J Microbiol Immunol Infect
2001;34:301-304

Fish allergy in atopic children

Ya-Hsuan Peng, Shyh-Dar Shyur, Ching-Long Chang, Chung-Lin Lai, Suz-Hung Chu, Wen-Chiu Wu, Cheng-Yu Wu

Department of Pediatrics, Mackay Memorial Hospital, Taipei, Taiwan, ROC

Received: August 21, 2000 Revised: November 1, 2000 Accepted: November 12, 2000

The prevalence of fish allergy among 11 atopic children with elevated levels of specific immunoglobulin (Ig) E for cod was determined. None of the children had a history of fish allergy. All of the children had asthma and allergic rhinitis and 5 of them had also atopic dermatitis. The children underwent allergy skin tests (codfish, tuna, catfish, salmon, flounder, and bass), specific IgE tests (salmon, trout, tuna, eel, and mackerel), and food challenge tests. Skin tests in cod-specific IgE-positive children were positive for codfish in 4 children, tuna in 2, catfish in 2, salmon in 6, flounder in one, and bass in 2. Three children had elevated specific IgE for salmon, 5 for trout, 8 for tuna, 4 for eel, and 4 for mackerel. Oral fish challenge with 10 g of fish did not result in positive reaction in any of the children. In conclusion, a positive food challenge test provided the only definitive confirmation of fish allergy, whereas positive allergy skin tests or positive specific IgE tests were less reliable. Skin tests and *in vitro* specific IgE assays were not correlated with clinical symptoms of fish allergy, and the results of these 2 tests did not correlate with each other in this study.

Key words: Atopic child, fish allergy

The amount of fish consumption is increasing all over the world. The most commonly consumed fish belongs to only a few orders: Salmoniformes (salmon, trout), Perciformes (tuna, perch), Gadiformes (codfish, hake), Pleuronectiformes (flounder, sole), Clupeiformes (herring, anchovy), Cypriniformes (carp, catfish), and Scorpaeniformes (rockfish) [1]. Ingestion of fish or inhalation of vapors from the cooking of fish are common causes of both immunoglobulin (Ig) E-mediated and non-immunologic adverse reactions. Immunoglobulin E-mediated reactions to fish are among the most commonly encountered food allergies. The sensitivity often appears at an early age, and in most patients, persists for life. Codfish allergy is the most widely studied fish allergy [2,3]. In 1990, de Martino *et al* [4] demonstrated that cod allergy might be a reliable index of fish allergy in general. They also demonstrated the presence of cross-reacting antigens in cod, bass, dentex, eel, sole, and tuna, but not dogfish [4]. Hansen [5] reported that cod, mackerel, herring, and plaice also share a common antigenic structure. We evaluated the cross-reactivity with other fish species of 11 patients who were serologically positive for IgE against cod by history, skin testing, specific IgE level, and oral fish challenges. The correlation between fish allergy skin tests and *in vitro* specific IgE results and the results of food challenges were also assessed.

Corresponding author: Dr. Shyh-Dar Shyur, Department of Pediatrics, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei 104, Taiwan, ROC.

Materials and Methods

Case collection

Eleven children with atopic diseases who had undergone routine specific IgE testing for inhalants and food allergens, including mites, cat dander, dog dander, cockroaches, cow's milk, egg white, and cod (Gadus morrhua) using the CAP system (Pharmacia, Sweden) were enrolled in this study. All 11 children had asthma and allergic rhinitis, and showed positive reactions to cod in *in vitro* IgE test. Five had atopic dermatitis.

Skin testing

Skin testing was performed for codfish, tuna, catfish, salmon, flounder, and bass (1:20 wt/vol, Greer Laboratories, Lenoir, NC, US) along with histamine (1 mg/mL) and negative controls (glycerin 50%). Raw fish extracts or control substances were applied to the palmar surface of the forearm by a puncture method. The mean diameters of the wheal-and-flare lesions were recorded 20 min later. A wheal at least 3 mm larger than the wheal of the negative control was considered positive.

Specific fish IgE

Specific IgE to tuna, salmon, trout, mackerel, eel equal to or greater than Class 1 as assayed by the CAP system was defined as positive in this study.

Oral challenge test

Fish to which the patients had positive skin or IgE tests were eliminated from their diets for at least 2 weeks before challenge. Oral challenge was performed by giving more than 10 g of each fish (to which the children demonstrated positive tests) at 7-day intervals. The testing was non-blinded.

Results and Discussion

There were 9 boys and 2 girls aged from 2 to 9 years included in the study, with a mean age of 5 years. Their specific IgE levels for cod were equal to or greater than Class 2 as assayed by the CAP system (Table 1). All of the 11 atopic children had ingested fish previously without any adverse reactions, although they may not have ingested all of the tested fish species. Although all 11 children had IgE against codfish, only 4 (36%) were skin-test positive to commercial codfish extract. The other positive skin test results were as follows: 2 (18%) patients were positive to tuna, 2 (18%) to catfish, 6 (55%) to salmon, one (9%) to flounder, and 2 (18%) to bass. Specific IgE reactivity to different fish extracts is summarized in Table 1. Elevated specific IgE levels to salmon were found to salmon in 3 (27%) children, to trout in 5 (45%), to tuna in 8 (73%), to eel in 4 (44%), and to mackerel in 4 (44%). None of the patients had adverse reactions to ingestion of codfish or other fish species.

Fish are clearly among the most commonly implicated foods that induce hypersensitivity in fish-eating or -processing populations. In Norway, fish allergy is estimated to occur in about 1/1000 individuals, but the incidence may be greater in pediatric populations [6]. A study from Finland estimated that 3% of 3-year-old children were fish-allergic [7]. de Martino *et al* [4] found IgE antibodies to cod in 18% of children with food allergy, two-thirds of whom had clinical manifestations when cod was ingested or inhaled. The incidence of fish allergy in Taiwan has not been reported.

The major cod allergen, Gad c1 (Allergen M) serves as a model for fish allergy, and can be identified, purified, and characterized [1]. Gad c1 belongs to the parvalbumins, a group of vertebrate muscle calcium-chelating proteins that mediates the concentration of calcium in muscles. Gad c1 is a 12 328-kD acidic protein composed of 113 amino acid residues and a single residue of glucose. Specific tryptic cleavage of Gad c1 yields 2 polypeptide fragments (TM1 and TM2) that are allergenic. Gad c1 is a very stable allergen; its allergenic activity is dependent on the amino acid sequence, not necessarily on steric configuration [1]. This is why the allergen can resist prolonged cooking and the host's digestive acids and enzymes [6]

Cross-reacting antigens are found in cod, bass, dentex, eel sole, and tuna, but not dogfish [4]. Hansen *et al* [5] reported that serologic cross-reactivity to different fish species in clinically codfish-allergic patients exists, and that cod, mackerel, herring, and plaice share a common antigenic structure.

Table 1. Results of fish skin test and specific IgE test in atopic children

Patient no.	Age, year/month	Positive skin tests	Specific IgE level, kU/L[a] (Class)[b]					
			Cod	Salmon	Trout	Tuna	Eel	Mackerel
1	4/5	Negative	0.74 (2)	0	0	0.66 (1)	ND	ND
2	5/11	Negative	1.14 (2)	0	0	0	0	0
3	3	Salmon	0.78 (2)	0	0.37 (1)	0.36 (1)	ND	ND
4	3/7	Salmon	0.76 (2)	0	0	0	0	0
5	3/8	Tuna	0.80 (2)	0	0.41 (1)	0.47 (1)	0.37 (1)	0.49 (1)
6	2/11	Cod	3.53 (3)	3.63 (3)	4.87 (3)	2.34 (2)	4.3 (3)	5.68 (3)
7	3/8	Cod	1.18 (2)	0	0	0.75 (2)	0	0
8	8/5	Cod, catfish, salmon	12 (3)	10 (3)	9.59 (3)	6.56 (3)	8.4 (3)	9.24 (3)
9	3/9	Tuna, catfish, salmon, bass	0.80 (2)	0.73 (2)	1.61 (2)	0.54 (1)	1.16 (2)	0.80 (2)
10	9/7	Salmon	1.46 (2)	0	0	0.65 (1)	0	0
11	5/10	Cod, salmon, flounder, bass	1.11 (2)	0	0	0	0	0

Abbreviation: ND = not done

[a]Specific IgE levels were determined by the Pharmacia CAP system FEIA at a cut-off level of 0.35 kU/L.

[b]Class 0 = <0.35 kU/L; Class 1 = ≥0.35 kU/L, <0.7 kU/L; Class 2 = ≥0.7 kU/L, <3.5 kU/L; Class 3 = ≥3.5 kU/L, <17.5 kU/L; Class 4 = ≥17.5 kU/L, <50 kU/L; Class 5 = ≥50 kU/L, <100 kU/L; Class 6 = ≥100 kU/L.

Allergic symptoms in fish-sensitive individuals are usually of immediate onset, occurring within 1 h after ingestion. Symptoms can result following ingestion of fish or inhalation of fish cooking vapors. Fatal anaphylaxis has been induced by ingestion of French fries prepared in fish-contaminated oil [8]. Studies by Aas [2,6] confirmed cod as a cause of asthma and urticaria. Some fish species other than cod have also been reported to cause asthma [9]. Age at the first introduction of fish in the diet does not seem to affect the likelihood of developing fish allergy [7,10], and maternal avoidance of fish during lactation does not prevent the child from subsequent sensitization [11]. Adverse reactions in infants or children at the first introduction of fish are resulted from the passage of fish allergens through breast milk or the presence of these allergens in the indoor air and dust of houses where fish is frequently cooked and/or processed [12].

As with the diagnosis of most allergies, a precise and detailed medical history is important for diagnosing fish allergy. Fish allergy skin tests appear to have excellent sensitivity and negative predictive power, but poor specificity and positive predictive value [13]. A high prevalence of clinically irrelevant positive skin tests to fish extracts has been reported [13,14]. False-positive reactions caused by relatively high levels of histamine in fish extracts are one possible explanation [14]. *In vitro* allergy tests such as radioallergosorbent test (RAST), enzyme-linked immunosorbent assay (ELISA), or CAP sytsem fluoroenzyme immunoassay (FEIA) are nearly always less sensitive than *in vivo* tests. *In vitro* tests are helpful to establish cross-reactivity among species, and to determine the antibody response to individual components of complex antigen mixtures. Although the double-blind placebo-controlled food challenge (DBPCFC) is the gold standard for diagnosis of fish allergy, negative single open food challenge tests are often used to exclude the possibility of fish allergy. In this study, all the children had negative single open food challenge tests. Skin test and *in vitro* evidence of IgE-specific cross-reactivity does not necessarily correlate with symptomatic fish allergy [13].

The best treatment of fish allergy is avoidance. Fish challenge testing should be used to identify specific allergens before recommending avoidance. For sensitive individuals, avoidance includes avoiding both ingestion and inhalation of vapors during cooking. Fish-allergic patients should read carefully the list of ingredients of all processed, packaged foods.

Sensitivity to fish often persists or increases with age [15]. However, Kajosaari [10] reported that fish allergy subsides in most patients within 6 years. Changes in reactivity with age may be caused by a decreased absorption of immunogenic food proteins as a result of the maturation of the intestinal mucosa and the secretory immune system. A maturation of the cellular immune system develope with an increased number of T cells with suppressor activity against IgE-antibody production on antigen exposure [15]. Development of tolerance to food has little effect on B-cell function, because antibody production against food proteins is a universal phenomenon in both infants and adults, which is not necessarily related to hypersensitivity to the antigen [16]. That is why the children in this series had no response to oral fish challenge tests, although they had positive reactions in the skin tests or specific IgE tests. Dannaeus and Ignanas [15] found that in children with food allergy, a high fish-specific IgG/IgE antibody ratio seemed to be a good prognostic sign, indicating that IgG may act as a blocking antibody. The ratio increased during the development of tolerance. Clinical tolerance developed despite remaining IgE food antibodies.

Despite the varied positive skin tests and specific IgE levels in the 11 atopic children in this study, none of them had positive oral challenge tests. In conclusion, a positive food challenge test is required to diagnose fish allergy, whereas positive allergic skin test or positive specific IgE test are not definitive. Skin tests and IgE levels do not correlate with each other or with clinical symptoms.

References

1. O'Neil C, Helbling AA, Lehrer SB. Allergic reactions to fish. Clin Rev Allergy 1993;11:183-200.
2. Aas K. Studies of hypersensitivity to fish: a clinical study. Int Arch Allergy 1966;29:346-63.
3. Elsayed S, Apold J. Immunochemical analysis of cod fish allergen M: locations of the immunoglobulin binding sites as demonstrated by the native and synthetic peptides. Allergy 1983;38:449-59.
4. de Martino M, Novembre E, Galli L, de Marco A, Botarelli P, Marano E, Vierucci A. Allergy to different fish species in cod-allergic children: *in vivo* and *in vitro* studies. J Allergy Clin Immunol 1990;86:909-14.
5. Hansen TK, Bindslev-Jensen C, Skov PS, Poulsen LK. Codfish allergy in adults: IgE cross-reactivity among fish species. Ann Allergy Asthma Immunol 1997;78:187-94.
6. Aas K. Fish allergy and the codfish allergen model. In: Brostoff J, Challacombe SJ, eds. Food Allergy and Intolerance. London: Balhere Tindall; 1987:356-66.
7. Saarinen UM, Kajosaari M. Does dietary elimination in infancy prevent or only postpone a food allergy? A study of fish and cytrus allergy in 375 children. Lancet 1980;1:166-7.
8. Yunginger JW, Sweeney KG, Sturner WQ, Giannandrea LA, Teigland JD, Bray M, Benson PA, York JA, Biedrzycki L, Squillance DL, Helm RM. Fatal food-induced anaphylaxis.

JAMA 1988;260:1450-52.
9. Tomaszunas S, Weclawik Z, Lewinski M. Allergic reactions to cuttlefish in deep-sea fisherman. Lancet 1988;1:1116-7.
10. Kajosaari M. Food allergy in Finnish children 1-6 years of age. Acta Paediatr Scand 1982;71:815-9.
11. Hattevig G, Kjellman B, Sigurs N, Bjorksten B, Kjellman NI. Effect of maternal avoidance of eggs, cow's milk and fish during lactation upon allergic manifestations in infants. Clin Exp Allergy 1989;19:27-32.
12. de Martino M, Peruzzi M, de Luca M, Amato AG, Galli L, Lega L, Azzari C, Vierucci A. Fish allergy in children. Ann Allergy 1993;71:159-65.
13. Bernhisel-Broadbent J, Scanlon SM, Sampson HA. Fish hypersensitivity: *in vitro* and oral challenge results in fish-allergic patients. J Allergy Clin Immunol 1992;89:730-7.
14. Williams PB, Nolte H, Dolen WK, Koepke JW, Selner JC. The histamine content of allergen extracts. J Allergy Clin Immunol 1992;89:738-45.
15. Dannaeus A, Inganas M. A follow-up study of children with food allergy: clinical course in relation to serum IgE- and IgG-antibody levels to milk, egg and fish. Clin Allergy 1981;11:533-9.
16. Husby S, Mestecky J, Moldoveanu Z, Holland S, Elson CD. Oral tolerance in humans. T cell but not B cell tolerance after antigen feeding. J Immunol 1994;152:4663-70.