

図6 臨床症状

97%の症例が小麦摂取後にアレルギー症状を発症していた。

([http://www.jsaweb.jp/modules/news\\_topics/index.php](http://www.jsaweb.jp/modules/news_topics/index.php) より)

### 3. 臨床症状

#### 1) 洗顔後と小麦摂取後のアレルギー症状の組み合わせ

洗顔後に眼が腫れる、顔に蕁麻疹がでるなどのアレルギー症状と小麦摂取後アレルギー症状の両方の症状があった症例は67%、洗顔後の症状はなく小麦摂取後アレルギー症状ありが30%、洗顔後症状も小麦摂取後のアレルギー症状もなしが3%だった。つまり、97%の症例は小麦摂取後にアレルギー症状を発症していた(図6)。

#### 2) 洗顔後の症状

洗顔後に症状のないものが30%だった(図7)。眼瞼の腫脹、蕁麻疹、痒みが多くみられたが、呼吸困難、ショック症状をきたした症例はなかった。

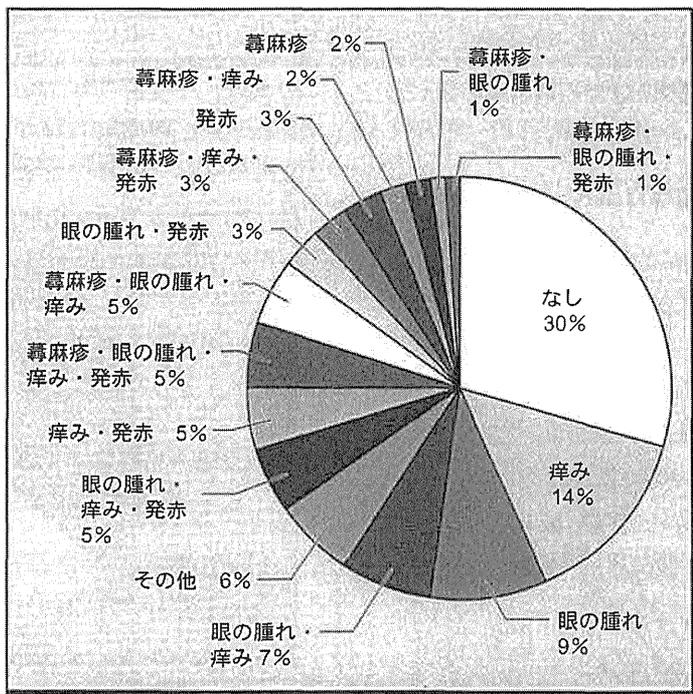


図7 洗顔中もしくは洗顔後の使用部位の皮膚症状

洗顔後に症状のない症例が30%であった。痒みや腫れ、蕁麻疹などはみられるものの、ショック症状を起こした症例はなかった。

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3) 小麦摂取後の症状

アナフィラキシーショックは25%、ショック症状はないが呼吸困難・嘔吐や下痢を生じた症例は27%あり、合計52%がアナフィラキシー症状を起こしていた(図8)。アナフィラキシー以外の蕁麻疹・眼の腫れ・鼻閉・鼻水・痒みなどは45%でみられた。

4) 運動や非ステロイド抗炎症薬内服での症状の誘発

(旧)茶のしずく石鹼コムギアレルギー症例も症状発現時に運動負荷ありが56%で、非ステロイド系抗炎症薬(NSAID)を内服していた人が16%いた。NSAID内服例は合計26例で、(旧)茶のしずく石鹼コムギアレルギー全体の10%を占め、アスピリンが11例で最も多く、次いでロキソプロフェン8例、イブプロフェン6例、ジクロフェナク1例などだった。また、抗アレルギー薬を内服していたが症状が誘発されたと答えた人は6例だった。

V. (旧)茶のしずく石鹼コムギアレルギーまとめ

- ・(旧)茶のしずく石鹼等に含まれたグルパール19S(GP19S)が原因物質である。当該石鹼の使用がコムギアレルギー症状発症に先行していた。
- ・94%が女性で大半を占めた。最年少1歳、最年長93歳であるが全体的には20歳代から60歳代に多く、ピークは40歳代であった。少人数ではあるが小児例も認められた。
- ・臨床症状は、眼瞼の著明な浮腫、顔面の全体的な腫脹、かゆみ、鼻汁などが特徴的であった。小麦摂取後にほぼ全例でこれらの顔面症状が出

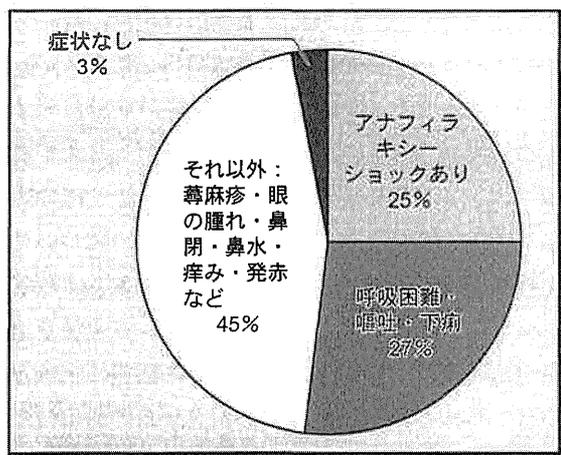


図8 アナフィラキシーショックの有無

アナフィラキシーショック症例25%、呼吸困難・嘔吐・下痢を生じた症例27%であり、52%がアナフィラキシー症状を起こしていた。

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現していたが洗顔時に症状がない症例が30%あった。小麦摂取後の即時型アレルギーは重症度が高く、25%でショック症状、それを含む52%でアナフィラキシー症状を呈していた。

従来の小麦依存性運動誘発性アナフィラキシーと異なり、買い物や家事などの軽度の運動で症状が誘発されたり、運動負荷がなくてもアナフィラキシー症状が誘発された症例もあった。

VI. 加水分解コムギ含有石鹼をはじめとする化粧品の安全性

今回の事例は、皮膚から吸収されたコムギ由来の加水分解タンパク質が経皮・経粘膜吸収されたことにより小麦に交叉反応するIgE (immunoglobulin E)を産生させ、小麦摂取で重篤な即時型アレルギーを発症させた。現在、化粧品や医薬

NSAID (非ステロイド系抗炎症薬)

IgE (immunoglobulin E)

部外品(薬用化粧品)の製造販売前の化粧品成分の即時型アレルギーの試験は必須項目には入っていない<sup>3), 4)</sup>。また、2009年から化粧品成分に対する動物実験の禁止、および化粧品の販売禁止が適用され、2013年よりその拡大が予定されている<sup>5)</sup>。経皮感作による即時型アレルギーについては動物実験もまだ十分には確立されておらず代替法もない。このような状況において、安全性を確保する市販前の試験法の標準化と市販後に化粧品の有害事象を早期に把握するシステムの構築は急務といえる。

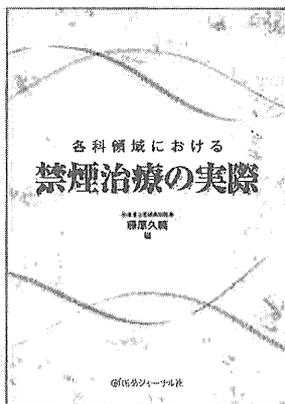
## おわりに

本稿では、同一の加水分解コムギ末を含有した石鹸により感作されたコムギアレルギーの疫学調査の結果を解説した。この一連の事象は、“経皮・経粘膜的に感作された食物アレルギー”として注目されるのみでなく、化粧品における安全性の評価において、評価項目にも入っていなかった“香

粧品における即時型アレルギーの評価の必要性”を我々に気づかせることとなった。今後、社会的な取り組みが進み、化粧品の安全性が確保されることを期待したい。

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# The Sensitivity and Clinical Course of Patients with Wheat-Dependent Exercise-Induced Anaphylaxis Sensitized to Hydrolyzed Wheat Protein in Facial Soap - Secondary Publication

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## ABSTRACT

**Background:** Recently, an increasing number of patients with wheat-dependent exercise-induced anaphylaxis (WDEIA) have been reported in Japan. Most of them had developed this condition during or after using hydrolyzed wheat protein (HWP)-containing soap (HWP-WDEIA).

**Methods:** To clarify the relation between WDEIA and HWP-containing soap and their prognosis, we retrospectively studied the patients who visited Hiroshima University Hospital and were diagnosed as WDEIA from January 2010 to June 2011. We took detailed clinical histories, performed skin prick tests, serum immunoassays for antigen-specific IgE and basophil histamine release test, and followed up their clinical courses after the diagnosis.

**Results:** Among 36 patients with WDEIA, 30 patients had used only one type of HWP-soap. The patients with HWP-WDEIA were mainly women and had developed facial symptoms and angioedema. They suffered from blood pressure reductions less frequently than patients with conventional WDEIA. The levels of gluten-specific IgE were higher than those of omega-5 gliadin in patients with HWP-WDEIA ( $P < 0.05$ , One-way ANOVA). All patients with HWP-WDEIA were positive against HWP in histamine release test. Among the conventional wheat antigens, glutenins induced the highest histamine release from basophils of patients with HWP-WDEIA. The sensitivities of patients against glutes and glutenins were reduced over months along with the discontinuance of HWP-soap.

**Conclusions:** The development of HWP-WDEIA is associated with the use of HWP-soap. The sensitivity to HWP that cross reacts with non-processed wheat may be reduced or possibly cured after the discontinuation of HWP-soap.

## KEY WORDS

clinical course, histamine release test, hydrolyzed wheat protein (HWP), IgE, wheat-dependent exercise-induced anaphylaxis (WDEIA)

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## INTRODUCTION

Hydrolyzed wheat protein (HWP) is obtained by hydrolyzing wheat with acids or enzymes. Because of its non-irritating and long-lasting foaming activity, HWP is widely used for numerous kinds of soaps, shampoos, creams, etc.<sup>1,2</sup> instead of chemical foaming compounds. Recently, cases of wheat allergy caused by HWP<sup>1-3</sup> have been reported. Snegaroff *et al.*<sup>3</sup> reported that some cases developed as wheat-dependent exercise-induced anaphylaxis (WDEIA). In Japan, many cases have been reported concerning patients who developed WDEIA after the use of HWP-containing soap,<sup>4,7</sup> and all of the patients reported to date have used the same product (A case of HWP-WDEIA<sup>5</sup> sensitized to HWP regarding another brand of soap was reported after the first publication of this article.).

In our hospital, the number of patients with WDEIA has greatly increased since 2010 and most cases had histories of HWP-containing soap usage. In this study, we report clinical characteristics, results of examinations, managements, and clinical courses of patients with WDEIA who visited our hospital in 2010 and 2011.

## METHODS

### SUBJECTS

Patients, who were diagnosed as WDEIA in Hiroshima University Hospital within 18 months (from January 2010 to June 2011), were evaluated, retrospectively. We classified WDEIA into two groups, one was a hydrolyzed wheat protein-WDEIA (HWP-WDEIA) group who had used HWP-containing soap before the development of WDEIA, and another was a conventional WDEIA (Co-WDEIA) group who had not used soap or cosmetics containing HWP. The diagnosis of WDEIA was made if a patient had a history of one or more incidences of anaphylaxis, and/or two or more allergic symptoms, after exercise, and showed a positive result in clinical examinations for wheat allergy, including, skin prick test, antigen-specific IgE, and histamine release test.

### METHODS

From interview sheets and charts, we checked age, sex, use of HWP-containing soap, past history (especially about allergic diseases), clinical symptoms (face symptoms, urticaria, angioedema, respiratory symptoms, abdominal symptoms, and blood pressure reduction), and its onset, history of hospitalization, and use of epinephrine.

The minimum quantity of exercise to develop symptoms was classified as grade 1: daily living activities such as bathing or housekeeping; grade 2: light exercise, such as walking or shopping; grade 3: jogging or other sports.

Clinical symptoms were classified as grade 1: only

skin symptoms; grade 2: anaphylaxis of non-cutaneous organs without reduction of blood pressure; grade 3: anaphylaxis accompanying a reduction of blood pressure.

Skin prick tests (SPT) for wheat and bread were examined using prick lancets (Yayoi Co., Ltd., Tokyo, Japan) and allergen scratch extracts (Torii Pharmaceutical Co., Ltd., Tokyo, Japan). The response was classified as semi-positive ( $\pm$ ), positive (+), when they were >25%, 50%, respectively, of the positive control response induced by histamine chloride at 10 mg/ml,<sup>7</sup> negative when the average wheal diameters were the same as those of the negative control (saline), or smaller than those of semi-positive after 15 minutes.

We collected data of the specific IgE against wheat, gluten, and omega-5 gliadin (Imuno-CAP<sup>®</sup> Phadia AB, Uppsala, Sweden).

For histamine release tests (HRT), basophils were obtained from the peripheral blood of patients and were incubated with antigens. We defined % histamine release as (histamine released into the buffer)/(total histamine). We defined as positive if net % histamine release (difference between % histamine release in response to antigens and that in buffer) was 5% or more. Basophils were stimulated by gliadin-mix (TCI, Tokyo, Japan), glutenin-mix (TCI), omega-5 gliadin<sup>8</sup> and HWP (Glupal-19S) (Katayama Chemical, Inc., Osaka, Japan) contained in the soap used by patients. Since we obtained HWP in May 2010, we performed HRT against HWP only when patients revisited our hospital after stopping the use of HWP-containing soap, except for one patient who first visited our hospital in June 2010.

All analyses were performed using Graph Pad Prism 5 (Graph Pad Software, San Diego, CA, USA).

This study was approved by the Ethics Committee of the Hiroshima University (No. 445).

## RESULTS

### CLINICAL CHARACTERISTICS OF PATIENTS WITH WDEIA-DEMOGRAPHY- (Table 1)

We diagnosed 40 patients as WDEIA, and 36 of them were checked for whether they had used the HWP-containing soap or not.

Among the 36 patients, 30 patients were diagnosed as HWP-WDEIA, 4 patients as Co-WDEIA, and 2 patients were unclassified because of uncertain histories. The HWP-containing soap used by the patients was the product of a company (Cha-no-Shizuku<sup>®</sup>, Yuhka, Fukuoka, Japan).

All patients with WDEIA consisted of 7 males and 33 females, and the mean age was 37.6 years old (male 24, female 40.5).

The patients with HWP-WDEIA consisted of 2 males and 28 females, and their mean age was 40.3  $\pm$  16.9 years old. The mean age of 2 males and 2 females with Co-WDEIA was 36.8  $\pm$  6.2 years old.

**Table 1** Clinical characteristics of patients with WDEIA -Demography-

	HWP-WDEIA	Co-WDEIA
Number of patients	30	4
Average of age (years)	40.3 (15-75) <sup>†</sup>	36.8 (30-43) <sup>†</sup>
Gender (Male : Female)	2 : 28	2 : 2
Use periods of HWP-soap by the onset (months)	12.8 (0.5-48)	none
Total use periods of HWP-soap (months)	18.1 (1-60)	none
Complication of eczema (History of eczema)	6/30 (10/30)	0/4 (1/4)

<sup>†</sup> Range of age; WDEIA, wheat-dependent exercise-induced anaphylaxis; HWP-WDEIA, hydrolyzed wheat protein-WDEIA; Co-WDEIA, conventional WDEIA.

Duration of the use of HWP-containing soap among 29 patients with HWP-WDEIA was from less than one month to 48 months and the average was 12.8 ± 13.1 months.

Regarding complication of other allergic diseases with HWP-WDEIA, six patients (4) suffered from atopic dermatitis, 2 (4), 4 (4), and 3 (2) patients were suffering from asthma, allergic rhinitis and allergic conjunctiva, respectively (the numbers in parenthesis mean the number of patients with respective complications only in the past history). In patients with Co-WDEIA, only one out of four patients had a past history of atopic dermatitis.

**CLINICAL SYMPTOMS OF PATIENTS WITH WDEIA**

Symptoms of patients with HWP-WDEIA were as follows: urticaria 27/30 (90.0%), angioedema 22/29 (75.8%), respiratory symptoms 22/28 (78.6%), facial symptoms 18/30 (60.0%), decreases of blood pressure 11/28 (39.3%), abdominal symptoms 7/30 (23.3%).

Six patients needed hospitalization and 3 patients had taken an injection of epinephrine.

We could evaluate the minimum quantity of exercise in 26 patients with HWP-WDEIA (grade 1: 6, grade 2: 15, grade 3: 5). Those in patients with Co-WDEIA were grade 2 in two patients and grade 3 in one patient.

Durations of symptoms in patients with HWP-WDEIA tended to be longer than those in patients with Co-WDEIA. In patients with HWP-WDEIA, 10 out of 24 patients suffered from symptoms for more than 3 to 4 days in each attack, eight patients for 2 hours to 1 day, and six patients for 2 hours or less. Durations of symptoms were confirmed in two patients with Co-WDEIA, and those of both patients were less than 2 hours.

**Table 2** Clinical characteristics of patients with WDEIA -Symptoms and skin reactions in prick test-

	HWP-WDEIA	Co-WDEIA
Urticaria	27/30 (90%)	4/4 (100%)
Angioedema	22/29 (76%)	1/3 ( 33%)
Respiratory symptom	22/28 (79%)	2/2 (100%)
Face flash or itchy	18/30 (60%)	1/4 ( 25%)
Blood pressure reductions	11/28 (39%)	2/3 ( 67%)
Abdominal symptom	7/30 (23%)	1/3 ( 33%)
Skin prick test Wheat (Tarii)	18/22 (82%)	2/2 (100%)
Bread (Tarii)	17/22 (77%)	3/3 (100%)

WDEIA, wheat-dependent exercise-induced anaphylaxis; HWP-WDEIA, hydrolyzed wheat protein-WDEIA; Co-WDEIA, conventional WDEIA

**SKIN PRICK TEST**

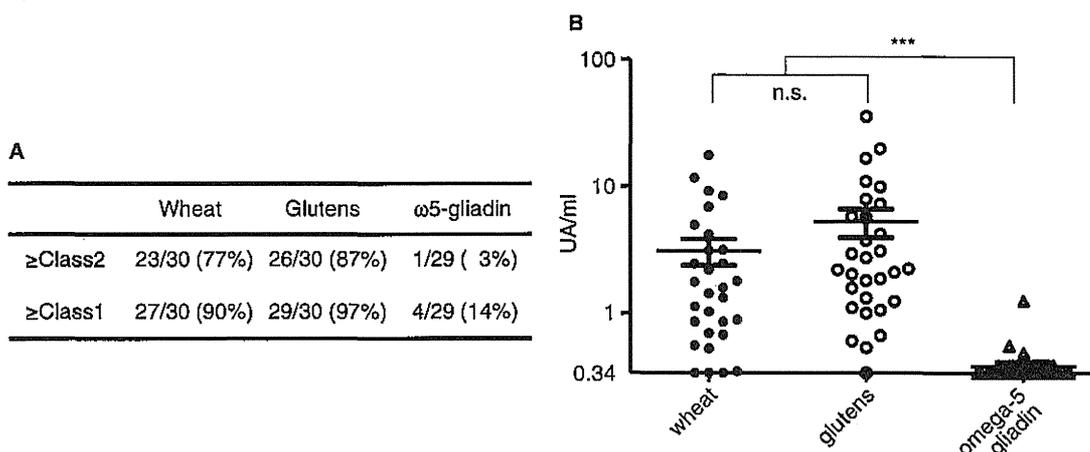
Patients with HWP-WDEIA presented high positive rates of skin prick test for wheat 18/22 (81.8%), bread 17/22 (77.8%), but three patients were negative for both antigens (Table 2).

**MEASUREMENT OF ANTIGEN-SPECIFIC IgE IN PATIENTS WITH HWP-WDEIA**

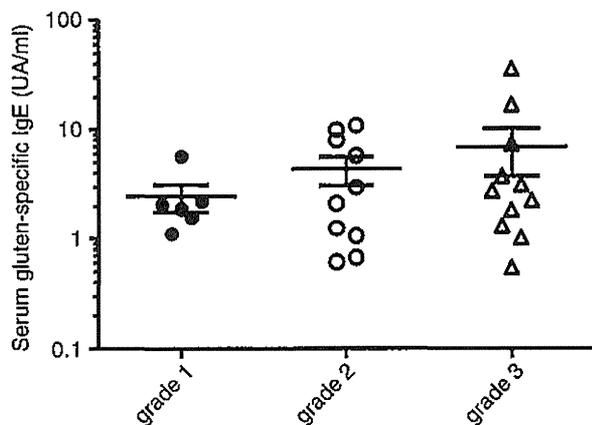
The antigen-specific IgE in patients with HWP-WDEIA were as follows; wheat-specific IgE (CAP-WEIA): class 2 or more 23/30 (76.7%), class 1 or more 27/30 (90.0%); gluten-specific IgE (CAP-GEIA): class 2 or more 26/30 (86.7%), class 1 or more 29/30 (96.7%); omega5-gliadin-specific IgE (CAP-WEIA): class 2 or more 1/29 (3.4%), class 1 or more 4/29 (13.8%) (Fig. 1A). The levels of omega5-gliadin-specific IgE were statistically lower than those of the other wheat antigens (one-way ANOVA, *P* < 0.05) (Fig. 1B). The levels of gluten-specific IgE tended to be high in correlation with the grade of symptoms. However, there was no statistical difference among gluten-specific IgE of patients in each clinical grade (one-way ANOVA) (Fig. 2), presumably due to a large dispersion of the values of specific IgE. The numbers of peripheral blood eosinophil and total IgE were 3.5% (1.1-13.3%) and 357.6 IU/ml (41.6-2459 IU/ml) on average, respectively.

**HISTAMINE RELEASE TEST (HRT) OF BASOPHILS FROM PATIENTS WITH HWP-WDEIA**

HRTs against wheat allergens were performed in 28 patients with HWP-WDEIA. Four out of 28 patients were low-responders (net % histamine release against anti-IgE was less than 5%) and they were excluded from the analysis of positive rates in HRTs. Out of 24 patients (excluded low-responders), 11 (45.8%), 17 (70.8%) and four (16.7%) patients were positive when stimulated by gliadin-mix, glutenin-mix and omega5-gliadins, respectively, indicating glutenin as a major antigen. The negative rates of reaction to omega5-gliadin was statistically higher than those to the other



**Fig. 1** Serum antigen-specific IgE levels with HWP-WDEIA. **(A)** Positive rate of specific IgE against wheat antigens. **(B)** Levels of antigen-specific IgE against wheat and those against glutens were significantly higher than those against omega-5 gliadin. Values less than 0.34 were accounted as 0.34 UA/ml for statistical calculations. WDEIA, wheat-dependent exercise-induced anaphylaxis; HWP-WDEIA, hydrolyzed wheat protein-WDEIA; \*\*\**P* < 0.001, one way ANOVA.



**Fig. 2** Relation between serum gluten-specific IgE levels and grades of clinical symptoms in patients with HWP-WDEIA. Mean levels of gluten-specific IgE in grade 3 is the highest among 3 groups. There was no statistical difference among 3 clinical groups (One-way ANOVA). Grade 1: Patients had only skin symptoms, Grade 2: Patients had anaphylaxis symptoms, but not blood pressure reduction. Grade 3: Patients had histories of anaphylactic shock. WDEIA, wheat-dependent exercise-induced anaphylaxis; HWP-WDEIA, hydrolyzed wheat protein-WDEIA.

wheat antigens (one-way ANOVA, *P* < 0.05) (Fig. 3A, B).

HRTs against HWP were performed in 16 patients with HWP-WDEIA. All of them were positive, except for one low-responder patient (Fig. 3C, D). On the other hand, all patients with Co-WDEIA (2), atopic

dermatitis (4), cholinergic urticaria (1) were negative in reactions to HWP (data not shown).

**GLUTEN-SPECIFIC IgE AND PERIODS USING HWP-SOAP (Fig. 4)**

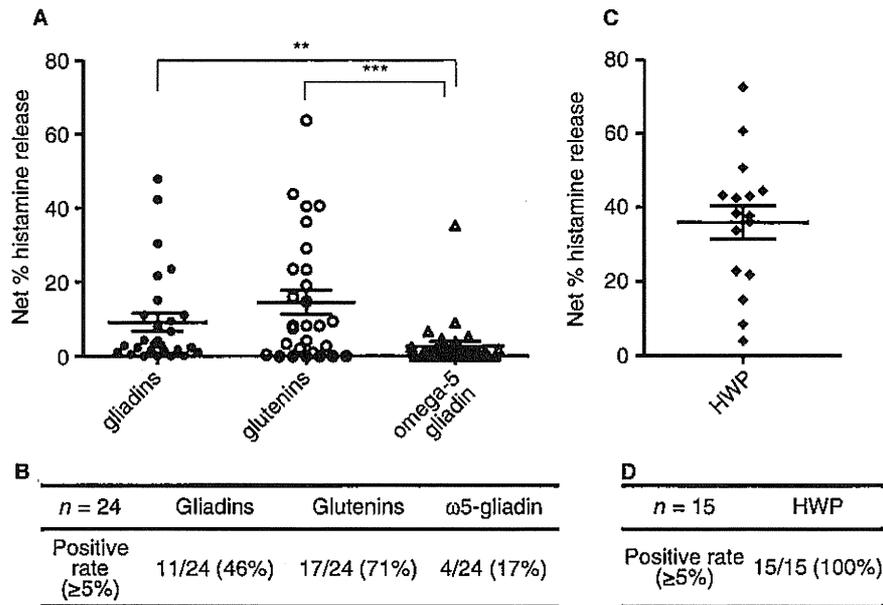
Levels of gluten-specific IgE were weakly correlated with periods using HWP-soap (*n* = 29).

**CHANGES OF HWP-HYPERSENSITIVITIES IN PATIENTS WITH HWP-WDEIA AFTER THE DISCONTINUATION OF HWP-SOAP USAGE**

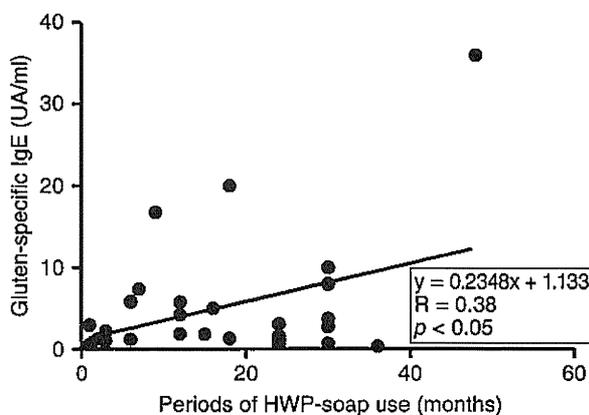
We could follow up gluten-specific IgE in 11 patients with HWP-WDEIA over subsequent months. Levels of gluten-specific IgE antibodies had slowly decreased after stopping the use of HWP-soap (Fig. 5A).

The ratio of net % histamine release in response to glutenin-mix over that of anti-IgE had significantly decreased after three months since stopping the use of HWP-containing soap (*P* < 0.05, Fig. 5B). HRT against three wheat antigens became completely negative in one of the six patients. We therefore had permitted her to take wheat and do exercise. She had one slight attack (mild angioedema and respiratory discomfort) when she exercised after eating some bread two weeks after the permission had been given. The symptoms were promptly cleared by taking an antihistamine. In the following five months, she did not suffer from any symptoms upon consuming wheat and exercising.

In total 12 patients revealed a decrease of wheat hypersensitivity represented by gluten-specific IgE or HRTs. Nine of them had been prohibited to eat wheat-containing food when they took oral NSAIDs



**Fig. 3** Histamine release tests in patients with HWP-WDEIA. (A) Histamine release in response to gliadins and that to glutenins were significantly higher than that against omega-5 gliadin ( $n = 28$ ).  $**P < 0.01$ ,  $***P < 0.001$ , one way ANOVA. (B) Positive rate of histamine release test against wheat antigens in patients with HWP-WDEIA. We defined  $\geq 5\%$  Net %histamine release as positive. The patients who had low response against anti-IgE ( $< 5\%$ ) were excluded from statistical calculations. (C) Histamine release against HWP containing soap that HWP-WDEIA patients used ( $n = 16$ ). Although some patients were already stopped the use of HWP-containing soap, levels of net% histamine release against HWP were still extremely high. (D) Positive rate of histamine release test against HWP in patients with HWP-WDEIA. All patients showed positive responses against HWP. We defined  $\geq 5\%$  Net %histamine release as positive. The patients who showed low responses against anti-IgE ( $< 5\%$ ) were excluded from statistical calculations. WDEIA, wheat-dependent exercise-induced anaphylaxis; HWP-WDEIA, hydrolyzed wheat protein-WDEIA; HWP, hydrolyzed wheat protein.

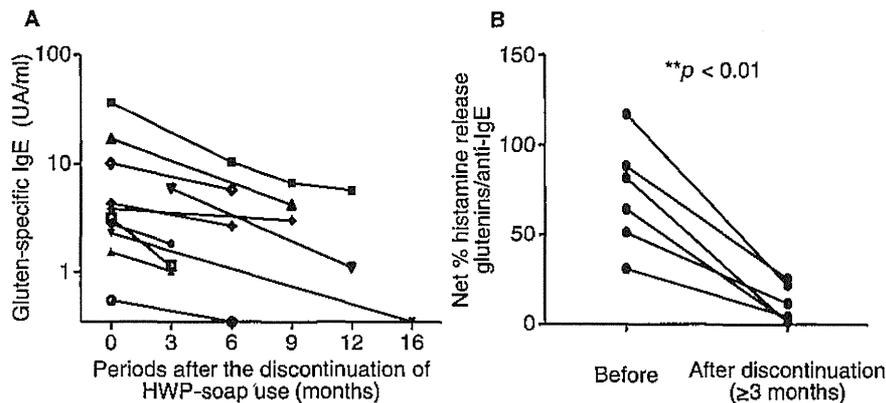


**Fig. 4** Gluten-specific IgE antibodies and periods of HWP-soap use ( $n = 29$ ). Levels of gluten-specific IgE were weakly correlated with periods of HWP-soap use. Values less than 0.34 were calculated as 0.34 UA/ml for statistical calculations. HWP, hydrolyzed wheat protein.

or exercise, but had been permitted to consume small amounts of wheat when they were resting. One patient consumed substantial amounts of wheat once a month and the other two patients were completely restricted from consuming wheat.

**DISCUSSION**

In this study, we demonstrated among our patients that: 1. The number of the patients with WDEIA increased and most of them were HWP-WDEIA; 2. the patients with HWP-WDEIA were mostly women, and older than the patients with Co-WDEIA; 3. the level of gluten-specific IgE tended to be high, and omega-5 gliadin tended to be low; 4. the same tendency was observed for HRT; 5. levels of gluten-specific IgE were weakly correlated with periods of HWP-containing soap usage; 6. the wheat-hypersensitivity of patients with HWP-WDEIA tended to decrease after stopping the usage of HWP-containing soap over months and could possibly be cured.



**Fig. 5** Changes of HWP-hypersensitivities in patients with HWP-WDEIA after the discontinuation of HWP-soap use. **(A)** Levels of gluten-specific IgE antibodies decreased after stopping the use of HWP-soap ( $n = 11$ ). **(B)** Histamine release in response to glutenins before and after the discontinuation of HWP-soap ( $n = 6$ ). WDEIA, wheat-dependent exercise-induced anaphylaxis; HWP, hydrolyzed wheat protein.

The number of patients with food-dependent exercise-induced anaphylaxis (FDEIA) who visited our hospital during a one year and six month period (from January 2010 to June 2011) was 46. In contrast, only five patients visited our hospital during an earlier 1 year and eight month period (from December 2003 to July 2005).<sup>9</sup> This observation indicated that the number of the patients with FDEIA had considerably increased recently. Moreover, the rate of WDEIA among FDEIA 87% (40/46) was larger than a previous report of Mochizuki, *et al* (57%).<sup>10</sup>

Hisamoto<sup>11</sup> reported that the mean age of 68 patients with FDEIA was 20.1 years, and that 48 (70.6%) were male and 20 (29.4%) were female. In our study, mean age of 46 patients with FDEIA was 37.6 years, and the numbers of male and female were 9 and 37, thus, relatively older and a higher rate being female. At first, we were not aware of the reason for such an increase in females, and age of patients with WDEIA. However, publications of similar reports about HWP-WDEIA in Japan prompted us to interview the patients about the use of particular soaps, resulting in the demonstration of a high rate (83.3% of whole WDEIA patients) of HWP-containing soap usage among the patients.

Many patients with HWP-WDEIA in our hospital had developed symptoms of face and angioedema, but the number of patients who had suffered from reduction of blood pressure and abdominal symptoms was small. Chinuki *et al.*<sup>12</sup> reported that the main symptoms of Co-WDEIA and HWP-WDEIA were urticaria (wheal) and angioedema (especially eyelids), respectively. They also reported that patients with Co-WDEIA experienced anaphylactic shock more often than patients with HWP-WDEIA. Another clinical difference between HWP-WDEIA and Co-WDEIA was the amount of exercise to evoke attacks. Six pa-

tients (22.2%) with HWP-WDEIA experienced attacks even after domestic work or taking a bath. Thus the symptoms of HWP-WDEIA may be induced easily by light exercise as compared with those of Co-WDEIA. Regarding the duration of attacks, those in patients with HWP-WDEIA tended to be longer (3-4 days in 41.7% patients), possibly due to the complication with angioedema.

SPT for wheat and bread were positive in 81.8% and 77.2% in patients with HWP-WDEIA, respectively. Namely, SPT was false negative in 18.2% patients with HWP-WDEIA. Most patients with HWP-WDEIA were negative in Immuno-CAP<sup>®</sup> for omega-5 gliadin-specific IgE. Even if omega-5 gliadin-specific IgE was positive, the levels of wheat- and gluten-specific IgE were higher than that of omega-5 gliadin-specific IgE. Fukutomi<sup>4</sup> and Chinuki<sup>7</sup> also pointed out that the levels of omega-5 gliadin-specific IgE were almost negative in patients with HWP-WDEIA. Therefore, positive wheat- and gluten-specific IgE and negative omega-5 gliadin-specific IgE may be taken as a proof to distinguish HWP-WDEIA from Co-WDEIA.

In accordance with antigen-specific IgE, histamine release in response to gliadins and glutenins were significantly higher than that to omega-5 gliadin. Even if patients had a positive response to omega-5 gliadin, the levels of histamine release were lower than that to glutenins in all-cases. HRTs against HWP were all positive except for one low-responder. These results suggest that patients with HWP-WDEIA were sensitized by HWP rather than by natural wheat.

One patient was entirely negative in SPT and antigen-specific IgE, but was positive in HRT against glutenins and omega-5 gliadin. Therefore, we diagnosed him as HWP-WDEIA with consideration of both positive HRT and his clinical history. In contrast, another patient was negative in SPT and a low-

responder in HRT, but both wheat- and gluten-specific IgE were positive. We diagnosed her as HWP-WDIEA with consideration of the detection of specific IgE by Immuno-CAP® and her clinical history. These results suggested that the importance of conducting multiple tests, especially when WDEIA was suspected based on their history, but a particular test gave a negative result against wheat and its components.

To clarify the relationship between the use of HWP-containing soap, and the onset of WDEIA, and/or their clinical data, we analyzed the correlation between the duration of HWP-soap usage and levels of gluten-specific IgE by regression analysis. It revealed that these factors were weakly, but significantly correlated ( $P < 0.05$ ). Fukutomi *et al.*<sup>4</sup> reported that the binding of specific IgE in sera from patients with HWP-WDEIA to HWP was fully inhibited by HWP, but not by natural wheat extracts. In our study, basophils from patients with HWP-WDEIA reacted substantially more strongly with HWP than that with other natural wheat antigens. These observations suggested that patients with HWP-WDEIA were previously sensitized to HWP via skin and mucosa by being exposed to HWP-containing soap. Chinuki *et al.*<sup>7</sup> speculated that one of the reasons for sensitization to HWP by the usage of HWP-containing soap was due to destruction of skin barrier function by detergents contained in the soap. Although they reported that only one out of 12 patients with HWP-WDEIA was complicated with atopic dermatitis, six out of 30 (20%) patients had been suffering from atopic dermatitis in this study. Taking into account that the prevalence of atopic dermatitis in Japan was 2.5% in the 50 to 59 year age group, 4.8% in 40 to 49 year age group, 8.3% in 30 to 39 year age group and 9.4% in 20 to 29 year age group,<sup>13</sup> patients with atopic dermatitis may be susceptible to the development of HWP-WDEIA.

Information about clinical course of wheat allergy in adult onset, including Co-WDEIA, was limited, especially about remission. Our data on the decreases of wheat-hypersensitivities in patients with HWP-WDEIA after the discontinuation of HWP-soap usage not only suggest the relation between the usage of HWP-containing soap and the onset of HWP-WDEIA, but also imply the possibility of improvement of such hypersensitivity against wheat. In our hospital, we recommend that patients with HWP-WDEIA avoid the combination of wheat and exercise rather than complete avoidance of wheat products. Nine out of 12 patients with gluten-specific IgE and/or the reactivity against glutenin in HRT continued to eat small amounts of wheat and decreased their sensitivities. We could not find a significant difference of remission rate of wheat-hypersensitivity between the group with complete avoidance of wheat and that with continuous taking of small amounts of wheat. It is feasible that continuous intake of wheat might have led a

tolerance rather than allergy.<sup>14</sup> Reports from multiple institutions are needed to clarify the influence of oral intake of wheat on the hypersensitivity against wheat after the discontinuation of HWP-soap usage.

All patients with HWP-WDEIA in this study and previously reported in Japan had used the same kind of soap (Cha-no-Shizuku®). However, this HWP (Glupal-19S) had also been contained in many other cosmetics of other companies. The reason why there are no reports about other cosmetics is unclear (A case of HWP-WDEIA<sup>15</sup> sensitized to HWP regarding another brand of soap was reported after the first publication of this article.). Since as many as forty-six million bars of Cha-no-Shizuku® were sold in Japan from 2004 to 2010, it may be simply due to such a very large number of people exposed to this soap. Alternatively, the composition of other ingredients and the way of using the soap might also be important and should be a subject for investigation. The company that sold Cha-no-Shizuku® has launched a self-imposed recall of the item and excluded HWP from the new lots of this soap. Moreover, the company that made Glupal-19S has already stopped making and distributing HWP. Therefore, the number of patients with HWP-WDEIA is expected to decrease in the future. However, since other types of HWP are still contained in many products such as cosmetics and foods, further analysis is needed to clarify whether only Glupal-19S among HWPs have a sensitizing capacity or other HWPs could also have such activity.

## ACKNOWLEDGEMENTS

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## Present state of Japanese cedar pollinosis: The national affliction

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Seasonal allergic rhinitis (SAR) caused by Japanese cedar pollen (JCP; ie, sugi-pollinosis) is the most common disease in Japan and has been considered a national affliction. More than one third of all Japanese persons have sugi-pollinosis, and this number has significantly increased in the last 2 decades. In our opinion the reason why sugi-pollinosis became a common disease in the last half century is the increased number of cedar pollens, with global climate change and forest growth caused by the tree-planting program of the Japanese government after World War II playing substantial roles; dust storms containing small particulate matter from China might also contribute to the increased incidence of sugi-pollinosis. To help minimize their symptoms, many Japanese wear facemasks and eyeglasses at all times between February and April to prevent exposure to JCP and aerosol pollutants. Forecasts for JCP levels typically follow the weather forecast in mass media broadcasts, and real-time information regarding JCP levels is also available on the Internet. Because a large amount of JCP is produced over several months, it can induce severe symptoms. Japanese guidelines for allergic rhinitis recommend prophylactic treatment with antihistamines or antileukotrienes before the start of JCP dispersion. Additionally, sublingual

immunotherapy will be supported by health insurance in the summer of 2014. However, many patients with sugi-pollinosis do not find satisfactory symptom relief with currently available therapies. Collaboration between scientists and pharmaceutical companies to produce new therapeutics for the control of sugi-pollinosis symptoms is necessary. (*J Allergy Clin Immunol* 2014;133:632-9.)

**Key words:** Seasonal allergic rhinitis, Japanese cedar, global climate change, prophylactic treatment, alternative complementary treatments

Allergic rhinitis (AR) represents a global health care problem that greatly affects daily activity, work productivity, learning, sleep, and quality of life (QOL) in persons of all ages. In the Allergic Rhinitis and its Impact on Asthma study, AR is divided into 2 categories: intermittent or persistent disease.<sup>1</sup> However, many otorhinolaryngologists in Japan use a perennial allergic rhinitis (PAR) and seasonal allergic rhinitis (SAR) classification system.<sup>2</sup> The major allergen contributing to SAR in Japan is pollen from the Japanese cedar (*Cryptomeria japonica*; ie, sugi). SAR is caused by Japanese cedar pollen (JCP; ie, sugi-pollinosis) and was first reported in 1963.<sup>3</sup> During the height of the allergy season (between February and April), a large number of patients with sugi-pollinosis experience more severe symptoms for longer periods of time compared with other pollen allergies (Fig 1, A). This might be because JCP is dispersed in large quantities over long distances (>100 km in some cases) and can remain airborne for more than 12 hours (Fig 1, B).<sup>4</sup> Furthermore, pollen from the Japanese cypress (*Chamaecyparis obtusa*), which also causes SAR, is dispersed in April and May, immediately after the release of JCP. Because Japanese cypress pollens are considered to contain several components that cross-react with JCP, 70% of patients with sugi-pollinosis also experience SAR caused by Japanese cypress pollen. Therefore allergic symptoms can last for as long as 4 months, from February to May, with some variation caused by annual climate differences.

A meta-analysis of 38 reports representing 27 prevalence subgroups and 134 sensitization rate subgroups showed that the prevalence of sugi-pollinosis increased 2.6-fold between 1980 and 2000.<sup>5</sup> The prevalence of sugi-pollinosis was 19.4% of the Japanese population in 2001.<sup>6</sup> We conducted a survey of 1540 persons aged 20 to 49 years in Fukui City between 2006 and 2007 that indicated the positive rate of serum JCP-specific IgE was 56.3% and the prevalence of sugi-pollinosis was 36.7%.<sup>7</sup> Additionally, the International Study of Asthma and Allergies in Childhood showed that Tokyo schoolchildren have an extremely high prevalence of SAR.<sup>8,9</sup> Specific to Japan, SAR-JCP is now called a national affliction. Manufacturers and

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*Abbreviations used*

AD:	Asian dust
apoA-IV:	Apolipoprotein A-IV
AR:	Allergic rhinitis
GWAS:	Genome-wide association study
JCP:	Japanese cedar pollen
PAR:	Perennial allergic rhinitis
PM:	Particulate matter
PM2.5:	Particulate matter less than 2.5 $\mu\text{m}$ in diameter
QOL:	Quality of life
SAR:	Seasonal allergic rhinitis
SLIT:	Sublingual immunotherapy
Sugi-pollinosis:	Seasonal allergic rhinitis caused by Japanese cedar

retailers are set to tap into a soaring demand for medications and related items, and the market for JCP prescription drugs has soared to 200 to 300 billion yen per season (2.1-3.2 billion US dollars). Also, the government will be required to take effective actions.

In this review we introduce sugi-pollinosis, the national affliction of Japan, with the intention of informing allergists about the spectrum of symptoms and treatment options available for patients with sugi-pollinosis.

## **PUTATIVE TRIGGER FACTORS, ENVIRONMENT, AND PATHOLOGY FOR THE INCREASED PREVALENCE OF SUGI-POLLINOSIS**

In Japan forests cover approximately 25 million hectares (ie, 66% of the total area of Japan). More than half of these trees were planted from the early 1950s to the early 1970s, and according to the Forestry Agency of Japan, an estimated 4.6 billion of these are Japanese cedar trees, covering nearly 18% of the total land area of Japan. The sugi trees are extremely straight and tall, making them ideal construction materials, but after wood tariffs decreased in 1964, imported wood put the sugi foresters out of business, and most sugi trees have been abandoned and grow taller and produce more pollen each year. With the exception of Hokkaido and Okinawa islands, this yellow-green dust is scattered throughout Japan. Airborne JCP levels have been monitored in Sagami-hara hospital (Kanagawa, Japan) since 1965. JCP counts can vary significantly from year to year because of weather conditions; however, the total JCP counts from 1995 to 2013 have been significantly greater than those in the initial period from 1965 to 1994 ( $P < .05$ ; Fig 2, A).

Epidemiologic studies have demonstrated that global climate change correlates with the number of symptomatic pollen-induced respiratory allergies and allergic diseases.<sup>10,11</sup> One of the fundamental effects of climate change is the potential for shifts in flowering phenology and pollen production associated with warmer seasonal air temperatures. As such, the length of the sugi-pollinosis season has increased since 1995.<sup>12</sup> Although the average global temperature has only increased by approximately 0.6°C in the 20th century, climate change in Japan has been more severe, with temperatures increasing by an average of 1.15°C in the past 100 years. Fig 2, B, shows the annual temperature change since 1960 in Japan.

Cedar pollen is released from male flowers on sugi trees (Fig 1, C). Hot summers usually affect sugi trees, promoting flower bud development and increasing pollen production; meanwhile, cool

summers have opposite effects. Ito et al<sup>13</sup> investigated the correlation between total JCP count and the previous years' summer weather conditions from 1987 to 2006. The annual cumulative level of airborne JCP was significantly related to the mean temperature and sunlight hours in late July before the start of the pollen season (see Table E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). The mean temperature in July during the 20th century has also significantly increased in Japan. Average temperatures in the Fukui area from 1974 to 1993 and 1994 to 2012 were  $25.1^\circ\text{C} \pm 0.3^\circ\text{C}$  and  $26.2^\circ\text{C} \pm 0.3^\circ\text{C}$ , respectively ( $P < .05$ ; Fig 2, C). The weather of late winter and early spring was not correlated with JCP counts; however, temperatures in January and February did influence the start of sugi pollen production and the pollen season (data not shown).

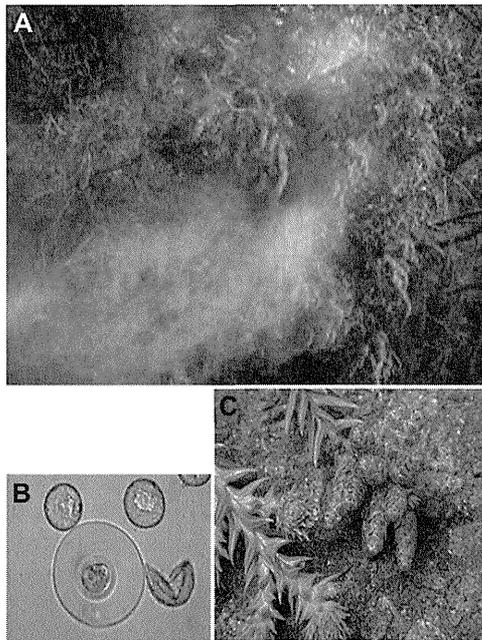
JCP counts were significantly associated with the prevalence of sugi-pollinosis. The mean JCP count in the mountainous area of Akita prefecture was 2 times higher than that in the coastal area of Akita from 1996 to 2006 (see Table E2 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). The prevalence of sugi-pollinosis in children (age, 10-11 years) in 2006 was higher in mountainous areas than in coastal areas, although the prevalence of PAR was not different between the 2 areas (see Table E3 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). The positive rate of serum anti-JCP-specific IgE in the mountainous area was also higher than in that in the coastal areas, but the positive rate of anti-mite IgE did not increase in the mountainous area.<sup>14</sup>

Asian dust (AD) and urban particulate matter (PM) are risk factors for sugi-pollinosis. AD storms originating in the deserts of Mongolia, northern China, and Kazakhstan are seasonal phenomena that affect much of Eastern Asia, including Japan, and occasionally spread around the globe, affecting the United States as well.<sup>15</sup> The number of spring dust storms has increased in the last 13 years. The frequency of the storms combined with increases in airborne pollution has led to an increase in the adverse effects of the storms. AD contains pollutants, such as sulfur dioxide and nitrogen dioxide, which stimulate immune cells through oxidative stress, enhancing inflammation-related cytokines.<sup>16</sup> AD enhanced nasal allergic reactions induced by repeated JCP administration in guinea pigs.<sup>17</sup> In fact, allergic symptoms have increased during AD storm events in Japan and Taipei.<sup>18,19</sup> Administration of AD plus allergen induced allergen-specific IgE production in mice,<sup>20</sup> suggesting that AD can bind to JCP and induce JCP sensitization in nonatopic or unsensitized atopic subjects.

The main pollutant in Japanese cities is fine PM. Particulate matter less than 2.5  $\mu\text{m}$  in diameter (PM2.5) is frequently reported in spring. PM2.5, a component of AD, induced asthma and enhanced sneezing and rhinorrhea in a manner of type I allergy.<sup>21</sup> Beijing has also recorded its worst levels of air pollution in recent years, and the onset and sensitization of sugi-pollinosis could be easily induced by PM2.5 from China. Environmental authorities in Japan, the United States, and other nations have adopted strict regulations to control PM levels. A wave of criticism, both at home and abroad, prompted Chinese officials to set their own standards in February 2012; however, air quality in China still remains an issue.

## **GENETIC FACTORS**

Genome-wide association studies (GWASs) and meta-analyses of GWASs have shown both common and distinct pathways that



**FIG 1.** The blooming Japanese cedar tree. **A**, Yellow-green pollen is scattered from male Japanese cedar flowers. **B**, JCP (magnification  $\times 400$ ). **C**, Male (right) and female (left) flowers of Japanese cedar.

might contribute to asthma and allergic diseases.<sup>22,23</sup> The first GWAS of asthma identified a novel asthma susceptibility locus on chromosome 17q21 including the *ORMDL3* genes.<sup>24</sup> Five polymorphisms in the *ORMDL3* gene are significantly associated with sugi-pollinosis.<sup>25</sup> Additionally, the matrix metalloproteinase 9 gene is involved in the pathogenesis of AR and asthma. The matrix metalloproteinase 9 gene confers susceptibility to sugi-pollinosis in children and might be associated with sensitization processes.<sup>26</sup> One of the polymorphisms in the gene for the IL-4 receptor  $\alpha$  chain, the Ile50 allele, might be involved in both sugi-pollinosis and atopic dermatitis.<sup>27</sup> IL-33 (an IL-1–like cytokine) is a ligand for IL-1RL1, an important effector molecule of the  $T_H2$  response. Serum levels of IL-33 are significantly higher in patients with sugi-pollinosis than in their nonallergic counterparts. In a genetic association analysis we found a positive association between the polymorphism of IL-33 and sugi-pollinosis.<sup>28</sup>

Complement systems are known to play an important role in allergic diseases. Decay-accelerating factor, which is involved in the regulation of the complement system, is one of the genes involved in conferring susceptibility to AR and sugi-pollinosis. Low levels of decay-accelerating factor might be associated with the enhanced specific IgE response that occurs in patients with allergic diseases in the Japanese population.<sup>29</sup>

Microarray analysis showed that JCP exposure increased IL-17 receptor  $\beta$  RNA expression in patients with sugi-pollinosis.<sup>30</sup>

### ASSESSMENT OF SEVERITY

Nasal symptom scores are assessed with a grading system that includes sneezing, rhinorrhea, and nasal congestion in Japan. Symptom scores are graded from 0 to 4. Grading of sneezing, rhinorrhea, and nasal congestion are evaluated based on the frequency of sneezing (number per day), frequency of nasal blowing (number per day), and duration of mouth breathing,

respectively (Fig 3).<sup>31</sup> Total nasal severity of sugi-pollinosis is evaluated by using the grading scores of nasal obstruction and sneezing/rhinorrhea as very severe, severe, moderate, and mild symptoms. According to Fig 3, of 795 patients with sugi-pollinosis, 22.6%, 29.4%, 31.3%, and 13.9% had very severe, severe, moderate, and mild symptoms, respectively.<sup>32</sup> Ninety-one percent of patients with sugi-pollinosis are classified as having moderate-to-severe AR.<sup>32</sup>

### ENVIRONMENTAL EXPOSURE UNITS

There are 4 environmental exposure units in Chiba, Tokyo, Wakayama, and Osaka City to investigate the effectiveness of medicine or devices on sugi-pollinosis (Fig 4).<sup>33</sup>

### ELIMINATION AND AVOIDANCE OF ANTIGENS

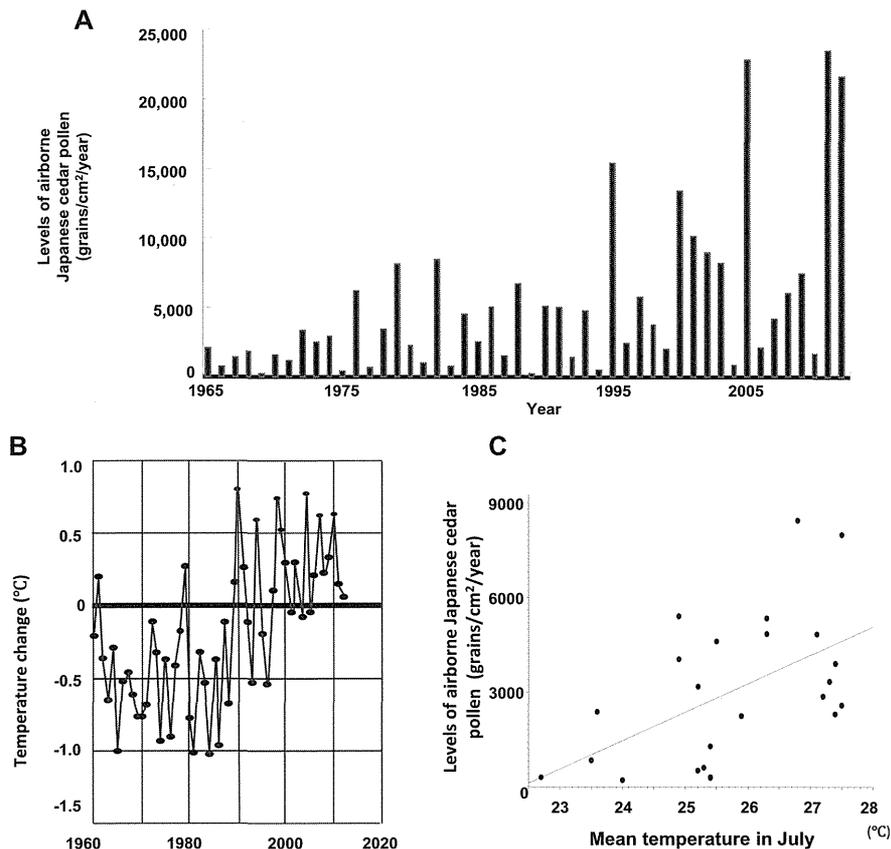
The most effective means of decreasing allergic inflammation reactions is avoidance of the aeroallergen.<sup>1</sup> Although the complete avoidance of pollen is impossible because of its ubiquitous nature, patients with sugi-pollinosis often wear protective face-masks between February and May (Fig 5); these masks have a significant protective effect on nasal JCP invasion.<sup>34</sup> This has created a large market for an array of related devices. Forecasting daily JCP dispersal conditions can help patients decide which prevention measures to take to protect them from pollen inhalation (see Fig E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). Using a service unique to Japan that has not been adopted in other countries, the amount of airborne JCP is automatically counted with equipment set up on the roofs of 1000 buildings and connected to the Internet (see Fig E2 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). The information is gathered from these sites and can be accessed for free using the Internet service. Furthermore, the success of these automatic pollen counters has led to their use to assess levels of other pollens, such as *Urticaceae*, *Poaceae*, and *Ambrosia* species.<sup>35</sup>

Ventilation systems can be equipped with appropriate filters to avoid drawing JCP into the house and car. Novel air-purification systems using positively and negatively charged cluster ions have been developed to create comfortable indoor living environments. Treatment with positive and negative cluster ions significantly decreased the *in vitro* and *in vivo* antigenicity of atomized JCP.<sup>36</sup> Treatment with low-concentration hypochlorous acid generated by means of electrolysis is also an effective method for significantly reducing the immunogenicity of JCP.<sup>37</sup>

### PHARMACOTHERAPY

Therapy for sugi-pollinosis is chosen based on severity (Fig 3) and disease type (Fig 6).<sup>2,38</sup> Because the severity of pollinosis markedly changes with the amount of dispersed pollen, the severity of a patient's symptoms is determined during a medication evaluation at peak pollen dispersal times and also takes into account the amount of dispersed pollen. Nasal antihistamine and mast cell stabilizers were not used for 1 decade in Japan.

Because there are a large number of patients with severe or very severe sugi-pollinosis, Japanese guidelines recommend the prophylactic treatment of sugi-pollinosis before pollen release.<sup>2</sup> Prophylactic treatment with oral antihistamines (olopatadine) significantly suppressed nasal symptoms by 40% and was



**FIG 2.** Correlation between increased JCP counts and climate change. **A**, Annual JCP counts from 1965 to 2013 in Kanagawa prefecture. **B**, Annual mean temperature change in Japan compared with baseline (mean temperature from 1960 to 2012). Data were provided by the Japan Meteorological Agency. **C**, Correlation between annual cumulative levels of airborne JCP and the mean temperature in Fukui, Japan. The mean temperature was taken in late July before the pollen season and from 1988 to 2012 (Spearman rank correlation coefficient = 0.531,  $P = .0067$ ). Pollen counts were determined from daily data with the Durham sampler (the standard gravity slide sampler) by counting the JCP particles dropped onto glass microscope slides.

associated with a high level of QOL during the peak of the JCP season in a randomized, double-blind, placebo-controlled study.<sup>39</sup>

Prophylactic administration of antileukotriene (pranlukast) 1 to 2 weeks before or at the start of the JCP season significantly reduced nasal symptoms by 50% at the peak of pollen dispersal compared with placebo.<sup>40</sup> Additionally, antileukotrienes reduces nasal congestion and allergic inflammation in patients with sugi-pollinosis.

Intranasal corticosteroids are the most effective drugs for controlling AR. In a double-blind, randomized, placebo-controlled study with mometasone furoate nasal spray (MFNS) as a prophylactic treatment for sugi-pollinosis, no worsening occurred in the MFNS group, whereas the placebo group showed a significant worsening of symptoms after the start of the continuous dispersion.<sup>41</sup> The 12-week mean total nasal symptom score in the prophylactically treated group was significantly lower than that in the postonset-treated group (which reduced the symptoms by 61%).<sup>42</sup> Intranasal corticosteroids should be administered prophylactically; with the addition of an oral antihistamine, they might improve outcomes in patients with severe sugi-pollinosis.<sup>43</sup> However, many Japanese persons prefer not to use intranasal

corticosteroids because of personal issues associated with using nasal sprays, including their smell.

## IMMUNOTHERAPY

Antigen-specific immunotherapy can change the natural course of AR and is recognized as a curative treatment without impaired performance. In the 1970s, subcutaneous immunotherapy for sugi-pollinosis was performed at university hospitals and medical clinics.<sup>44</sup> However, in the 1980s, the development of second-generation antihistamines and intranasal corticosteroids gradually decreased the frequency of application of subcutaneous immunotherapy. This decrease was also attributable to the fact that JCP extracts were not standardized until 1999.

In 2004, a multicenter, double-blind, randomized, placebo-controlled, parallel-group study of sublingual immunotherapy (SLIT) demonstrated the safer and more beneficial effects of immunotherapy for sugi-pollinosis than pharmacotherapy alone.<sup>45,46</sup> The mean of the daily total symptom scores was significantly lower in the SLIT group than in the placebo group. The QOL score in the SLIT group was almost half that in the placebo group.

Grading		Sneezing or rhinorrhea				
		Grade 4 (more than 21 times/day)	Grade 3 (20-11 times/day)	Grade 2 (10-6 times/day)	Grade 1 (5-1 times/day)	Grade 0 (none)
Degree of nasal obstruction	Grade 4 (completely blocked all day long)					
	Grade 3 (with much mouth breathing during the day)					
	Grade 2 (with some mouth breathing during the day)					
	Grade 1 (without mouth breathing, with nasal obstruction)					
	Grade 0 (none)					

**FIG 3.** Classification of the total severity of nasal symptoms of AR. Grading of sneezing, rhinorrhea, and nasal obstruction is evaluated based on the frequency of sneezing or the frequency of nasal blowing per day and the duration of mouth breathing. High grading scores are selected from sneezing or rhinorrhea. Uncontrollable severe symptoms are classified as very severe.



**FIG 4.** An environmental exposure unit.

Sera from 25 patients with sugi-pollinosis in a double-blind, randomized, placebo-controlled study for SLIT were analyzed by using 2-dimensional electrophoresis.<sup>47</sup> Sixteen proteins were found to be differentially expressed during the pollen season. Among the differentially expressed proteins, serum levels of apolipoprotein A-IV (apoA-IV) were significantly increased in SLIT-treated patients but not in placebo-treated patients. Higher levels of apoA-IV induction were correlated with lower clinical symptom-medication scores and better QOL scores in the case of SLIT-treated patients. The amount of histamine released from basophils *in vitro* was significantly reduced after addition of recombinant apoA-IV in the medium.<sup>47</sup> SLIT increased IL-10 production by monocytes and T cells in patients with sugi-pollinosis.<sup>48</sup> ApoA-IV and IL-10 might become clinical markers for the evaluation of the effectiveness of SLIT for sugi-pollinosis.

Uses of antigen-derived peptides that retain immunogenicity (but are insufficient in length to cross-link IgE on mast cells or basophils [immunotherapeutic peptides]) are a promising strategy



**FIG 5.** Persons on a train platform in a large Japanese city wearing facemasks during the JCP season.

for improved immunotherapy, and this concept has been applied to a variety of allergens. Cry-consensus peptide for sugi-pollinosis contains 6 major human derived T-cell epitopes. In an AR mouse model Cry-consensus peptide markedly inhibited Cry j 1-induced sneezing, eosinophil infiltration, and eosinophil peroxidase activity in nasal tissue.<sup>49</sup> Human immunodominant T-cell epitopes of the Cry j 1 molecule are being studied for peptide-based immunotherapy in patients with sugi-pollinosis.<sup>50</sup>

## ANTIBODY THERAPY

Omalizumab, a recombinant, humanized, anti-IgE mAb, has been shown to be effective for the treatment of SAR.<sup>51</sup> A randomized, placebo-controlled, double-blind study was conducted in Japanese patients with a history of moderate-to-severe sugi-pollinosis. The primary and all secondary efficacy variable scores were significantly lower in the omalizumab group than in the placebo group.<sup>52</sup> Retreatment with omalizumab is effective and safe when readministered in the second JCP season.<sup>53</sup>

## PROBIOTICS

Probiotics, including lactobacilli and bifidobacteria, might prevent several allergic diseases. Japanese persons are very interested in probiotics for the self-treatment of AR. A double-blind, placebo-controlled trial with lyophilized powders of *Bifidobacterium longum* BB536 for the treatment of sugi-pollinosis during the height of the pollen season indicated that BB536 intake alleviated subjective symptoms, reduced prescription of allergic medicines, and significantly suppressed the increase of plasma thymus and activation-regulated chemokine during the pollen season.<sup>54</sup> In another study BB536 reduced nasal symptoms from early allergic reactions in patients with sugi-pollinosis exposed to JCP in an environmental exposure unit outside of the normal JCP season.<sup>55</sup> Oral administration of heat-killed *Lactobacillus gasseri* OLL2809 reduced nasal

Severity	(prophylactic treatment)	Mild	Moderate		Severe or very severe	
Types			Sneezing rhinorrhea	Nasal blockage or combined	Sneezing rhinorrhea	Nasal blockage type or combined
Choice of therapy	Oral histamine H <sub>1</sub> antagonists (2 <sup>nd</sup> generation) or Oral Th2 cytokine inhibitors or Oral leukotriene receptor antagonists or Oral Prostaglandin D2/Thromboxane A2 receptor antagonists	Oral histamine H <sub>1</sub> antagonists (2 <sup>nd</sup> generation) + Eye drops, + Intranasal corticosteroid (when needed)	Oral histamine H <sub>1</sub> antagonists (2 <sup>nd</sup> generation) + Intranasal corticosteroid	Oral leukotriene receptor antagonists + Oral histamine H <sub>1</sub> antagonists (2 <sup>nd</sup> generation) + Intranasal corticosteroid	Intranasal corticosteroid + Oral histamine H <sub>1</sub> antagonists (2 <sup>nd</sup> generation)	Intranasal corticosteroid + Oral leukotriene receptor antagonists + Oral histamine H <sub>1</sub> antagonists (2 <sup>nd</sup> generation)
						+ Intranasal vasoconstrictor nose spray 7 to 10 days + oral corticosteroid 4-7 days (when needed, at the start of treatment)
		Histamine H <sub>1</sub> eye drops antagonists or mast cell stabilizer			Histamine H <sub>1</sub> eye drops antagonists, mast cell stabilizer, or steroids	
		Operation for cases of nasal blockage type with nasal deformities.				
	Specific immunotherapy					
Avoidance and elimination of antigens						

FIG 6. Algorithm for the treatment of sugi-pollinosis recommended by Japanese guidelines.<sup>2</sup>

symptoms and JCP-specific IgE levels.<sup>56</sup> Additionally, oral administration of *Lactobacillus paracasei* strain KW3110 decreased total symptom scores and serum eosinophil cationic protein levels and improved QOL scores at the start of the JCP production season.<sup>57</sup>

In addition, dietary intervention with nondigestible prebiotics might be effective for allergic diseases.<sup>58</sup> Administration of β-1, 4 mannobiose decreased sneezing frequency, histamine release, and IL-4 production in a sugi-pollinosis mouse model, suggesting a potential molecular therapeutic supplement in clinical trials for sugi-pollinosis.<sup>59,60</sup>

## FLAVONOIDS AND TEA

An appropriate intake of flavonoids might constitute a dietary preventative or therapeutic strategy for allergic diseases because flavonoids, which are abundant in plant foods, possess antioxidants and antiallergic activities. Analyses of structure-activity relationships of 45 flavones, flavonols, and their related compounds showed that luteolin, ayanin, apigenin, and fisetin were the strongest inhibitors of IL-4 production by basophils in mice because of their inhibitory action on the activation of nuclear factors in activated T cells and activator protein 1.<sup>61</sup> Additionally, prophylactic ingestion of enzymatically modified isoquercitrin significantly decreased levels of ocular symptoms and medication scores in patients with sugi-pollinosis in a double-blind, placebo-controlled study.<sup>62</sup>

Self-care with Ten-Cha (*Rubus suavissimus*, sweet Chinese tea) is the most common alternative complementary treatment for AR in Japan. Ten-Cha extract inhibited histamine release from rat peritoneal mast cells, as well as calcium ionophore-induced vascular permeability. However, the effects of drinking Ten-Cha beverages on sugi-pollinosis symptoms were considered low in an unblinded study.<sup>63</sup> Nevertheless, Ten-Cha has sold very well during JCP seasons.

## CONCLUSION

In Japan, 69.7% of the adult population has positive results for one of 7 aeroallergen-specific IgEs (JCP, 2 types of mite, ragweed, orchard grass, and *Aspergillum* and *Candida* species), and the prevalence of patients with AR is 44.2%.<sup>7</sup> In response to the increasing demand for AR relief, second-generation antihistamines have been approved for sale as over-the-counter medications. However, present therapies still do not offer sufficient relief for patients with sugi-pollinosis. In addition, the Japanese government has reduced the budget for AR research because they consider more lethal diseases, such as cancer, to be a more serious threat than sugi-pollinosis. Therefore cooperation between scientists and pharmaceutical companies will be needed to find new treatments that better control AR and its symptoms.

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# Indomethacin inhibits eosinophil migration to prostaglandin D<sub>2</sub>: therapeutic potential of CRTH2 desensitization for eosinophilic pustular folliculitis

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## Summary

Indomethacin is a cyclo-oxygenase inhibitor, and shows therapeutic potential for various eosinophilic skin diseases, particularly eosinophilic pustular folliculitis. One of the unique characteristics of indomethacin is that, unlike other non-steroidal anti-inflammatory drugs, it is a potent agonist of chemoattractant receptor-homologous molecule expressed on T helper type 2 cells (CRTH2), a receptor for prostaglandin D<sub>2</sub> (PGD<sub>2</sub>). This study investigated the pharmacological actions of indomethacin on eosinophil migration to clarify the actual mechanisms underlying the therapeutic effects of indomethacin on eosinophilic pustular folliculitis. Eosinophils exhibited chemokinetic and chemotactic responses to both PGD<sub>2</sub> and indomethacin through CRTH2 receptors. Pre-treatment of eosinophils with indomethacin greatly inhibited eosinophil migration to PGD<sub>2</sub> and, to a much lesser extent, to eotaxin (CCL11); these effects could be mediated by homologous and heterologous desensitization of eosinophil CRTH2 and CCR3, respectively, by agonistic effects of indomethacin on CRTH2. Indomethacin also cancelled a priming effect of  $\Delta^{12}$ -PGJ<sub>2</sub>, a plasma metabolite of PGD<sub>2</sub>, on eosinophil chemotaxis to eotaxin. Indomethacin down-modulated cell surface expression of both CRTH2 and CCR3. Hair follicle epithelium and epidermal keratinocytes around eosinophilic pustules together with the eccrine apparatus of palmoplantar lesions of eosinophilic pustular folliculitis were immunohistochemically positive for lipocalin-type PGD synthase. Indomethacin may exert therapeutic effects against eosinophilic skin diseases in which PGD<sub>2</sub>-CRTH2 signals play major roles by reducing eosinophil responses to PGD<sub>2</sub>.

**Keywords:** CCR3; chemoattractant receptor-homologous molecule expressed on T helper type 2 cells; desensitization; eotaxin; Lipocalin-type prostaglandin D synthase.

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## Introduction

Eosinophilic pustular folliculitis (EPF) is an eosinophilic inflammatory skin disease characterized by pruritic follicular papulopustules that tend to form in an annular configuration on the face, and occasionally on the trunk and extremities. Histopathologically, a number of eosinophils

infiltrate around and into hair follicles. Uncommonly, EPF also affects the palms and soles, which lack the hair follicle apparatus.<sup>1</sup> Our recent study demonstrated that, in palmoplantar lesions of EPF, intra-epidermal eccrine ducts may be the sites that are predominantly affected.<sup>2</sup> Occasionally EPF is resistant to topical or systemic corticosteroids, but, importantly, shows a consistently good

Abbreviations: CRTH2, chemoattractant receptor-homologous molecule expressed on T helper type 2 cells; EPF, eosinophilic pustular folliculitis; H-PGDS, haematopoietic prostaglandin D synthase; L-PGDS, lipocalin-type prostaglandin D synthase; PGD<sub>2</sub>, prostaglandin D<sub>2</sub>; Th2, T helper type 2