

Food-dependent Exercise-induced Anaphylaxis – A Review of 5 Cases

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Abstract

Introduction: Food-dependent exercise-induced anaphylaxis (FDEIA) is an uncommon and under-recognised syndrome that clinicians may not consider in a patient presenting with anaphylaxis. **Clinical Picture:** We describe here 5 patients aged 9 to 20 years old who presented at a local tertiary hospital over a 2-year period from August 2006 to July 2008. All presented with urticaria, 4 were hypotensive, 2 had angioedema and another 2 had dyspnoea. The symptoms occurred between 15 and 150 minutes (mean, 81) after exercising and consuming various food. All had consumed shellfish. All patients were admitted with the diagnosis of anaphylaxis of undefined aetiology. Diagnosis of FDEIA was only reached upon referral to an allergist. **Treatment and Outcome:** Patients were treated with standard medicines for anaphylaxis including adrenaline, antihistamines, steroids and fluid flushes. Symptoms resolved in 2 to 3 days with no further episodes. At discharge, patients were prescribed epinephrine auto-injectors and given written anaphylaxis management plans. **Conclusions:** More public awareness and strategies to ensure accurate diagnosis and management of this condition are necessary.

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Introduction

Anaphylaxis is a severe, potentially fatal, systemic reaction that occurs suddenly after contact with an allergy-causing substance, typically involving 2 or more systems: skin/mucosal, gastrointestinal, cardiovascular or respiratory systems.¹⁻⁴ It is an increasingly important emergency, notably in Western countries, especially among children.^{5,6} The age-sex standardised incidence of anaphylaxis was 6.7 per 100,000 person-years in 2001 and increased by 19% to 7.9 in 2005.⁷ In a large published series, the causes of anaphylaxis were found to be drugs (35.3%), food (21.3%), food-dependent exercise-induced (13.2%), idiopathic (13.2%), insect stings (11.8%), exercise-induced (2.9%), blood products (1.5%) and latex (0.7%).⁸

Food-dependent exercise-induced anaphylaxis (FDEIA) is a less commonly known differential diagnosis of severe allergic reactions, when anaphylaxis occurs shortly after a patient participates in exercise which is temporally associated with food intake. It was first described in 1979 by Maulitz et al⁹ as a late allergic reaction to shellfish induced by strenuous exercise. Symptoms of FDEIA include urticaria, angioedema, respiratory symptoms, gastrointestinal manifestations and hypotension/shock.^{10,11}

Patients may or may not have pre-existing allergy to the food. Food or exercise independently does not cause anaphylaxis³ and the reaction can be food-specific or non-food-specific (i.e. consumption of any food followed by exercise can cause anaphylaxis).¹² A study among Japanese students estimated the prevalence of FDEIA to be 0.012% in that population, with the food triggers being wheat (57%), prawns (18%), cuttlefish (5%), crabs (3%), grapes (2%), nuts (2%), buckwheat (2%) and fish (1%).¹² Males are twice as likely to be affected compared to females; young adults and adolescents are more affected, children less than 10 years old are affected less.^{4,13} Any level of exercise can induce FDEIA, but it occurs especially with prolonged endurance exercises.^{12,13}

It is pertinent to understand FDEIA because it is an important but frequently overlooked cause of anaphylaxis. It is difficult to diagnose due to the multiplicity of factors involved. We therefore conducted a 2-year retrospective review of all the cases of FDEIA presenting at our hospital between August 2006 and July 2008.

Case Reports

Five patients were diagnosed with FDEIA, 3 males

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and 2 females. There were 4 Singaporean Chinese and 1 Vietnamese aged 9 to 20 years. The patient characteristics, symptoms and management are recorded in Table 1. Three of the patients had had previous episodes of suspected FDEIA.

Patient 1, a 19-year-old Chinese male, developed hives, circumoral swelling as well as systemic symptoms – faintness, vomiting, diarrhoea and abdominal cramp after running and was brought into the Emergency Department (EMD). He had consumed a home-cooked meal prior to exercise. He has had 3 previous episodes of urticarial rashes which developed when exercising between 1 and 2 hours after eating. Previously, the patient also had rashes when ingesting clams.

Patient 2, an 18-year-old Chinese male presented to the EMD when symptoms of anaphylaxis occurred after jogging. He had consumed fish and prawns prepared at home 2 hours before jogging. This was his second episode of suspected FDEIA, the first being 6 months before.

Patient 3, a 20-year-old Chinese female, was jogging 1 hour after a home-cooked meal containing prawns when she suddenly felt itch, had rashes, nausea and subsequently lost consciousness. Three weeks prior to this, she had had a similar episode but without syncope when running at the same location shortly after consuming a meal containing prawns. She had run there without problems previously.

Patient 4, a 15-year-old Vietnamese boy, was playing basketball 15 minutes after ingesting the usual food at his hostel canteen when he started experiencing itch, rash and eventually lost consciousness. This was his first episode.

Patient 5, a 9-year-old Chinese girl, had a meal that contained shellfish prepared at home followed by a pineapple tart. This was her first time eating shellfish. She first felt a lump in her throat and later developed a rash and dyspnoea after swimming. The patient had a history of asthma and used a salbutamol metered-dose-inhaler whenever necessary. Her last episode of wheezing was 2 months before. Otherwise, she had been well and her exercise tolerance was good. She was found to be limpet and dust mite sensitised on skin prick test (SPT).

In all cases, patients were sent to the EMD and given various emergency treatments (Table 1). They were initially admitted with a diagnosis of anaphylaxis of unknown aetiology and subsequently referred to an allergist. FDEIA was diagnosed after careful consideration of the patient's history and exclusion of other causes. All patients were given an anaphylaxis management plan, asked to avoid exercise 4 hours after consuming food and to always carry an epinephrine auto-injector as well as oral antihistamines. Patients were taught to use the auto-injector and in the case of patient 5, her mother was instructed on how to use it. Symptoms resolved uneventfully in all cases and patients were discharged after a hospital stay of 2 to 3 days, with

follow-up consultations at the allergy clinic between 3 and 6 weeks later.

Discussion

In this study, we have described the characteristics of patients who presented to our hospital with FDEIA over a 2-year period. The patient demographics match that of the literature with more males than females. Also, our series shows that the most common age of presentation is in the late teenage years, consistent with data in other studies.^{4,13} The average time of symptom onset was 81 minutes, slightly longer than the 60 minutes suggested by Thong et al.¹¹

Most cases of FDEIA in the Asia Pacific region have been described in Korea and Japan. The most common cause of FDEIA among adults and children of Oriental descent is wheat followed by shellfish.^{3,12,14,15} The picture is similar among people of non-Oriental descent,^{3,10,13,16} with other less common allergens such as mustard,¹⁷ apple,¹⁸ tomatoes,¹⁹ peanuts¹⁹ and celery²⁰ being implicated in literature. In our patients, we suspected shellfish as the trigger as 4 had eaten prawns and 1 scallop and limpet before the development of symptoms. Wheat was not a cause in our population and this could be due to variations in dietary patterns.^{10,11} It is unlikely that unknown spices or food additives caused the reaction as the meals were prepared at home or in the hostel and 4/5 patients had consumed the suspected causative food before without problems. We performed SPTs on all subjects using commercial extracts of various foods. The tests were negative in all 4 patients tested for prawns, which is not surprising as a negative SPT does not rule out FDEIA. Patient 5, however, tested positive to limpet allergens. No further radioallergosorbent tests were conducted to measure allergen-specific serum IgE levels because RAST has similar or even lower sensitivity compared to SPT (85%) for older children and adults.¹⁴ To further confirm the SPT findings, 4 patients were contacted and were all consuming prawns without clinical reaction, in the absence of exercise. The remaining patient could not be contacted.

For the diagnosis of FDEIA, the first step is to take a good history to determine if there are other reasons for the symptoms. This is followed by allergy testing with SPT or in vitro serum food-specific Immunoglobulin E (IgE) assays.^{14,21} Open Exercise-Food challenge (OEFCh) and double-blinded, placebo-controlled food-exercise challenge (DBPCFEC) can also be performed, with DBPCFEC being the gold standard for the diagnosis of FDEIA.^{14,21} However, double-blind placebo-controlled food challenges are labour-intensive and may carry higher risks due to masking of oral symptoms, especially when food is packaged in capsules.²² There is a false negative rate of 1% to 3%.^{23,24} In each of our 5 cases, the diagnosis of FDEIA was reached based on the history of consumption of the

Table 1. Patient Characteristics, Symptoms and Management

Patient	Age	Gender	Race	History of atopy	Total no. of episodes	Food consumed prior to FDEIA	Exercise	Symptoms	Latent period	Skin prick test	Management	Length of hospital stay (days)
1	19	M	Chinese	Allergic rhinitis and eczema	4	Prawns Salad	Jog	Urticaria, syncope, angioedema, breathlessness, vomiting, diarrhoea	1 hour	Negative to extensive list of foods, including wheat, prawn Positive to Der p, Der f, Blo t	PO chlorpheniramine	2
2	18	M	Chinese	Nil	2	Prawns Fish	Jog	Urticaria, hypotension, light-headedness	2 hours	Negative to extensive list of foods, including crab, prawn, Blo t Positive to Der p, Der f	IM adrenaline IV hydrocortisone IV promethazine IV ranitidine	3
3	20	F	Chinese	Asthma	2	Prawns Rice Mushroom Vegetable	Jog	Urticaria, hypotension, syncope, angioedema	1 hour	Negative to prawn & crab Positive to Der p, Der f & Blo t	SC adrenaline PO prednisalone IM promethazine	2
4	15	M	Vietnamese	Nil	1	Prawns Fish cake Capsicum soup containing carrots	Basketball	Urticaria, hypotension, syncope	15 min	Negative to extensive list of food including crab, prawn, wheat, egg	IM adrenaline IV hydrocortisone IV diphenhydramine PO chlorpheniramine	3
5	9	F	Chinese	Asthma	1	Limpet Vegetable Scallop Duck Pineapple tart	Swim	Generalised urticaria, hypotension, wheezing and shortness of breath	2.5 hours	Negative to Blo t Positive to limpet, Der p, Der f	Nebulised salbutamol IM hydrocortisone IM diphenhydramine	2

IM: intramuscular; IV: intravenous; PO: per oral; SC: subcutaneous

* Latent period = Time between consumption of food and anaphylaxis

Table 2. Exercise-Induced Allergic Syndromes^{1,10,15}

	FDEIA	Cholinergic Urticaria	EIA
Stimuli	Food followed by exercise	Heat, stress, exercise	Only exercise
Symptoms			
-Dermatological	Diffuse urticaria (10-15 mm)	Transient punctuate pin-point sized wheals (2-4 mm)	Diffuse urticaria (10-15 mm)
-Cardiovascular	Hypotension	Rare	Hypotension
-Respiratory	Laryngeal oedema, bronchospasm	Rare	Laryngeal oedema, bronchospasm
Reproducible by same stimuli?	Yes	Yes	Variable. Episodic.
Management	Avoidance of exercise 4 hours post-prandial	Anti-histamines. No restriction to exercise.	Avoidance of exercise

causative food followed by exercise. This differentiated it from 2 similar conditions, exercise-induced anaphylaxis (EIA) and cholinergic urticaria (Table 2). Given the strong evidence from clinical history and the potential risks of anaphylaxis, both DBPCFEC and OEFC were not performed as supported by Du Toit et al and Morita et al.^{3,25}

Regarding treatment, adrenaline is the standard of care for anaphylaxis. Both Muraro and Fisher et al found that adrenaline most consistently caused improvement of symptoms but was frequently under-utilised.^{5,26} Subsequent management of FDEIA is largely preventive. The avoidance of exercise for 4 hours post-prandial is consistent with models suggested by many authors.^{3,4,10,12,21} This strategy seems to work as all our patients did not suffer any subsequent recurrence at up to 2 years of follow-up. Other studies suggest prophylactic anti-IgE therapy or using progressively higher exertions separated by rests to induce tolerance to exercise but both methods are as yet unproven.¹⁰

The exact pathophysiology behind FDEIA is still unknown.^{3,10,12} Stratbucker postulated that exercise lowers mast cell degranulation threshold.²¹ Other authors further suggest that exercise causes improper digestion and absorption of food, leading to an increase in allergenic proteins in the blood. This in turn results in IgE mast cell sensitisation and the rapid release of histamine and other mediators when the causative food is consumed.^{12,15,21} Histamine induces leukotriene release which contracts smooth muscle – causing difficulty in breathing and gastrointestinal symptoms. The mast cell mediators also cause vasodilatation, leading to urticaria, angioedema, hypotension and possibly even shock.²¹

Conclusion

The consumption of shellfish is commonplace in Singapore and exercise is increasing in popularity. Despite its low prevalence, FDEIA is an increasingly important differential to consider in anaphylactic events. Lack of

awareness will potentially lead to wrong diagnoses and management plans, possibly unnecessarily limiting the patient's diet and exercise routine. Further research into the pathophysiology behind this syndrome and developments into the method of accurate diagnosis and treatment are important areas for future research.

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