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Case Report

A Severe Case of Wheat-Dependent Exercise-Induced Anaphylaxis in Adulthood

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Abstract

Food-dependent exercise-induced anaphylaxis (FDEIA), is a severe form of allergy for which the ingestion of a specific food, usually before physical exercise induces symptoms of anaphylaxis. Patients typically have IgE antibodies to the food that triggers the reactions; however, the symptoms appear only if the co-factors act together. The most common reported cause of these reactions seems to be wheat. In some cases FDEIA is displayed even when the food is eaten immediately after exercise, showing that in FDEIA, not the sequence but rather the coincidence of triggering factors use, is of crucial importance. The risk to develop anaphylaxis in these patients depends on the presence and, in some cases, on the amount of cofactors of anaphylaxis. There are lots of evidences about the role of NSAIDs as cofactors of anaphylaxis.

Introduction

Food-dependent exercise-induced anaphylaxis (FDEIA) is a rare but severe allergic reaction, which is induced by exercise after the ingestion of wheat products [1, 2]. It is known that one of the most frequent causative food is wheat [3, 4], and the measuring of IgE specific for omega-5-gliadin (the major wheat allergen), is diagnostic for these patients [5]. Although the omega-5-gladin fraction in wheat allergen extracts is very small, it is proven that IgE detection has a high predictive value for WDEIA diagnosis [5-7]. The diagnosis of this disorder it is often missed, because neither the exercise nor the ingested food alone induces the symptoms. There are many reports supporting the fact that, aspirin intake is a contribution factor in some patients with FDEIA [2, 8, 9]. The risk to develop anaphylaxis in these patients depends not only on the presence, but in some cases, also on the amount of cofactors of anaphylaxis [5].

Patient history

A 43 years old woman was admitted in our clinic, after she had suffered of three severe allergic reactions. The first episode was observed 12 years ago, the second one 8 years ago and the third one a month ago. The initial symptoms of those episodes were nasal itching, sneezing, rhinorae, cutaneous itching and flushing, followed by whealing and generalized urticaria with angioedema, dyspnea, stridor, giving to the patient the feeling of choking, hypotension, and resulting to a collapse, thirty minutes later.

The patient hematological and biological blood tests were normal. The level of serum tryptase was 4.5 ng/mL (normal range values < 11.4 ng/mL). The detailed allergic and immunologic exams results were as following: Commercial SPT for inhalant and food allergens (Lofarma, Milan) showed positive response for wheat proteins 8-30 mm. The level of wheat-specific IgE detected by ImmunoCAP (UniCAP PHAD® Pharmacia & Upjohn, Uppsala, Sweden) was of class 3, and gluten-specific IgE were of class 2. Meanwhile, ω-5 gliadin-specific IgE was increased class 4. IgA anti-tissue transglutaminase, IgG anti-tissue transglutaminase, and IgG anti-gliadin were negative, whilst IgA anti-gliadin was positive. For SPT (prick by prick) with wheat, we used freshly made suspensions of flour and saline (1:10) and we got a positive response (6-32 mm).

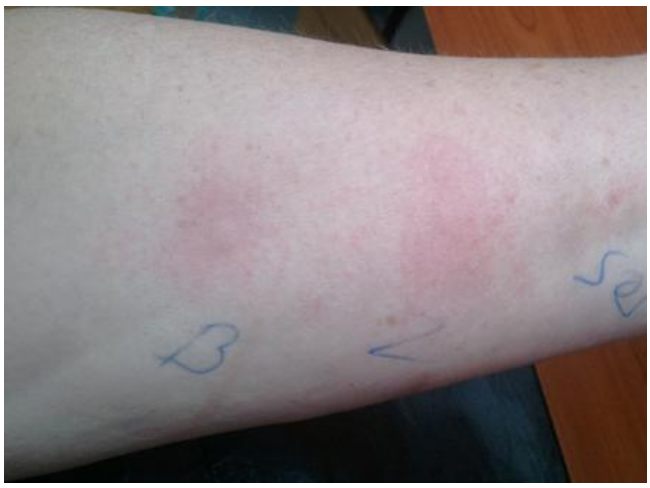

Figure 1: SPT (prick by prick) with wheat.

Even the patient has consumed in regular bases wheat products and its derivates, she did not reported any allergic reactions of them. In addition of the above-mentioned tests, prick testing with a commercially available crude gliadin (1 mg/mL in 20% ethanol) was performed, and the result was clearly positive (8-32 mm). We performed as well the challenge ingestion test for wheat flour and wheat pasta on separate days after an overnight fast. Wheat was eliminated from the diet at least 1 week before the challenge. Doses of wheat were administered at 20-minute intervals. A minimum starting dose of 100 mg raw wheat flour was given; then the next dose was 500 mg, followed by 1 g and 1.5 g, and the last dose was doubled (3 g, 6 g, 12 g) until the entire test's wheat flour was eaten. The next day 25 g cooked wheat pasta was given to the patient. We started with 1 g of pasta, and after that this amount was doubled every 20 minutes, until completion of the test meal. The final result was negative, without any clinical symptoms.

Thoroughly, we got a detailed history patient's disease, and our patient confirmed that in all three cases she had consumed flour products, followed by aspirin intake and an effort of moderate to high intensity (running) 10 minutes after the meal. She referred that she has used before those incidents quit often NSAIDs, without any allergic problem. She underwent to several challenge tests on specific dates separated from each other. Exercise challenge tests, Aspirin challenge test (base on standard protocols) showed negative responses.

Knowing the fact that these tests have clearly demonstrated high risk of anaphylactic and in some cases fatal reaction, we did not perform all three combined challenge tests together [6].

Discussion

We have diagnosed a patient with wheat-dependent exercise-induced anaphylaxis (WDEIA), with a history of recurrent anaphylaxis episodes, associated with wheat's ingestion. In order to establish the diagnosis, we relied on clinical data, disease history and skin tests with food allergens, which resulted positive for wheat peptides. The patient have clear positive IgE against food erupting reaction, in our case to the flour, but nevertheless, the consumption of food does not cause any symptoms, if it is not associated with physical exercise [10].

Although, this disorder seems to be the more representative case of EIA, its pathophysiology remains to be fully elucidated. Based on recent data, there are two major levels of cofactor-induced modulation leading anaphylaxis: increased absorption of the allergen and decreased activation threshold on the cellular level [11, 12]. Thus, the allergens in low doses, which cannot induce anaphylaxis alone, in the presence of cofactors, become dangerous triggers of anaphylaxis in sensitive patients. Also, current working hypotheses involve alterations in plasma osmolarity and pH, tissue enzyme activity, blood flow redistribution, altered gastrointestinal permeability and facilitated epitope recognition/allergen binding.

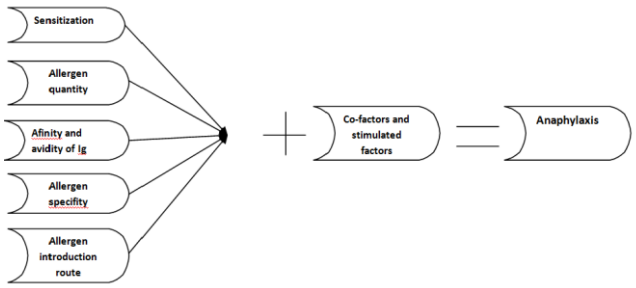

Figure 2: Risk to develop anaphylaxis.

Given that the food and physical exercise can be very well tolerated independently by the patient,

this suggests a pliable state of immunological tolerance [10, 12]. Referring to many recent European studies, it is observed that next to exercises, NSAIDs act as a cofactor in 6.1-9% of severe anaphylactic reactions. Epidemiological data show that cofactors are strongly important especially for food dependent anaphylactic reactions, revealing up to 39% of cases in adults [5, 11], (Fig. 2.).

Some authors suggest that alterations in transglutaminase (tTG) enzyme induced by exercises, lead in peptide aggregation, which increase the ability of IgE cross-linking. Many inflammatory mediators increase genetic expression of tTG, but one of the most important is interleukin-6 [12, 13].The most important tissues that produce interleukin-6 during exercises are: contracting skeletal muscles, central nervous system and peri-tendinous tissues, as well [12]. There are reports that blood gliadin levels correlate with clinical symptoms induced by exercise and aspirin intake in patients with WDEIA [3]. Peptides which derive from omega-5 gliadin are cross-linked by tTG and they cause a marked increase in IgE binding [14, 15]. Matsuo et al. could show that there is an increase uptake of gliadin after the ingestion of wheat meal followed by physical exercises [16].

Moreover, the biological study done on metabolism of gliadin in humans, have shown that 30 min after consuming wheat products, the absorption of gliadin is increased rapidly from fivefold, if it is accompanied at the same time with NSAID intake [14, 15]. Takahashi et al. have identified that, not only wheat omega- gliadin but also high molecular weight-glutenin subunit (HMW-glutenin) is an important major allergen in this patient. Detection of serum IgE to synthetic epitope peptides of these allergens diagnoses more than 90% of WDEIA patients [7]. A possible hypothesis supported by several studies in humans, also has shown that the mechanism of NSAID idiosyncrasy is involved as a cofactor, and systemic administration of NSAIDs may increase skin test reactions to food allergens. The NSAIDs not only modulate the intestinal absorption of allergens, but also modulates the function of effectors' cells present in this disorder [10].

Finally a following scenario is indicated: (a) the intensity of physical effort, (b) the level of sensitization and (c) allergen quantity co-regulate the intestinal absorption of allergens, resulting in the symptoms of anaphylaxis by contributing each of them on an individual level [11]. It is important to know that in WDEIA patients, the presence of exercise is an indispensable prerequisite to trigger anaphylaxis [5].

In conclusion, it was the first case of WDEIA diagnosed in our clinic, which in itself is a rare but very troubling condition. A careful step-by-step approach is required, as that is the reason why that disorder escapes so often the diagnosis. We recommend a gluten-free diet for treatment, or, at least, refraining from exercise for 4 to 6 h after wheat-products ingestion. Aspirin and other NSAIDs are to be included in diagnostic measures, and should not be taken in association with exercise. It should be especially recommended the avoidance of combined intake of identified food allergens, NSAIDs and effort.

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