

Case Report

Apple-Dependent Exercise-Induced Anaphylaxis: Three Cases in Children and Literature Review

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Abstract

Food-dependent exercise-induced anaphylaxis occurs with exercise, preceded in a few hours by food intake, being both independently tolerated. Apple-dependent exercise-induced anaphylaxis is very rare and we present a series of 3 cases. They occurred in five, 13 and 15 year-old males. All of them had allergic rhinitis. Anaphylaxis occurred during physical exercise, between one and two hours after eating apple, and was treated with intramuscular epinephrine. One patient had two further recurrences on identical circumstances. Skin prick tests (SPT) and specific Immunoglobulin E (sIgE) were positive to apple in all patients. Apple and exercise were tolerated separately and other possible causes of anaphylaxis, including exercise-induced anaphylaxis and apple allergy were excluded. An epinephrine auto-injector was prescribed and a four hour period free from exercise was recommended after eating apple. In a follow-up of 39±22 months, none had recurrence. So far, this is the largest series on apple-dependent exercise-induced anaphylaxis.

Keywords: Anaphylaxis; Exercise; Food Allergy; Food-Dependent, Exercise-Induced Anaphylaxis

Introduction

Anaphylaxis is an acute potentially fatal multissystemic reaction, generally IgE mediated. Food-dependent exercise-induced anaphylaxis (FDEIA) is rare in children [1], with a prevalence of 0,0017% [1,2]. FDEIA occurs during or shortly after exercise, few hours after ingestion of culprit food allergens. Typical symptoms include urticaria and/or angioedema, dyspnea, abdominal pain, fatigue and loss of consciousness [3]. Physical exertion and food are independently tolerated [1-7]. This can be explained by the fact that exercise increases the permeability, osmolality and absorption of food allergens in the gastrointestinal tract and the degranulation of mast cells [7,8]. The foods most commonly implicated in FDEIA are wheat, other grains, nuts and shellfish. Less frequently, fruits, vegetables, seeds, legumes, and even various meats, cow's milk, and egg have been reported [1,3,9]. Two forms of FDEIA have been described: the most common involves reactions after the ingestion of specific foods; rarely such reactions occur after the ingestion of any food [1,5,10,11].

Skin prick tests (SPT) and specific Immunoglobulin E (sIgE) are useful to identify allergen sensitization.[1-3] Prick-to-prick skin test can be used in the suspicious of sensitization to a raw fruit or vegetables [6]. A double-blind, placebo-controlled challenge test with the ingestion of the food followed by intense physical exertion is the gold standard method for confirming the diagnosis[12]. However, since anaphylactic episodes are rarely stereotypical, there is no widely accepted protocol for exercise testing and false negative results are common[1,3].

A correct diagnosis of this condition is essential to avoid unnecessary restricted diet, allow physical activity separately from the food trigger, and to manage attacks.

There are few reported cases of exercised-induced anaphylaxis after ingestion of apple, especially in children [13-15], although it is eaten widely over the world [13]. We present a case series of three pediatric patients with FDEIA after ingestion of apple, the largest series to date.

Cases Report

The first case is a 13-year-old boy, who presented to Emergency Department with generalized urticaria, facial angioedema and dyspnea, stridor and wheezing of rapid progression. This occurred in the first ten minutes of a football match, in an open field surrounded of vegetation. He was treated with intramuscular epinephrine with good response. Two

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Sub Date: October 7th, 2017, **Acc Date:** October 16th, 2017, **Pub Date:** October 16th, 2017.

Citation: Catarina Salgado, Catarina Carrusca da Silva, Patrícia Sá Ferreira and Candida Mendes, (2017) Apple-Dependent Exercise-Induced Anaphylaxis: Three Cases in Children and Literature Review. BAOJ Pediat 3: 049.

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similar episodes occurred four months later, during football matches, first at the same place and the second at an indoor field. These three events occurred about 30 minutes after ingestion of different foods, being raw apple the common one. He had intermittent seasonal allergic rhinitis in rural environment during spring and autumn and recently he had his first episode of asthma, in the context of pollen exposure. Later he had events of generalized urticaria after isolated ingestion of orange and crab but he had eaten apples without adverse reactions. SPT were performed to foods ingested before the events: spinach, cocoa, egg, chicken, kiwi, and apple. There was positivity to kiwi and apple.

The second case is a 15-year-old boy who suffered an anaphylaxis episode characterized by generalized urticaria, labial angioedema and dyspnea, ten minutes after beginning intense physical exertion, two hours after eating an apple. He presented to Emergency Department and received treatment with intramuscular epinephrine, with good response and no recurrence during 24 hours hospitalization. He had mild intermittent allergic rhinitis but no previous food reactions have been reported.

The last case is a 5-year old boy who presented a chin rash after eating an apple, two hours before practicing exercise. During exercise he developed facial edema, especially in eyelids, urticarial rash in back and arms. He also had abdominal pain, one vomit, dyspnea and stridor. He was assisted by his pediatrician who performed adrenaline muscular injection. He had rapid recovery of the respiratory and gastro-intestinal symptoms and was admitted to 24 hours hospital surveillance, with gradual disappearance of facial edema. This child had previous mild intermittent allergic rhinitis and perioral rash and pruritus after ingestion of peach (with or without skin).

In all the cases there wasn't previous reaction to ingestion of apple, similar amount of exercise had never resulted in symptoms and neither heat nor cold exposure caused urticaria. In all cases the ergometry test after four hours of fasting, with high intensity of exercise was reasonably tolerated, with appropriate cardiopulmonary response to the age.

Skin prick tests (SPT) and specific Immunoglobulin E (sIgE) were positive to apple in all patients. Prick to prick test to apple were also positive in the third case. There were other positive results in SPT and sIgE (**Table 1**) but none to food ingested previous to exercise.

Specific serum IgE in the cases reported.

Besides, the microarray-based assay ImmunoCAP® ISAC showed in the first case sensitization to different gramineae allergens and to lipid transfer proteins (LTP) of peach and hazelnut; in the second case was only positive do allergens of dust mite; in the third case there were multiple sensitizations identified (gramineae, aspergillus, dust mite), being the most relevant several LTP (from peanut, hazelnut, walnut, peach) We could find positive sIgE to Mald 3 (LTP from apple) in the second (6.21 KUL/L) and third (66.9 KU/L)

These three patients presented anaphylaxis following exercise. However, these never occur independently of food ingestion and once they had prior and ongoing exercise tolerance, exercise-induced anaphylaxis becomes unlikely. Being the clinical picture of anaphylaxis, exercise-induced asthma is ruled out. Given prior tolerance to apple and negative oral food challenge to apple, an apple allergy unrelated to exercise is unlikely.

Cholinergic urticaria (CU) is associated with an elevation in the core body temperature and can therefore also occur during exercise. The severe nature of the symptoms and the fact that in the absence of previous food ingestion all the subjects tolerated exercise, strongly argues against CU.

Given anaphylaxis following exercise, good tolerance to food without exercise and the continued ability to tolerate exercise without incident, FDEIA remains the most likely diagnosis.

An epinephrine auto-injector was prescribed and a four hour period free from exercise was recommended after eating apple. None had recurrence of anaphylaxis in five, 3,5 years and 15 months of follow up, respectively in first, second and third cases and been able to tolerate exercise without incident.

Discussion

These three cases are paradigmatic of FDEIA specific of apple because there was a typical multisystem reaction few minutes after physical exertion, being apple ingested in the previous two hours in all the cases. Furthermore, apple ingestion and physical exertion practiced separately did not trigger any reaction. It's largest series in pediatric population described in literature. In the first and third cases there were sensitization both to LTP of peach and apple, which might indicate a cross reactivity between these fruits. Besides, the third child also exhibited symptoms of oral allergy syndrome to peach previous to the FDEIA episode, being even more typical of an LTP syndrome. In vitro apple's sensitization is uncommon in literature [1], and apple has rarely been reported as cause of FDEIA, particularly in children [13 -15].

The gold standard diagnosis test of FDEIA is double-blinded, placebo-controlled food-exercise challenge (DBPCFEC)[5] which has not been performed in these cases. This was decided attending to the fact that some cases of FDEIA reported in literature have not been successfully induced by challenge tests, including a similar case of apple being the culprit food [13]. A negative exercise challenge test does not exclude the diagnosis of EIA since it is negative in about 30% of cases [3,6,16]. This is partly explained by the fact that in some cases the exposure to triggering actors are necessary to elicit reaction and they cannot be reproduced in the laboratory [17]. Induction of anaphylactic symptoms could be dependent on the amount of food allergen ingested [18], and another possible factor causing the false-negative test is an inappropriate type of exercise employed in the tests [3]. Likewise conditions as fatigue, cold, menstruation, stress and drugs (including alcohol and aspirin), that have

Table 1. Specific serum IgE in the cases reported.

Specific IgE (RAST)	Case 1		Case 2		Case 3	
	kU/L	Class	KU/L	Class	KU/L	Class
Apple (Malussylvestris)	93	5	2.81	2	7.75	3
Peach rPrup1	-	-	-	-	<0.01	0
Peach rPrup3	-	-	-	-	18.9	4
Orange	4.5	3	-	-	-	-
Cocoa	< 0.35	0	-	-	-	-
Egg yolk and white	< 0.35	0	-	-	-	-
Latex	< 0.35	0	-	-	-	-
Dermatophagoides pteronyssinus	<0.35	0	> 100	6	4.54	3
Dermatophagoides farinae	<0.35	0	83.9	5	1.5	2
Dactylis glomerata	18	4	<0.35	0	3.99	3
Lolium perene	5	3	<0.35	0	3.88	3
Phleum pratense	8	3	<0.35	0	3.25	2
Parietaria officinalis	0.4	1	-	-	-	-
Olea Europa (olive tree)	18	4	-	-	0.86	2
Total IgE PRIST (mean ± standard deviation adapted to age) UI/mL	200 (195±20.1)		832 (195±20.1)		421 (68.9±8.6)	
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Apple (Malussylvestris)	93	5	2.81	2	7.75	3
Peach rPrup1	-	-	-	-	<0.01	0
Peach rPrup3	-	-	-	-	18.9	4
Orange	4.5	3	-	-	-	-
Cocoa	< 0.35	0	-	-	-	-
Egg yolk and white	< 0.35	0	-	-	-	-
Latex	< 0.35	0	-	-	-	-
Dermatophagoides pteronyssinus	<0.35	0	> 100	6	4.54	3
Dermatophagoides farinae	<0.35	0	83.9	5	1.5	2
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been reported to augment FDEIA, cannot always be reproduced [3,9,13].

Therefore, It is accepted that FDEIA is a predominantly clinical diagnosis [1,4],and DBPCFEC is not absolutely required to diagnose FDEIA [1,3,5]. It can be skipped when the clinical and laboratory elements are consonant, considering the life threat event that is an anaphylaxis episode. In all the cases, laboratory tests confirmed sensitization to apple and exercise challenge without ingestion of apple in the previous four hours was tolerated. In second case open-labeled oral challenge test to apple without exercise was negative and in the first and third cases previous apple ingestion never caused adverse reactions.

Although rare, FDEIA is an increasingly important diagnosis to consider at anaphylactic events [17]. There are very few cases reported in international literature about apple-dependent exercise-induced anaphylaxis in children, which can be resumed in the table 2.

Cases reported by authors and cases reported in literature of apple dependent exercise induced anaphylaxis

A correct diagnosis of this condition is essential to avoid unnecessary restricted diet, allow physical activity separately from the food trigger (respecting the security time lapse) and to manage attacks. Authors highlight that although rare, apple may also be a cause of FDEIA.

Table 2. Cases reported by authors and cases reported in literature of apple dependent exercise induced anaphylaxis

Cases	Case 1	Case 2	Case 3	Morimoto et al. (2005) J Dermatol.	Morillas et al. (2003) Allergol et Immunopathol	Añíbarro B et al. (1994) Allergy
Age	13	15	5	14	14	12
Gender	male	male	male	male	female	female
Number of anaphylaxis episodes	3	1	1	4	9	1
Apple SPT	positive to apple	positive to apple	positive to apple and peach	positive to apple flesh	positive to apple	positive to fresh apple”
Total IgE (kU/L)	200	832	421	251	150	60
Specific apple IgE (KU/L)	93	2.81	7.75	0.88 (class 2)	not reported	“class 2”
Apple oral challenge	-	negative	-	negative	negative	negative
Exercise challenge	negative	negative	negative	negative	negative	negative
Exercise challenge after apple ingestion	-	-	-	negative	positive	positive
Allergic comorbidities	allergic rhinitis, asthma, crab and orange allergy	allergic rhinitis	allergic rhinitis Peach allergy	not reported	allergic rhinitis	allergic rhinitis

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