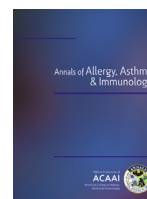




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Letter

Spice allergies in children

Spice allergy is rare in children.¹ Saffron allergy in particular has been described only in adults²; it occurs generally in occupational settings³ and is due to the Cro s 3 lipid transfer protein (LTP).⁴ We describe a case that is the exception to all these beliefs.

A 12-year-old boy followed up for allergic rhinitis to grass pollen, cat, and house dust mite also had oral allergy syndrome (OAS) and a positive skin prick test (SPT) result for apple, watermelon, and fennel. As is common in Milan, Italy, this patient often consumed risotto alla Milanese, with full tolerance. However, he experienced sneezing after smelling and eating a small amount of risotto. The reaction occurred almost immediately and was limited to nasal mucosa without OAS or asthma, but it was so severe that the patient gave up eating and needed nasal budesonide within 2 hours. The episode happened twice in a fortnight.

The results of a SPT with rice was negative, whereas a saffron powder SPT result was positive with a 5 × 5-mm diameter (histamine, 4 mm). His total IgE level was 2,872 kU/L; serum specific IgE determination by ImmunoCAP (ThermoFisher, Uppsala, Sweden) was 10.1 kU/L to saffron and 2 kU/L to rice. Specific IgE determinations also revealed polysensitization to several spices (thyme, cayenne pepper, black pepper, and oregano) and to possible ingredients in risotto alla Milanese, including peas, carrots, potatoes, celery, and parsley (range, 0.33–11.4 kU/L). At history, the patient tolerated all these foods and spices without any reaction.

To confirm the clinical suspicion, we performed a double-blind, placebo-controlled food challenge with saffron. A soft, custard-like, yellow cream colored with 7.5 mg of saffron (half bag; the equivalent of a dose used to prepare risotto alla Milanese for 2 people) was administered. Placebo was the same yellow cream colored with 3 yolks instead of 1. The boy reacted 10 minutes after ingestion of 1 coffee-spoon of saffron cream with sneezing, rhinorrhea, nasal obstruction, and conjunctivitis, without OAS or asthma. Again the patient recovered with nasal budesonide within 2 hours. No early or delayed systemic reaction occurred. We recommended strict saffron avoidance and extreme accuracy in reading labels of pre-packed food. Because rhinitis is not a potentially life-threatening reaction and saffron is easily avoidable in everyday life, no adrenaline was prescribed.

To estimate the possibility of severe reactions, molecular diagnosis was performed. Three allergenic molecules have been described in saffron: Cro s 1 (an Ole 1-like protein), Cro s 2 (a profilin),⁵ and Cro s 3 (an LTP).⁴ None is commercially available for immunodiagnosis. Therefore, we explored the patient's sensitization using cross-reactive available proteins in food and inhalant allergens. Many of the potentially instrumental foods did not contain a specific Ole 1-like protein, profilin, or LTP. In addition, not all of the described proteins were commercially available for specific IgE determination. When available, however, profilins

were positive on ImmunoCAP, suggesting that Cro s 2 is the responsible allergen. In particular, the levels of Pru p 4 from peach, Phl p 12, and Bet v 2 were 11.7 kU/L, 25.61 kU/L, and 2.21 kU/L, respectively.

This pediatric report of saffron allergy is also the first report, to our knowledge, of profilin-driven saffron reaction. Profilin-related allergens are responsible for type 1 allergy to many spice members of the Apiaceae family,⁶ but have never been found to be responsible of symptoms for spices of the Iridaceae family (which saffron belongs to). Saffron (from the Arabic word *zafaran*, meaning yellow) is a spice derived from the dried stigma of the flower of the saffron crocus (*Crocus sativus*). It arrived in Milan during the Renaissance as a coloring pigment used by the Flemish decorators of the stained glass windows of the cathedral. According to a Milanese legend, in 1574 a rice dish colored with saffron was served at a wedding dinner of a glazer's daughter. The rice prepared in that manner was enjoyed and became popular in Milan. Four and half centuries after, we report the first allergic reaction to it. From adult studies in occupational medicine, it is known that sensitization may occur to saffron pollen and stamen proteins; no allergenic components were demonstrated in pistils.² Saffron extracts contain Cro s 2, a 15.5-kDa allergen with a profilin nature.^{2,5} The sequence Cro s 2 displays a high degree of identity and similarity to other plant profilins, and its recombinant sequence may be used for target-specific diagnosis, structural analyses, and investigation of cross-reactivity of Cro s 2 with other vegetables. Profilins play a role in IgE-mediated allergy to anise, fennel, coriander, or cumin, members of the Apiaceae family. Specific IgE antibodies to birch (Bet v 2), latex (Hev b 8), and timothy (Phl p 12) profilins were also indicated as responsible in a case of allergy to curry.⁷

Using a similar approach, we infer that the reaction to saffron in our patient is due to Cro s 2. This indirect assumption is based on the boy's positivity to all profilin molecules tested and no LTP.

The lack of direct evaluation is not the only limiting factor in our observation. Saffron allergy could be variably expressed on the ground of different factors. Among them, the effect of cooking, heat treatment, and ripening. The saffron producers are well aware that the volatile composition of *C. sativus* changes notably, with each stigma's developmental stage characterized by a different volatile combination. The main protein compounds of the stigma, crocetin and picrocrocin, increase as stigmas reach a fully developed stage.⁸ Last, pollen hydration, pollen germination, and stigma papilla penetration are modifiable by fumigations with different gases used in the industrial process. At the end of industrial saffron production, it is not easy to know the precise amount of specific compounds in a saffron bag and their chemical properties.^{1,9}

Because clinical evolution is unpredictable and full knowledge of the spice allergies is still incomplete, strict saffron avoidance and

Disclosures: Authors have nothing to disclose.

accurate reading of labels of prepacked food are recommended. After 3 years of avoidance, no unintentional exposure occurred in this now 15-year-old boy. His only problem is that he has to avoid risotto alla Milanese, one of the culinary staples of Milan.

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