Food-Dependent Exercise-Induced Urticaria/Angioedema Caused by Lipid Transfer Protein in Two Children

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KEY WORDS: urticaria/angioedema (UA), exercise, lipid transfer protein, anaphylaxis, food-dependent exercise-induced anaphylaxis

IMAJ 2015; 17: 451–452

Acute urticaria/angioedema (UA) is a frequent manifestation of immunoglobulin E (IgE)-mediated food allergy (FA), although FA is not the most common cause of acute or recurrent UA. Symptoms mostly arise promptly after the specific food is ingested and abate soon after its withdrawal from the diet. A new ingestion of the food leads to a new and sudden onset of symptoms, sometimes accompanied by severe and generalized reactions. When the clinical history is supported by skin prick test or specific IgE positivity for the ingested food, it is easily diagnosed. In contrast, when acute or recurrent UA episodes develop in a child without a close temporal relationship with the ingestion of a food, especially if that food has been eaten on other occasions without apparent onset of symptoms, the diagnosis of food allergy is usually excluded. Unlike anaphylaxis, in acute or recurrent UA the possible role of exercise is usually not investigated [1].

We present two children with food allergy in whom UA developed only when the ingestion of the allergic food was followed by physical exercise.

PATIENT DESCRIPTIONS

PATIENT 1

A 6 year old girl was referred for an episode of UA that arose while she was walking. The clinical history revealed that 30 minutes before the onset of UA she had eaten a prepacked ice cream containing milk, egg, wheat, cocoa and traces of nuts. An ingestion of Ravenna cherries was also reported 2 hours before the same episode of UA. Skin prick tests and specific IgE (Thermo Fisher Scientific, Italy) performed at another allergy clinic were negative for several common foods, including milk, wheat, egg, peanut and walnut. Microarray assays for determination of specific IgE (ImmunoCAP ISAC™, Thermo Scientific) were positive only for Pru p 3 (4.21 ISU). The girl was thus advised to avoid some foods that contain lipid transfer protein (LTP), such as cherry, peach and peanut.

Two years later, she returned to our clinic for a reevaluation of her food allergy. For the last 2 years she has followed the diet and has been well. She has also been involved in sports activity, without any complaint. A detailed clinical history revealed that the girl had consumed Ravenna cherries several times, without any reaction, before the onset of UA. Prick-by-prick tests were positive for fresh cherry peel (mean wheal diameter 10 mm) and fresh cherry pulp (3 mm). Skin prick test (SPT) for cherry and peach commercial extracts were also positive (both with mean diameter 8 mm) and negative for wheat, egg, milk and other common food allergens. An oral food challenge (OFC) lasting an hour was performed with an increased quantity of cherries, without any clinical reaction. Thus, 4 hours after she began to eat the cherries, 24 in total (and 3 hours after finishing them), an exercise challenge (step test) was performed. Only 2 minutes after starting the step test a generalized UA developed. A thorough examination excluded respiratory, gastrointestinal or cardiovascular involvement. Symptoms disappeared about 1 hour after the exercise was stopped and oral antihistamine and steroids administered.

PATIENT 2

A 15 year old boy was referred for recurrent manifestations of UA. The first episode occurred at age 6, and reoccurred annually until the previous year when he had about six episodes – approximately one UA episode per month. The clinical history was negative for food allergies and revealed that these manifestations appeared only during exercise, and that the food ingested during the 2 to 3 hours before the occurrence of UA was wheat. The boy and his parents denied the presence of any other respiratory, gastrointestinal or cardiovascular symptoms, even mild, during previous episodes of UA. The SPTs were positive for wheat, peach and hazelnut commercial extracts (mean wheal diameter 6 mm, 5 mm and 5 mm, respectively) and negative for other common food allergens, such as milk, egg, soya, fish, peanut, nuts, tomato, etc. Microarray assays for the determination of specific IgE (ImmunoCAP ISAC™) were positive for some inhalants and, among the foods, for peach and hazelnut only. The boy had eaten those foods many times, both with and without physical exercise, with no complaint [Table 1].

He was advised not to eliminate wheat, hazelnut and peach from his diet, but to

Table 1. Immunologic responses to allergens in patient 2

	2011	2012
Art v 3 (ISU)	0.56	0.8
Cri J 1 (ISU)	5.4	5.5
Cup a 1 (ISU)	12.8	13
Par J 2 (ISU)	1.0	0.7
Ole e 7 (ISU)	0	0.7
Pla a 3 (ISU)	0	0.6
Cor a 8 (ISU)	0.5	1.4
Pru p3 (ISU)	1.88	2.3
Ara h 9 (ISU)	0	1.1
nJug r 3 (ISU)	0	1.1
Tri a 14 (ISU)	0	1.4
Tri a 19 (ISU)	0	0

avoid the ingestion of these foods during the 4 hours preceding physical exercise, paying special attention to wheat, which was the only food he had consumed before the previous episodes. Adhering to this recommendation, he has been well for 15 months, except on one occasion when he felt too tired to follow this advice and ate pizza with tomato and cheese and then went to play soccer. About 15 minutes after starting to play, he developed generalized UA with abdominal pain, vomiting, rhinitis and hoarseness. The symptoms disappeared 2 hours after administration of oral antihistamine and steroids. This time, microarray assays to determine specific IgE (ISACTM) were positive for wheat (Tri a 14) and several LTPs among foods and inhalants, but negative for Tri a 19, the most common molecular allergen implicated in wheat FDEIA [2]. SPTs were again negative for milk, tomato and other common food allergens.

COMMENT

It is well known that exercise may induce food-dependent exercise-induced anaphylaxis (FDEIA) in some children, but its role in children with acute or recurrent UA is less known, and usually not emphasized. FDEIA may be allergen specific or non-allergen specific (i.e., any ingested food may induce the reaction) [3]. Subjects affected by FDEIA are sensitized to the food responsible for anaphylaxis even if specific IgE blood levels are lower than in other food allergies. Ingestion of the suspected food provokes clinical manifestations only when followed by physical exercise. At the same time, physical activity does not induce adverse reactions if not preceded by food ingestion. In allergen-specific FDEIA, the role of exercise is crucial because it prompts the development of clinical reactions to a food that is commonly eaten by the patient, without any clinical manifestation. FDEIA seems to be a partial state of tolerance to food, whose pathophysiological mechanisms are complex and unclear [4]. Among Europeans, tomatoes, cereals and peanuts are the most frequent allergenic foods, whereas among Japanese, wheat and particularly the omega-5 gliadin allergen are the most frequent. LTPs and plant panallergens are the most frequent sensitizer in Italian subjects with FDEIA, and subjects with FDEIA sometimes also experience mild episodes of UA [5]. The causative role of exercise is usually suspected in FDEIA and not in non-anaphylactic food-allergic reactions.

These cases alert us to the fact that exercise may have a causative role not only in FDEIA but also in the most common manifestation of food allergy, such as UA. Therefore, the relationship with exercise should be investigated in acute or recurrent UA as well, and if found, a possible partial state of tolerance to food (mainly LTP) should be sought. In fact, exercise-induced UA may precede the onset of FDEIA, as shown in patient 2.

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