

CONCISE COMMUNICATION

Case of cholinergic urticaria accompanied by anaphylaxis

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ABSTRACT

Cholinergic urticaria occasionally occurs in combination with anaphylactic symptoms. However, this has not been widely reported. Herein, we report the case of a 14-year-old Japanese male who was diagnosed with cholinergic urticaria accompanied by anaphylaxis. The patient, who was suffering from atopic dermatitis and bronchial asthma, had developed wheals after exercising or bathing, which would have increased his core body temperature, since summer 2014. He experienced two episodes of severe systemic symptoms and wheal development when he took a bath after eating in December 2014 and the following January. His symptoms included wheezing, numbness of the lips, respiratory distress, blindness and fainting. Laboratory tests revealed the following results: serum IgE level, 7060 IU/mL; titers of specific immunoglobulin E antibodies against *Malassezia* and MGL_1304, 31.70 UA/mL and 112.5 ng/mL, respectively. A histamine release test against human sweat revealed a class 4 response. Skin prick and intradermal tests against autologous sweat produced immediate-type positive reactions. According to these findings, we diagnosed him with the sweat-hypersensitivity type of cholinergic urticaria accompanied by anaphylaxis. He was successfully treated with lafutidine, a histamine H₂ receptor antagonist, in combination with fexofenadine. It is important for dermatologists to be aware that cholinergic urticaria can progress to anaphylaxis.

Key words: anaphylaxis, anti-MGL_1304 immunoglobulin E antibody, autologous sweat, cholinergic urticaria, skin test.

INTRODUCTION

Cholinergic urticaria (CholU) is a form of hives, in which small pruritic wheals develop in association with sweating and/or an increase in core body temperature. It can be induced by factors including heat, exertion or emotional stress. Occasionally, this disorder causes systemic symptoms, such as angioedema, dyspnea, abdominal pain or loss of consciousness. While CholU occasionally occurs in combination with anaphylaxis, this is not widely known.

Herein, we report the case of a 14-year-old male who developed wheals followed by wheezing, respiratory distress, blindness and fainting when he took a bath after eating. Food-dependent, exercise-induced anaphylaxis was clinically suspected; however, no causative food antigen was identified, and detailed examinations concluded that the patient was suffering from CholU combined with severe anaphylactic symptoms. Skin tests, histamine release tests (HRT) and measurements of the patient's anti-MGL_1304 immunoglobulin (Ig)E antibody titer confirmed that he was hypersensitive to autologous sweat.

CASE REPORT

A 14-year-old male visited our clinic in January 2015 complaining of two episodes of severe systemic symptoms. He had developed wheals accompanied by wheezing and respiratory distress when he took a bath 30 min after eating ramen (soup containing wheat noodles) and takoyaki (a baked wheat cake with pieces of octopus) in December 2014. These symptoms were relieved via the inhalation of steroids, which he always carried for attacks of bronchial asthma. The second episode occurred 5 days later, during which the patient developed wheals combined with wheezing, numbness of the lips, blindness and fainting when he took a bath an hour after eating grilled meat. He was carried to hospital, and his symptoms disappeared spontaneously without treatment.

The patient's condition was complicated by atopic dermatitis, bronchial asthma and oral allergy syndrome due to kiwi fruit. An investigation of his detailed medical history revealed that he had developed wheals on a number of occasions during the 4 months before the above-mentioned episodes. Wheals had arisen when he was riding a bicycle to school, playing tennis, running, swimming or bathing. The wheals were

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numerous, small and non-follicular, and disappeared within 30 min (Fig. 1).

The patient's complete blood cell counts and liver and renal function levels were within normal limits. His serum IgE level was 7060 IU/mL, and his specific IgE antibody levels (ImmunoCAP™; Thermo Fisher Scientific, Tokyo, Japan) were as follows: mites and house dusts, more than 100 UA/mL; Japanese cedar pollen, 70.80 UA/mL; *Malassezia*, 31.70 UA/mL; *Pityrosporum*, 20.30 UA/mL; dog skin dander, 16.00 UA/mL; orchard grass pollen, 5.79 UA/mL; cat skin dander, 4.46 UA/mL; kiwi fruit, 0.80 UA/mL; and ragweed pollen, 0.23 UA/mL. Tests of the levels of specific IgE antibodies associated with the foods involved in the two above-mentioned episodes, such as antibodies against wheat, ω -5 gliadin, onion, egg white, egg yolk, pork, beef and octopus, all produced negative results.

The serum level of the IgE antibody against MGL_1304 was measured using a sandwich enzyme-linked immunosorbent assay, as described previously,¹ with a slight modification. In this study, 1 μ g/mL of recombinant MGL_1304 derived from *Pichia pastoris* was used as the standard sweat antigen, and the amount of IgE against MGL_1304 (weight/volume percentage) was determined using a monoclonal human IgE antibody against MGL_1304.² The patient's MGL_1304-specific IgE level was 112.5 ng/mL (3516.2 units/mL).

Prick-to-prick tests of the foods associated with the above-mentioned episodes were also all negative. The results of skin tests of acetylcholine, autologous sweat and serum are shown

in Table 1 and Figure 2. Stock ($\times 1$ dilution) acetylcholine solution was produced by diluting 100 mg acetylcholine chloride (Ovisot®; Daiichi-Sankyo, Tokyo, Japan) with 1 mL of distilled water. The prick and intradermal tests were conducted using acetylcholine at dilutions of $\times 1$ to $\times 1/10\ 000$, and autologous sweat and serum at dilutions of $\times 1$ to $\times 1/100$, and the sizes of wheals and erythemas that appeared were measured after 15 min. Our patient produced immediate-type skin reactions to autologous sweat at dilutions of $\times 1$ and $\times 1/10$ in the prick tests and at dilutions of $\times 1/10$ and $\times 1/100$ in the intradermal tests. The reactions to acetylcholine exhibited by the patient during the intradermal tests were smaller than those produced by healthy individuals, and no satellite wheals were noted around the injection sites.

An *in vitro* histamine-release test (HRT) against human sweat was performed using a commercial kit (Shionogi, Osaka, Japan), and it revealed a high histamine release ratio at a low concentration and even higher ratios at higher concentrations, which was indicative of a class 4 response. HRT against other allergens detected class 3 responses to mites and Japanese cedar pollen, and class 1 responses to dog and cat skin dander.

Our patient was finally diagnosed with anaphylaxis involving severe systemic symptoms, which had progressed from CholU. He was administered 120 mg/day fexofenadine, which is a H_1 receptor antagonist (H_1 RA), but it was ineffective. The further administration of 10 mg/day lafutidine, a H_2 receptor antagonist (H_2 RA), in combination with fexofenadine was successful at reducing his wheals.



Figure 1. Clinical findings of the patient's wheals. The patient developed numerous small and non-follicular wheals, which disappeared within 30 min.

DISCUSSION

Cholinergic urticaria has the following characteristics:³ (i) it usually appears by the second decade of life; (ii) it is induced by increases in core body temperature, for example, due to exercise, bathing, spicy food consumption or emotional stress; (iii) it usually results in wheals that are 1–3 mm in diameter with red halos; (iv) stinging or tingling pain and/or itching can occur at the onset of symptoms; and (v) the symptoms disappear within 30–60 min. Our patient demonstrated all of these characteristics, and also exhibited marked hypersensitivity to autologous sweat.

Recently, Fukunaga *et al.*⁴ proposed four types of CholU: (i) conventional sweat allergy-type CholU; (ii) follicular-type CholU; (iii) CholU with palpebral angioedema (CholU-PA); and (iv) CholU with acquired anhidrosis and/or hypohidrosis. Among them, CholU-PA is often accompanied by anaphylaxis. Washio *et al.*⁵ reported that seven out of 15 cases of CholU-PA had anaphylaxis. These cases were characterized by female predominance, a positive result in a HRT against sweat and atopic diathesis. There have only been a few other recent reports about CholU accompanied by anaphylaxis.^{6–8} According to the new classification mentioned above, our case should be classified as CholU-PA.

In their study of CholU, Fukunaga *et al.*⁹ reported that $\times 100$ diluted sweat was suitable for intradermal testing because $\times 10$ diluted sweat induced positive responses in normal subjects,

Table 1. Prick and intradermal tests with acetylcholine, autologous sweat and serum

		Our patient		Control 1	Control 2
Tested material	Concentration	Wheal (mm × mm)	Erythema (mm × mm)	Wheal (mm × mm)	
Prick test					
Acetylcholine	×1 (100 mg/mL)	4 × 4	5 × 4	0 × 0	0 × 0
	×1/10	1 × 1	2 × 2	0 × 0	0 × 0
	×1/100	0 × 0	2 × 2	0 × 0	0 × 0
	×1/1000	0 × 0	0 × 0	0 × 0	0 × 0
	×1/10 000	0 × 0	0 × 0	0 × 0	0 × 0
Autologous sweat	×1	10 × 8	20 × 20	0 × 0	0 × 0
	×1/10	5 × 4	12 × 10	0 × 0	0 × 0
	×1/100	2 × 2	5 × 5	0 × 0	0 × 0
Autologous serum	×1	0 × 0	0 × 0	0 × 0	0 × 0
	×1/10	0 × 0	0 × 0	0 × 0	0 × 0
	×1/100	0 × 0	0 × 0	0 × 0	0 × 0
Histamine dichloride (10 µg/mL)		7 × 8	13 × 10	7 × 6	7 × 6
Saline		0 × 0	0 × 0	0 × 0	0 × 0
Intradermal test					
Acetylcholine [†]	×1 (100 mg/mL)	5 × 5	10 × 10	7 × 6	10 × 10
	×1/10	6 × 5	10 × 10	7 × 6	7 × 5
	×1/100	0 × 0	0 × 0	0 × 0	5 × 4
	×1/1000	0 × 0	0 × 0	3 × 3	5 × 5
	×1/10 000	0 × 0	0 × 0	0 × 0	5 × 3
Autologous sweat	×1	N.T.	N.T.	7 × 5	8 × 5
	×1/10	17 × 11	35 × 25	5 × 4	5 × 4
	×100	10 × 10	20 × 20	0 × 0	3 × 2
Autologous serum	×1	0 × 0	0 × 0	0 × 0	0 × 0
	×1/10	0 × 0	0 × 0	0 × 0	0 × 0
	×1/100	0 × 0	0 × 0	0 × 0	0 × 0

[†]No satellite wheals were noted around the injection sites in our patient or healthy individuals. N.T., not tested.

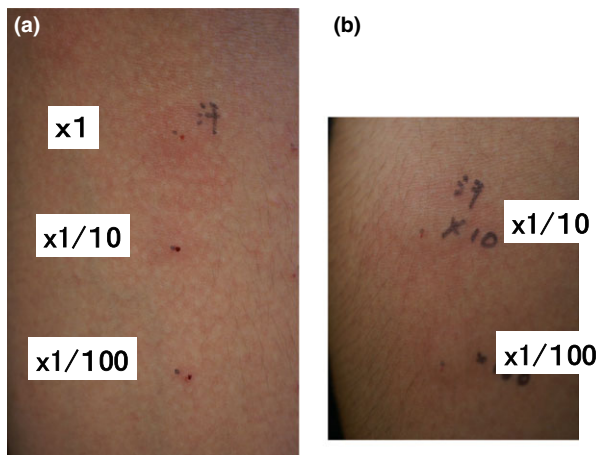


Figure 2. Results of prick and intradermal tests with autologous sweat. Immediate-type skin reactions were produced in response to autologous sweat at (a) dilutions of ×1 and ×1/10 in the prick tests and at (b) dilutions of ×1/10 and ×1/100 in the intradermal tests.

and our intradermal test results support their findings. However, they did not perform prick tests against autologous sweat. Our prick test results suggest that ×10 or ×1 diluted

autologous sweat may be the appropriate concentration for testing patients with CholU.

MGL_1304 is a fungal protein found in human sweat that is secreted by *Malassezia globosa*. It is now considered to be a major allergen for histamine release from basophils in patients with atopic dermatitis.¹⁰ Patients with atopic dermatitis or CholU exhibit significantly higher serum levels of the specific IgE against MGL_1304 than healthy individuals,^{1,11} and their levels of this antibody are correlated with the severity of their atopic dermatitis.¹¹ Our patient displayed higher level of the specific IgE against MGL_1304 than all of the patients with CholU described in a previous study.¹⁰ Recently, a case of angioedema involving excessive sweating and marked histamine release in response to MGL_1304 has been reported.¹²

The conventional treatment for CholU is H₁RA; however, some patients with severe symptoms respond poorly to such treatment. It was proposed that increased doses of H₁RA, H₂RA, montelukast and omalizumab should be administered to such refractory patients.⁴ Hatakeyama *et al.*¹³ demonstrated that the addition of lafutidine, a H₂RA, to H₁RA therapy was effective and safe in patients with refractory CholU that was unresponsive to H₁RA.

The present patient was diagnosed with the sweat-hypersensitivity type of CholU involving systemic symptoms, which was indicative of grade 4 anaphylaxis.¹⁴ The diagnosis was

confirmed based on skin tests of autologous sweat, a HRT of human sweat, and the patient's anti-MGL_1304 IgE antibody level. Clinicians should be aware that CholU can progress to anaphylaxis.

CONFLICT OF INTEREST: None declared.

REFERENCES

- Hiragun M, Hiragun T, Ishii K *et al.* Elevated serum IgE against MGL_1304 in patients with atopic dermatitis and cholinergic urticaria. *Allergol Int* 2014; **63**: 83–93.
- Ishii K, Hiragun M, Hiragun T *et al.* A human monoclonal IgE antibody that binds to MGL_1304, a major allergen in human sweat, without activation of mast cells and basophils. *Biochem Biophys Res Commun* 2015; **468**: 99–104.
- Horikawa T, Fukunaga A, Nishigori C. New concepts of hive formation in cholinergic urticaria. *Curr Allergy Asthma Rep* 2009; **9**: 273–279.
- Fukunaga A, Washio K, Hatakeyama M *et al.* Cholinergic urticaria: epidemiology, physiopathology, new categorization, and management. *Clin Auton Res* 2017; <https://doi.org/10.1007/s10286-017-0418-6>
- Washio K, Fukunaga A, Onodera M *et al.* Clinical characteristics in cholinergic urticaria with palpebral angioedema: report of 15 cases. *J Dermatol Sci* 2017; **85**: 135–137.
- Vadas P, Sinilaite A, Chaim M. Cholinergic urticaria with anaphylaxis: an underrecognized clinical entity. *J Allergy Clin Immunol Pract* 2016; **4**: 284–291.
- Antolin-Amerigo D, Vlaicu PC, Caballer BDLH, Cano MS. Anaphylaxislike cholinergic urticaria. *Can Fam Physician* 2013; **59**: 745–746.
- Handfield KS, Dolan CK, Kaplan M. Cholinergic urticaria with anaphylaxis: hazardous duty of a deployed US marine. *Cutis* 2015; **95**: 241–243.
- Fukunaga A, Bito T, Tsuru K *et al.* Responsiveness to autologous sweat and serum in cholinergic urticaria classifies its clinical subtypes. *J Allergy Clin Immunol* 2005; **116**: 397–402.
- Hiragun T, Ishii K, Hiragun M *et al.* Fungal protein MGL_1304 in sweat is an allergen for atopic dermatitis patients. *J Allergy Clin Immunol* 2013; **132**: 608–615.
- Kan T, Hiragun T, Shii K *et al.* Evaluation of recombinant MGL_1304 produced by *Pichia pastoris* for clinical application to sweat allergy. *Allergol Int* 2015; **64**: 266–271.
- Miyake M, Oiso N, Ishii K, Hide M, Kawada A. Angioedema associated with excessive sweating and sweat allergy. *J Dermatol* 2017; **44**: e58–e59.
- Hatakeyama M, Fukunaga A, Washio K *et al.* Addition of lafutidine can improve disease activity and lead to better quality of life in refractory cholinergic urticaria unresponsive to histamine H1 antagonists. *J Dermatol Sci* 2016; **82**: 137–139.
- Sampson HA. Anaphylaxis and emergency treatment. *Pediatrics* 2003; **111**: 1601–1608.