REVIEWS

Shellfish Allergy: Unmet Needs in Diagnosis and Treatment

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Abstract

Seafood is a major cause of food allergy and anaphylaxis worldwide. Shellfish is included among the "big eight" food groups, which are responsible for more than 90% of all cases of food allergy. Approximately 2.5% of the world's population has experienced an adverse reaction to seafood. Seafood allergy is one of the most frequent and lethal allergies that exist.
The several allergenic proteins involved in allergic reactions that have been described in recent years include tropomyosin, arginine kinase, myosin light chain, and sarcoplasmic calcium-binding protein. Despite all the data reported in the last few years, shellfish allergy is still diagnosed and treated as it was 50 years ago. The only effective treatment to prevent allergic reactions to shellfish is avoidance.
This review aims to update recently published data on shellfish allergy and to highlight those areas that have yet to be resolved.

Key words: Shellfish. Shrimp. Allergy. Allergens. Diagnosis. Food allergy.

Resumen

La alergia al marisco es una causa importante de alergia alimentaria y anafilaxia en todo el mundo. Los mariscos se incluyen entre los "ocho grandes" grupos de alimentos, responsables de más del 90% de todos los casos de alergia alimentaria. Aproximadamente el 2,5% de la población mundial ha experimentado alguna reacción adversa a los mariscos. La alergia al marisco es una de las alergias más frecuentes y letales que existen.
Se han descrito varias proteínas alergénicas involucradas en las reacciones alérgicas en los últimos años: tropomiosina, arginina quinasa, cadena ligera de la miosina, proteína de unión a calcio, entre otras. A pesar de la información obtenida en los últimos años, la alergia a los mariscos todavía se diagnostica y trata como hace 50 años. Actualmente, el único tratamiento efectivo para prevenir reacciones alérgicas a los mariscos es la evitación.
Esta revisión tiene como objetivo recoger todas las actualizaciones realizadas en las publicaciones de los últimos años y resaltar las cuestiones pendientes de resolver.

Palabras clave: Marisco. Gamba. Alergia. Alérgenos. Diagnóstico. Alergia a alimentos.

1. Introduction

Seafood is a major cause of food allergy and anaphylaxis worldwide. The terms seafood and shellfish are often used interchangeably, yet their meaning is different. Seafood refers to several distinct groups of edible aquatic animals including fish, crustaceans, and mollusks, whereas shellfish refers only to crustaceans and mollusks.

Shellfish is one of the "big eight" food groups that are responsible for more than 90% of all cases of food allergy. Approximately 2.5% of the world's population has experienced an adverse reaction to seafood [1]. The prevalence of shellfish allergy varies from 0% to 10.3% depending on the geographical area studied and is generally higher in regions where seafood is frequently consumed [2,3].

In Spain, shellfish is the third cause of food allergy in adults, behind fruit and nuts [4]. In children, the prevalence is lower than in adults.

Shellfish is defined as any edible marine invertebrate. Crustaceans belong to the phylum Arthropoda and are taxonomically classified alongside insects and arachnids [5]. The phylum includes prawn, crab, and lobster species, all of which may contain species-specific as well as common allergenic proteins, which are known as pan-allergens. These molecules have a high sequence homology, which favors cross-reactivity with other crustaceans and between crustaceans and other arthropods such as dust mites or cockroaches.

Mollusks belong to the phylum Mollusca [5] and are divided into bivalves (clams, scallops, cockles, mussels, oysters), gastropods (snail, abalone, limpet), and cephalopods (squid, octopus). The probability of cross-reactivity between these mollusks is not well established, and few proteins seem to be shared by crustaceans and mollusks. The shared proteins that have been described have a low amino acid sequence homology and are therefore less likely to cross-react.

For many years, tropomyosin has been thought to be the most important allergen in shellfish. However, in the last 15 years, several studies have shown the complexity and the variability of the allergenic composition of this food group. Today, there is clear evidence that several proteins are involved in the allergenicity and cross-reactivity of shellfish.

Within the shellfish family, the better studied group are the crustaceans. Most studies have been conducted with shrimp.

2. Shellfish Allergens

Shellfish allergens comprise a large and increasingly growing list of allergens that covers various species. The most important are presented in Table 1.

2.1. Tropomyosin

A 38-kDa thermostable protein identified in 1981 seemed to be responsible for shrimp allergy [6]. In the following years, several authors reported that patients with symptoms of immediate hypersensitivity after ingesting prawns had a positive skin prick test (SPT) result and circulating specific IgE to crustaceans [7,8]. Tropomyosin, the first allergen described in seafood, was identified in *Penaeus indicus* (Pen i 1), commonly known as Indian white prawn, in 1993 [9]. This pan-allergen is involved in invertebrate muscle contraction [10] and is considered one of the most important pan-allergens within allergens of animal origin [11]. Tropomyosin has been described in numerous invertebrate species; in addition to crustaceans, it has also been identified in mollusks, cockroach, nematodes such as *Anisakis simplex*, and dust mite [12-17]. Tropomyosin has also been described in vertebrates, although it is not allergenic [18,19].

Tropomyosin has been considered the most important allergen of shrimp for many years. Several studies show that in 72%-98% of patients sensitized to shrimp, IgE binds to the purified allergen [20-22], although a recent Italian multicenter study found that less than 50% of sensitized patients recognize it [23].

Shrimp tropomyosin, prawn tropomyosin, lobster tropomyosin, and crab tropomyosin share a sequence identity of 91%-100%. The sequence identity between crustacean and mollusk tropomyosin is lower, approximately 65% [11].

The tropomyosin of invertebrates is thermostable and resistant to digestion [24-27].

2.2. Arginine Kinase

Arginine kinase (AK) was the second shellfish allergen identified, in 2008. It was first identified in *Penaeus monodon* (Pen m 2) [28], commonly known as black tiger shrimp, and subsequently in many other crustaceans [29,30], such as crab [31], octopus [32], cockroach [33], and dust mite [34,35]. AK is more unstable and less resistant than tropomyosin [24,36]. Since it is thermolabile and volatile, it is considered one of the allergens responsible for respiratory symptoms induced by steam inhalation [37,38].

The percentage of patients sensitized to prawn who recognize AK is not well defined, although it is thought to range between 10% and 51% [22,39].

2.3. Myosin Light Chain

The third shellfish allergen described, in 2008, was myosin light chain (MLC). MLC was identified in American white shrimp, *Litopenaeus vannamei* (Lit v 3) [40], and later in other shrimp species, lobster [41], crab [42], and cockroach [20].

Like tropomyosin, it is highly resistant [24] and is considered a minor allergen, with a frequency of sensitization ranging from 19% to 55% [43,44], depending on the series. Although it usually accompanies tropomyosin in sensitization, there have been reports in patients with allergy due to shrimp intake, including anaphylaxis, in whom MLC was the only responsible allergen [39,40].

2.4. Sarcoplasmic Calcium-binding Protein

Described in 2008, immediately after Lit v 3, sarcoplasmic calcium-binding protein (SCP), was located first in *Penaeus monodon* (Pen m 4) [44]. It is highly resistant and stable [45] and has high sequence homology with crustaceans but low homology with mollusks [46,47]. As in the case of MLC, it is a minor allergen that could be clinically relevant regardless of sensitization to tropomyosin [39]. It is common in children, in whom the frequency of sensitization reaches 85% [46,22].

Table 1. Description of Shellfish Allergens

Component	Allergen Described	Route of Exposure	Molecular Weight	Resistance	Available for Diagnosis
Tropomyosin	Pen a 1 Lit v 1 Pen m 1 Cra c 1 Mel l 1 Pan b 1 Pen i 1 Met e 1 Por p 1 Hom a 1 Scy o 1 Scy p 1 Scy s 1 Cha f 1	Ingestion Inhalation	34-38 kDa	Highly thermostable and IgE-reactive	rPen a 1[a] nPen m 1[b]
Arginine kinase	Pen a 2 Pen m 2 Cra c 2 Lit v 2 Scy o 2 Scy p 2 Scy s 2 Cha f 2 Met e 2 Por p 2	Ingestion Inhalation	40-45 kDa	Labile Can elicit IgE binding	nPen m 2[b]
Myosin light chain	Pen m 3 Lit v 3 Cra c 3 Hom a 3	Ingestion	17-20 kDa	Stable	
Sarcoplasmic calcium-binding protein	Pen m 4 Lit v 4 Cra c 4 Mel l 4 Pon l 4 Scy p 4 Cha f 4 Met e 4 Por p 4	Ingestion	20-25kDa	Stable	nPen m 4[b]
Troponin C	Lit v 6 Cra c 6 Hom a 6 Pen m 6 Scy o 6 Pan b 6	Ingestion	20-21 kDa	Unknown	
Triose phosphate isomerase	Pen m 8 Cra c 8 Arc s 8 Pro c 8 Scy p 8	Ingestion Inhalation	26-29 kDa	Labile	
Hemocyanin	Lit v Hemocyanin Pan b Hemocyanin Mac r Hemocyanin	Ingestion	72-75 kDa	Stable	
Paramyosin	Myt g PM Oct v PM		100 kDa		
Fructose 1,6 Biphosphate aldolase		Ingestion Inhalation	39-43	Labile	

Abbreviations: Cha f, *Charybdis feriata* (crucifix crab); Cra c, *Crangon crangon* (common shrimp); Lit v, *Litopenaeus vannamei* (pacific white shrimp); Mac r, *Macrobrachium roserbergii* (giant freshwater prawn); Mel l, *Melicertus latisulcatus* (king prawn); Met e, *Metapenaeus ensis* (sand shrimp); Mit g, *Mytilus galloprovincialis* (black mussel); Oct v, *Octopus vulgaris* (common octopus); Pan b, *Panadalus borealis* (red shrimp); Pen a, *Penaeus aztecus* (brown shrimp); Pen i, *Penaeus indicus* (Indian white prawn); Pen m, *Penaeus monodon* (black tiger shrimp); Pon l, *Pontastacus leptodactulus* (narrow clawed crayfish); Por p, *Portunus pelagicus* (blue swimmer crab); Pro c, *Procambarus clarkia* (red swamp crawfish); Scy o, *Scylla olivacea* (mud crab); Scy p, *Scylla paramamosain* (green mud crab); Scy s, *Scylla serrata* (mangrove crab).
[a]Recombinant allergens: originally identified in native allergenic extracts and obtained by molecular biology techniques.
[b]Native allergens: obtained from the allergenic source.

2.5. Other Allergens

Other allergens reported during the last 15 years include troponin C [20,43,37,48-50], triose phosphate isomerase [20,22,51,52], hemocyanin [39,53-56], fructose biphosphate aldolase [34], fatty acid–binding protein, α-actinin and β-actinin [57,34], ubiquitin [34], paramyosin [58], and myosin heavy chain [54]. The clinical relevance of these allergens remains to be determined.

It is worth mentioning that hemocyanin, with unclear relevance in shellfish allergy, seems to have a very important role in cross-reactivity with mite, cockroach, and other invertebrates such as snails [59].

2.6. Epitopes

The study of peptides using microarray techniques has enabled us to identify linear peptides involved in sensitization to allergens. The epitopes described to date include 8 epitopes of tropomyosin [22,60-62], 7 epitopes of AK, 5 epitopes of MLC, and 3 epitopes of SCP [43].

Sensitization to various epitopes may account for the cross-reactivity between invertebrates and the variety of symptoms that patients experience [22,43,62].

3. Cross-reactivity Syndromes

3.1. Involvement of Tropomyosin

As previously mentioned, cross-reactivity between crustaceans, between crustaceans and mollusks, and between crustaceans and mollusks and mites or cockroaches, is mainly due to the high sequence identity of tropomyosin between the different species.

Cross-reactivity is attributed to the epitope that the patient recognizes. The 8 tropomyosin epitopes reported to date are epitopes 1, 2, 3a, 3b, 4, 5a, 5b, and 5c. In-depth analysis of these epitopes suggested that they can be classified into 3 groups. The first, comprising the 5a epitope, is highly conserved among crustaceans, mollusks, insects, and mites. The second, which comprises epitopes 2, 3, and 4, is found in arthropods but not in mollusks. And the third, which comprises epitopes 1, 5b, and 5c, seems to be specific to crustaceans [61-63].

Sensitization to tropomyosin can occur through the digestive route by consumption of shellfish or through the respiratory tract by inhalation of mites or by inhalation of shellfish vapors. Some studies have shown that sensitization to shellfish can trigger dust mite sensitization and vice versa. It seems that the prevalence of shrimp allergy is higher in regions with a high prevalence of house dust mite (HDM) allergy. In fact, in these regions, a positive SPT result is found in almost all patients sensitized to shrimp, and this may or may not be clinically relevant. Approximately 30% of HDM-allergic patients are sensitized to Der p 10 [64].

Wong et al [65] reviewed the evidence supporting the hypothesis that inhaled HDM tropomyosin is the main sensitizer for shellfish allergy in hot and humid tropical climates. A study conducted in the United States by Wang et al [66] showed a positive significant correlation between high specific IgE levels to shrimps and high exposure to cockroach allergens in urban children. Yang et al [67] obtained similar results in rural patients in southern China. Furthermore, Fernandes et al [68] reported a series of Orthodox Jews who presented sensitization to shrimp without ever being exposed to them. Thus, it seems that sensitization to shellfish may be explained by the presence of mites or cockroaches in the environment and the consequent sensitization to these arthropods. Conversely, there seem to be shellfish-allergic patients with positive SPT or specific IgE results against mite or cockroach without having had contact with these allergenic sources, although this finding is less frequent [34].

3.2. Involvement of Other Allergens

Allergens other than tropomyosin could explain cross-reactivity between dust mite and shrimp.

The proteins AK [28,34,69], SCBP [22,44,70], and hemocyanin [39,70] may also be involved in this cross-reactivity syndrome.

Yang et al [67] reported that in some cases of shrimp sensitization due to cross-reactivity with cockroaches, tropomyosin was not the dominant allergen responsible for the cross-reactivity.

Asero et al [23] conducted a multicenter study that included 116 Italian shrimp-allergic adults. Only 40% were positive to tropomyosin. In 52%, specific IgE binding to the >60-kDa component was detected.

Giuffrida et al [39] conducted a study to determine the clinical relevance of hemocyanin in patients allergic to shrimp and postulated that this allergen is a possible marker of cross-reactivity with mites.

Kamath et al [70] studied the importance of hemocyanin as an allergen in children, as well as its cross-reactivity with HDM.

Although sequence identity between shellfish hemocyanin and HDM hemocyanin has been demonstrated, Piboonpocanun et al [53] reported selective allergy to the giant freshwater shrimp *Macrobrachium rosenbergii* by exclusive sensitization to hemocyanin in patients tolerating *Penaeus monodon* [53].

More recently, Gámez et al [34] postulated that α-actinin and ubiquitin could be implicated in shrimp-mite cross-reactivity. Finally, according to Kamath et al [70], enolase could be a major allergen that explains cross-reactivity in infants.

3.3. Cross-reactivity Between Crustaceans and Mollusks

Although cross-reactivity between HDM and crustaceans is well documented, few studies have analyzed cross-reactivity between crustaceans and mollusks.

Vidal et al [71] recruited patients with anaphylaxis to crustaceans and noted that mollusk-allergic patients had higher levels of specific IgE to tropomyosin (rPen a 1) and more intense specific IgE binding in immunoblots to the shrimp extract. No differences were found between groups regarding AK, MLC, SCP, troponin C, and α/β actin [71].

No other trials have demonstrated the usefulness of biomarkers (level of IgE to prawn or tropomyosin, sensitization to specific allergens) to predict the likelihood of cross-reactivity between crustaceans and mollusks. Epitope mapping of the allergens seems to provide useful information (see above) [43,62].

3.4. Sensitization to Shellfish Induced by Allergen Immunotherapy

For many years, there has been an ongoing discussion about the possibility of inducing allergy to shellfish in previously tolerant patients receiving specific HDM immunotherapy. Several cases of patients who developed a new allergy have been reported [72]. Likewise, tolerance to seafood after HDM immunotherapy has been described in allergic patients who had previously presented severe allergy and even episodes of anaphylaxis [73,74]. Both reactions, the new induced shrimp allergy and the apparent desensitization to shrimp, have been reported for subcutaneous immunotherapy and for sublingual immunotherapy.

It is still unknown why food allergy improves in some patients, yet develops in others. Prospective studies suggest that it may depend on the level of tropomyosin in the immunotherapy extracts, but this level has not been identified [75,76]. The role of tropomyosin in HDM and shellfish allergies constitutes an important field of research, as it can provide new insights and strategies into immunotherapy for treatment of shellfish allergy [65].

4. Clinical Manifestations

There is no pathognomonic symptom of shellfish allergy. The clinical manifestations associated with an allergic reaction after the ingestion of shellfish are the same as those observed after ingestion of other foods.

The clinical manifestations may appear as oral allergy syndrome (OAS) or affect the skin in the form of rash, urticaria, or angioedema. They may involve the gastrointestinal, respiratory, or cardiovascular systems.

As in most food allergies, reactions begin immediately, in the first 15 or 20 minutes after intake. IgE-mediated allergic reactions are considered to occur within the first 2 hours, although there are always exceptions. The same is true of shellfish [77]. Late phase reactions have been reported from 2 to 8 hours after ingestion of shrimp, limpet, snow crab, and abalone [77-79].

Some studies suggest that shellfish is one of the foods most frequently involved in allergic reactions and that it can cause more severe reactions.

Alergológica 2015, an epidemiologic study based on the Spanish population, revealed that clinical presentations took the form of skin involvement in 72.9% of cases, OAS in 31.3%, digestive symptoms in 10.4%, asthma in 4.2%, rhinitis in 2.1%, and anaphylaxis in 12.5% [4]. A similar study conducted in Australia showed that patients experienced contact urticaria in 15% and anaphylaxis in 21% [80]. A review conducted in Hong Kong showed a high percentage of skin involvement (95.7%), followed by respiratory symptoms (29.9%), gastrointestinal symptoms (16.3%), cardiovascular symptoms (3.3%), and anaphylaxis (11.9%) [81,82].

In addition to the classic symptoms caused by the ingestion of a food, other symptoms have been reported for shellfish contact and steam inhalation. Exposure during processing in factories and in the home may cause other allergic symptoms, such as contact urticaria [83,84], contact dermatitis, and respiratory symptoms [85]. In the respiratory tract, the symptoms may result from the inhalation of the vapor/smell of the shellfish itself or from inhalation of steam during the cooking process.

There seems to be a strong correlation between a high concentration of allergens in the air and increased allergic sensitization [86]. Asthma induced by steam inhalation in fishermen and shellfish workers and in seafood industry processing factories is considered occupational asthma [38,85,87,88].

4.1. The Role of Cofactors

Physical exercise, nonsteroidal anti-inflammatory drugs, and alcohol consumption are enhancers of allergic reactions due to food intake [89-91]. The role of cofactors in shellfish allergy is not well established. Some cases of anaphylaxis after ingestion of shellfish followed by exercise have been reported [92-94].

Other factors that can increase the likelihood of an allergic reaction include stress, sleep deprivation, concomitant diseases, acute infections, and menstruation [89,95].

5. Diagnosis

As in all food allergies, the diagnosis of shellfish allergy is based mainly on the clinical history. After an exhaustive interview, additional tests are used to confirm the suspected diagnosis. These include SPTs, specific serum IgE determinations, and oral food challenge (OFC).

The first step is to perform SPT with one of the commercially available extracts. This procedure is safe and rapid, although it has been reported to be unreliable. Asero et al [96] analyzed 5 commercial crustacean extracts using SDS-PAGE and compared them with a fresh prawn extract. The authors found that the commercial extracts contained fewer protein bands than the fresh prawns and that molecular weight bands corresponding to the major shrimp allergens were lacking.

In a similar study conducted several years earlier by Jirapongsananuruk et al [82], 68 children diagnosed with prawn allergy underwent SPT with a commercially available extract and prick-prick testing with fresh and raw prawns. The authors demonstrated that crude extracts are useful when screening for sensitization to shrimp and better than commercial extracts.

Carnés et al [97] evaluated how the cooking process may alter the in vivo and in vitro allergenicity of the shrimp and lobster extracts and showed that more patients could be identified using boiled extracts of shrimp and American and spiny lobsters than using raw extracts. Additionally, wheal diameters and specific IgE levels were also significantly higher using boiled extracts. Jirapongsananuruk et al [82] found similar results (see above); therefore, the use of boiled extracts seems to be more effective in diagnosing seafood allergy. However, since some studies showed contradictory

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results concerning the effect of heat on these extracts [24,98], a negative SPT result could be a false negative. If real allergy is suspected, it is necessary to perform a prick-prick test with the food—both raw and cooked—to confirm sensitization [99].

In vitro diagnostic methods could also prove useful. The data provided during determination of specific IgE to the whole extract is similar to that of the SPT. The presence of specific IgE in serum implies sensitization but does not correlate with symptoms and/or severity [100].

Neither the size of the wheal nor the IgE level makes it possible to distinguish sensitized from allergic patients.

At present, OFC is the only test capable of differentiating an asymptomatic sensitized individual from an allergic patient. Double-blind placebo-controlled food challenge (DBPCFC) is considered the gold standard for diagnosis of food allergy [101], and several protocols have been proposed. Jirapongsananuruk et al [82] followed a 3-step protocol with 15-minute intervals between doses, starting with 500 mg of shrimp and reaching a cumulative dose of 15.5 g. Nordlee et al [102] conducted the DBPCFC with shrimp incorporated into a seasoned ground cooked beef matrix. Seven doses ranging from 7 μg to 4 g of shrimp were administered, and placebo was interspersed between the doses. While there is currently no standardized initial dose for the OFC, the European Academy of Allergy and Clinical Immunology recommends an initial dose of 5 mg of shrimp, increasing every 15-30 minutes until the daily recommended dose for the patient's age is reached [101]. These tests are not exempt from risk, and many can induce serious anaphylactic reactions [82,101,102].

The introduction of molecular diagnostic techniques during the last 20 years [103] has opened a new field in the study of allergy. In addition to revealing the complete allergenic source, molecular techniques make it possible to study the allergens individually. Applying single allergenic molecules from shellfish for allergen-specific IgE detection (ie, risk-associated molecules, markers of primary species, and indicators of cross-reactivity) could potentially modify test sensitivity and analytical specificity [104].

Component-resolved diagnosis and epitope mapping have been applied to a wide range of allergens to elucidate distinct sensitization profiles, which more accurately reflect clinical reactivity, and thus obviate, in some cases, the need to perform an OFC [105].

For some foods, such as peanut [106,107], milk [108,109], and egg [110], a positive connection has been found between the recognition of certain sequential IgE binding epitopes and the degree of allergic reactivity. It has been suggested that patients with persistent allergy or a history of more severe reactions recognize a larger number of sequential IgE epitopes. In addition, some pan-allergens have been correlated with greater or less severity.

Allergy to apple provides an example of the different manifestations of allergy symptoms regarding sensitization to different allergens from the same source. While sensitization to Mal d 4 (profilin) is associated with OAS, sensitization to Mal d 3 (lipid transfer protein) is associated with a risk of anaphylactic reactions after intake of apple.

In shellfish allergy, the significance of allergens is not clear. Patients with persistent allergy or a history of more severe

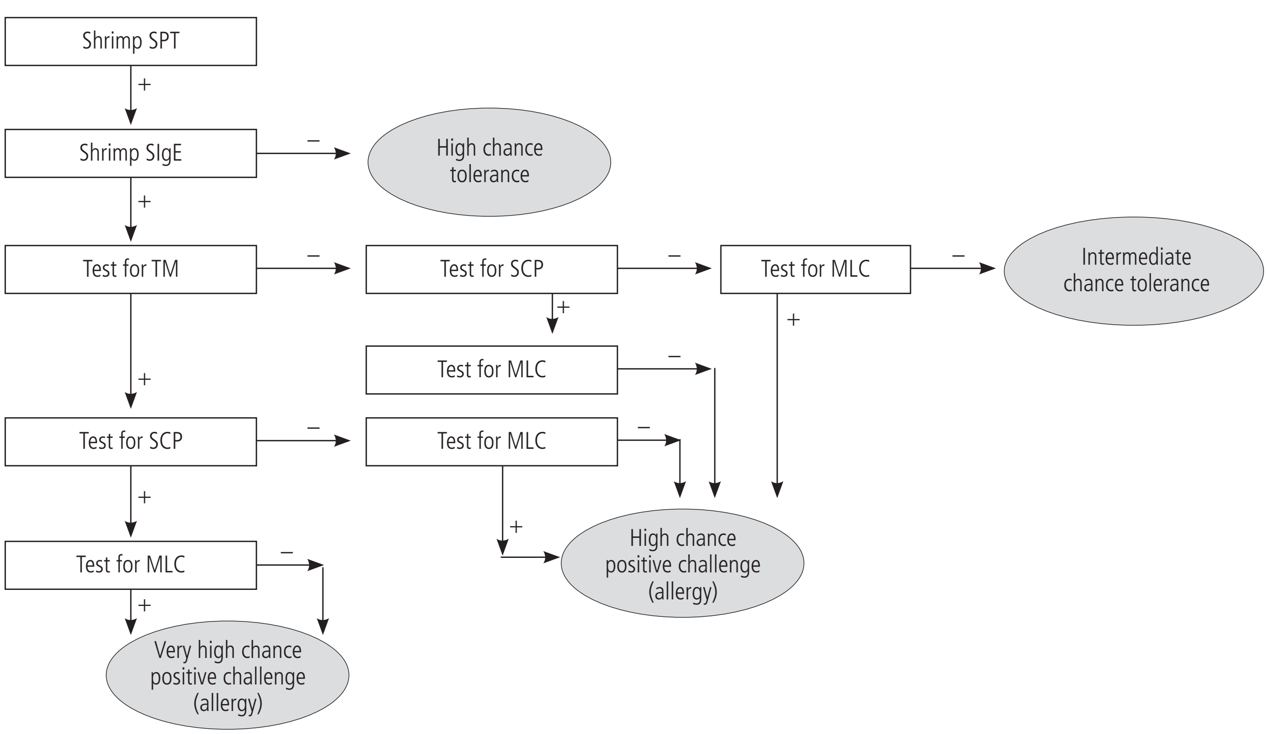

Figure. Flow diagram showing a protocol for diagnosis of shrimp allergy, as suggested by Pascal et al [43] in 2015. MLC indicates myosin light chain; SCP, sarcoplasmic calcium-binding chain; SPT, skin prick test; TM, tropomyosin.

reactions recognize many sequential IgE epitopes [67]. In addition, recognition of epitopes and allergens differs between children and adults [22]. According to the study conducted by Ayuso et al [22], 94% of children recognized tropomyosin, 70% MLC, 67% AK, and 59% SCP. In adults, tropomyosin was detected in 61%, MLC in 31%, AK in 21%, and SCP in 21%. Tropomyosin was the most frequently recognized allergen in both groups of patients. The other allergens were predominantly recognized by children. This might suggest that tropomyosin could be associated with the persistence of shrimp allergy into adulthood. However, as mentioned above, tropomyosin is a pan-allergen that cross-reacts with other common allergens, such as mite and cockroach. Therefore, the presence of crustacean tropomyosin may be due to cross-reactive sensitization, with no clinical relevance.

Determination of specific IgE against tropomyosin is the most specific protein-based approach and seems to have a higher positive predictive value in the case of oral provocation [111]. In addition to tropomyosin, SCP may be clinically relevant in children [39,44].

Pascal et al [43] conducted a study with the aim of identifying allergens and epitopes associated with clinical reactivity to shrimp. Patients with positive DBPCFC results recognized tropomyosin alone or in combination with SCP and/or MLC. AK and hemocyanin were recognized by patients with positive SPT results to HDM or cockroach and shrimp who never developed symptoms after ingestion of crustaceans. The authors believed that AK and hemocyanin could indicate cross-reactivity between shrimp and arthropods, albeit with no clinical significance. Based on results from 86 patients, the authors proposed a protocol to diagnose allergic patients based on a diagram that takes into consideration the outcome of SCP, specific IgE, and positive results for tropomyosin, SCP, and MLC (Figure).

The allergens currently marketed for in vitro diagnosis of crustaceans are nPen m 1 and rPen a 1 (both tropomyosin), nPen m 2 (AK), and nPen m 4 (SCP) (ImmunoCAP ISAC multiple 112 p, Thermo Fisher Scientific) and nPen m 1 (ALEX multiplex allergy test, MADX).

Finally, as in other conditions, knowing the genetic alterations that are associated with different types of allergy could facilitate diagnosis and treatment. Unfortunately, this type of study is still at a very immature stage in the allergy field. Several genome-wide association studies focused on samples from patients of European ancestry have identified food allergy-specific loci in the HLA class II region. Khor et al [112] conducted a study using data from 11 011 Japanese allergic women and identified shrimp allergy– and peach allergy–specific loci in the HLA-DR/DQ region, suggesting that allergy to certain foods may be related to genetic differences that tag both HLA alleles, with particular epitope-binding specificities, as well as variants modulating the expression of specific HLA genes.

6. Treatment

The only effective prophylaxis for allergic reactions to shellfish is avoidance [113].

Allergen-specific immunotherapy is proving successful in the treatment of patients with allergy to milk, egg, peanut, and wheat [114,115]. To our knowledge, none of the active groups studying shellfish allergy have conducted studies with oral immunotherapy.

The cross-reactivity of tropomyosins in arthropods and the clinical contribution of the other shellfish allergens hamper accurate diagnosis and design of allergen immunotherapy for shellfish allergy [116].

7. Discussion and Unmet Needs

Studying shellfish allergy is not an easy task. In addition, given that it is one of the most frequent and lethal allergies, we tend to advise avoidance in patients who have presented compatible symptoms, whether by intake, inhalation, or contact.

In the case of patients with suspected seafood allergy whose SPT result and specific IgE serum determination are negative, OFC (simple or DBPCFC) should be performed to demonstrate tolerance, although some OFC results may prove to be positive [117].

When sensitization is confirmed by positive SPT or by specific IgE, the same OFC should be performed as in the previous case, although very often it is not performed, sometimes because of patient refusal and sometimes because the physician does not wish the patient to undergo a risky procedure. Finally, challenge may not be possible owing to

Table 2. Research Needs in Shellfish Allergy

1. Determine the type of commercial extract with more sensitivity for detection of allergic individuals
   – Raw extract
   – Cooked extract
   – Single species
   – A mixture of species
2. Look for marks that determine the real probability of cross-reactivity between crustaceans, cephalopods, and bivalves.
3. Assess the possibility of using nasal provocation tests as a diagnostic tool:
   – As a previous step in the OFC
   – To replace the OFC
   – To confirm the diagnosis in patients who have experienced anaphylaxis and in whom OFCs are contraindicated

   Determine the type of extract to be used in a nasal provocation:
   – Cooked or raw extract
   – Single species or a mixture
   – The amount of protein to be applied
4. Carry out oral provocation studies with lyophilized extracts of different crustacean species containing all known allergens
5. Determine how individuals who have had an allergic reaction in the presence of a cofactor should be studied
6. Find a marker of mite-shrimp cross-reactivity in HDM-allergic patients who are not allergic to shrimp

Abbreviations: HDM, house dust mite; OFC, oral food challenge.

the lack of resources. It should be borne in mind that OFC requires adequate spaces within a hospital, skilled staff, and a long-term investment. Consequently, food allergy is generally diagnosed without assessment, and in many cases, patients may follow unnecessary avoidance diets.

In cases where the challenge can be performed, treatment is with avoidance diet if the challenge result is positive. Therefore, if the challenge is with shrimp, we must ask whether the avoidance diet should include all shellfish, or only crustaceans, or only shrimp. In addition, the decision to follow an avoidance diet or not may depend on the severity of the reaction or the results of the SPT carried out with other prawns or lobsters. No accurate answers have been proposed for these dilemmas to date.

Another scenario would involve a challenge yielding negative results. We would then have to ask whether patients who experienced a reaction did so in the context of a cofactor or whether the OFC was reliable. Therefore, in such cases, it would be necessary to ask whether patients could eat the foods they wished or only foods without the cofactor and whether tolerance to the crustacean used in the challenge implies tolerance for all crustaceans. Returning to the vegetable model, demonstrating tolerance to apple does not imply being tolerant to peach, even if both share the same pan-allergen.

We urgently require diagnostic tools to reduce the number of patients who avoid shellfish unnecessarily and to prevent fatal reactions in patients who are misdiagnosed (Table 2).

Commercial extracts must be perfected.

It is mandatory to continue working on molecular diagnostics in order to determine the significance of the allergens.

Alternative diagnostic challenges, for example, nasal provocation tests using acoustic rhinometry, should be investigated.

Finally, it is worth mentioning the need to find an option that enables patients to be cured. Maybe knowing the exact significance of each shellfish allergen would enable us to propose oral immunotherapy, as in the case of milk, egg, and peanut.

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Conflicts of Interest

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