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Letter to the Editor

A case of hen's egg-dependent exercise-induced immediate-type allergy

Dear Editor,

Hen's egg is a major food allergen among children in Japan, and the main source of allergens is the egg white rather than the yolk.¹ The major allergens in egg white are ovomucoid, ovalbumin, conalbumin, and lysozyme.² The antigenicity of ovomucoid does not change when exposed to heat or digestive enzymes. Chicken serum albumin (Gal d 5) has been reported to be an allergen in the yolk. Generally, patients with hen's egg allergy naturally acquire tolerance with age. We report a case of food-dependent exercise-induced immediate-type allergy caused by ingestion of hen's egg.

A 16-year-old girl with a history of hay fever experienced episodic eyelid swelling on three occasions. Each episode occurred during her commute to school by bicycle, after eating breakfast that included hen's egg. No other symptoms besides eyelid swelling had developed in any of the three episodes.

She had no history of hen's egg allergy in infancy, and no history of allergy to chicken or oral anti-inflammatory drugs.

Total immunoglobulin (Ig) E antibody titer was 216.7 IU/mL, and results of CAP fluorescent enzyme immunoassay (FEIA) for specific IgE antibodies to egg white, egg yolk, and ovomucoid were negative. Specific IgE antibodies to Japanese cedar, *Anthoxanthum odoratum*, and *Dactylis glomerata* were Class 3, and those to Japanese alder and Japanese white birch were Class 2. Skin prick test (SPT) yielded negative results for both egg white (raw and cooked; as is) and egg yolk (raw and cooked; as is).³ A positive control test (histamine dihydrochloride, 10 mg/mL; Torii Pharmaceutical, Tokyo, Japan) showed a 4 × 4 mm result, while a negative control test (physiological saline) showed a negative result. Exercise stress testing resulted in the development of pronounced eyelid swelling after ingesting 0.5 g of aspirin and 1 hot spring egg followed by running on a treadmill for 30 min, although this did not occur in exercise only, ingestion only, or exercise after ingestion of aspirin only (Fig. 1). After exercise stress testing, we diagnosed her episodic eyelid swelling as food-dependent exercise-induced immediate-type allergy caused by ingestion of hen's egg.

To identify the causative antigen in this case, hen's egg proteins were separated by two-dimensional electrophoresis, then immunoblotting was performed. The resulting protein was identified by mass spectrometry.⁴

This study was approved by the Ethics Committee of Fujita Health University School of Medicine (approval number HM16-371), and informed consent was obtained from this patient and the healthy controls who had never had a hen's egg allergy.

The patient's serum showed no specific response to egg white proteins, but a specific IgE antibody-binding protein band was identified in that bound to a 30-kDa protein in egg yolk. Mass spectrometry then identified vitellogenin-3 as the specific IgE antibody-bound egg yolk protein (Fig. 2).

Food dependent exercise-induced anaphylaxis (FDEIA) is a special case of allergy and considered to be a severe case of anaphylaxis in food-dependent exercise-induced immediate-type allergy. FDEIA is IgE-dependent food allergy,⁵ but it's a relatively rare. Many cases with FDEIA develop the symptoms with exercise performed within 2 h after eating the causative food. Wheat products and crustaceans often reported as causative foods of FDEIA, but other foods including peaches⁵ have also been reported as causes. Several potentiating factors are involved in food ingestion and exercise stress during the onset of FDEIA. Symptoms are often induced during periods when patients feel a strong sense of fatigue, suggesting fatigue as a potentiating factor.

Only few cases of FDEIA caused by hen's egg ingestion have been reported. Tewari *et al.* reported the case of a patient in whom FDEIA caused by egg ingestion was suspected based on the episode, but there was no mention of exercise stress testing.⁶ Asero *et al.* reported a patient with FDEIA caused by hen's egg and poultry, who showed a strongly positive result in SPT, but negative results from exercise stress testing. Immunoblotting identified conalbumin/ovotransferrin as antigens in that case.⁷

The present case report is the first case of food dependent exercise-induced immediate-type allergy caused by hen's egg ingestion in which a diagnosis was made by exercise stress testing and the causative antigen was identified.

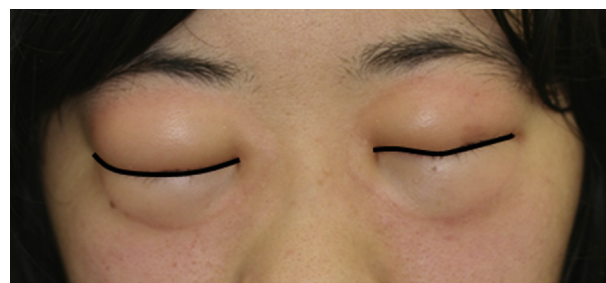


Fig. 1. Exercise stress testing resulted in pronounced eyelid swelling after ingesting 0.5 g of aspirin and 1 hot spring egg followed by running on a treadmill for 30 min. For use of the image, a permission from the patient was obtained.

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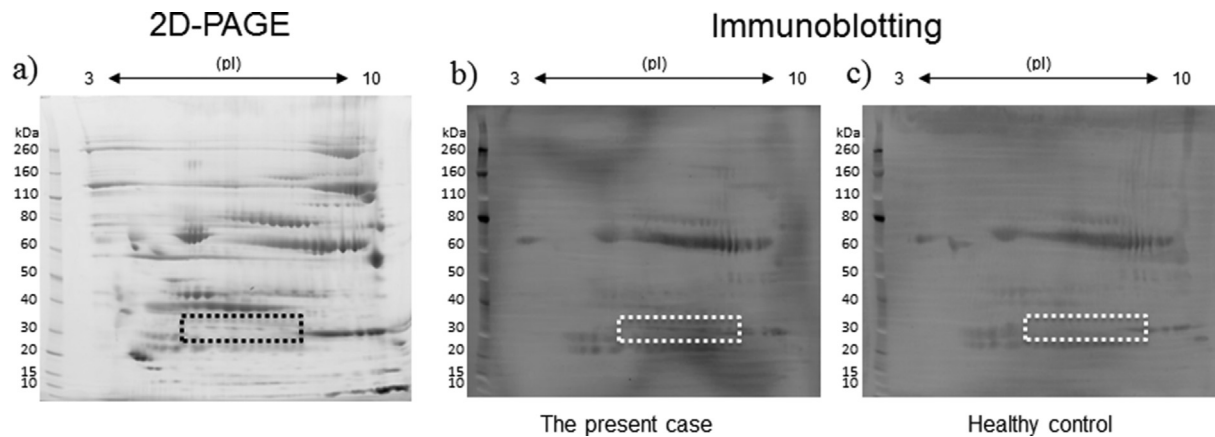


Fig. 2. Results of immunoblotting of egg yolk protein using IgE antibody from the patient's serum. Two-dimensional polyacrylamide gel electrophoresis (2D-PAGE) and immunoblotting were performed to identify the causative antigen in egg. Specific reaction to this case was detected for egg yolk, but not egg white. Specific IgE binding was predicted for vitellogenin-3 (XP_015146355) by mass spectrometry. **a)** Data of staining for all proteins. **b,c)** Data of detecting only proteins with bound IgE antibodies. **b)** in this case and **c)** in representative healthy control.

Vitellogenin, which we identified as the causative antigen, is a precursor egg yolk protein generally seen in egg-laying animals. In addition to hen's eggs, this protein has interestingly also been reported to be an antigen in salmon eggs (salmon roe) and sturgeon eggs (caviar).⁸ Cross-reactivity between fish eggs and hen's eggs was therefore also investigated in this case, but the patient was found capable of ingesting fish eggs without any problem. Gal d 6 has also been reported to be an antigen for hen's eggs and is a YGP42 glycoprotein derived from vitellogenin-1. The vitellogenin-3 that we identified has not been reported as an antigen, suggesting that differences in amino acid sequences between hen's eggs and fish eggs determine the presence or absence of symptoms.

Although most patients with hen's egg allergy develop allergic symptoms in childhood, our patient had no history of hen's egg allergy in early childhood. She first developed allergy caused by hen's egg ingestion at age 16 years. Recently, the mechanisms underlying the production of IgE antibodies to percutaneously absorbed proteins, and subsequent induction of allergic responses to orally ingested foods have gained attention, as in the cases of wheat allergy caused by using soap containing hydrolyzed wheat protein.^{9,10} Because our patient had never used cosmetic products containing egg components, further investigation into the mechanisms of allergy onset is warranted in this patient. She showed no positive response to hen's egg-specific IgE via CAP FEIA or SPT with egg white and yolk, but symptoms developed during exercise stress testing. We were able to reach a definitive diagnosis by exercise stress testing. Exercise stress tests are useful for diagnosis, but there is some degree of risk. We hope to establish serological or SPT methods to identify this pathology in the future, using candidate antigens such as vitellogenin-3.

Conflict of interest

YA, EH, MN are employees of Hoyu. The rest of the authors have no conflict of interest.

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