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Cross-reactivity between mites and snails

M.^a T. Server Costa

Al-lercen. Barcelona, Spain

The prevalence of allergy to snails is unknown, but it obviously depends on the alimentary habits of the population studied. Most publications on this particular subject have originated in southern Europe, where snails are frequently consumed.

Palma-Carlos et al¹, in Portugal, were the first to report an episode of bronchospasm in relation with snail intake. Prompted by this first case, they then carried out a survey on 5,000 atopic asthmatics in order to find out the prevalence of asthma related to snail intake. Thirty-six patients reported having developed asthma within 20 to 90 minutes after eating snails; among these 36 patients, 29 were allergic to dust mites. Skin tests with a commercial snail extract could be performed on only 26 patients, with positive results in 24.

Didier et al² performed skin tests with snail extracts on 312 young adult patients consulting for an allergological study because of respiratory complaints. In this population, 239 patients (77%) had at least one positivity to an airborne allergen, and 163 (52%) were allergic to dust mites. The prevalence of positive skin tests with snails among the atopic subjects was 4.5% (14/312). All but one of these were sensitized to dust mites (13/163). In other words, the prevalence of positive skin tests with snail extracts among dust mite-allergic patients was 8%. Among the fourteen snail-positive patients, six had consumed snails on some occasion, and four of them had had symptoms. Vuitton et al³, in a population of 169 children, found 38 who had positive skin tests to one or more snail species; 79% of these (30/36) were sensitized to dust mites. Among 72 patients who were not sensitized to dust mites, only 10% (8/72) had positive skin tests with snail, as compared to 31% (30/97) among those who were hypersensitive to dust mites. None of them reported having consumed snails previously.

The association of snail allergy in patients who are hypersensitive to dust mites is unusually frequent in Italy. Amoroso et al⁴, in the Palermo area,

found a 61% prevalence of positive skin tests with snails among individuals who were allergic to dust mites and pollens, and the RAST to snail was positive in 19% of them. However, only 15% of the patients had developed asthma after the ingestion of snails. Pajno et al⁵, in Sicily, reported a 67% prevalence of positive skin tests to snails in a population of 51 asthmatic children with *Dermatophagoides pteronyssinus* allergy; no data were given regarding previous snail consumption. A challenge test with 39 g of snails was performed on 15 children with positive skin tests to snail and on six with negative skin tests; the challenge test was positive in 73% of the former (11/15), and negative in all the cases with negative skin tests.

In Spain, De la Cuesta et al⁶ described ten atopic patients (80% with acarine sensitization) who evidenced severe anaphylaxis after eating snails (*Helix terrestris*). Two of them had also had reactions after eating limpets, and all of them tolerated other molluscs and crustaceans. All had positive skin tests with a raw snail extract and positive histamine release tests with snail. Muñoz et al⁷ published five cases of patients who developed asthma after eating snails; all had positive skin tests and RAST. Server et al⁸ published four further cases of patients with dust mite asthma who developed immediate hypersensitivity symptoms after eating snails. Roger⁹ carried out skin tests with a commercial snail extract on 50 asthmatics with dust mite sensitization and on a further 50 non-atopic asthmatics; the skin tests to snail were positive in 3/50 (6%) of the atopic asthmatics, and two of them had evidenced symptoms after eating snails; the skin tests were negative in all 50 non-atopic asthmatics. Cardona and Eseverri¹⁰, in a study of the prevalence of snail allergy in the paediatric population in the catchment area of the Vall d'Hebron Hospital, found it to be ca. 16% among patients with dust mite sensitization. Out of 37 patients studied six had positive skin tests, and two of them had developed asthma after eating snails.

CLINICAL MANIFESTATIONS

In most of the published cases, the reported reactions were potentially severe. The target organ is the bronchial tract, with asthma episodes after

the ingestion of snails; these were in some cases associated to cutaneous manifestations. The symptoms generally occurred within 5 to 60 minutes after eating snails.

Most of the patients with snail allergy had rhinoconjunctivitis and/or asthma due to dust mite sensitization. A high proportion of them receive immunotherapy with mites, and in some cases the local inflammatory reaction at the site of injection of the dust mite immunotherapy doses was quite remarkable after the ingestion of snails¹¹.

CROSS-REACTIVITY BETWEEN MITES AND SNAILS

Most of the patients with snail allergy have rhinitis and/or asthma due to dust mite sensitization. This coincidence might be related to the existence of cross reactivity between both. Several hypotheses have been postulated in an attempt to explain these observations: (1) parasitic infestation of the snail lungs by mites of the genus *Riccardoella limachum*; (2) presence of haemocyanin; (3) involvement of tropomyosin, and (4) a role of dust mite immunotherapy as inductor of the production of IgE antibodies to foodstuffs of invertebrate animal origin.

One of the first possible candidates proposed as an explanation was the mite *Riccardoella limachum* (group *Thrombidiformes*, family *Ereynitides*), which parasites the lungs of land snails and shares antigens with *Dermatophagoides pteronyssinus*. Industrially processed and packaged snails would exhibit a higher degree of acarine contamination than those collected in the fields and prepared at home. Thus, Banzet et al¹¹ observed that their patients tolerated the snails they themselves had collected and prepared, while they developed reactions with tinned snails. At present, however, there are arguments against this theory. Van Ree et al¹² performed skin tests and RAST with three different land snail extracts (*Eobania vermiculata*, *Helix aperta* and *Cernuella virgata*) and with two marine snail extracts (*Platella* spp. and *Bolinus brandaris*) to 28 patients who had developed asthma after the ingestion of snails, all of them allergic to dust mites. They observed a close correlation between the RAST results for land and marine snails as

well as cross-reactivity between them, yet marine snails are not parasited by the mite *Riccardoella*. A further argument against this theory is the fact that no reaction to *Riccardoella* extracts has been demonstrated *in vivo* in patients with snail and mite allergy. Thus, Vuitton et al³, in seven patients with mite allergy who had evidenced symptoms after eating snails, found that all of them had positive skin tests to snail, but none of them had such positive tests to *Riccardoella*.

Haemocyanin might be another source of allergens shared between mites, snails and crustaceans, as suggested by Mistrello et al¹³. Haemocyanin is the major component in snail haemolymph (representing 80-90% of its protein contents). It is also present in two further invertebrate families: arthropods and molluscs. Haemocyanin exists in the snail *Helix pomatia* in two forms, α - and β -haemocyanin, with molecular weights of 52.7 and 48.7 kDa, respectively. Vuitton et al¹⁴ have identified protein bands in the 49-53 kDa range in six out of seven patients with snail allergy; three of the patients who evidenced this type of reactivity *in vitro* also had positive skin tests with haemolymph, but only with the raw extract. A small epitope has been described in the haemocyanin from *Helix pomatia*, which is a complex glycane containing xylose. Xylose- or fucose-containing complex glycans are commonly found in plants and in some invertebrates and constitute important epitopes for the IgE antibodies of allergic patients. However, the antigen responsible for the cross-reactivity appears to be heat-stable, while the positive results achieved have only been observed with raw haemolymph extract, and not with the cooked one. This is clinically relevant depending on the culinary habits regarding the preparation of snails: in France, *Helix pomatia* is always consumed after protracted boiling, and this would seem to rule out haemolymph as the component involved.

Tropomyosin is an animal protein involved in the contractile "machinery" of cells. Tropomyosin, the major allergen in prawn, has been implicated as the possible responsible allergen in cross-reactivity processes between widely different allergenic sources, such as prawns, snails, mites and insects¹⁵. Its 36-kDa molecular weight and the observation that the sera from patients with snail allergy react with protein bands of molecular weights ranging between 33 and 34 kDa suggest

that tropomyosin is the main allergen involved in cross reactivity between mites and molluscs¹⁴. However, tropomyosin does not appear to play any role in the groups of patients studied by other authors, such as Van Ree et al¹² and De Maat-Bleeker et al¹⁶. These contradictory results suggest that more than one single allergen is implied in this cross reactivity.

The high prevalence of skin sensitization to snail among patients with dust mite allergy, the development of clinical manifestations in some patients upon eating snails for the first time and the observation that some patients evidence marked inflammatory reactivity in the site of injection of mite immunotherapy after having eaten snails all give support to the hypothesis of a role of mite immunotherapy as a risk factor, as it might induce the apparition of food allergy to invertebrate animal foodstuffs (snail, shrimp) through activation of tropomyosin IgE. Van Ree et al¹⁷ have followed 17 patients with dust mite allergy who received specific immunotherapy. The serum IgE to *Der p1*, *Der p2*, shrimp and snail was quantitated at the beginning of the dust mite immunotherapy. After 14-20 months of follow-up, the levels of *Der p1* and *Der p2* IgE had not changed, while the IgE response to snail had significantly increased. Specific IgE antibodies to tropomyosin were also detected.

In summary, all the studies confirm the existence of cross reactivity between mites and snails. This cross reactivity achieves particular relevance in atopic patients with dust mite allergy. Contrary to what has been reported in the case of patients with crustacean allergy, in whom tropomyosin plays an important role as a "panallergen", in patients with snail allergy the precise identity of the responsible allergen remains unknown. Possible candidates include haemocyanin, tropomyosin and a thermostable minor allergen from *Dermaphagoides pteronyssinus*, which might correspond to *Der pIV* (56-60 kDa), *Der pV* (15 kDa), *Der pVI* (60 kDa) or *Der pVII* (22-28 kDa).

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The hidden allergens

P. García-Ortega

Allergy Unit. "Joan XXIII" University Hospital. Tarragona, Spain

One of the main hurdles encountered in the practice of Allergology is that represented by unrecognised substances which may cause sensitization and allergic disease. Such substances could be termed "unknown" or "unreported" allergens, and only after being reported or described will they be incorporated into the diagnostic armamentarium. There is however another type of allergens which, although perfectly known, remain hidden both to the patient and to the allergist, as they are masked or hidden behind other more potent, better known or better foreseeable ones. They thus easily remain unnoticed in the diagnostic process. Over the last few years, the accumulation of new and surprising descriptions of such allergens, which could be termed "masked", "occult" or "hidden", has remarkably increased, and awareness of them is becoming indispensable for all allergists regardless of the level at which they carry out their professional activities.

RESPIRATORY ALLERGY: HIDDEN ALLERGENS IN HOUSE DUST

Beyond the protagonism of the major mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) and of the minor ones, or stora-