Proteins Responsible for Fruit allergies in the Northwest of Spain

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Key words: Fruits. Allergy. Proteins.

Plant allergies are a frequent cause of visits to the allergologist. In the Alergologica 2005 study carried out in Spain, fruits were the main cause of food allergies [1]. Plant allergies in a specific population are related to consumption habits and to the pollen pattern of the region under study.

The objective of this retrospective study was to determine the proteins responsible for fruit allergies in Asturias, a region situated on the Cantabrian Sea with an Atlantic climate and a pollen pattern different to that of the rest of Spain.

We recruited patients diagnosed with fruit allergy from a database of patients seen in an outpatient clinic between 2010 and 2013. To be included in the study, all patients had to present a clinical picture characteristic of IgE-mediated allergy to fruits, with a positive prick-prick test or skin prick test result (ALK-Abelló) with the culprit fruit. Sensitization to panallergens such as profilin, lipid transfer protein (LTP), and birch extract, as well as to Lolium extract was determined by skin prick test (ALK-Abelló), ImmunoCAP (Phadia) (rPhl p 12, rPru p 3, and nBet v 1), and ISAC 112 (Thermo Fisher Scientific). In vitro techniques were only used when the panallergen was not identified using the skin tests. The ImmunoCAP test was ordered for 10 patients and the ISAC test for 15.

The study sample comprised 56 patients (29 men) with a median age of 29 years (IQR, 20-40). Symptoms triggered by Rosaceae fruits were detected in 22 patients (39%), kiwi in 16 patients (29%), peach only in 12 patients (21%), melon in 6 patients (11%), and banana in 4 patients (7%). Less frequent reactions were observed for fig, apple only, and orange (2 cases each, 4%) and avocado, strawberry, cherry, and passion fruit (1 case each, 2%).

As for clinical manifestations, 63% of patients presented oral allergy syndrome (OAS), 16% urticaria/angioedema, 12% anaphylaxis, 5% contact urticaria, and 4% digestive symptoms.

The proteins responsible for the reactions were LTPs (17 cases [30%]), pathogenesis-related (PR) protein 10 (17 cases [30%]), profilins (6 cases [11%]). Act d 1 (5 cases [9%]), unknown proteins (5 cases [9%]), PR-10 and profilins (4 cases [7%]), thaumatins (1 case [2%]), and chitinases (1 cases [2%]).

The relationship between the type of fruit and the sensitization identified is shown in the Table.

Table. Culprit Allergens From the Fruits Involved in the Reactions

<table>
<thead>
<tr>
<th>Fruit</th>
<th>Allergen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosaceae (39%)</td>
<td>PR-10, profilin, LTP</td>
</tr>
<tr>
<td>Kiwi (29%)</td>
<td>Act d 1, PR-10, LTP, profilin, unknown</td>
</tr>
<tr>
<td>Peach only (21%)</td>
<td>LTP</td>
</tr>
<tr>
<td>Melon (11%)</td>
<td>Profilin, LTP, unknown</td>
</tr>
<tr>
<td>Banana (7%)</td>
<td>Profilin, thaumatins, unknown</td>
</tr>
<tr>
<td>Fig (4%)</td>
<td>PR-10</td>
</tr>
<tr>
<td>Apple only (4%)</td>
<td>PR-10, profilin</td>
</tr>
<tr>
<td>Orange (4%)</td>
<td>Profilin</td>
</tr>
<tr>
<td>Avocado (2%)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Strawberry only (2%)</td>
<td>PR-10</td>
</tr>
<tr>
<td>Cherry only (2%)</td>
<td>PR-10</td>
</tr>
<tr>
<td>Passion fruit (2%)</td>
<td>Chitinases</td>
</tr>
</tbody>
</table>

Abbreviations: LTP, lipid transfer protein; PR, pathogenesis-related.
*The percentages show the percentage of the allergic manifestations that each fruit was responsible for.
*The 2 most frequently involved proteins were PR-10 and LTP.
findings contrast with the previously cited article in which the pattern reported for southern Europe was one of sensitization to profilin and LTP. Allergy to kiwi triggered by Act d 1 led to systemic reactions in all the cases we report. The association between Act d 1 and severity of clinical symptoms has already been established in the literature [3,4].

The third most common fruit causing reactions was peach only. LTP was the protein responsible in 100% of patients, both in those presenting OAS and those experiencing systemic reactions. In a study from an area in the north of Spain close to ours, Gamboa et al [5] also reported LTP as the sole cause of systemic reactions or contact urticaria in patients with peach allergy. However, the authors found that in patients with OAS, profilin was the trigger in all cases and 60% were also sensitized to PR-10. This difference could be explained by the fact that these authors included patients with Rosaceae allergy in their series. However, in our “peach only” group, we excluded patients with sensitization to other members of the Rosaceae family.

We conclude that LTP and PR-10 are the proteins most commonly involved in allergy to fruits in our area and that they affect patients to the same extent. This situation is intermediate between that of the rest of Spain and the Mediterranean region in general, where LTPs predominate, and northern and central Europe, where PR-10 predominates. The results reported here are very similar to those reported in a recent study on nuts, in which we also found a predominance of PR-10 and LTP in very similar proportions [6]. The greater presence of PR-10 compared with the rest of Spain for both types of food is attributable to the presence of Betulaceae pollen in our region, although this is only slight in the overall pollen count.

In certain circumstances, providing figures on food allergies using a whole country as a frame of reference may not be appropriate, given the possible heterogeneity of pollen patterns across different regions. The various patterns of consumption in different geographical areas should also be taken into account, although the role of consumption patterns may be of scant relevance. In the case of fruits, consumption is most likely very homogeneous within any given country.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

Recurrent Anaphylaxis: A Case of IgE-Mediated Allergy to Carmine Red (E120)

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Key words: Carmine red. Anaphylaxis. IgE-mediated allergy. Tryptase.

Palabras clave: Rojo carmín. Anafilaxia. Alergia mediada por IgE. Triptasa.

Carmine (E120, color index No. 75470) is a natural red dye extracted from the dried bodies of females of the arthropod Dactylopius coccus var. Costa, which lives on the cochinheal cactus. It is widely used for coloring foods (eg, salami and shrimp), beverages (eg, orange juice, Campari Bitter), drugs, and cosmetics. Carmine is a low-molecular-weight compound that can act as a hapten and combine with proteins to induce an immunologic response [1].

There have been several reports of carmine-induced occupational respiratory diseases (eg, rhinoconjunctivitis, asthma, and extrinsic allergic alveolitis) in workers at spice blenders, butcher’s shops, and factories that manufacture natural dyes [1-5]. IgE-mediated anaphylactic reactions to ingested carmine have also been reported [6].

We report the case of 52-year-old woman who experienced “unexplained” anaphylactic reactions from December 2013 to April 2014. The patient had no history of allergic diseases or urticaria/angioedema.

The first reaction occurred a few minutes after the ingestion of pizza with mozzarella and tomato and a red nonalcoholic beverage. The patient experienced generalized flushing, angioedema of the face, and headache. Symptoms promptly resolved after treatment with oral prednisone and cetirizine. Twenty days later, the patient experienced abdominal pain, diarrhea, generalized itchy erythema, and loss of consciousness immediately after dinner (she did not remember what she had eaten). The third episode occurred after eating a red fruit candy and the fourth after drinking a fruit juice (ACE rosso). Again, the patient experienced skin and gastrointestinal symptoms and loss of consciousness.

In all cases except the first, the patient was treated by her husband, who is an anesthesiologist, with intramuscular epinephrine. She was also told to pay particular attention to food labelling in order to prevent potentially life-threatening reactions in food-allergic people.

Taking a detailed clinical history is the first step towards a correct diagnosis, especially in the case of allergic reactions after ingestion of foods or consumption of over-the-counter drugs. No diagnostic extracts for skin testing are available, but detection of specific IgE is now routinely possible.

The basophil activation test based on CD63 [5] or CD203c [9] has been used to confirm the diagnosis. In both cases, the result was concordant with those of skin tests and determination of specific IgE, and both sensitivity and specificity were good.

We would also like to underline the importance of detailed food labelling in order to prevent potentially life-threatening reactions in food-allergic people.

Finally, we recommend considering the possibility of dye allergy in all patients who experience anaphylaxis or life-threatening reactions classed as idiopathic.

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Allergic Reactions in Anesthesia: Do Diagnostic Studies Ensure the Safety of Reoperation?

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Key words: Anaphylaxis. Subsequent anesthesia. Skin test. Drug allergy. Neuromuscular blocking agents (NMBAs).


Anaphylactic reactions during anesthesia are rare, but when they do occur, they are unpredictable and potentially life-threatening [1]. For the last 20 years, the Allergy Departments of Hospital Universitario Araba, Vitoria, Spain and Hospital San Pedro, Logroño, Spain have performed active research on this topic. Our recent series revealed the most likely causes of anaphylactic reactions to be neuromuscular blocking agents (NMBAs), latex, nonsteroidal anti-inflammatory drugs (NSAIDs), and antibiotics [2].

Our practice involves giving patients a medical report with detailed results of their investigations and an action plan to pass on to their anesthetist in any further surgical procedures. In the present study, our aim was to quantify the effectiveness of our recommendations in terms of the safety of subsequent anesthesia.

We reviewed the histories of 85 patients treated at the allergy departments of both hospitals between 2000 and 2010. An identical protocol for adverse reactions during anesthesia was followed at both hospitals.

In a previous publication [2], we confirmed diagnosis using a combination of clinical examination and biochemical and skin tests. In all cases, we took a detailed clinical history with data from the anesthesia department and performed prick and intradermal skin tests with the culprit agents. All commercially available NMBAs were tested for cross-reactivity. In patients with positive results to NMBAs, a monovalent study (citicoline) was carried out to confirm a true allergic response [2].

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The action plan consisted of a report containing the clinical history, results of skin tests and biochemical tests, and recommendations for patients and the referring physician. A histamine release mechanism was proposed in cases labelled as nonallergic, and premedication with H1-receptor antagonists and avoidance of histamine-releasing drugs was recommended in these cases. In cases where the allergic mechanism was confirmed, our recommendations included avoidance of the culprit agent, use of alternative anesthesia (local/regional), and, in cases of mandatory general anesthesia, use of NMBAs that elicited negative results in skin tests.

The clinical history was reviewed to confirm that the patient had undergone further surgery, and the outcome of the
anesthesia used was recorded. Clinical data from the surgery and tolerance of anesthetic drugs were collected in electronic format or paper format depending on the time the history was taken. The study was approved by the Ethics Committee of Hospital Universitario Araba and was conducted according to the principles of the Declaration of Helsinki, Good Clinical Practice, and local regulations.

Eighteen of the 85 patients whose history we reviewed (21.2%) underwent further surgery. If these patients are classified as allergic and nonallergic, we recorded 10 IgE-mediated cases (8 females and 2 males) and 8 non-IgE-mediated cases (4 females and 4 males). One patient died. Details of the study are shown in the Table.

The 8 patients with a non–IgE-mediated reaction were managed using NMBAs and the least histamine-releasing drugs. No adverse events were observed in these patients (no previous diagnosis of allergy) when they underwent further surgery.

Similarly, no adverse events were observed among the 10 patients previously diagnosed with IgE-mediated anaphylaxis.

In this group, the diagnosis of allergy included 2 cases of allergy to antibiotics, 1 case of allergy to metamizole, 1 case of allergy to *Echinococcus granulosus*, and 6 cases of allergy to NMBAs. In the 6 NMBA-allergic cases, the NMBAs that previously induced a negative skin test was recommended and used safely during anesthesia. One patient with NMBA allergy had to undergo 3 operations, although no adverse events were recorded (Table). The time interval between the previous study and reoperation was heterogeneous, ranging from 1 to 13 years.

Adverse drug reactions are one of the most common causes of morbidity and mortality in patients receiving anesthesia [3]. Skin tests constitute the main tool for identifying the culprit agent and providing safe alternatives for future anesthesia. Unfortunately immediate reactions in skin tests with NMBAs can be due to an allergic reaction (IgE-mediated) and also to nonspecific histamine release (non–IgE-mediated). However, the relevant information from the clinical history and the monovalent additional study (citicoline) used in both hospitals proved very helpful [4].

### Table. Data From Allergic and Nonallergic Cases

<table>
<thead>
<tr>
<th>Culprit Drug</th>
<th>Sex</th>
<th>Age at Diagnosis, y</th>
<th>Time Since Diagnosis, y</th>
<th>Number of Operations</th>
<th>Alternative Drug Used in New Operations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergic Cases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuromuscular blocking agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rocuronium</td>
<td>Female</td>
<td>42</td>
<td>6</td>
<td>3</td>
<td>Suxamethonium</td>
</tr>
<tr>
<td>Vecuronium</td>
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<td>37</td>
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<tr>
<td>Mivacurium</td>
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</tr>
<tr>
<td>Rocuronium</td>
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<td>1</td>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
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<td>2</td>
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<td>13</td>
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<tr>
<td>Metamizole</td>
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<td>1</td>
<td>Cisatracurium</td>
</tr>
<tr>
<td>Echinococcus</td>
<td>Male 45</td>
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<td>1</td>
<td>1</td>
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</tr>
<tr>
<td><em>Echinococcus granulosus</em></td>
<td>Male 46</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>Cisatracurium</td>
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<tr>
<td><strong>NSAIDs</strong></td>
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<td>9</td>
<td>1</td>
<td>Suxamethonium</td>
</tr>
<tr>
<td>Male 80</td>
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<tr>
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<td>Male 40</td>
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<td>Female 61</td>
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<tr>
<td>Female 42</td>
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<td></td>
<td></td>
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<tr>
<td>Male 74</td>
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<td></td>
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<tr>
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<td>4</td>
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<td>Cisatracurium</td>
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</tbody>
</table>

| Abbreviations: NSAID, nonsteroidal anti-inflammatory drug. |
We recorded an outcome for all the cases of reoperation that we reviewed; therefore, our results confirmed the value of diagnostic studies and recommendations. The female predominance in NMBA allergy reported elsewhere [2] was confirmed in the present study, although there were no differences in the incidence of reoperation between the sexes (Table). Our main limitation was the number of cases, which is obtained from programmed reoperations. In the cases where the suspected agent was confirmed, avoidance of the agents with no further adverse events confirms the previous diagnosis. The good tolerance of NMBAs in subsequent anesthesia in this group of patients confirms the negative predictive value of skin tests (Table).

In the present study, the clinical outcome of patients diagnosed with allergy to NMBAs and who underwent further surgery with NMBA for which they had a negative skin test result was consistent with findings reported elsewhere [5-8]. Our results were also consistent with those of researchers who support the role of the skin tests as the main tool for identifying the culprit agent and for recommending a safe alternative drug for future use [9]. Moreover, the good tolerance to NMBAs in the 8 patients who were not allergic to NMBA and in the 4 patients with allergy to other entities (antibiotics, NSAIDs, and Echinococcus granulosus) clear up doubts about the reproducibility of negative skin test results with NMBAs. A major concern of clinicians is that of identifying a safe NMBA, although little is known about the outcomes in subsequent anesthesia in cases of negative results with NMBA [8-10]. Our main findings were the clinical outcomes of the course of new anesthesia over time and the 12 patients with negative skin test results to NMBA.

In summary, an allergological workup is useful in 2 senses: first, a negative result enables NMBA to be used for subsequent anesthesia; and second, a positive result helps to choose the safest drugs for allergic patients during anesthesia.

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

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**Previous Presentation**

This study was presented as a poster at the European Academy of Allergy and Clinical Immunology Meeting (EAACI) in Milan, 2013.

**References**

**Fixed Drug Eruption Due to Mesna**

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Key words: Fixed drug eruption. Mesna. Patch tests.

**Palabras clave:** Erupción fija medicamentosa. Mesna. Pruebas epicutáneas.

2-Mercapto-ethane sulfonate sodium (mesna) is the first-line prophylactic treatment for cyclophosphamide-induced hemorrhagic cystitis; it belongs to the family of thiol-based cytoprotective agents.

A 53-year-old woman (patient #1), a 45-year-old man (patient #2), and a 40-year-old woman (patient #3) with severe multiple sclerosis had been receiving monthly therapeutic doses of cyclophosphamide, mesna (Uromitexan) and methylprednisolone. Patients #2 and #3 were additionally receiving ondansetron. Nine, 24, and 20 months after starting this treatment, the patients respectively reported the development of red plaques with a burning sensation on the face 48, 24, and 24 hours after administration. Recovery was observed in all 3 patients within a few days, with residual pigmentation remaining in 1 case. Subsequent administration of the treatment triggered recurrence of the cutaneous lesions at identical and new sites less than 12 hours after administration in patients #1 and #3 and 6 hours after administration in patient #2, who experienced 2 recurrences. The results indicated a diagnosis of fixed drug eruption (FDE).

Skin biopsy was not performed owing to the facial location and the typical presentation.

Patch tests with mesna (30% in petrolatum), methylprednisolone (30% in petrolatum), cyclophosphamide (30% in petrolatum), and ondansetron (30% in saline solution for patients #2 and #3) were additionally receiving ondansetron. Nine, 24, and 20 months after starting this treatment, the patients respectively reported the development of red plaques with a burning sensation on the face 48, 24, and 24 hours after administration. Recovery was observed in all 3 patients within a few days, with residual pigmentation remaining in 1 case. Subsequent administration of the treatment triggered recurrence of the cutaneous lesions at identical and new sites less than 12 hours after administration in patients #1 and #3 and 6 hours after administration in patient #2, who experienced 2 recurrences. The results indicated a diagnosis of fixed drug eruption (FDE).

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Patch tests with mesna (30% in petrolatum), methylprednisolone (30% in petrolatum), cyclophosphamide (30% in petrolatum), and ondansetron (30% in saline solution for patients #2 and #3) were performed on affected and unaffected skin areas. The patch tests with mesna on affected skin were positive (Figure) at days 2 and 4 for all 3 patients. No other positive results were observed. The patients continued to take cyclophosphamide, ondansetron, and methylprednisolone, without recurrence of FDE.

Adverse effects related to mesna include fever, hemodynamic instability, pruritus, and maculopapular or urticarial eruptions with angioedema, and they appear within a few hours of drug administration [1-3]. The immunopathological mechanisms involved have not yet been elucidated. One case of a photodistributed eruption 1 month after starting mesna for Wegener granulomatosis has also been reported [4].

The incidence of adverse cutaneous effects with mesna therapy is not known. Autoimmune disorders treated with cyclophosphamide and mesna seem to be associated with a higher frequency of adverse skin reactions (about 50%). In 2 cases of generalized FDE after monthly pulses of cyclophosphamide and mesna for systemic lupus erythematosus, only patch tests performed in previously affected skin areas with undiluted Mesnex (mesna) showed a positive reaction, but an irritative reaction could not be ruled out [5]. More recently, another FDE with mesna for interstitial lung involvement of systemic sclerosis was reported. Intradermal (0.1% and 1% saline solution) and patch tests (50% in petrolatum) with mesna in previously affected skin areas showed a positive delayed reaction at days 2 and 4 [6]. As an alternative to mesna, hyperhydration to promote diuresis and prophylactic continuous bladder irrigation have been shown to be well tolerated and effective in the prevention of cyclophosphamide-induced cystitis [7].

We have reported 3 typical cases of FDE that appeared several months after starting mesna therapy, with patch test positivity to mesna in affected skin areas. Facial involvement was observed in all cases. Mesna-induced FDE is uncommon but physicians must be aware that hypersensitivity reactions of this type are possible with this drug.

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**Conflicts of Interest**

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The enormous number of people who use the Internet worldwide (an estimated 2 billion people) [1] and their increasing daily contact with social networks raises concerns about possible effects on physical and psychological health, with numerous recent studies focusing on the effects of social networks on psychophysical health [2-10].

Bronchial asthma is an increasingly common disease in the industrialized world, and psychological factors have been seen to play a role in increasing or reducing its severity [4].

The increased prevalence of asthma observed in developed countries at the end of the last century has raised concerns about the burden of this disease on society and individuals. Up to 37% of teenagers, for instance, are affected by asthma symptoms, making it one of the most common chronic diseases in childhood [2].

One of the main questions about the effects of social networks on psychophysical health is whether or not these represent a new source of psychological stress or a way to enhance self-esteem. The relationship between social network use and psychophysical health remains controversial, and research in this area raises numerous challenges. Social networking sites are designed to share information about oneself with others, including likes/dislikes, hobbies, and personal thoughts. While on the one hand, this information could make people aware of their limitations and shortcomings, possibly lowering self-esteem, on the other, it could represent...
selective and, therefore, positively biased aspects of the self, which could raise self-esteem [3,4].

Several studies and expert opinions have suggested that use of social media in general might have a beneficial effect on children and adolescents by enhancing communication, social connection, and even technical skills [5].

However, Internet use may also promote negative psychosocial well-being [6], including depression and loneliness. Researchers recently proposed a new type of depression, termed Facebook depression, which develops when preteens and teens start to experience symptoms of depression after spending long periods on social media sites. Teens and young adults with Facebook depression are at risk of social isolation and may seek online help, possibly leading to substance abuse, unsafe sexual practices, or aggressive or self-destructive behaviors.

Social media sites are also increasingly being used as online venues for the exchange of health-related information and advice. Nearly 60% of American adults and 80% of Internet users have sought health information online [7].

From a public health point of view, social networks are already showing potential benefits in terms of driving health care system reforms and improving patient networking. Some studies have demonstrated the effectiveness of social networks in disseminating public health messages, such as food safety, sex education, and general health [8].

The potential of social networks for health research is relevant to both researchers and participants. A systematic review of published research articles focusing on the use of social networks for youth health research [3-5, 7, 8] revealed numerous advantages, namely ease of access to youth, ease of intervention, cost effectiveness in recruitment, and reliable screening venue of mental status and high-risk behaviors. Therefore social networks may become a valuable platform for accessing, recruiting, and delivering health interventions in a cost-effective manner to youth populations as well as hard-to-reach minorities or underserved populations.

In 2010, we reported the first case of asthma exacerbation possibly triggered by the use of Facebook in which a young boy experienced asthma symptoms when connected to the personal profile of his former girlfriend [9]. We concluded that social networks in general could be a new source of psychological stress and trigger exacerbations in depressed asthmatic individuals, and suggest that triggers of this type be considered in the assessment of asthma exacerbations. The underlying hypothesis is that stressful life events may alter the psychological, immunological, and endocrine systems via mechanisms that are still largely unknown.

The association between psychological disorders and asthma has been observed in several epidemiological studies, particularly with respect to anxiety and depression [10]. In the context of social networks, a virtual emotional stressor might trigger an asthma exacerbation, especially in an individual with poorly controlled asthma because of a concurrent depressive state, as in the case we reported [9]. In clinical practice, asthmatic patients, and younger patients in particular, should undergo a thorough psychological evaluation, with consideration of potential virtual stressors. While the effect of social networks on asthma and on health in general cannot be considered exclusively negative, most of the data currently available suggest that certain aspects could act as psychological triggers for some diseases, including asthma. However, the potential positive effects of social networks on self-esteem should not be ignored.

Social network interactions may also have a role in asthma management. Care for asthma patients has shifted from physician-managed care to guided self-management in recent years. However, the effectiveness of written self-management plans and symptom diaries may be hampered by false reports, recall bias, and by both patient and doctor reluctance. Nonetheless, several studies have recently shown that a web-based self-management system for asthma is well tolerated and feasible and is as effective as and has similar costs to traditional management systems.

The role of the social media in the medical and health care sectors, including asthma, is far reaching, and many questions remain unanswered in terms of governance, ethics, professionalism, privacy, confidentiality, and information quality. Future research is required to understand the synergies between social media and evidence-based practice, and it is also necessary to develop institutional policies that benefit patients, clinicians, public health practitioners, and industry alike.

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Icatibant Exposure During Pregnancy in a Patient With Hereditary Angioedema

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During pregnancy, women with angioedema due to hereditary deficiency of C1 inhibitor (C1-INH-HAE) type I/II can experience changes in the frequency and location of acute attacks. A number of case series have reported an overall increase in the mean rate of attacks during pregnancy, although individual patients actually experienced a decrease or no change in frequency [1-4]. The most common location of attacks during pregnancy is the abdomen, which accounts for a higher proportion of attacks than in nonpregnant patients with C1-INH-HAE [3,4]. Although rare, laryngeal attacks do occur during pregnancy and, due to the potential for airway obstruction, they can be life-threatening [4].

The only therapeutic option currently available for pregnant women with C1-INH-HAE type I/II is plasma-derived C1 esterase inhibitor (pdC1-INH) concentrate, and its use in this setting is supported by substantial retrospective and observational data [4,5].

Icatibant is a bradykinin B2 receptor antagonist indicated for the treatment of acute angioedema attacks in adults with C1-INH-HAE [6,7]. There are no clinical data on the use of icatibant during pregnancy in humans, and as such, this drug should be used only if the benefit to the patient outweighs any potential risk to the fetus. The case reported here corresponds to a patient enrolled in the Icatibant Outcome Survey (IOS; Shire, Zug, Switzerland [NCT01034969]), an international observational study that monitors the safety and effectiveness of icatibant treatment. IOS is conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice, and approval was obtained from the ethics committees at all participating centers. This is the first case report of the use of icatibant during pregnancy to treat an attack of C1-INH-HAE.

A 31-year-old woman with C1-INH-HAE type I self-treated an angioedema attack with icatibant during pregnancy. The patient had been diagnosed with C1-INH-HAE type I at the age of 20 years based on a positive family history, clinical manifestations of cutaneous angioedema since the age of 16, and laboratory analyses showing low functional and antigenic levels of plasma C1-INH (C1-INH concentration <10%, functional C1-INH 13%, and C4 concentration 12% of normal values). The patient experienced very few angioedema attacks before her first pregnancy (approximately 1 cutaneous
In this case report, self-treatment with icatibant of a laryngeal attack, in which she reported voice changes and discomfort on swallowing, was trained at our clinic to self-administer icatibant. (almost complete control), but after 6 years of treatment, the patient was no longer taking any long-term prophylaxis, the patient experienced significant clinical improvement (almost complete control), but after 6 years of treatment, the danazol was discontinued due to adverse effects (headache and amenorrhea). The patient switched to on-demand therapy and was trained at our clinic to self-administer icatibant.

During a third pregnancy at the age of 31 years, when she was no longer taking any long-term prophylaxis, the patient experienced weekly cutaneous and abdominal attacks, which were treated with pdC1-INH. In the fourth month of this pregnancy (week 16), she experienced a laryngeal angioedema attack, in which she reported voice changes and discomfort on swallowing. The patient had previously been trained in the self-administration of icatibant and had the injection stored at home for use in the event of an attack. Ninety minutes after the onset of the attack, the patient self-administered a single injection of icatibant (30 mg/3 mL subcutaneously), with complete resolution of symptoms within 2 hours. She did not use any other rescue medication for this attack.

In a follow-up visit, the patient reported the use of icatibant during pregnancy and was advised not to use this drug again until the end of pregnancy as it is not approved for use during pregnancy in humans. The patient continued to experience frequent cutaneous and abdominal attacks and treated the latter with pdC1-INH. The pregnancy went to full-term and the patient delivered a healthy baby girl. She did not receive short-term prophylaxis before delivery or experience any attacks during delivery or immediately post-partum.

This is the first case report of the use of icatibant during pregnancy by a patient with C1-INH-HAE to treat an acute attack, in this case laryngeal. Although abdominal attacks are commonly reported by patients during pregnancy, potentially life-threatening laryngeal attacks that require prompt treatment can also occur [4]. The efficacy and safety of icatibant for the treatment of acute attacks in male and (nonpregnant) female adults with C1-INH-HAE has been established in 3 double-blind phase III studies [6,7], with evidence that icatibant shortens time to resolution for nonlaryngeal as well as laryngeal attacks versus placebo [7]. Based on the results of these phase III studies, current guidelines recommend icatibant as one of the available options for the acute treatment of attacks in nonpregnant adults, and also indicate that self-administration may be suitable for many patients [8-10]. Patients self-administering icatibant for laryngeal attacks are nevertheless advised to seek immediate medical attention at an appropriate medical institution. The current treatment of choice for attacks during pregnancy is pdC1-INH [5]; this recommendation is based on retrospective, observational data and case reports with pdC1-INH, and a lack of available data for other specific treatments. No other data were previously available on the use of icatibant during pregnancy in humans. Animal studies have shown effects on uterine implantation and parturition, but the potential risk for humans is unknown. In this case report, self-treatment with icatibant of a laryngeal attack in a patient with C1 INH-HAE during pregnancy was effective and no adverse effects on the pregnancy or the health of the newborn were reported. As this paper reports on a single injection of icatibant in a pregnant woman, no conclusions can be drawn on the use of icatibant in pregnant women with C1-INH-HAE.

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Conflicts of Interest
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References
Patients with respiratory allergy to fungi present symptoms when they inhale fungal particles present in air [1]. However, within this group, we have identified patients with the same symptoms when they ingest sunflower seeds, even though they are not sensitized to the seeds.

Since many foods undergo natural fermentation processes and become contaminated by organisms such as fungi [2], we hypothesized that sunflower seeds could also be contaminated and that fungi-allergic patients would therefore present symptoms when they were exposed to fungi-contaminated sunflower seeds.

We recruited 29 Alternaria-allergic patients with asthma but no food allergies.

The Ethics Committee for Clinical Research of University Hospital Arnau de Vilanova, Lleida, Spain authorized the study. Patients who gave their consent were asked to fill out a questionnaire with 4 questions about the symptoms they had experienced while eating sunflower seeds. They were asked whether they had ever experienced an asthma attack after eating sunflower seeds, the duration of the latency period (more than 1 hour, less than 1 hour, or did not remember), whether the attack had occurred when they ate peeled seeds or when they had to peel the seeds with their teeth before ingesting them, and whether they had experienced rhinitis, oral allergy syndrome, or urticaria/angioedema mediated by bradykinin. Part II. Treatment, follow-up, and special situations. J Investig Allergol Clin Immunol. 2011;21:422-41.

Description of Sunflower Seed–Fungus Syndrome

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Of the 29 patients, 11 (38%) had no clinical symptoms when they ate peeled seeds or when they had to peel the seeds with their teeth before ingesting them, and whether they had experienced rhinitis, oral allergy syndrome, or urticaria/angioedema with sunflower seeds, nuts, dried fruits, or other foods.

Of the 29 patients, 11 (38%) had no clinical symptoms and 18 (62%) reported asthma-like symptoms after ingesting sunflower seeds. Of the 18 symptomatic patients, 4 (22.2%) also experienced rhinitis, 12 (66.6%) had clinical reactions within the first hour after exposure to sunflower seeds, 4 (22.2%) developed symptoms after the first hour, and 2 (11.1%) did not remember the time of onset of their symptoms. All 18 developed symptoms when they ingested sunflower seeds or other foods.

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sunflower seeds after peeling them with their teeth. Seventeen (94.5%) tolerated peeled seeds, and 1 (5.68%) said that he had experienced symptoms both when he ate peeled seeds and when he had to peel the seeds before eating them. None of the patients experienced urticaria/angioedema or oral allergy syndrome when they ingested sunflower seeds, nor did they have reactions to other foods.

Using the blotter test [3,4], researchers from the Department of Plant Production and Forest Science at the University of Lleida, Lleida, Spain isolated the fungal strains found on sunflower shells from 3 commercially available brands. All the sunflower seeds analyzed had fungi on their shells. Strains from *Alternaria*, *Aspergillus*, *Cladosporium*, *Penicillium*, and *Rhizopus* were isolated.

The strains were grown on Czapek Dox media for 4 weeks at 25°C, and protein extracts were prepared from the cultures. A total of 18 extracts were prepared. Skin prick tests were performed using the fungal extracts obtained, and prick-prick tests were performed on 10 patients using both sunflower seeds and their shells. The remaining 8 patients did not consent to participate in the study. All skin prick tests were performed in duplicate on both arms in inverse order, and the larger and smaller diameters of the wheals were measured.

Skin prick test results were considered positive if the wheal was ≥3 mm [5]. All 10 patients presented positive skin reactions to *Alternaria*, *Cladosporium*, and *Penicillium*. Four patients (40%) also presented a positive skin prick result for *Aspergillus* and *Rhizopus*. Skin prick results for peeled sunflower seeds were negative in all patients, as were prick-prick tests against peeled seeds and their shells.

Serum specific IgE levels (ImmunoCAP and CAP-FEIA, Phadia) for extracts isolated from shells and peeled seeds were determined. Levels of specific IgE against rAlt a 1 were measured using the enzyme allergosorbent test (HYTEC Specific IgE EIA kit, HYCOR Biomedical Ltd). One patient dropped out of the study. Positive specific IgE values (>0.35 kU/L) were obtained for *Alternaria* in 9 of 9 sera studied (100%; mean, 17.31 kU/L) and for Alt a 1 (mean, 20.07 kU/L). Values were positive for *Aspergillus* in 8 of 9 sera (88.8%; mean, 4.69 kU/L) and *Cladosporium* in 6 of 9 sera (66.6%; mean, 4.98 kU/L). Serum specific IgE values were also positive for *Rhizopus* (mean, 2.79 kU/L) in 6 of 9 sera (66.6%) and for *Penicillium* in 7 of 9 sera (77.7%; mean, 2.91 kU/L). Determination of specific IgE against sunflower seed was negative (<0.35 kU/L) for all sera.

The 9 *Alternaria*-positive sera were analyzed using SDS-PAGE immunoblotting [6,7] to determine the profile of the IgE-binding bands present in the extracts. Strong IgE binding to Alt a 1 was detected with all 9 sera. Less intense IgE binding was also detected: 4 of the sera showed an IgE-binding band of 31 kDa, 3 showed a band of 28 kDa, and 2 showed a band of 18 kDa.

An immunoblotting-inhibition assay was carried out using extracts from the isolated strains of *Aspergillus*, *Cladosporium*, *Penicillium*, and *Rhizopus* on the solid phase. The results demonstrated specific IgE against *Alternaria* proteins, which cross-reacted with proteins from the other fungal species studied.

Five patients were exposed to sunflower seeds with shells using a spirometer (MasterScope Spirometer, Jaeger) to assess the fall in FEV1. Patients had to peal a maximum of 100 g of sunflower seeds with their mouth but could not ingest them. Peak flow was monitored (PF-CONTROL PLUS, Leti Alergia), and hourly measurements were taken over the 24 hours following the test (except during sleep) [8]. The test result was positive in all patients (falls of 15%-20% in FEV1) [8].

Our findings allow us to conclude that the respiratory symptoms patients present when they are cracking open sunflower seed shells are due to inhalation of fungal proteins, especially Alt a 1, which is the main allergen from *Alternaria*, a fungus isolated from sunflower seed shells.

Isolation of other fungi from the surface of the sunflower seed shell, the sensitization detected in patients studied, and the results of the immunoblotting-inhibition assays suggest that proteins from other fungi may contribute to the allergic symptoms detected through the presence of cross-reaction events.

This study was carried out in patients who were allergic to *Alternaria* species, as this is the most prevalent fungal allergen in our area. If we had selected patients allergic to other fungi (eg, *Aspergillus* and *Penicillium*), we suspect that these would have been the principal cause of the allergic symptoms shown.

<table>
<thead>
<tr>
<th>Patient</th>
<th>SPTa</th>
<th>IgE, kU/L</th>
<th>Peeled Sunflower</th>
<th>Immediate Symptoms</th>
<th>Provocation Test</th>
<th>Delayed Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Positive</td>
<td>20.4 14.9</td>
<td>100</td>
<td>Cough, dyspnea</td>
<td>22%</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Positive</td>
<td>12.8 12.8</td>
<td>100</td>
<td>Dyspnea</td>
<td>9%</td>
<td>Cough, wheezing, fall in FEV1 (26%)</td>
</tr>
<tr>
<td>3</td>
<td>Positive</td>
<td>22.5 14.6</td>
<td>72</td>
<td>Dyspnea, wheezing</td>
<td>20%</td>
<td>Cough, wheezing, fall in FEV1 (17%)</td>
</tr>
<tr>
<td>4</td>
<td>Positive</td>
<td>10.4 12.5</td>
<td>40</td>
<td>Dyspnea</td>
<td>20%</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Positive</td>
<td>15.8 16.6</td>
<td>70</td>
<td>Dyspnea, wheezing</td>
<td>20%</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: FEV1, forced expiratory volume in 1 second; SPT, skin prick test.

*Positive if >3 mm*
by allergic patients when they come in contact with fungi-contaminated sunflower seed shells. Therefore, this outcome is probably found both in patients allergic to *Alternaria* species and in patients allergic to other fungi that can grow on sunflower seed shells.

In summary, we observed 2 situations. On the one hand, we saw patients who experience allergic respiratory symptoms when exposed to foods, even when these are not ingested. The reaction occurs when patients use their teeth to crack open the sunflower seed shells, and the inhalation of fungal proteins contaminating the sunflower seeds triggers the symptoms. On the other hand, we determined the cause of bronchospasm over both shorter and longer time periods. Such attacks can destabilize asthma and require the patient to visit the emergency department, although both situations can be avoided once all relevant data are available.

Finally, it would be interesting to determine whether the situations presented here could occur after ingestion of other foods with shells or peel susceptible to fungal contamination.

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The authors declare that they have no conflicts of interest.

**References**

Rubber vulcanization additives have been frequently implicated in occupational dermatoses, and users of final products (eg, health care workers, housewives, car factory workers, printing machine manufacturer workers) are affected more often than those working in the latex industry [1-4]. Vulcanization is a chemical process for converting rubber or related polymers into more durable materials through the addition of sulphur or equivalent curatives or accelerators. These additives modify the polymer by forming crosslinks (bridges) between individual polymer chains. Vulcanized materials are less sticky and have superior mechanical properties [5]. Here we present a special case of sensitization to a rubber component.

A 47-year-old man was referred to our hospital in September 2013 because of hand dermatitis. He had been working for 25 years in a company manufacturing metal parts for printing machinery. The skin lesions had appeared 2 years earlier and had worsened over the 6 months prior to consultation. The patient was asymptomatic during holidays and periods of sick leave. He did not have diabetes or hypertension, and was not taking any medication. He had no history of previous allergic disease and he smoked 20 cigarettes a day.

His daily work routine involved making iron-plated metal parts in several stages that comprised sanding the part and cleaning its edges with paper containing perchloroethylene. Each part was then painted with gray adhesive paint and once dry covered with a new layer of black paint. The part was then placed in presses to vulcanize the painted area and finally cleaned, lacquered, and stored. The patient used to wear latex gloves but stopped doing this when the skin lesions appeared. The dermatitis, however, persisted.

Physical examination revealed acute eczematous lesions across the finger pads of the right hand, particularly affecting the thumb and middle fingers (Figure). Mild scaling was also observed on the thumb of the left hand. The patient was prescribed Batmen (prednicarbate) and instructed to stay away from work until the study was completed.

Skin patch testing was carried out with standard series of contact allergens (T.R.U.E test, 2 panels) as well as all the materials used by the patient at work (provided by the company Mutua Activa 2008). These materials included perchloroethylene, Chemosil 411, the metal part, sawdust, gray, black, and green paints, gums, and lacquer (numbered from 1 to 10). Readings were performed at 24, 48, 72, and 96 hours (Figure).

The only positive result was found for Chemosil 411 at 24, 48, 72 and 96 hours (numbers 2, 3, and 4). No reactions to the remaining compounds were recorded in the patient or in his wife and 4 patients without contact dermatitis.

The patient handled Chemosil 411 during application of the layers of paint and, following vulcanization, during the cleaning, lacquering, and storing of the metal parts.

Given these findings and the severity of the dermatitis, the patient needed 2 weeks away from work to completely recover. When he returned, he was relocated to another job without exposure to vulcanization processes or Chemosil-coated metal parts. He has been asymptomatic ever since.

Sensitization to rubber compounds, especially due to accelerators added during vulcanization, has been frequently reported [1-4]. These substances have been traditionally classified into 3 main groups: thiurans, dithiocarbamates and mercaptobenzothiazoles. New allergens, however, have also been identified in the final products after this complex procedure [1,2]. A literature search using the MedLine Plus Database revealed reports on allergic contact dermatitis to latex proteins and the previously mentioned substances [6-10], but no cases of sensitization to chemosil were identified.

Chemosil 411 (LORD Germany) is a versatile heat-activated bonding agent that links a variety of rubber compounds to metal and polar polymeric substrates. It is actually a mixture of various compounds, including xylene, ethyl benzene, zinc compound, nitrogen-substituted aromatic, imide, and carbon black. Chemosil 411 may sometimes be applied as a single coat. This material bonds elastomer compounds based on natural rubber, butadiene, isoprene, styrene-butadiene, nitrile, chloroprene, ethylene-propylene, and butyl rubber to most metals, alloys, and polar polymeric substrates. Bonding occurs during the vulcanization of the rubber. Typical cure temperatures for molding processes range from 130°C to 180°C. Bonds made with Chemosil 411 exhibit good resistance to oil and other aggressive media.

Initially, the case described in this report seemed to be another case of delayed hypersensitivity to latex gloves in an occupational setting, but the skin lesions persisted on both hands.

An Unusual Case of Contact Dermatitis to Vulcanization Additives

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Key words: Contact Dermatitis. Occupational dermatoses. Vulcanization additives. Rubber Allergy. Chemosil.

after the patient stopped using the gloves. Thus other diagnostic possibilities had to be considered and we thoroughly investigated his everyday tasks [1,2], testing all suspect materials. This is the first reported case of sensitization to Chemosil 411. When occupational contact dermatitis is suspected, patch testing should include standard series of contact allergens as well as all substances found in the work environment [1-4].

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**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

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We report the case of a 41-year-old woman, born in Colombia, who had worked as a dental assistant for 10 years. Over the past 5 years, she had experienced several episodes of edema associated with generalized pruritus, respiratory distress, and dry cough immediately after eating. In all cases, cassava had been present in the food. She had been forced to seek emergency care for 4 episodes of severe angioedema and respiratory distress. She also reported symptoms after salpingectomy and cystopexy. In addition, she experienced generalized hives and respiratory distress after contact with latex balloons, latex gloves, and ingestion of avocado.

Using commercial extracts (Laboratorios Leti), skin prick tests (SPTs) were performed for 43 food allergens that were all part of the patient’s regular diet. We also skin tested most of the common aeroallergens in our area. SPTs with commercial latex and prick-by-prick tests with fresh and cooked cassava yielded a strongly positive reaction (wheal diameters of 14.5 mm, 12 mm, and 6.5 mm, respectively). The SPTs were also positive to avocado, banana, kiwi, peach, mites, and fungus extract (Alternaria alternata, Aspergillus

**Cross-reactivity Between Cassava and Latex in a Colombian Patient With an Anaphylactic Reaction**

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**Key words:** Cross reactivity. Latex. Allergy. Cassava.

**Palabras clave:** Reactividad cruzada. Latex. Alergia. Yuca.

**Figure.** A, Silver stained sodium dodecyl sulfate polyacrylamide gel electrophoresis of fresh Cassava extract prepared at home and latex extract (line 2). B, IgE immunoblot of Cassava (line 1), latex (line 2) and IgE cassava immunoblot after <n inhibition assay with latex extract (line 3). IgE binding to cassava extract was almost completely inhibited (approximately 80%) by the latex extract. MW indicates molecular weight.
enzyme immunoassay (FEIA-CAP, Phadia) revealed positive results for fumigatus, Fusarium, Penicillium chrysogenum. Total IgE levels were higher than 20 kU/L.

SDS-PAGE and immunobLOTS were performed with proteins extracted from fresh cassava tuberous root tissue, as previously reported by Li et al [1] and Ibero et al [2] (Figure A). The same tests were performed with commercial extracts for avocado, banana, and latex (Laboratorios Leti). For SDS-PAGE, the protein extracts were quantified using BCA Protein Assay Reagent (bicinchoninic acid, Thermo Scientific) and separated on 12% denaturing polyacrylamide gels. Proteins were visualized by silver staining.

SDS-PAGE was performed with cassava, avocado, banana, and latex. Cassava extract contains multiple IgE-binding protein bands between 10 and 75 kDa. IgE-binding bands of between 23 and 40 kDa were also detected for the latex extract and one band of around 60 kDa was observed for the avocado extract. No IgE-binding bands were observed for the other extracts (fungi and banana). Two-dimensional gel electrophoresis with cassava extract was performed for high-resolution profiling of proteins using the method described by Sheffield et al [3]. Using this method, gels of high quality showing well-resolved spots and little streaking were obtained with a mass of between 20 and 39 kDa (data not shown). We also tested 2 individuals as controls. IgE immunoblotting assay for cassava and latex proteins showed negative results in both individuals (data not shown). Inhibition assays were performed using 2 approaches: IgE immunoblotting inhibition and the FEIA-CAP inhibition test. IgE binding to cassava proteins was largely inhibited (by approximately 80%) by the latex extract (Figure B). In addition, the patient’s serum was incubated with cassava extract (1 g of fresh cassava disrupted mechanically with a mortar in the presence of protease inhibitors) for 2 hours at room temperature with sporadic agitation. Inhibition with cassava extract reduced the levels of specific IgE for latex by approximately 60%.

Cassava, also known as yucca, manioc, mandioca, or tapioca, is the common name for the tuber Manihot esculenta. It is widely eaten in different countries, mainly South American [4,5] and is also important in the textile, cosmetics, and pharmaceutical industries.

Studies have been performed to identify and classify the proteins present in cassava roots [3]. The participation of these proteins in allergic reactions, however, has been poorly studied and there have few reports of anaphylaxis after the ingestion of boiled cassava, namely in individuals from Africa (Mozambique), Europe (Spain), and Brazil [2,6-8]. Our case is the first report of allergy to cassava in Colombia.

Specific IgE immunodetection has permitted the identification of IgE-binding components with a wide range of molecular sizes in cassava root [2,6,8]. IgE immunoblotting analysis has shown 3 protein bands of around 35, 42-44 and 50 kDa [6] and 30 and 40 kDa [8], and at least 5 IgE-binding bands of 89, 46, 26, 21, and 19 kDa [2]. Our results were similar in that we also observed multiple bands ranging between 75 and 25 kDa.

Interestingly, all patients with cassava allergy described to date have had latex cross-reactivity. Some of those patients were first diagnosed with allergy to latex and subsequently to cassava [2,6,7], indicating that cassava allergy might be a consequence of primary latex sensitization. We detected IgE reacting with latex by SPT, FEIA-CAP, and immunoblotting. With IgE immunoblotting we observed bands of between 23 and 40 kDa. In our study, in order to confirm the existence of cross-reactivity between cassava and latex, immunoblotting, and FEIA-CAP inhibition assays were performed, showing considerably reduced recognition of cassava proteins by IgE from serum treated with latex extract or latex proteins by IgE from serum treated with cassava extract.

In the study by Ibero et al [2], the extensive cross-reactivity between fruits, vegetables, and latex was attributed to class I chitinases, which are plant defense proteins with an N-terminal domain similar to that of prohevein (Hev b 6) in latex. Interestingly, these chitinases are present in banana, avocado, and chestnut, and are now considered “panallergen” proteins responsible for latex-fruit syndrome [9,10]. Tuber root and latex also share other proteins in addition to chitinases that could be involved in what was recently called latex-manioc syndrome by Santos and colleagues [8]. Pt214, a glutamic acid–rich protein, was identified in the cassava extract by the allergic patient serum. This protein has moderate sequence identity (41.9%) to Hev b 5 from latex. In another study, Santos et al [8] recently described 3 new IgE-binding proteins.

In conclusion, the natural course of allergy in the patient described in this report could be oral sensitization to cassava due to occupational exposure to latex. The extensive use of materials made from latex and the widespread intake of fruit and cassava in our country means that we can expect an increasing number of cases of allergy to cassava in the coming years. Therefore, it is important for clinicians to be alert to the fact that cassava is a source of allergens involved in the latex-fruit syndrome.

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