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

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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 pre-packed 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 recurred 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 wheat 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...
Case Communications

Wheat (Tri a 14) and several LTPs among specific IgE (ISACTM) were positive for oral antihistamine and steroids. This disappeared 2 hours after administration.

About 15 minutes after eating the pizza, he started to feel too tired to follow this advice and ate more pizza. He then played soccer. During the game, he started to feel itchy and sneeze. He ran home to take an antihistamine and a steroid. However, his symptoms did not disappear immediately. He was able to go to bed but woke up several times during the night with abdominal pain, vomiting, rhinitis and hoarseness. The symptoms disappeared 2 hours after administration of oral antihistamine and steroids. Adhering to this recommendation, he has been well for 15 months, except on one occasion when he 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 common food allergens.

The role of exercise in the development of food allergy has been studied in several reports [1]. Le et al. found that patients with food-dependent exercise-induced anaphylaxis (FDEIA) may be allergen specific or non-allergen specific (i.e., any ingested food may induce the reaction) [2]. 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 tomatoes, cereals and peanuts are more frequent. LTPs and plant panallergens are among the most frequent sensitizer in Italian subjects with FDEIA, and subjects with FDEIA sometimes also experience mild episodes of UA [5].

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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References

Table 1. Immunologic responses to allergens in patient 2

<table>
<thead>
<tr>
<th>Allergens</th>
<th>2011</th>
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</tr>
<tr>
<td>Cri j 1 (ISU)</td>
<td>5.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Cup a 1 (ISU)</td>
<td>12.8</td>
<td>13.8</td>
</tr>
<tr>
<td>Par j 2 (ISU)</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Ole e 7 (ISU)</td>
<td>0</td>
<td>0.7</td>
</tr>
<tr>
<td>Pla a 3 (ISU)</td>
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</tr>
<tr>
<td>Cor a 8 (ISU)</td>
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<td>1.4</td>
</tr>
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<tr>
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(Capsule)

(Mis)matching tumors to immunotherapy

Despite the amazing success stories seen in some patients receiving cancer immunotherapy, the sobering reality is that not all patients or cancer types respond. For instance, colorectal cancer does not respond in the dramatic way that melanomas and other cancers do to the so-called immune checkpoint inhibitors. A subset of colorectal cancers cannot repair mismatched bases in DNA and therefore harbor high levels of somatic mutations. In a small clinical trial, Le et al. found that patients with mismatch repair-deficient colorectal tumors responded more favorably to an immune checkpoint inhibitor than those with mismatch repair-proficient tumors. The greater response observed in the former group is probably due to a higher abundance of mutation-associated neoantigens that boost antitumor immunity.