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

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Entomophagy, i.e. 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 are still poorly understood.

We report the case of a 47-year-old man who presented anaphylaxis after the first consumption of crickets (*Acheta domestica*) and mealworm (*Tenebrio molitor*). This patient reported as the only history, anaphylactic reactions occurring at the age of 20 and 24 years following consumption of crab, mussels and ground snails. These reactions manifested as hives, digestive disorders and breathing difficulties which led to spontaneously practicing an enlarged exclusion of all crustaceans, mollusks and gasteropods. More recently, the patient consumed for the first time a teaspoonful of cricket and mealworm (approximatively 5 g). In less than 30 min, he developed nausea, erythema of the neck, cough and difficulty of breathing, requiring the use of antihistamines, corticosteroids and epinephrine followed by a 24-hour hospitalization. No co-factors, such as alcohol, NSAIDs, or exercise were reported by the patient.

Allergy workup evidenced positive skin prick test (SPT) to native cricket, mealworm, crab, mussel and snail, reinforcing the hypothesis that the reactions presented by the patient were IgE mediated (supplementary data). SPT were positive for shrimp despite the absence of any clinical reaction and negative for house dust mites (HDM). Serum IgE were positive to

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shrimp extract, but undetectable to Pen a 1 tropomyosin and HDM. No sensitization to shrimp allergens Pen m 1 (tropomyosin), Pen m 2 (arginine kinase) or Pen m 4 (sarcoplasmic calcium binding protein) was found with the ISAC® allergen microarray. In addition, no IgE(s) toHDM, cockroaches or *Anisakis simplex* allergens wasdetectedwith ISAC® (Table E1).

Cross-reactivity was further investigated with basophil activation tests (BAT) carried out using in-house or commercial cricket, mealworm, shrimp and snail extracts (supplementary data). All but shrimp extract induced basophil activation (TableE1). In this context, an open oral food challenge test was carried out and was negative up to 100g of shrimp, confirming that the allergen responsible for the anaphylaxis in the patient was absent from the shrimp muscle. Taken together, the investigations suggested that the occurrence of an anaphylactic reaction upon the first consumption of insect was explained by cross allergy between crickets, mealworm, mussel, crab and snail without involvement of shrimp or HDM. In addition, the culprit allergen did not appear to be either tropomyosin, arginine kinase or the sarcoplasmic calcium binding protein of crustaceans.

In order to better characterize the patient's sensitization profile, IgE Western blots (WB) were performed (supplementary data). Sera from two patients allergic to shrimp and sensitized to Pen a 1 were used as controls (controls 1 and 2). These two controls displayed IgE to crab, mussel, snail and mealworm extracts, probably related to sensitization to the panallergenic tropomyosin (supplementary data). Interestingly, although these controls' IgE bound to several protein bands ranging from 25 kDa up to 150 kDa, their WB profiles were different (FIG. 1). The index patient's IgE strongly bound to a protein band around 60 kDain the cricket extract. Similar binding, although of less intensity, was also present at 60 kDa in the mealworm, mussel and snail extracts, but completely absent for the shrimp extract. This profile was different from controls which mainly exhibited IgE reactivity to proteins between 35 and 40 kDa in all extracts. These bands could correspond to tropomyosin or arginine

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kinases. We hypothesize than an allergen of around 60 kDa might be involved in these specific reactions between crickets, mealworm, mussels and snails. However, the presence of this allergen in the shell or hepatopancreas of shrimp cannot be eliminated. Some allergens around 60 kDa has been identified in mealworm. In the case of our patient, the allergen involved of this cross reactivity might be a catalase[2] or an ATP synthase subunit alpha[3].

Food allergies to insects can be distinguished into primary allergy and cross allergy[4]. Cross allergies are thought to be due to the presence of allergens homologous between different invertebrates and can explain the reactions to the first consumption of insects. Interestingly, different allergens might be involved depending on whether the allergy to edible insects is primary or not. Indeed, Broekman and his team suggested that the Larva Cuticle Protein (LCP) could be a major allergen in the case of primary allergy to mealworms[4]. The cockroach allergen-like protein could also be important in this context[5,6]. However, in patients with cross allergies to mealworms, 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. Certain allergens seem to be shared only by some insects such as the LCP found only in 3 edible insects out of 7 tested in a study[7]. Conversely, cross-reactivity may not occur between all members of a biochemical family, e.g. the arginine kinases of *Acheta domestica* and *Tenebrio molitor*[8]. Finally, some allergens may be present only in certain parts of the invertebrate, such as the hemocyanin identified in the hepatopancreas of the shrimp and absent from the muscle usually consumed[9]. These elements underscore the complexity of cross-reactivity within invertebrates.

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Through this case, we highlight that specific cross-reactivities between cricket, mealworm, snail and mussel can occur without cross reactivity to shrimp or HDM. This opens up perspectives in the more precise characterization of allergy risks 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 delivered to patients with allergies to mollusks and gastropods in addition to arthropods, in the current context of entomophagy development.

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Conflict of interests

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

Raphael Piarroux is currently employed by ldbio diagnostics.

The remaining authors have no conflict of interests to declare.

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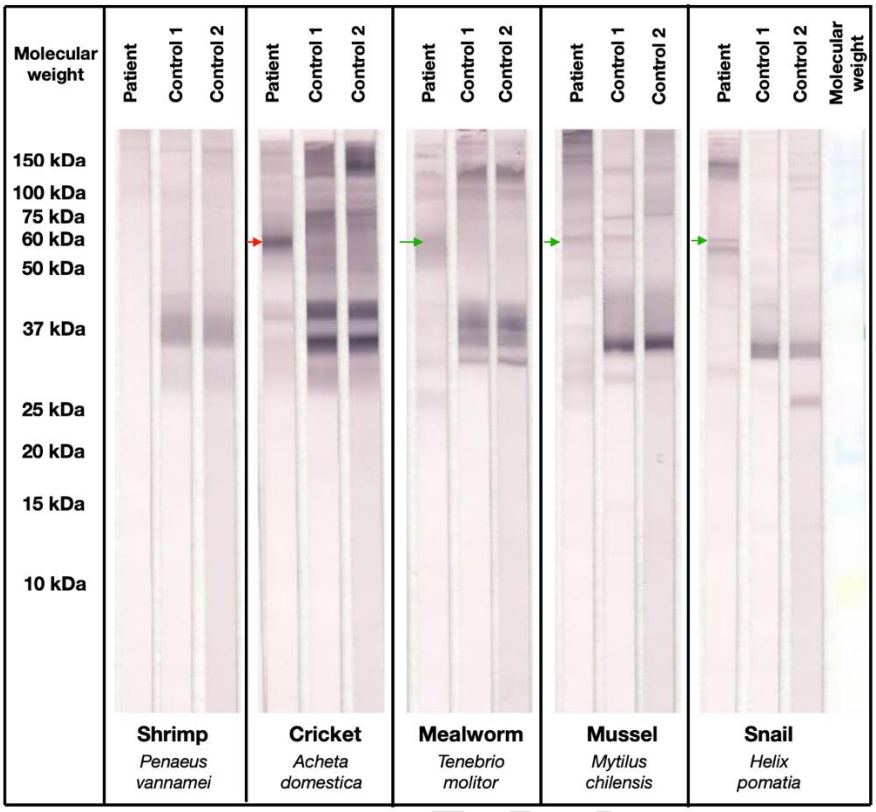
Figure legend

Figure 1: IgE Western Blot of the patient and two controls.



Patient and controls show IgE bound to several protein bands ranging from 25 kDa up to 150 kDa with two different profiles of fixation.
The index patient's IgE strongly bound 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 for the shrimp extract.
The control's serum mainly exhibited IgE reactivity to proteins between 35 and 40 kDa in all extracts who could correspond to tropomyosin or arginine kinases in these controls sensitized to Pen a 1.
However, the index patient's IgE bound also to other bands between 50 and 150 kDa. These other bands could also be involved in cross reactivity between cricket, mealworm, mussel and snail.

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