Review of Wheat Dependent Exercise Induced Anaphylaxis with Two Cases, and a New Co-Factor - Myorelaxant

Ayse Baccioglu*, Fusun Kalpaklıoglu, and Gulben Altan
Kirikkale University Medical Faculty, Department of Pulmonary Diseases, Turkey

INTRODUCTION
Anaphylaxis defines an acute, life-threatening reaction with presentations that concern skin, respiratory, gastrointestinal, or cardiovascular systems [1]. It may be caused by a variety of triggers, and called idiopathic with no identification of causes [2,3]. The number of diagnosis of this kind of anaphylaxis is declining, due to the increasing recognition of new disorders, such as wheat dependent exercise induced anaphylaxis (WDEIA) [4]. The prevalence of this rare condition is increasing steadily [5]. It may be seen in both children and adults, and develops after physical activity within 1-2 hours of food consumption [4]. Its’ mechanisms include both IgE mediated with foods, and non-IgE mediated with exercise that lead to an increased mast cell degranulation due to hyperosmolality, and an increased intestinal absorption of allergens [6]. Some of the cases with EIA are associated with co-factors, and the most common one is food especially wheat ingestion [7]. Here, we present two cases which are a good model for “co-factor mediated” anaphylaxis. Written informed consents were obtained.

CASE 1
Thirty-eight years old male patient had experienced anaphylaxis attacks for three years. His last attack was two months ago with a sudden onset of itching, generalized urticaria, dyspnea, dizziness, and hypotension. He reported three different foods in each attack as ravioli, hamburger, and toast, and use of myorelaxant (fenyramidol hcl). However, he was able to ingest these foods and used the same drug with no problem between the attacks. The patient didn’t have a history of atopy, allergy, food, and/or drug intolerance.

In Allergy Department, an examination of idiopathic anaphylaxis was started with skin prick tests (SPT)s with aeroallergens and foods which were found to be positive only with wheat. SPTs using fresh flours (wheat, barley, corn, rice, rye, oat) were positive to wheat and barley, and intradermal tests (ID)s were resulted positive to all, except rice. Oral challenge tests with these flours, and 6-minute walking test (6MWT) were negative. He was diagnosed WDEIA with a result of anaphylaxis after 6MWT within 10 minutes of wheat ingestion.

Serum specific IgE to gluten and to flours were negative, whereas it was positive to ω-5 gliadin (1.87kUA/l) (Immuno CAP). Since the patient was consuming gluten, celiac disease screening tests with serum anti-gliadin and tissue transglutaminase IgA-G were negative.

Finally, WDEIA was treated with a prescription of adrenalin auto-injector, and he was advised not to exercise one hour after meal or not to eat wheat products as well as myorelaxant three hours before and one hour after exercise.

CASE 2
Twenty-two years old male patient had experienced two anaphylaxis attacks in a year. In the last one, he was admitted
to the emergency department with generalized urticaria, angioedema, and hypotension within one hour of onset. He was treated with adrenalin, methyl prednisolone, and feniramin. He didn’t have any history of atopy, food or drug intolerance. He reported pastry food in each attack, and last one happened during a rush walking after wheat ingestion. On the other hand, pastry was his every day meal without causing any problem.

One month after anaphylaxis, SPTs were found to be positive to wheat. Diagnostic search was negative by means of oral challenge test with wheat, 6MWT, 6MWT after wheat ingestion. We suggested a treadmill test since the exercise’s intensity might had been low which he refused. He was overweight (BMI: 38.2kg/m²), and it seemed hard for him to cycle/run. However, serum specific IgE to ω-5gliadin (1.87kIU/l) was positive, whereas gluten and flours mix specific IgE, celiac serum screening tests were all negative (Immuno CAP). He was diagnosed WDEIA, and was treated as the same as the above case.

DISCUSSION

The prevalence of WDEIA is unknown but we may accept it as rare since the prevalence of EIA was detected less than 1%, and about 30% of cases with EIA were associated with food ingestion [4,5,8]. Age of subjects with EIA in the literature were reported within a range of 4-74 years [5,8].

There may be several mechanisms in WDEIA. Even though mast cell degranulation is induced by wheat IgE antibodies which is observed in skin biopsies and in serum [6,7]. On the other hand, food ingestion alone is unable to trigger the reaction despite the patient being sensitized to specific foods. Therefore, other mechanisms are likely to be involved. European Academy of Allergy and Clinical Immunology (EAACI) position statement on EIA had proposed the following hypothesis [6]; 1- Gastrointestinal permeability is altered during thermal changes, drug intake, and prolonged exercise, by relaxation of intestinal tight junctions which leads to an increase in transport of allergens, 2- Prolonged exercise increases plasma osmolality that rises basophil releasibility and histamine production, 3- Finally, exercise reduces cellular pH, triggering mast-cell degranulation.

First, it is advised to perform SPTs with common inhalant and food allergens [9]. Gluten is not only found in wheat but is related to cereal grains e.g. wheat, rye, barley, triticale. This is why SPTs and intradermal tests showed positivity to most of the cereals in our cases. SPT responses to native gluten flour were concordant with positive specific ω-5 gliadin IgE levels which show that it could be a screening test for the disease. If negative, prick-prick test with fresh suspected food is done. An oral challenge test with the suspected food starting with minimal dose to increasing doses should be performed (Figure 1). If the challenge is positive, food allergy is diagnosed. However, if the oral challenge is negative, there are two possibilities [4]; Firstly, the patient may not have a sensitivity to that food which can be confirmed with serum food specific IgE. Secondly the mechanism may be non-IgE mediated with co-factors. In this regard, an exercise test on fasting should be performed for EIA. If positive, the diagnosis of EIA is achieved; if negative, an exercise test after 1 hour from the assumption of the suspected food should be followed [9]. Still, the test may give false-negative results. The need of concomitant factors, such as cold/warm temperature, acetylsalicylic acid, alcohol, or other reasons may partly account for such outcome by increasing plasma gliadin levels [7]. Brockow, et al., reported 36% of positivity in suspected cases of WDEIA by wheat plus exercise challenge [10]. They also advised that WDEIA can be

**Figure 1** Diagnostic approach to WDEIA is presented. Although there are no definite diagnostic criteria, most common possible positive tests are shown as “±” accompanied with an absolutely negativity as “-” in exercise and wheat challenge alone.
Wheat “Triticum aestivum”

Soluble part
(e.g. α-amylase inhibitors*, lipid transfer protein*.*, peroxidase, and others)

Insoluble part
(Glutens)

Glutenins
(High** and low*** molecular weight)

Gliadins
(α***, β****, γ, ω***)

Transglutaminase****

**Figure 2 Components of wheat and associated diseases (*: Baker’s asthma, **: WDEIA, ***: Type 1 hypersensitivity to wheat, ****: Celiac disease by IgA and IgG antibody to transglutaminase enzyme).**

### Table 1: *In vitro* IgE diagnostic tests of wheat components (ISAC; Immune solid-phase allergen chip) [14]

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Allergen Code</th>
<th>Available in ISAC</th>
<th>IgE positivity rates [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat</td>
<td>f4</td>
<td>-</td>
<td>41</td>
</tr>
<tr>
<td>Gluten</td>
<td>f79</td>
<td>-</td>
<td>43.5</td>
</tr>
<tr>
<td>ω 5-gliadin</td>
<td>f416</td>
<td>+</td>
<td>82</td>
</tr>
<tr>
<td>Lipid transfer protein</td>
<td>f433</td>
<td>+</td>
<td>28</td>
</tr>
</tbody>
</table>

*elicited with high allergen doses, even in the absence of exercise and other cofactors.*

Any kind of physical activity may elicit EIA with different system symptoms. We asked our patients to walk quickly for 6 minutes on a 30-meter corridor. Even though 6MWT was improved to measure exercise tolerance for chronic lung diseases, it is also used in other conditions such as rheumatic [11]. We preferred this test since it was simple that requires no equipment or advanced training for technicians. However, patient chooses his own intensity of exercise, and may not reach the maximal exercise capacity. 6MWT was successful to prove the diagnose in 1st case, but in the 2nd case it was insufficient which might be due to its submaximal level or duration of exercise. On the other hand, we didn’t think negative result excluded the diagnosis of anaphylaxis, since he had a history of anaphylaxis after food and exercise combination. In this case, authorities suggest to re-test with high gluten doses and add other cofactors which results to increase plasma gliadin levels sufficiently to induce symptoms [6,12]. Unfortunately, patient refused to be retested due to fear of its life-threatening condition. Furthermore, the exercise intensity able to elicit symptoms is reported to be variable, even in the same subject [11]. However, since most daily activities are performed at submaximal levels, 6MWT is a reliable test to reflect the level of daily physical activities, and may be used in the diagnosis of WDEIA.

The most important cofactor seems to be food ingestion in EIA. Even though any food before exercising was able to trigger reactions, wheat seems to be one of the common besides nuts and sea food [7]. Co-factors other than food in EIA reported in the literature were cold/warm temperature, infectious disease, alcohol assumption, menstrual cycle, dental amalgams, proton pump inhibitors, and non-steroidal anti-inflammatory drugs [7]. As we know, myorelaxant drug is the first reported co-factor in WDEIA as seen in 1st case. However, we didn’t think that he was sensitized individually to both wheat and myorelaxant drug, since he was able to use the same drug after the event. Furthermore, WDEIA is characterized by elicitation of anaphylaxis only in the presence of at least one such cofactor. These conditions augment the onset of anaphylaxis by lowering the allergen dose necessary for triggering anaphylaxis.

*In vitro* tests are used as a confirmation tool besides
Wheat or "Triticum aestivum" as taxonomic name is mainly composed of soluble and insoluble parts. Soluble part such as α-amylase inhibitor plays a role in baker’s asthma [13], whereas 80% of it is composed of insoluble proteins as glutenins which include glutenin and gliadin (Figure 2). Gluten, glutenin, and gliadin contain a large number of 2 particular amino acids - glutamine and proline with different amounts. Type 1 hypersensitivity to wheat is associated with low molecular weight glutenin, and WDEIA is associated with IgE to high molecular weight glutenin or ω-5 gliadin in the majority of cases [12]. Of interest in some the responsible allergen was identified as lipid transfer protein (LTP), and not ω-5 gliadin [14]. The other responsible epitopes have been identified as wheat, gluten, glutenin, gliadin, proline, and LTP (Table 1) [10].

Most patients with WDEIA think that they may have celiac disease. In celiac disease gluten does not get properly digested into single amino acids, and gliadin passes through the cell undigested. Gliadin peptides linked to secretory IgA getting taken through the cell and transglutaminase enzyme deaminates these peptides in creating immunogenic neoepitopes, enhancing antigentic presentation of gliadins. Celiac disease differs from wheat allergy by IgA and IgG antibodies to gliadin and tissue transglutaminase which are used for screening. If the blood tests used for screening showed that the patient might have celiac disease, endoscopic biopsy from intestine was needed to confirm the diagnose [15].

The acute treatment of EIA includes classic treatment of anaphylaxis as epinephrine, corticosteroids and antihistamines [1]. Also, patients with EIA must carry an epinephrine auto-injector to be used in case of a reaction [3]. Prophylaxis of WDEIA is educating the patients to avoid ingestion of wheat products before exercise or within 1-3 hour after exercise [4]. Prophylactic use of antihistamines, leukotriene antagonists, and corticosteroids is lacking.

As a conclusion, WDEIA is a rare disorder that should be kept in mind in case of exercise or food intake alone does not constitute a clinical picture. The mainstay of management is prevention of further episodes by keeping away from the wheat specific triggers and other possible co-factors before exercise. These cases were interesting in terms of positivity of specific IgE ω-5gliadin but negativity of gluten as well as the fact that myorelaxant was found to be a rare co-factor for the first time, and negative challenge with combination of wheat and exercise might not exclude the diagnosis.

Cite this article

References