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Cholinergic urticaria: epidemiology, physiopathology, new categorization, and management

Atsushi Fukunaga[1], Ken Washio[1, 2], Mayumi Hatakeyama[1], Yoshiko Oda[1], Kanako Ogura[1], Tatsuya Horikawa[3], Chikako Nishigori[1]

[1]Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

[2]Division of Dermatology, Nishi-Kobe Medical Center 5-7-1, Koji-Dai, Nishi-ku, Kobe, 651-2273 Japan

[3]Ueda Dermatology Clinic, 1654-5 Harima-cho Nozoe, Nishi-ku, Kako-gun 675-0151, Japan

Correspondence: Atsushi Fukunaga, MD

Division of Dermatology, Department of Internal Related

Kobe University Graduate School of Medicine

7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

Tel: +81-78-382-6134; Fax: +81-78-382-6149

E-mail: atsushi@med.kobe-u.ac.jp

ORCID: 0000-0003-2026-8154

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Abstract

Purpose The aim of this study was to review the evidence on the epidemiology, physiopathology, categorization, and management of cholinergic urticaria. We specifically focused on several subtypes of cholinergic urticaria and investigated the relationship between cholinergic urticaria and idiopathic anhidrosis.

Methods Using an integrative approach, we reviewed publications addressing the epidemiology, clinical features, diagnostic approach, physiopathology, subtype classification, and therapeutic approach to cholinergic urticaria.

Results Multiple mechanisms contribute to the development of cholinergic urticaria. This disorder should be classified based on the pathogenesis and clinical characteristics of each subtype. Such a classification system would lead to better management of this resistant condition. In particular, sweating function should be given more attention when examining patients with cholinergic urticaria.

Conclusions Because cholinergic urticaria is not a homogeneous disease, its subtype classification is essential for selection of the most suitable therapeutic method.

Keywords: cholinergic urticaria, acetylcholine, hypohidrosis/anhidrosis, sweat allergy

Introduction

Cholinergic urticaria (CholU), first described by Duke [1] in 1924, is a frequently occurring skin disorder characterized by unique clinical features. Pinpoint, highly pruritic wheals with surrounding erythema occur after sweating induced by an increase in the core body temperature, which occurs in response to hot bathing, physical exercise, and/or emotional stress [2, 3]. Although the symptoms usually subside rapidly, commonly within 1 hour, most patients with CholU complain that they feel stinging or tingling pain and/or itching at the onset of symptoms, and these feelings appear to disturb their quality of life [4, 5]. Severe symptoms such as angioedema, respiratory symptoms, and/or anaphylaxis often accompany CholU [2, 4, 6-8]. Although CholU affects up to 20% of young adults, the precise underlying mechanism of the whealing response remains incompletely understood with the exception of the involvement of acetylcholine, poral occlusion, cholinergic receptor M3 (CHRM3), sweat allergy, serum factors, and dyshidrosis [9-11]. We and other research groups recently proposed four subtypes of CholU based on the pathogenesis and clinical characteristics of this condition: (i) conventional sweat allergy-type CholU, (ii) follicular-type CholU with a positive autologous serum skin test (ASST) result, (iii) CholU with palpebral angioedema (CholU-PA), and (iv) CholU with acquired anhidrosis and/or hypohidrosis [9, 12-16]. The European Academy of Allergy and Clinical Immunology / Global Allergy and Asthma European Network (GA^2LEN) / European Dermatology Forum (EDF) / Urticaria Network e.V. (UNEV) recommend defining CholU as a subtype of chronic inducible urticaria [17]. CholU should be treated as a physical urticaria/angioedema syndrome according to the American Academy of Allergy, Asthma & Immunology /

American College of Allergy, Asthma & Immunology [18]. CholU is classified as inducible urticaria in the Japanese Dermatological Association guidelines for the diagnosis and treatment of urticaria [19].

In the present review, we focus on the classification of CholU, especially with respect to the relationship between CholU and sweating function, and present an overview of the current knowledge of the pathogenesis and therapeutic methods of CholU.

Clinical features, provocation test, and differential diagnosis of CholU

Clinical features

CholU is characterized by the development of numerous distinct small hives, usually 1 to 3 mm in diameter, with red halos (Fig. 1). However, these hives may occasionally become larger in size and coalesce with one another (Fig. 1). The eruptions may occur anywhere on the body except for the palms, soles, and axillae, but the most commonly affected part of the body is the trunk [2, 3, 11]. Because active or passive warming leads to the development of pinpoint wheals and itching, the symptoms rarely occur at bedtime. In contrast to other types of urticaria, many patients with CholU complain that they feel stinging or tingling pain, but no itching. Severe symptoms such as angioedema, respiratory distress, dizziness, and/or anaphylaxis often accompany CholU. Although the prevalence of CholU does not generally show a large sex-related difference, serious symptoms including anaphylaxis seem to more frequently occur in female patients [8, 13, 14]. Most patients' symptoms become exacerbated in hot summer weather, whereas some patients exhibit exacerbation during exercise and bathing in cold weather [20]. CholU is most prevalent in

the second and third decades of life [2, 11]. The estimated prevalence of CholU is 4.16% to 11.2% of the general population [11, 21]. CholU is frequently related to atopic diathesis including atopic dermatitis, allergic rhinitis, and bronchial asthma [13, 22, 23]. Patients with moderate to severe CholU seem to show high rates of atopy [13, 23].

Provocation test

Because the symptoms of CholU develop only after an increased body temperature has been stimulated in a repetitive manner and the appearance of the eruption is characteristic, the clinical diagnosis of CholU is usually not difficult. However, a provocation test should be performed to confirm the diagnosis of CholU and rule out other types of urticaria. Provocation tests for the diagnosis of CholU are performed by increasing the body temperature through exercise (treadmill or stationary bicycle) or the use of a hot bath (42°C for 15 min) [24-26]. The EAACI/GA^{2}LEN/EDF/UNEV consensus panel recommends the following criterion for confirming the diagnosis of CholU: the core body temperature has increased by >1.0°C over the baseline as indicated by a passive warming test involving sitting for up to 15 min in a bath full of water at 42°C [17, 24]. However, the problem associated with this test is the inaccuracy of body temperature measurement. Although the use of an esophageal or rectal thermometer is more accurate than the use of an oral thermometer, the former is invasive and unsuitable for outpatients. Therefore, a standardized protocol for diagnosing and measuring CholU thresholds using pulse-controlled ergometry has been proposed [27]. Interestingly, pulse-controlled ergometry demonstrated that the critical trigger of CholU development is sweating rather

than a rise in the mean body temperature. Intradermal injection of cholinergic drugs such as acetylcholine or methacholine may produce small satellite wheals surrounding the injection sites in certain patients with CholU (Fig. 2) [14, 26]. This test is a supplementary test for the diagnosis of CholU because this examination is not necessarily positive in all patients with CholU. One advantage is that local sweating function can be simultaneously observed by the intradermal injection of cholinergic drugs such as acetylcholine [14, 28].

Differential diagnosis

Based on whether the clinical episode has developed secondary to exercise and/or heat stimulation, CholU must be differentiated from food-dependent exercise-induced anaphylaxis (FDEIA) and heat urticaria (HU). FDEIA is a unique form of food allergy induced by exercise after food ingestion [29]. FDEIA, in which symptoms do not appear without food ingestion and which usually involves a specific IgE antibody against causative food allergens, is clearly distinguishable from CholU. Skin prick tests, measurement of specific IgE, and provocation tests including challenges with the suspected foods, exercise, aspirin intake, and combinations of these challenges are valuable for differentiating between CholU and FDEIA. HU is defined by the appearance of wheals after contact heating of the skin within minutes of exposure. Localized HU is characterized by itchy erythema and well-demarcated wheals restricted to the heated area (Fig. 3) [30, 31]. The diagnosis of HU is confirmed by a heat provocation test involving the placement of metal/glass cylinders filled with hot water (Fig. 3). Localized HU can be differentiated from CholU by the characteristic clinical images that develop after the provocation tests.

Because similar clinical images develop after many different types of stimulation excluding exercise and/or heat stimulation, CholU should be differentiated from aquagenic urticaria, adrenergic urticaria, and cold-induced CholU. Aquagenic urticaria is a rare form of urticaria in which contact with any source of water at any temperature evokes small pruritic wheals surrounded by flare [32]. Diagnosis of aquagenic urticaria should be differentiated from other types of urticaria including CholU, cold urticaria, and HU before testing for aquagenic urticaria. Adrenergic urticaria is a rare type of stress-induced physical urticaria characterized by widespread pruritic urticarial papules [33]. Although the clinical picture of adrenergic urticaria resembles that of CholU, adrenergic urticaria can be distinguished from CholU by the presence of a white halo of vasoconstriction surrounding small red or pink wheals [34]. Diagnosis can be made by intradermal injection of adrenaline or noradrenaline, which produces the characteristic rash [35]. A positive noradrenaline test result and negative acetylcholine skin test result are useful for the differential diagnosis of adrenergic urticaria and CholU [35]. In cold-induced CholU (generalized reflex cold urticaria), widespread wheals occur in response to cooling of core body temperature [6, 25]. Cold-induced CholU is an unusual disorder characterized by small pin-point urticarial lesions induced by a systemic cold challenge rather than a local cold challenge [28].

The diagnostic workup in CholU is summarized in Fig. 4.

Pathogenesis

Although the physiopathological mechanism of CholU has not been well clarified, it is thought that histamine, cholinergic agents (e.g., acetylcholine), sweat allergy, serum factors,

poral occlusion, and anhidrosis are related to the development of symptoms of CholU [14, 36-39].

Histamine

Previous studies have shown that the serum histamine level increases during the development of symptoms and after exercise in patients with CholU [37, 40]. Second-generation non-sedating histamine H1 receptor antagonists (H1RAs) are recommended as the first-line therapy in patients with CholU; in contrast to patients with conventional urticaria, however, some patients do with CholU not respond to standard H1RA therapy [4, 10, 17, 41]. H1RA up-dosing in patients with CholU refractory to standard H1RA therapy substantially improves the disease activity of CholU in fewer than half of all patients [41]. In one study, addition of the histamine H2 receptor antagonist (H2RA) lafutidine to H1RA therapy in patients with refractory CholU that was unresponsive to up-dosing of H1RA reduced the itch severity, frequency of whealing, and size of the wheals [4]. These findings suggest that histamine plays an important role in the development of CholU but that additional mediators other than histamine may also be closely associated with the development of CholU.

Cholinergic agents

The sweat glands receive sympathetic innervation but express muscarinic acetylcholine receptors, which are normally expressed in the parasympathetic nervous system. Thus, stimulation of cholinergic postganglionic sympathetic nerves by acetylcholine is considered

to be a central signal mediator of sweat secretion (Fig. 5) [10]. Intradermal injection of cholinergic agents can reproduce the symptoms of CholU, but not all patients (Fig. 2) [14, 26]. Pilocarpine iontophoresis can reportedly induce wheals that are localized near the electrode. The acetylcholine antagonists atropine and scopolamine inhibit the development of CholU in a minor population of patients with CholU. Thus, acetylcholine appears to play an essential role in the development of CholU. In fact, it has been demonstrated that not only sweat glands but also mast cells express CHRM3, which is responsible for the initiation of sweating [5, 15]. The authors of these papers proposed a schematic model in which acetylcholine released from postganglionic sympathetic nerves cannot be trapped by the acetylcholine receptors of eccrine glands because of decreased expression of these receptors and overflow of acetylcholine to adjacent mast cells secondary to decreased expression of acetylcholine esterase. Although this schema is very interesting, this phenomenon is limited to the hypohidrotic area of CholU in patients with accompanying acquired generalized hypohidrosis and does not apply to patients with CholU who have normal sweating function. Moreover, this schema indicates that acetylcholine can finally activate mast cells and induce their degranulation in the hypohidrotic area of CholU. In our experience, however, H1RAs seem to be ineffective in inhibiting whealing formation in the hypohidrotic area of CholU (Fukunaga A et al., unpublished data). Additionally, whether acetylcholine can induce degradation of human mast cells *in vivo* remains controversial [5, 9]. Thus, although cholinergic agents are undoubtedly involved in the pathological mechanism of CholU, the detailed roles of these cholinergic agents in pathogenesis of CholU require further study.

Sweat allergy

Several studies have suggested the involvement of sweat allergy in the occurrence of CholU [14, 42-44]. In 1994, Adachi et al. [42] reported that patients with CholU showed positive immediate-type skin reactions and histamine release from their basophils in response to contact with autologous diluted sweat. That study also demonstrated that after transfer of the patient's serum into a normal subject, skin tests with autologous sweat (autologous sweat skin test; ASwST) showed positive results, suggesting that these patients with CholU have a type I allergy to their own sweat. In 2005, we reported that 11 of 17 patients with CholU showed immediate-type skin reactions and confirmed that the level of histamine release from basophils in the response with autologous sweat was well correlated with response of ASwST [14]. In 2009, Takahagi et al. [22] demonstrated that 23 of 35 patients with CholU showed histamine release from basophils in response to semipurified sweat antigen. Most recently, Hiragun et al. [45] identified a putative protein, MGL_1304 of *Malassezia globosa*, as a major allergen in human sweat of patients with atopic dermatitis. Moreover, in another study, the concentrations of purified MGL_1304-specific IgE in the sera of patients with CholU were significantly higher than those of normal controls, and 14 of 24 patients with CholU were positive for purified MGL_1304-specific IgE [46]. These findings suggest that MGL_1304 in sweat is an important antigen in most patients with CholU. A commercial histamine release test for MGL_1304 in sweat is available in Japan. We recently used this commercial histamine release test to detect sweat allergy in a characteristic case series of patients with CholU-PA [13].

Serum factor

Half of patients with chronic spontaneous urticaria have IgG autoantibodies to FcεRIα or FcεRIα-bound IgE on dermal mast cells and basophils, which crosslink FcεRI molecules to induce histamine release [47]. The ASST is useful to detect these autologous serum factors [47, 48]. Sabroe et al. [48] reported that one of nine patients with CholU had a positive ASST result. We previously showed that 8 of 15 patients with CholU had a positive ASST result [14]. In our and other institution, one-third or fewer of all patients with CholU seem to have associated serum factors [49].

Poral occlusion

Several reported cases indicate that CholU is caused by poral occlusion. Kobayashi et al. [39] showed that biopsy specimens from two patients with CholU and hypohidrosis exhibited occlusion of the superficial acrosyringium. The authors assumed that poral occlusion leads to the leakage of sweat containing numerous inflammatory enzymes and cytokines and induces local inflammation and lymphocytic inflammation around the upper sweat duct. They proposed that the occlusion and subsequent leakage of sweat from the sweat duct are responsible for the development of CholU accompanied by hypohidrosis. Rho [50] reported that the incidence of hypohidrosis in patients with CholU, most of whom complained of symptoms only in the winter season, is relatively high and that topical application of antikeratolytic agents to the affected area may be helpful. These reports suggest that poral occlusion is involved in the etiology of hypohidrotic CholU. We also described a patient

with acquired idiopathic generalized anhidrosis (AIGA) accompanied by CholU, whose histopathology showed an occlusion of the superficial acrosyringium and infiltrates composed of lymphocytes and mast cells around the sweat glands [51].

Hypohidrosis/anhidrosis

Previous studies have established that some patients with CholU have acquired generalized hypohidrosis/anhidrosis with various pathogeneses [38, 39, 52]. The various etiologies include autoimmunity to sweat glands or acetylcholine receptors, degeneration of post-ganglionic sympathetic skin nerve fibers, and poral occlusion (see above) [53, 54]. AIGA is a sweating disorder characterized by inadequate sweating in response to heat stimuli and is caused by sudomotor failure, which is probably a dysfunction on the postsynaptic side of the nerve–sweat gland junction [38]. From the viewpoint of hypohidrosis, approximately 30% to 60% of patients with AIGA show complications of CholU, also known as idiopathic pure sudomotor failure or hypohidrotic CholU. The relationship between CholU and anhidrosis is described in more detail in the next section, which describes CholU subtype classification (see below).

Subtype classification

Four pathogenesis- and/or clinical feature-based subtypes of CholU were recently proposed: (i) conventional sweat allergy-type CholU without angioedema, (ii) follicular-type CholU with a positive ASST result, (iii) CholU-PA, and (iv) CholU with acquired anhidrosis and/or hypohidrosis [10, 13, 14]. It is particularly important to differentiate subtypes (i),

(ii), and (iii) from subtype (iv), especially in terms of sweating function, because the clinical therapeutic approach appears to be very different. A thermoregulatory sweat test, drug-induced sweat test, quantitative sudomotor axon reflex test, and thermography should be used to evaluate sweat function [55]. The characteristics of the four subtypes of CholU are summarized in Table 1.

Conventional sweat allergy-type CholU without angioedema

In 2005, we proposed classification of CholU into two subtypes: (1) the sweat-hypersensitivity type (nonfollicular type), which is characterized by nonfollicular wheals, development of satellite wheals following local acetylcholine injection, a positive ASwST result, and lack of a positive ASST result; and (2) the follicular type, which is characterized by follicular wheals, lack of development of satellite wheals following local acetylcholine injection, and a positive ASST result [14, 49]. Indeed, generalized anhidrosis was completely examined and excluded in that paper. However, we and other research groups confirmed that almost all patients with CholU with anhidrosis or hypohidrosis, such as AIGA, lack sweat hypersensitivity [12, 16]. Thus, the sweat hypersensitivity type of CholU in the old classification is assumed to be consistent with conventional CholU without angioedema with sweat allergy among the four new subtypes because these patients lack angioedema and anaphylaxis. In this subtype, certain satellite wheals that developed after the acetylcholine test were coincident with perspiration points [14]. Therefore, conventional sweat allergy-type CholU without angioedema could be associated with leakage of sweat from sweat ducts (Fig. 5) [9, 14].

Follicular-type CholU with positive ASST result

This type of CholU is characterized by pinpoint wheals coincident with follicles. Wheals accompanied by aquagenic urticaria and follicular dermographism are also coincident with the follicles [56, 57]. Although the etiology of this urticaria has not been clarified, some authors have postulated that a water-soluble antigen located in the epidermis may cause mast cell degradation in patients with aquagenic urticaria and that friction force may release unknown antigens from the bloodstream to trigger focal urticaria at sites of high-density mast cells, namely around follicles, in patients with follicular dermographism. A report describing a patient with both CholU and aquagenic urticaria suggests that these two diseases may be related. Notably, follicular-type CholU is mainly associated with a positive ASST result and lack of sweat allergy. With respect to the relationship between follicular wheals and serum factors, we assume that the existence of both serum factors and acetylcholine and/or particular antigens located in the epidermis can activate mast cells and induce focal urticaria around follicles at sites of high-density mast cells (Fig. 5).

CholU-PA with sweat allergy

Exercise-induced angioedema without a food trigger has been reported as an uncommon manifestation of CholU, although the causative allergen and clinical characteristics remain poorly understood. We recently reported a case series of patients with characteristic CholU-PA [13]. This characteristic CholU-PA was accompanied by angioedema around the eyelids and often anaphylaxis, and it was closely related to atopic diathesis (14 of 15

patients) and female sex (all 15 patients). Furthermore, patients with CholU-PA had a high prevalence of sweat allergy (all 15 patients), whereas only four patients had a positive ASST result. Notably, wheals in these patients with CholU-PA often appeared in lesions exhibiting an eczematous reaction consistent with atopic dermatitis. This implies that sweat leaking easily occurs in these lesions; this induces sensitization to sweat, and the subsequent sweat allergy induces an eczematous reaction and urticarial reaction in the lesions. Additionally, patients with CholU-PA respond poorly to H1RA therapy. Vadas et al. [8] recently described 19 patients with CholU with anaphylaxis as an under-recognized clinical entity. Similar to patients with CholU-PA, those with CholU with anaphylaxis showed strong female predominance (78.9%; 15 of 19 patients) with moderate to severe reactions recurring about once per month. Although female predominance is seen in patients with idiopathic anaphylaxis, severe multisystem reactions accompanying CholU can be also easily develop in female patients.

CholU with acquired anhidrosis and/or hypohidrosis

As described above, CholU is often accompanied by acquired anhidrosis and/or hypohidrosis. AIGA is an acquired disorder characterized by a reduced amount of sweat without a clear cause and is associated with neither dysautonomia nor any neurological abnormalities except sudomotor dysfunction. AIGA is assumed to be associated with three pathological conditions: sudomotor neuropathy, idiopathic pure sudomotor failure, and sweat gland failure [55]; idiopathic pure sudomotor failure accounts for a large proportion of cases of AIGA. These pathological conditions are predominant in men and are likely to

be complicated by pain, paresthesia, and CholU; however, psychogenic sweating is preserved. Because almost all patients with CholU who develop acquired anhidrosis and/or hypohidrosis are assumed to have AIGA, the comment on AIGA is explained as follows. No epidemiological data on AIGA have been published to date; therefore, the prevalence and morbidity of AIGA remain unknown. AIGA is assumed to be rare because only approximately 100 cases have been reported. However, patients with AIGA may be misdiagnosed, and a precise diagnosis may be achieved in only a small proportion of patients because the presence of AIGA is not well recognized. Indeed, the first case of AIGA in our facility was diagnosed and reported in 2009 [51]. During the next 8 years, approximately 20 patients were newly diagnosed with AIGA in our facility (Fukunaga et al., unpublished data), implying that more patients with AIGA might exist. Therefore, an epidemiological survey was conducted by a committee comprising members commissioned by the Japanese Dermatological Association, Japan Society of Neurovegetative Research, and Japanese Society for Perspiration Research [55]. In total, 145 cases of AIGA were identified among 94 departments of neurology or dermatology at Japanese university hospitals from 2010 through 2015. The incidence was significantly higher in men (126 men and 19 women), like a previous report. The inhibition of sweating, which is essential for body temperature regulation, results in discomfort, hyperthermia, nausea, vomiting, headache, and heat stroke. AIGA is frequently accompanied by CholU with symptoms of tingling, unpleasant sensation, and severe pruritus. We reported that untreated AIGA was associated with considerably reduced quality of life; the impact of AIGA on quality of life was greater than that of other skin diseases [16].

As described above, decreased expression of CHRM3 in the sweat gland has been observed in patients with AIGA [5]. Decreased expression of acetylcholine esterase was observed in patients with CholU with anhidrosis or hypohidrosis; their condition was equivalent to AIGA [15]. These findings suggest that excess acetylcholine stimulates sensory nerve terminals to produce pain and acts on CHRM3 in mast cells in the vicinity of sweat glands, causing wheals. Because some studies have revealed that few patients with AIGA exhibit sweat allergy, sweat allergy is infrequently associated in the pathogenesis of AIGA accompanied by CholU [12, 16]. A recent report showed that elevated serum carcinoembryonic antigen might be a marker of disease activity of AIGA [58].

The herein-described categorization and characteristics of the various subtypes of CholU are illustrated in Table 1.

Therapeutic management

The therapeutic approach to CholU largely differs based on the presence of sweating dysfunction. Differential diagnosis of subtypes based on the presence of sweating dysfunction is essential before treatment. However, almost no previous reports focused on the therapeutic approach with respect to the presence of sweating dysfunction.

H1RAs are the first-line therapy in patients with CholU, but many patients show only a mild to moderate response to standard H1RA doses [4, 41, 59]. Increasing the dose of an H1RA in patients with CholU that is refractory to standard doses may improve the disease activity, but this occurs in fewer than half of all patients [41]. The effectiveness of adding an H2RA was reported in patients with refractory CholU that was unresponsive to

up-dosing of an H1RA [4]. There are also reports on the efficacy of scopolamine butylbromide (an anticholinergic agent) [60]; combinations of propranolol (a β2-adrenergic blocker), antihistamines, and montelukast [61]; and treatments and injection with botulinum toxin [62]. High doses of danazol (600 mg daily) are also reportedly effective. However, the side effect profile of danazol restricts its use [17]. Several studies have shown that omalizumab (a recombinant humanized IgG1 monoclonal antibody that binds to IgE) was effective for severe CholU [63, 64], whereas a case of omalizumab treatment failure was also reported [65]. Desensitization protocols involving regular physical exercise and/or bathing or treatment with autologous sweat in patients with sweat-allergy type CholU have been described [9, 10, 43].

In contrast, systemic administration of corticosteroids such as intravenous high-dose (500–1000 mg) steroid pulse therapy for AIGA appears to merit recommendation based on the findings presented in numerous case reports despite an insufficient level of research-based evidence [16, 55, 66]. A trial of oral immunosuppressants is worthwhile in patients who do not respond to steroid pulse therapy [55]. In patients with AIGA, H1RAs can be administered at increased doses appropriate to the symptoms experienced [67]. Topical application of keratolytic agents is reportedly effective in treating hypohidrotic CholU, which is associated with the occlusion of sweat ducts [50].

These recommended therapeutic management approaches are summarized in Fig. 6.

Conclusions

This review has presented the clinical features, provocation tests, and differential diagnoses

of CholU. Four new pathogenesis- and/or clinical feature-based subtypes of CholU have been described and summarized. Although the underlying mechanism of CholU has not been fully clarified, the understanding of its pathological mechanism has gradually increased based on this subtype classification. Therapeutic management using this classification can lead to better control of treatment-resistant CholU.

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Ethical standards: The manuscript does not contain clinical studies or patient data.

Conflicts of interest: The authors declare that they have no conflict of interest.

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Figure Legends

Fig. 1 (a) Typical appearance of cholinergic urticaria: pinpoint-sized, highly pruritic wheals with surrounding erythema occur on the trunk after sweating. (b) Occasionally, the wheals become larger in size and coalesce with one another

Fig. 2 Satellite urticarial response induced by intradermal acetylcholine (Ovisot®) injection. Arrow head; small satellite wheal. Arrow: intradermal injection site of acetylcholine.

Fig. 3 Typical appearance of localized heat urticaria. A well-demarcated localized wheal was induced by exposure to a beaker filled with water at 40°C for 10 min

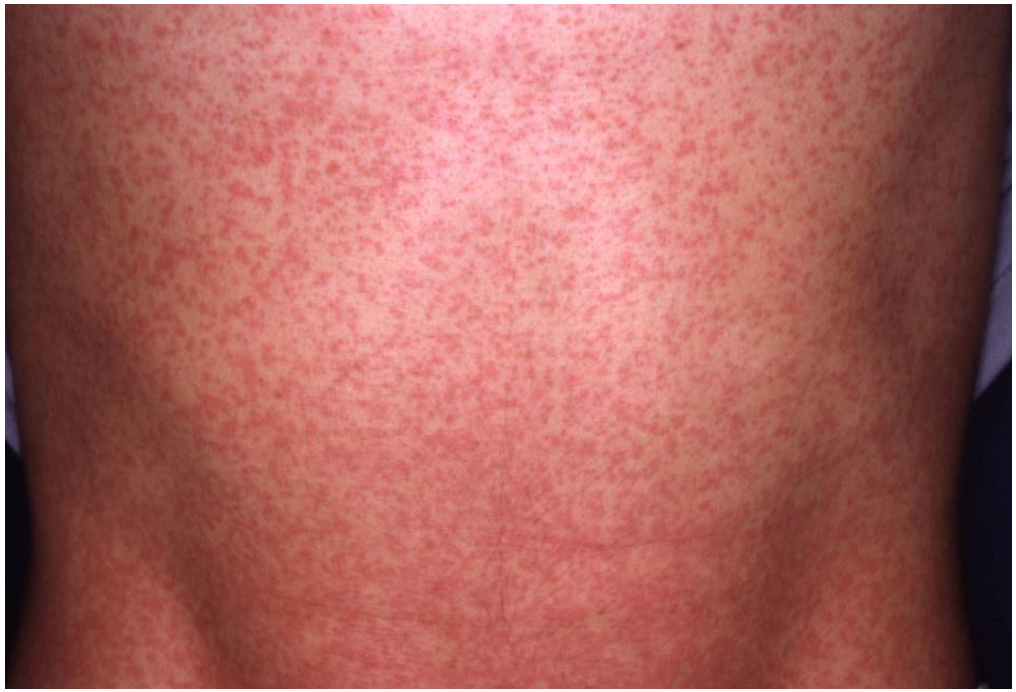
Fig. 4 The flowchart in the diagnostic workup of CholU. ASST; autologous serum test. ASwST; autologous sweat test.

Fig. 5 Schema of pathogenesis-based mechanism of onset in patients with sweat allergy-type and follicular-type cholinergic urticaria

Fig. 6 Proposed therapeutic algorithm for cholinergic urticaria with and without hypohidrosis. Sweating promotion, which does not cause serious symptoms, can be recommended in both subtypes

Fig1

A



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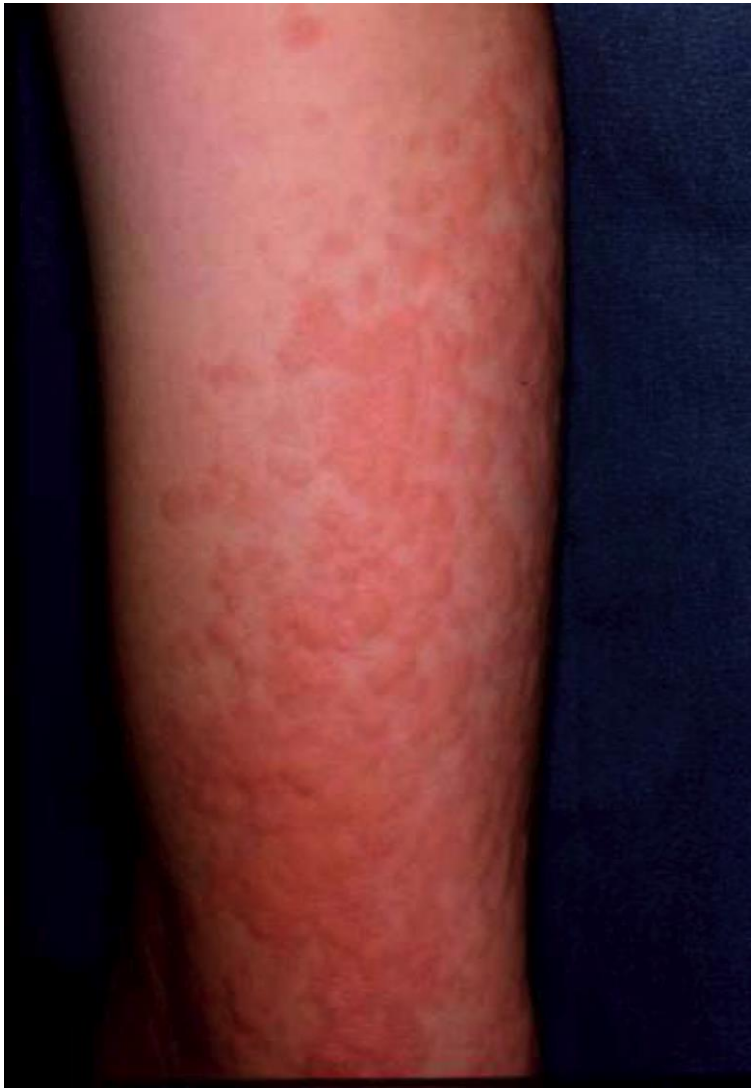

Fig2

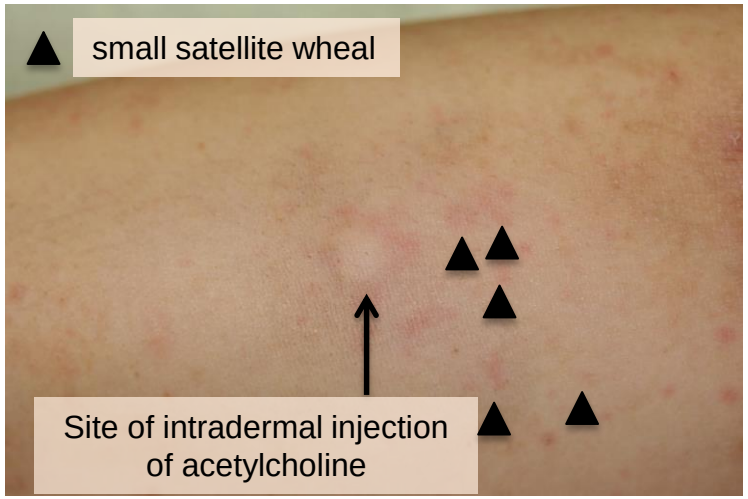
small satellite wheal
Site of intradermal injection
of acetylcholine

Fig3

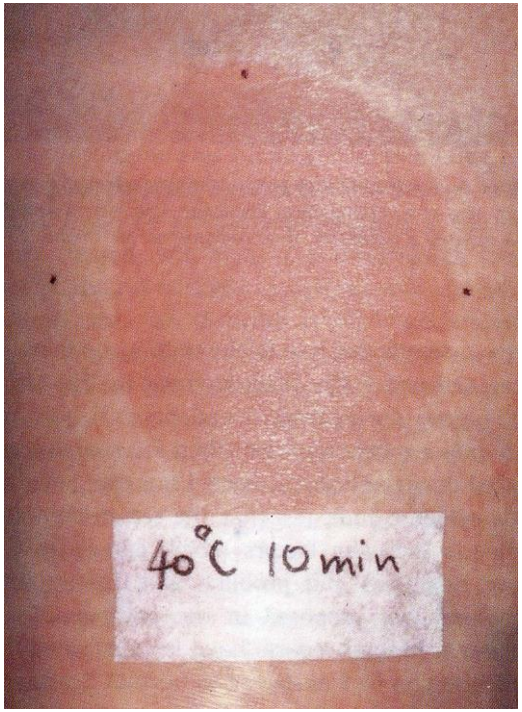

Fig4

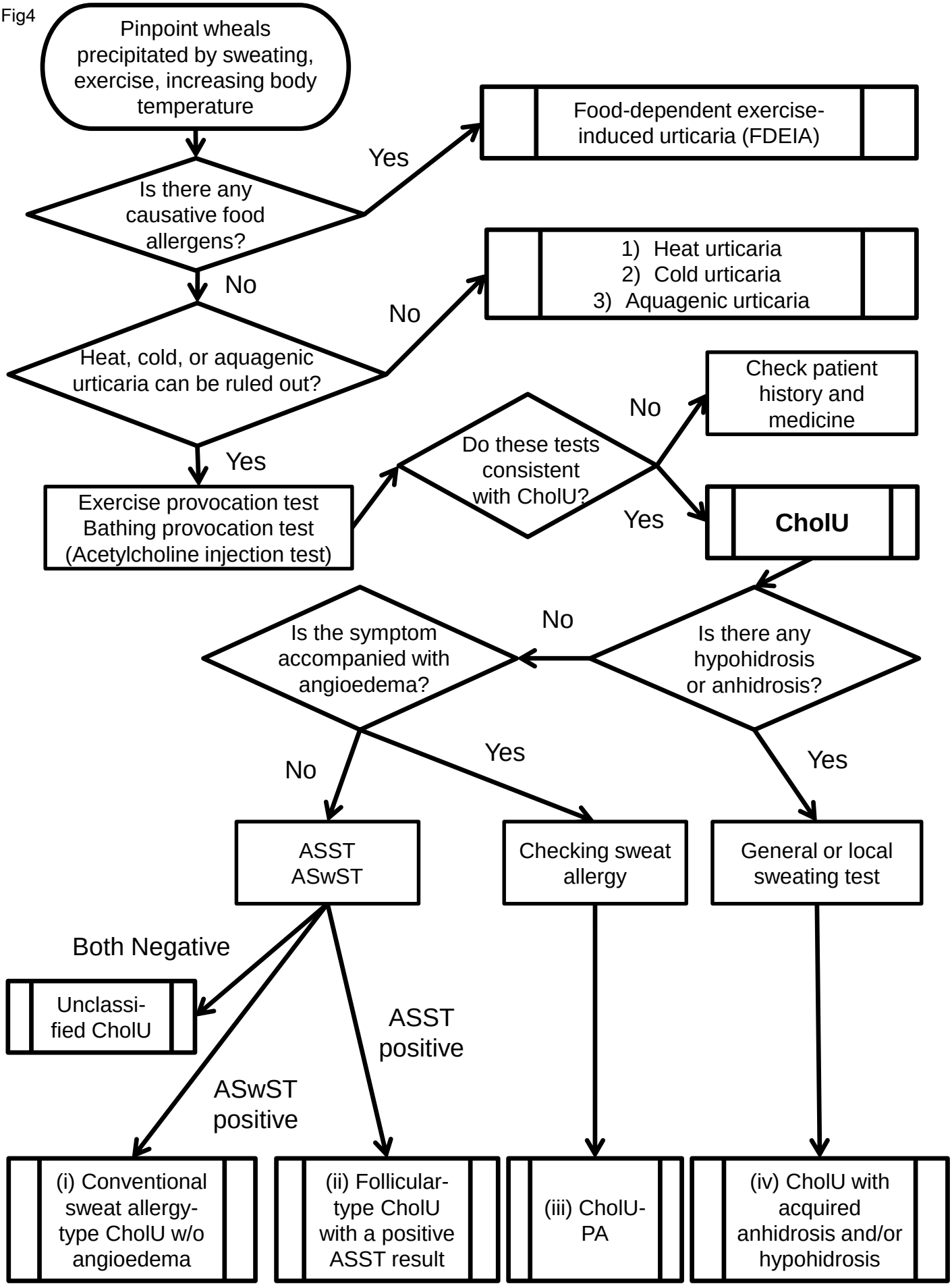
Pinpoint wheals precipitated by sweating, exercise, increasing body temperature
Is there any causative food allergens?
Yes
Food-dependent exercise-induced urticaria (FDEIA)
No
Heat, cold, or aquagenic urticaria can be ruled out?
No
1) Heat urticaria
2) Cold urticaria
3) Aquagenic urticaria
Yes
Exercise provocation test
Bathing provocation test
(Acetylcholine injection test)
Do these tests consistent with CholU?
No
Check patient history and medicine
Yes
CholU
Is the symptom accompanied with angioedema?
No
Is there any hypohidrosis or anhidrosis?
No
Yes
Yes
Yes
ASST
ASwST
Checking sweat allergy
General or local sweating test
Both Negative
Unclassi-fied CholU
ASST positive
ASwST positive
(i) Conventional sweat allergy-type CholU w/o angioedema
(ii) Follicular-type CholU with a positive ASST result
(iii) CholU-PA
(iv) CholU with acquired anhidrosis and/or hypohidrosis

Fig5

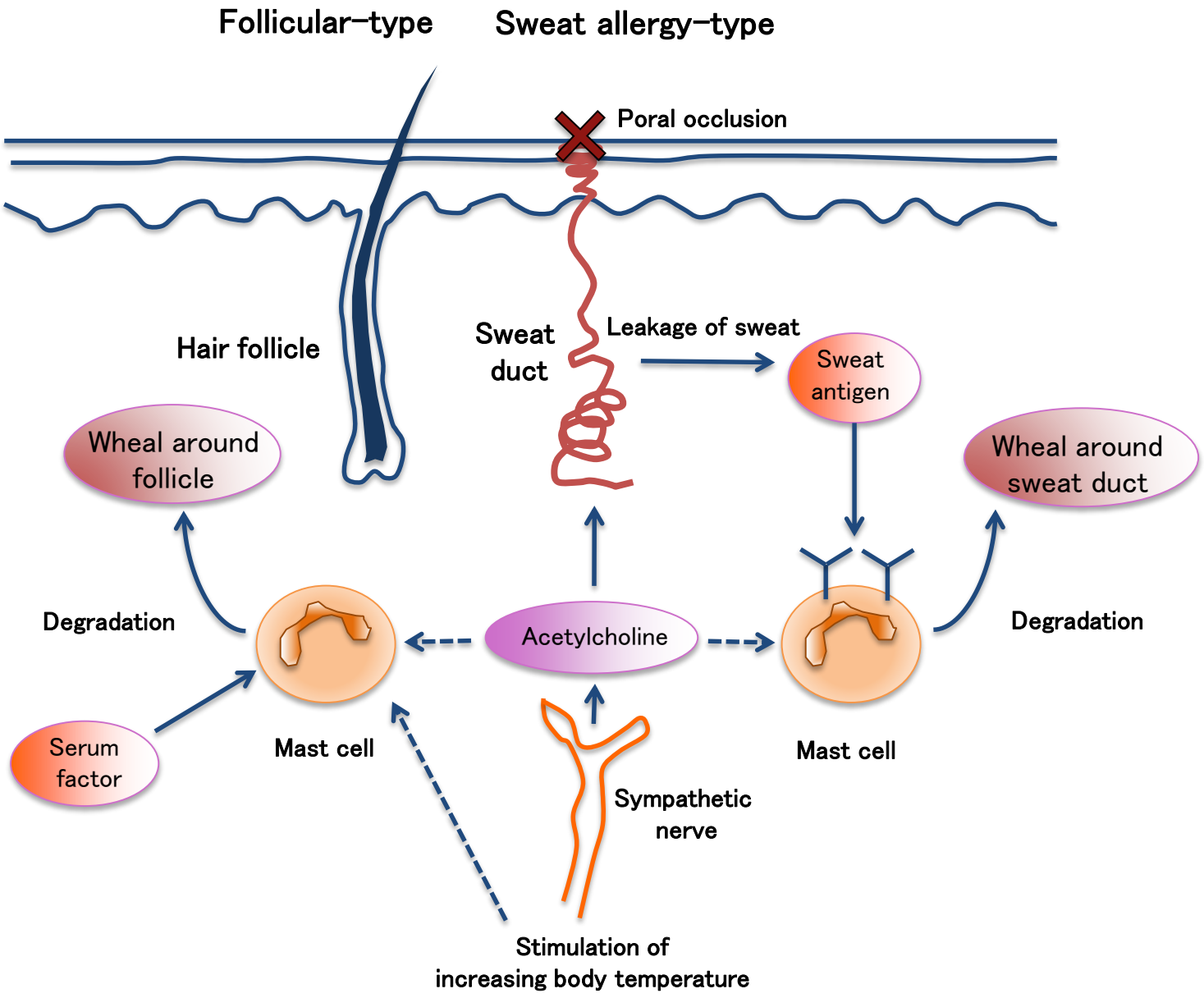
Follicular-type
Sweat allergy-type
Poral occlusion
Hair follicle
Sweat duct
Leakage of sweat
Sweat antigen
Wheal around follicle
Wheal around sweat duct
Degradation
Degradation
Acetylcholine
Serum factor
Mast cell
Mast cell
Sympathetic nerve
Stimulation of increasing body temperature

Fig6

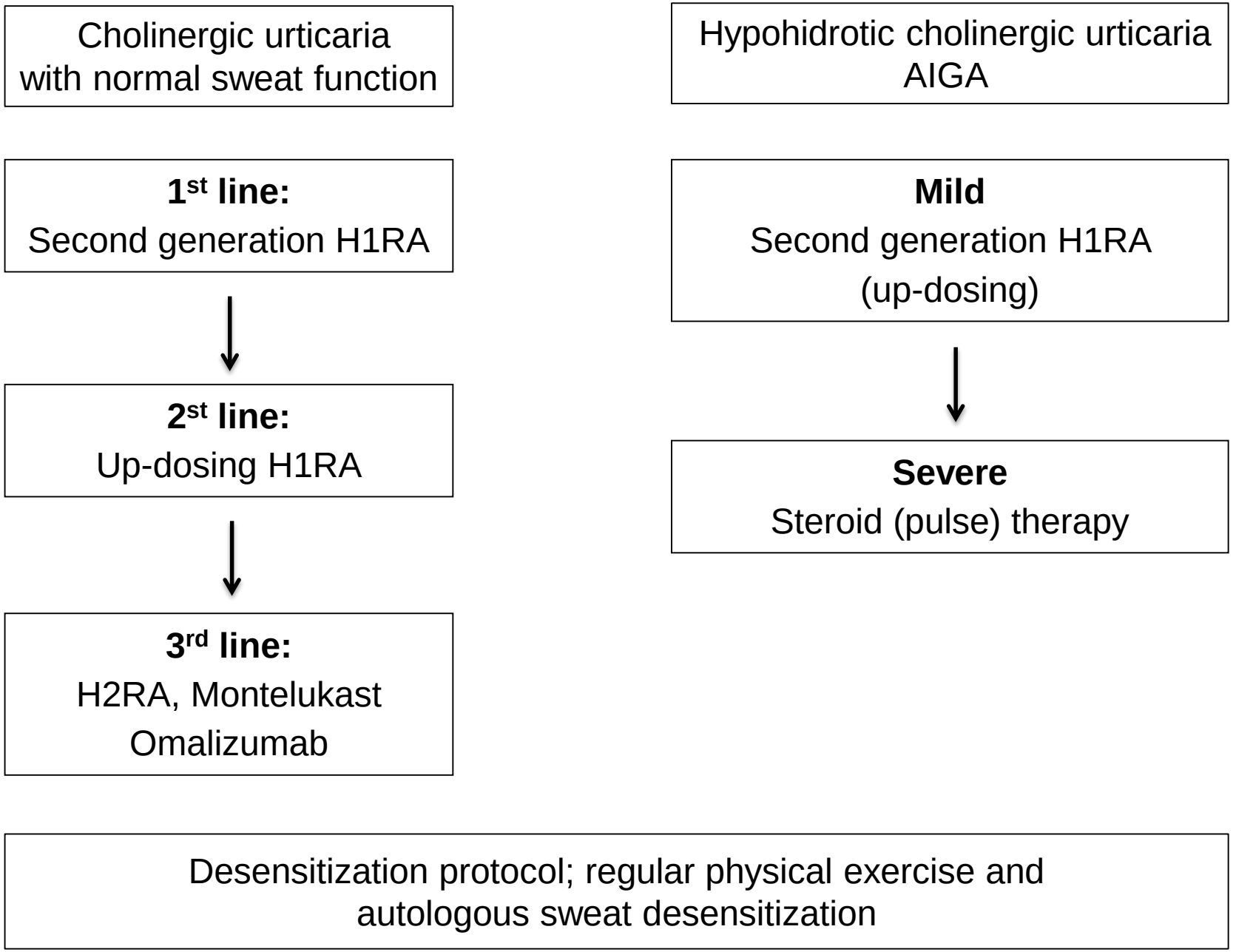
Cholinergic urticaria
with normal sweat function
1st line:
Second generation H1RA
2st line:
Up-dosing H1RA
3rd line:
H2RA, Montelukast
Omalizumab
Hypohidrotic cholinergic urticaria
AIGA
Mild
Second generation H1RA
(up-dosing)
Severe
Steroid (pulse) therapy
Desensitization protocol; regular physical exercise and
autologous sweat desensitization

Table1

Table 1 Cholinergic urticaria: Pathogenesis and/or clinical feature-based four subtypes

Subtype	sweat allergy	autologous serum skin test	sexual predominance	atopic predisposition	hypohidrosis	pathology	severity
conventional sweat allergy without angioedema	positive	negative	none	ND	none	sweat allergy, sweat leaking	moderate
peripebral angioedema-type	positive	negative	female	strong	none	sweat allergy, preexistence of eczema	severe
follicular-type	negative	positive	none	ND	ND	serum factor	mild
acquired anhidrosis and/or hypohidrosis-type	negative	ND	male	weak	always	excess acetylcholine folllowing decrease of CHRM3 expression	severe

ND: not determined