

Cross-reactivity between terrestrial snails (*Helix* species) and house-dust mite (*Dermatophagoides pteronyssinus*). I. *In vivo* study

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Clinical reports have suggested an unusual frequency in the number of patients with food allergy to snails who are also allergic to the house-dust mite (HDM). As allergy to HDM is one of the most frequent sensitizations in atopic patients of Western countries, evaluation of the relevance of the concomitant sensitization to *Dermatophagoides pteronyssinus* and to snails is an important consideration. To evaluate the responsibility of different snail components and of snail mites for inducing *in vivo* hypersensitivity in patients allergic to HDM, the *in vivo* reactivity of patients with clinical symptoms after ingestion of snails was assessed by skin prick tests with extracts and hemolymph from four different *Helix* species snails, and extracts from the snail parasitic mite, *Riccardoella limacum*. In addition, to obtain epidemiologic data on cosensitization to HDM and snails in allergic patients, the frequency of snail sensitization and its relationship to HDM sensitization were determined in a population of 169 allergic children. All patients allergic to snails had positive skin prick tests to the snail extracts and none to *R. limacum* extract. The number of positive skin reactions did not significantly differ whatever the species, snail part, or heating procedure used. The strongest reactions were obtained with *Helix pomatia* (Burgundy snail). Among the 169 prospectively tested children, 38 had a positive prick test to snail extracts; 79% of the snail-sensitized children had sensitization to HDM; and 31% of the children allergic to HDM were found to be sensitized to snails. These results show that snail components, and not the mite *R. limacum*, were responsible for the *in vivo* hypersensitivity. These snail components reacting *in vivo* are present in different parts of snails, including the hemolymph. One-third of the children allergic to HDM were sensitized to snails without any previous ingestion of snails: this observation suggests that HDM was the sensitizing agent and that the cross-reaction could be clinically relevant in countries where eating snails is common.

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In the past decade, a number of allergens have been shown to be involved in cross-reactions between ingested food and inhaled particles (1). Usually, these cross-reactions have been described in patients with pollen hypersensitivity where most of the allergens involved were those of fruits and vegetables (2–4). More recently, animal allergens

have been shown to exhibit cross-reactivity, such as unusual cases of egg allergy associated with sensitization to inhaled avian allergens (5), or cross-reactions between crustaceans and mollusks (6).

Allergy to the house-dust mite (HDM), especially *Dermatophagoides pteronyssinus* (D. pt), is one

of the most frequent sensitizations in atopic patients of Western countries. Some Italian studies suggest that food allergy to shellfish and snails such as *Euparipha pisana*, *Bolinus brandaris* ("Ragusa shellfish"), *Helix* species, or *Limax agrestis* was unusually frequent in patients with HDM allergy, and that true cross-reactivity could be involved (7–12). This kind of association was also suggested for the "vineyard" snail, *Eobania vermiculata*, in The Netherlands (13).

In Franche-Comté, a region of eastern France between Switzerland and the region of Burgundy, France, the snail ("Burgundy snail") is commonly eaten by both children and adults, especially at Christmas and New Year's Eve/Day dinners. Since 1984, when the first case came to our attention, we have observed asthmatic attacks and other types of allergic reactions, including anaphylactic shock, during or immediately after such meals in patients who were likewise allergic to HDM (14). In some of these patients, we also observed delayed and long-lasting inflammatory reactions at sites where patients had received subcutaneous injections of *D. pt* extracts for specific immunotherapy (14). These observations prompted us to analyze further the origin, cause, and characteristics of potential cross-reacting antigens and the epidemiologic aspects of snail sensitization in HDM-allergic patients. The aims of this study were as follows:

- 1) to assess the *in vivo* reactivity of patients with clinical symptoms after snail ingestion:
 - a) to various extracts from different species of terrestrial snails
 - b) to extracts from a small mite *Riccardoella limacum* (Schränk) which lives on the surface and inside the mantle cavity of these mollusks (15)
- 2) to determine the frequency of snail sensitization and its relationship to HDM sensitization in a population of allergic children who live in a French region (Bordeaux) where eating snails is quite unusual, and who thus would have had no previous digestive contact with snails.

Material and methods

Snail aqueous extracts

Extracts were prepared from four *Helix* species (class Gasteropodae, family Helicidae) bred in the laboratory of the Research Group on snail biology, University of Franche-Comté in Besançon: *H. aspersa aspersa* (small gray snail), *H. aspersa maxima* (large gray snail), *H. lucorum* (Turkish snail), and *H. pomatia* (Burgundy snail). A native crude extract (NE) was prepared from each species. The whole

body of the snail was separated from the spiral shell. The two parts of the whole body, the foot and the visceral mass, were crushed in phosphate-buffered saline (PBS), and the mixtures were centrifuged at 8000 g for 15 min. The raw supernatant (R extract) was divided into two volumes. One volume was heated in a water-bath for 15 min at 100°C (H extract).

Hemolymph was obtained through a direct puncture of the snail heart, and mucus by gentle pressure on the snail. Hemolymph and mucus were also divided into two volumes. One volume was heated in a water-bath for 15 min at 100°C.

Snail-parasite extracts

Specimens of the snail parasite, *R. limacum*, class Arachnidae, family Ereynetidae (15), were collected from snail skin with a paintbrush soaked in absolute ethanol. Their presence was verified with a magnifying glass. The dry extract was diluted in PBS. Extracts were centrifuged in ethanol.

Dermatophagoides extracts

D. pt extracts were purchased from Stallergènes, Fresnes, France. For skin prick tests, *D. pt* extracts were diluted at 1/10 (w/v) in saline.

Patients allergic to snail

The seven patients under study (Table 1) had developed clinical manifestations after eating snails and were known to be allergic to *D. pt*. All of them were positive to prick tests with commercial *D. pt* extract as well as to those performed with a Stallerpoint® lancet (Stallergènes, Fresnes, France) according to the prick+prick technique (16) with commercially preserved *H. pomatia* snails (Romanzini, La Rivière-Druegeon, France). Ten healthy, nonallergic subjects were used as controls. Informed consent was obtained from all patients and controls.

Skin prick tests with various extracts of snail and *R. limacum*

Skin prick tests were performed in duplicate on the volar side of the forearm of seven patients (patients 1–7) with the different raw (R) and heated (H) snail extracts and *R. limacum* extracts prepared as described above. On evaluation at 15–20 min, those skin test sites with a wheal diameter ≥ 3 mm larger than the negative control site and at least 1/2 the diameter of the positive control codeine test were considered positive. Comparison between the results obtained with the different

Table 1. Clinical manifestations of allergy to house-dust mites and to snails in seven patients under study

Patient no.	Clinical manifestations of allergy to house-dust mites	Specific IgE anti-D. pt (*) (kU/l)	Clinical manifestations of allergy to snails
1	Rhinitis/conjunctivitis, spastic cough, dyspnea	11	a) b) Erythema and swelling at injection site of D. pt immunotherapy (arms)
2	Eczema, rhinitis	13	a) Anaphylactic shock, cough, facial edema; b) anaphylactic shock
3	Rhinitis, asthma	12	a) b) Pruritus, asthma, erythema, induration (arms)
4	Rhinitis, asthma	25	a) Pruritus, asthma, induration, erythema, pain and swelling (arms); b) erythema and induration (arms)
5	Rhinitis, asthma	43	a) Asthma, anaphylactic shock
6	Rhinitis, exercise-induced asthma	73	a) b) Facial edema, asthma, urticaria, anaphylactic shock
7	Rhinitis, conjunctivitis	16	a) Malaise, asthma, rhinitis, urticaria; b) rhinitis, urticaria

D. pt (*): *Dermatophagoides pteronyssinus*. a: first clinical manifestation. b: second clinical manifestation.

extracts was done with the nonparametric Mann-Whitney and Wilcoxon tests.

Epidemiologic study

From August 1994 to January 1995 (6 months), a systematic study of snail sensitization was performed in a population of 169 children and adolescents (aged 3–18 years). They were patients from a pediatric allergy outpatient clinic in southwest France, an area where consumption of snails is rare, especially by children. Prick tests were done with a commercial snail extract (CE) (Allerbio®, Varennes-en-Argonne, France) and the native crude extract (NE) of heated *H. aspersa aspersa* and fresh *Buccinum undatum*. Those skin test sites with a neat wheal diameter ≥ 3 mm larger than the negative control site and at least 1/2 the diameter of the positive control codeine test were considered positive. Thirteen children had a labial food challenge using the native snail extract. Informed consent was obtained from the children's parents.

Results

Snail-related symptoms in patients allergic to *D. pteronyssinus* and snails

All seven patients had allergic episodes after consumption of snails. Five patients had asthmatic episodes. In three cases, the reaction was severe, leading to anaphylactic shock. Rhinitis and urticaria were observed in one and two cases, respectively. A local reaction, presenting as erythema with swelling and/or induration and pain, appeared at the site of previous mite immunotherapy injections

in three patients, and recurred after a second ingestion of snails in all three patients.

Prick tests with *R. limacum* and snail extracts in patients with clinical symptoms of snail allergy

In 10 control subjects, the skin prick tests were negative for snail extracts and *R. limacum* extracts.

The results obtained with the different extracts in D. pt- and snail-allergic patients are given in Table 2. In 7/7 allergic patients, the prick tests were negative for *Riccardoella* extracts, while they were positive for at least one of the extracts from snails, whether or not infestation by *R. limacum* had been proven (Table 2). The number of positive skin reactions did not markedly differ whatever the species, snail part, or heating procedure used. However, wheal diameters were significantly higher when *H. pomatia* and *H. lucorum* visceral mass and foot extracts were used than when visceral mass and foot extracts from *H. aspersa aspersa* ($P < 0.03$ and $P < 0.04$) and *H. aspersa maxima* ($P < 0.02$ and $P < 0.01$), respectively, were used. A positive reaction was observed in 4/6 patients tested with pure hemolymph; this result was obtained only with unheated hemolymph. The strongest reactions observed were obtained with *H. aspersa aspersa* and *H. pomatia* hemolymph.

Sensitization to snails in allergic children and adolescents without symptoms of allergy to snails

Among the 169 tested children, 38 had a positive prick test to snail extracts: 28 prick tests were positive to the native heated crude *H. aspersa* extract (73.6%), and 19 to the commercial extract

Table 2. Results of prick tests with snail extracts in seven patients allergic to *D. pteronyssinus* and to snails

Patients	1		2		3		4				5				6				7				
Snail extracts	R		R		R		R		H		R		H		R		H		R		H		
	E	W	E	W	E	W	E	W	E	W	E	W	E	W	E	W	E	W	E	W	E	W	
<i>Haa</i>																							
VM	4	0	0	0	0	0	9	4	7	3	0	0	0	0	4	0	0	0	0	0	0	0	
F	0	0	10	4	0	0	8	3	7	5	0	0	0	0	2	0	0	0	20	4	5	0	
He	ND	ND	0	0	0	0	0	0	ND	ND	10	8	0	0	20	4	0	0	6	5	10	0	
												Pruritus	Pruritus										
<i>Ham</i>																							
VM	3	0	0	0	0	0	0	0	0	0	15	7	0	0	0	0	0	0	10	3	15	7	
F	10	0	0	0	0	0	0	0	14	5	0	0	0	0	0	0	0	0	5	0	0	0	
He	ND	ND	0	0	0	0	0	0	ND	ND	0	0	0	0	0	0	0	0	6	0	0	0	
<i>Hlu</i>																							
VM	10	4	10	0	0	0	0	0	8	3	0	0	12	5	8	3	5	1	9	0	16	6	
F	15	6	12	5	0	0	7	2	12	5	0	0	0	0	5	3	3	2	10	3	5	0	
He	ND	ND	0	0	0	0	0	0	ND	ND	0	0	0	0	20	4	0	0	0	0	0	0	
<i>Hpo</i>																							
VM	3	0	5	0	0	0	10	5	7	3	0	0	15	6	7	5	0	0	6	2	10	6	
F	0	0	8	3	0	0	9	5	7	3	0	0	0	0	12	8	0	0	6	4	10	2	
He	ND	ND	12	4	0	0	ND	ND	ND	ND	0	0	0	0	0	0	0	0	8	5	0	0	
C	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	4	0	
<i>R. limacum</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Haa: *Helix aspersa aspersa*; Ham: *Helix aspersa maxima*; E: erythema (mm); W: wheal (mm); C: control prick tests (with PBS); Hlu: *Helix lucorum*; Hpo: *Helix pomatia*; H: heated; R: raw; VM: visceral mass; F: foot; He: hemolymph; ND: not determined.

(50%) (Table 3). Nine of them also had a positive prick test to *B. undatum* extract. All of them had asthma and six also had food allergies (mustard: three; salmon: one; chicken: one; egg: one; sesame: one; shrimp: one). The better sensitivity of the prick tests performed with the native extract, compared to the commercial extract, confirmed similar observations in other types of food allergy (16). Thirty of the 38 snail-sensitized children (79%) were sensitized to HDM, as confirmed by a positive prick test and/or the presence of serum specific IgE to *D. pt.* Among the 72 patients with no sensitization to *D. pt.*, only eight (10%) were found to be sensitized to snail. However, among those 97 children presenting asthma or rhinitis who were sensitized to *D. pt.*, 30 (31%) were also sensitized to snail. None of the 38 snail-sensitized children of this series had ever eaten snails.

The sensitization to snails was confirmed in 6/13 tested cases by positive labial food challenge (Table 3).

Discussion

Associations between snail, other mollusks, and dust-mite allergies have been described in several

European studies, and cross-reactivity between snail and dust-mite allergens is now confirmed (17). Cross-reactivity may be of clinical significance in atopic patients allergic to *D. pteronyssinus*. Cross-reactivity has been proposed on clinical grounds for various species of terrestrial as well as sea snails (7, 9–14, 17, 18), and its existence has been studied in allergenic extracts from *E. pisana*, *B. brandaris*, *E. vermiculata*, *Helix aperta*, *Cernualla virgata*, and *D. farinae* and/or *D. pteronyssinus* allergens (7, 10, 13, 17). Although tropomyosin was initially suspected, identification of the common allergen has not yet been made. In the group of snail-allergic patients recently studied by van Ree et al., tropomyosin did not play an important role, and the different results indicate that no single allergen is responsible for cross-reactivity between snails and mites (17). Moreover, even if the responsibility of those parasitic mites which live in the lung of snails has been partially ruled out (17), direct evidence of their nonresponsibility has never been produced. Terrestrial snails frequently serve as hosts of a trombidiform mite of the Ereyetidae family, *R. limacum* (Schrack) (15–19), which may share antigens with *D. pteronyssinus*. We were thus interested in a possible *in vivo* reactivity of patients to

Table 3. Main characteristics of 38 children and adolescents sensitized to snails in population of 169 allergic patients

Patient No.	Age (years)	Sex M/F	Prick tests		Dust-mite sensitization	Other allergic sensitizations
			CE (mm)	NE (mm)		
1	10.6	M	0	3	+	
2	15.6	M	4	9	+	
3	9.8	F	0	3	+	
4	8.7	F	0	5	—	
5	10	M	3	3	+	Pollens
6	9	M	1	3	+	Pollens
7	5	M	0	3	+	
8	4	F	0	3	—	
9	8	M	0	3	+	
10	4.8	M	0	3	+	
11	13.8	M	0	8	+	Pollens
12	6.4	M	0	7	+	Pollens
13	18	F	3	0	—	Pollens
14	3	M	0	5	—	Mustard, egg
15	10.6	M	0	3	+	Chicken, fish
16	6.5	F	0	3	—	
17	16.1	M	4	3	—	Pollens, horse
18	7.6	M	4	0	+	Cat
19	4.4	M	3	0	+	
20	4	F	3	0	—	Pollens, cat
21	7.8	M	3	0	—	Pollens, cat
22	6.7	M	1	4	+	Pollens
23	10.2	M	0	3	+	Pollens
24	8.3	M	3	3	+	Pollens, cat
25	6.2	M	3	3	+	Pollens
26	4.3	F	3	0	+	Pollens
27	10	F	0	3	—	
28	8.3	M	0	2	+	
29	11.6	M	3	0	—	Pollens
30	3	M	3	0	+	Pollens
31	13.6	M	3	0	+	Mustard
32	11	M	0	2	+	Pollens
33	16	F	4	5	+	Pollens, cat
34	14.7	M	0	7	+	Pollens, mustard
35	12.6	F	3	11	+	Pollens, cat, shrimp
36	7.11	M	3	2	+	
37	9.2	M	3	4	+	Pollens, sesame
38	5.2	M	0	8	+	

mm: diameter of wheal; ND: not determined; CE: commercial extract; NE: native extract.

Riccardoella extracts. The results we consistently obtained definitely rule out this hypothesis; they confirm that cross-reactivity occurs between *D. pteronyssinus* and the mollusk itself.

The lack of marked differences between the skin reactions obtained with the extracts prepared from different *Helix* species suggests that the shared allergens are not species-specific. Similar results have been obtained by measuring specific IgE, present in patients allergic to snails and dust mite, using extracts from three related species of the Helicidae family. They showed a strong correlation confirmed by weighted regression analysis (17). Cross-reactivity has also been proposed for other

sea mollusks (limpet, abalone, squid) because clinical manifestations after ingestion have been mainly observed in patients with HDM allergy (20–23). The close correlation observed between the RAST for land snails and sea snails in 28 Italian patients allergic to dust mite and snail strongly suggests that a group of allergens is probably shared by snail, limpet, and other mollusks (17). In our study, 4/7 patients with clinical manifestations of allergy to land snail also had symptoms after eating sea mollusks, and 2/7 after eating shrimp. Nine of the 38 children with positive prick test to the land-snail extracts also had a positive prick test to the sea-snail extract.

The clinical relevance of cross-reactivity is strongly suggested by the high prevalence of snail sensitization in our population of children allergic to HDM (30%). In these children, who had never eaten snails before skin testing and did not complain of any allergic reactions to shellfish, snail sensitization is probably due to a primary sensitization to HDM. A similarly high frequency of snail sensitization in children (11, 18) and adults (7) with HDM allergy has been reported for other snail species; our study, however, is the first systematic study of snail sensitization in a population of allergic children. Some reported cases of snail allergy in HDM-allergic patients involved clinical manifestations at the first ingestion of snails (13, 14). Many of these patients had a semidelated inflammatory reaction at the site of previous *D. pteronyssinus* immunotherapy, whether or not associated with other clinical symptoms after eating snails (14). These observations reinforce the hypothesis of a latent presensitization to HDM. The role of mite immunotherapy in the emergence of sensitization and/or clinical manifestations to snail (or mollusks in general) is not clear. Many reported patients had previous subcutaneous immunotherapy (13, 17) (6/7 in our series of patients). A clear increase in IgE reactivity to snail has been recently reported in mite-allergic patients after 1 year of immunotherapy (24). This information must be assessed by prospective epidemiologic studies on larger populations of allergic patients. As mite body components contain relatively more tropomyosin (the presumed shared allergen) than mite excreta, the use of mite excreta-rich extracts has been proposed for immunotherapy in patients with concomitant allergy to Crustacea (25). The relevance of such advice for patients concomitantly sensitized to mollusks and mites must be evaluated.

The identification of cross-reacting allergens has yet to be made, and, as already mentioned, tropomyosin is no longer the only candidate (17). As suggested previously by Mistrello et al., hemocyanin would also be a good candidate (8). Hemocyanin,

the major component of snail hemolymph (90–98% of hemolymph protein content), occurs in two phyla of the invertebrates, the Arthropoda (including both Crustacea and Arachnida) and the Mollusca (26), in which it serves as oxygen-carrier. Four among the six patients who were skin-tested with pure hemolymph obtained by cardiac puncture of the snails had a positive prick test. However, unlike the results obtained with the different extracts, heated or not, that suggest that other potentially allergenic components are thermostable, the positive results obtained with only unheated hemolymph suggest that hemolymph-contained allergens (hemocyanin?) may be inactivated by heat. This could have clinical relevance, since, depending on the type of snail and cooking habits of different countries or regions, snails are eaten either raw or boiled. In France, *H. pomatia* is always eaten after prolonged boiling, and this could preclude any role of such an allergen in the clinical symptoms.

Abnormally increased IgG4 primary as well as secondary responses to keyhole limpet hemocyanin (KLH) have been described in atopic patients (27). This observation has been interpreted as an abnormal isotype regulation, parallel to that observed with IgE, in response to protein antigens in atopic patients. However, as KLH is a hemocyanin from the inedible Pacific mollusk *Megathura crenulata*, a hidden sensitization through HDM in some of the patients under study cannot be ruled out. Cross-reaction between KLH and antigens from an unrelated species, *Schistosoma mansoni*, has already been described (28). It should be noted that the cross-reacting antigen belongs to the “protective” antigens that have been shown to elicit the immune response involved in resistance to the parasite in human schistosomiasis (28). Besides the effect it would have clinically, a further analysis of the exact nature of snail-mite cross-reactivity may also give additional insight into the still puzzling relationship between undesirable allergic reactions and useful IgE-dependent immune responses in parasitic diseases.

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