

## Remission of Wheat-dependent Exercise-induced Anaphylaxis after the Cessation of Hydrolysed Wheat-containing Soap Usage

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Patients with wheat-dependent exercise-induced anaphylaxis (WDEIA) develop anaphylaxis when exercise is performed within a few hours after ingestion of wheat products, such as bread and pasta (1).

It is now apparent that WDEIA may also develop after the use of cosmetics and/or soap that contain hydrolysed wheat protein (HWP) (2), which is prepared by the digestion of gluten using enzyme or acid treatment. Although the major antigens of WDEIA have been elucidated as  $\omega$ -5 gliadin and high molecular weight glutenin (1), newly occurring WDEIA in association with HWP-containing soap (HWP-WDEIA) has shown no, or only low, levels of specific IgE against  $\omega$ -5 gliadin (3, 4). On the other hand, it has shown reactivity of serum IgE against hydrophilic wheat proteins, which contain albumin and globulins, and gluten that consists of gliadins and glutenins, as well as artificially-produced wheat proteins of a wide range of molecular weights, produced by hydrolysis (3, 4).

Previously reported cases of HWP-WDEIA have described patients who developed symptoms only when they ate HWP-containing food, such as paté and ham (2). However, many patients with HWP-WDEIA recently diagnosed in Japan have been shown to develop allergic reactions not only with the use of artificial HWP-containing soap, but also on exercise after the ingestion of a variety of natural wheat products (3). Such patients have to avoid not only HWP-containing soap and cosmetics, but also a wide range of wheat products. Therefore, they experience a large burden in their daily lives. No information has been available regarding the prognosis of HWP-WDEIA, especially the decrease in, and remission of, reactivity against natural wheat products in the diet. We report here a case of a young woman who developed HWP-WDEIA, but whose symptoms remitted after the cessation of use of HWP-containing soap. Sensitization of the patient to HWP was demonstrated by all skin test, solid-phase immune-binding assay for serum specific IgE and Western blotting. Remission was most clearly reflected by a histamine-release test for glutenin in the patient's basophils.

### CASE REPORT

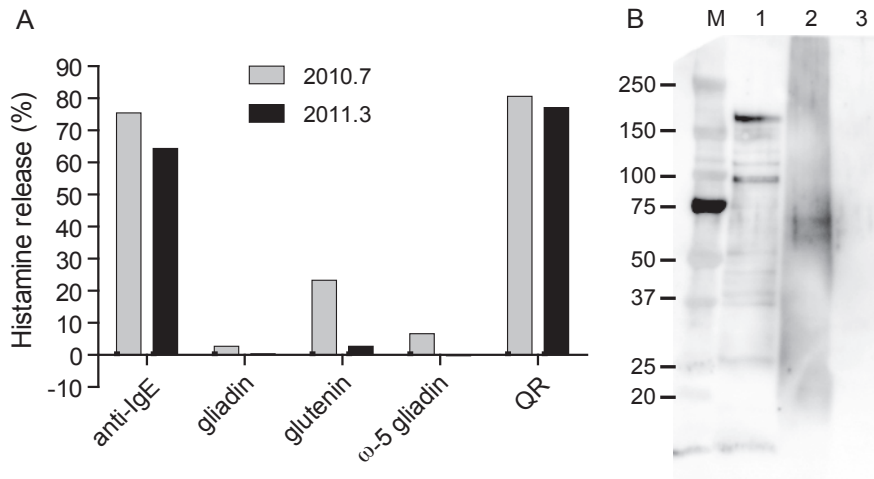
A 16-year-old female, who had atopic dermatitis, developed widespread itching and wheals on the body when she rode a bicycle after eating pasta in December

2008. She also developed dyspnoea and hypotension following the skin symptoms. Since then she has developed similar symptoms during exercise on 6 or more occasions, and was referred to our hospital in March 2010. A skin prick test with wheat and bread antigens (Torii Pharmaceutical Co., Tokyo, Japan) were both positive. A serum allergen-specific IgE test (ImmunoCAP<sup>®</sup>; Phadia, Uppsala, Sweden) for wheat, was 3.11 kUA/l. A histamine-release test performed on July 2010, using basophils (5) of the patient revealed 23.3% release of histamine by glutenin (TCI, Tokyo, Japan) extracted from wheat and 6.3% by recombinant  $\omega$ -5 gliadin (6) (Fig. 1A).

Based on the diagnosis of WDEIA, the patient was instructed not to eat wheat products before exercising. She took 20 mg bepotastine, an anti-histamine, in case she might embark on exercise within 3 h after eating wheat products. In December 2010, it became apparent that she had been using HWP-containing facial soap, Chano-Shizuku<sup>™</sup> (Yuhka, Fukuoka, Japan) for washing her whole body, including her face since December 2007, and she stopped using it. Western blotting with the patient's serum revealed a smear-like IgE-binding to HWP contained in this soap, but not a clear blotting for  $\omega$ -5 gliadin (Fig. 1B, lanes 2 and 3), as reported in other patients with HWP-WDEIA (2, 4). Re-examination 4 months after the final diagnosis revealed that her serum IgE level against wheat had decreased to 2.2 kUA/l, but the reactivity in the histamine-release test against wheat constituents had completely diminished, whereas the reactivity against sweat antigen (5) and anti-IgE antibody remained the same (Fig. 1A). The patient was then allowed to eat natural wheat products and to exercise, but she experienced no further anaphylaxis over the following 6 months, except for one occurrence of mild urticaria, which appeared during exercise and disappeared shortly after taking bepotastine.

### DISCUSSION

The mechanism of antigen sensitization and the prognosis of conventional WDEIA have not been fully elucidated. It has become apparent recently that the number of patients with HWP-WDEIA is increasing abruptly in Japan and most of them have developed symptoms after the use of a recently commercialized brand of soap that contains HWP (Chano-Shizuku<sup>™</sup>) (3, 4).



**Fig. 1.** (A) Histamine-release test (HRT) using basophils of the patient with wheat-dependent exercise-induced anaphylaxis (WDEIA) in response to wheat antigens (gliadin, glutenin,  $\omega$ -5 gliadin) and semi-purified sweat antigen (QR) and anti-IgE (positive control). Gliadin, glutenin and  $\omega$ -5 gliadin were individually prepared by sonication in distilled water and diluted to 1.0  $\mu$ g/ml in buffer for the HRT. Shaded and filled bars show data in July 2010 and March 2011, respectively. (B) Western blot using patient's serum. Lane 1: mite-Df (LSL Co., Tokyo, Japan). Lane 2: hydrolysed wheat protein (HWP). Lane 3:  $\omega$ -5 gliadin (6). Lane 1 contained 1.6  $\mu$ g protein of mite-Df, lanes 2 and 3 contained 10  $\mu$ g protein, respectively. HWP was prepared by incubating 100 mg/ml glutenin in 2% HCl at 100°C for 90 min.

The reason for such a large increase in the number of patients with HWP-WDEIA is unclear. It may be due either to the rapid increase in use of the soap, or to the combination of HWP and a particular detergent, which may effectively peel the corneal surface, reducing the barrier function of the skin.

The case reported here suggests that the continual use of HWP-containing soap may sensitize individuals, such that they react to a wide range of wheat proteins and develop HWP-WDEIA. Importantly, this patient remitted from the reactivity after 6 months of avoiding exposure to HWP, with a mild restriction against eating wheat just prior to exercise. Furthermore, a histamine-release test with basophils and wheat proteins, especially glutenin, reflected the change in reactivity of the patient against HWP better than a serum allergen-specific IgE test, as observed in infant food allergy (7). It is tempting to speculate that the sensitivity against artificially produced HWP, which may cross-react with natural wheat antigen, might be developed and preserved by continual exposure of the skin to HWP together with soap, but remitted by the cessation of further exposure of the skin to HWP, even if the gut membrane continues to be exposed to a natural wheat diet. Large-scale studies of the prognosis, the manner of desensitization in HWP-WDEIA, and the means of its evaluation are expected not only to lead to means of prevention of HWP-WDEIA, but also to improved understanding of the mechanisms underlying WDEIA.

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