

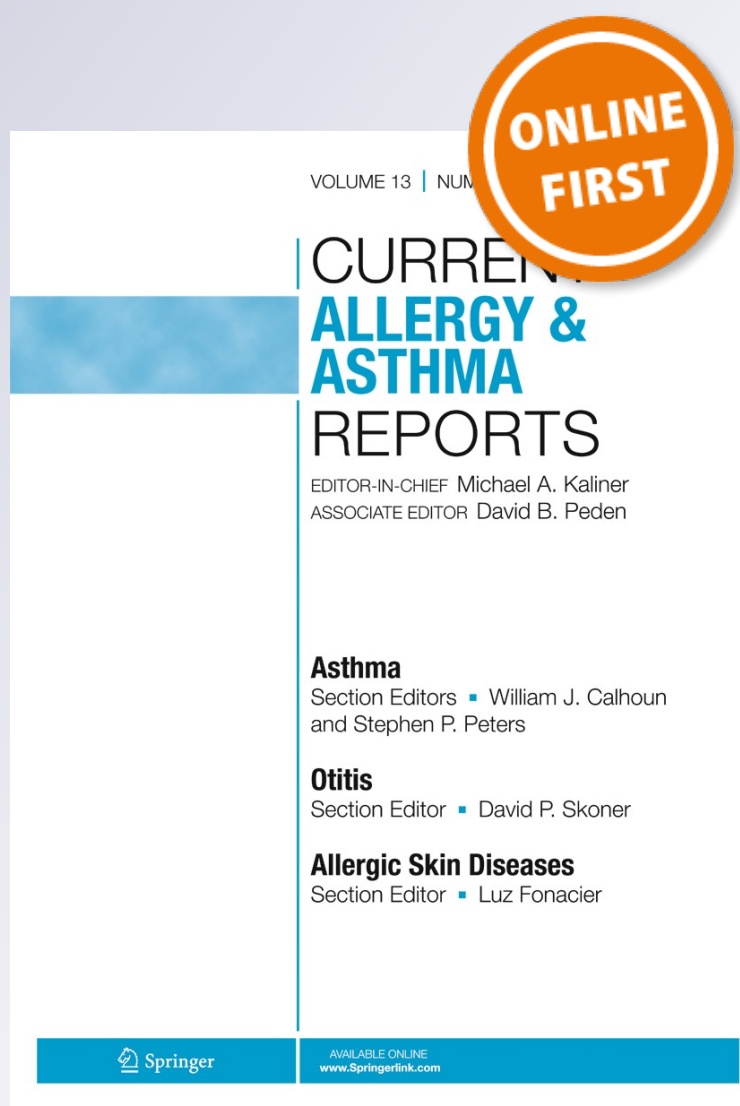
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Current Allergy and Asthma Reports

ISSN 1529-7322

Curr Allergy Asthma Rep
DOI 10.1007/s11882-013-0388-2



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Food-Dependent Exercise-Induced Anaphylaxis: Is Wheat Unique?

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Abstract This review draws comparisons between wheat-dependent exercise-induced anaphylaxis (WDEIA) and other food-dependent exercise-induced anaphylaxis (FDEIAs) and discusses the importance of co-factors in its pathophysiology. FDEIA remains an enigmatic condition since it was first described 30 years ago. The sporadic and unpredictable nature of its reactions has puzzled clinicians and scientists for decades, but recent studies on WDEIA have enlightened us about the pathophysiology of this condition. The identification of defined allergic epitopes such as Tri a 19, α -gliadin, β -gliadin and γ -gliadin in WDEIA enables it to become the perfect model for studying FDEIA, but WDEIA is by no means a unique condition. On a larger scale, FDEIA represents a crucial link between IgE-mediated and anaphylactoid reactions and provides supportive evidence for the concept of ‘summation anaphylaxis’ and the need to overcome the ‘allergen threshold’. Future work should focus on identifying more of the FDEIA epitopes and understanding their distinct molecular properties. The development of a biomarker in order to identify patients susceptible to co-factor influences would be invaluable.

Keywords Food-dependent exercise-induced anaphylaxis · Wheat · Wheat-dependent exercise-induced anaphylaxis · Summation · Anaphylaxis · Omega-5-gliadin · Serum-specific IgE · Anaphylactoid reactions

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Introduction

Food-dependent exercise-induced anaphylaxis (FDEIA) was first reported in 1979 by Maulitz et al. when a patient’s anaphylaxis was triggered by a combination of shellfish ingestion and exercise [1]. In the past 30 years, our understanding of this condition has improved, and a number of foods have now been associated with this clinical syndrome [2]. FDEIA is IgE-mediated; classical symptoms of type 1 hypersensitivity and serum-specific IgE (ssIgE) to culprit allergens are often detectable in patients [3]. Patients are usually able to tolerate exercise and ingestion of the offending food allergen independently as long as they are at least 4–5 h apart. The delayed onset of symptoms is unusual but can be seen in other IgE-mediated reactions such as tick bites and red meat allergy [4]. Although it was originally thought that the combination of food ingestion and exercise was crucial for a reaction to occur, a number of studies have now shown that a combination of food with aspirin or alcohol was also able to trigger a reaction [5, 6].

Wheat-dependent exercise-induced anaphylaxis (WDEIA) is without doubt the best-studied sub-type of FDEIA in the last decade. Many distinct clinical and laboratory features related to WDEIA have been described. In particular, omega-5-gliadin and many other newly discovered epitopes have revolutionised our diagnostic approach to this condition [7]. In this review, we will summarise the current reports on FDEIA and will draw comparisons between WDEIA and other FDEIAs. Finally, we will discuss the importance of co-factors in the pathophysiology of FDEIA and how they challenge the traditional concept of allergic disorders.

Common Foods Associated with FDEIA

Both plant and animal proteins are known to be associated with FDEIA. Wheat, shellfish and nuts are responsible for the

majority of FDEIA, but this syndrome has now been extended to a never-ending list of plant and animal proteins such as celery, oranges, apples, rice, tomatoes and cow's milk [2, 8, 9]. The sensitisation pattern varies depending on the geographical location. For example, tomato FDEIA was frequently reported from Southern Europe, but not in other regions [10, 11]. On the other hand, shellfish FDEIA is relatively common in the Far East [12]. Similar to oral allergy syndrome [13], this geographical variation suggests that local diet, environment and immunogenetics may play a role in the sensitisation process of patients with FDEIA.

WDEIA as the Best-Studied Subtype of FDEIA

Over the last decade, studies on WDEIA have represented over half of all publications related to FDEIA, and there has been an explosion of interest since the millennium. WDEIA differentiates itself from the rest of FDEIAs by having a set of clearly defined and well-studied allergen epitopes. Wheat proteins are subdivided into water-soluble and -insoluble proteins (gluten) [14, 15]. Gluten is further subdivided into glutenins and gliadins, which may be of alpha, beta, gamma or omega isoforms [16]. Sensitisation to different fractions of the wheat protein can result in distinct clinical syndromes; for example, patients with baker's asthma are sensitised to α -amylase, but not gliadins [17]. In 1999, Palosuo et al. identified a gamma-like gliadin as the major allergen for WDEIA [8]. This protein was later known to be omega-5-gliadin (Tri a 19) and its diagnostic benefits had since been confirmed by other research groups [18–20]. Serum-specific IgE (ssIgE) to Tri a 19 was shown to have a sensitivity of up to 80 % and specificity of >95 % in WDEIA, with levels often undetectable in patients with atopic eczema and healthy controls [21]. The favourable performance of ssIgE to Tri a 19 in WDEIA led quickly to its use in routine clinical practise. However from our clinical experience, ssIgE to Tri a 19 may be detectable in some individuals without WDEIA when applied to a wider allergy cohort, emphasising the importance of pre-test probability with accurate clinical history in order to ensure maintenance of high performance of this test. Nevertheless, WDEIA is one of the few conditions that has benefited enormously from component resolved diagnostics. Other less dominant wheat subunits such as high-molecular-weight glutenin (HMW-glutenin), alpha gliadin, beta gliadin and gamma gliadin were associated with patients with WDEIA who were negative for ssIgE to Tri a 19 [22, 23]. Combination testing has shown promising results, but the usefulness of these newly identified epitopes remains to be tested in clinical practice [22]. As with other IgE-mediated conditions there does not appear to be a correlation between the level of ssIgE and severity of allergic reactions.

WDEIA exhibits a wide range of clinical presentations in comparison to other allergic disorders. In addition to those conventional symptoms of anaphylaxis that occur any time between 10 min to 4 h of food intake [24], rhinoconjunctivitis and peri-orbital angioedema were reported in a new variant of WDEIA (hydrolysed wheat protein WDEIA) [25]. Those patients were thought to be sensitised by hydrolysed wheat protein (HWP) via the cutaneous route and had immediate facial urticaria, rhinoconjunctivitis and angioedema to soap products containing HWP, in addition to symptoms of conventional WDEIA. Although the clinical presentation is variable, all patients with HWP-WDEIA were skin prick test positive to soap supplement with HWP. However, ssIgE to Tri a 19 is not a feature of this variant. Whether this facial presentation is an extension of WDEIA or merely an associated condition remains to be seen.

WDEIA Shares Many Fundamental Features with FDEIA

The variable clinical nature of WDEIA can also be observed in other FDEIAs. Despite the condition's name, generalised systemic urticaria is the commonest presentation of FDEIA and not all patients present with anaphylaxis. As previously mentioned, because of the disproportional interest in WDEIA, the majority of the clinical features of FDEIA are derived from case reports, or case series, of WDEIA. In WDEIA, reactions occur sporadically and unpredictably, as the combination of food and exercise may not trigger a reaction on every occasion. Moreover, the threshold of exercise required to trigger a reaction may be variable within an individual [8, 26]. Although detailed large case series of other FDEIAs are not available, indication of this variable nature is evident in the literature. For example, Teo et al. reported five patients with shellfish FDEIA following moderate to vigorous exercise. All reactions were unpredictable and occurred from 15 to 180 min following shellfish intake [27]. Another patient with chickpea FDEIA was reported to develop a biphasic reaction 5 h following the initial reaction [28] and another with tofu FDEIA had symptoms lasting for 2 days [29]. Moreover, Caffarelli and colleagues had previously reported a case of facial angioedema with tomato and exercise that closely resembles the recently described HWP-WDEIA [11]. Finally, both WDEIA and FDEIA (shrimp) can be triggered by food and aspirin, without exercise, during direct provocation test [5, 30].

Because of the intense molecular and proteomic work on wheat protein in the past decade, it is widely accepted that WDEIA is an IgE-mediated reaction. Similar work can now be seen in other FDEIAs, such as soybean, with the interim results resembling those data generated from earlier wheat experiments. Adachi et al. demonstrated that the serum IgE of

a patient with tofu (soy bean) FDEIA showed specific reactivity to β -conglycinin of soybean. Although interesting, it is important to highlight that this is a single case report and a larger study cohort is required to confirm the value of this finding. Recently, two separate case reports from the Mediterranean described patients with nectarine FDEIA, for which both were positive to nectarine ‘prick to prick’ test, but negative to ssIgE to Pru p 3, indicating an unidentified epitope [31, 32].

Although wheat is the commonest food reported in FDEIA, it maybe over emphasised. Some reports included patients who had only experienced one previous reaction [33]. Because of the sporadic nature of FDEIA, it is impossible to exclude other idiopathic causes in such a situation. Another important point is that wheat is a dietary staple in many cultures and a 4-h window period following breakfast, lunch and dinner can occupy a significant proportion of the day. Therefore, more vigilance is required to make an accurate diagnosis, especially when the positive predictive value of ssIgE to omega-5-gliadin is constantly being challenged [34]. Our recent work has suggested that ssIgE to omega-5-gliadin alone is suboptimal in predicting the outcome from a diet-exercise modification, and we strongly advocate a combined clinical and laboratory approach [35]. Therefore, in our practise, we are cautious with patients presenting with a single episode of anaphylaxis/allergic reaction and a positive ssIgE omega-5-gliadin (>0.89 kU/l); a ‘wait and watch approach’ with specific advice to maintain food-activity diary to record future episodes is employed.

Therefore, although less well documented, other FDEIAs demonstrate similar clinical and laboratory features to WDEIA. At present, WDEIA can be seen as a model of FDEIA, but it is by no means a unique presentation.

FDEIA Provides a Crucial Link Between IgE-Mediated Anaphylaxis and Anaphylactoid Reactions

FDEIA consists of two major components: (1) allergen exposure and (2) the presence of co-factors such as exercise, NSAIDs or

hormonal changes. The allergen component, as discussed, is IgE-mediated, but the co-factor component is less well understood. In certain situations, co-factors can trigger reactions in their own right in susceptible individuals, historically known as anaphylactoid reactions. Anaphylactoid responses are reactions that cause direct release of mast cell mediators and activation of the inflammatory cascade without crosslinking surface IgE antibodies on mast cells. It is clinically indistinguishable from anaphylaxis, and histamine and mast cell tryptase levels are also elevated following a reaction [36].

Exercise-induced anaphylaxis (EIA) is closely associated with FDEIA, and the two may be considered as a continuum. In contrast to FDEIA, exercise alone is sufficient to trigger a reaction in EIA. A number of hypotheses regarding the pathophysiology of EIA exist, including a change in serum osmolality, pH, gut permeability and redistribution of blood flow [37]. However, more convincing evidence is still required to confirm these hypotheses. Studies on exercise-induced broncho-constriction have shown that mast cells and eosinophils release leukotrienes and prostaglandins in the airways immediately after exercise [38, 39•].

NSAIDs hypersensitivity is one of the most common drug hypersensitivities. These are usually non-IgE mediated, although rarely an individual may be specifically allergic (IgE-mediated) to a particular NSAID. It was hypothesised that the COX-1 inhibition property of NSAIDs might also lead to imbalance of arachidonic acid metabolites, resulting in an anaphylactoid reaction and bronchospasm [40]. Other drugs such as opiates and muscle relaxants are known to cause intrinsic histamine release from mast cells [41].

Chronic spontaneous urticaria is six times more common in females, and hormones such as oestrogen and progesterone are thought to play a role [42]. The potential pathological role of female hormones was further highlighted by case reports of breast-feeding anaphylaxis, where occurrence of symptoms was closely related to the timing of lactation and could be significantly worsened by active breast feeding [43]. Similarly, anaphylaxis during general anaesthesia shows adult female predominance, i.e., such a pattern is not reported in children

Table 1 Transition between IgE-mediated reactions to anaphylactoid reactions

Clear IgE mediated reactions	Transitions	Anaphylactoid reactions
Food allergy	FDEIA	Exercise-induced anaphylaxis
Wheat allergy	WDEIA	NSAIDs sensitivity
Oral allergy syndrome	OAS worsen by exercise	Breast-feeding anaphylaxis
Venom allergy	Refractory cases of venom allergy/ anaphylaxis with primary exposure	Exercise-induced broncho-constriction/NSAIDs asthma
Allergic asthma		(Minor factors: menstrual cycle, concurrent infection and inflammation, stress, change in temperature, D816V C-kit mutation)

[44]. The mechanisms underpinning the influence of female hormones on mast cell or basophil function are not clear at the present time. Female mice are more prone to develop allergic inflammation than male mice and estradiol has been shown to enhance histamine release of uterine mast cells [45, 46]. In human mast cell lines, degranulation is shown to be greater under the influence of estradiol [47]. However, a study of eight patients with idiopathic anaphylaxis found that oestrogen and progesterone had little or no effect on basophil function [48].

Because of the involvement of mast cells, both anaphylaxis and anaphylactoid reactions are likely to share a final pathophysiological pathway, although the initiation processes for these reactions appear separate. However, in the case of FDEIA both IgE-mediated and non-IgE mediated mechanisms appear to work synergistically to exceed the allergen threshold. 'Summation anaphylaxis' is a phenomenon where accumulation of a number of stimuli results in symptoms of anaphylaxis [49]. In addition to exercise and drugs, other minor factors such as menstrual cycle, hormonal changes, concurrent infections, stress and changes in temperature are also known to contribute to anaphylaxis. FDEIA fits well with this concept and the overall picture could perhaps be more fluid than we previously thought (Table 1).

In WDEIA, a number of studies have shown that the addition of aspirin to wheat ingestion and exercise increases the chance of provoking a reaction [5, 50]. The transitional nature of patients' reactions also supports this concept. For example, we previously reported a patient with type 1 hypersensitivity to wheat, but her symptoms can be significantly worsened with the addition of exercise [20]. In 2008, Bito et al. demonstrated how the combination of cow's milk, exercise, aspirin and ovulation phase could eventually provoke an allergic reaction in a 24-year-old patient with eczema [51]. Fiedler et al. reported another case of FDEIA following a confirmation challenge with a combination of wheat flour, exercise, food additives and alcohol [6]. Finally, a single case of D816V c-kit mutation was found in a patient with FDEIA, suggesting that underlying mast cell hyper-responsiveness could contribute to the development of FDEIA [52].

Epitope mapping in the past decade has identified unique allergen epitopes for WDEIA. However, it is not clear why Tri a 19 is not associated with classic type 1 hypersensitivity. We favour the possibility that the epitopes for FDEIA are less immunogenic and therefore only manifest as disease in the presence of other co-factors, whereas more immunogenic epitopes such as Ara h 1, 2 and 3 in peanut allergy directly provoke an allergic reaction [53]. There may also be a natural variability within the population regarding the susceptibility to co-factor influences. The requirement for the combination of a number of weak stimuli in order to overcome the allergen threshold offers a suitable explanation for the sporadic and unpredictable nature of FDEIA.

Conclusions

WDEIA was the best studied FDEIA over the past few decades. Through its popularity, it has become a perfect clinical model for FDEIA, but it is by no means a unique condition. Many lessons may be learnt from the studies on WDEIA. Not only have they helped us understand the clinical presentation of FDEIA, they have also demonstrated that component testing could be beneficial outside pollen-food syndrome. FDEIA represents a crucial link between IgE-mediated and anaphylactoid reactions and provides supportive evidence for the concept of 'summation anaphylaxis' and the need to overcome the 'allergen threshold'. Future work should focus on identifying more of the FDEIA epitopes and understanding their distinct molecular properties. The development of a biomarker in order to identify patients susceptible to co-factor influences would be invaluable.

Compliance with Ethics Guidelines

Conflict of Interest Mamidipudi T. Krishna has received grant support/honorarium from ALK Abello, Allergy Therapeutics, Meda Pharmaceuticals and Phadia; has received publishing royalties from Nova Biomedical; and is lead for national audits and member of the Standards of Care Committee for the British Society for Allergy and Clinical Immunology.

Gabriel K. Wong 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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