

Educational case report

The difficulties of diagnosing food-dependent exercise-induced anaphylaxis in childhood – a case study and review

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We describe a case report of peanut and hens egg-dependent exercise-induced anaphylaxis in a 13-yr-old child, and assess the fundamental importance of careful investigations to differentiate food-dependent exercise-induced anaphylaxis from other forms of allergic reactions.

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Food allergy/hypersensitivity is an adverse reaction to a food component causing allergic reactions including generalized urticaria, angioedema and type 1 anaphylaxis. Epidemiological studies (1) indicate that the prevalence of food allergies is greatest in the first few years of life, affecting approximately 6% of infants <3 yr of age and decreasing over the first few decades to approximately 2% of the adult population. Eighty-five per cent of food allergies in children are due to egg, milk and peanuts (2) whilst the common foods causing allergies in adults are shellfish, tree nuts and egg.

Exercise-induced anaphylaxis (EIA) is a form of physical allergy in which exercise precipitates attacks of anaphylaxis. In 1979, Maulitz et al. (3) reported a case of EIA that occurred only when the ingestion of shell fish preceded exercise. This syndrome was named food-dependent EIA (FDEIA) and is an unusual clinical syndrome requiring both intake of an allergenic food and exercise to induce anaphylaxis. It is vital that this diagnosis is not overlooked when an otherwise healthy exercising person develops anaphylactic type symptoms without an obvious inciting event.

Case history

A 13-yr-old MW (initials) was referred to our clinic after suffering numerous episodes of

angioedema, urticaria and difficult breathing during vigorous exercise. There was no history of prior medication intake such as aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) or episodes of being stung or bitten, and his mother describes no allergies to medications. The first of these major episodes occurred during Tai Kwon Do training approximately 2 h after a meal containing processed turkey and an egg and nut containing sauce. It responded immediately to chlorphenamine 4 mg and 10 puffs of Salbutamol inhaler. The second episode of anaphylaxis also occurred during Tai Kwon Do and was preceded by a meal containing eggs, banana and peanut. Anaphylactic symptoms included generalized urticaria, angioedema, wheezing and dyspnoea, and he immediately required an epinephrine autoinjector and diphenhydramine. Additionally MW has had numerous other episodes of less severe urticarial episodes occurring during exercise and associated with wheezing.

Review of symptoms was negative for recent viral colds, chest pain, abdominal pain, vomiting or diarrhoea. Other allergic diseases included eczema since 4 yr of age, asthma (which is well controlled on a steroid inhaler) and hay fever during the summer months. There is no other family history of food allergies or allergic reactions during exercise.

Clinical examination

General examination revealed a child in good health with evidence of chronic flexural eczema. The oropharynx, cardiovascular and respiration examinations were normal, and there were no features of mastocytosis.

Investigations

Skin prick testing (SPT) returned negative for peanut, a selection of treenuts, hens egg, wheat flour, banana and gluten. Specific immunoglobulin (Ig)E tests demonstrated a raised total IgE (750 IU/ml, normal range <120) and Class-1 (0.65 IU/ml) specific IgE to peanut and egg white.

The family was informed about the possible association of specific foods with exercise. It was noted that MW tolerated significant quantities of peanut and egg in the absence of exercise. After he was advised to avoid eggs and peanuts 2–3 h pre-exercise, symptoms completely resolved confirming a relationship of nuts and egg with exercise. However 6 months later, MW presented to the emergency department with the third major episode. This again occurred during strenuous exercise following ingestion of a peanut containing chocolate bar, a snack that he normally tolerates in the absence of exercise. He was once again educated to separate ingestion of nuts and egg from exercise. One year on, MW exhibits no anaphylactic type symptoms and continues to excel at Tai Kwon Do. The history and asymptomatic period following dietary elimination proves egg- and peanut-dependant EIA and an oral food challenge were not indicated. Lung function tests were performed at clinical assessment when asymptomatic and on asthma therapy. Predictive values for peak expiratory flow and forced expiratory volume were normal with no significant post-salbutamol reversibility demonstrated.

Discussion

Diagnosis

Detailed clinical history of exercise induced anaphylactic symptoms with a preceding history of all food intake is fundamental for diagnosis (4). SPTs and radioallergosorbent test may be useful as it is important to test to a broad range of food allergens including wheat, peanut and treenut (5). Those foods used for seasoning, such as garlic or parsley (6) may also prove beneficial. Although MW was only weakly positive to egg white and peanut, exclusion of these food aller-

gens prior to exercise eliminated all further reactions.

Food-dependent EIA is predominantly a clinical diagnosis, and it is essential that other food-induced allergic reactions are ruled out during the history. These include the following.

Food allergy. Food hypersensitivities can be IgE mediated or cell mediated responses. IgE mediated reactions typically develop within minutes to 2 h of consumption of the responsible food allergen with cutaneous, respiratory and gastrointestinal manifestations. These include urticaria and angioedema, bronchospasm, abdominal pain, vomiting and diarrhoea. Exercising in the interim may complicate the diagnosis, however, it is important to note that patients with type 1-mediated food allergies will become symptomatic independent of physical exertion.

Egg- and peanut-dependent patients may present with diarrhoea, vomiting and failure to thrive (4). MW did not illustrate any gastrointestinal manifestations of allergy.

Exercise-induced anaphylaxis. Affected individuals typically experience a sensation of warmth, flushing, generalized itching and the development of urticaria or hives during vigorous exercise (7). This can lead to a full-blown life-threatening anaphylactic attack with airway obstruction and signs of shock. EIA tends to affect females around the time of menstruation, or with aspirin or NSAIDs use. There is a positive family history but no association with food. Although MW has an atopic status, suffering from eczema and asthma, we exclude EIA as his anaphylactic symptoms do not occur each time he exercises. There is also an association with particular food groups as exclusion of egg and peanut several hours prior to physical activity eliminates symptoms.

Cholinergic urticaria. Cholinergic urticaria (CU) is associated with an elevation in the core body temperature and can therefore also occur during exercise (8). A rise of core body temperature by 1°C will reproduce symptoms of urticaria and angioedema and so unlike EIA, which only occurs on exposure to exercise, an increase in core body temperature is the inciting stimulus. The urticaria of CU are punctate and small in size (1–3 mm), whilst those of EIA are typically larger (10–15 mm) and more diffuse. The airway symptoms of EIA may include choking, stridor secondary to obstruction and bronchospasm whilst CU patients may experience wheezing from spasm of the smaller airways but no

life-threatening angioedema or vascular collapse. The severe nature of the symptoms and the characteristic features of the rash and the fact that in the absence of food MW tolerates exercise, strongly argues against CU.

Exercise-induced asthma. Exercise-induced asthma develops when vigorous physical activity triggers airway narrowing in people who have heightened bronchial reactivity, resulting in cough, wheezing, dyspnoea, and/or chest tightness. This may be the sole manifestation of asthma or may present in uncontrolled persistent asthmatics. If there is absence of rash or anaphylaxis then we differentiate this condition from FDEIA.

Cold urticaria. Cold urticaria is a physical urticaria where exposure to cold temperature can rapidly induce the onset of hives on the face, neck or hands. Common cold triggers include swimming, cold water bathing and environmental cold exposure. The low temperature is thought to induce a massive histamine release which may even result in low blood pressure, fainting and shock (9). It is important to note that it is the temperature rather than the co-associated exercise that initiates these changes and during the history it is important to question the environment in which symptoms began.

Allergic reactions associated with exercise. Here the relationship between exercise and allergic symptoms is not causal, with exercise being described as a cofactor for anaphylaxis, thereby worsening allergic symptomatology. Exercise may be coincidentally associated with symptoms such as when a child develops urticaria and wheezes whilst running outdoors in the grass during summer. Pollen and pet dander are acknowledged allergens causing significant morbidity. An interesting review (10) discussed three case reports where young children developed symptoms of rhinitis, conjunctivitis and wheeze in unforeseen circumstances. On further analysis, all detailed a history of exposure to horses or horse dander which emphasizes the necessity to look for less obvious allergens that may be precipitating an allergic episode. Although MW has hay fever, his symptoms also occurred in winter where exposure to inhaled allergens is minimal.

Treatment

Treatment of acute symptoms includes epinephrine and H1 receptor antagonists, with B₂ agon-

ists providing benefit for milder symptoms. However, identification and avoidance of precipitating foods at least 3–4 h prior to exercise is the mainstay of treatment for FDEIA. Patients should be instructed to carry antihistamines and auto-injectable epinephrine when performing vigorous activity. In any event they should always exercise with others who understand their condition and can administer epinephrine.

Pathophysiology

In FDEIA, IgE cross-linking by a particular food allergen in combination with exercise lowers the threshold of mast cell degranulation resulting in histamine release and the progression of allergic symptoms from pruritus and urticarial rash to angioedema and anaphylaxis. The exact mechanism is unknown, however, other considerations include the following.

Gut permeability. Gut permeability improves during exercise, thus allergenic proteins may have greater access to the hosts gut-associated immune system (11). Low molecular weight peanut allergens (e.g. Ara h 3, glycinin, which consists of a series of polypeptides ranging approximately from 14 to 45 kDa) may be rapidly absorbed through the mucosal barrier, accounting for the rapid onset of reactions during exercise.

Increased activity of tissue enzymes. Coeliac disease research has highlighted the importance of the tissue enzyme transglutaminase (tTG), localized beneath gut epithelium (12). This enzyme is able to modify specific glutamine residues in wheat allergens, resulting in the formation of large peptide aggregates with more intense IgE binding and cross-linking. During exercise there is widespread release of interleukin (IL)-6, IL-1 β and tumour necrosis factor- α by contracting skeletal muscle. IL-6 is thought to be a potent tTG activator. As a result exercise-induced IL-6 release may activate tTG to modify protein peptides and facilitate Ig cross-linking and mast cell histamine release. At present, no studies have been performed assessing the activity of tTG towards peanut or egg allergenic peptides.

Conclusion

MW reports three clear episodes of anaphylaxis during vigorous exercise following ingestion of peanut and hens egg, and numerous other episodes of urticaria in the interim. All allergic

symptoms were absent with dietary exclusion of peanut and hens egg 2–3 h pre-exercise. This confirms peanut and egg-dependent EIA. However, all other possibilities must first be excluded before this diagnosis can be made. FDEIA in childhood is an uncommon but important consideration when ‘exercise associated’ anaphylactic reactions occur. Given that the prevalence of food allergy among children is increasing, and in particular allergy to peanuts (13), FDEIA may become a more common clinical scenario.

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