Immediate Hypersensitivity to Mealworm and Cricket: Beyond Shrimp and House Dust Mite Cross-Reactivity

Mankouri F[1], Sereme Y[2,3], Michel M[2,3], Piarroux R[4], Pahus L[1,5,6], Chanez P[1,6], Vitte J[2,3], Gouitaa M[1]

[1]*Aix Marseille University, APHM, Clinique des bronches allergies et sommeil, Marseille, France*

[2]*Aix-Marseille University, IRD, APHM, MEPHI, Marseille, France*

[3]*IHU Méditerranée Infection, Marseille, France*

[4]*LDBio Diagnostics, Lyon, France*

[5]*Aix Marseille University, CNRS, EFS, ADES - Marseille, France*

[6]*Aix Marseille University, INSERM U1263, INRA 1260 (C2VN), Marseille, France*

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Entomophagy, that is, consumption of insects by humans, is a common practice in parts of Asia, Africa, and South America. Less common in Western countries, this diet could become more widespread in the years to come, especially in view of the nutritious properties of insects. Although cross-reactions between insects, shrimps, and mites have been described [1,2], the potential for allergic reactions linked to the consumption of edible insects is still poorly understood.

We report the case of a 47-year-old man who experienced anaphylaxis the first time he ate crickets (*Acheta domestica*) and mealworm (*Tenebrio molitor*). His history was remarkable only for anaphylactic reactions at age 20 and 24 years following consumption of crab, mussels, and ground snails. These reactions manifested as hives, digestive disorders, and breathing difficulties, thus leading him to exclude all crustaceans, mollusks, and gastropods from his diet. More recently, the patient consumed a teaspoonful of cricket and mealworm (approximatively 5 g) for the first time. In less than 30 minutes, he developed nausea, erythema on the neck, cough, and difficulty breathing. He was treated with antihistamines, corticosteroids, and epinephrine, followed by hospitalization for 24 hours. No cofactors such as alcohol, nonsteroidal anti-inflammatory drugs, or exercise were reported by the patient.

Skin prick test (SPT) results were positive to native cricket, mealworm, crab, mussel, and snail, thus reinforcing the hypothesis that the reactions were IgE-mediated (Supplementary Data). SPT results were positive for shrimp despite the absence of a clinical reaction and negative for house dust mite (HDM). Serum IgE was positive to shrimp extract, but undetectable for Pen a 1 tropomyosin and HDM. The ISAC allergen microarray revealed no sensitization to the shrimp allergens Pen m 1 (tropomyosin), Pen m 2 (arginine

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kinase), or Pen m 4 (sarcoplasmic calcium binding protein). In addition, no IgE to HDM, cockroach, or *Anisakis simplex* allergens was detected with ISAC (Table E1).

Cross-reactivity was further investigated using the basophil activation test with in-house or commercial cricket, mealworm, shrimp, and snail extracts (Supplementary Data). All but shrimp extract induced basophil activation (Table E1). In this context, an open oral food challenge test was negative up to 100 g of shrimp, confirming that the allergen responsible for anaphylaxis was absent from shrimp muscle. Taken together, the findings pointed to an anaphylactic reaction upon the first consumption of insects. This could be explained by cross-reactivity between crickets, mealworm, mussel, crab, and snail, with no involvement of shrimp or HDM. In addition, the culprit allergen did not appear to be tropomyosin, arginine kinase, or the sarcoplasmic calcium-binding protein of crustaceans.

In order to better characterize the patient's sensitization profile, IgE Western blot (WB) analysis was performed (Supplementary Data). Sera from 2 patients who were allergic to shrimp and sensitized to Pen a 1 were used as controls (controls 1 and 2). Both displayed IgE to crab, mussel, snail, and mealworm extracts, probably associated with sensitization to the panallergen tropomyosin (Supplementary Data). Interestingly, although the controls' IgE bound to several protein bands ranging from 25 kDa up to 150 kDa, their WB profiles were different (Figure). The index patient's IgE bound strongly to a protein band of around 60 kDa in the cricket extract. Similar, albeit less intense, binding was also present at 60 kDa in the mealworm, mussel, and snail extracts, but completely absent from the shrimp extract. This profile differed from that of controls, who mainly exhibited IgE reactivity to proteins between 35 kDa and 40 kDa in all extracts. These bands could correspond to tropomyosin or arginine kinases. We hypothesize that an allergen of around 60 kDa might be involved in these reactions between crickets, mealworm, mussels, and snails. However, the presence of this allergen in the shell or hepatopancreas of shrimp cannot be eliminated. Allergens of around 60 kDa have been identified in mealworm. In the present case, the allergen involved in cross-reactivity might be a catalase [2] or an ATP synthase subunit α [3].

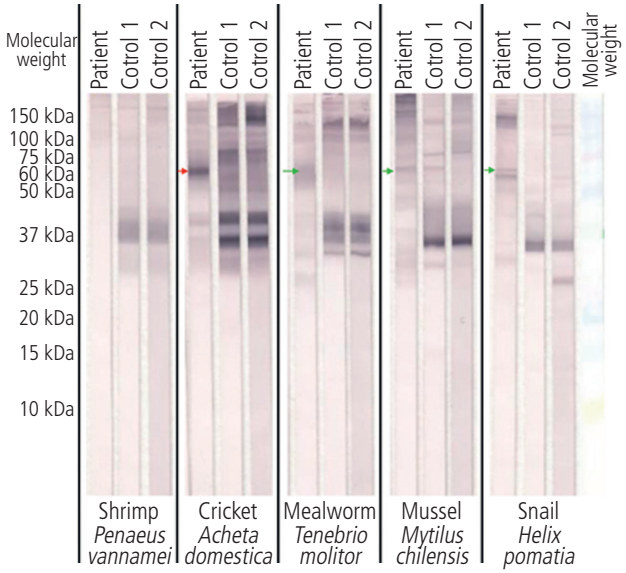

Figure. IgE Western blot of the patient and 2 controls. Patient and control IgE bound to several protein bands ranging from 25 kDa up to 150 kDa, with 2 different fixation profiles. The index patient's IgE bound strongly to a protein band around 60 kDa in the cricket extract (red arrow). Similar binding, although of lower intensity, was also present at 60 kDa in the mealworm, mussel, and snail extracts (green arrow), but completely absent from the shrimp extract. The controls' serum mainly exhibited IgE reactivity to proteins between 35 and 40 kDa in all extracts. These could correspond to tropomyosin or arginine kinases in controls sensitized to Pen a 1. However, the index patient's IgE also bound to other bands between 50 and 150 kDa. These bands could also be involved in cross-reactivity between cricket, mealworm, mussel, and snail.

Food allergy to insects can be classified as primary allergy and cross-allergy [4]. Cross-allergy is thought to be due to the presence of allergens that are homologous between different invertebrates, thus accounting for the reactions to the first intake of insects. Interestingly, various allergens might be involved, depending on whether the allergy to edible insects is primary or not. Indeed, Broekman et al [4] suggested that the larva cuticle protein could be a major allergen in primary allergy to mealworm. The cockroach allergen–like protein could also be important in this context [5]. However, in patients with cross-allergy to mealworm, tropomyosin and arginine kinase appear to be the most frequently involved allergens [1]. Other allergens, such as actin, troponin T–like protein, or the myosin-like light chain, are also identified as being at risk of cross-reactivity between crustaceans and mealworm [2].

Identifying the risks of cross-reactivity within invertebrates according to the allergens involved remains complex. Broekman et al [6] found that certain allergens seem to be shared only by some insects such as the larva cuticle protein found in only 3 edible insects out of 7 tested. Conversely, cross-reactivity may not occur between all members of a biochemical family, eg, the arginine kinases of *Acheta domestica* and *Tenebrio molitor* [7]. Finally, some allergens may be present only in certain parts of the invertebrate, such as the hemocyanin identified in the hepatopancreas of *Macrobrachium rosenbergii* (giant freshwater prawn) and absent from the muscle [8]. These elements underscore the complexity of cross-reactivity within invertebrates.

Our findings show that specific cross-reactivities between cricket, mealworm, snail, and mussel can occur without cross-reactivity to shrimp or HDM. This finding paves the way for more precise characterization of the risks of allergy associated with entomophagy. Indeed, the study of patients allergic to invertebrates other than shrimp could lead to the characterization of new cross-reactive allergens. Personalized exclusion advice should therefore be given to patients with allergies to mollusks, gastropods, and arthropods who wish to consume insects.

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Conflicts of Interest

Joana Vitte reports personal fees from Thermo Fisher Scientific, Meda Pharma (Mylan), Beckman Coulter, and Sanofi outside the submitted work.

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Raphael Piarroux is currently employed by ldbio diagnostics.

The remaining authors declare that they have no conflict of interests.

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Marion GOUITAA
APHM, Hôpital NORD
Cliniques des bronches, allergies et sommeil
Chemin des Bourrely
13015 Marseille
E-mail: marion.gouitaa@ap-hm.fr

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