



Contents lists available at ScienceDirect

Allergology International

journal homepage: <http://www.elsevier.com/locate/alit>

Letter to the Editor

Two cases of angioedema without wheals induced by exercising or bathing

Dear Editor,

Angioedema without wheals is caused by C1 inhibitor deficiency, drugs and various diseases¹ but is rarely induced by a specific physical stimulus.² Here, we report two cases of angioedema without wheals, clearly related to exogenous stimuli including bathing and exercising. Additionally, we examine fluctuations in plasma histamine levels and complement parameters before and after a challenge test.

Case 1: An 18-year-old woman presented with a two-year history of recurrent episodes of eyelid swelling without wheals. The swelling occurred when bathing or exercising for approximately 30 min, persisting for two days before improving spontaneously. There were no subjective symptoms of hypohidrosis or other symptom-related factors such as drugs, foods, the timing of meals, season or her menstrual cycle but the high air temperature was a precipitating factor. She had atopic dermatitis (AD) as a child, but no history of urticaria or family history of angioedema.

Blood test results of c-reactive protein, immunoglobulin E (IgE), C1q, C3, C4, C1 inhibitor activity, thyroid function, anti-nuclear antibody and coagulation factor 12 activity were within respective normal ranges. Results of antigen-specific IgE antibodies are shown in [Supplementary Table 1](#). Provocation tests in accordance with international consensus recommendations³ for symptomatic dermographism and heat urticaria were negative. After taking a bath at 42 °C for 30 min as a challenge test, eyelid itching and swelling and redness, conjunctival swelling, tears, nasal obstruction and nasal mucus developed ([Fig. 1](#)). Symptoms other than eyelid swelling disappeared 40 min after bathing, with the swelling disappearing after two days. No other symptoms including wheals occurred. Blood tests were performed before the provocation test and during the presence of symptoms to observe the fluctuations in plasma histamine and complement parameters ([Table 1](#)). The patient was treated with tranexamic acid, rupatadine fumarate and pranlukast. Despite some relief, symptoms persisted.



Fig. 1. Skin manifestations of the patient before and after the challenge test consisting of bathing at 42 °C for 30 min. (a) No swelling of eyelid before the challenge test. (b) Swelling and redness of eyelid after the challenge test. A permission from the patient for the use of the images was obtained.

Peer review under responsibility of Japanese Society of Allergy.

<https://doi.org/10.1016/j.alit.2020.04.011>

1323-8930/Copyright © 2020, Japanese Society of Allergy. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Table 1

Plasma histamine levels and complement parameters before and after a challenge test of bathing at 42 °C for 30 min.

	Normal range	Case 1		Case 2	
		Before	After	Before	After
C1q (mg/dL)	8.8–15.3	8.9	10.3	10.7	9.8
C3 (mg/dL)	80–165	147	156	81	78
C4 (mg/dL)	14–42	35	37	15	14
C1 inhibitor activity (%)	70–130	99	99	88	86
Histamine (ng/mL)	0.15–1.23	2.28	2.32	1.40	4.14

Case 2: A 20-year-old woman presented with an 18-month history of recurrent episodes of eyelid swelling without wheals when bathing or exercising. Respiratory discomfort gradually accompanied the swelling. Similar to Case 1, there were no subjective symptoms of hypohidrosis and no other symptom-related factors, but the high air temperature was a precipitating factor. She had a history of bronchial asthma and AD and exhibited mild eczema in the extremities. She had no history of inducible urticaria such as cholinergic or heat urticaria. She had no family history of angioedema. Serum IgE was 706 IU/mL (normal range: 0–450 IU/mL). Other blood test results of c-reactive protein, C1q, C3, C4, C1 inhibitor activity, thyroid function, anti-nuclear antibody and coagulation factor 12 activity were within respective normal ranges. After confirming the patient was negative for provocation tests of symptomatic dermatographism and heat urticaria, we performed the challenge test (42 °C bath). After bathing for 30 min, eyelid and lip swelling, eyelid itching and redness, conjunctival swelling, tears, nasal obstruction, nasal mucus and respiratory discomfort developed. Symptoms other than eyelid and lip swelling disappeared 40 min after bathing; lip swelling disappeared 5 h after bathing, and eyelid swelling disappeared two days after. No other symptoms occurred. Blood tests were performed before the provocation test and during the presence of symptoms (Table 1). The patient was treated with tranexamic acid and rupatadine fumarate. Despite responding to the treatments, symptoms persisted.

In our patients, results of the challenge tests indicated that angioedema was induced by an elevation of body temperature. To our knowledge, there is only one reported case similar to ours,² in which Kobayashi *et al.*² advocated a new diagnosis “thermal angioedema”. The 20-year-old woman in this study developed eyelid swelling and itching when showering the whole body at 41 °C.² Interestingly, patients in all three cases not only showed similar clinical courses, but also shared similar background characteristics including age, gender and co-morbidities. Moreover, all three patients had a past history of AD and two (Case 2 in the present study and the patient in the previous case) had accompanying respiratory discomfort. These findings suggest that our patient’s form of angioedema is a severe type of angioedema often accompanied by respiratory discomfort that has a predilection for young women with AD.

Elevation of body temperature is well known as a trigger in patients with cholinergic urticaria (CholU),³ showing angioedema as an uncommon manifestation.^{4,5} A recent report proposed CholU with angioedema as a severe subtype of CholU with sweat hypersensitivity, mainly occurring in women with AD.⁶ Antigen-specific IgE antibodies against *Malassezia*, previously reported as being able to predict sweat allergy,⁶ were positive in both cases (Supplementary Table 1), suggesting a possibility that they had sweat allergy related complications. This new subtype of CholU has a clinical course and patient background characteristics similar to our cases.

Plasma histamine levels before the provocation in both cases were already beyond their normal limits. This might be due to the complications of AD, similar to previous reports of elevated basal plasma histamine levels in AD.⁷ Case 1 did not show

fluctuations in either plasma histamine or complement parameters, whereas plasma histamine in Case 2 increased mildly during the symptoms compared to that before the challenge test. Our hypothesis is that no observation of fluctuations in the plasma histamine level in Case 1 was due in part to the mild symptoms and the brevity of the half-life of histamine. The symptoms in Case 2 were severe, suggesting a possibility of high values in the plasma histamine level, thereby allowing us to detect elevated plasma histamine levels. However, both cases showed poor responses to H1 receptor antagonists. Similarly, CholU with angioedema has also been reported to be associated with increased plasma histamine⁸ but the H1 receptor antagonist may be less effective.⁶ Many features observed in our cases were reminiscent of CholU with angioedema except the occurrence of wheals. Our cases and previously reported thermal angioedema might be an abortive form of CholU with angioedema in which the symptoms of wheals are less prominent. Future studies are needed to clarify whether exercise- or bathing-induced angioedema without wheals is a manifestation of CholU with angioedema or represents a new entity.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2020.04.011>.

Conflict of interest

The authors have no conflict of interest to declare.

Tomoyuki Minowa, Yasuyuki Sumikawa, Ayako Kumagai, Takafumi Kamiya, Hisashi Uhara *

Department of Dermatology, Sapporo Medical University School of Medicine, Sapporo, Japan

* Corresponding author. Department of Dermatology, Sapporo Medical University School of Medicine, South 1, West 16, Chuo-ku, Sapporo 060-8543, Japan. E-mail address: uharah@sapmed.ac.jp (H. Uhara).

References

- Zingale LC, Beltrami L, Zanichelli A, Maggioni L, Pappalardo E, Cicardi B, et al. Angioedema without urticaria: a large clinical survey. *CMAJ* 2006;**175**:1065–70.
- Kobayashi A, Uhara H, Ashida A, Kuniwa Y, Okuyama R. Thermal angioedema induced by hot water. *Acta Derm Venereol* 2011;**91**:343–4.
- Magerl M, Altrichter S, Borzova E, Giménez-Arnau A, Grattan CE, Lawlor F, et al. The definition, diagnostic testing, and management of chronic inducible urticarias - the EAACI/GA(2) LEN/EDF/UNEV consensus recommendations 2016 update and revision. *Allergy* 2016;**71**:780–802.
- Kaplan AP, Natbony SF, Tawil AP, Fruchter L, Foster M. Exercise-induced anaphylaxis as a manifestation of cholinergic urticaria. *J Allergy Clin Immunol* 1981;**68**:319–24.
- Kato T, Komatsu H, Tagami H. Exercise-induced urticaria and angioedema: reports of two cases. *J Dermatol* 1997;**24**:189–92.
- Washio K, Fukunaga A, Onodera M, Hatakeyama M, Taguchi K, Ogura K, et al. Clinical characteristics in cholinergic urticaria with palpebral angioedema: report of 15 cases. *J Dermatol Sci* 2017;**85**:135–7.
- Ring J. Plasma histamine concentrations in atopic eczema. *Clin Allergy* 1983;**13**:545–52.
- Lewis J, Lieberman P, Treadwell G, Erffmeyer J. Exercise-induced urticaria, angioedema, and anaphylactoid episodes. *J Allergy Clin Immunol* 1981;**68**:432–7.

Received 19 February 2020

Received in revised form 10 April 2020

Accepted 19 April 2020

Available online xxx