



Food-dependent exercise-induced reactions: lessons from a 15-year retrospective study

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Abstract

Background Food-dependent exercise-induced anaphylaxis (FDEIA) is a life-threatening disorder in which the signs and symptoms of anaphylaxis occur if physical exertion occurs within a few hours of exposure to a food.

Aims The aim of this study was to characterise patients diagnosed with FDEIA and related disorders.

Methods A retrospective review of electronic clinical data from 2001 to 2016 was carried out. Fifty-seven cases were identified and analysed to establish clinical features, triggering factors and sensitisation patterns.

Results The number of patients per annum diagnosed with FDEIA or related reactions increased from 1 in 2001 to 18 patients in 2016. Sixty-nine percent reported systemic symptoms consistent with anaphylaxis, and 31% had skin manifestations only. In 33% of cases, the level of triggering exercise was mild. Forty-four percent of patients were sensitised to the omega-5-gliadin fraction of wheat.

Conclusions FDEIA is an increasingly recognised serious allergic disease. The clinical diagnosis is supported by targeted sensitisation testing and molecular-based allergy diagnostics. These tools allow implementation of effective dietary and lifestyle modifications that mitigate against future serious reactions. Given the limited access to physicians with specialist allergy training in Ireland, increased awareness of this condition amongst sports medicine specialists and general physicians is required.

Keywords Allergy · Anaphylaxis · Exercise-induced anaphylaxis · Food allergy · Food-dependent exercise-induced anaphylaxis

Introduction

Anaphylaxis is an acute life-threatening disorder, with a variety of clinical manifestations affecting multiple systems, primarily cardiovascular, respiratory, gastrointestinal and the skin [1]. Exercise-induced anaphylaxis (EIA) is a disorder in which signs and symptoms of anaphylaxis occur within the setting of physical exertion [2]. Food-dependent exercise-induced anaphylaxis (FDEIA) is a subset of this disorder in which clinical manifestations only occur if physical exertion occurs within a few hours of exposure to a food [3]. If food ingestion and exercise are independent of each other, symptoms do not occur [4].

The prevalence of anaphylaxis ranges from 1.6 to 5.1% in adults [5] and is less than 2% in children [2, 6]. EIA is estimated to account for 5 to 15% of all cases of anaphylaxis [7]. The prevalence of FDEIA is not well studied; however, it is approximated to account for one third to one half of EIA patients [1]. A 2001 study of Japanese high school students suggested a prevalence of 0.03% of EIA and 0.0017% of FDEIA; importantly, this study predates wide availability of molecular-based sensitisation testing [8].

In FDEIA, it is the combination of both food and exercise that precipitate the signs and symptoms of anaphylaxis [1, 9]. A vast array of foods are implicated in the diagnosis of FDEIA, with wheat as one of the most commonly diagnosed allergens worldwide [1, 3, 9]. The consumption of the trigger food typically occurs within 4 h of commencing exercise [10]; however, in some cases, exposure to the food may be after exertion [1, 9]. When the food is consumed without a temporal relationship to exercise, it does not precipitate allergic symptoms [1, 3, 4, 9].

The signs and symptoms of this disorder typically manifest within the initial stages of commencing exercise [11, 12];

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however, they may occur at any time throughout the exercise period [1]. Clinical presentation is varied, with some patients displaying systemic symptoms and others reporting skin manifestations only, such as urticaria, flushing and pruritus [1, 2, 11]. Skin-limited manifestations do not fulfil the diagnostic requirements of anaphylaxis but are specified here as related disorders such as urticaria and angioedema. The intensity and duration of physical exertion also contribute to the varying clinical picture [12, 13].

The exact pathogenesis of FDEIA is not fully established, and there are a number of underlying mechanisms likely to play a role, including increased intestinal permeability, raised tissue transglutaminase levels, reduced gastric acid activity and altered blood distribution [1, 4, 9, 14]. Cofactors such as temperature, alcohol, NSAID use, inhaled allergens and menstruation [12, 15–19] are thought to contribute to this process by both increasing allergen absorption and reducing threshold for mast cell degranulation [20].

The diagnosis of FDEIA can be challenging. It requires a suggestive clinical history and supportive allergy sensitisation testing. Symptoms must be typical for an anaphylactic reaction, and accurate details of the setting in which the event occurred, including details of contemporaneous food exposure, and any potential cofactors need to be carefully recorded.

Sensitisation testing to the implicated foods should be carried out. This may be performed via skin prick testing or food specific IgE immunoassays [3]. These tests can be supported by molecular-based allergy diagnostics, which allow identification of IgE antibodies directed against specific recombinant protein allergens. The gold standard for diagnosis is a food-exercise challenge [21]. This, however, is a clinically challenging procedure that lacks standardisation, is not widely available and carries significant risk.

Methods

We carried out a retrospective review of patients attending a large adult immunology clinic in Ireland. The immunology clinic provides services for patients with primary and secondary immune deficiency disorders, vasculitis, autoimmune disorders and complex allergic disease. It is a public clinic taking referrals from primary care and hospital physicians from public and private sectors. The clinic takes referrals from across Ireland but has a notional catchment area population of 1.2 million. Due to waiting times, assessments typically take place several months after initial referral.

A database of electronic clinical data from 2001 to 2016 was analysed using the search terms ‘exercise’, ‘exercising’ and ‘exercise-associated’ to identify possible cases. Records were analysed retrospectively, including a review of the structured allergy-focussed clinical history, and supportive sensitisation tests. Allergy sensitisation tests were selected based on

exposure history, with molecular-based allergy diagnostics employed based on this history. Patient demographics, reaction characteristics and exposure history were noted. Anaphylaxis was diagnosed where the patient history and referral details indicated that a rapidly evolving reaction was associated with features suggestive of respiratory or cardiovascular compromise. The term ‘related disorder’ was applied to cases where skin-limited urticaria and angioedema were precipitated by the combination of food and exercise, but extra-cutaneous symptoms were not present. Cases of exercise-induced anaphylaxis, where a food trigger was not clinically suspected, and cases of cholinergic urticaria were not included in this study. Exercise intensity was subjectively and retrospectively graded by a single researcher based on the recorded history as mild (brisk walk or equivalent), medium or intensive (more sustained cardiovascular exertion).

Results

A total of 57 cases were identified over the 15-year period.

The number of cases identified progressively increased from 2001, when a single case was identified, to 2016, when 18 cases were identified (Fig. 1).

Of the 57 cases identified, there was a female predominance with a female to male ratio of 3:2. The ages ranged from 16 to 64 in this adult cohort, with a mean age of 35 years (Table 1). Atopic disease, particularly allergic rhinitis, was common in this cohort.

Most patients (69%) reported systemic systems, whilst the remaining 31% had symptoms limited to the skin that would not be classified as anaphylaxis.

The triggering exercise was graded as mild in 33% of cases and medium/intensive in 60%. In 4 cases (7%), the records lacked sufficient detail to grade exercise intensity. The mean

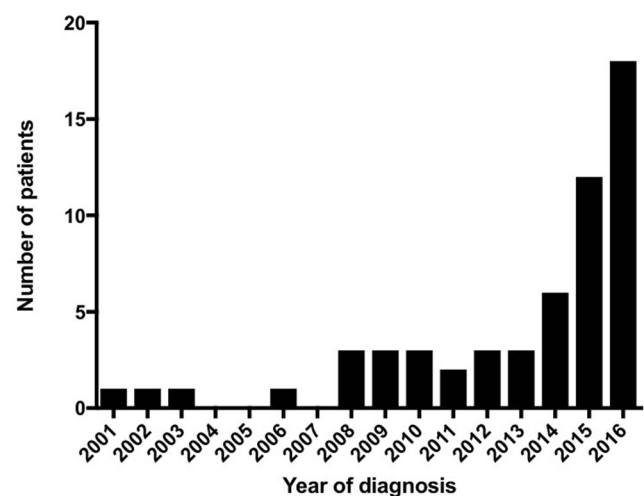


Fig. 1 Number of patients diagnosed from 2001 to 2016

Table 1 Diagnosis of 57 patients with FDEIA from 2001 to 2016

Number of cases	57
Female:male	3:2
Mean age	35
Atopic comorbidities	Atopic disease, 44 (77%) Asthma, 20 (35%) Allergic rhinitis, 33 (58%) Eczema, 11 (19%) No atopic disease 13 (23%)
Intensity of exercise	Mild 19 (33%) Mid/intensive 34 (60%) Not graded 4 (7%)
Mean number of episodes	2.1 (1–8)
Skin-limited symptoms	11 (31%)
Systemic symptoms	46 (69%)
Wheat molecular tests	Omega-5-gliadin 25 Tri a14 1
Plant food molecular tests	Storage protein 3 PR-10 positive 2 Lipid transfer protein 11

number of episodes prior to presentation at the specialist clinic was 2.1 (Table 1).

Sixty-two percent of patients self-reported a food association with their symptom onset. Wheat was the most commonly reported food, and associations with fish, peanut and tree nuts were also reported (Fig. 2). A total of 4 patients with a history suggestive of FDEIA had negative sensitisation tests to all foods. The remainder did not self-report a link with food prior to the detailed allergy history.

Patients underwent food specific IgE testing, guided by the exposure history. Molecular-based allergy diagnostics to exposed foods were carried out where available. Diagnosis of FDEIA was made based on a suggestive history and positive

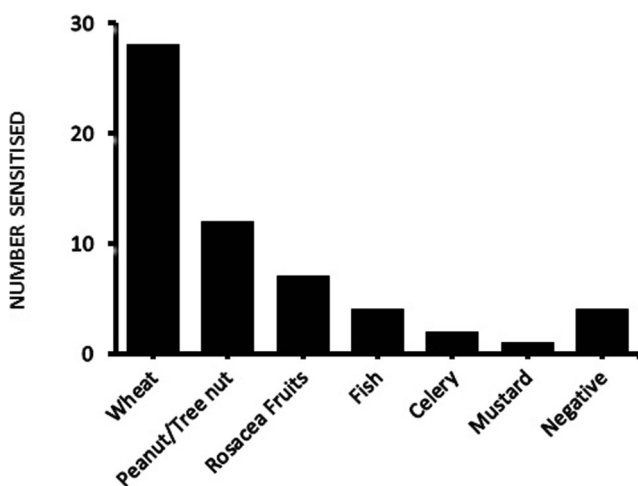


Fig. 2 Number of patients who self-reported a food association with their symptom onset

sensitisation testing including molecular testing. The majority of patients were shown to be positive for wheat IgE. 43.9% of patients were found to be sensitised to the omega-5-gliadin fraction of wheat. One patient tested wheat specific IgE positive, omega-5-gliadin negative and Tri a14 negative. One patient was sensitised to Tri a14 only. Sensitisation to fish, nuts, rosacea fruits, celery and mustard was also noted. Patients sensitised to peanuts, tree nuts and fruits had additional molecular-based diagnostics carried out in 14 cases. Sensitisation to PR-10 proteins was noted in 3 cases (Ara H8 (2), Mal D1) and storage proteins in 2 cases (Cor a9, AraH2). Lipid transfer protein (LTP) sensitisation was noted in 11 cases (Ara H9 (6), Cor a8 (3), Pru P3 (4)). Cross-reactive sensitisation was noted in this group, but we did not identify sensitisation to the wheat LTP, Tri a14, in this small cohort. In 3 cases, molecular testing results were not available.

In all cases, patients were carefully counselled and given a written management plan, including exclusion of the sensitised food before (−4 h) and immediately after (+2 h) exercise, and a recommendation not to exercise alone. Avoidance of other cofactors including NSAIDs and alcohol at the time of exercise was also recommended. Patients were prescribed adrenaline autoinjectors in all cases, including those where the presenting features did not fulfil anaphylaxis. Patients were also given standard management of atopic comorbidities in particular asthma. Adherence to the management plan resulted in resolution of symptoms in 93% of cases (53). Four (5%) patients discontinued the culprit food entirely (3 wheat, 1 peanut) against advice. No anaphylaxis occurred during the period of follow-up, and no patients completely discontinued exercise.

Discussion

There has been a marked increase in the diagnosis of FDEIA in this adult immunology centre over the course of the study period. One new case was diagnosed in 2001, whereas in 2016, 18 new cases were identified. This may represent a true increase in prevalence; however, it is possible that other factors have influenced this rise.

Advances in diagnostic laboratory techniques, especially in the area of molecular testing, have aided the identification of new cases of FDEIA over the last decade. Molecular food specific IgE testing allows clinicians to thoroughly investigate suggestive food triggers and identify food sensitisation in cases that may previously have been labelled as simple exercise-associated anaphylaxis. Awareness of the condition may also have increased amongst specialists and referring physicians. Referrals to the immunology clinic for assessment of allergic disease have also increased dramatically over the intervening period. More research is required to determine

whether the increase in numbers observed in this study represents a true increase in disease.

A number of different food types have been implicated in the diagnosis of FDEIA, with wheat as the most commonly identified allergen worldwide [1, 3, 9, 10, 22]. The cases of FDEIA identified in our centre are in line with this trend; 43.9% of patients diagnosed with FDEIA were positive for omega-5-gliadin. Exercise may induce tissue transglutaminase production under the influence of IL-6 [23]. This may cause aggregation of omega-5-gliadin facilitating sensitisation and specific IgE production [24, 25]. In addition, alterations in acid-base balance and alterations in blood flow with possible redistribution of allergens to the muscle and skin may act to facilitate mast cell degranulation. Finally, exercise may induce changes in intestinal permeability allowing passage of intact molecules across the gut barrier facilitating sensitisation [14, 20, 26–28].

Whilst wheat was the dominant allergen in this cohort, other foods were implicated. These included peanuts and tree nuts, fruits from the rosacea family, celery and mustard. Fish was the only non-plant-based allergen implicated. Where possible, molecular-based sensitisation testing of allergen components was used to further inform the diagnosis. These tests are increasingly used to complement more traditional sensitisation tests [29]. In this study, we found that sensitisation to the lipid transfer protein (LTP) component of plant food was unexpectedly common in this Northern European cohort. LTP sensitisation is a known cause of LTP syndrome and FDEIA but is most frequently described in Mediterranean populations [30]. Storage protein sensitisation and PR-10 protein sensitisation were also noted indicating heterogeneity in the way patients sensitised to these proteins can present. Interestingly, we did not find corresponding sensitisation to the wheat LTP Tri a14. This may reflect the limited sequence homology between wheat LTP and LTPs from fruit such as Pru P3 [31].

One major weakness of the diagnostic approach used in this cohort is the absence of a food-exercise challenge. Such challenges are not always necessary, and the degree of variability involved in these reactions means their clinical utility remains unclear. Their use in resource constrained healthcare systems with limited access to allergy specialists is likely to be perpetually limited even if methodological challenges are overcome. A high index of suspicion along with an allergy-focussed clinical history supported by judicious targeted use of sensitisation tests, including molecular diagnostics is likely to remain the most practical way of making a diagnosis of FDEIA.

FDEIA is a potentially life-threatening condition that is increasingly identified. It is vital that healthcare professionals recognise this condition, are aware of the diagnostic pathways and understand the management guidelines so as to avoid potentially devastating consequences. This is of particular concern amongst

healthcare professionals working alongside athletes, especially in Ireland and other countries, where there is a limited availability of healthcare professionals with experience in allergy.

Management of acute episodes of FDEIA involves the same emergency care as is standard for anaphylaxis: adrenaline, antihistamines, bronchodilators and steroids, along with fluids and supportive care [1, 32]. It is imperative that all patients diagnosed with FDEIA should be supplied with a self-injectable adrenaline pen and educated on its use and correct administration [33]. Close contacts should also be trained in the use of self-injectable adrenaline and recognition of the signs and symptoms of anaphylaxis [3]. Affected athletes should not exercise alone, should carry an adrenaline autoinjector at all times, in particular when partaking in exercise or, if this is not possible, a competent close contact should retain possession during periods of exertion [3]. The good outcomes in this cohort suggest that current management strategies are useful in modifying the risk of future reactions, but long-term follow-up data is required. Furthermore, whether adrenaline autoinjectors are required for patients with a history of food-exercise reactions that are not anaphylactic merits further prospective study.

Soyer and Sekerel have stressed the importance of implementing preventative measures and patient education as the ongoing management for this disorder [34]. All efforts should be made to avoid activity limitation for these people, and with certain lifestyle and dietary modifications, our data indicates that this is entirely possible.

Conclusion

There has been a progressive increase in the diagnosis of FDEIA in this Irish immunology centre. This may be explained by a true increase in prevalence, referral bias or improved detection with molecular diagnostics. All patients were offered specific IgE based on their exposure history with supportive molecular diagnostics where available. Sensitisation to omega-5-gliadin in wheat is the most commonly detected food factor noted. The management of FDEIA involves dietary modification, provision of adrenaline autoinjectors and a comprehensive written management plan. This is effective in reducing the risk of further reactions. Increased awareness of this fascinating condition is required especially amongst healthcare professionals working with athletes.

Compliance with ethical standards

Ethical statement This study was approved by the research ethics committee in St James's Hospital and informed consent was obtained. The authors state full compliance with ethical standards in completing this study.

Conflict of interest The authors declare that they have no conflict of interest.

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