Responsiveness to autologous sweat and serum in cholinergic urticaria classifies its clinical subtypes

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Background: It has been reported that patients with cholinergic urticaria have a type 1 allergy to autologous sweat; however, the pathogenesis of that disorder has not been fully elucidated.
Objective: We investigated the responsiveness to autologous sweat and serum in patients with cholinergic urticaria in relation to their clinical characteristics. We further classified the clinical subtypes that are clearly characterized by responsiveness to *in vivo* and *in vitro* tests as well as their clinical features.
Methods: Intradermal tests with autologous sweat and serum were performed in 18 patients with cholinergic urticaria. Histamine release from peripheral blood basophils induced by autologous sweat was measured.
Results: Eleven of 17 patients with cholinergic urticaria showed positive reactions in skin tests with their own diluted sweat. Substantial amounts of sweat-induced histamine release from autologous basophils were observed in 10 of 17 patients. Eight of 15 patients with cholinergic urticaria showed positive reactions in the autologous serum skin tests. All 6 patients who developed satellite wheals after the acetylcholine test showed hypersensitivity to sweat. Further, patients whose eruptions were coincident with hair follicles showed positive responses to the skin test with autologous serum, whereas patients whose eruptions were not coincident with hair follicles did not.
Conclusion: On the basis of these findings, we propose that cholinergic urticaria should be classified into 2 distinct subtypes. The first (nonfollicular) subtype shows strong positive reactions to autologous sweat and negative reactions to autologous serum. The second (follicular) subtype shows weak reactions to autologous sweat and positive reactions to autologous serum. (J Allergy Clin Immunol 2005;116: 397-402.)

Key words: *Cholinergic urticaria, sweat, autologous serum, skin test, histamine release test, acetylcholine test*

Abbreviations used
CU: Cholinergic urticaria
ASST: Autologous serum skin test

Cholinergic urticaria (CU), which was first described by Duke[1] in 1924, is characterized by unique clinical features: pinpoint sized, highly pruritic wheals with surrounding erythema that occur after sweating during physical exercise, taking a bath, raising the body temperature, and emotional stress. In typical cases, this disorder usually occurs in young adults. Occasionally, this disorder is accompanied with angioedema and anaphylactic reactions.[2,3]

The pathogenesis of CU has not yet been well clarified despite the fact that numerous investigators have described its clinical characteristics and possible pathogenesis. In patients with CU, injection of acetylcholine (mecholyl) into normal-appearing skin produces a wheal and flare reaction, often surrounded by smaller satellite lesions that are similar to the skin symptoms of CU.[4] Acetylcholine is thus believed to play a significant role in the development of the symptoms of CU. Another aspect of the pathogenesis of CU has focused on sweat itself on the basis of evidence that this unique eruption occurs after sweating. Adachi et al[5] found that 20 patients with CU showed immediate-type reactions after an intradermal skin test with autologous sweat. Kobayashi et al[6] presumed that the leakage of sweat into the dermis because of ductal occlusion at the superficial acrosyringium causes CU. Kaplan et al[7] and Sigler et al[8] demonstrated plasma histamine elevations after exercise challenge of patients with CU.

We performed this study to clarify further the possible involvement of sweat-mediated and autoimmune-mediated mechanisms in CU and in its clinical features. Skin responsiveness was evaluated after the intracutaneous injection of autologous sweat and serum. We assessed the correlation between the degrees of skin reactions and amounts of *in vitro* histamine released from basophils after stimulation with autologous sweat. We further analyzed the relationship between the clinical symptoms of CU and the characteristics of these tests.

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METHODS

Subjects

Eighteen patients with CU were enrolled at the Dermatological Institute of Kobe University Hospital. CU was confirmed by the development of numerous small wheals after exercise until sweating.[9] All of the patients had no aquagenic urticaria. The characteristics of patients with CU are described in Table I. Their age ranged between 15 and 31 years (mean, 21.8 years). Nine patients had a past history of atopic diseases (6 atopic dermatitis and 3 allergic rhinitis). Five patients were accompanied with cold urticaria. Healthy control subjects were enrolled from the staff at Kobe University Hospital. All subjects provided oral consent for this study after oral and written explanations. Relevant drugs such as histamine H1-receptor antagonists were withdrawn for at least 24 hours before the examination. All of the patients had never had systemic corticosteroids for at least 3 months before the examination.

Materials

Venous blood was taken into sterile glass tubes and allowed to clot at room temperature for 30 minutes. Serum was separated by centrifugation at 500*g* for 20 minutes and passed through a 0.45-μm MILLEX HV membrane (Millipore, Molsheim, France). Sweat was collected from each patient's forearm after exercise. The sweat was sterilized after collection by using a 0.45-μm MILLEX HV membrane, and it was preserved at −80°C before use. Sweat samples were diluted with saline (1/100 dilution) before the skin test. Histamine contents of sweat samples (1/100 dilution) from healthy control subjects and patients with CU were less than 10 nmol/L.

Skin test technique

Samples of autologous diluted sweat (0.02 mL), autologous serum (0.05 mL), and 0.9% sterile saline (0.02 or 0.05 mL) were separately injected intradermally into the volar aspect of the forearm of each subjects when they were quiet and with no wheal. The diameters of wheals and erythema were measured after 15 minutes. Reactions were assessed as positive if the diameter of the wheal induced by sweat and serum was equal to or larger than 6 mm. The sterile saline-induced wheals of all subjects were below 4 mm and 2 mm when the amounts of 0.05 and 0.02 mL were injected, respectively.

Local provocation test

Responses to acetylcholine chloride (Ovisot; Daiichi, Tokyo, Japan) were evaluated. Acetylcholine (0.1 mL) was intradermally injected at a concentration of 100 μg/mL diluted with saline. The development of satellite wheals around the injection site was considered as positive. Simultaneously, we checked sweating around the injection site by the iodine-starch technique, and all patients tested showed sweating by this test.[10] All of the normal controls tested showed a significant number of tiny sweating points by this method.

Basophil histamine release test

A histamine release test was performed *in vitro* by using HRT (Shionogi, Osaka, Japan) as previously described.[11] Venous peripheral blood samples from patients with CU and normal healthy controls, 20 μL, and antibasophil antibodies conjugated to magnetic beads were added to each well of a 96-well plate and incubated for 10 minutes at room temperature on a plate mixer. Antibody-binding basophils in each well were then trapped with a chandelier-shaped magnet and transferred to another microplate, where the basophils were stimulated at 37°C for 1 hour with autologous sweat, anti-IgE antibody, and digitonin, respectively. Histamine released into the medium was measured by an ELISA with a characteristic detection profile.[12]

Statistical analysis

The statistical significance of differences was determined by using the Student *t* test. Some data were analyzed by regression analysis by using the statistical package StatView J (Abacus Concepts Inc, Palo Alto, CA). A difference was considered statistically significant at $P < .05$.

RESULTS

Skin tests for autologous sweat

Of 17 patients with CU, except for 1 patient who showed mechanical urticaria in skin test for autologous sweat, 11 (64.7%) showed positive reactions to their own 1/100 diluted sweat by measuring the diameter of wheals (Table II). In contrast, all 10 healthy controls showed negative reactions to their own 1/100 diluted sweat, whereas a few healthy controls had positive reactions to their own 1/10 diluted sweat (data not shown). Sweat-induced wheals in the skin tests were significantly greater for patients with CU than for healthy control subjects (Fig 1, *A*).

Sweat-induced histamine release from basophils

We investigated the histamine release from basophils of 17 patients with CU and of 10 healthy controls after incubation with autologous sweat. Of 17 CU patients' basophils, 10 (58.8%) showed positive responses (more than 5% histamine release) after incubation with 1/100 diluted autologous CU sweat, whereas none of the 10 healthy controls' basophils did with 1/100 diluted autologous normal sweat. Four of the CU patients' basophils showed positive responses to 1/1000 diluted CU sweat. The overall values of percent histamine release from basophils of patients with CU were significantly larger than those from healthy control subjects (Fig 1, *B*).

Correlation of skin tests for autologous sweat with sweat-induced histamine release from basophils

We examined whether sweat-induced histamine release from CU basophils correlates with skin tests for autologous CU sweat in 16 patients. As shown in Fig 1, *C*, % histamine release correlated positively with the area in wheal using skin tests on 1/100 diluted sweat. These results indicate that the degree of percent histamine release for autologous sweat represents the responsiveness of skin tests for autologous sweat.

Autologous serum skin tests

Of 15 patients with CU, 8 (53.3%) showed a positive response in the autologous serum skin test (ASST; Table II). In contrast, all 6 healthy controls showed a negative response for ASST. Most patients with CU who had a negative response for ASST tended to show a positive

TABLE I. Clinical characteristics of patients with cholinergic urticaria

Patient	Age (y)	Sex	History	Accompanying symptoms	Total IgE (IU/mL)	IgE RAST
1	26	Female	Atopic dermatitis	None	919	Mite, *Candida*
2	25	Female	Atopic dermatitis	Asthma	5518	Cedar, orchard grass
3	22	Male	None	Cold urticaria	432	Wheat
4	20	Male	None	None	85	Not done
5	21	Male	Atopic dermatitis	None	4080	Mite, *Candida,* wheat
6	20	Male	None	None	250	Not done
7	22	Female	Allergic rhinitis	Cold urticaria	1842	Mite, *Candida*
8	19	Male	None	None	Not done	Not done
9	22	Male	None	None	116	Not done
10	26	Male	None	None	Not done	Not done
11	31	Male	Allergic rhinitis	None	194	Not done
12	19	Female	Atopic dermatitis	Cold urticaria, angioedema	342	Mite
13	24	Female	Atopic dermatitis	None	907	Mite
14	15	Male	None	Cold urticaria	1302	Mite, *Candida,* orchard grass
15	26	Female	None	None	144	Negative
16	18	Female	Atopic dermatitis	None	118	Mite
17	19	Male	Urticaria	Cold urticaria	Not done	Not done
18	17	Male	Allergic rhinitis	None	423	Not done

TABLE II. Details of results for skin tests, histamine release test, acetylcholine test, and clinical chracterization

Patient	Autologous sweat skin test (Erythema*)	Autologous sweat skin test (Wheal†)	% Histamine release by sweat 1/100‡	% Histamine release by sweat 1/1000‡	Autologous serum skin test§	Acetylcholine test‖	Characteristics of eruption
1	31 × 16	20 × 14	100	36.6	Negative	Not done	Nonfollicular
2	25 × 20	10 × 10	89.6	23.6	Negative	Positive	Nonfollicular
3	11 × 10	9 × 8	0.5	0	Negative	Positive	Nonfollicular
4	23 × 20	8 × 8	7.3	0.4	Negative	Positive	Nonfollicular
5	11 × 10	11 × 10	21.4	6.5	Negative	Positive	Undetermined
6	10 × 10	7 × 7	Not done	Not done	Negative	Positive	Nonfollicular
7	24 × 23	10 × 8	40	3.9	Not done	Positive	Nonfollicular
8	25 × 22	9 × 9	48.8	0.2	Not done	Not done	Nonfollicular
9	20 × 15	7 × 6	54.8	6.7	Positive	Not done	Undetermined
10	15 × 13	6 × 5	63.2	4.6	Positive	Not done	Undetermined
11	0 × 0	0 × 0	10.6	1.3	Positive	Not done	Follicular
12	10 × 8	10 × 8	2.1	0.2	Positive	Negative	Follicular
13	9 × 9	0 × 0	1	0	Positive	Negative	Follicular
14	Mechanical urticaria		0.2	0	Not done	Not done	Follicular
15	0 × 0	0 × 0	0.4	0	Positive	Negative	Follicular
16	7 × 6	0 × 0	0	0	Positive	Negative	Nonfollicular
17	0 × 0	0 × 0	0.4	0.4	Positive	Negative	Follicular
18	7 × 7	4 × 4	1.1	0	Negative	Negative	Nonfollicular

*†Long axis and short axis of oval area are presented. 1/100 diluted sweat is used in autologous sweat skin test.
‡Dilution of sweat.
§Autologous serum was injected intradermally into the volar aspect of the forearm.
‖Acetylcholine was intradermally injected 0.1 mL in concentration of 100 μg/mL diluted with saline.

response for skin tests and for the histamine release test with autologous CU sweat. In contrast, a few patients with a positive response for ASST tended to show hypersensitivity for sweat (Table II).

Intradermal acetylcholine test

After intradermal injections of relatively high concentrations of cholinergic agents, the typical satellite pinpoint wheals around the central large wheal were seen only in patients with CU.[4] However, these satellite wheals seemed to develop only in a few patients with CU.[13] We therefore examined whether the patients with CU showed satellite wheals by acetylcholine injection. In this study, 6 (50%) of the 12 patients with CU tested showed a positive response for acetylcholine (Table II). Almost all of the patients who were checked for sweating by iodine-starch method

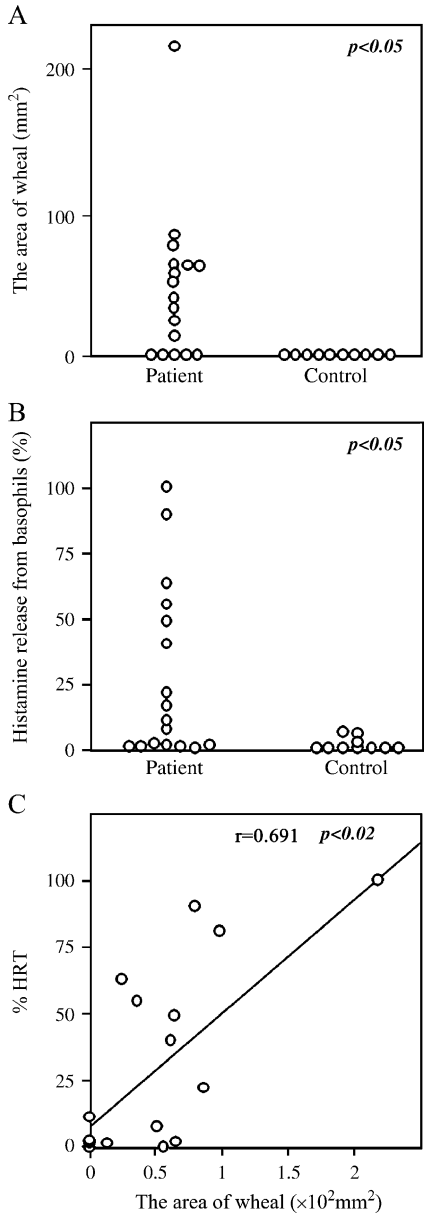


FIG 1. Differences in responses to sweat in patients with CU and normal controls. **A,** The areas of wheals induced by intradermal injection with autologous sweat. **B,** Values of the histamine release from basophils stimulated with CU sweat or normal sweat. **C,** The relationship of responsiveness of skin tests with CU sweat and CU sweat-induced histamine release from CU basophils.

showed sweating after acetylcholine injection in our series, indicating that the absence of the satellite wheals by the agent is not attributed to the dyshidrosis. Compared with patients who showed a negative response for the acetylcholine test, the areas of CU sweat-induced wheals in the skin tests were significantly greater in patients who showed satellite wheals for the acetylcholine test (Fig 2, *A*). The values of CU sweat-induced histamine released from basophils of patients who showed positive responses for the acetylcholine test were significantly greater than those from patients who showed negative responses for the acetylcholine test (Fig 2, *B*). In addition, certain satellite wheals after the acetylcholine test were recognizable as coincident with perspiration points when sweating points were detected by the starch-iodine method (Fig 2, *C*).

Characterization of the clinical phenotype

When patients with CU developed wheals after exercise, we observed that the wheals sometimes coincided with hair follicles. Of 16 patients with CU, 6 (37.5%) had wheals coincident with follicles (the follicular type), and 8 (50%) had wheals that were not coincident with follicles (the nonfollicular type). Compared with the follicular type, the areas of CU sweat-induced wheals in the skin test were significantly greater in the nonfollicular type (Fig 3, *A*). The values of CU sweat-induced histamine released from basophils of the nonfollicular type tended to be greater than those released from basophils of the follicular type (Fig 3, *B*). A representative clinical picture of wheals consisting of follicles is shown (Fig 3, *C*).

DISCUSSION

We demonstrated that the majority of patients with CU are highly sensitive to autologous sweat. The heterogeneous responses in skin tests with autologous sweat suggest that patients with CU have various degrees of hypersensitivity to sweat. We further observed that various amounts of histamine were detected in the medium when basophils were incubated in the presence of autologous sweat, which suggests that autologous sweat itself contains factors that can induce histamine release. The amounts of histamine released from CU basophils correlated relatively well with the degree of response in the skin tests to autologous CU sweat. In contrast, normal healthy controls did not respond to intracutaneous challenge with autologous sweat and did not show histamine release from basophils by stimulation with autologous sweat. These results indicate that patients with CU have various degrees of hypersensitivity to sweat and that *in vitro* histamine release tests using autologous sweat correlate with the intracutaneous test. Previously, Adachi et al[5] reported that all patients with CU examined showed immediate-type skin reactions to intradermal tests with sweat at various dilutions (2^0-2^9). We observed that a few healthy controls had positive reactions after intradermal injection of 1/10 autologous sweat, whereas no healthy controls showed a positive reaction to their own 1/100 diluted sweat. Certain patients who showed a negative response at 1/100 dilution might have shown a positive response at higher concentrations (1/10 and higher dilutions). In other words, those patients with CU who showed positive skin responses in this study might represent the presence of strong hypersensitivity to sweat.

Interestingly, Hide et al[14] recently reported that patients with atopic dermatitis show hypersensitivity to autologous sweat antigens. They speculate that this phenomenon is

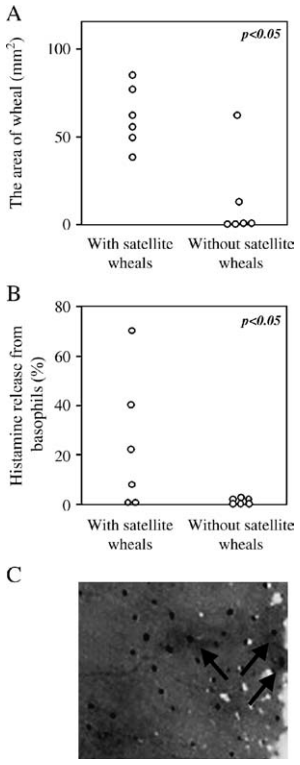


FIG 2. The relationship between responses to sweat and acetylcholine tests in patients with CU. **A,** The areas of wheals induced by intradermal injection with CU sweat in patients with CUs with or without satellite wheals. **B,** The CU sweat-induced histamine release from basophils in patients with CU with or without satellite wheals. **C,** A representative clinical picture that satellite wheals are coincident with perspiration points.

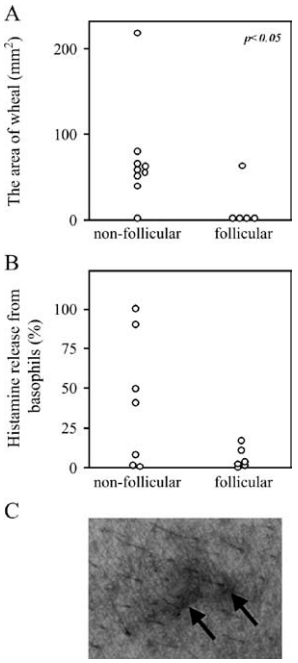


FIG 3. The difference of response to sweat in the relationship between follicles and eruption in patients with CU. **A,** The areas of wheals induced by intradermal injection with CU sweat in patients with CU with nonfollicular or follicular wheals. **B,** The CU sweat-induced histamine release from basophils in CU patients with nonfollicular or follicular wheals. **C,** A representative picture of wheals consisting of follicles.

an IgE-mediated response, because histamine release was impaired by removal of IgE from patients' basophils and myeloma IgE blocked the sensitization of basophils with the patient's serum. It is of interest to note that patients with CU frequently have atopic dermatitis.[5,15] Adachi et al[5] have shown that leukocytes from a normal healthy donor did release histamine on sweat challenging after being sensitized with a patient's serum. Therefore, it might be possible that, similar to atopic dermatitis, hypersensitivity to sweat in patients with CU could be an IgE-mediated response.

An attractive hypothesis for the pathomechanisms of CU is that sweat leaks from the sweat duct into the dermis.[6,16] Several cases of CU have been described that are associated with hypohidrosis/anhidrosis.[6,16] Occlusion of the superficial acrosyringium might result in sweat leakage into the dermis in patients with CU and anhidrosis.[6] If those patients with CU are hypersensitive to sweat, the leaking sweat possibly induces urticarial symptoms around the sweat ducts, resulting in small pinpoint wheals. Commens and Greaves[4] examined 12 patients with CU by intradermal testing with methacholine and found that satellite wheals were induced in only 6 of them. It is not yet clear why only some patients with CU develop satellite wheals after injection of cholinergic agents. We showed here that patients developing satellite wheals in the acetylcholine test had significantly enhanced responses to sweat in the skin tests and in histamine release tests (Fig 2). This means that those with hypersensitivity to sweat tend to develop satellite wheals after stimulation with acetylcholine, a sweat inducer. Moreover, we observed that satellite wheals after the acetylcholine test were coincident with perspiration points by the iodine-starch method (Fig 2, *C*). These results are compatible with the idea that sweat leakage from sweat ducts induces small wheals in certain patients with CU.

Circulating functional histamine-releasing autoantibodies reactive against either the α-subunit of the high-affinity IgE receptor (FcεRIα) or IgE have been identified in more than one third of patients with chronic idiopathic urticaria.[17-22] The ASST is now recognized as a suitable screening test for such autoantibodies in such patients.[4] However, it is still unclear whether the wheal-inducing factors in the patient's sera in this study are these autoantibodies, and this issue should be further clarified in the future. Sabroe et al[23] have reported that only 1 of 9 patients with CU had a positive ASST. In contrast, we showed here that 8 of 15 patients had a positive ASST. The discrepancy of the ratio of responsiveness in ASST between their findings and ours might be attributed to the patient population; that is, the majority of the patients in their study might have had the nonfollicular type. So far, it is unclear whether we might enroll more follicular-type

patients than the usual population in CU. Therefore, this issue should be further studied in the future.

We observed that certain patients with CU develop wheals in association with hair follicles, whereas the other patients do not. This phenomenon is similar to that seen in aquagenic urticaria, in which follicular wheals develop after contact with water. We found that patients with nonfollicular-type CU tend not only to show satellite wheals after the acetylcholine test but also to have hypersensitivity to sweat as determined by skin tests and by histamine release tests (Table II). On the other hand, most of the patients with follicular-type CU showed a positive reaction to ASST and no satellite wheals by acetylcholine or hypersensitivity to sweat (Table II). On the basis of these findings, we strongly believe that CU should be classified into 2 subtypes from the clinical and pathological aspects. The relationship between CU and hair follicles should be examined further.

In summary, 2 subtypes were identified in patients with CU. The first subtype shows nonfollicular wheals, a hypersensitivity to autologous sweat, satellite wheals in the acetylcholine test, and negative reactions to autologous serum. The second subtype shows follicular wheals, a very weak hypersensitivity to sweat, no satellite wheals in the acetylcholine test, and positive reactions to autologous serum. Thus, we suggest that the pathogenesis of CU involves hypersensitivity or autoimmunity to sweat. In considering the pathogenesis of CU, the classification presented here may be useful to this unique disorder.

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