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Fish allergy: is cross-reactivity among fish species relevant? Double-blind placebo-controlled food challenge studies of fish allergic adults

Arthur Helbling, MD; Robert Haydel, Jr, MD; Marjorie L McCants; Jon J Musmand, MD; Jane El-Dahr, MD; and Samuel B Lehrer, PhD

Background: Allergic reactions to fish are a common cause of food allergy in many areas of the world where fish is a major source of protein. Although different species of fish may be consumed, possible cross-reactivity has received limited investigation.

Objective: The aim of this study was to assess potential cross-reactivity to different **species** of fish species using double-blind, placebo-controlled food challenges (DBPCFC) in fish-allergic adults and to compare skin test and RAST reactivity with the challenge response.

Methods: Nine skin prick test tired/or RAST-positive adult individuals with histories of all immediate-type reaction following fish ingestion were challenged with different fish species using double-blind, placebo-controlled food challenge.

Results: Of a total of 19 double-blind, placebo-controlled fish challenges performed, 14 challenges (74%) resulted in the induction of objective signs that were consistent with an lgE-mediated response. The most common sign observed was emesis (37%); the most prevalent subjective symptoms reported were compatible with the oral allergy syndrome (84%)). Three subjects reacted to at least three fish species and one subject reacted to two fish species tested. In regard to the positive challenges, predictive accuracy of skin prick test and RAST was 84% and 78%, respectively.

Conclusion: Our results indicate that clinically relevant cross-reactivity among various species of fish may exist. Advising fish-allergic subjects to avoid all fish species should be emphasized until a species can be proven safe to eat by provocative challenge.

Ann Allergy Asthma lmmtmol 1999:83:517 523.

INTRODUCTION

Ingestion of fish or occasionally, inhalation of vapors generated when fish are cooked are potential causes of both lgE-mediated and nonimnmnologic adverse reactions to fish. An adverse reaction following exposure to fish call be due to fish proteins or to contaminants in fish such as scombroid, toxins, or parasites. Allergic symptoms following fish ingestion of sensitized individuals are usually immediate. Most subjects demonstrate cutaneous symptoms, such as urticaria or angioedema, followed by respiratory difficulties, gastrointestinal complaints, or oven

cardiovasculatory symptoms including shock. The exact prevalence of fish allergy is not known, but can be significant in populations where fish is a major component of the diet. In Norway, Aas estimated that 1/1000 of the general population is hypersensitive to fish; De Martino et al determined that 4 to 5 out of 1000 Italian children have cod-fish-specific IgE antibodies. In Sweden and Spain, of all pediatric patients with food allergy, up to 39% are allergic to fish. Due to current health concerns about fat and cholesterol levels in beef and pork products, fish is becoming increasingly more important as a food source, particularly in the Western World. The per capita fish consumption in tile United Staten has steadily increased from 4.7 *kg* in 1960 to 7.0 kg in 1990. Sensitivity to fish may also become more important in this country.

Most studies of fish allergy have been performed on pediatric subjects, although fish is considered one of the most important food allergens in adults. Despite the huge variety of fish species, the most commonly consumed fish species belong to a few orders. Allergy to cod is tine best studied. Unfortunately, clinically significant cross-sensitivity among different species of fish has received limited investigation and the few published studies have yielded conflicting results. Some authors reported clinical cross-reactivity to most fish species while others demonstrated sensitivities limited to only one or two species. Fish-allergic individuals are therefore usually advised to avoid all species or' fish.

The double-blind, placebo-controlled food challenge (DBPCFC) is considered to be the only reliable procedure for diagnosing allergy to specific foods. The purpose of the current study was to challenge fish-sensitive subjects in order to verify reported symptoms by BPCFC, to assess potential reactivity to different fish species, and to determine possible correlation between skin tests, and RAST with the food challenge response.

MATERIAL AND METHODS

Patients and Control Subjects

Based on histories of an immediate and recurrent systemic reaction within an hour after ingestion of fish, nine adult subjects (mean age 31 years, range 17 to 39 years) were enrolled in the study. These subjects were recruited from the allergy clinics at Tulane and Charity Hospitals or were referred by local physicians in practice. Informed consent was obtained from all individuals.

Skin Prick Tests

All subjects were prick skin tested with 12 common inhalant allergens and three commercial fish extracts: channel catfish *(Ictalurus punctatus)* [Greer Labs], codfish *(Gadus callarivus)* [Center Labs], and snapper *(Sebasto-ces* spp.) [Hollister-Stier] as well as with turkey meat extract and A-1 sauce for control, prepared in our laboratory. A positive skin prick test (SPT) was defined as a mean wheal diameter of 3 mm or greater to the test antigen in subjects who reacted with at least 3-mm wheal to the positive control (1 mg/mL histamine diphosphate) and did not react to

the negative diluent control (50% glycerol in PBS). Results were recorded 15 minutes after application of the extracts.

Specific lgE Determinations (RAST)

Commercial extracts of catfish, codfish, and snapper were dialyzed against 0.1 M borate buffer (pH 8.0), concentrated by dialysis with Ficoll 400 (Pharmacia LKB, Upsala, Sweden), and stored at -20°C until use. Protein concentrations were measured using a commercially available phenol reagent method (Sigma Diagnostics, St. Louis, MO).

Cyanogen bromide-activated paper disks, coated with fish extract (50 ug protein/disc) were incubated overnight in duplicate with 100 uL undiluted serum. After washing with saline (0.9% NaCl), 100uL l-labeled anti-IgE (15,000 cpm/disc) (Kallestad, Chaska, MN) was added to discs, and they were incubated overnight. Disc were washed and bound. Radiolabeled 1251 (cpm) was measured in a gamma counter (Gamma 5500; Beckman, Ir-vine, CA). Results were expressed as a mean percent binding of total radioactivity added. RAST values ->3% of total radioactivity added were considered positive.

Preparation of Fish and Placebo Challenge Samples

Through test trials with fish-tolerant volunteers, the texture and taste of catfish, codfish, and snapper were found to be masked effectively in ground turkey meat, salt, and A-I steak sauce (Nabisco Brands, Inc, East Hanover, NJ). Samples were prepared by cooking ground turkey and fish separately at 350°C for 20 to 30 minutes. The two food items were then pureed separately in a food processor. Four challenge doses offish (l, 4, 16, and 64 g) plus turkey (31, 28, 48, and 64 g), respectively, and four turkey (placebo) doses (32, 32, 64, and 128 g) were prepared with salt and A-1 steak sauce added proportionately. Challenge and placebo dose samples were individually mixed, formed into patties, and stored frozen until utilized.

PROCEDURE OF DBPCFC

All challenges were performed and completed within a single 8-hour testing period in two phases at the General Clinical Research Center (GCRC), at the Medical Center of Louisiana, New Orleans, LA. The challenge protocol was approved both by the GCRCs human subjects committee and by the Tulane Committee on the Use of Human Subjects. Short-acting antihista-mines were discontinued for I week, and 132-agonists were withheld for 6 hours before the challenges in asthmatic patients. None of the study subjects were being treated with glucocorticosteroids or long-acting antihistamines. For the challenge, study subjects had been in good health and had not eaten since midnight. Prior to any challenge, informed consent, physical exam, vital signs, and baseline peak expiratory flow rates (PEFR) were performed and intravenous access was procured. The first phase of testing was a DBPCFC with either in-creasing amounts of fish or placebo randomly administered at hourly intervals. The fish doses administered during this challenge were 1, 4, 16, and 64 g prepared as described. The first two

catfish subjects were tested with a starting dose of 0.25 mg. The DBPCFC was considered positive if the subject manifested an objective sign consistent with IgE-mediated symptoms such as urticaria, decrease of PEFR of -> 15%, drop in blood pressure (>30 mm Hg systolic), or eme-sis after a challenge dose containing fish. If no objective signs occurred during the blinded phase, the second phase, an open fish challenge with approximately 2 ounces (64 g) of the baked fish in question, was performed. One hour following completion of the challenge, patients were provided with emergency medical access information and a questionnaire to report any delayed signs or symptoms occurring within 24 hours after discharge and allowed to leave.

RESULTS

Study subjects' characteristics and SPT and RAST reactivity to the fish under study are detailed in Table 1. All participants were atopic based on personal and/or family history and positive SPT to at least two common inhalant aeroallergens. None of the study subjects reported allergy to turkey or had positive SPT to the turkey extract or A-1 sauce. All fish-allergic subjects had a positive SPT to the fish alleged to induce their allergic reactions. Five of six study subjects (# 1-5) who reacted by SPT to all three fish species also reported an immediate reaction to each of these species. RAST reactivity varied, but was detected in 6/6 subjects sensitized (by skin prick test and history) to catfish, in 5/7 (71%) sensitized to cod, and in 5/6 (83%) sensitized to snapper. RAST reactivity of eight study subjects to species of different fish is shown in Table 2. Because the quantity of serum obtained from several subjects was limited and no further serum was available, only those sera in sufficient quantities were tested to all fish species.

Table 1. Demographic Data of the Fish-Allergic Subjects, Skin Prick Test (SPT) and RAST Reactivity to the Fish Under Study

Subject	Clinical Symptoms Reported	Age (yr)	Sex	Catfish		Codfish		Snapper	
				SPT	RAST %bound	SPT	RAST %bound	SPT	RAST %bound
1	OA,* hives, cramps, nausea, emesis	38	M	--	26.5	+	28.9	+	4.9
2	OA, gen. puritus, nausea, emesis	35	F	+	18.4	+	24.2	+	6.2
3	OA, wheezing	39	F	+	16.8	+	26.7	+	25.0
4	OA, nasal congestion, chest tightness	20	F	+	6.4	+	4.0	+	1.1
5	OA, hives, chest tightness	36	M	--	25.3	+	23.2	+	23.0
6	OA, hives, nausea (>24 h)	35	M	+	3.9	+	nd*	+	1.8
7	Puritus, emesis	39	F	-	nd	+	1.2	-	nd
8	OA, emesis	20	F	-	nd	+	1.7	+	8.8
9	OA, chest tightness	17	F	-	nd	-	nd	+	nd

* OA = oral allergy syndrome and nd = not determined.

Table 2. RAST Reactivity (positive ~3% bound) to Different Fish Species in Eight of the Nine Subjects Studied

	Subjects Studied

Fish Order	Fish Species	#1	#2	#3	#4	#5	#6	#7	#8
Salmiformes	Salmon	15	13	nd*	nd	7	5	nd	nd
	Trout	18	15	nd	nd	12	3	nd	nd
	Whitefish	23	26	nd	nd	17	2	nd	nd
Perciformes	Bass	25	24	nd	nd	22	nd	nd	nd
	Mackerel	2	12	nd	nd	5	17	nd	nd
	Perch	25	28	nd	nd	21	0	nd	nd
	Snapper	5	6	25	1	23	2	nd	9
	Tuna	2	7	nd	nd	1	0	nd	nd
Gadiformes	Codfish	29	24	27	4	23	nd	1	2
	Haddock	23	24	nd	nd	16	nd	nd	nd
	Pollock	20	19	nd	nd	11	1	nd	nd
Pleuronectiformes	Flounder	11	27	nd	nd	13	2	nd	nd
	Sole	14	21	nd	nd	15	2	nd	nd
Clupeiformes	Anchovy	2	8	nd	nd	2	0	2	nd
	Herring	5	12	nd	nd	3	18	1	nd
Cypriformes	Catfish	27	18	17	6	25	4	nd	nd

nd = not determined due to insufficient quantities of serum.

Patients had a history of an imme-diate-type allergy to fish; this was objectively studied by DBPCFC (Table 3). Of 19 DBPCFC performed in nine fish-sensitive subjects, 14 challenges (74%) were considered positive based on objective signs/symptoms that occurred following fish ingestion, but **not** during placebo challenge. Subjective symptoms were perceived in all positive challenges and these preceded objective signs. Doses eliciting symptoms in DBPCFC varied between 0.25 and 64 g. Most objective signs (79%) appeared at doses between I and 4 g, one at 16 g, and two at 64 g following the fish challenge. In five positive challenges (26%) objective signs/ symptoms were registered at the same dose (0.25 to 1 g) as subjective symptoms. Two of the five open challenges (40%) were positive. Generalized urticaria developed after catfish and snapper challenge in subject 1. Emesis following placebo challenge (although after several doses of fish and placebo) was seen in 2/19 DBPCFC (11%). Overall, 16 of the total 24 challenges performed with fish (66.6%) were positive.

Three of four subjects (1-4) tested with three species of fish reacted with objective signs to all three species of fish, and one of two subjects challenged with two fish species reacted to both species tested. All three subjects (6,7,9) challenged with a single fish species had symptoms. The most commonly reported symptom in 7/9 study subjects (78%) and in 16/19 DBPCFC (84%) was local pruritus of the lips and oropharynx, leading to erythema and swelling (oral allergy syndrome). These oral symptoms were always the very first observed in fish-

allergic subjects who had positive challenges. The second most frequent subjective symptom was dyspnea, followed by nasal irritation, and gastrointestinal cramps. Of the objective signs, emesis was the most frequent, followed by respiratory signs (rhinitis in three, and decrease of

Table 3. Reported Symptoms, Objective Signs, and Corresponding Dose During DBPCFC in Nine Subjects with Fish Allergy

	Catfish			Codfish			Snapper					
Subject	Subjective Symptoms*	At Dose	Objective Signs/ Symptoms	At Dose	Subjective Symptoms	At Dose	Objective Signs/ Symptoms	At Dose	Subjective Symptoms	At Dose	Objective Signs/ Symptoms	At Dose
1	OA, P, Gl	0.25 g	Negative*	64 g	OA, P, D	4 g	U	64 g	OA, F, Gl	4 g	Negative	64 g
2	OA, C, I	0.25 g	C, R, E	0.25 g	OA	1 g	E	1 g	OA	1 g	E	1 g
3	OA	1 g	PEFR 20%	1 g	OA	1 g	PEFR 31%	4 g	OA, I	1 g	U	1 g
4	OA, D, t	1 g	C, F, R	16 g	OA, D, P	1 g	Negativet	64 g	Gl	4 g	Negative	64 g
5	OA, D, N	1 g	R	64 g	OA	4 g	Negativet	64 g	NC		NC	
6	N, Gl	1 g	B, E	4 g	§		§		NC		NC	
7	NC§		NC		P, N, H	1 g	E	4 g	NC		NC	
8	NC		NC		OA, N	1 g	E	4 g	OA	1 g	E	4 g
9	NC		NC		NC§		NC§		OA, N	1 g	PEFR 23%	4 g

* Open challenge: generalized urticaria.
1' Open challenge: negative.
:i; Reaction after placebo challenge.
§ Not challenged.
Abbreviations:

B = belching	C Conjunctititis	D – Dyspnea	E - Emesis
F = flushing	Gl = Cramps	H = Headache	I = nasal irritation
N = nausea	OA - Oral Allergy	P gen. Pruritus	PEFR = Peak expiratory flow rate
R = rhinitis	U = Urticaria	N = Nausea	

more than 15% of the PEFR with notable wheezing in two subjects), and urticaria was seen less commonly.

One subject (6) withdrew from the study after the first challenge, because he disliked the fish challenge procedure. He also was the only patient who recorded nausea during the next 24 hours after catfish challenge. All other subjects had no residual symptoms after discharge.

Correlation of SPT, RAST, and the DBPCFC is shown in Table 4. Positive predictive value of SPT was 73.8% compared with 73.3% with RAST. In

Table 4. Correlation Between SPT, RAST, and the DBPCFC

		DBPCFC	
		+	-
SPT	+	14	5
	-	**0**	**0**
RAST*	+	11	4
	-	2	1

*RAST % binding ->3% was considered positive. In one DBPCFC-positive subject RAST was not done.

contrast, negative predictive value of SPT was 100% and with RAST 33%. Concordance of positive SPT and positive RAST was 74%. Taking the open challenges into account, positive predictive value of SPT and RAST increases to 84% and 78%.

DISCUSSION

The present study is relevant for individuals with a convincing history of fish allergy. In all subjects, fish hypersensitivity was confirmed by DBPCFC which provoked symptoms that are characteristically associated with an IgE-mediated allergic response. Compared with other DBPCFC studies that report a 50% nonreaction rate to the suspected food, our 74% rate confirming history to different fish species is high. Our results however, are similar to those of Hansen and Bindslev-Jensen, in which 70% of patients studied had a positive challenge response to codfish? The high rate of positive challenge tests identifying fish-allergic subjects is probably due to the careful selection of our study population and the precise preparation of fish challenge doses and challenge procedure performance.

Fish texture and taste were undetect-able to investigators and volunteers. The majority of fish-allergic or sensitive subjects, however, could identify masked fish at low doses by oropharyngeal symptoms. This complex of oral symptoms has been described as the oral allergy syndrome and is well known in pollen-related food allergic individuals. Oral allergy symptoms can occur in DBPCFC if the challenge food is not encapsulated, a procedure which inhibits the contact with the oropharyngeal mucosa.

Emesis was the most frequent objective sign in our study and was considered an IgE-mediated response. In all challenges, oropharyngeal symptoms or generalized pruritus preceded emesis. In those subjects who did not experience emesis, a full spectrum of IgE-mediated manifestations such as urticaria or respiratory symptoms was observed. We believe some of our patients may not have developed more systemic signs due to emesis which prevented absorption of sufficient amounts of allergen.

Oral allergy symptoms were the best predictors of developing further IgE-mediated signs. Patients should be cautioned to take oral symptoms seriously and to stop ingesting the fish at that point. Manifestation of upper and lower airway symptoms, commonly observed during food-allergic reactions were perceived in half of the study subjects. Significant acute obstruction of the lower airways, as demonstrated by a decrease of PEFR of more than 15% was documented in only two patients during three challenges.

Most challenges were objectively positive at doses between 0.25 and 4 g of fish. The quantity of fish eliciting symptoms, occasionally at very low amounts of fish proteins, as well as the pattern of reactions observed during the challenges are consistent with an IgE-mediated mechanism and are similar to other reports using DB-PCFC. 1.3.5.19.22.31

This study looked at challenge-proven fish hypersensitivity in adults, in contrast to previous fish challenge studies in children. It is well documented that the majority of children with hypersensitivities to milk, egg, wheat, and soy outgrow their clinical reactivity by school age. Those sensitized to shellfish, peanuts, or tree nuts only rarely outgrow these. Additionally, food sensitivities that appear alter preschool age are less like to resolve with time. Allergy to fish has not yet been sufficiently studied longitudinally to determine the frequency of outgrowing it. Our study subjects clearly demonstrated substantial symptoms to multiple fish species even after years (in some >20 years) of consciously avoiding fish, suggesting that fish allergy may persist for many years following cessation of exposure. Similar results were reported in DBPC shrimp challenge studies. While Aas found a spontaneous resolution to fish hypersensitivity over time in some children, the natural course of allergy to fish was followed only in the minority of children, and two had evidence for an increased hypersensitivity. Further studies will be necessary to determine the persistence of fish allergy into adulthood, but it appears as though adults may react more strongly and more broadly across fish species.

In this study, two of the five open challenges were positive. Our experience suggests that an open challenge should be performed whenever the blinded part of the challenge is negative; although, in the literature, the subsequent open challenge rarely is found to be positive.31 Since all subjects had subjective oral allergy symptoms, it is conceivable that exposure to a larger quantity of fish or perhaps fish exposure in combination with substances that can increase the absorption of intact proteins, such as alcohol or ingestion of nonsteroidal anti-inflammatory drugs, may precipitate an allergic reaction.

There is disagreement in the literature with regard to cross-sensitivity and abstinence among different orders of fish for fish-allergic patients. Is abstinence to all fish species necessary for fish allergic subjects'? Although several in vitro studies have demonstrated the existence of common allergens between different fish species, only a few investigations, mainly with codfish-allergic children, have shown clinical relevance of hypersensitivity reactions to different fish. From those studies, it has been concluded that some fish-allergic children may tolerate fish from taxonomically distinct orders than the one to which they are allergic. The study of

Bernhisel-Broadbent et al3 demonstrated 3 of l l fish-allergic children reacted to two or three fish species of different orders. In our study, four of six subjects who were challenged with more than one fish species reacted to more than one species of taxonomically different fish orders. Our results concur with those data that clinically significant hypersensitivity to different fish species can occur. The advice of eschewing all fish species until proven otherwise is probably safer and should be emphasized to all subjects with a convincing history of immediate reaction following fish ingestion. Any known fish-sensitive patient who considers eating a variety of fish species in an attempt to pinpoint which should be eliminated, should be cautioned that serious reactions could occur and that it would be best to do this under medical supervision with epinephrine available.

In our investigation, a relatively high concordance between SPT with challenge responses was observed, suggesting that there are sufficient amounts of fish proteins and allergens in commercial fish extracts. Our data are in accordance with the finding of other authors using a purified codfish allergen. Significant levels of serum fish-specific IgE were noted in the majority (73%) of the positive and in one of four of the negative challenges. Although the magnitude of the RAST did not predict the occurrence of a positive challenge, our results suggest that measurements of fish IgE antibodies may provide diagnostically useful information, eg, identifying individuals at risk for hypersensitivity reactions following fish ingestion. High RAST reactivity to a particular food has been shown to correlate with a history of severe allergic reactions to many foods including cod and shrimp. To date, however, no diagnostic procedure can replace the accuracy of DBPC food challenges.

In conclusion, our data support clinically relevant allergy among various fish species of taxonomically dist subjects with a history of an immediate reaction after fish exposure should abstain from all fish species until it is definitely demonstrated that they can safely eat other fish species. Fish-allergic individuals should also inquire at restaurants whether seafoods listed are substituted with a fish-based product (eg, imitation crabmeat). The individuals should always carefully read ingredients of all processed and packaged foods since processed fish meat (surimi) is used as a basis for a variety of imitation non-fish products such as beef or pork substitutes?

Skin testing and RAST with commercial fish extracts may assist in assessing relative risk for fish-sensitive subjects. Food challenge in a clinical setting, however, remains the only safe and reliable way to diagnose an IgE-mediated sensitivity and ascertain the true risk for fish-sensitive individuals who wish to consume fish in their diet. Skin testing and RAST, however, identify patients at risk for true fish hypersensitivity.

Finally, since the symptoms of the oral allergy syndrome were the first reported by our patients and these symptoms always occurred prior to the onset of more severe reactions, food-allergic patients should be alerted to this manifestation when eating meals. The development of more serious reactions may be prevented if the food-sensitive individual is educated about these early symptoms and subsequent appropriate interventional management is practiced, eg, immediate cessation of the suspect meal and, if needed, immediate initiation of emergency

treatment including antihistamines, epinephrine, or corticoste-roids.

ACKNOWLEDGEMENTS

This project was supported by a grant from the National Fisheries Foundation and in part by NIH grant 5MO1 RR05096-03 from the Division of research resources, NIH. The helpful comments of Drs Rosalia Ayuso and Gerald Reese and word processing by Ms Pat Constant are greatly appreciated.

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