

Life-threatening fish allergy successfully treated with immunotherapy

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Manifestations of fish allergy can include near-fatal anaphylactic reaction. In very sensitive patients, fish odors and cooking vapors may have some allergenic activity. We reported a case of life-threatening fish allergy in a girl of 39 months referred for three episodes of Quincke edema with wheezing, cyanosis and severe urticaria after fish consumption or inhalation. Reagins were found against codfish and direct skin prick test with fresh food (codfish) showed important local reaction. Strict avoidance of fish in the diet is usually the only recommended procedure. However, in this particular case, the life-threatening nature of the allergic reaction was the major consideration to perform a desensitization. The child was treated by RUSH immunotherapy using codfish extracts from BENCARD company, following the schedule for insect venom allergy described by Pharmacia. Immunotherapy was performed immediately after determination of the threshold of sensitivity by specific skin prick tests and intra-dermal injections. Desensitization was initiated with a 1/10 dilution of the cut-off solution and 5 subcutaneous injections were administered daily. When important local reactions were observed, additional doses were necessary to obtain tolerance. After the RUSH therapy, the child was submitted to uncooked codfish odors without any reaction. No reaction has been observed even when the child has accidentally eaten a little piece of codfish.

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Fish consumption is increasing worldwide, partly due to rapid fish-processing and transport to the different nations. Unfortunately, fish-hypersensitivity is also increasing. Estimations of the prevalence of fish allergy in Europe range from 1 in 1000 to 4–5 per 1000 individuals (1,2) and is most prevalent in Scandinavian countries. Manifestations of adverse reaction include atopic dermatitis (1,3), urticaria-angioedema either by contact or ingestion (1,2), asthma by inhalation (1), and near-fatal anaphylactic reactions (4). Aas (1987) and Elsayed and Apold (1983) have previously investigated and extensively characterized Gad c1 (previously known as allergen M), a parvalbumin from codfish (*Gadus callarias* L.) recognized to be the major codfish allergen (5). However, there is little information on the allergenic determinants in other fish species (1). Gad c1 is known to be a remarkably heat and acid stable protein, resistant to partial proteolysis. Skin prick tests and *in vitro* evidence of IgE-specificity show high levels of cross-reactivity amongst fish species be-

longing to the subclass actinopterygii suggesting the existence of a common antigenic structure (1).

The presence of specific reagins, in contrast to the results of oral challenge, do not always correlate with symptomatic fish hypersensitivity (6). Fish sensitivity depends partly on the processing of the fish which can alter the structure of the major allergens (7). Fish odors and cooking vapors may also have some allergenic activity (8). "Outgrowing" seafood allergy is less likely than with other food hypersensitivities; however, a total fish elimination diet may be unnecessary since some patients can eat unrelated fish species without experiencing any adverse allergic reaction (3). In addition, fish is one of the foods which release significant amounts of histamine.

Case report

A girl of 39 months was treated at the Department of Allergy and Pulmonology at the University Chil-

dren's Hospital Queen Fabiola for three acute episodes of Quincke edema with wheezing, cyanosis, and severe urticaria. The first episode occurred five minutes after the consumption of codfish. The two other episodes followed inhalation of odors in a fish-market during the holidays, the second of which required naso-tracheal intubation when the emergency unit arrived. The second episode occurred just three months after the first and the third 15 days after the second. It was unfortunately not known if the girl had already been exposed to the offending food before the reported incidents.

At her first visit, when she had been referred from another hospital, she was asymptomatic. The familial history of allergy was positive: the father was allergic to penicillin; the brother and sister of the mother were asthmatics. Total IgE concentration was 141 IU/ml (range for age: 1–178; geometric mean: 21); total eosinophilia 364 cells/mm³. Reagents were found against codfish (a score of 2+, by the Pharmacia Cap system classification) but not against any other seafood tested (e.g. tuna, lobster, shrimp, sole). A direct skin prick test was performed in the intensive care unit, with fresh food (codfish) using « Stallerpoint »R: the test was positive, showing a red indurated area of 38 mm (induration) and 49 mm (erythema) diameter. The procedure involved pricking the fish meat and then pricking the skin making two perpendicular scratches. A double-blind placebo-controlled challenge with the offending food was not performed, despite being considered the most reliable method of confirming fish-allergy and identifying the putative species (13) because the risk of life.

It was decided to try desensitization to codfish protein using the RUSH procedure with a solution of 10,000 Noon U/ml codfish extracts from BEN-CARD Company (Cat. no. 5601) and following the schedule for insect venom allergy described by Pharmacia (Pharmalgen R). The child's threshold of sensitivity was determined firstly by specific skin prick tests and then intradermal injections with the extract. To initiate this determination, a dilution of 2°/° of the basic extract solution was used. Table 1 summarizes the schedule: a reaction was only observed for the intradermal test using a 1/100 dilution of the basic extract solution (i.e. solution 2). The cut-off solution was a 1/100 dilution of basic extract with a reaction of 8 mm erythema and 4 mm induration. Immunotherapy was performed immediately after determination of the threshold of sensitivity. Desensitization was initiated with a 1/10 dilution of the cut-off solution and 5 subcutaneous injections were administered daily. Serious local reactions appeared after the three last injections delaying the procedure (Table 2). In each case (following injections of 0.4, 0.8 and 1.0 ml of the basic solution, res-

Table 1. Determination of the threshold of sensitivity

Prick test
solution 1 = dilution 1 : 1000 of the basic solution
solution 2 = dilution 1 : 100
solution 3 = dilution 1 : 10
solution 4 = basic solution
Intra-dermal reaction
solution 5 = dilution 1 : 100,000 of the basic solution
solution 6 = dilution 1 : 10,000
and then solutions 1 to 4, as for prick tests

pectively) a local reaction corresponding to an induration of more than 5 cm was observed. The same dose was therefore repeated following recommendation in the Pharmalgen Schedule and in each case one additional dose was necessary to obtain tolerance (i.e. a reaction with an induration < 5 cm).

After the complete RUSH therapy, the child was submitted to uncooked codfish odors in the hospital without any local or anaphylactic reactions. Desensitization was continued for the ambulatory patient as described for the treatment of insect allergy (1 ml of the solution of 100 mcg/ml each six weeks). Since then, the parents have been able to cook fish at home and, furthermore, no reaction has been observed even when the child has accidentally eaten a little piece of codfish. Controls for the presence of reagents against codfish were carried out at 2, 6 and

Table 2. Schedule of rush desensitization

Day	Concentration (microg/ml)	Dose (ml)	Total dose (microg)
1	0.00001	0.1	0.000001
	0.0001	0.1	0.00001
	0.001	0.1	0.0001
	0.01	0.1	0.001
2	0.1	0.1	0.01
	1.0	0.1	0.1
		0.2	0.2
		0.4	0.4
3	1.0	0.8	0.8
	10.0	0.1	1
		0.2	2
		0.4	4
4	10.0	0.8	8
	100	0.1	10
		0.2	20
		0.4	40
		0.8	80
		1.0	100

18 months after the end of RUSH treatment resulting in class 1 reactions at 2 and 6 months and the disappearance of specific reagins at 18 months. Reaction to the skin prick test with fresh food also decreased gradually, with a reaction of 18 mm/ 26 mm at 2 months and 11 mm/ 19 mm at 18 months.

Discussion

Desensitization is usually not recommended in food allergy as on the rare occasion it has been applied it has been unsuccessful. Also, many food allergens are spontaneously outgrown. Although this is true for milk, it is usually not the case for fish (9). Thus strict avoidance of fish remains the only recommended procedure.

In this particular case, the life-threatening nature of the allergic reaction was a major consideration. Complete eviction of the allergens is very difficult since there are hidden fish-proteins in various food-preparations, and inhalation of volatile allergens cannot be afforded. Therefore along with the strictest eviction procedures possible, we tried to reduce sensitivity by specific desensitization, in order to minimize the potential consequences of accidental contact with the offending allergen. Desensitization can be used to reduce the expression of allergic symptoms in case of food allergy, but not suppress them completely (10, 11, 12). This case documents improvement of a critical allergy after specific hyposensitization. The duration of the induced tolerance is at present unknown. Theoretically, it would have been possible to dilute an oral challenge material to whatever degree seemed appropriate, and thus to determine the patient's reaction threshold by the oral route, but a validated schedule for performing oral challenge with such potent allergens does not exist in the literature. However, treatment by injection is well described for tolerance induction in allergies to penicillin and to insect venom (Pharmalgen), both life-threatening allergies. For this reason, we chose injection treatment.

The described desensitization had to be performed in the hospital, with all the necessary precautions (hospitalization in a pediatric intensive care unit, perfusion as well as permanent supervision by an allergologist and a nurse).

A decrease in specific IgE antibodies was observed along with clinical improvement. In the literature, it has been reported that there is no clear relationship between the level of specific IgE and the clinical result of desensitization (13). However, there are some reports describing decreases in specific IgE and /or released mediators with improved clinical status. Discrepancies between the results of specific reagins (RAST or CAP) and skin prick test may often be observed because:

- the two tests do not use the same antigen preparation. A reduced response to RAST or CAP could be explained by partial or total degradation of the specific epitope during the engineering and preparation of the antigen
- the specific antigen could be volatile
- the offending antigen is not the major antigen contained in the RAST or CAP test and this specific antigen is not preserved if the fish is not fresh.

Final evidence for the successful management of the reported case of fish allergy was provided by the observed tolerance of the patient to fish allergens *in vivo*.

References

1. DE MARTINO M, PERUZZI M, DE LUCA M, AMATO AG, GALLI L, AZZARI C. Fish allergy in children. *Ann Allergy* 1993; 71: 159–65.
2. AAS K. Fish allergy and the codfish allergen model. In: BROSTOFF J, CHALLACOMBE S (Eds): Food allergy and intolerance. London: Balliere Tindall, 1987: 356–60.
3. SAMPSON HA. Natural history of food hypersensitivity in children with atopic dermatitis. *J Pediatr* 1989; 115: 23–7.
4. SAMPSON HA, MENDELSON L, ROZEN JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992; 327: 380–4.
5. ELSAYED S, APOLD J. Immunochemical analysis of codfish allergen M; location of the immunoglobulin binding sites as demonstrated by the native and synthetic peptides. *Allergy* 1983; 38: 449–59.
6. BERNHISEL-BROADBENT J, SCANLON SM, SAMPSON HA. Fish hypersensitivity. I. *In vitro* and oral challenge results in fish-allergic patients. *J Allergy Clin Immunol* 1992; 89: 730–7.
7. BERNHISEL-BROADBENT J, STRAUSS D, SAMPSON HA. Fish hypersensitivity. II. Clinical relevance of altered fish allergenicity caused by various preparation methods. *J Allergy Clin Immunol* 1992; 90: 622–9.
8. AAS K. Studies of hypersensitivity to fish. *Int Arch Allergy Appl Immunol* 1966; 29: 536–52.
9. SAMPSON HA, METCALFE DD. Food allergies. *JAMA* 1992; 268: 2840–4.
10. GRILLIAT J, MONERET-VAUTRIN D. Traitement de l'allergie alimentaire. In: CHARPIN J, VERVLOET D.eds. *Allergologie*. Flammarion 1992: 1110–15.
11. MONERET-VAUTRIN D, NICOLAS J, GUEANT J, BENE M. Immunotherapie et allergie alimentaire. *Jordana Internacional de Alergia Alimentaria* 1987: 97–104.
12. DANNAEUS A, INGANAS M. A follow-up study of children with food allergy. Clinical courses in relation to serum IgE and IgG antibody levels to milk, egg and fish. *Clin Allergy* 1981; 11: 533–9.
13. O'NEIL C, HELBLING A, LEHRER SB. Allergic reactions to fish. *Clin Rev Allergy* 1993; 11: 183–200.
14. ARMENTIA A, FERNANDEZ A, TAPIAS J, MENDEZ J, DE LA FUENTE R, SANCHEZ PALLA P, et al. Immunotherapy with allergenic extracts in geriatric patients: evaluation of the effectiveness and safety. *Allergol Immunopathol (Madr)* 1993; 21: 193–6.
15. JUNG CM, PRINZ JC, RIEBER EF, RING J. A reduction in allergen induced Fc epsilon R2/ CD 23 expression on peripheral B cells correlates with successful hyposensitization in grass pollinosis. *J Allergy Clin Immunol* 1995; 95: 77–87.