

LITERATURE REVIEW

Fish allergy: a general perspective

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FOOD ALLERGIES

Food allergy is a form of adverse reaction to food, in which the cause is an immunological response to a food.

The history of food allergy begins with Sir Thomas More (1478-1535) – an English philosopher, statesman and humanist at King's Henry of England court – who describes in his work “The History of King Richard III” about a condition suffered by the king. After Richard III had enjoyed a bowl of strawberries, his body was covered by spots – it was urticaria. Later, in 1586, Marcello Donati, a doctor from Italy, described a case of angioedema, caused by eggs. In 1914, Fernand Widal writes about a patient who developed generalized acute urticaria, every time he ate meat. Occupational allergic reactions to seafood were first reported by De Beshce (1937), when he described a fisherman who developed asthma, angioedema and conjunctivitis when handling codfish. At the beginning of the 20th Century, the role of food in allergology was recognized and actively studied.

Over the past 2 to 3 decades, there has been a significant increase in the prevalence of allergic diseases. Food allergies affect almost 4% of the general population, irrespective of age¹. Most common food triggers are eggs, cow's milk, wheat, soy, peanuts, tree nuts, fish and shellfish.

The etiology and pathogenesis of food allergy are not fully understood. Immune reactions to foods can be IgE-mediated, cell-mediated or result from a combination of IgE and non-IgE mechanisms.

Symptoms of food allergy vary from abdominal discomfort to life-threatening anaphylactic shock reactions. Food allergy reactions involve the intestinal tract, skin, airway and cardiovascular system^{2,3}.

Clinical features include immediate reactions, occurring within minutes (usually up to 2 hours) after of ingestion (**urticaria** - nettle rash, **angioedema**, **rhinitis** - sneezing, nasal discharge, blocked nose, **worsening of pre-existing atopic eczema**, **asthma** - wheezing, coughing, tightness of the chest, shortness of breath, **vomiting**, **abdominal pain**, **diarrhoea**, and **anaphylactic shock**), and delayed reactions that occur over hours to days⁴. These delayed reactions involve the gastrointestinal tract (food protein induced enteropathy, proctocolitis or eosinophilic oesophagitis) or skin (eczema)⁴.

Diagnosis of food-allergy is a clinical procedure that depends on clinical history, determination of specific IgE (in vivo or in vitro), patch tests, an appropriate exclusion diet and blinded food challenges.

Avoidance of the causal food is a widely accepted form of managing IgE-mediated and non-IgE-mediated disorders. Several strategies are currently being investigated, both allergen-specific and allergen non-specific.

ALLERGY TO FISH

Fish allergy is one of the most common food allergies in populations where fish is a major part of the diet.

TAXONOMY

The class of fish is represented by 50 orders, comprising 445 families, more than 4000 genera and

20000 species. It is a very heterogeneous class, which includes two superclasses of the phylum Chordata.

The superclasses are Agnatha the jawless vertebrates, and Gnathostomata (vertebrates with jaws).

Superclass Agnatha (vertebrates without jaws):

- Class Myxini - hagfish
- Class Cephalaspidomorphi – lampreys

Superclass Gnathostomata (vertebrates with jaws):

- Class Chondrichthyes (cartilaginous fish - sharks and rays)

- Class Osteichthyes (bony fish), which has two subclasses:
 - Actinopterygii (ray-finned fish)
 - Sarcopterygii (lobe-finned fish)

ALLERGENS

Parvalbumins (PVs) form a major part of the fish skeletal muscle sarcoplasm, and were identified as the major food allergens, in fish and other vertebrates like frog, for example. PVs are calcium-binding albumin protein with low molecular weight (10 - 12.5kD). PV bind free Ca²⁺ reducing the intracellular [Ca²⁺] in muscle. These proteins have highly conserved Ca²⁺-binding sites. PV distribution varies in different fish species. Most fishes are found to express three to five isoforms of PV throughout their development, though the number of PV-isoforms can range from two to eight⁵

According to several studies cross-reactivity exists between different fish species and from different sources also, therefore one patient allergic to one fish could be sensitized by other PV sources.

It is demonstrated that PV is a very stable albumine, it can resist in conditions like heat, acidic pH, under denaturing effects of the digestive enzymes from the gastrointestinal system. In conclusion, cooking (boiling) can't avoid an allergic response in a previously sensitized individual, or an immune reaction in a new person⁵.

At present three PVs appear in the nomenclature: Gad c 1, Gad m 1 (gadus callarias, cod) and Sal s 1 (Salmo salar, salmon).

Collagen was recently identified as a new allergen in the muscle and in the skin of several species of fish. The collagen molecule is approximately 300 nm long and 1.5 nm in diameter. It is made up of three alpha chains, each possessing the conformation of a left-handed helix, that are twisted together into a super helix, a cooperative quaternary structure stabilized by numerous hydrogen bonds. So far, 29 types of collagen have been identified and described.

According to Hamada et al. some fish-allergic patients have specific IgE to fish muscle collagen⁶. Fish muscle collagen is a cross-reactive allergen among various species of fish also, but no cross-reactivity with the collagen of other animal species.

An important aspect is that the collagen is degraded by heating, but the peptide fragments derived from heated collagen are significantly IgE reactive. This way, studies have shown that allergenic activity of fish muscle collagen is dependent on aminoacid sequence, and steric conformation independent.

From an allergological point of view 4 categories are distinguished:

- Squalidae (shark),
- Gadidae (cod, whiting),
- Scombridae (tuna, mackerel),
- Pleuronectidae (lemon sole, sole).

But as we established, cross sensitization exists between different species, including Sicherer estimated that the risk of an allergy to other fish in a patient already allergic to a particular fish is 50%. It was demonstrated that almost all patients allergic to one or more fish have positive skin tests to other types of fish too, but the frequency and intensity of clinical reactions are much lower¹.

EPIDEMIOLOGY

Fish allergy is prevalent in coastal countries, where fish consumption is high. European Community Respiratory Health Survey announces a prevalence of adverse reactions for fish on average 2.2%. Sicherer found a prevalence of 0.4% for fish only, comparative with allergies to seafood estimated at 5.9%.

Fish allergy affects up to 3% of children in the Scandinavian population.

In Spain, Rivas found in his study a percentage of 9.8%⁷

SYMPTOMS

The symptoms of a fish allergy are the same as for a food allergy and allergies in general:

- skin and mucosal symptom
 - urticaria
 - atopic dermatitis
 - angioedema
- digestive symptoms
 - nausea, vomiting, stomach ache
 - abdominal pain, diarrhea
- respiratory symptoms
 - rhinitis (associated or not with conjunctivitis)
 - asthma

Concerning symptoms, a very important subject is represented by life-threatening symptoms like anaphylaxis, anaphylactic shock and coma.

In case of anaphylaxis, first symptoms are the mucocutaneous ones: palmoplantar / generalized purities, flushing, erytema, urticaria, angioedema, conjunctivitis. More serious are the symptoms involving the respiratory system (swelling of the uvula, edema of the

tongue/ pharynx, laryngeal/ bronchial spasm), the cardiovascular system (cardiac rhythm disorders, low blood pressure, loss of consciousness), the digestive tract (vomiting, intense abdominal pain).

The anaphylactic shock can induce coma. Death is also possible if medical measures are not taken.

DIAGNOSIS

Any food can produce an allergic reaction, so a clinical history that includes the nature of symptoms and the time elapsed between exposure and the first symptoms, intensity of allergic response and the reaction to treatment, is very important.

The first step in fish-allergy diagnosis is skin testing. It consists of putting dermal mast cells in contact with allergens. A positive skin test indicates a sensitization to food allergens.

Food patch tests are used to identify reactions to food (fish), in patients with atopic dermatitis or digestive symptoms, reproducing the mechanism of eczema experimentally.

Biological investigations includes eosinophilia (which has no relevance), tests with multiple allergens, total IgE antibodies, specific IgE antibodies.

Challenge tests, LCT (labial challenge tests) and OCT (oral challenge tests) are the gold standard in food-allergy diagnosis. The aim is to reproduce the clinical history of the allergy. Anyway, OCT is used in situations where the diagnosis is uncertain.

Jeebhay et al. recommends using serum determination of omega 3-fatty acids².

The elimination diets could be considered a diagnosis test and also a prophylaxis method.

In clinical situations where digestive symptoms are dominant it should be practiced an intestinal biopsy or an intestinal permeability test.

Unconventional diagnostic methods are: food specific IgG tests, cytotoxic food testing, ALCAT test, sublingual/intradermal provocation tests, applied kinesiology and electrodermal testing. These tests are not recommended because they're associated with higher risks of systemic reactions, including fatal anaphylactic reactions.

CONDITIONS OF EXPOSURE TO ALLERGENS

Allergic symptoms appear after **inhalation** of, **contact** with, **ingestion** of fish allergens.

Inhalation of allergenic fish particles could lead to im-

mediate symptoms of conjunctivitis, rhinitis, asthma, urticaria and sometimes even acute anaphylaxis. Several studies show the importance to this type of allergenic exposure – Crespo et al. studied 21 children who were suffering from an allergy to fish and 19 of these developed symptoms after accidental inhalation of fish particles (frequently, the accidents happened at home when fish was cooked / eaten by others)⁸.

Carral et al. showed in his study that workers at frozen and smoked fish factories can develop occupational asthma generated by passive evaporation of aerosols⁹.

Skin or mucosal contact with fish also provokes allergic reaction. Most common symptoms include urticaria, contact dermatitis² and angioedema¹.

Occupational allergic reaction to seafood can manifest as rhinitis, conjunctivitis, asthma, urticaria, protein contact dermatitis, and occasionally systemic anaphylactic reactions. Studies has demonstrated that workers involved in fish processing (pilchard, anchovy) are at increased risk of becoming sensitized to fish and developing work-related asthma symptoms. 24 out of 291 employees in a factory developed occupational asthma after exposure to salmon protein².

Ingestion of fish / fish products (surimi, caviar) remains the most common trigger for allergic reactions. Several studies suggest that disruption of normal gut barrier functions, such as gastric acid pH and commensal bacteria, can increase the risk of food allergies. Gut importance can be revealed also by the fact that food allergies are more frequent in children who have not an optimum gut development.

Normally, a gastrointestinal mucosal immune system can distinguish between harmless food allergens, beneficial commensal bacteria and potentially harmful pathogens¹⁰.

Very important is that, as we before mentioned, the fish allergens are able to preserve their allergic properties even after cooking⁵.

DIFFERENTIAL DIAGNOSIS

False allergies to fish could be caused by a natural richness in histamine, non-specific histamine-release, special preparations, a bacterial infection or a parasitosis¹.

Anisakis simplex is a Nematode that infest patients after consumption of raw or undercooked bony fish – the problem is particularly important in countries which are big consumers like Spain and Japan.

Scombroid poisoning is caused by fish which contain large quantities of histamine (50 mg/100g or over) like tuna, mackerel and sardines.

Cigua-toxin is fat-soluble toxin that herbivore sea fish absorb while eating algae attached to coral. Ciguatera fish poisoning produce digestive, cardiovascular and neurotoxic (paralysis, coma) symptoms.

TREATMENT

Strict dietary elimination is recommended, also skin contact and respiratory contact with allergens.

Emergency treatment for the symptoms of food allergy, including fish, involves antihistamines, corticosteroids, bronchodilatory and adrenaline therapies for anaphylactic shock.

Further studies must demonstrate if some of today's researcher's approaches could represent a treatment for fish allergy in the future.

Immunotherapy implies gradual exposure to allergens hoping for desensitization and/or promoting tolerance. However, the attempts of using **subcutaneous immunotherapy** for food allergies demonstrated high rates of severe adverse reactions. Alternative routes of administering immunotherapy are being investigated to improve the risk-benefit ratio, and the **sublingual immunotherapy** appears to be a promising one.

Modified recombinant vaccines decrease IgE binding capacity and protein's ability to stimulate T cell in order to decrease adverse effects.

Peptide immunotherapy use peptide fragments that contain T cell epitopes that are not of sufficient length to cross-link IgE decreasing the adverse effects of immunotherapy related to mast cell or basophile activation.

Immunostimulatory sequence-conjugated protein immunotherapy bound to proteins to promote switching to a Th1 response, in fact to make the proteins less allergenic.

Plasmid DNA immunotherapy - allergen gene immunization is another approach to immunomodulate the allergic response.

Anti-IgE decreased circulating free IgE, inhibits the early and late phase allergic response, suppresses inflammation and provides improved control for allergic diseases^{10,11}.

Cytokine/Anti-cytokine - Strategies to block pro-allergic cytokines have been investigated as potential therapeutic approach.

CONCLUSIONS

Fish is one of the most common triggers for allergy. Major fish allergen is considered parvalbumin and collagen. The developed symptoms in this kind of allergy follow the general pattern of allergies.

The skin tests and oral challenge are considered to be the cornerstone in fish-allergy diagnosis. Avoidance is most easy way to manage an allergy and the treatment concerns only symptomatic situations.

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