

Educational Clinical Case Series

Fish allergy in childhood

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Fish and its derived products play an important role in human nutrition, but they may also be a potent food allergen. Fish can be an ingested, contact, and inhalant allergen. Gad c I, a Parvalbumin, the major allergen in codfish, is considered as fish and amphibian pan-allergen. Prevalence of fish allergy appears to depend on the amount of fish eaten in the local diet. In Europe, the highest consumption occurs in Scandinavian countries, Spain and Portugal. In Spain, fish is the third most frequent allergen in children under 2 yr of age after egg and cow's milk. An adverse reaction to fish may be of non-allergic origin, due to food contamination or newly formed toxic products, but the most frequent type of adverse reactions to fish are immunologic-mediated reactions (allergic reactions). Such allergic reactions may be both IgE-mediated and non-IgE-mediated. Most cases are IgE-mediated, due to ingestion or contact with fish or as a result of inhalation of cooking vapors. Some children develop non-IgE-mediated type allergies such as food protein induced enterocolitis syndrome. The clinical symptoms related to IgE-mediated fish allergy are most frequently acute urticaria and angioedema as well as mild oral symptoms, worsening of atopic dermatitis, respiratory symptoms such as rhinitis or asthma, and gastrointestinal symptoms such as nausea and vomiting. Anaphylaxis may also occur. Among all the species studied, those from the Tunidae and Xiphiidae families appear to be the least allergenic.

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Fish and its derived products play an important role in human nutrition. They are a very valuable source of protein; however, fish protein may also be a potent food allergen (1).

The report of fish allergy by De Besque in the 1930s was the first to describe reactions as a result of ingestion, contact or inhalation of fish allergen (2). Ten years later a paper was published describing the antigenic relationships between different fish species. In the late 1960s, Aas published the most extensive study about fish allergy and Elsayed characterized Gad c I, as the major allergen in codfish, to be considered as a fish pan-allergen (3–5).

Fish is the third most frequent allergen after egg and cow's milk in parts of Europe (6–8). Most of the cases are IgE-mediated due to ingestion, contact or inhalation of cooking vapors. Re-

cently, the number of new fish allergy cases during the first year of life appears to have diminished. This may reflect a parental tendency to delay the introduction of fish into the infant diet, although there is no public health advice to support this. Cases of non-IgE-mediated allergy, such as food protein induced enterocolitis syndrome (FPIES) to fish have also been reported. In this paper, we will review the four most common patterns of fish allergy in our outpatient clinic (9–12).

Case 1: An infant boy with urticaria after contact with sea bass

An 11-month-old boy with mild eczema was referred for possible allergy to foods which had not yet been introduced into his diet. From 5 months of age, each time the mother handled

fish and afterwards touched him, he developed contact urticaria. Direct skin contact with sea bass reproduced similar symptoms. He had never eaten fish.

He was exclusively breast fed for 4 months and was tolerating cow's milk formula, cereals with gluten, fruit, vegetables, beef, and corn by the age of presentation.

Skin prick tests using commercial extracts were positive for tuna, swordfish, hake, megrim, and sole. After allergy testing, the patient was advised to have a diet free from fish and until further evaluation. At follow up at 2 yr of age, skin tests were positive for tuna, swordfish, hake, megrim, and sole. Specific IgE results were: hake (5.7 kU/l), megrim (2 kU/l), sole (1.7 kU/l), salmon (2.4 kU/l), tuna (0.9 kU/l), swordfish (≤ 0.35 kU/l). Due to the absence of IgE antibodies against swordfish, an oral challenge test with 25 g ($\frac{1}{2}$ portion) was performed which resulted in moderate erythema and angioedema around the mouth 5 min later. The test was considered positive and his diet was recommended to be free of fish until the next review.

Discussion about case 1: IgE-mediated fish allergy

The vast majority of IgE-mediated allergic reactions to fish result from ingestion, however, a few cases of allergic reactions to fish through inhalation have also been reported in children. Some cases may present with contact urticaria even prior to ingestion, as in this case described above. Adverse reactions to fish may result from non-allergic responses due to food contamination or newly formed toxic products (1) although these are less common than allergic reactions. Allergic reactions may be IgE-mediated or non-IgE-mediated. Prevalence of fish allergy appears to relate to the amount of fish in the local diet. In Europe, the highest intake is found in the Scandinavian countries, Spain and Portugal (1) (Box 1).

Box 1. Key features of all fish allergy

Usually presents between 9 and 12 months of age, often associated with other food allergies

Symptoms on first ingestion, which may include contact urticaria

Usually first contact with white fish (hake, megrim)

Urticaria, rash, worsening of atopic dermatitis, and delayed symptoms even with vapor

Diagnosis is via clinical history; skin prick tests and/or serum fish-IgE positivity

Food challenge is necessary if relationship with species is not well established

The clinical symptoms related to IgE-mediated fish allergy are most frequently acute urticaria and angioedema as well as mild oral symptoms, worsening of atopic dermatitis, respiratory symptoms such as rhinitis or asthma, and gastrointestinal symptoms such as nausea and vomiting. Anaphylaxis may also occur. In one study of 197 children diagnosed with IgE-mediated fish hypersensitivity, 21 patients showed allergic reactions upon incidental inhalation of fish vapors or fumes (9), and 18 had immediate symptoms with fish contact (10). Upon inhalation, fish allergens elicited respiratory symptoms. These infrequent reports refer mainly to cases of occupational exposure, including fish processing, handling, and cooking activities (11). However, as reported for other foods, non-occupational exposure to fish odors and fumes could potentially play a role in eliciting clinical manifestations in subjects with IgE-mediated hypersensitivity to fish (12).

In Spain, the age of presentation of fish allergy reaches a maximum incidence at 6 months to 1 yr of age, which coincides with the time of fish introduction in the diet amongst Spanish children. In our study, the fish species provoking the strongest IgE response is hake, followed by megrim. Among all the species studied, Bonito (*Thunus alalunga*), Tuna (*Thunus thunnus*), and swordfish had the lowest IgE response (13, 14). These findings have recently been confirmed by other groups (15, 16). These results may be considered when introducing fish into the diet of highly allergic patients; as has been done inadvertently by tradition in some countries such as USA where the most popular fish species is tuna (17, 18).

The most frequently consumed fish in childhood diets in Spain are fat-poor, white fish (whiff/megrim, sole, and hake). Later in life there is a higher intake of Bonito, Tuna fish (both tunidae), and Swordfish (*Xiphias gladius*) from Xiphiidae family. Among all the species studied those from the Tunidae and Xiphiidae families appear to be the least common to cause allergic reactions (13, 19). This is the rationale for starting fish challenges with swordfish in our case report. As the patient tested positive with the species of lowest IgE response, he was very unlikely to tolerate any of the other tested species. In this case a complete fish exclusion diet was required.

Fish allergy is persistent, around 80% of patients are still allergic even 10 yr after the initial diagnosis. Many people with fish allergy avoid shellfish too. Shellfish (Crustaceans and mollusks including cephalopods) allergy is

mostly caused by tropomyosin and is common in children over 3-yr -old. Whilst some multiple food allergic children may be allergic to both fish and shellfish, they are not the same entity. Those with either fish or shellfish allergy need not routinely avoid the other.

Fish allergy should not be confused with other adverse reactions to fish, such as gastro-allergic anisakiasis and scombroid poisoning. Fresh raw fish consumption can produce gastroallergic anisakiasis which is characterized by a colic-type abdominal pain in the epigastrium. This may be associated with nausea, vomiting or even changes in the intestinal rhythm if the small bowel is involved. 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. The clinical signs of anisakiasis depend on where in the digestive tract the larva is deposited. Symptoms may develop as a result of an inflammatory response occurring in the gastric wall mucosa where the larva enters it (20, 21) (Box 3).

Box 2. Key features of FPIES

Mostly occurs around the first birthday
 Profuse vomiting (within 2–4 h) and diarrhea causing dehydration and lethargy upon ingestion
 Resolution of symptoms with exclusion of causal food
 Negative skin prick tests and *in vitro* IgE tests for fish
 Treatment of acute reactions with intravenous rehydration
 Challenge with the suspected food under close physician supervision with intravenous via
 A 25% chance of resolution in 4 yr

Box 3. Key features of gastroallergic anisakiasis

Usually occurs in adults on ingestion of raw or under-cooked fish
 Range from urticaria/abdominal discomfort to anaphylaxis
 Definitive diagnosis by endoscopy
 Specific IgE for anisakis positive and negative to fish

Many asymptomatic subjects show high levels of specific IgE against *A. simplex*. It is often difficult to diagnose an allergy to *A. simplex*, due to the cross-reactivity with other allergens. Positive skin tests to *A. simplex* usually correspond to subjects with positive results to other

allergens such as crustaceans or mites (22). The high cross-reactivity between this and other parasites prevalent in infants would be responsible for this confusion when an accurate diagnosis is to be obtained. The secretory–excretory antigen is more specific for recognizing patients who actually have parasites. This antigen could be used for indicating real parasitisation in the differential diagnosis of this type of sensitization. This type of parasitisation is frequent and sometimes severe in adults, but is practically non-existent in infants and small children in Europe, due to currently adequate food handling.

To prevent this condition, raw fish left less than 48 h since frozen, or fresh fish not cooked for at least 20 min above 60°C, should not be consumed.

Scombroid poisoning is another type of pathology due to fish consumption, although it is relatively uncommon. Scombroid poisoning occurs when people eat scombridae fish (tuna, mackerel, skipjack, bonito, marlin) that have been inadequately preserved. Non-scombroid fish (amberjack, mahi-mahi) may also be implicated. 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 (23, 24). 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 (Box 4).

Box 4. Key features of scombroidosis

Rare, particularly in small children
 Occurs after ingestion of spoilt scombridae fish
 Symptoms mostly begin in 10–30 min after fish ingestion. Generally starts by flushing, nausea, vomiting, and abdominal cramps. Itching, hives, diarrhea, headache, fever, and burning mouth may occur
 Tachycardia, palpitations and may include hypotension, wheezing, and dizziness
 Treatment includes antihistamines

Case 2: Fish allergy with Tunidae and Xiphidae tolerance

A 15-month-old boy, with a background of eczema and egg allergy presented after eating

fish for the first time. After eating hake, he immediately developed facial erythema and urticaria. His mother avoided giving him any further fish. On allergy testing, he had positive skin prick tests for hake and sole. The skin prick tests were negative for tuna and swordfish. Specific IgE was measured for hake (4.74 kU/l), sole (5.07 kU/l), tuna (0.67 kU/l), and swordfish (≤ 0.35 kU/l). Given the low allergic sensitivity to tuna and swordfish, provocation tests were done for both fish, and both were well tolerated. The patient was advised to introduce tuna and swordfish into the diet whilst continuing to avoid other fish.

Discussion of case 2: Fish allergy with partial tolerance

This child presented with urticaria upon first fish intake which was hake, one of the most IgE responding species, but often mother's first choice to feed small children in Spain. He tolerated tuna and swordfish introduced after challenge and depending on future specific IgE measurements, more species could be added to his diet. In this pattern of fish allergy, evolution tends towards tolerance of all fish over the subsequent years.

In 1966, Aas (25) found 89 cases of fish sensitization out of 711 children with food allergy. He described a high degree of immunologic cross-reactivity among fish species, but he reported other patients, clinically sensitized to cod who tolerated other fish species. Fifteen years later, De Martino et al (26) reached similar conclusions and noted a degree of excess hypersensitivity with skin testing as a diagnostic procedure in fish allergy. Bernhisel-Broadbent et al (27) found through skin testing, immunoblotting, and double-blind placebo-controlled food challenges, that sera of his patients showed specific IgE antibodies to fish species that were clinically tolerated. Sachs and Yunginger (28) confirm this finding and conclude that only those fish species not clinically tolerated should be withdrawn from the diet.

Our own group studied a group of 79 children diagnosed with fish allergy based on a convincing history and IgE antibodies to six fish species. This group was drawn from an area of central Spain where fish was consumed by most children on a daily basis (13). In all the patients, skin prick tests were positive (3×3 mm larger than control, and even larger than the 5×5 mm average of histamine control) for all six investigated fish species. This suggests a low specificity of skin prick tests because of the cross-reactivity:

31 of 79 patients selectively tolerated one of the studied species (14). Only a few subjects had high levels of specific serum IgE antibodies to White tuna or Albacore (*Thunnus alalunga*), and 29 of the patients clinically tolerated ingestion of it.

All these studies have been replicated in the last 3 yr (15). An additional finding is that dark muscle, which tuna is very rich in, contains relatively less parvalbumin than white muscle (16). This could be one explanation for the tolerance of this fish in people who react to others. It is also noteworthy that parvalbumin is a thermo-resistant protein; hence cooking fish will not significantly alter its allergenicity. However, the canning process has been shown to destroy or alter proteins recognized by IgE so may effect its allergenicity in some patients (31).

As there is an increasing demand to include fish-derived fatty acids in the diet, due to their possible beneficial effects in atopic disease, it is important to elucidate the most likely species to accomplish both goals: low allergenicity and high amounts of omega 3 (32, 33).

Case 3: Monospecies fish allergy

A 3-yr -old boy background of egg allergy and atopic dermatitis presented to the clinic. He had tolerated hake from 18 months of age without any problems. Over the following year he successfully introduced sole, sea bass, halibut, salmon, tuna, and swordfish into his diet. His parents also noted that on numerous occasions he developed immediate peri-oral erythema and itching of the mouth and tongue when he ate megrim. Skin prick tests to commercial extracts were positive to megrim but negative to hake, sole, salmon, swordfish, and tuna. Measurement of specific IgE revealed positive results to megrim (0.8 kU/l) but negative results to hake and sole. The diagnosis of monospecies fish allergy was made. Recommendations included avoidance of megrim and follow-up evaluation in approximately 1 yr.

Discussion of case 3: Monospecies fish allergy

In the last 5 yr, there have been some reports of new fish allergens other than parvalbumin, as well as cases of patients who are only allergic to one fish type. Some cases involve mono-sensitization to those species considered less allergenic (31, 34, 35). In some species, allergens other than parvalbumin have been recognized by some mono-sensitized patients (36).

The differences in clinical response to fish species suggests that allergenicity is not only

related to the presence of parvalbumin. A better understanding of the allergenic characteristics of different fish will help to better predict cross-reactivity (13, 16).

Unlike some authors, we have not found patients mono-sensitized to tuna or swordfish, but in our practice, megrim (*Lepidorhombus whiffiagonis*), is the fish we most commonly see mono-sensitization to. Immunoblotting, demonstrates IgE binding to a 20 kDa band with no band corresponding to parvalbumin.

Case 4: Non-IgE-mediated fish allergy

A 12-month-old girl presented for evaluation. At 11 months of age, after eating a puree of boiled hake and potatoes, she repeatedly vomited 2–3 h later. Her gastrointestinal symptoms included lethargy and later diarrhea. She was admitted for observation and discharged after 2 days without a firm diagnosis. Two weeks later, the same symptoms occurred after the first ingestion of sole (no fish was consumed between episodes).

She was an atopic girl but weaning had been uneventful prior to first exposure to fish. Allergic evaluation with skin prick tests to commercial extracts of hake, sole, megrim, swordfish, and tuna were negative. Specific IgE to hake, sole, megrim, and tuna were negative. Based on her clinical manifestations and the negative results of the tests, she was diagnosed with FPIES. A diet free of all fish was recommended until her next review, in 1 yr. At this point, skin prick and specific IgE tests were still negative for hake, sole, megrim, salmon, tuna, and swordfish. Given her age and negative allergy tests, a provocation test with tuna was performed. This resulted in vomiting within 3–4 hours (later followed by diarrhea) as well as a marked increase in peripheral white blood cell count and leukocytes in the stool. It was therefore recommended to continue with a diet free of fish until the next review.

Discussion of case 4: Non-IgE mediated fish allergy

This last type of clinical pattern associated with fish ingestion is the least common, but may account for between 5% and 10% of all cases of fish allergy (37). It is a non-IgE-mediated allergy syndrome known as FPIES. This is characterized mostly by excessive vomiting and diarrhea that can progress to acidosis and shock if supportive treatment is not instituted (38). It is usually described as induced by cow's milk and soy protein but there are reports of FPIES induced

by egg, whey or chicken. There have been an increasing number of publications implicating different solid foods such as rice, grains, vegetables, and peanuts (39, 40) that could trigger this syndrome. Fish as a causative food was first noted in a case 25 yr ago and has been described again since (41). Even though fish is often clinically suspected in pediatric patients by allergists, no further cases were reported until a group from Madrid studied 14 infants with FPIES due to dietary fish protein (37) (Box 2).

The pathogenesis of FPIES is not well defined, although some studies point to a delayed, cell-mediated Th 2 type reaction to certain foods. Some cases it first occurs after recovering from an intestinal viral infection and in others an underlying eosinophilic mechanism is suspected. Recent studies suggest that tumor necrosis factor- α from T cells upon food stimulation is involved in the pathophysiology of FPIES (42).

As FPIES is not an IgE-mediated disorder, prick skin tests are usually negative, but if skin tests are positive to the causal food, reports suggest that these children may have a lower probability of developing tolerance. Atopy patch tests (APT) are positive in some of these patients but the sensitivity and specificity of this test is different depending on the reporting group (43–45). The diagnostic and predictive value of the APT is currently considered to be too limited to be of any real clinical value to some experienced allergology groups (43) whilst others use the positive APT as a predictor of a positive food challenge. However, some patients with positive test do have negative challenges (45). This test will need more validation before being recommended for use in the clinical diagnosis of FPIES patients.

The appropriate treatment is avoidance of the offending food. Development of tolerance occurs in 25% by 4 yr from diagnosis (37). Oral food challenges must be done before any attempt to introduce the food and should be performed carefully in a controlled environment under physician supervision and with a prepared kit of emergency equipment, medication, and intravenous fluids.

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