

Review Article

Sea Food Allergy

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Fish and shellfish play an important role in human nutrition and in the world economy. Unfortunately, they also can be important causes of severe acute hypersensitivity reactions, including fatal anaphylaxis. Food-related anaphylaxis is a growing problem worldwide and is now estimated to be the most frequent cause of anaphylaxis treated in emergency departments.¹ Fish and shellfish are two of the most common causes of IgE-mediated food-allergic reactions in both children and adults. A number of major allergens and important potential cross-reacting allergens have been identified within the fish family, and between shellfish and major inhalant allergens in arachnids and insects.² The edible fish include more than 20000 species; however, the most commonly consumed belong to only a few orders of the ray-finned fish (Actinopterygii). Fish-sensitive patients are often allergic to multiple species of fish and are therefore advised to avoid consuming fish in general.³

Epidemiology and prevalence

Fish is a major source of dietary protein, especially in coastal areas. It is generally considered that crustaceans and fish are among the four food groups most commonly provoking severe food anaphylaxis. The consumption of seafood has increased worldwide, and therefore, the imports of seafood from other countries often surpass the own productions.⁴ A recent analysis of food-related reactions in emergency departments in the USA established that shellfish was the most frequently implicated food in persons aged 6 years or older.⁵ Fish allergy accounts for an estimated 0.1% and 0.4% of food allergies in US children and adults, respectively. Shellfish are responsible for 0.1% of food allergies in children and are the number one cause of IgE-mediated food allergy in US adults, affecting an estimated 2% of the adult population.⁶ Seafood allergy is common not only in western but also in Asian countries where allergic reactions to seafood and particularly shellfish are significant among children and adults.⁷ A study from Singapore on 227 children with food hypersensitivity confirmed that crustaceans and fish were significant sensitizers in about 40 and 13% of children, respectively.⁸

Sensitization to sea food

It is well accepted that the major route of sensitization to sea food is through the gastrointestinal tract. This mechanism was confirmed for codfish allergens in animal and human studies. The use of antacid medication that increased the stomach pH can result in incomplete digestion and thereby increase exposure to and uptake of allergenic fish proteins or protein fragments. Challenge experiments on patients without clinical sensitivity demonstrated absorption of biologically active fish allergens already 10 min after ingestion.^{4,9-10}

There is little information on the establishment of threshold values for elucidating allergic reactions to seafood. For codfish, very small amounts of less than 3 mg protein could trigger allergic reactions,¹⁰ which is less than that previously reported.¹¹ Double-blind placebo-controlled studies with shrimp demonstrated allergic reactions after ingestion of at least two to four shrimps (4 g each, 16 g total) equivalent to 32 mg of extracted shrimp proteins.¹²

Although most food-allergic individuals have knowledge of their allergy and thus can make attempts at strict avoidance, many unknowingly ingest or inhale the offending food as a hidden allergen.¹ Fish and shellfish allergic individuals may not be aware of the various forms of potential exposure, because the seafood content of some foods is not obvious.¹³

Allergens in fish and shellfish

In the late 1960s, Aas¹⁴ published the most extensive study about fish allergy and Elsayed¹⁵ characterized Gad c 1, as the major allergen in codfish, to be considered as a fish pan-allergen. During the past several years, many new allergens and important potential cross-reacting allergens have been identified within the fish family and between shellfish, arachnids, and insects. Codfish and shrimp have been the models used to study allergy to fish and shellfish, respectively.¹⁶

The major allergens responsible for cross-reactivity among distinct species of fish and amphibians are Parvalbumins. These proteins control calcium flow in the muscular sarcoplasm of the white meat and have a molecular weight of

approximately 12 kD. Parvalbumins are resistant to thermal and enzymatic degradation.¹⁷

The major one of these, Gad c 1, is a Parvalbumins that was first identified in Baltic cod (*Gadus callarias*). Another parvalbumin, the major allergen in the white muscle of Atlantic salmon, was identified and named *Salmo salar* (*Sal s 1*). In the Atlantic cod (*G. morhua*), an oligomeric parvalbumin encoded by a distinct gene was identified as *Gad m 1* and found to have greater homology with *Sal s 1* than with *Gad c 1*. Interestingly, *Gad m 1* shares 75% homology with *Sal s 1* and only 62.3% homology with *Gad c 1*.¹⁸

Hamada et al.¹⁹ identified the major allergens, *Sco j1*, *Sco a1*, and *Sco s1*, from three species of mackerel (*Scomber japonis*, *S. australasicus*, and *S. scombrus*, respectively). Swoboda et al.²⁰ identified The major allergen in carp (*Cyprinus carpio*) was found to inhibit IgE binding to parvalbumins of several other fish species and, therefore, contains most of the fish-specific IgE epitopes.²⁰ Because carp Parvalbumins contains 70% of the IgE epitopes present in natural extracts of cod, tuna, and salmon, recombinant carp parvalbumin may prove to be a very important tool in the diagnosis and treatment of fish-allergic subjects.²¹ In addition to the well-known major fish-allergen parvalbumin, gelatin (type I collagen) was identified as an important novel allergen in the muscle and skin of several species of fish.²²

The major allergen of shellfish is the muscle protein, tropomyosin, in crustaceans and mollusks. In addition to tropomyosin, other allergens have been identified and characterized in crustaceans such as the 40 kDa arginine kinase which might be a new class of invertebrate pan-allergens.²³ A recent study demonstrated IgE binding to a 20 kDa allergen in 55% of patients reacting to the white pacific shrimp (*Litopenaeus vannamei*).²⁴

Importantly, tropomyosin is not only a crustacean allergen but has been confirmed in a number of mollusk species. It has become apparent that mollusks such as mussel, oyster, squid, limpet and abalone are significant food allergens in exposed population. In addition to tropomyosin, mollusks contain allergens such as myosin heavy chain, hemocyanin and amylase.^{25,26}

Cross-reactivity with other allergens

Patients with seafood allergy are frequently reported to also have allergic reactions to mites and insects.²⁷ This cross-reactivity is probably due to the high amino acid homology of these invertebrate tropomyosins and may have significant clinical implications. Fernandes et al.²⁸ demonstrated

sensitization to shrimp tropomyosin in orthodox Jews who are prohibited by religious dietary laws from eating shellfish; however, as they were never exposed to crustacean allergens, this sensitization to tropomyosin is probably due to a noncrustacean source, such as house dust mites (HDM), cockroaches or both. Clinically relevant cross-reactivity between crustacean and HDM allergens was described in the early 1990s by Witteman et al.²⁹ The primary sensitization is believed mostly to be 'respiratory' allergy to dust mites, which in some individuals may cause food-allergic reactions to crustaceans or mollusks. This view is supported by recent observations during immunotherapy to HDM in which some patients developed clinical sensitization to shellfish tropomyosin, which did not exist before therapy. In contrast, sensitization to HDM in Iceland, where exposure to mites is extremely rare, is strongly correlated with specific IgE to shrimp.³⁰

In the group of arthropods, the crustaceans are more phylogenetically related to the 'insects' than to the group of 'mites' (arachnids).⁴ Other possible IgE reactivities to tropomyosin-containing allergen sources have been documented, such as the cross-reactivity with the nematode parasite, *Anisakis* found in many seafood species.³¹

Clinical features

Hypersensitivity reactions to fish and shellfish can result from ingestion, contact, or even inhalational exposures. Many reactions have been described in allergic consumers after the ingestion of or direct contact with the offending seafood. In a double-blind, placebo-controlled oral fish challenge study, emesis was the most frequent objective sign in patients with a positive challenge. Oropharyngeal symptoms or generalized pruritus preceded emesis in all patients.¹⁶ In another study, the most frequently reported signs/symptoms were pruritus and hives, wheezing and chest tightness, and angioedema. Although symptoms can develop up to 60 minutes after ingestion, most reactions (85%) occur within 30 minutes of ingestion of the culprit food.³²

In addition to allergy in the consumer, fish and shellfish have also been recognized as important allergens in occupational environments. In the occupational setting, reactions are most commonly associated with direct contact or inhalational exposure rather than with ingestion. Often these workers are unable to handle raw food but are able to ingest the food once it is cooked, suggesting a heat-labile allergen.³³

Adverse reactions in infants or children at the first introduction of fish may result from the passage of fish allergens through breast milk or the presence of these allergens in the indoor air and dust of houses where fish is frequently cooked and/or processed.³⁴

Seafood allergy is potentially severe, and because it is often noted in adults, it is often considered long-lived.³⁵ A follow up study by Priftis et al.³⁶ demonstrated that 65.5% of fish-sensitized children maintained their sensitization and are at increased risk for wheezing illness and hyperactive airways in school age.

Monospecific allergy to fish was reported³⁷. However, Sicherer et al.³⁸ noted that among patients with allergy to any fish, there is allergy to other types of fish in 67%; Crustacea in 38%, and mollusks in 49%; only 14% with crustacean allergy reported a mollusk allergy.

There are some adverse reactions to fish that mimic fish protein allergy. A negative skin test result or in vitro test result should alert the physician to possible reactions to substances in fish other than fish protein allergens. Bacterial spoiling of certain fish can produce histamine and cause scombroid fish poisoning. In rare cases the allergy might be to a roe protein rather than fish muscle allergen.³⁹ Fresh raw fish consumption can produce gastroallergic anisakiasis; a parasitic infestation which is characterized by a colic-type abdominal pain in the epigastrium. The diagnosis can be confirmed by endoscopy from which the parasite can be seen. The larva of *Anisakis simplex* can also cause an immediate allergic reaction, resulting in systemic signs ranging from urticaria or angioedema to anaphylactic shock. *Anisakis simplex* is a worldwide-distributed nematode that infects consumers of raw or under-cooked fish.⁴⁰ Scombroid poisoning occurs when people eat scombridae fish (e.g. tuna and mackerel) that have been inadequately preserved. Symptoms are caused by the ingestion of biogenic amines, especially histamine, that are produced by the bacterial decarboxylation of histidine, which is normally found in fish. Symptoms of scombroid poisoning mostly begin 10–30 min after ingestion of the implicated fish. Generally, it begins by flushing, nausea, vomiting, and abdominal cramps, followed by diarrhea and headache. Itching and hives, fever, burning mouth, and tachycardia sensation may also appear. If the reaction is severe, it may include wheezing, dizziness, and hypotension.⁴¹

Diagnosis

The medical history continues to be the mainstay of the diagnostic process. The history relies on the patient's recollection of events surrounding the development of symptoms. Unfortunately, this assumes the patient was able to identify the offending food, which is not always easy with complex foods with multiple and sometimes "hidden" allergenic ingredients.²

Prick skin testing with a history suggestive of IgE-mediated fish and/ or shellfish hypersensitivity is indicated. It is extremely important that caution be exercised in interpreting skin test results when the history is poor, because potential cross-reacting allergens may result in positive skin tests with unclear clinical relevance.²⁸ A recent study convincingly demonstrated that a wheal diameter of 30 mm after skin prick test (SPT) provided an 80 to 95% predictive probability of positive food challenge in patients allergic to the black tiger prawn (*Penaeus monodon*) and the giant fresh water prawn (*Macrobrachium rosenbergii*), respectively.⁴² SPT was also successfully correlated with positive food challenge when using cooked instead of raw extracts of shrimps and lobster for skin testing.⁴³

Radioallergosorbent testing (RAST) has generally been considered a less sensitive and more expensive method for the diagnosis of food allergy compared with the skin prick test. Diagnostic IgE levels were identified at 20 kUA/L for fish allergy. This level is predictive of clinical reactivity with more than 95% certainty.⁴⁴ Although the diagnostic levels of IgE for predicting crustacean allergy have yet to be determined, the ImmunoCAP-RAST FEIA was considered to be a safe and predictive test when considered in combination with the clinical history for the diagnosis of food allergy.²

Treatment

The only proven therapy for fish and shellfish hypersensitivity is strict avoidance. Unfortunately, strict avoidance is not always possible. As a result, new approaches to the treatment of food allergy are being investigated and developed. Although a few cases of successful rush immunotherapy with foods have been described, this form of therapy is very risky compared with other forms of immunotherapy and should be considered experimental.⁴⁵

Immunotherapy for food allergy was first described by Freeman in 1930.⁴⁶ Casimir et al.⁴⁷ desensitized a young girl with a standard rush immunotherapy protocol with codfish. After the rush therapy, the child was submitted to uncooked codfish odors without any reaction. Rush immunotherapy is the administration of multiple

injections either in a single day or over several days in an attempt to reach maintenance dose more rapidly. The risk of adverse reactions, including systemic reactions, is higher than with traditional allergen immunotherapy schedules. These patients are often pretreated with antihistamines and corticosteroids. Children are at even greater risk for adverse reactions with rush immunotherapy and the benefits versus the risks should be fully considered.⁴⁵

Many alternative approaches, including food-allergen plasmid DNA vaccines, mutated less allergenic recombinant food proteins, and anti-IgE with or without conventional immunotherapy are under study. These novel approaches to fish and shellfish allergy may offer the potential of safely desensitizing patients with less risk for systemic reaction.²

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Test yourself in sea food allergy

1. Mark the incorrect statement:

- a) Some workers are unable to handle the raw fish but are able to ingest it once cooked
- b) Hypersensitivity reactions to shellfish result only from ingestion.
- c) More than half of the fish-sensitized children are at increased risk for wheezing illness in school age
- d) The patient is sometimes unable to identify the offending food because of complex foods with multiple ingredients or hidden allergenic ingredients

2. Scombroidosis is due to:

- a) Allergy to mackerel fish
- b) Ingestion of histamine produced by the bacterial decarboxylation of histidine in fish
- c) Ingestion of toxins in rotten fish
- d) Ingestion of inadequately preserved crustaceans

3. The following are true about Anisakiasis except:

- a) It is caused by ingestion of the larvae of the nematode *Anisakis simplex* in raw or under-cooked fish
- b) It is characterized by a colic-type abdominal pain in the epigastrium.
- c) The SPT with fish extract is positive
- d) The diagnosis can be confirmed by endoscopy

4. In the diagnosis of sea food allergy:

- a) The medical history is the mainstay
- b) SPT is a good negative test
- c) Diagnostic IgE levels were identified at 20 kUA/L
- d) All of the above

5. The following may show cross reactivity with crustaceans:

- a) Nuts
- a) Cockroach
- b) Ragweed
- c) Beef

6. One of the following is true about sea food allergens:

- a) Tropomyosin is the major allergen in fish and is considered as a fish pan-allergen
- b) Gad c I, as the major allergen in shrimp and mollusks
- c) The use of antacid medications may decrease the sensitization to sea food
- d) Allergy at the first consumption may result from the passage of fish allergens through breast milk

7. The approved treatment of sea food allergy is:

- a) Avoidance
- b) Rush immunotherapy with sea food allergens
- c) Standard immunotherapy with sea food allergens
- d) Sea food-allergen plasmid DNA vaccines
- e) All of the above

(Answers on page 90)