

# A rare case of wheat-dependent exercise-induced anaphylaxis induced by exercise 5 hours after wheat ingestion.

Tomoki Yaguchi<sup>1</sup>, Katsutoshi Nakano<sup>1</sup>, and Tadayuki Kumagai<sup>1</sup>

<sup>1</sup>Yaizu Shiritsu Sogo Byoin

April 14, 2024

**A rare case of wheat-dependent exercise-induced anaphylaxis induced by exercise 5 hours after wheat ingestion.**

Tomoki Yaguchi<sup>1</sup>, Katsutoshi Nakano<sup>1</sup>, Tadayuki Kumagai<sup>1</sup>

Department of Pediatrics, Yaizu City Hospital, Shizuoka, Japan

Corresponding author

Tomoki Yaguchi, 1000, Dobara, Yaizu-shi, Shizuoka 425-0055, Japan. Phone: +81-54-623-3111, Fax: +81-54-624-9103, E-mail: ravvvvish@gmail.com

Word Count for Main Text; 916

The number of Table; 1, Figure; 0

Keywords: wheat-dependent exercise-induced anaphylaxis, food allergy, aspirin, sensitization, anaphylaxis

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## FUNDING INFORMATION

None.

## Informed consent

Written informed consent for publication was obtained from the patient's parents.

## MAIN TEXT:

To the Editor:

Food-dependent exercise-induced anaphylaxis (FDEIA) is an immunoglobulin E (IgE)-mediated food allergy triggered by physical exertion following the ingestion of the causative food. Foods causing FDEIA differ by culture and eating habits, and wheat and shrimp are commonly reported causative foods in Japan. In 95% of patients, the duration between food consumption and exercise is shorter than 3 h<sup>1</sup>. Here we report a unique case of wheat-dependent exercise-induced anaphylaxis (WDEIA) in a 12-year-old boy who experienced exercise-induced anaphylaxis 5 h after wheat ingestion and required intramuscular adrenaline administration.

A 12-year-old boy presented to our emergency department with systemic urticaria, nasal discharge and dyspnea after running for 20 min. He had ingested tempura containing wheat and shrimp 5 h before running. He was administered intramuscular adrenaline by his mother 30 min after the onset of symptoms.

On arrival at the hospital, the patient had diffuse urticaria and wheezing accompanied by hypoxemia, was diagnosed with anaphylaxis, and administered hydrocortisone, antihistamines and intravenous hydration.

The patient had a history of three prior anaphylactic episodes starting at 7 years of age, with each episode requiring intramuscular adrenaline injection (Table 1). Prior to all three episodes, he had exercised within 1 h of wheat ingestion. Other than exercise, none of the common triggers of FDEIA<sup>1</sup> were identified. Although rice, cow's milk, beef, pork, chicken, fish, shrimp and vegetables were also consumed prior to some of the episodes, only wheat was consumed prior to all four anaphylactic episodes. He regularly consumed wheat and performed intensive exercise for judo, both of which were always well tolerated. He had a history of hay fever to cedar and ragweed but no history of bronchial asthma, other food allergies, or atopic dermatitis. The anaphylactic episodes were not seasonal; one episode was in March, one episode was in May, and two episodes were in October. He was diagnosed with WDEIA and instructed to refrain from exercise for 3 h after wheat ingestion and to carry an adrenaline auto-injection for use in case of WDEIA symptoms.

The results of allergen-specific IgE (ImmunoCAP, Thermo Fisher Scientific, Uppsala, Sweden) were negative for wheat,  $\omega$ 5-gliadin, gluten, shrimp, cow's milk, beef, pork, chicken and orchard grass (cutoff, 0.35 UA/mL). The skin prick test (SPT) using commercial allergen extracts of wheat (Torii Pharmaceutical, Tokyo, Japan) and the prick-to-prick method with shrimp revealed a negative reaction with no measurable wheal.

After obtaining informed consent from his parents, the patient was admitted for a provocation test using wheat with and without aspirin and exercise. The test protocol was based on the Japanese guidelines for food allergy 2020<sup>2</sup>. He experienced no symptoms after ingesting 5.5 g of wheat protein and running for 15 min. However, a second provocation test with the combination of 11.0 g of wheat protein and 500 mg of aspirin followed by a 25-min run induced itching in the face. The provocation test results confirmed the diagnosis of WDEIA, and the patient was instructed not to exercise on days of wheat consumption. However, one month after the positive provocation test, the patient developed anaphylaxis due to exercising 30 min after wheat ingestion, which was consistent with the diagnosis of WDEIA (Table 1).

In patients with anaphylactic episodes, identifying the causative foods based on the clinical history and allergy testing is important before performing a provocation test<sup>3</sup>. However, allergen-specific IgE and SPT are not sufficiently accurate for the diagnosis of FEDIA, especially in children and young adult patients. The reported sensitivities of the omega-5 gliadin-specific IgE test and SPT for WDEIA in children are 46% and 40%, respectively<sup>3,4</sup>. In cases where the causative food cannot be identified through history taking or allergy testing, determination of the causative food by provocation testing can prevent the recurrence of anaphylaxis and improve the patient's quality of life. The present case was diagnosed with WDEIA based on a positive provocation test although allergen-specific IgE and SPT did not revealed wheat sensitization.

The Japanese guidelines for food allergy 2020 recommend that patients with FDEIA should avoid the ingestion of causative foods within 2 h prior to exercise<sup>2</sup>. Only two cases of FDEIA induced by exercise performed more than 4 h after eating have been reported<sup>5,6</sup>. No information regarding the need for intramuscular adrenaline injection has been provided in either case. In the present case, despite the recommended instructions to refrain from exercise within 3 h of wheat ingestion due to the high frequency of anaphylactic episodes, the patient exercised 5 h after wheat ingestion, which triggered the fourth anaphylactic episode and required the administration of intramuscular adrenaline. Therefore, exercise restriction for 3 h after wheat ingestion was considered inadequate. The mechanism of FDEIA remains unclear, and exercise may be one of the many factors lowering the threshold for food allergy. In the present case, no known FDEIA triggers except for exercise were identified across the five anaphylactic episodes, and it remains unclear why the induction of symptoms could not be prevented despite exercise restriction for 3 h after wheat ingestion. Future studies are warranted to elucidate the mechanism of FDEIA and the aggravating factors.

The present case illustrates the unique presentation of anaphylaxis triggered by exercise 5 h after wheat ingestion, which required adrenaline self-injection, although allergy tests did not demonstrate wheat sensitization. This case highlights that severe symptoms can be triggered even after a long interval between food ingestion and exercise in patients with FDEIA and that the diet consumed in the 5–6 h before exercise

should be reviewed in patients who develop anaphylaxis during or after exercise.

**Author contribution**

Tomoki Yaguchi: Conceptualization; Data Curation; Investigation; Writing – Original Draft Preparation. Katsutoshi Nakano: Writing – Review & Editing (equal). Tadayuki Kumagai: Writing – Review & Editing (equal). All authors read and approved the final manuscript.

**Acknowledgements**

None.

**REFERENCES**

1. Kulthanan K, Ungprasert P, Jirapongsananuruk O, et al. Food-Dependent Exercise-Induced Wheals, Angioedema, and Anaphylaxis: A Systematic Review. *J Allergy Clin Immunol Pract.* 2022;10(9):2280-2296.

2. Ebisawa M, Ito K, Fujisawa T, et al. Japanese guidelines for food allergy 2020. *Allergol Int.* 2020;69(3):370-386.

3. Asaumi T, Yanagida N, Sato S, Shukuya A, Nishino M, Ebisawa M. Provocation tests for the diagnosis of food-dependent exercise-induced anaphylaxis. *Pediatr Allergy Immunol.* 2016;27(1):44-49.

4. Morita E, Matsuo H, Chinuki Y, Takahashi H, Dahlström J, AkiraTanaka. Food-Dependent Exercise-Induced Anaphylaxis—Importance of Omega-5 Gliadin and HMW-Glutenin as Causative Antigens for Wheat-Dependent Exercise-Induced Anaphylaxis—. *Allergol Int.* 2009;58(4):493-498.

5. Shiratsuki R, Chinuki Y, Fukushima S, Morita E. A Case of Pork-cat Syndrome That Developed as Food-dependent Exercise-induced Anaphylaxis. *Acta Derm Venereol.* 2020;100(15):1-2.

6. Medrala W, Cieřlik K, Barg W, Skotny A, Siwak E, Wolanczyk-Medrala A. Naproxen increases the severity of food-dependent exercise-induced anaphylaxis: a case report. *J Investig Allergol Clin Immunol.* 2014;24(6):461-462.

**TABLES**

**Table1 Episodes of Food-Dependent Exercise-Induced Anaphylaxis**

	Episode 1	Episode 2
Foods other than wheat	Beef, pork	Cow’s milk, chick
Age	7 yo	7 yo
Season	May	October
Augmenting factors	–	–
Exercise	Running	Running
Time from intake of culprit food to exercise	1 hour	20 minutes
Onset of anaphylaxis after exercise	1 hour	20 minutes
Symptoms of anaphylaxis	Urticaria, nausea, cough	Eyelid edema, dy
Treatment	Intramuscular adrenaline, β2-stimulant inhalation, steroid	Intramuscular ad