Allergy to Strawberry in Children From the Mediterranean Area: Is It Really Allergy?

Cabrera-Freitag P1,2, Bermejo Becerro A1, Abreu Ramírez MG1, Álvarez-Perea A1,2, Infante Herrero S1,2, Fuentes-Aparicio V1,2, Zapatero Remón L1,2
1Pediatric Allergy Unit, Hospital General Universitario Gregorio Marañón, Madrid, Spain
2Gregorio Marañón Health Research Institute (IISGM), Madrid, Spain

Key words: Strawberry allergy. Children. Rosaceae family.

Members of the Rosaceae family are the most frequent cause of allergic reactions to fruits in the Mediterranean area [1]. Strawberry, which belongs to the Rosoideae subfamily of Rosaceae, has an apparently unjustified poor reputation among the general population, as self-reported symptoms after ingestion of strawberry are very common [2,3]. However, few cases of true allergy have been reported in the literature [4-7].

The aim of our study was to make a descriptive analysis of pediatric patients with a history of self-reported strawberry allergy and to investigate whether they had true allergy.

Patients from the Pediatric Allergy Department of Hospital General Universitario Gregorio Marañón, Madrid, Spain were retrospectively analyzed on the basis of a clinical history of strawberry allergy, specific IgE (sIgE) to strawberry, and age under 17 years.

The data we recorded included demographic and clinical characteristics, specific IgE (sIgE) values to strawberry (ImmunoCAP 250, Thermo Fisher Scientific), skin prick test (SPT) results with a commercial strawberry extract (Leti), sensitization to profilin by prick and peach nonspecific lipid transfer protein (nsLTP) by prick (peach extract enriched with Pru p 3 [ALK-Abelló] or Pru p 3 [ImmunoCAP]), and tolerance to strawberry in oral food challenge (OFC). sIgE values to birch PR-10 (Bet v 1) were not analyzed, as sensitization to birch pollen is not common in our area. SPT wheals ≥3 mm and sIgE values ≥0.35 kU/L were considered positive.

Qualitative variables are expressed as a frequency and quantitative variables as median (IQR). Categorical variables were compared using the χ² test and Fisher exact test; quantitative variables were compared using the Mann-Whitney test.

The study population comprised 43 children with a clinical history of strawberry allergy. Of these, 29 (67%) had a positive SPT and/or sIgE result to strawberry (group 1) and 14 (33%) had negative results in both tests (group 2).

Median time between self-reported symptoms related to strawberry intake and the allergological work-up was 4 (3-6) months; median time from symptoms to the assessment of
tolerance was 6 (4-9) months. Cofactors such as concomitant exercise, infectious disease, and nonsteroidal antiinflammatory drug intake were excluded in all patients.

Among patients belonging to group 1 (58.6% male, median age 9 [6-12] years), the most frequently reported symptoms were pruritus of the oral mucosa (oral allergy syndrome [OAS]) and cutaneous symptoms (48.3% and 37.9%, respectively). Three patients (10.3%) reported gastrointestinal symptoms and 1 anaphylaxis (3.4%). All patients also had concomitant atopic diseases: 23 patients (79.3%) were allergic to other foods (mostly other fruits [n=20], with peach the most frequently involved [39.3%] in fruit-allergic patients), 16 (55.1%) had rhinoconjunctivitis and/or bronchial asthma related to aeroallergens other than birch, and 13 (44.8%) had atopic dermatitis.

Symptoms at onset in patients belonging to group 2 (57.1% male, median age 4.5 [2-12] years) comprised OAS (50%) and cutaneous symptoms (50%). All but 1 patient had at least another atopic disease: 7 (50%) had atopic dermatitis, 6 (42.8%) had at least 1 other food allergy (with fruits being the most frequently involved [n=4]), and 5 (35.7%) had rhinoconjunctivitis and/or bronchial asthma related to aeroallergens but not birch.

No statistical differences were observed regarding gender, age, or type of symptoms between groups. Patients in group 1 were more frequently allergic to other foods and fruits than those in group 2 (p=0.03 and 0.01 respectively), although no differences were observed for other atopic diseases.

The results of the allergological work-up are shown in the Table. Tolerance was assessed in 28 children (65.1%, 16 belonging to group 1 and 12 to group 2), with a dose proportionate to their age, and all but 1 tolerated strawberry (96.4%). There were no significant differences between patients belonging to group 1 in whom tolerance to strawberry was assessed and those in whom it was not regarding age, clinical symptoms, concomitant atopic diseases, sIgE values to strawberry, and SPT results with strawberry, profilin, and LTP. These data were not analyzed for patients belonging to group 2 owing to the small sample (12/14 tested for tolerance vs 2/14 not tested).

All but 1 child in group 1 (16/29 tested) tolerated strawberry (93.7%); 3 were not allergic to other fruits, 7 were allergic to peach, 3 to Rosaceae fruits other than peach, and 2 to fruits other than Rosaceae. The patient who did not tolerate strawberry had a clinical history of anaphylaxis with strawberry, a positive SPT and ImmunoCAP result to strawberry (2.47 kU/L), and a positive SPT to profilin (sensitization to LTP not tested). This boy was also allergic to apple, house dust mite, and plane tree pollen. All children tested in group 2 tolerated strawberry.

Consistent with other studies carried out in southern Europe, most of the patients in our study who self-reported symptoms after strawberry consumption experienced mild symptoms (OAS and cutaneous symptoms) and were allergic to other fruits, mostly peach [4,5,7]. Moreover, 96% of the children in our study with symptoms after strawberry intake tolerated the fruit in a subsequent OFC, thus supporting the idea that true allergy to strawberry is not as frequent as it seems. Since this was independent of whether or not they were sensitized to strawberry, neither SPT nor CAP seem to have good sensitivity, although specificity was good, as all patients with negative results in both diagnostic tests tolerated strawberry.

The high percentage of patients sensitized to peach LTP (61.3% [19/31 tested]) and profilin (41.4% [12/29 tested]) could partly explain the patient’s sensitization to strawberry due to cross-reactivity [4].

Our study suggests that true allergy to strawberry in our part of the Mediterranean area is rare. Therefore, we believe that, in our region, OFC should be considered in children who report mild symptoms (OAS and/or cutaneous symptoms) after strawberry intake, regardless of whether or not they are sensitized to strawberry, and even in those who are sensitized to LTP. Nevertheless, in patients with more severe symptoms, true allergy to strawberry might be considered.

Further studies involving more patients are needed in order to analyze whether severity of the symptoms and strawberry allergen sensitization profile are associated with true strawberry allergy.

<table>
<thead>
<tr>
<th>Table. Result of the Allergological Work-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
</tr>
<tr>
<td>(n=29)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Strawberry sIgE</td>
<td></td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>≥0.35 kU/L, No. (%)</td>
<td>26 (89.7)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>2.53 (1.05-8)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>&lt;0.35 kU/L, No. (%)</td>
<td>3 (10.3)</td>
<td>14 (100)</td>
<td></td>
</tr>
<tr>
<td>Strawberry SPT, No. (%)</td>
<td></td>
<td>.003</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>9 (31)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>9 (31)</td>
<td>14 (100)</td>
<td></td>
</tr>
<tr>
<td>ND</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peach LTP</td>
<td></td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>Positive, No. (%)</td>
<td>17 (58.6)</td>
<td>2 (14.3)</td>
<td></td>
</tr>
<tr>
<td>No. positive by SPT/No.</td>
<td>13/20</td>
<td>2/8</td>
<td></td>
</tr>
<tr>
<td>tested by SPT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. with Pru p3 ≥0.35 kU/L/No.</td>
<td>11/15</td>
<td>0/2</td>
<td></td>
</tr>
<tr>
<td>tested for Pru p3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>7.35 (2.04-15.6)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Profilin by SPT, No. (%)</td>
<td></td>
<td>.21</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>12 (41.4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>9 (31)</td>
<td>8 (57.1)</td>
<td></td>
</tr>
<tr>
<td>ND</td>
<td>8 (27.6)</td>
<td>6 (42.8)</td>
<td></td>
</tr>
<tr>
<td>OFC with strawberry, No. (%)</td>
<td>.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1 (3.4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>15 (51.7)</td>
<td>12 (85.7)</td>
<td></td>
</tr>
<tr>
<td>ND</td>
<td>13 (44.8)</td>
<td>2 (14.3)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; ND, not done; OFC, oral food challenge; SPT, skin prick test.
Anaphylaxis to Mepolizumab and Omalizumab in a Single Patient: Is Polysorbate the Culprit?

Bergmann KC, Maurer M, Church MK, Zuberbier T

Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin, Germany

doi: 10.18176/jiaci.0492

Key words: Anaphylaxis. Asthma. Mepolizumab. Omalizumab.

The past decade has seen an increase in the use of biological agents such as mepolizumab and omalizumab for the treatment of severe asthma. These agents reduce the frequency of exacerbations, allow for reduced oral corticosteroid use, and increase quality of life. Their safety profile is generally very good. Beside local adverse effects, which are comparable in placebo-controlled clinical trials, there are very few reports on anaphylactic reactions to these biologics [1,2].

Pivotal studies indicate that the anti-IL-5 antibody mepolizumab is well tolerated, with no reports of anaphylaxis or treatment-related deaths [2]. The anti-IgE monoclonal antibody omalizumab binds to the constant region of free IgE only and, therefore, does not cause mast cell degranulation. However, omalizumab has been reported to cause anaphylaxis in <0.1% of patients, with reactions being delayed in many cases [3]. The mechanism for these reactions is, however, unclear [3]. Here, we report an anaphylactic response after 13 months of treatment with mepolizumab and following the subsequent first injection of omalizumab in a patient with severe asthma.

The patient was a never-smoking woman (born 1989) who, since childhood, had had allergic asthma due to sensitization to cat and dog dander, house-dust mite, and tree and grass pollen. Sublingual immunotherapy for chronic rhinosinusitis without polyps due to mite allergy was attempted but discontinued because of unwanted adverse effects. There were no other clinically relevant comorbidities. During the 12 months before starting mepolizumab, the patient experienced 4 serious asthma exacerbations despite using a high-dose inhaled corticosteroid (fluticasone 1500 µg), a long-acting β mimetic, a long-acting muscarinic antagonist, and a leukotriene receptor antagonist. Her symptoms were severe, with nightly awakening (3-5 times/wk) and exercise-induced dyspnea after climbing about 20 stairs.

Before starting mepolizumab on November 1, 2017, the patient had a total blood IgE of 1109 kU/L, sIgE against grass pollen (class 4), tree pollen (class 5), and *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (class 6). Her eosinophil count was 540/µL (without oral corticosteroids). FEV₁ was 2.5 L (65% predicted). Following initiation of treatment, her symptoms improved, and she was able to discontinue oral corticosteroids. After 1 year of treatment, she continued to experience 1 serious asthma exacerbation per year despite maintaining a high-dose inhaled corticosteroid regimen. She was referred for additional treatment with omalizumab to further improve her control.

Before starting omalizumab, the patient was given her first injection of mepolizumab (75 mg) without incident. She was instructed to take diphenhydramine 25 mg 1 hour before the injection and had no prior history of anaphylaxis. One hour after the injection, she experienced itching and flushing of the face and mouth, followed by angioedema of the lips and tongue. She was treated with epinephrine and antihistamines, and her symptoms resolved within 30 minutes. After her second injection of mepolizumab, she was started on omalizumab (150 mg) with no incident.

The patient was referred to our department for further evaluation. She denied any history of exposure to the agent of concern (mepolizumab or omalizumab). A skin test with mepolizumab and omalizumab was negative. A nasal challenge with mepolizumab was performed, and she did not experience any adverse effects. A patch test with omalizumab was also negative. A blood test for immediate-type hypersensitivity with mepolizumab and omalizumab was negative.

The patient reported that she had previously been exposed to polysorbate 80, a surfactant used in the formulation of mepolizumab and omalizumab. She had previously developed mild urticaria after exposure to this agent. However, she denied any previous reaction to polysorbate 80 while on mepolizumab or omalizumab. The patient underwent a challenge with polysorbate 80, which was well tolerated. A diagnosis of anaphylaxis was made based on the clinical presentation and the timing of the reaction.

The patient was treated with epinephrine and antihistamines, and her symptoms resolved within 30 minutes. She was instructed to avoid exposure to polysorbate 80. She was also referred for desensitization to polysorbate 80, although this was not pursued due to the patient's preference.

The patient's symptoms improved with the addition of omalizumab, and she was able to discontinue oral corticosteroids. She continued to experience 1 serious asthma exacerbation per year despite maintaining a high-dose inhaled corticosteroid regimen. She was referred for additional treatment with omalizumab to further improve her control.

**Funding**

The authors declare that no funding was received for the present study.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**References**


Manuscript received September 25, 2019; accepted for publication January 30, 2020.

**Paula Cabrera Freitag**

E-mail: paula.cabrera@salud.madrid.org