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Molecular allergology in practice: an unusual case of LTP allergy

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SUMMARY

The authors describe an unusual case of LTP allergy. A 35 years old patient presented repeated episodes of angioedema after food intake and complained 10 years ago of contact urticaria and rhinoconjunctivitis when exposed to cannabis leaves and to marijuana smoke. The suspected responsible foods, such as wheat flour in bread, are known to contain LTP. Oral syndrome occurred after ingestion of walnuts. Cutaneous tests confirmed immediate responses to several flours and nuts and also to cannabis leaf and flower. A few months later he had similar accidents following peach ingestion and drinking of beer and several wines which all induced positive skin tests. Serological investigations using ImmunoCAP and ISAC microarray confirmed IgE positivity for n Pru p3, r Cor a 8 and n Art v3. It was assumed that sensitization to LTP, the major allergen of cannabis, was responsible of the primary sensitization and induced further LTP food allergies.

Introduction

Lipid transfer proteins (LTP) are pan-allergens present in many edible plants and in certain pollens. It is now accepted that, unlike homologous proteins of Bet v 1, profilin and polcalcins, the clinical manifestations of LTP sensitization are most often severe. This is the allergenic protein most commonly responsible for primary allergy to edible plants in Southern Europe (1, 2). While systemic manifestations associated with peach LTP are widely known, other less common allergies to LTP are more rarely reported; this is illustrated by the case reported here. Molecular arguments allowed us to establish the sensitization profile of the patient, thus permitting more accurate diagnosis as well as adapted therapeutic management.

Case report

MCP, aged 35, consulted in March 2009 following several episodes of facial and trunk angioedema associated with post-prandial urticaria. He had a family history of atopy and had complained of mild persistent rhinitis over the past fifteen years. Ten years ago, he developed contact urticaria with cannabis leaves and a few years later, he complained of rhinoconjunctivitis when exposed to marijuana smoke. Regarding postprandial events, potentially responsible foods were: fig jam and bread (either wheat flour or rye, barley, oats, corn, spelt, millet, flax, sesame); amylase and other enzymes could also be suspected. It was impossible for the patient to clearly specify which bread was implied in the different episodes. He also reported an oral

Table 1 - Arguments for the etiological diagnosis obtained by assays using molecular allergens.

Clinical symptoms	Etiologies	Arguments obtained by assays using molecular allergens
Urticaria and angio-oedema	LTP (grape, peach, hazelnut, fig, cannabis, beer)	Pru p 3, Cor a 8 and not Pru p 1 or Cor a 1 sensitizations
No pollen symptoms	LTP	Sensitization to Art v 3 and not to Art v 1

syndrome after intake of walnuts and felt a strong dislike for hazelnuts.

The first allergological investigations showed cutaneous sensitization to house dust mites, while skin tests to other aeroallergens were all negative. Concerning food allergens, positive skin tests were observed for flax flour (4 mm), maize flour (3 mm), fig (6 mm), hazelnut (2 mm), nuts (3 mm), Brazil nut (2 mm) and pecan nut (4 mm). Moreover cutaneous tests were positive both for cannabis leaf and flower (4 mm in each case). All these tests were performed with native materials. No sensitizations were detected for ficus, rubber and fruits of the latex family. The average size of the wheal obtained with 9% codeine phosphate (9%) was 4 mm. Specific IgEs for fig and hazelnut were 0.84kU/l and 0.59kU/l respectively (ImmunoCAP System; Phadia, Uppsala, Sweden).

To begin with, the patient was recommended to avoid consumption of the foods responsible for positive cutaneous tests and an emergency kit was prescribed.

A few months later, the patient consulted for similar accidents following peach ingestion and intake of several drinks: champagne (Pinot Noir/Chardonnay), red wine (Merlot, Côte de Provence, Côtes du Rhône) and homemade beer. Renewed allergological investigations confirmed cutaneous sensitisation to champagne and to involved red wines; peach skin tests were also positive [both for skin (3 mm) and pulp (4 mm)].

The hypothesis of LTP sensitization was raised and was confirmed by positivity of specific IgE antibodies to rPru p 3 (0.96kU/l) (ImmunoCAP, Phadia). Allergy to sulfites was ruled out by an oral challenge with sulfites. These results allowed us to hypothesize that the patient could have contracted cannabis allergy followed by allergies to several foods (peach, grape, maize, barley, figs, hazelnuts) which all contain LTP. In order to support the hypothesis of a common molecular family allergen involved in these multiple allergies, other LTP sensitisations were searched by ISAC microarray (Phadia) which revealed positivity for the three LTP available on the chip: nPru p3 (0.4 ISU),

rCor a 8 (1.7 ISU) and n Art v 3 (0.6 ISU), corresponding to LTP of peach, hazelnut and mugwort pollen. There was also positivity for Group 1 and 2 of mite allergens (n Der p1:1,2 ISU, n Der p 2: 2.8 ISU, n Der f 1: 3.5 ISU, r Der f2: 2.8 ISU). No positivity either for profilins or storage proteins present on the chip, or for thaumatin-like kiwi protein was found.

Comments

LTP belonging to the superfamily of prolamins are pan-allergens. They have been found in many edible plants as well as in certain pollens (mugwort, plane, ragweed, wall-pellitory, oleaceae) (3). In plants, they are concentrated in the aerial parts (flowers, leaves, pollen and stem) (4). They are usually not present in the root (4).

In the case reported, we believe that LTP sensitisation was initiated by repeated contact with cannabis plants. LTP cannabis (Can s 3) was isolated and sequenced; it is currently considered as the major allergen of cannabis (5). LTP sensitization can occur transdermally or by inhalation (5). This has been shown in individuals handling fruits known to contain a high amount of LTP (6). The history of our patient seems to illustrate these data. Only later did the patient develop severe food allergies that could be the consequence of sensitization to LTP, as the foods involved (corn, figs, grapes, beer, peach) contain LTP (7-11). The resistance of LTP to cooking temperature could also explain the clinical manifestations after ingestion of fig jam (12). LTPs are also resistant to proteolysis, which accounts for their presence in fermented beverages such as champagne, wine or beer (13, 14). In our clinical case, the multiplicity and severity of food allergies, the absence of pollinosis, the difference in skin reactivity between peach skin and flesh (consequent to the preferential accumulation of LTP in the skin of the peach) suggest that allergy to wine and champagne may also be attributable to LTP. If usually wine allergy is mainly attributed to chitinases and thaumatin-like proteins, the

role of LTP in wine allergy, especially in severe clinical presentations, has been reported by several groups (13-16). Some methods of winemaking, some grape varieties (e.g. Fragolino) could promote the presence of LTP in wine (14). Young wines are most often concerned, there would still be allergenic proteins in solution prior to later polymerization induced by polyphenols (14). Sensitization to Art v 3, without clinical symptoms of pollinosis is suggested by Pastorello et al. (17). Some Spanish authors have found that sensitization to Art v 3, which only shares a 40% sequence homology with Pru p 3 is often associated with a broader recognition of LTP (unpublished data). Our patient is sensitized to Art v 3 (0.6 ISU, biochip IgE ISAC) and to several LTPs. Sensitization to hazelnuts (which he had never eaten due to his aversion), is not related to sensitization to PR10 (Cor a 1), or to profilin, but also relies upon LTP sensitization.

The clinical arguments above and the demonstration of sensitization to several LTP lead us to retain the diagnosis of multiple LTP food allergies induced by a primary sensitization by cannabis LTPs (Tab. 1). However, only inhibition studies would allow confirmation of this diagnostic hypothesis.

The patient, informed that his food allergies are probably mediated by LTPs, was made aware of the potential severity of clinical symptoms and of the necessity of the prescribed emergency kit containing adrenaline.

Conclusion

Allergy to cannabis and alcoholic beverages such as wine, champagne or beer might be an unusual revelation of the classical LTP syndrome. Cannabis could be the allergenic source of a primary sensitization to LTPs, introduced either by inhalation or by a transdermal pathway. A recent article by Asero and Antonicelli can support this statement (18).

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