

Sweat antigen induces histamine release from basophils of patients with cholinergic urticaria associated with atopic diathesis

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Summary

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Conflicts of interest

None declared.

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Background We previously demonstrated that the semipurified human sweat antigen causes skin reactions and histamine release from basophils via specific IgE in patients with atopic dermatitis (AD). Patients with cholinergic urticaria (ChU) also develop skin reactions and histamine release of basophils in response to autologous sweat.

Objectives To study whether or not patients with ChU share sensitivity for the sweat antigen with patients with AD and to study the clinical characteristics among patients with ChU and the relationship with histamine-release activity of basophils.

Methods The sweat antigen that induces histamine release from basophils of patients with AD was prepared by Con-A, anion-exchange and reverse-phase chromatography. Relationships between histamine-release activity against the sweat antigen and clinical features of patients with ChU were analysed.

Results Twenty-three of 35 patients with ChU showed > 5% net histamine release in response to the semipurified sweat antigen, whereas none of healthy controls did so. In patients with ChU, histamine release in response to semipurified sweat antigen significantly correlated with the level of serum IgE and eosinophil numbers in peripheral blood. Incidence of each atopic disease in patients with ChU tended to be higher than in the general Japanese population. When the patients were categorized according to their responses in the histamine release test, the positive group tended to show a higher incidence of AD and bronchial asthma compared with the negative group.

Conclusions ChU and AD may share hypersensitivity to common antigens in sweat. The sweat allergy and atopic diathesis are associated with each other.

Cholinergic urticaria (ChU) is a distinctive type of urticaria and appears in association with rising body temperature and sweating. The involvement of an immediate-type allergy to autologous sweat has been suggested in certain populations of patients with ChU. Adachi *et al.* reported that autologous 'crude' sweat induced immediate-type reactions in intradermal skin tests and histamine release from basophils in patients with ChU.¹ They suggested an IgE dependency of these reactions using the Prausnitz-Küstner test and histamine release from leucocytes treated with acid and sensitized with serum of the patient. Fukunaga *et al.* recently reported that ten of 17 patients with ChU released histamine from their basophils as well as having positive skin reactions in response to autologous 'crude' sweat.²

Many patients with atopic dermatitis (AD) also showed immediate-type reactions in response to intradermal injections of autologous 'crude' sweat, and their basophils induced histamine release in response to the sweat samples.³ The sensitization of basophils obtained from a healthy individual with sera of patients with AD rendered them sensitive to sweat but not myeloma IgE.⁴ Because ChU in patients is often complicated by AD,⁵ it is feasible that patients with ChU may be sensitive to the same antigen in sweat as patients with AD.

Recently, we semipurified the sweat antigen, which induced histamine release from mast cells and basophils via antigen-specific IgE in patients with AD.⁶ In the present study, we examined the histamine release from basophils of patients with ChU in response to the semipurified and standardized

sweat antigen. We also assessed the correlation between the amount of histamine release and atopic diathesis, the incidence of atopic diseases, serum IgE concentrations and numbers of eosinophils in peripheral blood.

Materials and methods

Thirty-five subjects with ChU (males : females, 18 : 17; mean age 26.0 years, range 10–56) were enrolled in this study. ChU was confirmed by the development of numerous characteristic small weals during or after exercise with sweating. Fourteen healthy control subjects (males : females, 6 : 8; mean age 30.2 years, range 22–44) were recruited from the staff at Hiroshima University Hospital. All subjects provided informed consent for the study. This study was approved by the ethics committee in Hiroshima University Hospital.

The semipurified and standardized sweat antigen that induced histamine release from basophils of patients with AD was prepared by concanavalin A (Con-A) chromatography, anion-exchange chromatography and reverse-phase chromatography, as described previously.⁶ Histamine release tests with basophils obtained from peripheral blood were performed as described previously.⁴

Statistical analysis was performed and $P < 0.05$ was considered statistically significant.

Results

Twenty-three (66%) of 35 patients with ChU showed $> 5\%$ net histamine release in response to semipurified sweat antigen, whereas none of healthy controls did so. Net percentage of histamine release of patients with ChU (mean $\pm$ SEM, $24.56 \pm 4.00\%$) was significantly higher than that of healthy controls ($-0.10 \pm 0.36\%$; $P = 0.0003$) (Fig. 1). Moreover, both the level of serum total IgE and numbers of eosinophils in peripheral blood correlated significantly with histamine release in response to semipurified sweat antigen (Fig. 2).

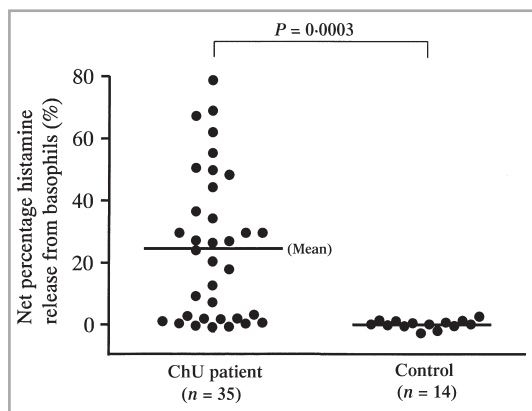


Fig 1. Histamine release in response to semipurified sweat antigen from basophils of patients with cholinergic urticaria (ChU) and normal controls (using the t-test; $P < 0.05$ was considered statistically significant).

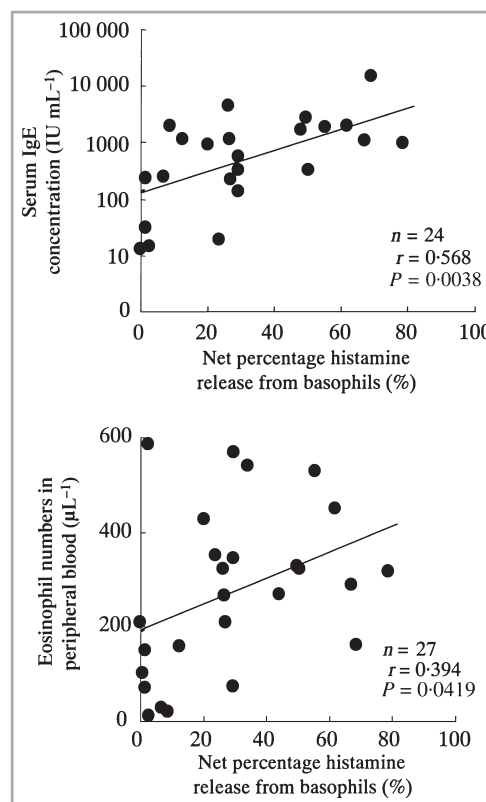


Fig 2. The relationship of serum IgE concentrations and number of eosinophils in peripheral blood and histamine release (using regression analysis; $P < 0.05$ was considered statistically significant).

The incidence of each atopic disease in patients with ChU was higher than that in the general Japanese population,^{7,8} namely AD, bronchial asthma, allergic conjunctivitis and allergic rhinitis (Table 1). The difference is especially apparent in AD and bronchial asthma. When they were categorized in terms of responses in histamine release tests, patients in the positive group (net histamine release $> 5\%$) tended to show more association with AD and bronchial asthma than those in the negative group (net histamine release $\leq 5\%$). On the other hand, the association of allergic conjunctivitis and allergic rhinitis with the histamine release test-positive group was almost equal or smaller than that with the histamine release test-negative group. However, statistical analysis did not prove any significance in these differences.

Discussion

In this study, we demonstrated that 23 of 35 (66%) patients with ChU were sensitive to the 'semipurified' sweat antigen as are many patients with AD. Fukunaga *et al.* reported 'crude' autologous sweat induced significant histamine release in 59% of patients with ChU.² Because the amounts of histamine-release activity in 'crude' sweat vary widely among donors of sweat, the 'semipurified' and standardized sweat antigen allowed us to compare quantitatively the degree of sweat

Table 1 The incidence of atopic diseases in patients with cholinergic urticaria (ChU) and reactivity to the sweat antigen detected by histamine release tests (using χ^2 test to study correlation between positive and negative groups; $P < 0.05$ was considered statistically significant)

	AD	P-value	BA	P-value	AC	P-value	AR	P-value
Prevalence in the general Japanese population, %	8.2–13.2 ^b		3.0–6.4 ^b		15.0–20.0 ^b		27.1 ^c	
Prevalence in ChU patients (n = 35), %	51.4		20.0		31.4		34.2	
Histamine release test ^a , %								
Positive group (n = 23)	60.9	n.s.	30.4	n.s.	30.4	n.s.	30.4	n.s.
Negative group (n = 12)	33.3		0		33.3		41.6	

^aPositive group: net histamine release > 5%; negative group: net histamine release ≤ 5%; ^bfrom reference 7; ^cfrom reference 8.
AD, atopic dermatitis; BA, bronchial asthma; AC, allergic conjunctivitis; AR, allergic rhinitis; n.s., not significant.

hypersensitivities among subjects using histamine release tests. Moreover, the 'semipurified' sweat antigen was equal or superior to 'crude' sweat in terms of histamine release-inducing activity, suggesting that the semipurified sweat antigen contains major sweat antigens, to which patients with ChU are sensitive.

Recently, Metz *et al.* reported a case of ChU, successfully treated with omalizumab.⁹ As the recombinant humanized monoclonal antibody targets the high-affinity receptor-binding site on the IgE antibody, omalizumab is useful for the treatment of asthma and allergic rhinitis, in which IgE antibody plays an important role.¹⁰ The effectiveness of omalizumab for ChU supports the hypothesis that ChU is mediated by IgE antibody. If the pathogenic IgE antibodies target the sweat antigen, histamine release tests with the semipurified sweat antigen would be useful to identify patients with ChU who might be treated with omalizumab.

In terms of the incidence of atopic diseases, we could not find a significant difference between ChU patients with sweat allergy and those without sweat allergy. However, the incidence of atopic diseases, especially AD and bronchial asthma, in all patients with ChU was higher than that in the general population. Moreover, the histamine release in response to the sweat antigen correlated significantly with levels of serum IgE and peripheral eosinophil numbers, suggesting the association of atopic diathesis and sweat allergy in patients with ChU.

Although clinical manifestations of ChU and those of AD are different, our results suggest that ChU and AD may share hypersensitivity to common antigens in sweat. The identification of sweat antigen and further studies with a larger popula-

tion of patients with AD and those with ChU should help us understand the relationship of these two diseases in their pathogenesis.

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