



Shrimp-Induced Anaphylaxis

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Abstract

Purpose of Review Shrimp and other crustaceans and molluscs are one of the most frequent causes of food allergy and anaphylaxis at all ages. Molecular biology has paved the way to a better understanding of the allergen profile of invertebrates that is much more complex than thought only one decade ago.

Recent Findings While tropomyosin has been traditionally considered as the dominating major allergen in crustaceans and other invertebrates, recent research demonstrated that IgE to this allergen can be detected in about 50% of shrimp-allergic patients only. Many of these allergens are conserved ones and, hence, potentially cross-reacting across different invertebrates, including house dust mites. Patients not sensitized to tropomyosin frequently experience anaphylactic reactions, suggesting that also the so-called *minor allergens* may have an extreme clinical relevance.

Summary This review focuses on the clinical features of shrimp allergy and highlights the recent findings on shrimp allergens. The use of epinephrine, which remains a cornerstone of the treatment of anaphylaxis, is reviewed as well.

Introduction

Anaphylaxis is an acute, dramatic clinical event characterized by the abrupt onset of an illness involving the skin, mucosal tissue, or both associated with either

respiratory compromise, reduced blood pressure and associated symptoms of end-organ dysfunction (collapse, syncope, incontinence), or persistent

gastrointestinal symptoms [1]. Food allergy represents one of the most frequent causes of anaphylaxis worldwide [2–4], and food-induced anaphylaxis is responsible for hundreds of fatalities every year [4]. Crustaceans and shellfish rank among the main offending foods virtually in all countries where anaphylaxis recordings exist, including the USA [5, 6], the Far East [7], and Australia [8]. In Italy, crustaceans represent the second cause of primary food allergy [9] and the second cause of food-induced anaphylaxis [10] after the plant food panallergen LTP, the nonspecific lipid transfer protein. This observation is confirmed by epidemiologic studies carried out in different geographical areas [6, 11]. Further, Spanish epidemiologic studies suggest that shellfish allergy is on the rise [12]. A very recent analysis on a continental basis found that shrimp allergy is also frequent in the European pediatric population, particularly in the Mediterranean area [13].

However, the discrepancy between self-reported allergy and real allergy cannot be underrated. In a meta-analysis of food allergy in Europe, the self-reported prevalence of shellfish allergy was 1.3% but the real prevalence dropped to 0.1% following food challenge [14]. Similarly, a systematic review carried out in extra European countries showed that the prevalence of self-reported allergy to crustaceans ranged between 0.1 and 5.5% with an IgE positivity ranging from 0 to 10.3%. However, when food challenge was used for an estimate, the prevalence fell to 0 to 0.9% for crustaceans [15]. This shows that a diagnosis cannot be based on patients' perceptions or IgE reactivity only. When the clinical history is not correlated to IgE reactivity and the anaphylactic episode is not reported by an Emergency Department visit, the oral food challenge represents the only "gold standard" for the diagnosis of shellfish allergy.

The recent developments in molecular biology have clearly shown that crustaceans represent one of the most complex allergen sources [16, 17]. No less than 15 allergens, eight of which are currently registered in the WHO/IUIS database, have been detected so far, and other invertebrates, including house dust mites, share many of these allergens, which thus represent potential respiratory and food pan-allergens [17•]. Nonetheless, the allergen list of crustaceans is far from being complete [18].

As for many other food sources, the clinical effects of crustaceans ingestion by sensitized individuals show large variability, ranging from the total absence of symptoms to an array of immediate reactions including cutaneous symptoms, oral allergy syndrome, digestive complaints, asthma, rhinitis, exercise-induced asthma, exercise-induced anaphylaxis, and anaphylaxis [19, 20]. The clinical expression of sensitization is largely dependent on the level of specific IgE to tropomyosin [21–23] although also other allergens such as sarcoplasmic calcium-binding protein seem to play a role [24]. Another factor influencing the clinical expression of shrimp allergy is the amplitude of epitope recognition by patients' specific IgE [24]. Of course, the physical and chemical characteristics of the allergen protein(s) play a relevant role also; for instance, some shrimp allergens appear heat-labile and may induce severe respiratory symptoms when the patient inhales them in an aerosolized form while shrimps are cooking, whereas the shrimp is tolerated without any problem once cooked [25].

Table 1 reports the crustaceans allergens identified up to now [26, 27], and a phylogenetic tree showing the relationships among various allergenic crustaceans, molluscs, and invertebrates is shown in Fig. 1.

Clinical Studies of Shrimp-Induced Anaphylaxis

Several multicenter studies of food allergy have been carried out in Italy during the last decade or so. In one study [9], 13% of about 500 patients with primary food allergy were allergic to shrimp, 90% of them having a history of systemic reactions following the ingestion of crustaceans. Ten of these, corresponding to 15% of the total shrimp-allergic population, experienced a shrimp-induced anaphylactic reaction [10]. Such proportion is in line with that observed in other countries [12, 16] and was confirmed in a subsequent multicenter study, where 15/116 (13%) shrimp-allergic patients had a clear-cut history of anaphylaxis [28]. Interestingly, more than half of those who experienced a shrimp-

Table 1. Updated list of crustaceans allergens

Name	Species	Allergen	MW	Biochemical name	Heat stability
Brown shrimp	<i>Penaeus aztecum</i>	Pen a 1	36	Tropomyosin	Yes
Black tiger shrimp	<i>Penaeus monodon</i>	Pen m 1	38		
Shrimp	<i>Penaeus indicus</i>	Pen i 1	34		
White shrimp	<i>Litopenaeus vannamei</i>	Lit v 1	36		
Giant freshwater prawn	<i>Macrobrachium rosenbergii</i>	Mac r 1	37		
King prawn	<i>Melicerus laticulatus</i>	Mel l 1	38		
American lobster	<i>Homarus americanus</i>	Hom a 1	38		
North sea shrimp	<i>Crangon crangon</i>	Cra c 1	38		
Shrimp	<i>Metapenaeus ensis</i>	Met e 1	34		
Northern shrimp	<i>Pandalus borealis</i>	Pan b 1	37		
Red swamp crayfish	<i>Procambarus clarkii</i>	Pro c 1	36		
Crab	<i>Charybdis feriatus</i>	Cha f 1	34		
Spiny lobster	<i>Panulirus simpsonite</i>	Pan s 1	34		
North sea shrimp	<i>Crangon crangon</i>	Cra c 2	45	Arginine kinase	Yes
White shrimp	<i>Litopenaeus vannamei</i>	Lit v 2	40		
Black tiger shrimp	<i>Penaeus monodon</i>	Pen m 2	40		
Red swamp crayfish	<i>Procambarus clarkii</i>	Pro c 2	40		
Mud Crab	<i>Scylla paramamosain</i>	Scy p 2	40		
White shrimp	<i>Litopenaeus vannamei</i>	Lit v 3	20	Myosin light chain 2	Yes
Black tiger shrimp	<i>Penaeus monodon</i>	Pen m 3	20		
North sea shrimp	<i>Crangon crangon</i>	Cra c 5	17.5		
American lobster	<i>Homarus americanus</i>	Hom a 3	23		
Red swamp crayfish	<i>Procambarus clarkii</i>	Pro c 5	18	Myosin light chain 1	Yes
White shrimp	<i>Litopenaeus vannamei</i>	Lit v 4	20		
Black tiger shrimp	<i>Penaeus monodon</i>	Pen m 4	20	Sarcoplasmic calcium-binding protein	Yes
North sea shrimp	<i>Crangon crangon</i>	Cra c 4	25		
Crayfish	<i>Pontastacus leptodactylus</i>	Pon l 4	24		
Mud Crab	<i>Scylla paramamosain</i>	Scy p 4	20		
Black tiger shrimp	<i>Penaeus monodon</i>	Pen m 6	16.8	Troponin C	Yes
North sea shrimp	<i>Crangon crangon</i>	Cra c 6	21		
American lobster	<i>Homarus americanus</i>	Hom a 6	20		
Narrow-clawed crayfish	<i>Pontastacus leptodactylus</i>	Pon l 7		Troponin I	Yes
Crayfish	<i>Archaeopotamobius siberiensis</i>	Arc s 8	28		
North sea shrimp	<i>Crangon crangon</i>	Cra c 8	28	Triose-phosphate isomerase	No
Mud Crab	<i>Scylla paramamosain</i>	Scy p 8	28		
Red swamp crayfish	<i>Procambarus clarkii</i>	Pro c 8	28		

Table 1. (Continued)

Name	Species	Allergen	MW	Biochemical name	Heat stability
Giant freshwater shrimp	<i>Macrobrachium rosenbergii</i>	Mac r 2	72–75	Hemocyanin	Yes

Other allergens	MW	Other allergens	MW
Tritin	70	α -Actin	31–42
Fructose 1,6 biphosphate aldolase	39–48	Smooth endoplasmic reticulum Ca^{++} ATPase (SERCA)	113
Paramyosin	100	Glyceraldeide phosphate dehydrogenase (GDPH)	37
Myosin heavy chain	225	Ubiquitine	8.5

induced anaphylactic episode (8/15) did not show any IgE reactivity against the major shrimp allergen tropomyosin (Pen a 1). In these patients, the immunoblot analysis showed IgE reactivity to a large array of shrimp allergens suggesting that several allergens other than tropomyosin may be potent enough to induce life-threatening reactions upon ingestion [28].

Further, a novel syndrome -called “Fish-shrimp-meat syndrome” exists, where the similarity between chicken Myosin Light Chain and the homologous allergens from various fish species and crustaceans justifies the clinical association of poultry meat allergy with fish and crustaceans allergy [29].

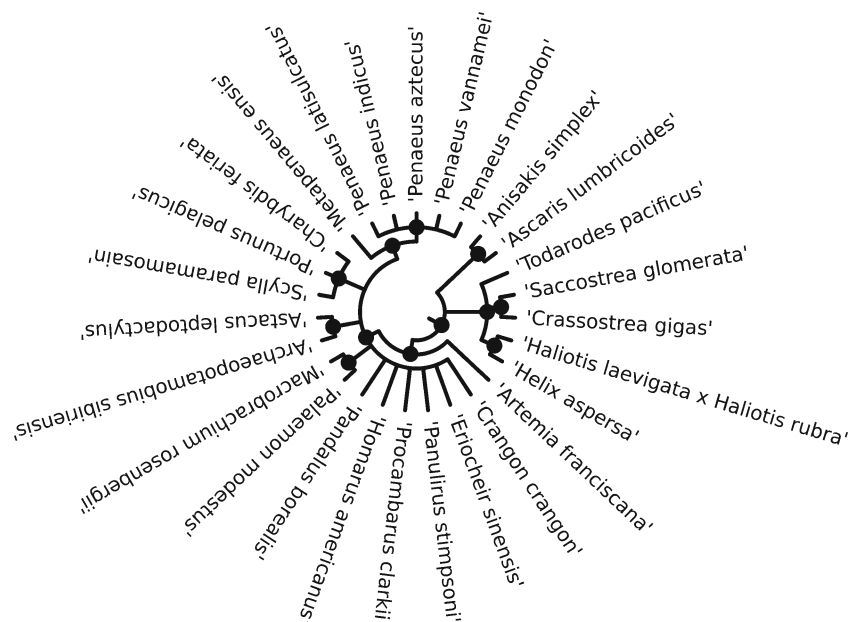


Fig. 1. Phylogenetic tree showing the relationships among shrimp, other crustaceans, and molluscs sources containing the molecules identified as allergens to date

Threshold Dose in Shrimp-Allergic Patients

Although anecdotal data of patients reacting to traces of shrimp suggest an elevated level of reactivity in allergic patients, in a study where adult shrimp-allergic patients underwent DBPCFC with cooked shrimp doses, doses almost 100-fold greater than those of the other foods studied were needed to induce significant objective symptoms [30]. Very recently, Remington and coworkers showed that the eliciting doses (ED) required to predict an allergic reaction in 1% (ED01) and 5% (ED05) of the shrimp-allergic population were 26.2 mg and 280 mg, respectively [31]. This might suggest that the traces of cooked shrimp that might be found in some manufactured food products should pose much less of a risk to allergic subjects than the equivalent for foods such as peanut, hazelnut, celeriac, and fish for whom the ED01 and ED05 are by far lower [31].

Management and Treatment

The patient with a history of shrimp-induced anaphylaxis should be always investigated for IgE cross-reactivity to other invertebrates, such as cephalopods and molluscs [32]. This is because, although many shrimp allergens show a high level of cross-reactivity, crustacean-allergic patients are not necessarily sensitized to other invertebrates [33, 34]. Of course, the foods scoring frankly positive on SPT or on specific IgE measurements where these are available should be excluded from the patient's diet due to the risk of allergic reactions. Most allergens in invertebrates appear heat- and pepsin-stable (see Table 1). Shrimp-induced allergic reactions have been recorded in subjects that had never eaten shrimps before due to cross-reactivity with house dust mite and cockroach allergens [35]. This might pose a question whether house dust mite allergic patients should be investigated for shrimp hypersensitivity regularly to identify those at risk of food allergy [36]. In effect, the unexpected finding of shrimp sensitization is all but rare in mite allergic subjects.

However, the diagnosis of shrimp allergy remains in some cases difficult. Indeed, the commercial extracts for skin prick test are largely unsatisfactory [37], and only a few allergens are available for the component-resolved diagnosis (tropomyosin for monoplex assays; tropomyosin, arginine kinase, sarcoplasmic Ca^{++} BP, and more recently myosin light chain 1 and Troponin C for multiplex assays). For these reasons, prick by prick test with fresh shrimp remains the most sensitive diagnostic assay, although in many cases double-blind, placebo-controlled food challenge may become mandatory to achieve a correct diagnosis.

As for all other primary food allergies, shrimp allergy management relies mainly on avoidance. Although the labelling of foods containing seafood proteins has become mandatory in many countries (e.g., Europe, USA, and Japan), the risk for accidental cross-contamination is always present, particularly when the meals are consumed in public places such as restaurants.

The treatment of shrimp-induced anaphylaxis follows the same rules as for all other types of food-induced anaphylaxis. Systemic anaphylaxis is the most dramatic clinical manifestation of an acute allergic reaction to shrimp. Rapid recognition and treatment often only with minimal anamnestic data can be life-saving. Even mild itching, urticaria, or oedema of the lips can rapidly worsen towards complete airway obstruction with hypotension and, therefore, deserve an aggressive treatment. Perioral angioedema can rapidly involve oropharynx and require intervention. Many fatal reactions begin with modest symptoms, which rapidly progress towards cardiovascular collapse. It is therefore essential to start the treatment as early as possible. A written emergency protocol for recognition and treatment of anaphylaxis to be verified regularly is essential. Patients should be placed in the supine position, with the legs raised, to minimize the hypotensive state and the abrupt reduction of venous return.

There are plenty of guidelines highlighting the importance of epinephrine in the treatment of anaphylactic reactions [37]. Epinephrine has to be injected intramuscularly in the central area of the vast lateral muscle of the thigh at a dose of 0.01 mg/kg of a 1:1000 solution (1 mg/mL) up to a maximum of 0.3 mg in children (0.5 in adults). The dose can be repeated after 5–15 min, if necessary. Most patients respond after 1 or 2 doses. Oxygen therapy is indicated at high flows (6–8 L/min), and venous access, using needles or catheters with the largest possible diameter, should be prepared. At any time, one must be ready to start cardio-pulmonary resuscitation. Blood pressure, heart frequency and heart functionality, respiratory function, and oxygenation should be checked at regular intervals.

Patients knowing to be allergic to crustaceans should always carry one or two ampoules of epinephrine autoinjectors to be used as soon as one is aware of accidental ingestion of the offending food. In case of inadvertent ingestion of shrimp or molluscs, the self-administration of epinephrine should be followed as soon as possible by a visit at the ER to exclude and treat properly possible prolonged or delayed adverse reactions. Although epinephrine is the first-line treatment, tablets of corticosteroid and antihistamines can be taken by the patient although their indication in anaphylaxis is less clear [38–40].

Patients with systemic anaphylaxis on chronic treatment with beta-blockers present peculiar problems. In these cases, there can be resistance to normal therapeutic regimens. Beta-blockers can induce marked hypotension and bradycardia. Hypotension may be refractory; tachycardia replaced by bradycardia and biphasic or late reactions are common. In these cases, atropine (0.3–0.5 mg every 10 min up to 2 mg) is useful for increasing the heart rate. The amount of fluids required to restore blood volume is much higher in patients in treatment with β -blockers, up to 5–7 L. For the above reasons, patients treated with β -blockers, even with mild anaphylactic shock, should be transferred to the intensive care unit as soon as possible until clinical stabilization. The observation period of a patient with anaphylactic shock cannot be established a priori. Bearing in mind the possibility of a biphasic and protracted course of anaphylaxis, asymptomatic periods of 1–8 h may occur followed by a relapse of symptoms. Patients on β -blocker therapy, those who have ingested antigens that continue to be absorbed for hours or those with late symptoms after exposure, are at risk of recurrent symptoms and should, therefore, be hospitalized. The best predictive indicator of a prolonged or severe reaction is a significant early reaction, with respiratory or cardiovascular impairment.

Conclusions

Crustaceans are one of the most complex allergen sources. Much expertise is required to diagnose properly sensitization and allergy to these foods, particularly in view of the high stability of their allergenic proteins, their broad potential cross-reactivity, and the fact that they are a main cause of anaphylaxis worldwide.

Compliance with Ethical Standards

Conflict of Interest

Riccardo Asero declares that he has no conflict of interest.

Valerio Pravettoni declares that he has no conflict of interest.

Enrico Scala declares that he has no conflict of interest.

Danilo Villalta declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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