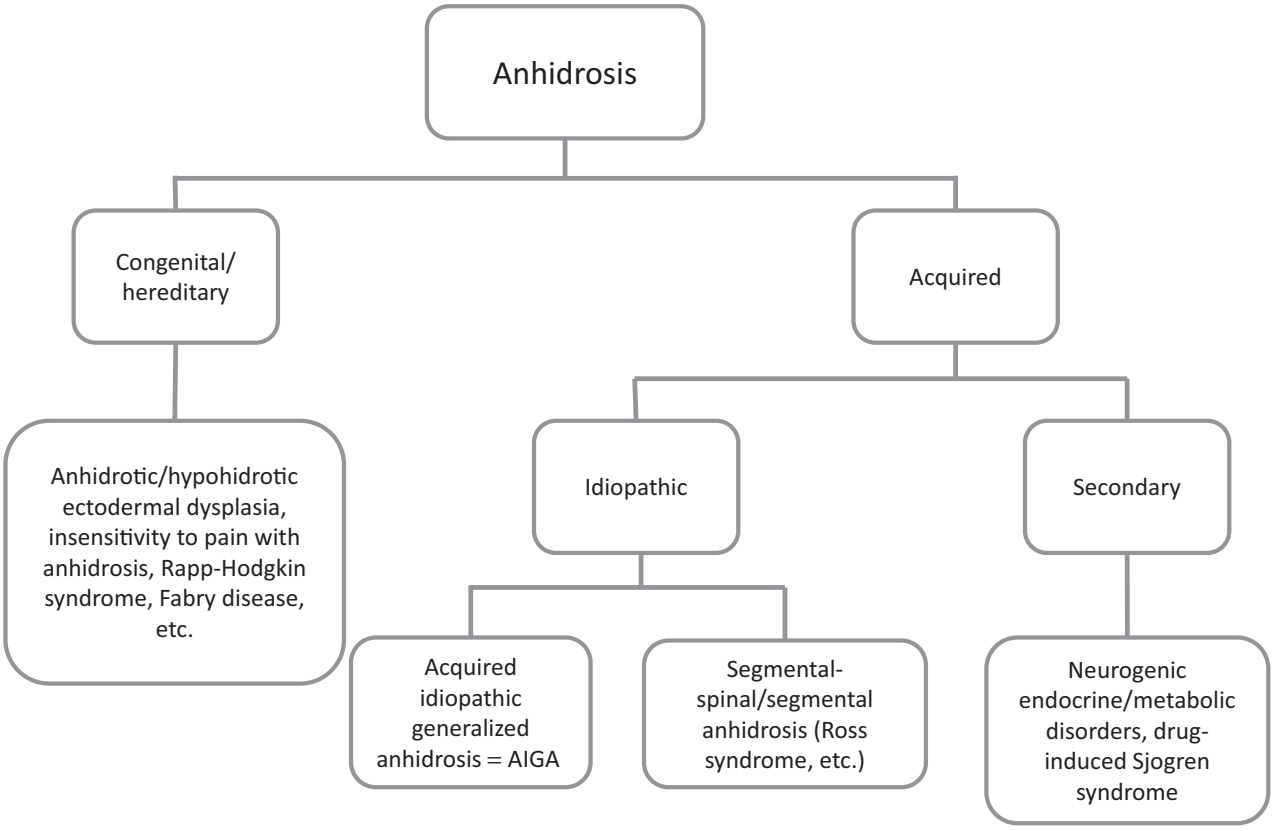

Figure 1. Classification of anhidrosis.

Symptoms of AIGA, especially IPSF

Anhidrosis or hypohidrosis has widespread effects throughout the body. Sudomotor function, however, is quite frequently preserved in some parts of the body, especially in the head, face, axillae, palms and soles of the feet. Sweating, which is important in regulating body temperature, is inhibited in these patients. As such, exercise or a hot environment results in heat accumulation. These patients may present with hot flush sensations involving the whole body, hyperthermia, weakness, lassitude, facial flushing, nausea, vomiting, headache, dizziness or palpitations. Heatstroke may occur in some patients. The pricking pain and rash of cholinergic urticaria are also frequently observed. Although spontaneous resolution may occur in some cases, these symptoms often follow a chronic course.

Diagnostic criteria for AIGA (devised by the preparation committee for the guidelines for the pathological analysis and treatment of AIGA)

A: Although lesions of idiopathic anhidrosis or hypohidrosis are widely distributed in a non-segmental spinal pattern, no other autonomic or neurological symptoms are observed.

B: Anhidrotic or hypohidrotic areas affect 25% or more of the entire body. These are defined as areas that do not turn black with the thermoregulatory sweat test (based on the Minor method using the iodine–starch reaction) and other methods, or hyperthermic areas detected by thermography.

Acquired idiopathic generalized anhidrosis is diagnosed when both criteria A and B have been satisfied.

Reference items

1 When sweating is induced, the pricking pain and rash of cholinergic urticaria are frequently observed on the skin.
2 The hypohidrotic areas are symmetrically distributed. Sweating in the axillae and psychogenic sweating on the palms and the soles of the feet are frequently preserved.
3 Atopic dermatitis may manifest concurrently with AIGA and should not be considered as part of the exclusion criteria.
4 Some patients may have histopathological findings such as lymphocytic infiltration around sweat glands, atrophy of sweat glands and keratotic plugs in sweat pores.
5 Reactions on the acetylcholine skin test and the quantitative sudomotor axon reflex test (QSART) are decreased.
6 Sjögren's syndrome (SS) has been excluded by the absence of anti-SS-A and anti-SS-B antibodies, the absence of exocrine gland dysfunction, and other findings.

Differentiation and tests for AIGA

Thermoregulatory sweat test

This involves the use of an artificial temperature-controlled room, makeshift sauna, electric blanket or other heating devices to raise patients' body temperatures and promote sweating. Anhidrotic areas may then be observed. The Minor method,[14] wrapping-film, alizarin and other methods facilitate a clearer assessment of anhidrotic areas. In healthy individuals, sweating occurs throughout the body after approximately 15 min of heat exposure. However, in patients with AIGA, although sudomotor function is frequently preserved in the face, neck, axillae, palms, soles and other parts of the body, non-segmental spinal distributions and broad distributions of anhidrotic areas are observed.

Drug-induced sweat test

This test is used to diagnose AIGA lesions.

Local administration: Acetylcholine chloride (Ovisot®) 1–10 mg/mL is injected i.d. at a dose of 0.1–0.3 mL.[15] In healthy individuals, piloerection and sweating are observed a few seconds after the injection. Sweating centered on the injection site can be observed within 5–15 min.[16] In patients with AIGA due to a sweat gland disorder, no sweating is observed.

QSART

After acetylcholine is administrated to the skin by iontophoresis, only sweating due to the axon reflex is quantified.[17] Sweating is not induced in patients with AIGA.

Skin biopsy (light and electron microscopy)

In patients with AIGA due to IPSF, although light microscopy does not reveal marked morphological defects of sweat glands, lymphocytic infiltration may sometimes be observed around sweat glands.[5] Some cases of AIGA due to sweat gland failure may demonstrate swelling of the secretory cells of the sweat glands, hyperkeratosis of the horny layer and other findings.[13]

Measurement of total serum IgE levels

Total serum IgE is elevated in some cases of IPSF.

Thermography

When thermography is performed in combination with the thermoregulatory sweat test, areas of increased body temperature are found to correspond to anhidrotic areas.

Of these tests, only the general thermoregulatory sweat test is covered by the Japanese national health insurance system. The drug-induced sweat test and QSART are not.

Severity classification of AIGA (devised by the preparation committee for the guidelines for the pathological analysis and treatment of AIGA)

Criteria for determining the severity of AIGA are provided in Table 2.

TREATMENT AND CLINICAL QUESTIONS

Is systemic administration of corticosteroids effective for AIGA?

Recommendation grade: C1

Recommendation: Despite insufficient high level of evidence, systemic administration of corticosteroids is recommended on the basis of findings presented in numerous case reports.

Corticosteroid therapy is recommended in the early stages of AIGA. Patients delayed treatment initiation or degeneration

Table 2. Criteria for determining AIGA severity

Item score	Area of anhidrotic/ hypohidrotic lesions†	Area of painful skin or wheal† (cholinergic urticaria may be included)	Symptoms of heatstroke
0	<25%	<25%	Asymptomatic in not environment or after exercise
1	25% to <50%	25% to <50%	Orthostatic dizziness, myalgia or muscular rigidity in hot environment or after exercise
2	50% to <75%	50% to <75%	So-called heat exhaustion (headache, discomfort, nausea, vomiting, malaise, collapse) in hot environment or after exercise
3	>75%	>75% Anaphylaxis	Impaired consciousness, convulsion, dyskinesia of the limbs and high body temperature in hot environment or after exercise

Mild, 0–2; moderate, 3–5; severe, 6 or more. †Areas are determined by thermoregulatory sweating tests using iodine–starch reaction, such as Minor method. AIGA, acquired idiopathic generalized anhidrosis.

of sweat gland tissue reportedly respond poorly to corticosteroids.

However, this is not covered by the Japanese national health insurance system.

Explanation: Steroid therapy was initiated in more than half of the 100 previously reported cases, the majority of whom experienced improvement or cure (level V evidence).[2,13,18,19] Thus far, there have been no reports of randomized controlled trials examining the efficacy of steroids in AIGA. However, steroid therapy appears to merit recommendation on the basis of findings described in numerous case reports.

The forms of steroid therapy described in these reports include steroid pulse therapy alone, steroid pulse therapy followed by p.o. administration of prednisolone and p.o. administration of steroids alone. With regard to steroid pulse therapy, 1–2 courses of a 3-day i.v. infusion of methylprednisolone (500–1000 mg/day) were typically administrated. In those receiving steroid pulse therapy followed by prednisolone, oral prednisolone was often administrated p.o. at 30–60 mg/day.[2,13,18,19] In the reports on oral steroid monotherapy, although a common regimen is 30–60 mg/day of prednisolone followed by tapering this dose, some reports also described improvement even at very low doses of just 2.5–5 mg/day.[20] However, there is no consensus on the most appropriate dose of steroids, and future investigations are required to establish this.

Regarding the time to onset for symptom relief, steroid pulse therapy achieves early improvement immediately to a few days after treatment initiation.[2,13] Thus, it may be appropriate for cases in which rapid effectiveness is needed. However, there is no consensus on the number of courses of steroid pulse therapy required or the need for post-treatment oral prednisolone.

Regarding factors associated with therapeutic responsiveness, it has been reported that patients with early onset AIGA and concurrent cholinergic urticaria may respond well to steroids.[19] Some reports have also indicated that patients with delayed treatment initiation[19] or severe parenchymal changes in sweat gland tissue may respond poorly to steroids.[18,19] However, the evidence for this is not sufficiently robust, and further accumulation of cases is required.

The long-term prognosis of AIGA has yet to be elucidated. In some cases, remission is maintained even after the completion of steroid therapy, whereas AIGA recurs in others when steroid doses are tapered. There have also been cases of treatment-resistant AIGA. Moreover, cases in which spontaneous remission is achieved have also been reported.[2,13] The optimal duration of steroid administration must be carefully examined in future studies.

Is p.o. administration of immunosuppressants effective for AIGA?

Recommendation grade: C1

Recommendation: It is worthwhile to attempt a trial of oral immunosuppressants in patients not responding to steroid pulse therapy. However, this treatment is not covered by the Japanese national health insurance system.

Explanation: Oral administration of immunosuppressants has been reported in only one case in Japan (level V).[21] The patient was a 22-year-old man with AIGA. Anhidrotic areas were detected in the extensor and flexor aspects of both forearms, the chest, the entire face and parts of the dorsum of both hands using the Minor method. The distribution of anhidrotic areas, normal serum IgE level, presence of cholinergic urticaria and absence of underlying disease led to the diagnosis of AIGA. After two courses of steroid pulse therapy (methylprednisolone at a dose of 1000 mg/day for 3 days) had been administrated, sweating was temporarily observed, but the patient subsequently experienced a relapse of AIGA. Although four further courses were administrated, the anhidrotic areas increased. p.o. administration of cyclosporin was commenced at a dose of 250 mg/day, and sweating was observed 1 week later. Oral cyclosporin was gradually reduced and stopped after 4 months. The anhidrotic areas did not increase during the 3 months of follow up after treatment discontinuation.

Although sweating was not completely achieved, this case suggests that oral immunosuppressants may be effective in patients with expanding anhidrotic areas refractory to steroid pulse therapy. Oral immunosuppressants may be effective in

glandular disorders due to the CD-4-positive cells infiltrating the tissues around eccrine glands. However, p.o. administration of immunosuppressants has only been reported in this one case. There are no other reports of such cases in Japan or even worldwide. As such, further studies are needed.

Is administration of antihistamines appropriate for relieving symptoms of AIGA?

Recommendation: Antihistamines can be administrated at increased doses appropriate to the symptoms experienced.

Recommendation grade: C1

Explanation: AIGA may be accompanied by cholinergic urticaria. Histamine is a factor common to both pathological conditions. It plays a major role in the pathogenesis of urticaria and also inhibits acetylcholine-induced sweating.[22] Through histamine H1 receptors, histamine inhibits secretion of sweat from secretory cells of sweat glands to suppress sudomotor activity.[22,23] As a result, antihistamines are expected to be effective in treating anhidrosis, and have been studied in patients with AIGA resistant to steroid pulse therapy.[24] When increased doses of antihistamines were administrated to two patients with AIGA confirmed by QSART and the general sweat test (using the Minor method), sweating at levels detectable by QSART was confirmed. Bathing and exercise gradually promoted sweating noticeable to the patients, until sweating recovered.[24] Despite the low level of evidence for this treatment, given the limited treatment options currently available, appropriately increased antihistamine doses and instructions to promote and manage sweating can be considered in patients unresponsive to or intolerant of corticosteroid pulse therapy. However, it should be noted that antihistamines are not covered by the Japanese national health insurance system for the treatment of AIGA.

Are there any other effective treatment options for AIGA?

Recommendation grade: C1

Recommendation: Given the large number of intractable cases, other treatment options may be attempted. However, none are adequately evidence-based or covered by the Japanese national health insurance system.

Explanation: One case report described the amelioration of AIGA with a combination of oral *Saireito*, a traditional Japanese medicine, and topical steroids (level V).[25] *Saireito* (minor bupleurum decoction plus five ingredient powders with poria) has anti-inflammatory effects and promotes endogenous steroid secretion by stimulating the secretion of corticotropin-releasing factor from the hypothalamus. As such, this report suggested that it may be worthwhile to administrate *Saireito* in patients with inability to tolerate p.o. administration of steroids.

Regarding cholinergic drugs, which are also used as systemic therapy for glandular symptoms experienced in SS, there have been reports of the effectiveness of oral pilocarpine hydrochloride (level V).[26,27] The use of cevimeline hydrochloride hydrate has not been reported. Warm bath therapy, exercise therapy[28,29] and the topical application of keratolytic agents[30] are reportedly effective in treating hypohidrotic cholinergic urticaria, which is associated with the occlusion of sweat ducts (level V). The effective treatment of hypohidrotic cholinergic urticaria with exercise loading in patients with no parenchymal histological abnormalities has also been described (level V).[31]

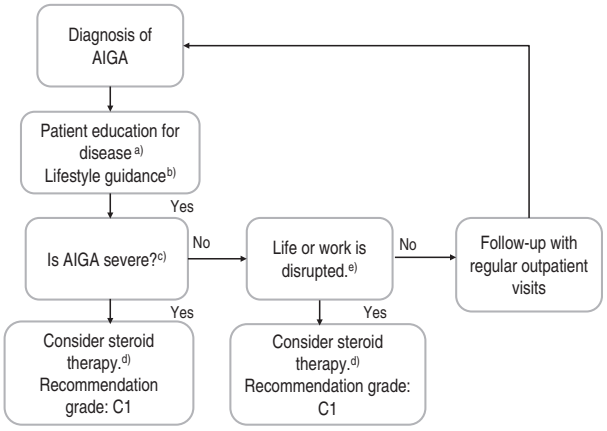

Figure 2. Proposed algorithm for the treatment of acquired idiopathic generalized anhidrosis (AIGA) in Japan.

Proposed algorithm for the treatment of AIGA in Japan

1 As part of patient education, AIGA should be adequately explained to patients, such that they understand the high risk of heatstroke due to the thermoregulatory disorder associated with decreased sweating (Fig. 2).
2 As part of lifestyle guidance, patients should be instructed on techniques for preventing heatstroke. These include avoiding hot environments, limiting exercise and cooling their bodies (e.g. proper use of air conditioning, wearing a cooling vest and carrying bottled cold water).
3 Steroid therapy should be considered for patients with a severity score of 6 points or higher (according to the criteria for determining the severity of AIGA).
4 Commonly administrated forms of steroid therapy include steroid pulse therapy (1–2 courses of a 3-day i.v. infusion of methylprednisolone at a dose of 500–1000 mg/day) alone, steroid pulse therapy followed by oral prednisolone at 30–60 mg/day and oral prednisolone at 30–60 mg/day followed by dose tapering.[2,13,18,19] However, there is no sufficiently robust evidence regarding appropriate doses and administration routes. For cases of AIGA that do not respond to steroid therapy, treatment with other agents such as cyclosporin, *Saireito* and pilocarpine can be considered. However, none of these treatments are covered by the Japanese national health insurance system.
5 Steroid therapy should be considered for patients with pain or symptoms of heatstroke that disrupt daily life or work.

ACKNOWLEDGMENTS: This work was supported by a Grant-in-Aid for Research for Incurable Disorders from the Ministry of Health, Welfare and Labor of Japan (H26-069).

CONFLICT OF INTEREST : None declared.

REFERENCES

1 Saida T, Manabe M, Takenouchi T *et al.* Guidelines for management of skin cancer. *Jpn J Dermatol* 2012; **122**: 1725–1740. (in Japanese).
2 Iwase S. Acquired idiopathic generalized anhidrosis. *Jan Med J* 2003; **4136**: 1–10. (in Japanese).
3 Fujimoto T, Yokozeki H, Sato T. Establishment of guideline for the treatment and analysis of etiology of AIGA in Japan. Research for incurable disorders. Ministry of health, Labor and welfare in Japan. 2012: 28–37. (in Japanese)
4 Murakami K, Sobue G, Iwase S, Mitsuma T, Mano T. Skin sympathetic nerve activity in acquired idiopathic generalized anhidrosis. *Neurology* 1993; **43**: 1137–1140.
5 Sawada Y, Nakamura M, Bito T *et al.* Decreased expression of acetylcholine esterase in cholinergic urticaria with hypohidrosis or anhidrosis. *J Invest Dermatol* 2014; **134**: 276–279.
6 Nakazato Y, Tamura N, Ohkuma A, Yoshimaru K, Shimazu K. Idiopathic pure sudomotor failure: anhidrosis due to deficits in cholinergic transmission. *Neurology* 2004; **63**: 1476–1480.
7 Asahina M, Sano K, Fujinuma Y, Kuwabara S. Investigation of antimuscarinic receptor autoantibodies in patients with acquired idiopathic generalized anhidrosis. *Intern Med* 2013; **52**: 2733–2737.
8 Watanabe T, Iwase S, Saito K, Nagatani T, Yoshida J. Altered sympathetic thermoregulation in patients with hypothalamic dysfunction following resection of suprasellar tumors. *Auton Neurosci* 2004; **112**: 80–87.
9 Nakazato Y, Shimazu K, Tamura N. Neurology of perspiration - anhidroisis. *Neurological Medicine* 1996; **44**: 131–136. (in Japanese).
10 Nakazato Y, Tamura N, Araki N. Drug induced perspiration. *Journal of the Japan Society of Neurovegetative Research* 2010; **47**: 428–431. (in Japanese).
11 Nakazato Y. Idiopathic anhidrosis. *Annual Review of Neurology*, Tokyo: Chugai-igakusha, 2006; 309–317. (in Japanese).
12 Nakazato Y. Idiopathic segmented anhidrosis. *Journal of the Japan Society of Neurovegetative Research* 2004; **40**: 327–334. (in Japanese).
13 Nakazato Y. Idiopathic generalized anhidrosis. *Neurol Ther* 2001; **18**: 141–149. (in Japanese).
14 Minor V. Ein neues verfahren zu der klinischen untersuchung der shweissabsonderung. *Z Neurol* 1927; **101**: 302–308.
15 Sato K, Takemura T, Saga K. Practical approach to sweat tests for dermatologists. *Jpn J Clin Dermatol* 1989; **43**: 889–896. (in Japanese).
16 Saito H. Examination for perspiration. *Journal of Clinical and Experimental Medicine* 1999; **state of art 1**: 228–231. (in Japanese).
17 Nakazato Y. Quantitative sudomotor axon reflex test (QSART). *J Jpn soc Neureveg Res* 2006; **43**: 327–333. (in Japanese).
18 Kita K, Shimoe Y, Kasahata N, Hirayama K. Corticosteroid therapy for idiopathic generalized anhidrosis -Quantitative analysis of sudomotor function. *Neurological Therapeutics* 1994; **11**: 619–624. (in Japanese).
19 Ooshima Y, Itoh K, Tamada Y, Watanebe D. Treatment of patients with acquired idiopathic generalized anhidrosis. *Jpn J persp Res* 2010; **18**(1): 3–6. (in Japanese).
20 Itakura E, Urabe K, Yasumoto S, Nakayama J, Furue M. Cholinergic urticaria associated with acquired generalized hypohidrosis: report of a case and review of the literature. *Br J Dermatol* 2000; **143**: 1064–1066.
21 Yagi Y, Kio P, Fujisawa A *et al.* Acquired idiopathic generalized anhidrosis successfully treated with cyclosporine A. *Rinsho derma* 2010; **52**: 863–868. (in Japanese).
22 Matsui S, Murota H, Takahashi A *et al.* Dynamic analysis of histamine-mediated attenuation of acetylcholine-induced sweating via GSK3beta activation. *J Invest Dermatol* 2014; **134**: 326–334.
23 Matsui S, Murota H, Ono E, Kikuta J, Ishii M, Katayama I. Olopatadine hydrochloride restores histamine-induced impaired sweating. *J Dermatol Sci* 2014; **74**: 260–261.
24 Suma A, Murota H, Kitaba S *et al.* Idiopathic pure sudomotor failure responding to oral antihistamine with sweating activities. *Acta Derm Venereol* 2014; **94**: 723–724.
25 Iketaki K, Kawai K, Togashi K, Ito M. Acquired idiopathic generalized anhidrosis. *Jpn J Clin Dermatol* 1999; **53**: 34–38. (in Japanese).
26 Furuta J, Ito M, Onizawa S, Kawauchi Y, Ootsuka F. Two cases of successful treatment of Pilocarpine for acquired idiopathic generalized hypohidrosis. *Jpn J Dermatol* 1990; **120**(1): 84. (in Japanese).
27 Kubota N, Ito M, Onizawa S, Furuta J, Kawauchi Y, Ootsuka F. Four cases of successful treatment of Pilocarpine for acquired idiopathic generalized hypohidrosis. *Jpn J Dermatol* 2011; **121**: 746. (in Japanese).
28 Shiraishi K, Murakami S, Hashimoto K. Cholinergic urticaria associated with hypohidrosis: report of a case and review of the literature. *Nishinihon J Dermatol* 2007; **69**: 359–364. (in Japanese).
29 Kobayashi H, Aiba S, Yamagishi T *et al.* Cholinergic urticaria, a new pathogenic concept: hypohidrosis due to interference with the delivery of sweat to the skin surface. *Dermatology* 2002; **204**: 173–178.
30 Rho NK. Cholinergic urticaria and hypohidrosis: a clinical reappraisal. *Dermatology* 2006; **213**: 357–358.
31 Ohnuki M, Hashimoto H, Horio T. Cholinergic Urticaria associated with hypohidrosis. *Skin Res* 1996; **38**: 505–510. (in Japanese).