

Allergic reactions associated with airborne fish particles in IgE-mediated fish hypersensitive patients

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We evaluated the clinical characteristics found in 21 children who showed allergic reactions upon incidental inhalation of fish odors or fumes, from 197 diagnosed with IgE-mediated fish hypersensitivity. Allergic reactions to fish via ingestion began in most patients (86%) within the first 24 months of life. The vast majority (19/21) of patients showed cutaneous symptoms, either alone or, less frequently, associated with other clinical manifestations. Hake and flounder were the species of fish most frequently implicated in eliciting clinical manifestations upon ingestion. After diagnosis, all these patients were placed on a strict fish-avoidance diet. During this period of avoidance, patients reported allergic reactions (mean age 7 years) after incidental exposure to airborne fish odors or fumes. Clinical manifestations through inhalation were respiratory (mainly wheezing) in 12 patients and cutaneous (mainly urticaria) in nine patients. Nineteen of 21 patients reported three or more episodes upon exposure to fish aerosols; in most cases, these episodes occurred at home when other people were eating fish. In conclusion, incidental inhalation of fish odors or fumes could play an important role in accidental and unknown encounters with fish in children on fish-avoidance diets for fish IgE-mediated hypersensitivity. Such exposures could elicit clinical symptoms and could have some effect in delaying the development of tolerance.

J. F. Crespo, C. Pascual, C. Dominguez, I. Ojeda, F. M. Muñoz, M. M. Esteban

Allergy Service, La Paz Children's Hospital, Madrid, Spain

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Dr J. F. Crespo
Laboratorio de Inmunoalergia
Hospital Infantil La Paz
Castellana, 261
28046 Madrid
Spain

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Fish has been reported to be an important cause of IgE-mediated hypersensitivity reactions to foods. In our area, fish has been implicated in 17.8% of allergic reactions to foods (3). Extrapolated results from Martino et al. showed that about 4–5/1000 children may have allergy to codfish (5).

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. Upon inhalation, fish allergens elicited respiratory symptoms. These infrequent reports refer mainly to cases of occupational exposure, including fish processing, handling, and cooking activities (6). However, as reported for other foods (9), nonoccupational exposure to airborne fish odors and fumes could have a potential role in provoking clinical manifestations in subjects with IgE-mediated hypersensitivity to fish.

The present investigation constitutes an extension of previous research on fish hypersensitivity. In this work, we report clinical characteristics found in 21

children diagnosed with IgE-mediated fish hypersensitivity who showed allergic reactions upon incidental inhalation of fish allergens.

Material and methods

Subjects

We selected our study population from 197 children diagnosed with IgE-mediated fish hypersensitivity at La Paz Children's Hospital (Madrid, Spain). Twenty-one of these 197 patients were selected to be included in this study because they reported immediate symptoms after exposure to fish odors or fumes.

All these patients had been diagnosed as having IgE-mediated fish hypersensitivity and placed on a strict fish-avoidance diet. These patients were followed-up for periods of 2–14 years. Fish hypersensitivity was re-evaluated after every 2 or 3 years of a fish-avoidance diet. In these re-evaluations, patients were specifically asked about accidental or incidental contacts with fish.

Materials

Fish antigens. The antigens utilized were of two kinds: 1) commercial extracts of codfish, trout, and tuna (Bencard-Bayer, Germany; Leti, Spain); 2) extracts produced from fish not commercially available, such as hake, flounder, sole, swordfish, and sardine. Fish extracts prepared in the La Paz Children's Hospital immunoallergy laboratory were extracted in PBS, defatted if necessary, dialyzed, and lyophilized. Extracts were reconstituted to 10 mg/ml in PBS-glycerol for prick test and to 1 mg/ml in PBS for binding to cellulose CNBromide activated disks.

Procedures

Diagnosis of allergic reactions to fish through ingestion. The diagnosis of IgE-mediated fish hypersensitivity was accomplished on the basis of the clinical history, open fish challenge, and fish-specific IgE demonstrated by skin prick test and/or RAST. We evaluated the appearance of clinical symptoms described elsewhere (12), less than 2 h after ingestion of food. Open fish challenge had been carried out in 12 subjects included in this study. Open food challenges were performed as outlined in a previous publication (7). Briefly, the patients had to be symptom-free and to have discontinued antihistamines or corticosteroids at least 1 week prior to challenge. Patients were given increasing amounts of food every half hour if no symptoms were elicited, until the standard diet amounts for their ages were reached.

Diagnosis of allergic reactions to fish through inhalation. Patients on a fish-avoidance diet were asked specifically during follow-up about accidental or incidental contacts with fish. Reported symptoms after the exposure to airborne fish odors or fumes were accepted only when patients, previously asymptomatic, developed symptoms only after this type of exposure.

Skin testing. Glycerinated fish extracts (10 mg/ml) were applied to the patient's forearm by the prick technique. Isotonic glycerol saline was used as a negative control and 0.1 mg/ml histamine chloride as a positive control. All tests were applied and measured by one of two trained nurse clinicians. The result was considered to be positive when a fish allergenic extract elicited a wheal at least 3 mm greater than the negative control prick.

In vitro testing. The serum concentration of specific IgE was determined by an immunoenzymatic method, Phadezym RAST (Pharmacia Diagnostics, Sweden). The results were expressed by classes (0–4) and PRU/ml (0.35–17.5 PRU/ml), according to the manufacturer's instructions.

The total serum IgE was determined with the Phadezym PRIST (Pharmacia Diagnostics, Sweden) immunoenzymatic method with an IgE detection level of 0.5–100 IU/ml (using a 1:10 dilution of the sample sera), according to the manufacturer's instructions.

Results

Of 197 children diagnosed as having IgE-mediated fish hypersensitivity related to eating fish, 21 also showed immediate clinical symptoms upon exposure to fish odors or fumes. In addition, 20 of these 21 patients were diagnosed as having the following other allergic disorders: allergic asthma and atopic dermatitis (eight patients); allergic asthma and/or rhinitis (eight patients); atopic dermatitis and egg allergy (one patient); atopic dermatitis only (one patient); shellfish allergy (one patient); and cold urticaria (one patient) (Table 1).

Allergic reactions to fish through ingestion

Clinical manifestations. The symptoms observed during the allergic reactions are enumerated in Table 1. Fourteen of 21 (66%) subjects had only cutaneous reactions, including mainly generalized acute urticaria and/or angioedema. Four (19%) had acute skin reactions associated with gastrointestinal symptoms. One (5%) had both skin reactions and respiratory symptoms. Interestingly, two patients showed only oropharyngeal symptoms after ingesting fish, including tingling, pruritus, angioedema of the lips, and throat tightness. They were diagnosed as having oral allergy syndrome.

Reactions occurred during ingestion of hake (11 patients), flounder (eight patients), codfish (two patients), tuna (two patients), sole (one patient), trout (one patient), and sardine (one patient) (Table 1). All adverse reactions occurred within 2 h of ingestion of fish, and most occurred from within a few minutes to an hour. The age at onset of clinical manifestations was from 3 months to 7 years, mean 17 months (18, SE).

Fish-specific IgE. All 21 children exhibited sensitizations to multiple species of fish (Table 1). Seventeen of 21 subjects showed sensitizations at least to flounder, codfish, sole, hake, and tuna.

Allergic reactions to fish through inhalation

Clinical manifestations through inhalation or exposure to fish airborne particles, without physical contact, were as follows: 1) respiratory manifestations only (patients 1, 2, 4, 5, 6, 9–12); 2) dermatologic symptoms only (patients 13–21); and 3) respiratory

Table 1. Clinical characteristics of 21 patients diagnosed with fish hypersensitivity who showed also clinical symptoms upon inhalation of fish allergens

Patient no.	Age at onset (mo)	Symptoms upon ingestion	Fish-specific IgE	Other allergic disorders
1	36	Urticaria, angioedema	F, C, S, <u>H</u> , <u>T</u> , Sa	Atopic dermatitis Allergic asthma
2	9	Urticaria, angioedema, vomiting	F, C, S, <u>H</u> , T, Sa, Sw	Shellfish allergy
3	7	Oral allergy syndrome	<u>F</u> , C, S, <u>H</u> , T	Allergic asthma
4	6	Urticaria, angioedema, vomiting	F, C, S, <u>H</u> , T, Sw, Sa	Atopic dermatitis Allergic asthma
5	19	Urticaria, angioedema	<u>F</u> , C, S, H	Atopic dermatitis Allergic asthma
6	6	Urticaria, angioedema	<u>F</u> , C, T, Sa	Allergic rhinitis
7	84	Wheeze, angioedema	F, C, S, H, T, <u>Tr</u> , Sa	Cold urticaria
8	36	Urticaria, angioedema	F, C, S, H, T, <u>Sa</u>	Allergic asthma
9	6	Urticaria, angioedema	F, C, <u>S</u> , <u>H</u> , T, Tr, Sa	Atopic dermatitis Allergic asthma
10	12	Oral allergy syndrome	F, <u>C</u> , S, H	Atopic dermatitis
11	6	Angioedema, vomiting	F, C, S, <u>H</u> , T, Tr, Sw	Allergic asthma
12	24	Urticaria, angioedema	F, C, S, <u>H</u> , T, Sa	Atopic dermatitis Allergic asthma
13	5	Urticaria	F, C, S, <u>H</u> , T, Tr, Sa	Allergic rhinitis
14	12	Urticaria, angioedema	<u>F</u> , C, S, H, T, Sw	Atopic dermatitis Allergic asthma
15	6	Urticaria, angioedema	<u>F</u> , C, S, H, T, Sa	Atopic dermatitis Allergic asthma
16	7	Urticaria, angioedema	<u>F</u> , C, S, <u>H</u> , T, Sw, Sa	Atopic dermatitis Allergic asthma
17	12	Urticaria, angioedema	<u>F</u> , C, S, H, T, Sa	Atopic dermatitis Egg allergy
18	10	Urticaria, angioedema	<u>F</u> , C, S, <u>H</u> , T, Tr, Sa	Allergic asthma and rhinitis
19	24	Urticaria, angioedema, vomiting	F, <u>C</u> , S, H, T, Sa, Sw	Allergic asthma
20	24	Urticaria, angioedema, hoarseness	F, C, S, H, <u>T</u> , Sa	Allergic asthma
21	3	Urticaria, angioedema	C, S, <u>H</u> , T, Tr	

mo: month; F: flounder; C: codfish; S: sole; H: hake; T: tuna; Tr: trout; Sa: sardine; Sw: swordfish. Underlined: fish species implicated in clinical manifestations by ingestion.

and dermatologic manifestations (patients 3, 7, and 8). Symptoms reported for nine patients with only respiratory symptoms following aerosol exposure to fish are enumerated in Table 2. Seven of the nine patients with respiratory symptoms showed severe manifestations, such as wheezing. Nine patients had only dermatologic symptoms after exposure to fish airborne particles (Table 2). Most of these patients reported acute urticaria and angioedema.

As shown in Table 2, the age at onset of clinical manifestations upon fish inhalation was from 24 months to 18 years, mean 7 years (0.9, SE). Regarding the number of reactions, nineteen of 21 (90%) patients reported three or more episodes. Clinical manifestations elicited by inhalation or exposure to fish particles occurred mainly at home. Thirteen patients were exposed outside the kitchen, when other

people were eating fish, and seven were exposed in the kitchen, when someone was cooking or handling fish.

The reported methods of exposure to fish airborne particles were as follows: in 14 patients, through fumes generated while fish was being fried; in six patients, through water vapor released during boiling of fish; and in five patients, through simple exposure to fish (Table 2).

Discussion

IgE-mediated hypersensitivity to fish is a clinically relevant problem, particularly in some European countries. In Spain, it is the second most commonly implicated food, after eggs, in food-induced allergic reactions (3). In addition, fish hypersensitivity has

Table 2. Respiratory manifestations upon inhalation of fish particles

Patient no.	Age at onset (mo)	No. episodes	Symptoms upon inhalation	Method	Place
1	105	≥3	Wheeze	V	Kitchen
2	130	≥3	Rhinitis	F	Kitchen
3	42	≥3	Urticaria, rhinitis	F	Kitchen
4	120	≥3	Wheeze	F	Kitchen
5	71	≥3	Wheeze	V, F, E	Home
6	216	≥3	Rhinitis, conjunctivitis	F, E	Home, fish shop
7	96	≥3	Wheeze, urticaria	n.r.	Home
8	120	≥3	Wheeze, urticaria, angioedema	V, E	Home
9	60	≥3	Wheeze	F	Home
10	162	≥3	Wheeze	F	Home
11	24	≥3	Wheeze	F	Home
12	96	≥1	Wheeze	n.r.	Restaurant
13	106	≥3	Urticaria	V	Home, fish shop
14	57	2	Urticaria	F	Kitchen
15	68	≥3	Urticaria	F, E	Kitchen
16	60	≥3	Urticaria/angioedema	F	Kitchen, home
17	34	≥3	Urticaria/angioedema	V, E	Home, fish shop
18	34	≥3	Urticaria/angioedema	E	Home, fish shop
19	24	≥3	Urticaria/angioedema	F	Home
20	72	≥3	Urticaria/angioedema	V, F	Home
21	74	≥3	Urticaria/angioedema	V, F	Home

mo: month; V: vapor; F: fumes; E: exposure; n.r.: not reported.

been reported to be a cause of fatal and near-fatal allergic reactions (11). These facts directed us to study in depth the clinical implications of fish hypersensitivity.

Allergic reactions to fish via ingestion began in most patients (86%) within the first 24 months of life. The vast majority (19/21) of patients showed cutaneous symptoms, either alone or, less frequently, associated with other clinical manifestations. Only two patients demonstrated oropharyngeal symptoms related to fish ingestion. This could be interpreted as oral allergy syndrome. This syndrome is frequently seen immediately after ingestion of certain foods, namely fresh fruits and raw vegetables, and it occurs mainly in patients with pollinosis (1).

Hake and flounder were the species of fish most frequently implicated in eliciting clinical manifestations. This could be because the most common fish in children's diets in our area are flounder, sole, and hake. However, all patients showed sensitization to multiple species of fish, a fact which can be attributed to the high degree of cross-reactivity reported previously (10).

As described early on by De Besche (4), fish is an inhalant allergen that can trigger asthma. However, allergic reactions through inhalation of airborne fish particles have mainly been reported in fish workers, and, in all cases, industrial exposure was shown (6). Outside occupational exposure, some allergic reactions to foods through inhalation have been reported mainly in housewives exposed to the steam from cooking legumes, such as chickpeas or lentils, as well

as from potatoes (9). But the extent of this problem has not been thoroughly evaluated in large groups of subjects.

In our study, all patients originally had generalized symptoms after fish ingestion (mean age 17 months) and were diagnosed as having fish hypersensitivity, and then placed on a strict fish-avoidance diet. After a significant period, 20 patients (mean age 7 years) showed clinical manifestations upon exposure to airborne fish. These patients probably became sensitized via the gastrointestinal route. Twelve of 21 patients reported respiratory symptoms immediately after exposure to airborne fish. Since most of these reactions occurred in the uncontrolled environment of the home, lung-function measures would have helped to evaluate the symptomatology in these patients. However, further challenge was not carried out since these patients were previously challenged, diagnosed as hypersensitive to fish, and placed on a strict avoidance diet. Eight of these 12 patients had allergic asthma, and exposure to airborne fish could be a nonspecific trigger for respiratory symptoms. These eight patients were reported to be reactive only after inhalation of fish, and not with other food allergens. The other seven asthmatic patients showed only dermatologic reactions upon exposure to airborne fish particles. No late reactions were reported after the inhalation of fish.

Nine of 21 patients showed only immediate cutaneous symptoms upon exposure to fish. Cutaneous symptoms were not due to direct contact because patients strictly avoided physical contact with fish.

Most of these allergic reactions to fish through inhalation occurred at home, with exposure mainly through steam from the cooking of fish, and not from industrial exposure.

The inhalation of steam from fish could be a means of inadvertent exposure to fish allergens, producing accidental reactions in fish-allergic children. In addition, it represents an important limitation on complete compliance with the allergen-avoidance diet, and it could be relevant to the fact that fish-hypersensitive patients rarely lose their clinical reactivity (2).

Lehrer has previously documented significant amounts of antigen present in the processing fluid after boiling, as well as cross-reactivity among shrimp, crab, crawfish, and lobster antigens (8). Our ongoing studies are being directed to characterize allergenic substances present in steam from fish and to study its antigenic relation with raw and boiled fish allergenic extracts.

In conclusion, we report 21 patients diagnosed as having IgE-mediated fish hypersensitivity who, despite an ongoing strict fish-avoidance diet, reported immediate allergic symptoms upon nonoccupational exposure to fish odors or fumes. Therefore, the inhalational route could play an important role in accidental and unknown contacts with fish allergens. It could elicit clinical symptoms and could have some effect in delaying the development of tolerance.

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