

## Letter to the Editor

**Outbreak of immediate-type hydrolyzed wheat protein allergy due to a facial soap in Japan***To the Editor:*

Wheat proteins in hydrolyzed form have been widely used in cosmetic products. The number of patients allergic to hydrolyzed wheat protein (HWP) in cosmetic products seems to be small in Western countries (see [Table E1](#) and this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). However, in Japan, Fukutomi et al<sup>1</sup> first reported 5 Japanese patients with wheat-dependent exercise-induced anaphylaxis (WDEIA) after using the facial soap containing 0.3% of a specific type of HWP, Glupearl 19S, in 2009, and thousands of subjects showed allergic contact urticaria, anaphylaxis, and/or WDEIA after using the soap.

Here, we provide an overview of the outbreak of immediate-type wheat allergy caused by a specific HWP (HWP-IWA) by facial soaps in Japan.

A nationwide survey for HWP-IWA was conducted to collect the information on Glupearl 19S-containing soaps. A flowchart of the patient registration and the diagnostic criteria are shown in [Fig E1](#) and [Table E2](#), respectively, and details are also described in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org).

On the basis of the diagnostic criteria listed in [Table E2](#), the number of patients who satisfied the diagnostic criteria was 2111 (2025 females, 86 males; age, 1-93 years; average age,  $45.8 \pm 14.5$  years). The age group with the largest share consisted of those in their 40s (see [Fig E2](#) in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). Because sales of the soap containing Glupearl 19S were discontinued in May 2011, the number of reported patients has gradually decreased, and the nationwide survey for HWP-IWA ended in October 2014 ([Fig 1](#)).

The symptoms typically appeared 1 year after starting use of the soap. Most patients used the soap only for their faces, but some used it on other body parts as well. Symptoms observed in patients are listed in [Table I](#). No patients had shown apparent wheat allergy before using this soap. Twenty-five percent of patients experienced anaphylactic shock, 43% experienced dyspnea, and 11% experienced vomiting. Most of the patients with food ingestion-related symptoms reacted to traditional wheat products such as bread and pasta. This was in contrast to non-Japanese patients allergic to HWP in cosmetic products, who tolerated traditional wheat products but showed the symptoms of allergic reaction after eating processed food such as ham and pâté (see [Table E1](#) and Online Repository). Initial symptoms of anaphylaxis in the patients were facial symptoms, including swelling of the eyelids, urticaria/itchiness of the face, and runny nose, which were distinct from conventional WDEIA with initial symptoms of systemic reaction of itching and urticaria.

In contrast to conventional wheat allergies that react mainly with gliadin and high molecular weight glutenin in wheat protein,<sup>2</sup> immunoblot analysis and ELISA revealed that sera from patients allergic to the HWP-containing soap showed a pattern distinct from that of conventional wheat allergy.<sup>1</sup> Glupearl

19S that was produced by acid treatment of gluten (pH, 0.5-1.2) at 95°C for 40 minutes is the HWP responsible for the allergenicity of the soap. The SDS-PAGE analysis of Glupearl 19S showed a smear staining pattern from the low to high molecular weight range in contrast to the staining pattern of gluten. [Fig E3](#) in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org) shows the SDS-PAGE of Glupearl 19S and IgE reactivity against Glupearl 19S by ELISA<sup>3</sup> (see this article's [Methods](#) section in the Online Repository at [www.jacionline.org](http://www.jacionline.org)) using sera obtained from conventional patients with WDEIA, patients with HWP-IWA who satisfied the diagnostic criteria, subjects who had used soaps containing Glupearl 19S but did not meet the diagnostic criteria, and healthy controls. As shown in [Fig E3](#), strong IgE reactions were observed only in those patients who satisfied the diagnostic criteria, and none of the sera obtained from patients with conventional WDEIA reacted with Glupearl 19S.

Because patients used the soap repeatedly on the face, it is likely that allergen exposure occurred through the eyelids and noses, leading to the strong allergic reactions with their eyelids that were not commonly observed in patients with conventional wheat allergy. Airaksinen et al<sup>4</sup> reported 2 patients of occupational rhinitis, asthma, and contact urticaria due to a sprayable hair conditioner containing HWP, and both of them showed exercise-induced eyelid edema and other symptoms after eating wheat-containing food.

Glupearl 19S was produced by acid treatment of gluten (pH, 0.5-1.2) at 95°C for 40 minutes. It has been reported that gluten treated with 0.1 N hydrochloric acid for 30 minutes at 100°C markedly increased IgE-binding capacity of patients' sera, indicating that neopeptides on the gluten might be generated after the treatment.<sup>5</sup> The acid treatments at high temperature for a short time produce random degradation of gluten, and mixed short and long peptides, leading to smear pattern by electrophoresis ([Fig E3](#)). Because most food products do not contain HWP, it was speculated that gastrointestinal enzyme reaction after ingestion of wheat protein might be responsible for acquiring allergenicity. Glupearl 19S itself is not deamidated by transglutaminase in the body, but deamidated peptides were produced during the process of acid and heat treatment of gluten,<sup>6</sup> and then specific IgE antibodies against Glupearl 19S were produced when patients used the soap repeatedly ([Fig E3](#)). Nakamura et al<sup>7</sup> showed that tissue transglutaminase treatment of gluten dramatically increased reactivity against IgE from the patients' sera by cell-based assay (EXiLE). Yokooji et al<sup>8</sup> reported that IgE-binding epitope QPQQFPQ in  $\gamma$ -gliadin reacted more strongly with IgE of the patients in its deamidated form, PEEPFP.<sup>8</sup> Ingested wheat food product such as bread and/or pasta might be deamidated by transglutaminase in the body, and specific IgE antibodies against Glupearl 19S could cross-react with deamidated peptide derived from food gluten, which may lead to anaphylactic/allergic reaction in the patients.

The detailed analysis of allergenicity of HWP and predisposition to type I allergy against HWP will lead to the safe use of cosmetic products containing wheat protein.

Hiragun et al<sup>9</sup> reported the status of remission of 110 patients with IWA-HWP who were part of the 2111 patients mentioned above, and the remission rate of 110 patients was still 56.1% at 60 months after stopping usage of HWP-containing soap.

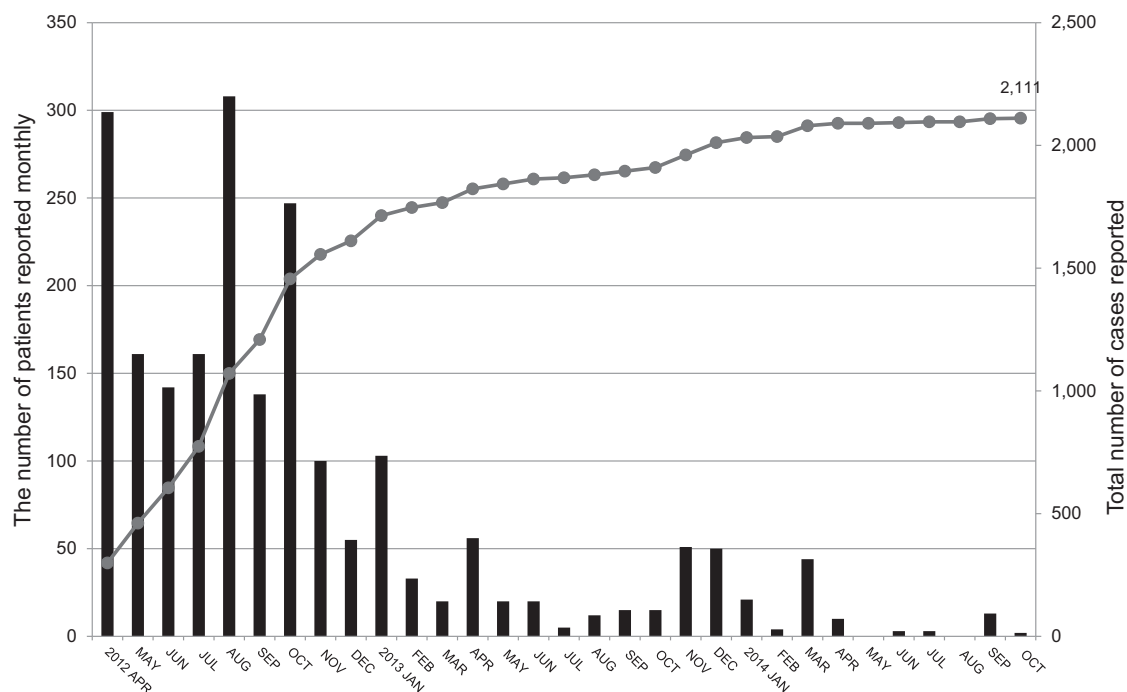


FIG 1. The number of patients registered per month and cumulative total number between 2012 and 2014.

TABLE I. Symptoms observed in immediate-type wheat allergy caused by Glupearl 19S (n = 899)

Skin symptoms during or after using soap, n (%)	
Skin symptoms	640 (71)
Swelling of eyelids	360 (40)
Urticaria, itching, and rubefaction	280 (31)
Skin symptoms negative	246 (27)
Unknown	13 (2)
Symptoms after eating wheat products, n (%)	
Swelling of eyelids	694 (77)
Urticaria	537 (60)
Dyspnea	385 (43)
Erythema	344 (38)
Itching	278 (31)
Anaphylactic shock	227 (25)
Diarrhea	148 (16)
Nausea	122 (14)
Nasal discharge	117 (13)
Vomiting	103 (11)
Nasal congestion	95 (11)

Therefore, it is necessary to find effective treatment for the long-lasting and refractory cases. Discovering the molecular mechanisms underlying the HWP-IWA, in comparison with conventional WDEIA and wheat intolerance such as celiac diseases, may lead to better understanding of the molecular basis of wheat protein-related diseases.

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This study was partly supported by Grant-in-Aid of the Ministry of Health, Labour, Welfare of Japan (Study on Quasi Drug/Cosmetic Additives Safety, 2012-2014) and the

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