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## Letter to the Editor

### Clinical characteristics in cholinergic urticaria with palpebral angioedema: Report of 15 cases

Angioedema is characterized by localized swelling of sudden onset affecting the skin and/or mucosa [1] and can be classified as bradykinin-mediated or mast cell mediator-mediated [2]. Angioedema with wheals is usually histamine (mast cell)-mediated. Exercise-induced angioedema without trigger foods has been reported as an uncommon manifestation of cholinergic urticaria (CholU) [3,4], although the causative allergen and clinical characteristics are poorly understood. Here, we report a characteristic case series of CholU with palpebral angioedema (CholU-PA).

Fifteen patients who had palpebral angioedema accompanied by CholU were consecutively enrolled in this retrospective study (Table 1). CholU-PA was confirmed by the development of angioedema mainly around the eyelids and/or numerous small wheals after exercise or bathing until sweating. Fig. 1a shows a typical clinical image, in which the patient manifests a prominent swelling of the eyelids with small wheals on the forehead. To note, CholU-PA patients tended to demonstrate more wheals in lesions where adult atopic dermatitis often involves (Fig. 1b). The institutional ethics committee approved this study and all subjects provided written informed consent. The mean age of patients was 31.9 years. Surprisingly, all patients were female: 11 had a history of atopic dermatitis, six had bronchial asthma, and five had allergic rhinitis. The high frequency of atopic disease (14/15) might reflect the pathogenesis of CholU-PA. Notably, seven patients experienced anaphylaxis (less than grade III) accompanied with CholU-PA, and four had concomitant cold urticaria. Because hypersensitivity to sweat and serum is involved in the pathogenesis of CholU, an autologous sweat skin test (ASwST) and autologous serum skin test (ASST) were performed as previously described [5,6]. Sweat was collected and reactions were determined to be positive as previously described [5]. All CholU-PA patients had a positive reaction to ASwST, whereas only four patients were positive for ASST, indicating that all CholU-PA patients had hypersensitivity to autologous sweat. A commercial histamine release test (HRT) against sweat was performed *in vitro* using an HRT kit (Shionogi, Osaka, Japan) [5]. Results were expressed as an index value (0: negative, 1: weakly positive, 2: positive, 3–4: strongly positive) according to the manufacturer's instructions. Nine of 13 examined patients showed positive HRT reactions to sweat. The levels of complement (C3, C4, and CH50) in 13 patients, or C1-INH in two patients were within the normal limits if applicable (data not shown). Because elevated serum IgE against MGL\_1304 derived from *Malassezia globosa* in patients with CholU was reported [7,8], a radioallergosorbent test (RAST) to detect fungal allergy and a non-specific serum IgE test were also performed. Of note, we found a positive correlation ( $r=0.663$ ,

$p=0.026$  by linear regression analysis) between IgE-RAST titers against *Malassezia* species, and HRT with sweat (Fig. 1c), but no correlation ( $r=0.064$ ,  $p=0.852$  by linear regression analysis) between *Candida* species or HRT with sweat (Fig. 1d). Of the 15 patients, 9 patients responded poorly to treatment with up-dosing of conventional H1 receptor antagonists (H1RA). Patients whose HRT values to sweat were more than three (strongly positive) and/or had a positive result of 1/1000 diluted ASwST were characterized as exhibiting strong sweat hypersensitivity. All four cases without strong sweat hypersensitivity responded well to the H1RA alone, whereas of 11 patients with strong sweat hypersensitivity, only two patients responded to the H1RA ( $p=0.0110$  by two-tailed Fisher's exact test) (Table S1; see Supporting information). Among 9 patients unresponsive to the H1RA, six received an H2 receptor antagonist (H2RA) and their clinical symptoms gradually improved. Of two patients that were administered cyclosporine A, one showed clinical remission and the other showed no response. Two patients with CholU-PA were treated successfully by the local administration of olopatadine.

In this report, we demonstrated that CholU-PA is a characteristic subgroup of CholU with serious symptoms. CholU-PA is different from ordinary CholU because it is accompanied by angioedema around the eyelids and often anaphylaxis. This characteristic CholU-PA is closely related to atopic diathesis and female sex; in contrast, ordinary CholU was not reported to have a significant gender difference [5]. Furthermore, our CholU-PA patients had a high prevalence of sweat allergy. Our findings support the hypothesis that allergy to *Malassezia* species is also related to sweat allergy in CholU-PA patients. To note, wheals by CholU-PA often appeared in lesions where there were eczematous reaction as atopic dermatitis, implying the possibility that sweat leaking easily occur in the lesions, induce sensitization to sweat and subsequently sweat allergy induces eczematous reaction and urticarial reaction in the lesions. In contrast, conjunctival sensitization with hydrolyzed wheat protein in soap induced a marked angioedema of the eyelids in cases of wheat-dependent exercise-induced anaphylaxis sensitized with hydrolyzed wheat proteins [9]. In addition, the mean age of patients with CholU-PA was higher than in those with ordinary CholU (mean age=21.8 years), indicating that a strong hypersensitivity to sweat might be acquired by repetitive facial sensitization to sweat [5].

Some patients with severe CholU often respond poorly to H1RA [10], and our data demonstrated that strong hypersensitivity to sweat in CholU-PA patients tended to be refractory to H1RA therapy. The addition of H2RA to H1RA treatment improved clinical symptoms in some of the refractory patients with CholU-PA, confirming the findings of a previous study that reported the benefit of H2RA for refractory CholU [10]. Furthermore, we found that some patients were successfully treated with

**Table 1**  
Clinical characteristics of patients with cholinergic urticaria with palpebral angioedema.

| Patient | Age | Sex | History      | Accompanying symptoms | EPT              | ASwST  | ASST | Serum IgE [IU/ml] | HRT <sup>b</sup> (Sweat) | IgE-RAST ( <i>Malassezia</i> ) [UA/ml] | IgE-RAST ( <i>Candida</i> ) [UA/ml] | Effect of H1-antagonist alone |
|---------|-----|-----|--------------|-----------------------|------------------|--------|------|-------------------|--------------------------|----------------------------------------|-------------------------------------|-------------------------------|
| 1       | 45  | F   | AD, AR       | None                  | (+)              | 1/1000 | (–)  | 1590.1            | 3                        | 2.89                                   | <0.10                               | (–)                           |
| 2       | 28  | F   | AD           | CoU, An               | (+)              | 1/1000 | (–)  | 2170              | 4                        | 25.90                                  | 2.20                                | (–)                           |
| 3       | 18  | F   | AD, BA       | An                    | (+)              | 1/1000 | (–)  | 2279.8            | 3                        | ND                                     | ND                                  | (–)                           |
| 4       | 28  | F   | BA           | An                    | (+)              | 1/100  | (–)  | 1305              | 4                        | 12.00                                  | 0.45                                | (–)                           |
| 5       | 41  | F   | AD, alopecia | CoU                   | (+)              | 1/100  | (–)  | 114.2             | 1                        | 0.56                                   | <0.10                               | (+)                           |
| 6       | 45  | F   | BA, AR       | None                  | (–) <sup>a</sup> | 1/100  | (–)  | 716.2             | 0                        | 0.63                                   | 3.16                                | (+)                           |
| 7       | 37  | F   | AD           | An                    | (–) <sup>a</sup> | 1/100  | (–)  | 247               | 0                        | 2.52                                   | 0.19                                | (+)                           |
| 8       | 34  | F   | AD, AR       | CoU                   | (+)              | 1/100  | (–)  | 364               | 4                        | ND                                     | ND                                  | (–)                           |
| 9       | 27  | F   | AD           | None                  | (–) <sup>a</sup> | 1/100  | (–)  | 1010.6            | 3                        | 10.90                                  | 2.02                                | (+)                           |
| 10      | 30  | F   | AD           | None                  | (+)              | 1/1000 | (+)  | ND                | 0                        | 1.25                                   | 2.09                                | (–)                           |
| 11      | 42  | F   | None         | CoU                   | (+)              | 1/1000 | (+)  | 113.3             | 0                        | ND                                     | ND                                  | (+)                           |
| 12      | 17  | F   | AD           | An                    | (+)              | 1/100  | (–)  | 82                | 0                        | <0.10                                  | <0.10                               | (+)                           |
| 13      | 45  | F   | AD, BA       | An                    | (+)              | 1/100  | (–)  | 4147              | 3                        | ND                                     | ND                                  | (–)                           |
| 14      | 27  | F   | AD, BA, AR   | An                    | (+)              | 1/1000 | (+)  | 1020.3            | 4                        | 12.00                                  | 1.90                                | (–)                           |
| 15      | 15  | F   | AR, BA       | None                  | (+)              | 1/1000 | (+)  | ND                | 0                        | 8.60                                   | 0.37                                | (–)                           |

EPT: exercise provocation test, ASwST: autologous sweat skin test, ASST: autologous serum skin test, HRT: histamine release test, RAST: radioallergosorbent test, AD: atopic dermatitis, AR: allergic rhinitis, BA: bronchial asthma, CoU: cold urticaria, An: anaphylaxis, ND: not done.

<sup>a</sup> All patients with negative EPT showed a positive reaction in the bathing provocation test.

<sup>b</sup> Results were expressed as an index value (0: negative, 1: weakly positive, 2: positive, 3–4: strongly positive) according to the manufacturer's instructions.

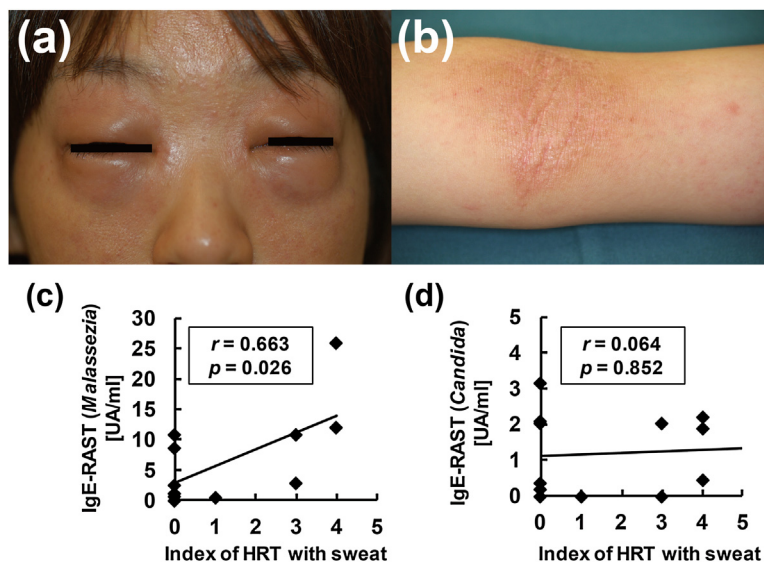


**Fig. 1.** (a) Typical appearance of cholinergic angioedema: prominent edema of eyelids with small (2–3 mm) wheals on the face. (b) Coalescent wheals developing around cubital fossa where eczematous lesions with atopic dermatitis remain. (c) Correlation between serum IgE-RAST levels for *Malassezia* species and index of HRT with sweat. (d) Correlation between serum IgE-RAST levels for *Candida* species and index of HRT with sweat. Data were analyzed by linear regression analysis using Prism6 software (GraphPad Software, Inc., San Diego, CA). A *p* value of <0.05 was considered statistically significant.

local olopatadine eye drops, suggesting that secreted histamine in the eyelids might be involved in the pathogenesis of the symptoms.

The main strength of our study was the identification of a new characteristic subtype, CholU-PA, which mainly occurs in females who have atopic diathesis. CholU-PA is a severe subtype of CholU with sweat hypersensitivity. A high value of IgE-RAST for *Malassezia* species might predict sweat hypersensitivity, which in turn might indicate a condition refractory to H1RA treatment. Further studies are needed to clarify the allergenicity of *Malassezia* antigens for CholU-PA patients.

## Conflicts of interest

The authors have no conflict of interest to declare

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jdermsci.2016.11.001>.

## References

- [1] M.W. Greaves, F. Lawlor, Angioedema: manifestations and management, *J. Am. Acad. Dermatol.* 25 (1991) 155–165.

- [2] A.P. Kaplan, M.W. Greaves, Angioedema, *J. Am. Acad. Dermatol.* 53 (2005) 373–388.
- [3] A.P. Kaplan, S.F. Natbony, A.P. Tawil, L. Fruchter, M. Foster, Exercise-induced anaphylaxis as a manifestation of cholinergic urticaria, *J. Allergy. Clin. Immunol.* 68 (1981) 319–324.
- [4] T. Kato, H. Komatsu, H. Tagami, Exercise-induced urticaria and angioedema: reports of two cases, *J. Dermatol.* 24 (1997) 189–192.
- [5] A. Fukunaga, T. Bito, K. Tsuru, A. Oohashi, X. Yu, M. Ichihashi, C. Nishigori, T. Horikawa, Responsiveness to autologous sweat and serum in cholinergic urticaria classifies its clinical subtypes, *J. Allergy. Clin. Immunol.* 116 (2005) 397–402.
- [6] J.E. Kim, K.H. Jung, H.H. Cho, H. Kang, Y.M. Park, H.J. Park, J.Y. Lee, The significance of hypersensitivity to autologous sweat and serum in cholinergic urticaria: cholinergic urticaria may have different subtypes, *Int. J. Dermatol.* 54 (2015) 771–777.
- [7] M. Hiragun, T. Hiragun, K. Ishii, H. Suzuki, A. Tanaka, Y. Yanase, S. Mihara, Y. Haruta, N. Kohno, M. Hide, Elevated serum IgE against MGL\_1304 in patients with atopic dermatitis and cholinergic urticaria, *Allergol. Int.* 63 (2014) 83–93.
- [8] T. Hiragun, K. Ishii, M. Hiragun, H. Suzuki, T. Kan, S. Mihara, Y. Yanase, J. Bartels, J.M. Schröder, M. Hide, Fungal protein MGL\_1304 in sweat is an allergen for atopic dermatitis patients, *J. Allergy. Clin. Immunol.* 132 (2013) 608–615.
- [9] Y. Fukutomi, Y. Itagaki, M. Taniguchi, A. Saito, H. Yasueda, T. Nakazawa, H. Hasegawa, H. Nakamura, K. Akiyama, Rhinoconjunctival sensitization to hydrolyzed wheat protein in facial soap can induce wheat-dependent exercise-induced anaphylaxis, *J. Allergy. Clin. Immunol.* 127 (2011) 531–533.
- [10] M. Hatakeyama, A. Fukunaga, K. Washio, K. Ogura, Y. Yamada, T. Horikawa, C. Nishigori, 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.* 82 (2016) 137–139.

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Table S1. Contingency table for sweat hypersensitivity and effect of H1 receptor antagonists (H1RA)

|                                    | Cases | H1RA effective | H1RA resistant |
|------------------------------------|-------|----------------|----------------|
| Strong sweat hypersensitivity: Yes | 11    | 2              | 9              |
| Strong sweat hypersensitivity: No  | 4     | 4              | 0              |

$p = 0.0110$  by two-tailed Fisher's exact test. We defined "strong sweat hypersensitivity" as cases with a positive result of 1/1000 diluted ASwST or with HRT values  $\geq 3$ .