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CASE REPORT

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Allergy to Gibberellin-regulated proteins in an adolescent: A case of orange-induced anaphylaxis mediated by cofactors

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Abstract
This report is a case of anaphylaxis in an adolescent due to allergy to gibberellin-regulated proteins mediated by cofactors, in probable relation to a pollen/food allergy syndrome. It should also emphasizes the importance of obtaining a faithful clinical history, especially when it comes to adolescent patients as they tend to initiate toxic habits.

Introduction

Anaphylaxis is an acute and potentially life-threatening allergic reaction that must be promptly recognized and managed immediately. The diagnosis of anaphylaxis is clinical; thus, consideration for anaphylaxis is based on the effect of two or more organ systems, including the skin or mucous membranes, the respiratory system, the gastrointestinal system, and the cardiovascular system.[1] The diagnosis of anaphylaxis is even more challenging in children and adolescents because of the inability of children to accurately describe their symptoms and difficulties in obtaining truthful information.[2]

Gibberellin-regulated proteins (GRPs) are an emergent family of allergens that belong to the cysteine-rich plant peptide families involved in antimicrobial and homeostatic functions in plants, with high physicochemical resistance. GRPs can be found in fruits and pollen. The clinical features may include systemic reactions and, less frequently, cofactor dependence.[3] Clinical cross-reactivity has been proven and it might be related to pollen/fruit allergy syndrome (PFAS).[4]

Case Report

We report the case of a 15-year-old adolescent male affected by a mild intermittent rhinoconjunctivitis, the episodes of which coincided with the cypress pollen season, who developed two anaphylactic reactions in 2016. In the two episodes, he had eaten macaroni with tomato

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and an orange. He also took ibuprofen for headache, recognized alcohol intake, and smoked cannabis. The second time, he had also been exercising simultaneously.

The allergological study [skin prick test (SPT), determination of specific Immunoglobulin E (sIgE), and molecular study (Figure 1)] was positive for pollen, epithelia, and orange. In more detail, the resulting analytical values were as follows: total IgE 79.3 KiloUnits/liter (KU/l), timothy grass sIgE 10.40 KU/l, cypress sIgE 2.60 KU/l, dog dander sIgE 7.8 KU/l, and orange sIgE 1.59 KU/l.

The SPT to *Cannabis sativa* was also positive (with negative controls), although less so than histamine wheal. An elevation of tryptase was determined with a normal basal tryptase [3.58 micrograms/liter (µg/l)]. After the reactions, the patient tolerated the intake of macaroni and tomato. Oral food challenges (OFC) to orange and ibuprofen were performed with negative results. Immunoblotting only detected one band [<14 kiloDaltons (kDa)] toward the orange extract. No major protein previously described as an orange allergen was identified in Liquid Chromatography with tandem mass spectrometry (LC-MS-MS) (Figure 2).

In 2022, the patient reports not having experienced any new reactions and maintains tolerance to all the allergens involved in the previous reactions when ingested separately and without the cofactors previously described. On the other hand, the allergological and molecular restudy provides new results (negative for cannabis sIgE and Can s 3, and positive for Pru p 7) (Table 1). A new LC-MS/MS was performed providing evidence of a protein with sequence identity with a GRP present in the citric fruit, which is the orange in our case (Figure 3).

Discussion and conclusions

GRP isolated from peach, also known as Peamaclein, was the first GRP to be described as a food allergen and was named Pru p 7; up to now, it is the best characterized. Nevertheless, there are other identified allergens among them, such as sweet orange GRP, Cit s 7, which has been demonstrated to be clinically relevant, although this allergy seemed to be milder than Pru p 7[4] and without

Table 1. Second molecular study to allergen-specific IgE (ImmunoCAP ISAC® 112).

Cannabis sativa, Hemp	**0,02 kU/l**
Allergen component rCan s 3	0,00 kU/l
Citrus sinensis, Orange	1,34 kU/l
Allergen component rPru p 7	6,22 kU/l
Cupressus arizonica, Arizona Cypress	3,55 kU/l
Allergen component nCup a 1	6,98 kU/l

[kU/l: kilounits/liter]

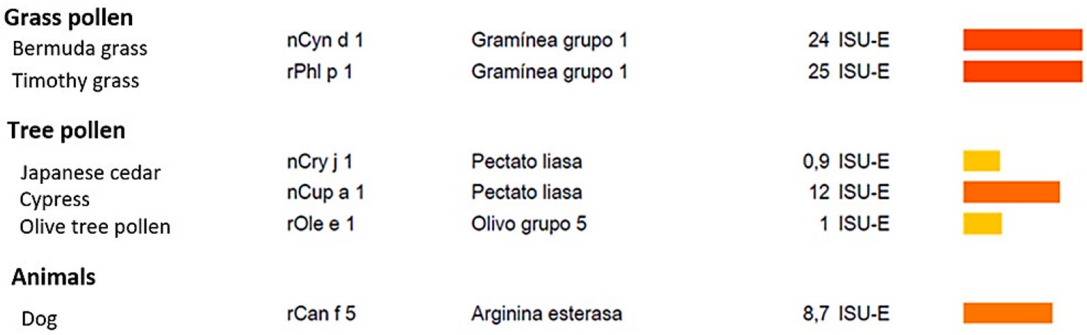

Figure 1. First molecular study to allergen-specific IgE (ImmunoCAP ISAC® 112).

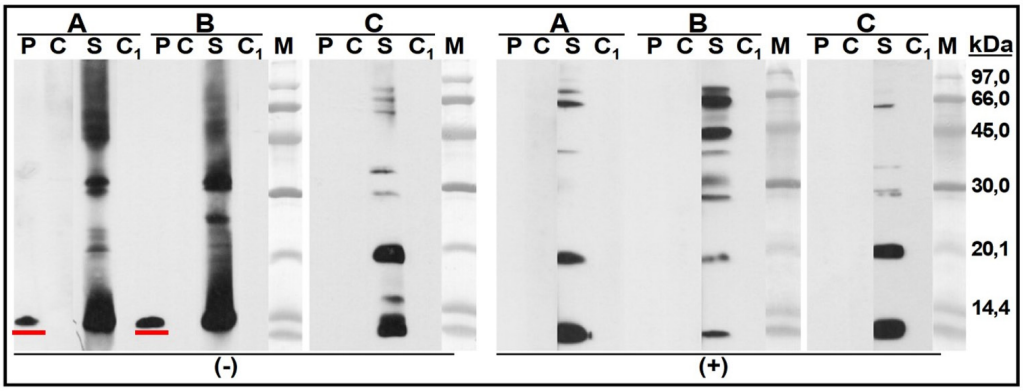

Figure 2. Liquid chromatography with tandem mass spectrometry (LC-MS-MS). (A) Orange peel extract, (B) Orange pulp extract, and (C) Cannabis bud extract. Lane P: patient serum. Lane C: control serum (mix of serum of nonatopic people). Lane S: anti-Pru p 3 rabbit serum. Lane C1: negative control serum of rabbit. M: molecular mass pattern. (-) Nontreated sample with 2-mercaptoethanol. (+) Treated sample with 2-mercaptoethanol. Red lines: < 14 kDa band.

Accession	Description	MW [kDa]	calc. pI	Coverage [%]
A0A067GPB8	Gibberellin regulated protein OS=Citrus sinensis OX=2711 GN=CISIN_1g039784	9,7	8,24	23

# Peptides	# Protein Uniqu	Score Mascot: N	# PSMs	PSMs/Mw
2	0	98	7	0,722

Figure 3. Protein characterization using liquid chromatography with tandem mass spectrometry (LC-MS-MS).

any reported cases of anaphylaxis shock.[6] In this case, the exposed adolescent patient showed positive reactivity toward Pru p 7, GRP of the peach, and also sensitization to cypress pollen. This may suggest a probable PFAS.[4]

To ascertain the factors that could explain the present cross-reactivity, on one side, we detected Cup a 1 and Cry j 1 from cypress, albeit in the literature the PFAS related to GRPs is mainly described with Cup s 7[5], a molecule that cannot be determined yet. However, to support the hypothesis, we base it on the positivity of the complete cypress extract. On the other side, about the detected GRP molecule in our case, which is Pru p 7 (peach allergen), it can be found that there is high homology, and 87% identity, with orange Cit s 7[5] which reactivity has been proven.[6]

With regard to the clinical aspects, PFAS frequently induces oral allergy syndrome (OAS). However, there is evidence that symptoms of PFAS are not limited to OAS but can be more severe and can thus progress to systemic symptoms and anaphylaxis[7], especially if the involved protein families have physical-chemical resistance, such as lipid transfer proteins (LTP) or GRPs, which are involved in the present report of anaphylaxis. Furthermore, if associated with cofactors such as physical activity and the intake of nonsteroidal anti-inflammatory drugs, the symptoms may be more severe and even include anaphylactic shock.[7]

Concerning cannabis, it is confirmed that patients sensitized to Can s 3, the LTP in cannabis, may develop sensitization and relevant clinical symptoms.[8] Other proteins, such as Can s 2, Can s 4, and Can s 5, have also been described but with less knowledge about their clinical relevance. In this regard, we found a unique publication that reports food-dependent exercise-induced anaphylaxis (FDEIA) that proposes a possible role of cannabis acting as a cofactor, postulating the release of cytokines as a mechanism.[9] However, nowadays there is a lack of evidence on the potential role of cannabis as a cofactor.

This report is a good illustration to highlight the importance of obtaining a faithful clinical history to ensure the accuracy of clinical data, especially when it comes to adolescent patients since in this age range they tend to initiate drug and alcohol consumption and other risky behaviors. Furthermore, this population becomes more independent from their parents and this consequently makes the anamnesis more difficult for the lack of awareness of the parents and because these patients tend to hide information. Thus, these expositions, as potential allergens or cofactors, can remain undetected.

Therefore, we present a case of anaphylaxis in an adolescent due to allergy to GRPs mediated by cofactors (exercise, nonsteroidal anti-inflammatory drugs, alcohol), in probable relation to a PFAS (cypress-orange). GRPs have gained increasing attention as allergens so we should increase the knowledge of the immunological and clinical features of GRPs allergies.

ETHICAL DISCLOSURES

Data Confidentiality

The authors declare that no patient details appear in this article.

Privacy rights and informed consent

The authors declare that no patient details appear in this article.

CONFLICTS OF INTEREST

We declare that we do not have any financial or personal relationship concerning the submitted publication.

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