

Wheat-Dependent Exercise-Induced Anaphylaxis

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Opinion statement

Wheat-dependent exercise-induced anaphylaxis (WDEIA) is presently gaining attention. Patients with WDEIA experience allergic symptoms when they exercise following wheat consumption. Some patients may be advised to restrict wheat consumption or exercise because of repeated allergic symptoms without adequate diagnosis or examination. Japanese guidelines recommend that WDEIA should be diagnosed using provocation tests with wheat and exercise. After wheat consumption, patients exercise using a treadmill or an ergometer during provocation tests. Once WDEIA is diagnosed, patients should not consume wheat before physical activity. Exercise is allowed at least 4 h after wheat intake. They may consume wheat if they do not exercise after wheat consumption, and they may exercise without consuming wheat before exercising. All WDEIA patients should be instructed regarding use of adrenaline auto-injector and should carry one with them. Some patients may respond to prophylactic treatment with anti-histamines. However, there is no established drug for preventing WDEIA; moreover, there is inadequate evidence for routine administration of these prophylactic drugs. Cofactors like nonsteroidal anti-inflammatory drugs (NSAIDs) may directly modulate immune reactions and could exacerbate the condition. Hence, patients should avoid these cofactors. The emergency treatment of WDEIA does not differ from that of immediate-type food allergy or anaphylaxis. Exercise should be stopped when patients show food allergy symptoms. When patients show anaphylactic reactions, adrenaline should be quickly administered. Indications for adrenaline auto-injector use are severe symptoms like persistent coughing, breathing with wheeze, persistent abdominal pain, and confusion. However, there is no evidence that

anti-histamines and corticosteroids have lifesaving effects. Consequently, it is important that adrenaline auto-injector is used in an appropriate setting and that the patient is transferred to a hospital immediately. The mechanisms of WDEIA development are unknown. Further research is needed to clarify the mechanisms involved so that it can be treated.

Introduction

Food-dependent exercise-induced anaphylaxis (FDEIA) is a special type of food allergy induced by exercise after ingestion of a specific food [1–3]; it is not caused by exercise or food alone. Maulitz reported the first case of FDEIA in 1979 [1]. FDEIA patients typically present with pruritus, generalized urticaria, angioedema, dyspnea, repetitive cough, wheezing, gastrointestinal symptoms, or hypotension. Symptoms are usually triggered by strenuous exercise like running, aerobics, or ball games [4].

Most patients show FDEIA development in their teens or twenties [5, 6]. Studies have shown that FDEIA-related morbidity was 0.02% in junior high school students in Japan in 1998 and 2012 [7, 8]. However, several FDEIA cases may be underdiagnosed.

While every food can be an allergen, wheat is a common allergen in FDEIA cases, followed by shrimp and fruits [9–15]. Major studies on wheat-dependent exercise-induced anaphylaxis (WDEIA) have been performed mostly in Asia [6, 16]. In some cases, consumption of two food items may be needed to induce WDEIA [17•]. Symptoms are induced only when they consume a combination of foods like wheat and umeboshi (a type of plum) along with exercise [18].

The mechanisms involved in FDEIA are not fully understood. We cannot predict when the first episode of WDEIA will occur. To prevent the development of further WDEIA episodes, accurate diagnosis and education of patients are crucial. Once WDEIA is diagnosed, patients should not consume wheat before physical activity [19].

The aim of this review is to inform physicians that precise diagnosis is important and provocation tests are needed to diagnose.

Special type of WDEIA

Hydrolyzed wheat protein (HWP) is made from gluten and used in many cosmetics worldwide [19]. After the use of facial soap with HWP, 2169 patients developed WDEIA (HWP-WDEIA) [20]. It represents an important

social problem in Japan. Most patients were adults and females [21]. HWP-WDEIA is due to sensitization via percutaneous or rhinoconjunctival route to HWP. An angiotensin-converting enzyme genotype was reported to be a risk factor for HWP-WDEIA [21]. The most common symptom of HWP-WDEIA is angioedema of the eyelids [5]. This may be because angioedema is a symptom consistent with changes related to the angiotensin-converting enzyme or bradykinin.

A previous study reported that the median duration from the discontinuation of soap use to remission was 59.8 months [21]; the only prognostic factor reported was younger age and patients showed that HWP-WDEIA may be clinically cured in many cases.

Diagnosis

While the accurate diagnosis of WDEIA is very important, physicians and patients often are not aware about WDEIA. At the start of the diagnostic procedure, the patient's allergic history data are recorded via a medical examination. To allow free exercise and to avoid unnecessary food elimination, a precise diagnosis is necessary. The available diagnostic tests are blood tests, skin prick tests, and provocation tests. The most important factors for the diagnosis are a precise medical interview and suspicion of WDEIA.

Blood tests and skin prick tests

Although wheat-specific IgE or skin prick tests are not sufficient for the diagnosis of WDEIA [22], omega-5 gliadin-specific IgE is useful for identifying WDEIA [22]. The positive rate with the use of omega-5 gliadin-specific IgE was 93% among adult patients, but only 46% among pediatric patients. In the case of HWP-WDEIA, omega-5 gliadin-specific IgE was not detected in most cases [5]. Similar results were observed in basophil activation tests using omega-5 gliadin [23]. In HWP-WDEIA, the causal protein will differ because of direct percutaneous sensitization by HWP.

The skin prick test does not have adequate efficiency to diagnose WDEIA either. Its sensitivity is 40%, and

specificity is 74% [17•]. This may be because the commercial prick extract contains an unrelated protein rather than an allergic component.

Provocation tests

Provocation tests with the food and exercise are gold standard tests to confirm FDEIA [24]. One protocol is that patients consume a large amount of wheat (e.g., 5.2–10.4 g wheat protein) and aspirin, which is a cofactor involved in FDEIA. Sixty minutes later, they exercise using an ergometer [17•]. The amount of exercise depends on the patients' athletic abilities. If the patients are unable to continue exercising, they stop, because the exertion level may influence the result. A treadmill ergometric stress test is also used (Table 1) [18, 25].

As tests may induce systemic symptoms [26], they should be performed in the presence of allergy specialists in a hospital. One study showed that physicians administered adrenaline in 20% of cases with positive results in provocation tests using food and exercise because of severe symptoms (Fig. 1) [17•]. The initial symptoms were induced within 30 min of exercise initiation in patients who needed adrenaline.

While provocation tests using wheat and exercise should be performed to confirm the diagnosis in WDEIA patients, exercise could be replaced by high gluten doses and other cofactors [27••, 28]. Provocation test results could be false negative because of unknown reasons [27••]. In these cases, repeated tests or additional tests using cofactors may be needed. Plasma histamine levels during provocation tests may be helpful for diagnosis [18, 29].

Differential diagnosis

When diagnosing WDEIA, the possibility of mite ingestion-associated exercise-induced anaphylaxis should be eliminated [30, 31]. A 17-year-old boy developed anaphylaxis owing to exercise after consuming okonomiyaki (Japanese savory pancake with various ingredients) [30]. WDEIA was suspected, but he tested negative for specific IgE to wheat, and provocation test result for wheat and exercise was negative too. He had elevated levels of specific IgE to *Dermatophagoides*, and microscopy revealed several mites in the rest of the okonomiyaki powder. The powder was stored for months after opening the package. He was finally

diagnosed with mite ingestion-associated exercise-induced anaphylaxis.

Augmenting factors

Nonsteroidal anti-inflammatory drug

Aspirin and other nonsteroidal anti-inflammatory drug (NSAIDs) should not be taken in association with wheat or exercise [32]. Aspirin is thought to increase gastrointestinal permeability [33]. Furthermore, aspirin has direct effects on mast cell activation because skin prick test reactions to wheat after aspirin consumption increase [34]. Thus, aspirin and other NSAIDs could exacerbate the condition (Table 2).

Other cofactors

Cofactors other than NSAIDs may directly modulate immune reactions (Table 2). Optimal management of WDEIA based on prospective data is not established, but we should assess the risks involved and plan management based on the medical history [9, 35••, 36].

In some cases, to prevent WDEIA episodes, patients should not exercise in extremely cold or hot weather, in the patients' allergic season, or in humid weather [37]. A cold or warm environment may exacerbate allergic reactions [38–40]. Alcohol consumption may lower the symptom threshold or augment allergic reactions [41, 42]. Antacids like proton pump inhibitors may be augmenting factors for WDEIA through gastric function impairment [43]. Estrogen and progesterone have been reported to influence WDEIA [44, 45], but the mechanism involved has not been established. Infection or hyperthermia may also augment anaphylactic reactions or food allergic symptoms [35].

Exercise as an augmenting factor

In some cases, exercise has augmented food allergy. A previous study reported exercise with wheat-induced anaphylaxis after oral immunotherapy [46] or during oral immunotherapy [47].

Brockow reported on the use of provocation tests using aspirin and alcohol instead of exercise [27••]. They concluded that "Exercise is not an essential trigger for the onset of symptoms in patients with WDEIA."

Table 1. Method of provocation tests and prognosis

Subjects	Number of subjects	Food	Age (years)	Country	Method of provocation tests	References
FDEIA	21	Multiple	5–22	Japan	Aspirin + foods + ergometer (+ running)	[17•]
WDEIA	16	Wheat	23–76	Japan	Aspirin + gluten + alcohol	[27••]
WDEIA	6	Wheat	15–61	Japan	Wheat + treadmill/aspirin	[33]
WDEIA	6	Wheat	7–16	Japan	Wheat + treadmill/running/aerobics (+ aspirin)	[25]
Prognosis						
WDEIA	1	Wheat	65	Japan	Symptoms of FDEIA were caused for 30 years.	[67]
FDEIA	18	Mainly wheat	9–43	Japan	All patients were free of symptoms after avoiding foods or exercise or using medicines.	[56]
HWP-WDEIA	102	Wheat	44 (Mean)	Japan	The median duration from discontinuation of soap use to remission was 59.8 months.	[20]
EIA _n	279	Multiple	13–77	America	Improvement appears to result from individual modification of exercise and avoidance of known environmental and ingestible precipitants.	[37]

FDEIA food-dependent exercise-induced anaphylaxis, WDEIA wheat-dependent exercise-induced anaphylaxis, HWP-WDEIA hydrolyzed wheat protein-sensitized wheat-dependent exercise-induced anaphylaxis, EIA_n exercise-induced anaphylaxis

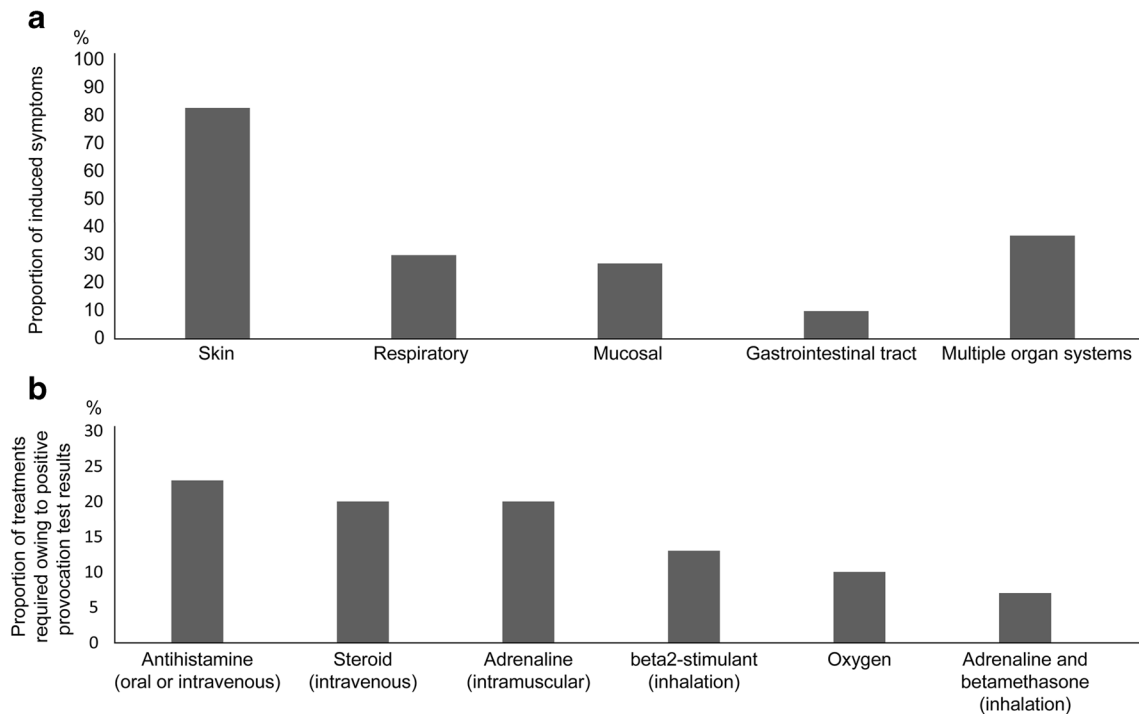


Fig. 1. Symptoms and treatment of provocation tests. **a** Location of symptoms noted after provocation tests with positive results. **b** Level of treatment required in cases of positive provocation test results [17•]. The symptoms and treatment required in patients undergoing provocation tests are summarized. In the 30 cases with positive test results, cutaneous symptoms were seen most frequently (noted in 25 cases [83%]). Medical treatment was provided after tests in 9 cases (30%), including the use of adrenaline after tests in 6 cases (20%). No patient who underwent the test required more than one adrenaline dose.

Matsuo performed provocation tests in which some patients had symptoms with wheat and aspirin without exercise [33]. However, whether these cases can be considered as WDEIA is still debatable because symptoms were induced without exercise.

The mechanism involved in WDEIA remains unknown. Exercise or NSAIDs may be just one of the augmenting factors of food allergy through increased gastrointestinal permeability or some other factors [32, 35••]. In a few decades, the terms WDEIA and FDEIA may change.

Management (Treatment)

Diet and lifestyle

Avoidance of wheat or exercise

Patients should not consume wheat before physical activity. Physical activity within 4 h of wheat consumption should be prohibited [24]. If they have not consumed wheat, they can exercise freely. If they do not intend to exercise later, they can consume wheat. Exercise should always be performed in the presence of a partner who is aware of the patient's condition and is capable of providing emergency assistance including adrenaline administration using an auto-injector.

Table 2. Augmentation factors for food-dependent exercise-induced anaphylaxis

Augmenting factors		References
Drugs	NSAIDs	[27••, 37]
	ACE inhibitors	[35••]
	Beta-blockers	[35••]
	Antacids	[35••]
	Ganja (cannabis)	[6]
Weather	Cold temperature	[38, 39]
	Hot temperature	[40]
	Humid	[37]
General condition	Hyperthermia	[35••]
	Infection	[35••]
	Psyche	[35••]
	Fatigue	[22]
	Stress	[22]
Others	Menstruation	[6]
	Pollen season	[37]
	Alcohol	[27•, 41]
	Bathing	[15]

Action plan and emergency drugs

An action plan for anaphylaxis should be made (see “Emergency treatment” section).

WDEIA patients as well as their companions and schoolteachers should be instructed in the use of an adrenaline auto-injector, and patients should carry one. Patients are also encouraged to carry anti-histamines, corticosteroids, and short-acting beta-2 agonist inhalers. The action plan and information regarding when or how to use the adrenaline auto-injector should be reviewed every year [24].

Pharmacologic treatment

Some authors have reported sodium cromoglycate [48], anti-histamines, leukotriene receptor antagonists, omalizumab, or sodium bicarbonate to be effective treatment of WDEIA [49]. However, no drug that can prevent WDEIA has been established [3], and there are inadequate data to support other drugs [24].

Anti-histamines

Choi reported a case of a 20-year-old woman who, for 7 years, had experienced dyspnea and wheals after ingesting some foods [50]. Based on the provocation test result, she was diagnosed with WDEIA. On taking ketotifen before wheat consumption, the provocation test result was negative. She did not experience recurrent wheals or dyspnea with ketotifen after tests. This is a case of WDEIA with successful prevention by ketotifen.

Leukotriene receptor antagonists

Increased cysteinyl leukotriene production during anaphylaxis has been reported [51, 52].

Peroni reported the effectiveness of montelukast, a leukotriene receptor antagonist, in FDEIA prevention [53]. A 17-year-old adolescent underwent a provocation test using peach and exercise. He had cough, wheeze, nausea, and urticaria after the test. After daily montelukast administration for 3 days, he tested negative on the provocation test with peach and exercise.

Misoprostol

Misoprostol is a derivative of prostaglandin E1 (PGE1). Aspirin inhibits the synthesis of PGE1, which protects the gastrointestinal mucosa.

Inoue examined if misoprostol could prevent an increase in serum gliadin levels and prevent allergic reactions in aspirin-induced WDEIA [54]. On provocation tests, patients' symptoms and serum gliadin levels were monitored. Misoprostol inhibited the symptoms and the increase in serum gliadin levels, which were caused by aspirin, wheat, and exercise. However, sodium cromoglycate did not suppress the symptoms or elevation of serum gliadin levels. Thus, misoprostol or PGE1 may inhibit allergen absorption and prevent allergic reactions in patients with aspirin-induced WDEIA.

Sodium cromoglycate

In food allergic patients, sodium cromoglycate is thought to stabilize mast cells in the gastrointestinal tract and inhibit allergen absorption [55].

Juji and Suke reported a case of WDEIA in which exercise after wheat consumption caused a decrease in forced expiratory volume in 1 s (FEV1) of 19% and increased plasma histamine levels along with urticaria and dyspnea [29]. Sodium cromoglycate administration before bread ingestion and exercise challenge increased the FEV1, but there were no symptoms or an increase in the plasma histamine levels.

Furthermore, Kano et al. performed basophil activation tests on FDEIA patients. The rate of histamine release on anti-IgE stimulation decreased after sodium cromoglycate administration [56].

On the other hand, Benhamou et al. showed the effectiveness of anti-histamine and sodium cromoglycate in patients with FDEIA [57]. Patients had symptoms when they consumed wheat and swam in a cold water pool, but not in a hot water pool. Thus, fexofenadine and sodium cromoglycate could prevent WDEIA in a cold water pool.

Omalizumab

Omalizumab is a recombinant humanized anti-IgE monoclonal antibody approved for the treatment of severe asthma or chronic spontaneous urticaria [58, 59]. Omalizumab suppresses anaphylaxis [60]. The mechanism of action of omalizumab is thought to be a decrease in serum IgE concentrations as well as the stabilization of mast cells by downregulation of IgE receptor expression.

Bray reported on the successful treatment of exercise-induced anaphylaxis using omalizumab [61]. A 14-year-old boy had repeated exercise-induced

anaphylaxis episodes. Adrenaline was administered in some cases. Food restriction before exercise and the use of montelukast, fexofenadine, or sodium cromoglycate were ineffective even in cases of minimal exercise. However, after omalizumab administration, he had no symptoms after strenuous exercise.

The pathophysiology of exercise-induced anaphylaxis remains unknown. However, the effects of omalizumab may be applicable to WDEIA.

Immunotherapy

In the recent decade, oral immunotherapy has been studied in many clinical trials although it has many disadvantages including a low efficacy for real tolerance and a high rate of induced symptoms [62, 63].

Oral immunotherapy using interferon-gamma was administered in two WDEIA cases in Korea [64]. Both patients with WDEIA experienced remission. After treatment, both patients could freely consume wheat.

The authors concluded that oral immunotherapy using interferon-gamma was effective for treating WDEIA. However, the patients showed allergic symptoms many times during the immunotherapy. Emergency treatment was done when they showed anaphylactic reactions. Because of many adverse reactions, oral immunotherapy for FDEIA using interferon-gamma is not recommended in clinical practice.

Emergency treatment

Exercise discontinuation

Emergency treatment of FDEIA does not differ from that of immediate-type food allergy or anaphylaxis. As emergency treatment, patients should stop exercising when they note the earliest warning signs. Anaphylaxis is a severe, systemic hypersensitivity reaction. It is characterized by rapid onset with life-threatening airway, breathing, or circulatory problems, usually accompanied by urticaria or cough [65].

First line treatment

Adrenaline is potentially lifesaving and has to be used quickly as the first-line treatment for the emergency management of anaphylaxis. It reverses hypotension through vasoconstriction and increasing cardiac output and induces bronchodilation. Severe symptoms like persistent coughing, breathing with wheeze, persistent abdominal pain, and confusion can be treated using an adrenaline auto-injector [3]. The patient should be placed in a supine position with the legs raised, and adrenaline should be rapidly administered using the auto-injector [66]. Adrenaline should be administered at least 5 min apart if the patient requires subsequent adrenaline doses [65]. The patient should be maintained in the supine position and quickly transported to the hospital for further treatment and management.

Second line treatment

Inhaled short-acting beta-2 agonists should additionally be given to relieve airway obstruction symptoms [65]. Patients may initially be treated with in-

haled short-acting beta-2 agonists alone when the symptom is only mild wheeze.

Anti-histamines and corticosteroids can also be used in patients with FDEIA. Anti-histamines are commonly administered for anaphylaxis, but they only ameliorate cutaneous symptoms [65]. Similarly, corticosteroids are thought to possibly suppress protracted anaphylaxis symptoms and biphasic reactions. There is no evidence that these drugs have lifesaving effects.

Treatment in medical facility

In addition to the previous treatment, high flow oxygen, normal saline bolus, and call for staff are required. Repeat intramuscular adrenaline, repeat fluid bolus, and set up adrenaline infusion are sometimes necessary.

Prognosis

Prognosis of FDEIA is not clear, but some studies have reported on prognosis (Table 1). Terao reported a patient who had experienced WDEIA for 30 years without an accurate diagnosis [67]. Kano followed 18 FDEIA patients who had been educated regarding food avoidance or drug use [56]. All patients were free of symptoms between 1 and 9 years. Shadick surveyed 279 patients with exercise-induced anaphylaxis including WDEIA [37]. Half of them (47%) said that the anaphylaxis episodes had decreased since onset after they avoided the triggers, whereas 46% of patients stated that the episodes had remained the same since onset. Only 7% of the patients mentioned that these episodes had increased. Furthermore, during follow-up, 41% of the patients said that symptoms of exercise-induced anaphylaxis had completely disappeared. However, in both studies, provocation tests with food and exercise were not performed. Thus, prognosis is unclear, but most WDEIA patients would be free of symptoms by avoiding some foods or taking medications.

Conclusions

FDEIA should be diagnosed using provocation tests. Once WDEIA is diagnosed, patients can consume wheat if they do not intend to exercise. We should repeatedly educate patients regarding when and how to use an adrenaline auto-injector. While the prognosis of FDEIA is unclear, patients should not fear the attacks. Adequate preparation will save lives. An individualized action plan and a strategy for management considering cofactors should be made based on the medical history.

The mechanisms related to WDEIA remain unknown. Hence, further studies need to be performed. Exercise or NSAIDs may be just one of the augmenting factors.

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Compliance with Ethical Standards

Conflict of Interest

Tomoyuki Asaumi declares that he has no conflict of interest. Tetsuharu Manabe declares that he has no conflict of interest. Noriyuki Yanagida declares that he has no conflict of interest. Sakura Sato declares that she has no conflict of interest. Motohiro Ebisawa declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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