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# Exercise-food challenge test in patients with wheat-dependent exercise-induced anaphylaxis

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## Abstract

**Background:** Wheat-dependent exercise-induced anaphylaxis (WDEIA) is a severe and potentially life-threatening food allergy. Diagnosis of WDEIA is challenging because reactions are not always reproducible.

**Objective:** This study aimed to evaluate the positivity rate of exercise-food challenge test at our allergy unit in order to confirm the diagnosis, and to investigate the effect on the episode of reactions after the test.

**Methods:** This retrospective evaluation included patients aged 5-60 years who presented at the pediatric and adult allergy units of Siriraj Hospital during 2014-2018 with a convincing history of WDEIA and who underwent a 4-day exercise-food challenge test. Demographic data, challenge test result, and episodes of the reaction before and after the challenge test were obtained.

**Results:** Fourteen of the 17 patients that were enrolled were included in the analysis. The 3 excluded patients were found to have IgE-mediated wheat allergy. Median age and time to diagnosis was 18.3 years (range: 10.5-43.4) and 1.8 years (range: 0.3-6.2). History of recurrent acute urticaria before the onset of anaphylaxis was reported in 5 patients (35.7%). Exercise-food challenge test was positive in 10 patients (71.4%). Median mean number of exacerbations per year before and after the confirmation test was 2 (range: 1-10) and 1 (range: 0-3), respectively.

**Conclusion:** For WDEIA, time to diagnosis was delayed, and one-third of patients had recurrent acute urticaria proceeding anaphylaxis onset. Our exercise-food challenge test could be utilized safely in both children and adult and able to elicit symptoms in two-third of patients.

**Key words:** Adult, anaphylaxis, children, exercise-food challenge test, wheat allergy, wheat-dependent exercise-induced anaphylaxis

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## Introduction

Wheat-dependent exercise-induced anaphylaxis (WDEIA) is a distinct form of food allergy that occurs after a combination of wheat ingestion and exercise. The symptoms can range from generalized urticaria to severe and potentially life-threatening anaphylaxis.[1,2] The time between wheat ingestion and exercise normally ranges from 30 minutes to 4 hours; however, food exposure after exertion can also cause a reaction.[3,4] Other factors, such as nonsteroidal antiinflammatory drugs (NSAIDs), e.g., acetylsalicylic acid (ASA), alcohol, stress, and infection, can also promote onset of symptoms, and can sometimes elicit a reaction without physical exercise.[5-7] Although, the pathophysiology is not fully understood, NSAIDs has been shown to increase intestinal absorption and permeability of allergens, and augment the degranulation of mast cells.[2,3]

It has been shown that skin tests and measurement of specific IgE (sIgE) to wheat, gluten, and particularly omega-5-gliadin (ω5G) might help to determine the diagnosis.[8,9]

However, the sensitivity and specificity of those investigations are not always satisfactory, so exercise-food challenge test remains the gold standard to confirm diagnosis. This provocation test is usually performed by providing a large amount of suspected food to the patient with or without the use of cofactors, followed by exercise challenge test in a hospital setting. Even though this test is considered the gold standard diagnostic test, reactions are not always reproducible because multiple factors involved in trigger a reaction and this makes diagnosis of WDEIA very challenging.[10] Patients usually develop multiple episodes of the reaction, and a delay in WDEIA diagnosis is common due to a lack of awareness among both patients and physicians,[8,11] particularly in patients with a negative challenge test result.

Moreover, standardization of the test protocol has not yet been established, so the protocols used vary widely among centers, and this variation can affect the positivity rate of the challenge test.

This retrospective study was conducted to evaluate the positivity rate of an exercise-food challenge test protocol that is used in both children and adults at our center to confirm the diagnosis, and to investigate the effect on the number of episodes of the allergic reaction before and after conducting the challenge test.

## Materials and Methods

Patients aged from 5 and 60 years with a history of WDEIA who came or were referred to the pediatric or adult allergy clinic of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during 2014 to 2018 were enrolled in this study. A diagnosis of WDEIA was made based on convincing clinical history of having an immediate allergic reaction after wheat ingestion followed by exercise within 4 hours or vice versa, with the last episode of the reaction having occurred during the past one year before enrollment combined with either skin prick test (SPT) result to wheat ≥ 3 mm using wheat extracts (1:10 w/v) in Coca's solution and 10% alcohol[12] and/or level of sIgE to wheat and/or ω5G > 0.35 $kU_A/L$ using the ImmunoCAP System (Phadia, Uppsala, Sweden) during the past six months. The protocol for this study was reviewed and approved by the Human Ethics Committee of the Faculty of Medicine Siriraj Hospital (COA no. Si 822/2018). Written informed consent from parents or guardians and assent from children older than 7 years of age were obtained.

Demographic and clinical data, including gender, age at enrollment, age of onset, time to diagnosis, duration of disease (defined as the time from onset of disease until the enrollment period), other food allergy and allergic diseases, family history of allergic diseases, the initial and the most severe clinical reaction of WDEIA, onset of symptoms after wheat ingestion and exercise, and mean number of episodes of the reaction before and after provocation test per year, were collected and recorded. Diagnoses of other allergic diseases and other types of food allergy were made by allergists. Allergy to other foods was defined as a patient having had a clear symptomatic reaction to food with a positive SPT and/or sIgE to specific foods. Anaphylaxis was defined according to the clinical criteria from the World Allergy Organization anaphylaxis guidelines, and anaphylaxis severity was classified using the Brown system for grading hypersensitivity reactions including anaphylaxis.[13] All patients suspected of having WDEIA (either positive or negative provocation result) were instructed to strictly avoid consuming wheat products followed by exercise/cofactors within at least 4 hours, in addition to receiving a prescription for an adrenaline auto-injector or an adrenaline prefilled syringe.

### *4-day challenge protocol*

All patients underwent a medically supervised 4-day wheat-exercise challenge protocol during hospital admission (**Figure 1**). An intravenous catheter was placed before the start of the challenge test in all patients. ASA graded challenge test was performed on the first day using a total dose of

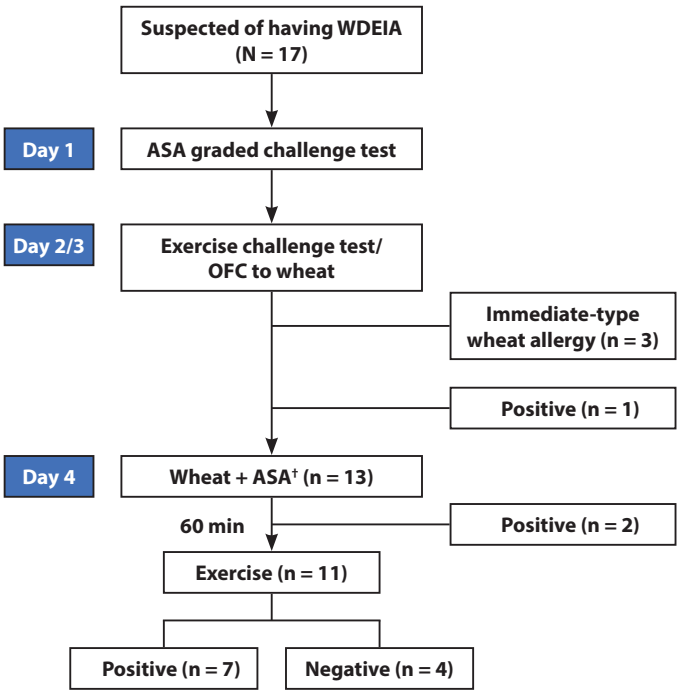


**Figure 1. Flow diagram of study subjects and challenge result**

Among 17 patients suspected of having WDEIA, 3 were excluded because they developed immediate reaction after OFC to wheat. The remaining 14 patients were included in our analysis. One patient (patient 5) developed a reaction after consuming wheat on the second day, followed by exercise on the third day of the challenge test (24 hours apart). Repeated exercise challenge test was performed with negative result; therefore, she was diagnosed as WDEIA. The remaining 13 patients were given the challenge test on day 4. Of those, 2 patients developed a reaction after receiving only wheat + ASA (patients 2 and 13); 7 patients developed a reaction after wheat + exercise (+ASA) (patients 1, 3, 4, 6, 10, 11, and 12); and, the other 4 patients (patients 7, 8, 9, and 14) had a negative provocation test result.

**Abbreviations:** ASA, aspirin; OFC, oral food challenge; WDEIA, wheat-dependent exercise-induced anaphylaxis
†ASA was given to these 11 patients (patients 1, 2, 3, 4, 6, 9, 10, 11, 12, 13, and 14) on the final day of testing

10 mg/kg/dose (maximum 300 mg) for children, and 300-381 mg for adults (except in patients who had a hypersensitivity reaction to anti-inflammatory drugs). Either oral food challenge (OFC) test to wheat or exercise challenge test was performed the following day, depending on the availability of the challenge room and physicians. OFC to wheat was conducted in an open fashion with a cumulative dose of 4 slices of bread (60 gm of wheat or 7.6 gm of wheat protein) in children and 5 slices of bread (75 gm of wheat or 9.5 gm of wheat protein) in adults. Exercise challenge test was performed using a motor-driven treadmill with slope and speed adjustment to achieve 80% of maximum heart rate during the first two to five minutes with subsequent maintenance this targeted heart rate for at least 4 minutes in children, for at least 15 minutes in adults,[14,15] or for as long as could be tolerated. The temperature and humidity in the testing room was kept at 25-30°C and 40-50%, respectively. Spirometry was performed at baseline (before test) and at 5, 10, 15, and 30 minutes after the test. After each challenge test, the patient was closely observed for 2 hours, after which the patient was normally observed in the ward for the remaining 22 hours to complete a 24-hour observation period. The result was determined to be positive if any type of allergic reaction consistent with IgE-mediated symptoms occurred. If no reaction developed, then the patient underwent a combination provocation test on the final day of testing. Administration of ASA as a cofactor (to increase the sensitivity of the test), and then administration of 4-5 slices of bread, and then exercise challenge test was conducted with a 30-60-minute period between each of the 3 tests. A positive challenge test result was determined as described above.

### *Statistical analysis*

All data analyses were performed using SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA). Data are presented as median and range, median and interquartile range (IQR), number and percentage, or percentage. Chi-square test was used to compare categorical variables between groups and Mann-Whitney U test was used to compare non-normally distributed continuous variables. A *p*-value less than 0.05 indicates statistical significance.

Patients who underwent the challenge test, but who were confirmed to have a classical immediate type reaction to wheat allergy (positive wheat challenge test result), and those with exercise-induced anaphylaxis (positive exercise challenge test result) without wheat ingestion were excluded from the analysis.

## Results

Seventeen patients were initially enrolled; however, 3 of those patients were subsequently determined to have IgE-mediated reactions to wheat. After exclusion of those 3 patients, the 14 remaining patients were included in the final analysis (**Figure 1**). The median age at enrollment was 18.3 years (range: 10.5-43.4), and the median time to diagnosis was 1.8 years (range: 0.3-6.2). The median age of onset and duration of disease was 14 years (range: 5-40) and 3.5 years (range: 0.8-14.4), respectively. Other food allergies were found in only one patient (7.1%), while allergic rhinitis (AR) was reported in 7 patients (50.0%). No patients reported having asthma or atopic dermatitis. Family history of any allergic diseases was reported in 2 patients (14.3%) (**Table 1**).

Comparison between groups according to the age of onset [< 15 years (n = 9) from the pediatric allergy unit, or ≥ 15 years (n = 5) from the adult allergy unit] revealed no statistically significant differences for gender, time to diagnosis, duration of disease, or personal and family history of allergic diseases (**Table 1**).

History of clinical reaction and allergy testing to wheat for each patient is shown in **Table 2**. Cutaneous symptom (urticaria with or without angioedema) was the most common presentation (100% of patients), followed by cardiovascular symptoms (syncope, hypotension, diaphoresis, loss of consciousness) (85.7%), respiratory symptoms (dyspnea, chest tightness) (78.6%), and gastrointestinal symptoms (vomiting, abdominal pain) (28.6%). Using the Brown grading system, the severity of the presenting symptom was classified as severe in 11 patients (78.6%), moderate in 2 patients (14.3%), and mild in 1 patient (7.1%). Recurrent acute urticaria related to wheat ingestion and exercise was reported to precede the onset of anaphylaxis in 5 patients (35.7%) with a median

**Table 1. Demographic and clinical characteristics of study patients**

| Characteristics | Total (N = 14) | Age of onset < 15 years (children: n = 9) | Age of onset ≥ 15 years (adult: n = 5) |
|---|---|---|---|
| Male gender, n (%) | 6 (42.9%) | 4 (44.4%) | 2 (40.0%) |
| Current age (y), median (range) | 18.3 (10.5-43.4) | 15.8 (10.5-21.4) | 31.8 (22.3-43.4) |
| Age of onset (y), median (range) | 14 (5-40) | 10 (5-14.5) | 30.4 (17-40) |
| Time to diagnosis (y), median (range) | 1.8 (0.3-6.2) | 1.8 (0.4-3.8) | 1.8 (0.3-6.2) |
| Duration of disease (y), median (range) | 3.5 (0.8-14.4) | 4 (1.3-14.4) | 3.1 (0.8-7.6) |
| Allergic diseases, n (%) | | | |
| Other food allergy | 1 (7.1%) | 1 (11.1%) | 0 (0.0%) |
| Allergic rhinitis | 7 (50.0%) | 3 (33.3%) | 4 (80.0%) |
| Family history of any allergic diseases, n (%) | 2 (14.3%) | 2 (22.2%) | 0 (0.0%) |

**Table 2. History of clinical reaction and allergy testing to wheat**

| Patient no. | History of clinical reaction | Brown grading | Onset of reaction (min) | Allergy testing to wheat | | |
|---|---|---|---|---|---|---|
| | | | | MWD of SPT (mm) | SIgE to wheat ($kU_A/L$) | SIgE to ω5G ($kU_A/L$) |
| 1 | CU, CVS, RS | 3 | 5-220 | 5.5 | 1.16 | 5.19 |
| 2 | CU, CVS | 3 | 30-60 | 14 | 4.45 | 9.41 |
| 3 | CU, CVS, RS | 2 | 20-60 | 2 | 5.12 | 0.07 |
| 4 | CU, CVS, GI, RS | 3 | 5-60 | 10 | 0.29 | 2.56 |
| 5 | CU, CVS, GI, RS | 3 | 30 | 5 | 3.03 | 13.2 |
| 6 | CU, CVS, RS | 3 | 10-180 | 6 | 1.71 | 1.70 |
| 7 | CU, CVS, RS | 3 | 5-210 | 5.5 | 0.77 | 7.02 |
| 8 | CU, CVS, GI, RS | 3 | 5-10 | 10.5 | 1.49 | 3.02 |
| 9 | CU, CVS, RS | 3 | 5-180 | 9.5 | 1.78 | 8.43 |
| 10 | CU, CVS | 3 | 20-30 | 10.5 | 0.09 | 2.75 |
| 11 | CU | 1 | 30 | Negative | 0.43 | 1.26 |
| 12† | CU, CVS, GI, RS | 3 | 20-120 | 6.5 | 0.54 | 4.52 |
| 13 | CU, RS | 2 | 30-60 | 16.5 | 14.2 | 57.3 |
| 14† | CU, CVS, RS | 3 | 30-480 | 4.5 | 0.28 | 0.01 |
| Total | CU 100%<br>CVS 85.7%<br>RS 78.6%<br>GI 28.6% | Severe 78.6%<br>Moderate 14.3%<br>Mild 7.1% | 5-480 min | 6.3 mm<br>(4.9-10.5) | 1.3 $kU_A/L$<br>(0.4-3.4) | 3.8 $kU_A/L$<br>(1.6-8.7) |

† Data in patient no. 12, and 14 had also been published elsewhere (reference 15)
Data presented as median (IQR), percentage, or range
**Abbreviations:** MWD, mean wheal diameter; SPT, skin prick test; sIgE, specific IgE; ω5G, ω-5 gliadin; CU, cutaneous; CVS, cardiovascular; GI, gastrointestinal; RS, respiratory

**Table 3. Exercise-food challenge test results**

| Patient no. | Challenge test | Onset of reaction | Reaction | Brown grading |
|---|---|---|---|---|
| 1 | ASA + wheat + exercise | 10 min | Generalized urticaria, flushing, dyspnea (CU, RS) | 2 |
| 2 | ASA + wheat | 30 min | Angioedema at perioral area (CU) | - |
| | Wheat + exercise | 18 min | Generalized urticaria, angioedema (CU) | 1 |
| 3 | ASA + wheat + exercise | 18 min | Generalized urticaria, flushing (CU) | 1 |
| 4 | ASA + wheat + exercise | 7 min | Generalized urticaria, hypotension, dyspnea, desaturation (CU, CVS, RS) | 3 |
| 5 | Wheat (day 2) + exercise (day 3) | 24 h | Vomiting, syncope, hypotension (CVS, GI) | 3 |
| | Exercise | - | No reaction | - |
| 6 | ASA + wheat + exercise | 16 min | Generalized urticaria, angioedema, hypotension (CU, CVS) | 3 |
| 7 | Wheat + exercise‡ | - | No reaction | - |
| 8 | Wheat + exercise‡ | - | No reaction | - |
| 9 | ASA + wheat + exercise | - | No reaction | - |
| 10 | ASA + wheat + exercise | 30 min | Urticaria (CU) | - |
| 11 | ASA + wheat + exercise | 5 min | Urticaria (CU) | - |
| 12† | ASA + wheat + exercise | 15 min | Generalized urticaria, hypotension (CU, CVS) | 3 |

**Table 3. (Continued)**

| Patient no. | Challenge test | Onset of reaction | Reaction | Brown grading |
|---|---|---|---|---|
| 13 | ASA + wheat | 45 min | Generalized urticaria, angioedema, dyspnea (CU, RS) | 2 |
| 14† | ASA + wheat + exercise | - | No reaction | - |

† Data in patient no. 12, and 14 had also been published elsewhere (reference 15)
‡ ASA was not given due to a history of hypersensitivity reaction to anti-inflammatory drugs
**Abbreviations:** ASA, aspirin; CU, cutaneous; CVS, cardiovascular; GI, gastrointestinal; RS, respiratory

**Table 4. Mean episodes of the reaction per year in patients with wheat-dependent exercise-induced anaphylaxis (WDEIA) before and after diagnosis**

| | Episodes of the reaction before diagnosis | | Episodes of the reaction after diagnosis | |
|---|---|---|---|---|
| No. of episodes | Challenge positive (n = 10) | Challenge negative (n = 4) | Challenge positive (n = 10) | Challenge negative (n = 4) |
| 0 | 0 (0.0%) | 0 (0.0%) | 5 (50.0%) | 1 (25.0%) |
| 1-2 | 6 (60.0%) | 2 (50.0%) | 5 (50.0%) | 2 (50.0%) |
| 3-4 | 4 (40.0%) | 1 (25.0%) | 0 (0.0%) | 1 (25.0%) |
| ≥ 5 | 0 (0.0%) | 1 (25.0%) | 0 (0.0%) | 0 (0.0%) |
| Median | 2 (range: 1-10) | | 1 (range: 0-3) | |

duration of 3 years (range: 1-7). The time between wheat ingestion and onset of the reaction ranged from 5-480 minutes. The median mean wheal diameter (MWD) of SPT to wheat was 6.3 mm (IQR: 4.9-10.5). The median level of sIgE to wheat and ω5G was 1.3 $kU_A/L$ (IQR: 0.4-3.4) and 3.8 $kU_A/L$ (IQR: 1.6-8.7), respectively. The median level of sIgE to wheat and ω5G, and median MWD of SPT to wheat were not significantly different among the three grading groups.

Exercise-food challenge test result was positive in 10 patients (71.4%) (**Figure 1**). Among those patients, positive reaction after taking only ASA and wheat (without exercise) occurred in 2 patients (patients 2 and 13). Onset of the reaction occurred within 45 minutes after the challenge test in all patients except for patient 5 who developed a reaction after consuming wheat on the second day, followed by exercise with no reaction on the third day of the challenge test (24 hours apart). This patient underwent exercise challenge test on the following visit and no reaction occurred. According to Brown grading, severe reaction occurred in 4 patients (40%), and moderate reaction occurred in 2 patients (20%). Adrenaline was given to all patients with a moderate to severe reaction (60%), and no further exacerbations were observed (**Table 3**).

The median number of mean reactions per year before and after the diagnosis was 2 (range: 1-10) and 1 (range: 0-3), respectively. Of the 10 patients with a positive challenge test, 5 (50%) had no additional episodes of the reaction after the confirmation test. One patient (25%) in the negative challenge test result group had no additional episodes of the reaction after the confirmation test (**Table 4**).

## Discussion

Very few studies have reported the results of provocation testing for WDEIA in children.[16,17] The majority of studies have reported provocation testing for WDEIA in adult population,[2,5,6,18] including protocol used for our adult WDEIA patients.[15] In the present study, we demonstrated that the exercise-food challenge test protocol used at our center can be performs uniformly in both children and adult patients. It was also shown to have good efficacy for confirming the diagnosis, and for reducing subsequent episodes of the reaction after the test, particularly among those with positive challenge test result.

Our study showed that children and adults with WDEIA share similar clinical characteristics, which has never been compared before. Among those, time to diagnosis was delayed by about 2 years. This finding is similar to that reported by Wong G K Y, et al.[19] who found that diagnosis took ≥ 32 months in half of their adult patients with WDEIA, and similar to that reported by Kennard L, et al.[18] who reported that diagnosis took 1-5 years in 40% of patients with WDEIA, and longer than 5 years in 29% of patients. We found the median duration of disease to be 3.5 years in our study population; however, little is known about the natural history of this disease. The median age of tolerance among children with IgE-mediated wheat allergy was reported to be approximately 6 years of age.[20,21]

Interestingly, recurrent acute urticaria was reported to be the initial clinical presentation before the onset of anaphylaxis in approximately one-third of our patients (35.4%). Though only cutaneous symptom does not fulfill the diagnostic criteria for anaphylaxis, it is known to be a manifestation of WDEIA.[1,2,11,19] Allergic rhinitis was found in half of our patients, whereas other allergic diseases and family history of

allergic diseases were surprisingly low when compared to a study in IgE-mediated wheat allergy children from the same race.[22] Nevertheless, it remains unknown whether these factors are risk factors in this disease condition.

Cutaneous symptoms were the most common presenting symptom in this study (100% of cases); however, cardiovascular and respiratory symptoms were not uncommon, which explains why the majority of our patients were classified as severe reaction (78.6%). This result is similar to those reported from several previous studies.[6,18,19] Although the terminology is called "wheat-dependent exercise-induced anaphylaxis", the symptoms can range from pruritus and urticaria to anaphylaxis. Despite, allergy testing for wheat are useful in the diagnosis of WDEIA, our study showed that their SPT size and/or the sIgE level were not correlated with the severity of patient reactions.

The exercise-food challenge test protocol that is used at our center could elicit symptoms in two-thirds of patients (71.4%). This is similar to reports from Fukunaga A, et al.[23] that revealed a positivity rate of 77.8% among 9 adults with food-dependent exercise-induced anaphylaxis (FDEIA) and studies from Thongngarm T, et al.[15] and Pacharn P, et al.,[17] whom reported 65% and 80% positivity among 12 adults and 5 children with WDEIA, respectively. However, this rate is higher than the 49% rate reported by Asumi T, et al.[16] in pediatric patients with positive provocation test result among FDEIA patients. This difference between studies may be due to the fact that their study included WDEIA and other types of food allergies, and they also used a different challenge protocol. ASA is routinely used at our center to increase the sensitivity of the exercise-food challenge test as previously demonstrated in several studies.[2,5,7,16,23] In addition, using ASA and wheat without exercise was able to elicit symptom in two of our patients (14.3%). Furthermore, the high positivity rate elicited by our provocation protocol might be due to the consistent control of the room temperature and humidity in the challenge room, and the intensity of the exercise. Warmer environment, higher humidity, and higher intensity of exercise were all reported to be factors that can trigger a reaction.[4,11,24] Although the mechanism of these cofactors facilitate the reaction are uncertain, but current hypotheses include changes in intestinal permeability, alteration of blood flow redistribution, and acid-base balance.

Of note, there were three patients who had a negative sIgE to wheat (but positive sIgE to ω5G, patients 4 and 10), or negative sIgE ω5G (but positive sIgE to wheat, patient 3), and subsequently reacted during the exercise-food challenge test. Therefore, in case of having an evocative clinical history to WDEIA, but negative or doubtful of the *in vivo* or *in vitro* test, exercise-food challenge test remains mandatory to confirm the diagnosis.

Onset of the reaction typically occurred within the first hour after the challenge test; however, one patient developed symptom 24 hours after the test (patient 5). Similarly, a study from China reported a 51-year-old man who experienced two episodes of anaphylaxis within 10 to 24 hours after wheat ingestion and exercise.[25] The precise mechanism of this delayed onset is unknown, but it may be due to delayed gastric emptying time. This patient had a compatible clinical history of WDEIA, with the positive *in vitro* (sIgE to wheat 3.03 $kU_A/L$, sIgE to ω5G 13.2 $kU_A/L$) and *in vivo* testing (SPT size to wheat of 5 mm) to wheat. Despite, an unusual delayed of the onset of reaction during the food exercise challenge test with an imprecise mechanism, this patient is currently avoidance of eating wheat-containing food for 4-6 hours before and after physical exertion, and she also tolerates from the isolated physical exertion and isolated wheat consumption without any reaction.

Even though this challenge test is considered safe to perform, it induced a reaction severe enough to require adrenaline administration in more than half of our patients, particularly among children (3 from 9 children developed severe reaction during the test vs. only 1 from 5 adult patients). This challenge should, therefore, be performed in appropriately screened patients after obtaining written informed consent to do so, and it should only be performed by a team of experienced allergists who have all necessary resuscitation drugs and equipment at their disposal.

Multiple episodes of the reaction occurred among our WDEIA patients, but these episodes were reduced after confirmation of WDEIA diagnosis. Half of patients with positive challenge test result had no further episodes of the reaction compared to only a quarter of patients among the negative result group despite both groups receiving the same management instruction. This finding seems to suggest increased awareness and vigilance among positive result patients. This observed benefit of reduced episodes of the reaction may outweigh the risks associated with performing this challenge test. Furthermore, regards to our clinical observation and this result, this could explain the reason that we routinely used ASA in our center, in order to increase the sensitivity of the test, and raise patient awareness after the positive test.

The limitations of this study include its small study population and its retrospective design. However, WDEIA is not a common disease, particularly among children. Further prospective multicenter study in a much larger sample is needed to confirm the findings of this study.

In conclusion, time to diagnosis was delayed, and one-third of patients had recurrent acute urticaria proceeding the anaphylaxis episode of WDEIA. Our exercise food challenge test could be utilized safely in both children and adult and able to elicit symptoms in two-third of patients, and episodes of the reaction were also decreased after the test.

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## Conflict of interest declaration

All authors declare no personal or professional conflicts of interest relating to any aspect of this study.

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