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Severe biphasic anaphylaxis to bigarreau cherry in a child

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Partially funded by Ricerca Corrente - Italian Ministry of Health

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The cherry is the fruit of the cherry-tree belonging to *Rosaceae* family. There are two main cherry-trees: *Prunus avium* (the fruit is the sweet cherry, with two main varieties: wild cherry and bigarreau cherry) and *Prunus cerasus* (the fruit is the sour cherry). *Rosaceae* fruits may cause two allergic clinical patterns: i) oral allergy syndrome (OAS) sustained by sensitization to pathogenesis related proteins (PR-10) proteins family (Bet v1 homologous) or lipid transfer proteins (LTP) and ii) systemic reactions, including anaphylaxis, caused by LTP or thaumatin-like proteins (TLP) (1).

Four principle molecular allergens of the sweet cherry have been described (www.allergome.org). Pru av 1 is a Bet v 1-homologous protein (PR-10) with 67% homology with Bet v 1, a pan-allergen shared by many *Rosaceae* fruits. It is responsible of mild allergic reactions. Pru av 2 is a thaumatin-like protein, a common pan-allergen present in many fruits. Pru av 2 is the main protein in ripe cherry and shares high homology with TLP of grape and apple. It may cause also severe symptoms. Pru av 3 is a LTP, pan-allergen with high homology with peach and apricot and maize. Pru av 3 does not cross-react with PR-10. It is localized in the peel. LTP allergy may induce severe reactions. Pru av 4 is a profilin, a pan-allergen present in many pollens and fruits. Generally, it causes mild allergy.

Cherry allergy is rather rare and usually may induce mild symptoms, including OAS and gastrointestinal complaints, even though anaphylactic reaction may occur.

Anaphylaxis is a "severe; life-threatening, generalized or systemic hypersensitivity reaction" as reported by a systematic review on its epidemiology in Europe (2). The most quoted work definition was proposed by Sampson and colleagues: anaphylaxis is likely when any of 3 criteria are fulfilled: i) acute onset of an illness with involvement of skin/mucosal tissue and airway compromise or reduced blood pressure or associated symptoms; ii) 2 or more of the following after exposure to known allergen for the patient: history of severe allergic reaction, skin/mucosal tissue, airway compromise, reduced blood pressure, gastrointestinal symptoms (for food allergy); iii) hypotension after exposure to known allergen for the patient (3). Infants and teenagers have increased vulnerability to anaphylaxis (4). Food is the most important trigger in childhood (5). Food anaphylaxis typically occurs after ingestion, more rarely after skin contact or inhalation. Diagnosis is performed using validated criteria (3,4). Clinical diagnosis is based on consideration of presenting signs and symptoms and on excluding other sudden-onset multisystemic diseases. However, there is still no biomarker confirming the diagnosis. Clinical history and serum allergen-specific IgE and/or

skin prick test remain the cornerstone for diagnosing food allergy. Recently, molecular-based allergy diagnostics improved the work-up, as it allows defining the profile of proteins involved in anaphylactic reaction (7). Fortunately, only few foods, mainly including egg, milk, peanut, fish, soybean, wheat, are usually cause of anaphylaxis in children and adolescents. However, 6 cases of cherry anaphylaxis have been reported till now. The first description of cherry anaphylaxis was reported by Subiza and colleagues, but they did not detect serum specific IgE either to cherry or to other *Rosaceae* fruits (8). Escribano and colleagues reported an adult case (36 years) with cherry anaphylaxis and hay fever (sensitization to grasses, olive tree, and mugwort): he had a negative prick-prick test for cherry, but high serum specific IgE to cherry (8 kU/L) and also to other *Rosaceae* fruits (9). Vieira et al. described a case referring cherry anaphylaxis occurred 20 years before (at 11 years): she had sensitization to plane and mugwort pollens, serum specific IgE were positive for LTP proteins, such as Pru p 3 (35.2 kU_A/L) and Cor a 8 (14.0 kU_A/L), but both prick test and serum specific IgE measurement were negative for cherry (10). Bianchi and colleagues reported a child (12 years) with food-dependent exercise-induced anaphylaxis, who experienced two episodes: the first after eating peach with peel, the second after eating some cherries (11). Prick-prick test was positive for cherry and peach (and also for other *Rosaceae* fruits), but serum specific IgE were negative for both raw peach and cherry extracts, as well as for LTP and PR-10 proteins (11). A survey on the incidence of anaphylaxis in Alcorcon (Spain) reported 1 case of cherry anaphylaxis, but without details (12). Another survey on Piemonte Region (Italy) reported 1 adult case of cherry anaphylaxis (13). It is to note that all these subjects lived in Spain or Italy: this fact is not surprising, as it is well known that LTP syndrome has some peculiarities, such as geographical distribution (Mediterranean basin), being frequently symptomless, symptoms occurrence needing co-factors, absence of pollen allergy favoring severe reactions (1).

Case Description

A 5 year-old boy living in southern Piemonte (Italy) in a rural area, without any relevant illness, experienced two distinct anaphylaxis episodes, both immediately after eating bigarreau cherries. The first episode occurred in May 2012; (few minutes after eating some cherries picked from the tree) he presented ocular hyperemia, swelling of eyelids and auricles, breathlessness, syncope, and sphincter release. He was rapidly moved to local Emergency Room, where he was treated with adrenaline, corticosteroids, and antihistamines. Symptoms disappeared within few hours. Thereafter, he enjoyed good health. Exactly one year later (in May 2013), he experienced a second episode immediately after eating half bigarreau cherry. Initially, he presented wheezing, perioral and glottis angioedema, and

drowsiness. At local ER, he was treated with the same medications; clinical remission was quickly achieved. However, breathlessness and fainting appeared after 4 hours, adequate treatment was administered and recovery occurred.

He was visited at Centro Malattie Allergiche of Istituto Giannina Gaslini (Genoa, Italy) for thorough assessment and management.

Skin tests

They were not performed for the risk of severe reactions. In fact, we previously reported a case of anaphylaxis after prick-by-prick with pine nut in a child with previous severe anaphylaxis to pesto, sauce containing pine nut (14).

Serum specific measurement

ImmunoCAP and ISAC tests (ThermoFisher, Milan, Italy) were performed. ImmunoCAP showed a mono-sensitization to the raw cherry extract (11.3 kU_A/L). ISAC test showed positivity for 2 proteins families: i) LTP, such as Pru p 3 (1.7 ISU), Jug r 3 (1.3 ISU), and Ole e 7 (0.8 ISU); and ii) thaumatin-like protein, such as Act d 2 (0.9 ISU) and Alt a 1 (0.7 ISU), which is an acid glycoprotein that interacts with PR5, a TLP (15).

Food challenge

Oral food challenge was not obviously performed for ethical reasons. However, it is noteworthy that the child tolerated wild cherry, also after these two anaphylactic episodes.

Management

Adrenaline autoinjector was prescribed for severe symptom occurrence, antihistamine and steroid for milder complaints.

Discussion

Diagnosis of food anaphylaxis is based on validated criteria (2,3,4), such as: i) suggestive clinical history, ii) allergen-specific IgE detection for the suspected food, and iii) symptoms consistent with sensitization, i.e. the demonstration of a cause/effect dependence between ingestion of sensitizing food allergen and occurrence of anaphylaxis clinical features (*post hoc ergo propter hoc*). According to this work-up, we made the diagnosis of bigarreau cherry anaphylaxis.

Our findings are consistent with the remark that cherry anaphylaxis is prerogative for the Mediterranean area (1). The cases reported in literature occurred only in Spain and Italy (8-16). In addition, our case presented sensitization to two molecular protein families, such as LTP and TLP, peculiar for severe hyper-reactivity. It was also remarkable that there was no pollen sen-

sitization, and molecular allergy diagnostics confirmed absence of sensitization to PR-10 and profilins. These findings confirm the assumption that LTP syndrome is severe and characterized by sensitization to pan-allergens, mainly Pru p 3 that is the genuine allergen for peach, namely a *Rosaceae* fruit. TLP is another proteins family involved in food allergy (17).

Anyway, the most important outcome of the present case are its peculiar characteristics: i) sensitization to dangerous proteins (LTP and TLP), ii) biphasic anaphylaxis at the second episode, iii) tolerance of different cherry variety, iv) precocious age of onset. These aspects underline the concept that pediatric anaphylaxis is a complex and complicated disorder, that should be carefully investigated and managed, and deserves adequate attention as it requires specific and in-depth competence.

The main limitation of the present experience is that information about the molecular profile of wild and bigarreau cherry is lacking. In addition, the parents will be advised to perform an immunoblotting to define the IgE profile to bigarreau and wild cherry proteins.

In conclusion, the present case report that cherry allergy may be also life threatening and adequate workup is mandatory.

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