

Possible consequences of elimination diets in asymptomatic immediate hypersensitivity to fish

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The natural history of IgE antibodies to food without related symptoms is unknown. We have followed the progress of 7 children with various atopic diseases and asymptomatic immediate hypersensitivity to fish, treated with elimination diet in spite of full alimentary tolerance. During the diet period, between 24 and 113 months, all 7 patients presented immediate symptoms upon accidental exposure to or challenge tests with fish (skin symptoms in all 7 cases, digestive in 5, respiratory in 4, and anaphylaxis in 2), which differed from those related to atopic diseases previously present. The levels of fish-specific IgE (prick test, RAST) remained unchanged or were increased. These findings suggest that during elimination diet, and perhaps due to minimal and hidden contact with the allergen, the patients' degree of sensitization may increase, turning an asymptomatic into a symptomatic immediate hypersensitivity.

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A strict elimination diet is the only effective therapy currently available for control of immediate-type food allergy (25). For the correct application of such a diet, a previous diagnostic work-up of immediate hypersensitivity is essential (by means of skin tests, RAST, etc.). However, the existence of patients with positive specific IgE to a given foodstuff, but who tolerate its ingestion without problem is well known (18, 20, 30). For this reason, and provided it is not hazardous to the patient, a challenge test seems required in order etiologically to correlate the sensitizing foodstuff with the presenting symptoms (20, 26).

An elimination diet is not a harmless procedure: apart from possible nutritional problems, particularly in infants and small children (3, 8, 13), there have been reports of severe anaphylactic reactions when attempting to reintroduce the sensitizing foodstuff (7). Sometimes, an elimination diet is prescribed for patients without symptoms clearly related to foodstuffs to which they are skin- or RAST-sensitive. This practice, not scientifically proven, has led us to investigate the effects of elimination diets on this type of patient.

This study is a follow-up of children with immediate hypersensitivity to fish who, although they show no evidence of apparently related symptoms, have been subjected to elimination diets. We aimed to assess whether this situation might cause a modifi-

cation in the degree of sensitization and in the clinical picture.

Material and methods

Among 62 children previously diagnosed to have immediate fish allergy (positive skin prick tests and high specific serum IgE levels) and placed on a fish elimination diet, the relationship between ingestion of fish and the appearance of symptoms prior to the beginning of the diet was prospectively followed.

In 55 cases there was a clear-cut cause/effect relationship between fish ingestion and the appearance of symptoms. In the other 7 cases such a relationship did not exist; that is, at the moment of deciding an exclusion diet, because of positive skin tests and high specific IgE to fish, they were consuming fish on a regular basis without symptoms, but a fish-free diet was started without a previous controlled challenge test.

Thus, only these 7 patients were selected for the present study as only they fulfilled all of the following selection criteria:

1. Presence of specific IgE antibodies against fish.
2. Lack of symptoms related to fish ingestion.
3. On fish elimination diet.

The selected patients were regularly reviewed, and the following aspects investigated: a) dietary compliance, b) evolution of the initial symptoms not re-

lated to fish intake, and c) possible occurrence of other symptoms directly related to exposure to fish, dietary transgression, contact, or other means.

Total serum IgE (Phadezym PRIST, Pharmacia, Sweden) was measured, before and at the end of the follow-up. At the same time, skin prick tests and specific serum IgE determinations (Phadezym RAST, Pharmacia, Sweden) were carried out for different fish species among those most usual in Spain (hake, cod, sole, whiff, witch and Spanish tuna – albacore, bonito –), using extracts prepared as described elsewhere (23). Briefly, fish meat was shredded and stirred in phosphate-buffered saline (10% w/v) for 24 h; after paper filtration and centrifugation, the supernatant was defatted with ether, dialysed (10 mM glycine) and lyophilised, and the protein content measured (16).

For the prick tests, allergens were used at a final concentration of 1 mg protein/ml, and a wheal $\geq$ than that of the histamine (1/100 w/v) control was classed as positive (3+ to 4+). To determine specific serum IgE, dilutions of the stock, extracts of the various fish species were bound to paper disks activated with cyanogen bromide (a generous gift of Alergia e Inmunología Abelló, S.A., Spain), as described by Ceska (5) and modified by Løwenstein (14). The results were recorded as classes (0 to 4), and a class 2 or higher was considered positive.

Challenge tests were performed at the end of the follow-up when fish-related clinical symptoms were not readily ascertainable, but not if, according to the clinical data, a test might trigger severe acute symptoms. The challenges had been planned in single blind modality with boiled hake, ground and mixed with potatoes and carrots, at increasing doses (25, 50 and 100 g, with an optional initial dose of 10 g of boiled hake). The challenge test would be considered positive when clinical signs occurred which had been absent at the physical examination immediately prior to the challenge: urticaria and/or angioedema, vom-

iting with or without diarrhoea, rhinoconjunctivitis, cough and wheezing, or a reduction of the PEF $> 20\%$ of the baseline value.

Results

Retrospective data of the selected patients

The reason for the initial consultation in these 7 patients was other atopy-related diseases (Table 1): asthma in 4 cases, atopic dermatitis in 6, and immediate acute urticaria following the ingestion of other foodstuffs in 5 (egg in 4 and nuts in one). There were no asymptomatic positive skin tests or RAST values to other foodstuffs.

All patients consumed fish on a regular basis without problems at least once a week. In all cases there was no direct correlation between the symptoms causing the consultation and the ingestion of fish (Table 1).

Total serum IgE was high in 4 patients, and above the mean + 2 SD for age in the remainder. The skin tests with fish extracts prior to instituting the fish elimination diet and the determination of specific IgE to fish (Table 1) were positive in the 7 patients.

The fish elimination diet was started when the patients were 8 to 48 months old (mean 24 months). No patient was being breast-fed at that time. The apparent causes for instituting a fish-free diet were (Table 1) positive skin prick tests to fish in all cases, with associated atopic dermatitis in 5, and associated atopic dermatitis plus asthma in one.

Clinical progress: occurrence of fish-related symptoms during elimination diet

All patients received conventional therapy for their underlying disease: skin hygiene and hydration, antihistamines and topical steroid courses during outbreaks of atopic dermatitis, and bronchodilator management with beta-mimetics and theophylline, plus

Table 1. Patients' status prior to institution of the diet

Patient no.	Age (months)	Reason for consultation	Total IgE (kU/L)	Other sensitizations	Fish				
					Symptoms	ST*	RAST* (class)	Challenge	Reason for diet
1	18	A/AD	740	Inh/E, M, L	No	4+	2	ND	ST/A/AD
2	30	AD/U(E)	5000	E, M, L, N/Inh	No	4+	2	ND	ST/AD
3	14	A/U(E)	150	E, M/Inh	No	4+	2	ND	ST
4	45	A/AD/U(N)	1280	E, L, N/Inh	No	4+	3	ND	ST/AD
5	11	AD/U(E)	52	E	No	4+	3	ND	ST/AD
6	48	AD/A	5700	E, M/Inh	No	4+	4	ND	ST/AD
7	25	AD/U(E)	115	E/Inh	No	4+	2	ND	ST/AD

ST=skin tests; A=asthma; AD=atopic dermatitis; U=urticaria; E=egg; M=milk; L=legumes; N=nuts; Inh=inhalants; + = positive; ND=not done. The letter in parentheses shows the foodstuff responsible for the related symptoms.

(*) Only the highest result is indicated from among those observed with the various fish species tested.

Table 2. Progress of the nonfish-related fish symptoms (present at time of first consultation) during the fish elimination diet, up to first fish re-exposure

Patient no.	Elapsed time (months)	Symptoms	Progress
1	72	asthma – AD	unchanged
2	40	AD egg urticaria	unchanged diet
3	16	asthma egg urticaria	unchanged outgrown
4	9	AD – asthma nuts urticaria	unchanged diet
5	1	AD egg urticaria	unchanged diet
6	96	AD asthma	well unchanged
7	20	AD egg urticaria	well diet

AD=atopic dermatitis.

therapy for added complications, when asthma was present.

The time elapsed between the institution of fish-free diet and the appearance of the first fish-related symptoms (Table 2) ranged between 1 and 96 months (mean 36 months). In no case was there a significant change in baseline symptoms during the first month of diet; later, improvement was observed in 2 patients with atopic dermatitis, with no noteworthy changes in the remainder (Table 2).

After this initial period immediate symptoms were observed in all cases, in at least one instance in relation to fortuitous exposure to fish, in spite of maintaining the diet for 24 to 111 months (mean 70 months) (Table 3) at the time of the termination of follow-up.

During the follow-up, fish was accidentally ingested on 5 occasions (3 patients), and this coincided with the most severe symptoms. Symptomatic inhalatory exposure occurred on 7 occasions (4 patients), and symptomatic skin (contact) exposure on 7 occasions (4 patients). All patients had acute skin symptoms, such as urticaria and angioedema. Gastrointestinal symptoms (vomiting or diarrhoea) were observed in 2 cases. Three patients presented respiratory symptoms (asthma or rhinoconjunctivitis) (Table 3).

Through this follow-up period no ingestion of fish occurred without symptoms, but there were 7 reported asymptomatic exposures in 4 patients after accidental contact (2 occasions) and inhalation (5 occasions). It is difficult to say whether any of these patients had had other unreported accidental exposure to fish without symptoms.

The total serum IgE increased over the follow-up

Table 3. Total duration of elimination diet and immediate symptoms upon accidental exposure to fish

Patient No.	Duration (months)	Exposure pathway*:			No. exposures	
		Digestive	Inhalatory	Cutaneous	Total	Symptomatic
1	96		Urt/RcA (1)		1	1
2	64	Urt/Dig/RcA (1)	No (1)	No (1)	3	1
3	74		RcA, No (2), (1)	Urt (4)	7	6
4	24	Urt (3)		Urt (1)	4	4
5	29	Urt/Dig (1)			1	1
6	111		Urt, No (1), (1)	Urt, No (1), (1)	4	2
7	94		Urt, No (3), (2)	Urt (1)	6	4

(*) Clinical signs in relationship with the exposure to fish. The number in parentheses shows the number of contacts in this way.

Urt=urticaria and/or angioedema; Dig=vomiting and/or diarrhoea; RcA=rhinoconjunctivitis and/or asthma; No=exposure without symptoms.

period at least 2-fold in 5 of the 7 patients, and decreased in the remaining two (Table 4).

Skin tests were performed in the first year after the occurrence of the first immediate symptoms directly related to fish, and were strongly positive (4+) in all patients for several fish species (Table 4). The skin tests have continued to be positive in later visits.

In the quantification performed at the time of the first symptoms and/or at later visits, the specific serum IgE levels were high in all 7 patients (Table 4).

Challenge test

This test was positive in 3 patients at the first challenge with fish (Table 4). One patient (Case 2) had urticaria and vomiting a few minutes after the intake of 25 g of boiled hake. Two patients (Cases 1 and 3) developed systemic anaphylaxis requiring emergency therapy; neither had eaten fish since the beginning of the diet, but they had evidenced symptoms on contact or inhalation. For this reason, challenge testing was considered inadvisable in 2 more patients (Cases 6 and 7), who also had had symptoms on contact or through inhalation while on fish-free diet, without having transgressed (Table 3). No challenge was performed in the remaining 2 patients, as they had already shown evidence of severe symptoms during the diet period obviously related to the accidental ingestion of fish, and not to any other foodstuff to which they were allergic. The severity of the symp-

Table 4. Sensitization status as assessed by skin tests and RAST, and results of challenge tests before and after the fish elimination diet follow-up

Patient No.	Total IgE (kU/L)		Skin tests (before/after)						RAST* (before/after)						Challenge**
	Before	After	Cod	Hake	Witch	Sole	Whiff	Tuna	Cod	Hake	Witch	Sole	Whiff	Tuna	After
1	740	1730	4+/4+	2+/4+	2+/3+	4+/3+	ND/0+	2+/4+	2/2	ND/0	ND/1	ND/2	ND/ND	ND/0	25 [†]
2	5000	14720	3+/3+	4+/4+	4+/4+	3+/3+	ND/3+	3+/4+	2/2	ND/2	ND/2	ND/2	ND/2	ND/2	25 [§]
3	150	364	4+/4+	ND/4+	ND/4+	ND/4+	ND/4+	2+/4+	2/4	ND/4	ND/4	ND/4	ND/3	ND/2	10 [†]
4	1280	7200	0+/4+	0+/4+	4+/3+	2+/2+	ND/4+	1+/2+	ND/3	ND/3	2/3	ND/4	ND/3	ND/1	ND
5	52	380	3+/3+	3+/4+	4+/4+	0+/4+	ND/4+	ND/3+	3/4	ND/4	2/4	ND/4	ND/4	ND/0	ND
6	5700	1930	4+/4+	4+/4+	4+/4+	4+/4+	4+/4+	4+/4+	4/4	3/4	2/4	2/3	3/2	3/2	ND
7	115	51	4+/4+	ND/4+	ND/4+	ND/4+	ND/4+	4+/4+	2/3	ND/0	ND/0	ND/0	ND/2	ND/0	ND

* RAST in classes.

** Challenge test with hake. Number indicates weight (g) of boiled hake that induced symptoms.

[†] Immediate systemic anaphylaxis. [§] Immediate acute urticaria, angioedema and vomiting. ND=not done.

toms at the single-blind challenge rendered the double-blind placebo controlled procedure inadvisable.

Discussion

All 7 patients showed typical signs of immediate hypersensitivity upon exposure to fish after a variable period of elimination diet. These signs differed entirely from those shown when the previously tolerated foodstuff (fish) was removed from the diet. However, their sensitivity to fish, as documented by skin testing and RAST, had also increased. Total serum IgE increased in 5 of the 7 patients.

These facts could simply reflect the natural course of food hypersensitivity in these patients, that is, both with or without exclusion diet, they would have developed these symptoms. Unfortunately, there were no patients with skin or RAST sensitization, without symptoms and not on diet, or with other subclinical food sensitization not on diet, who could serve as controls. Most studies on the natural history of food sensitization are based on symptomatic patients (4, 22), and none of them has accounted for the course of subclinical sensitization.

There are no evident data on asymptomatic hypersensitivity as an obligatory previous step towards the development of symptoms. There are reports of the occurrence of immediate-type symptoms with previously tolerated foodstuffs, particularly in adults (2), yet the usual pattern in children is for the symptoms to appear after the first few contacts with the foodstuff (18), and even after the first known contact (29). In contrast, in adults with symptoms after ingesting previously tolerated foodstuffs there is no overt evidence of the previous asymptomatic sensitization; further, in some cases this sensitization appears to be due to cross-reactivity to aeroallergens (15, 17).

Another possible explanation would be to relate the appearance of symptoms and the increased sen-

sitivity to a feature common to all patients, i.e. the institution of an elimination diet. In this case, the elimination diet could act as the responsible or facilitating factor for the appearance of clinical symptoms.

There are reports that suggest that exposure to large doses of antigen might produce a suppression of the specific IgE response (24, 27, 28). If this is so, the daily intake of an antigen could suppress, or at least not induce, the appearance of an immediate hypersensitivity. Firer et al. have detected, in children with cows' milk allergy and minimal previous exposure to this antigen (breast-feeding), higher levels of total IgE and specific IgE to cows' milk antigens than in allergic children with high previous intake (formula-feeding) (9). At the same time, immediate type allergy to cows' milk proteins appears to be less frequent in children who have been formula-fed from birth (19).

These facts suggest that, in some individuals, exposure to large doses of antigen could produce suppression of specific IgE response, reflected in clinical tolerance. However, an IgE response against food antigens might be easier to achieve with small doses. Probably, when the amount of absorbed antigen is below the threshold required to stimulate the T-suppressor cells engaged in the down-regulation of IgE synthesis, the production of specific IgE is favoured. This threshold seems to be higher in atopsics (as were those in the present series) than in normal subjects (10). Thus, contact with minimal quantities of the allergen may favour the production of specific IgE and, even more, the maintenance of this response over time (6, 11, 12).

Minimal or hidden contact with an allergen can be diverse; regarding fish, some workers have found minimal but detectable quantities of fish in the house dust of individuals sensitized to this allergen (1). In such a case, an elimination diet, as it does not prevent minimal and hidden contact with the allergen, might act as a "pro-sensitizing" diet, favouring the

transformation of an asymptomatic sensitization into an overtly symptomatic one.

Thus, in the present group of patients the elimination diet might have played an important role in the increased degree of sensitization and in the occurrence of immediate symptoms upon renewed exposure to fish. For this reason, this possible effect should be considered, together with others already mentioned (3, 7, 8, 13), when deciding on an elimination diet. These findings support the idea that an elimination diet not based on challenge procedures, or on severe symptoms closely related to a specific food, is inadvisable and might be potentially harmful.

It is quite possible in daily practice to encounter patients who are in a situation similar to that described. It is therefore recommended that the deleted foodstuff be reintroduced with caution.

These observations show that, except for well-documented exceptions (21), a controlled challenge test is the only valid method to establish the relationship between the patient's complaints and the sensitization detected. Only the existence of such a relation will justify an elimination diet.

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