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Fish allergy: Evaluation of the importance of cross-reactivity

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Fish constitute one of the most important groups of allergens in the induction of immediate (type I) food hypersensitivity. In our environment, fish allergy is present in 22% of all patients with a diagnosis of food hypersensitivity. We studied the allergenic significance of the fish species considered most representative because of their greater consumption in our environment (flatfishes: Pleuronectiformes such as sole, whiff, and witch; Gadiformes such as hake; and Scombriformes such as albacore) or because of the results of previous studies of Gadiformes such as cod. Through the use of isoelectric focusing and sodium dodecyl sulfate-polyacrylamide gel electrophoresis immunoblotting, we have observed that several allergens common to all these species are able to bind specific IgE from the sera of sensitized patients. This allergenic community has been confirmed by radioallergosorbent inhibition. Another group of species-specific allergens focuses in the regions at about pH 5 and with molecular weights less than 14 kilodaltons; these allergens correspond to sarcoplasmic parvalbumins. From the results observed, which have been confirmed by various procedures and techniques, we conclude that hake is the fish with the capability to induce the strongest IgE response, followed by whiff; the witch seems to be the least allergenic of all flatfishes. Among all species studied, albacore was the least allergenic. These results may be considered when one introduces supplementary feeding with fish in infants, most particularly in infants at high risk for atopy. (*J PEDIATR* 1992;121:S29-S34)

Fish and its derived products play an important role in human nutrition. They are a valuable source of high-assimilation proteins; their fats have a high concentration of polyunsaturated fatty acids and fat-soluble vitamins. However, fish may also be potent alimentary allergens.

The prevalence of immediate fish allergy is higher when the consumption of fish plays a greater part in the diet of the community. In Norway, where a large percentage of the population works for fishing and associated industries, and where fish (particularly cod) is a mainstay of the daily diet, the prevalence of fish allergy reaches 1/1000 of the general population.¹ In Sweden, 39% of all pediatric patients with food allergy have fish allergy.² In an assessment carried out in our own environment 6 years ago, 18% of all pediatric patients with food hypersensitivity were allergic to fish,³ and

this allergen was third, in order of importance, after eggs and cow milk. In a more recent study,⁴ 30% of children with food allergy had symptoms related to the ingestion of fish; in this series, fish held second place (after egg) in prevalence among sensitizing foods.

IEF	Isoelectric focusing
kd	Kilodalton
MW	Molecular weight
PAGE	Polyacrylamide gel electrophoresis
RAST	Radioallergosorbent test
SDS	Sodium dodecyl sulfate

De Besche,⁵ in Norway, published the first report describing fish as an alimentary allergen, as an inhalational allergen able to trigger asthma, and as an allergen that caused immediate skin symptoms on contact. He also described patients with selective sensitization to a single species who tolerated other kinds of fish. About 10 years

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Table I. Incidence of increased serum IgE antibodies to each of six fish species studied

Order	Family	Species	Patients	
			No.	%
Gadiformes	Merlucciidae	Hake (<i>Merluccius merluccius</i>)	75	94.9
Pleuronectiformes	Scophthalmidae	Whiff (<i>Lepidorhombus whiffiagonis</i>)	73	92.4
Gadiformes	Gadidae	Cod (<i>Gadus callarias</i>)	72	91.1
Pleuronectiformes	Pleuronectidae	Witch (<i>Glyptocephalus cynoglossus</i>)	71	89.9
Pleuronectiformes	Soleidae	Sole (<i>Solea solea</i>)	65	82.3
Scombriformes	Scombridae	Albacore (<i>T. alalunga</i>)	17	21.5

Table II. Fish allergy in children: age at onset of clinical manifestations in 79 patients

Age (mo)	Patients	
	No.	%
0-6	19	24.1
7-12	40	50.6
13-18	6	7.6
19-24	5	6.3
>24	9	11.4

Table III. Clinical features related to fish hypersensitivity in 79 patients

Description	Patients	
	No.	%
Urticaria/angioedema	73	92.4
Atopic dermatitis	14	17.7
Asthma (inhalation related)	11	13.9
Acute digestive (vomiting, diarrhea)	9	11.4
Systemic anaphylaxis	1	1.3

later, Tuft and Blumstein,⁶ by means of skin tests and passive transfer, studied the antigenic community among different fish families (flounder, cod, mackerel, carp, salmon, and shark) and concluded that there is cross-reactivity among all fish. The clinical manifestations in the patients may be combined: urticaria and angioedema on contact or ingestion, and asthma on inhalation when handling or cooking fish. Twenty years later, Aas⁷ started publishing his studies on fish allergy. He found 89 cases of fish sensitization in a series of 711 children with food allergy, for a high degree of cross-reactivity among fish species, although there were also patients, clinically sensitized to cod, who could tolerate species other than cod.⁸ Later, Elsayed et al.⁹ characterized the major allergen in cod, which is today designated *Gad c 1*.

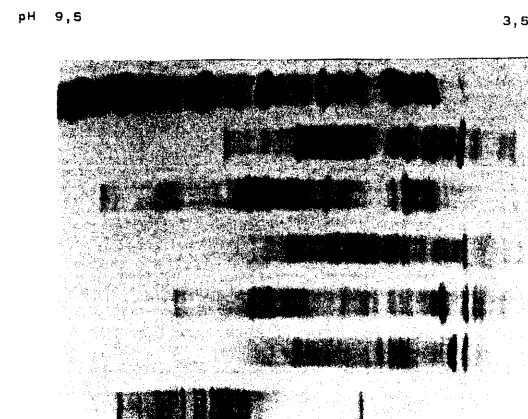
Other researchers have also studied cross-allergenicity

Table IV. Frequency of highest specific IgE response with six fish species studied

Species	Patients	
	No.	%
Hake (<i>M. merluccius</i>)	28	35.4
Whiff (<i>L. whiffiagonis</i>)	23	29.1
Cod (<i>G. callarias</i>)	20	25.3
Sole (<i>S. solea</i>)	7	8.9
Witch (<i>G. cynoglossus</i>)	1	1.3
Albacore (<i>T. alalunga</i>)	0	0.0

among various fish species and their clinical significance. DeMartino et al.¹⁰ reached conclusions similar to those of Aas⁷ and emphasized a certain degree of excess hypersensitivity in using skin tests as a diagnostic procedure in fish allergy. Frick and Barker¹¹ used sera from two patients with anaphylactic sensitization to halibut (a scophthalmid) and to tuna to assess cross-reactivity to 16 fish species; they found that the IgE binding patterns became more similar as the species became more closely related taxonomically. In five fish-allergic patients, Bernhisel-Broadbent and Sampson¹² ascertained, through skin tests, immunoblotting, and double-blind, placebo-controlled food challenge, that the sera of these patients contained specific IgE antibody to fish species that were clinically tolerated. In a recent review on immediate food allergy, Sachs and Yunginger¹³ assessed these articles and concluded that only those fish species not clinically tolerated should be withdrawn from the habitual diet. They recommended that if it is not possible to carry out skin tests with various fish species, all fish should be removed from the diet of sensitized people.

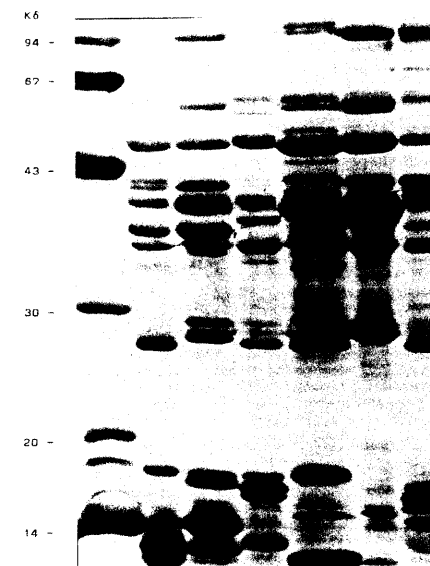
Our group has been working on this subject for the past 10 years. In our environment, the most significant fish in children's diets are those which are fat poor; the most commonly consumed species are whiff, sole, and hake.¹¹ For this reason, adverse reactions to fish are usually related to these species, which are largely unknown to allergists in other countries. In our country, by contrast, the consumption of

**Fig. 1.** Analytic IEF of six fish species (Table I). From the top down: pH standard (pH 4.65 to 9.60) and then, in succession, whiff, sole, witch, hake, cod, and albacore.

fresh or dried codfish, more widely known as an allergen elsewhere, is infrequent in children and relatively uncommon in adults. We have thus addressed the features of immediate hypersensitivity to various fish species and assessed the significance of each as an etiologic agent of immediate-type allergy.

CLINICAL AND IMMUNOLOGIC RESPONSES IN FISH ALLERGY

We studied a group of 79 children with immediate fish hypersensitivity,¹⁴ including the clinical features and IgE antibody response to six fish species, among them those already mentioned as having the highest intake among children in our area¹ (Table I). The onset of fish-related abnormalities among these children usually occurs during the early school years (Table II). The most frequently occurring clinical syndromes are acute cutaneous urticaria-angioedema, followed—far behind—by atopic dermatitis and by respiratory and digestive symptoms; polysystemic involvement occurs frequently. A point to note is the incidence of respiratory syndromes (rhinoconjunctivitis, asthma) related to inhalation of fish fumes during cooking, regardless of whether the fish is then eaten (Table III). In all patients, skin prick tests yielded reactions greater than the positive histamine control for all six investigated fish species. This observation seems to indicate a low diagnostic efficiency of skin prick tests because of cross-reactivity: 31 of 79 patients selectively tolerated one of the studied species.¹⁵

**Fig. 2.** Vertical electrophoresis (SDS-PAGE) of six fish species. Left to right: MW standard (14 to 94 kd), cod, sole, whiff, hake, albacore, and witch.

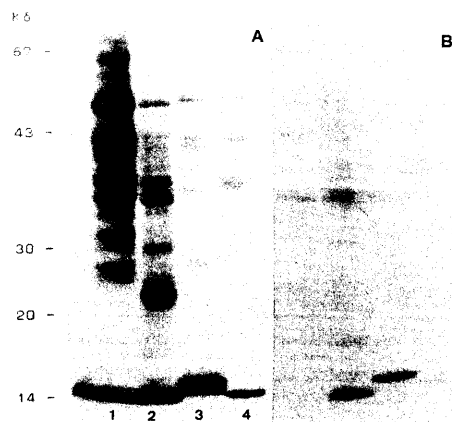


Fig. 3. A, Autoradiography of SDS-PAGE immunoblot corresponding to hake (1), whiff (2), cod (3), and albacore (4). Protein bands from each fish species binding specific IgE from the positive reference serum (pool of sensitized patients) are clearly observed. B, The same system and in the same order as in A, but with previous incubation of the positive reference serum with hake extract (1 mg protein per milliliter serum). In the inhibition control (hake blotting, B-1), practically total inhibition has been achieved, particularly in the low MW bands. The inhibition, however, is not so intense for the other fish species (B-2 to B-4), most particularly in the low MW zone corresponding to parvalbumins.

Table V. RAST inhibition for all six fish species with *Gad c 1* allergen and total cod extract

Species	Allergen		
	A	B	C
Cod (<i>G. callarias</i>)	52.23	89.80	39.73
Hake (<i>M. merluccius</i>)	28.20	67.85	72.00
Whiff (<i>L. whiffiagonis</i>)	16.63	51.74	43.80
Sole (<i>S. solea</i>)	46.55	73.46	0.74
Witch (<i>G. cynoglossus</i>)	28.51	77.08	4.47
Albacore (<i>T. alalunga</i>)	32.78	83.70	8.18

A, Inhibition percentage achieved with previous incubation of a pool of sera of patients sensitized to fish with purified *Gad c 1* (major allergen of cod) (100 µg protein/ml pool serum); B, inhibition percentage achieved with previous incubation with total cod extract (100 µg protein/ml pool serum); C, required amount (in micrograms) of total cod extract protein per milliliter pool serum for 50% RAST inhibition.

On the other hand, the quantification of specific serum IgE antibodies to each fish species might yield a more exact idea of the significance of the sensitization; only 20% of the patients in our previous study¹⁴ had high levels of specific serum IgE antibodies to all six fish species, whereas 61% had such antibodies for five species and the remainder to isolated species. In agreement with the clinical situation, only a few subjects had a high titer of specific serum IgE antibody to

albacore (Table I). We found no direct evidence that a given species causes a stronger specific serum IgE response than do the others, although albacore was not identified as the cause of maximal sensitization (Table IV).

These results might indicate that because albacore consumption is lower, there are fewer sensitizations; however, although ingestion is lower, sensitization does not have to be of a lesser degree than for other fish species, unless albacore is, in fact, less sensitizing. On the other hand, albacore sensitization detected through skin testing might be due to the presence of antigens common to those of other fish species, which are clinically less relevant.

ANTIGENIC AND ALLERGENIC CHARACTERISTICS OF FISH

Antigenic characteristics. When an isoelectric focusing study of the various fish species is carried out, each species demonstrates a particular characteristic pattern of protein bands, especially in the pH zone below 4.6 (Fig. 1). Nevertheless, even in this zone there are some similar bands for whiff, witch, and gadiforms. Contrarily, albacore lacks almost any bands in this pH zone.

Studies with SDS-PAGE (Fig. 2) also highlight the differences among the species studied. At a molecular-weight area below 20 kd, the patterns for each of the species differ,

albacore again having the lowest number of bands at this level.

These protein bands, with pH below 4.7 and MW below 15 to 20 kd, correspond to parvalbumins^{16,17} (sarcoplasmic proteins from muscle tissue of fish and amphibians that are absent in mammals). All have similar biologic properties, although the amino acid sequence is particular to each species.¹⁸ One is *Gad c 1*, described by Elsayed et al.⁹ as the major allergen in cod. The reported structural differences may be related to the varying capability for immediate hypersensitivity induction observed in these fish species.¹⁴

Allergenic characteristics. The distribution of specific IgE binding, as studied through immunoblotting, is also different according to species, mainly in the areas below pH 5 and below MW 14 kd (corresponding to parvalbumins). Among the three species of flatfish considered (whiff, witch, and sole), whiff binds the greatest amount and witch the lowest amount of IgE. Among gadiforms (hake and cod), there is a greater similarity in the higher MW protein allergens, but binding in the bands with MW less than 20 kd varies for both species. Albacore, the species with the lowest IgE antibody response, also has the lowest binding of IgE at the low MW protein level and shows no binding on the more acidic bands on IEF (data not shown).

Allergenic community among various fish species. As shown by RAST inhibition,¹⁹ there are several common antigens among the fish species; yet, with some specifications among the flatfish, whiff is the richest in common allergens. Hake is the gadiform species with the most allergens in common with other species and, at the same time, the species that is, among those studied, richest in such common allergens. The scombriform albacore is the species with fewer allergens in common with all others.²⁰ Because hake and whiff are the two species most frequently consumed by children, these data may explain why, in fish-sensitized patients, positive skin test reactions to many species are so frequent. Probably the greatest allergenic differences among the various fish species are to be found in proteins with MW less than 20 kd, as could be surmised from autoradiography inhibition experiments (Fig. 3).

It has been demonstrated that the *Gad c 1* antigen from cod has great allergenic significance,¹¹ and it has even been considered the "reference" sensitization in fish allergy.²¹ However, because of the structural differences in the parvalbumins among various fish species, its significance may not be the same for other species.

When RAST inhibition is performed with *Gad c 1* antigen against the mentioned fish species, we observed that, although this parvalbumin is important as an allergen in cod, it does not hold for another gadiform (hake) and even less so for flatfishes. Albacore also has fewer allergens that are similar to *Gad c 1* (Table V).

PROPHYLAXIS AND THERAPY FOR FISH ALLERGY

The data presented above suggest that hake is the fish species able to provoke the strongest IgE response, followed by whiff. Among all the species studied (Table I), albacore is the least allergenic. These results should be considered when fish is introduced into the diet of patients (children) at risk for allergy. In fact, this is inadvertently being done in some countries such as the United States, where the most popular fish species is tuna, which is practically identical to albacore.

Therapeutically, when immediate hypersensitivity to one fish species is demonstrated with symptoms related to contact or ingestion, the most adequate therapy is an elimination-avoidance diet. Frequently, however, despite the presence of hypersensitivity (e.g., the presence of specific IgE antibodies in skin or serum), patients will tolerate some fish species.^{12,13} In some atopic fish-sensitized patients²² who undertook an elimination diet, even though they clinically tolerated the "inculcated" fish, reintroduction of that fish several months later might be followed by anaphylactic—and sometimes severe—clinical manifestations.

Thus, even in the presence of specific IgE sensitization, if good clinical tolerance is evident and demonstrated, it seems advisable to continue with the ingestion of such fish. A therapeutic elimination diet should be instituted only when a proven correlation can be demonstrated between the particular fish and the patient's symptoms.

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Session I: Discussion

ANNE FERGUSON, FRCP, FRCPATH, FRSE: Definitions and diagnosis of food intolerance and food allergy: Consensus and controversy (see pp. S7-S11)

DR. STROBEL: In your Edinburgh study of atopy and skin test sensitivities, did you accept only positive skin test results as an indicator of atopy? How did you define atopy? About 8% to 10% of the population have positive skin test reactions to antigens but have no symptoms associated with these antigens at the time of testing.

DR. FERGUSON: We defined atopy as a positive skin test reaction because this indicates the presence of IgE antibodies to one or more antigens.

DR. SCHMITZ: Dr. Ferguson, you said that type I hypersensitivity led to increased permeability in the gut, which would make it possible for cell-mediated or delayed-type reactions to occur. Is this an opinion or a fascinating hypothesis? Are there solid experimental data to support that?

DR. FERGUSON: Increased permeability creates the circumstances in which these reactions could develop. Normally, very little IgG is in and around the gut. If the permeability increases, IgG pours into the gut lumen. Then there are certainly the conditions for producing immune complexes, complement activation, and deposition.

Regarding cellular immunity, lymphocytes and mast cell precursors do migrate from the blood vessels into the lamina propria and quickly reenter the lymph and leave again. With increased permeability, it is likely that the traffic of these cells would be greater.

DR. SCHMITZ: That could very well explain the mixture of type I and type IV hypersensitivities that we observe in cow milk protein intolerance.

DR. FERGUSON: That is right. Of course, cells and molecules associated with suppression will also pour in. Bacterial products that get into the tissues may up- or down-regulate local immunity.

ERKKI SAVILAHTI, MD: Allergenicity of cow milk proteins (see pp. S12-S20)

DR. BUSINCO: You mentioned the adapted formulas that contain 60% whey and 40% casein proteins. However, it is not possible just to change the proportions of whey and casein to get a formula that is more similar to human milk.

The protein specificity of cow milk whey protein is totally different from that of human milk whey protein. To obtain a blood amino acid profile closer to that found in breast-fed infants, recent studies have shown that it is important to decrease the protein concentration significantly rather than change the proportion of casein and whey.

You have shown that the whey protein β -lactoglobulin is the most allergenic protein. I am not convinced that increasing the proportion of the proteins that are considered by many to be the most allergenic is advantageous in terms of allergy. Do you still believe that whey-predominant formulas have an advantage over casein-predominant formulas?

DR. SAVILAHTI: Our results showing that β -lactoglobulin was the most allergenic protein do not have any basis in the literature. I do not agree that it has been shown to be the most allergenic in many studies. Several people have speculated about that, but I do not find any clear reason for that speculation.

The nutritional values of these formulas have been very carefully studied. For instance, in our hospital about 10 to 15 years ago, these casein- and β -lactoglobulin-based formulas were compared. The blood amino acid profiles of the infants fed the β -lactoglobulin-predominant or whey-predominant formula were very close to those of infants fed human milk. I do not believe that the small differences in amino acid concentrations are significant. The whey-predominant formulas are good formulas nutritionally and there may be some advantage to whey proteins, but I believe that there is no major difference in the allergenicity of the formulas.

DR. STROBEL: My understanding is that gut closure is complete at 3 months of age and then gut permeability to protein molecules stays the same. Would you comment on gut permeability after that period?

DR. SAVILAHTI: We have been studying that recently, and we have found that a very small amount of human lactalbumin crosses the intestinal barrier during the first 2 months. After 2 or 3 months, we do not see this at all. Similarly, about 7 years ago, we measured the absorption of antibodies from human milk. It has been claimed that as much as 15% of these antibodies are absorbed, but when we measured this in healthy infants and premature infants, we found no absorption of IgA antibodies and we estimated that it was less than 0.1%. I agree that the human intestine is closed at birth but that there is some permeability.