The spectrum of allergy to South African bony fish (Teleosti)

Evaluation by double-blind, placebo-controlled challenge

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Objective. The aim of this study was to assess the spectrum of allergy to South African bony fish (Class Teleosti), crustaceans and molluscs and to confirm or refute suspected allergy, specifically to bony fish, by double-blind, placebo-controlled food challenge (DBPCFC).

Design. Patients were recruited by means of a seafood allergy questionnaire. Subjects with reported allergy to hake, yellowtail, salmon and mackerel were investigated by means of skin-prick tests, RASTs and Western blot analysis. For those subjects with test results that were either all negative or equivocal, a definitive diagnosis of clinical sensitivity was made on the basis of DBPCFC.

Setting. Volunteer population-based cohort in the Western Cape.

Participants. 105 volunteer subjects with suspected fish allergy were recruited by advertising in the local press.

Main outcome. Species-specific bony fish allergy was confirmed or refuted by DBPCFC.

Results. The four most common seafood species reported to cause adverse reactions were prawns (46.7%), crayfish (43.8%), abalone (35.2%) and black mussels (33.3%). The four most common bony fish species to cause reactions were hake (24.8%), yellowtail (21.9%), salmon (15.2%) and mackerel (15.2%).

Seven DBPCFCs were performed and two open challenges. Skin-prick tests produced one false-negative result. Western blots produced one false-negative and one false-positive result. The RAST had a 100% correlation with DBPCFC.

Conclusions. Local bony fish represent a significant cause of clinical reactions to seafood in the Western Cape. Although skin-prick tests, RASTs and Western blotting tests assist in the documentation of an IgE responder state, confirmation of clinical sensitivity can only be made with certainty by means of DBPCFC.

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Adverse food reactions to seafoods are frequently reported, but the prevalence of seafood allergy in South Africa has not been determined. Adverse food reactions include true food allergy, which is an IgE-mediated hypersensitivity, and food intolerance, which is a non-immunological hypersensitivity.[1,2]

Seafood represents one of the most important groups of allergens in the induction of food allergy worldwide. Most of the published studies assessing the prevalence of fish allergy have been performed in the Scandinavian countries and Spain. It is estimated that 3% of 3-year-old Finnish children are allergic to fish.[3,4] In Norway, a large percentage of the population works in fishing and related industries, and fish forms a large part of the daily diet. The prevalence of fish allergy approaches 1/1 000 in the general population of Norway.[4] In Spain, fish is the second most commonly implicated food, after eggs, to induce allergic reactions.[4] With the increased consumption of seafood, the rate of adverse reactions is believed to be rising.[5-9]

Scombroid fish poisoning (SFP) is a form of ichthyosarcotoxism caused by the consumption of 'spoiled' fish. Clinically, SFP resembles an IgE-mediated allergic reaction. Ten incidents involving 22 subjects have been documented in Cape Town. In each case, Cape yellowtail, *Seriola lalandi*, was involved.[10] Fish affected by SFP are usually from the families *Scombridae* and *Scomberescidae*, i.e. tuna, mackerel and bonito. Non-scombroid fish such as yellowtail, anchovy, sardines and herring have also been implicated as causes of scombrotoxism.

From previous studies it is apparent that a conclusive diagnosis of IgE-mediated food hypersensitivity to different fish cannot be confirmed with a single test. Skin-prick tests, the radio-allergosorbent test (RAST) and immunoblotting have been used to diagnose allergy in both children and adults,[11,12-19] but there is still disagreement as to which test is more accurate in identifying food hypersensitivity.[11,12-19] Therefore, today it is accepted worldwide that verification of food allergy is only possible with the gold-standard — double-blind, placebo-controlled food challenge (DBPCFC).[11-17]

This study had three aims. The first was to investigate, by means of a detailed questionnaire, the spectrum of adverse seafood reactions in a sample of volunteers in South Africa. Secondly, the study aimed to compare the results of various diagnostic procedures (skin-prick test, RAST and Western blot) with the clinical diagnosis in a cohort of 22 subjects with suspected bony fish allergy. The third aim was to confirm or refute immediate fish hypersensitivity to yellowtail, hake and snoek in a sample of 9 of the candidates in whom equivocal results were obtained in the tests, using DBPCFCs.

Methods

Patients

Patients were recruited for the study by advertisements in a daily newspaper, the hospital newsletter and local medical journals. A questionnaire was distributed to individuals who volunteered to participate in the study. The questionnaire sought details of the seafoods that were thought to be problematic, the symptoms produced upon ingestion of the

suspected foods, the time between food ingestion and symptom onset and the ingredients used for the preparation of the seafood dish. Other details such as a family history of food allergy and whether or not the subjects were atopic were also obtained. Individuals who were willing to undergo a series of diagnostic tests signed a consent form and had a blood sample taken. Twenty-one subjects with perceived allergy to bony fish (either yellowtail and/or hake and 1 subject with perceived allergy to snoek) (Class Teleosti) were selected for detailed investigation. Individuals younger than 16 years and those who reported previous anaphylaxis were not subjected to any *in vivo* tests.

Skin-prick tests

A panel of 19 different seafood species was used on each subject. The panel consisted of 12 in-house extracts prepared from fresh raw fish: hake, yellowtail, Cape salmon, snoek, kingklip, prawn, calamari, crayfish, black mussel, white mussel, perlemoen, oyster and seven commercial glycerinated extracts (Soluprick, ALK Laboratories, Horsholm, Denmark: crab, cod, herring, shrimp, plaice, mackerel and mussel). Histamine dihydrochloride 10 mg/ml was used as positive control and a diluent of glycerol/sodium chloride as a negative control. Subjects were requested not to take any antihistamines on the day prior to and on the day of the skin tests. Blood pressure, pulse and peak expiratory flow rate (PEFR) were measured prior to and half hourly following skin tests. The reaction to the skin test was considered positive when the weal induced by the fish extract had a diameter 3 mm greater than that of the negative control.

Skin tests to the in-house allergens were performed on four non-allergic members of our laboratory staff who served as negative controls prior to our performing the tests on the subjects.

RASTs

Fish allergen-specific IgE was determined using the Pharmacia AB (Uppsala, Sweden) CAP RAST system (RIA) for hake, salmon and mackerel. Snoek and yellowtail RASTs were not available. A positive result was classified as any value greater than 0.35 kU/l, according to the CAP RAST scoring system. An in-house RAST for yellowtail was performed. In this procedure, yellowtail extract was coupled with sepharose beads prior to incubation with serum. The standard RAST procedure was followed. The radioactive antibody used was I^{125} rabbit antihuman IgE and reactivity was measured with an automatic gamma counter (LKB 1272 Clinigamma). A positive result was classified as any value more than 3.0 times the value of the nonspecific binding.

Western blots

Extracts were made by adding finely chopped raw fish to phosphate-buffered saline in a weight-to-volume ratio of 1:3. The mixture was placed on a shaker, agitated overnight at 4°C and then centrifuged (with a Beckman GPR centrifuge) at 2 000 rpm for 30 minutes. The resultant supernatant was filtered through 3 filters: a 1.6 µm prefilter, a 1.2 µm filter and a 0.45 µm sterile filter. The final mixture was aliquoted into 50 ml portions and frozen at –20°C; 10 µg of the seafood extract were separated by means of a polyacrylamide gel and blotted onto a Hybond-Polyvinylidene difluoride membrane. Nonspecific binding sites were blocked by immersion of the membrane in a 5% blocking reagent in PBS-Tween for half an hour at room temperature. The membrane was then incubated overnight with the serum of the subject. Enhanced chemiluminescence (ECL), Western blotting and detection reagents (Boehringer) were then used with the secondary antibody (HRP-labelled streptavidin complex). Protein bands were visualised in the dark room on X-ray film.

Challenge tests

Nine subjects were selected for challenge testing. Subjects with test results, which were either all negative or equivocal, were challenged.

DBPCFC procedures

Forty-five grams of fresh raw fish (yellowtail and hake) were homogenised in 400 ml distilled water. This was then mixed with 200 ml Fruitmate concentrated blackcurrant juice (without dyes or preservatives). This produced approximately 600 ml fish/blackcurrant juice mixture. A series of cups were made up in which sequentially increasing amounts of fish extract were used. The final volumes in each cup were reached by adding dilutions of blackcurrant juice/distilled water (1:4). The placebo drinks consisted solely of blackcurrant juice and distilled water. A total of 9 fish challenges were performed, 7 of which were DBPCFCs. All challenge procedures were prepared and randomised by the same person.

On the day of the challenge, the subjects were told to arrive at the hospital after having fasted. The procedures and risks involved were explained to each subject and informed consent was obtained. Cups were administered every 20 minutes. Before each ingestion, PEFR, blood pressure and pulse were measured. Any symptoms experienced by the subjects were recorded. Challenges were continued until either objective symptoms were observed or the maximum dose had been reached. A challenge was considered negative if a single dose of 8 g or a cumulative dose of 15 g was tolerated. The solutions were served cold in paper cups with a lid and straw. Subjects used a nose-clip while drinking in order to minimise any potential fish taste. The subjects were allowed home 1 hour after the last active dose had been administered. The challenges were performed in a setting where full resuscitation equipment was available.

A pilot fish challenge was performed on a control subject in order to assess the palatability of the fish/blackcurrant juice mixture as well as the degree to which the fish had been disguised.

A different fish challenge protocol was individually designed for each subject.

Ethics approval

Ethical approval for the study was obtained from the Ethics and Research Committee of the University of Cape Town, and written consent was obtained from each of the patients studied.

Results

Patient demographics

The ages of the patients ranged from 7 to 74 years, the mean age being 41.2 years.

Seafood species

The questionnaire specifically enquired about 9 seafood species, crayfish, prawns, perlemoen, black mussel, oyster, yellowtail, hake, salmon and mackerel, and snails. Subjects were asked to list any other species that caused adverse reactions.

From the first group of seafood phylla (crustacea and molluscs) (Fig. 1), prawns were frequently reported to cause adverse reactions (46.7%), followed in descending order by crayfish (43.8%), abalone (35.2%), black mussel (33.3%), oyster (23.8%), snails (16.2%), shrimp (13.3%), crab (12.4%) and squid (11.4%). The last four seafood types in Fig. 1, viz. limpet, alikreukel, white mussel and scallop were each reported by 1 individual. Their contribution was 0.9% each.

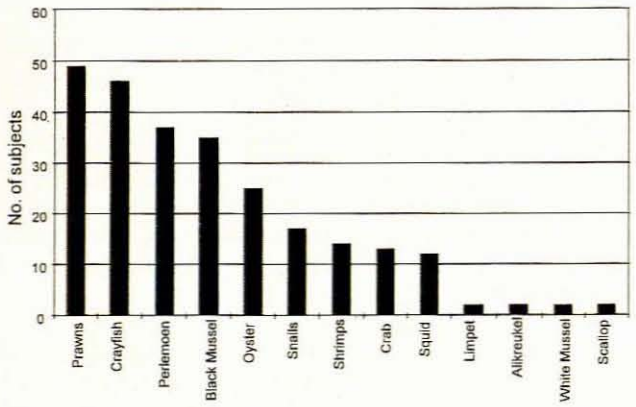

Fig. 1. Numbers of subjects reporting adverse reactions to crustaceans or molluscs following ingestion of seafood, in the 105-patient cohort.

From the second group (bony fish/Teleosti), 24.8% of people reported an allergy to hake (Fig. 2). This was followed by yellowtail (21.9%), salmon and mackerel (each contributing 15.2% to the total), kingklip (13.3%), snoek (10.5%) and tuna (2.8%). Haddock, cob and sole each contributed 1.9% and carp, trout, maasbanker and pilchard 0.95%.

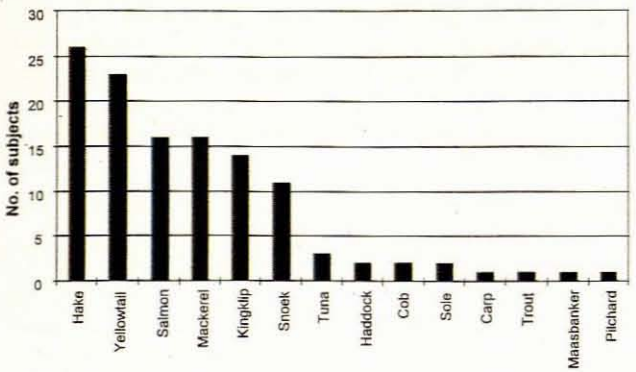

Fig. 2. Numbers of patients reporting adverse reactions following ingestion of bony fish (Teleosti) in the 105-patient cohort.

Symptoms

Subjects in the cohort of 105 were asked to describe the symptoms they experienced during an adverse reaction. Symptoms were divided into 4 categories: cutaneous, gastro-intestinal, respiratory and miscellaneous. The distribution of symptoms is summarised in Table I.

Table I. Reported signs and symptoms of 105 subjects with perceived seafood allergy

Symptoms	No. of subjects (% of total)
Cutaneous	
Pruritus/swelling of throat	53 (51%)
Pruritus of lips/tongue	45 (43%)
Urticaria	41 (39%)
Pruritus/swelling of body	12 (11%)
Eczema	10 (10%)
Pruritus/swelling of eyes/face	9 (9%)
Gastro-intestinal	
Nausea/vomiting	57 (54%)
Abdominal pain	36 (34%)
Diarrhoea	36 (34%)
Bloating	1 (1%)
Respiratory	
Wheezing	38 (36%)
Shortness of breath	28 (27%)
Throat closing	21 (20%)
Other	
Anxiety	40 (38%)
Flushing	35 (33%)
Headache	22 (21%)
Dizziness	22 (21%)
Cold/sweaty/shivering	3 (3%)
Collapse/anaphylaxis	2 (2%)
Chest pain	2 (2%)
Blurred vision	1 (1%)
Tachycardia	1 (1%)
Confusion	1 (1%)

Of all symptoms 32.9% were cutaneous, 25% were gastro-intestinal, 16.8% were respiratory and 25% were in the miscellaneous category. The most common symptom experienced in the 105 subjects was nausea/vomiting, and it was reported in 54% of cases.

Twenty-one patients who suspected allergy to either yellowtail and/or hake were studied in detail. Some of these patients also suspected allergy to mackerel and/or salmon. One patient with suspected allergy to snoek was also studied in detail.

Table II provides the details of the 22 individual subjects who underwent further testing and the results of the tests performed on the fish suspected by the history: skin-prick test, RAST and Western blot.

Of the subjects who reported allergy to hake, 29% had typical histories of type I allergy as well as strong positive results on all the tests performed. A typical history was considered to be a reaction within 2 hours of fish ingestion with symptoms characteristic of the immediate-type reaction (oropharyngeal itching and swelling, urticaria, angio-oedema and asthma). Fifty per cent of the subjects had all negative test results and 21% had equivocal results.

Table II. Subject details based on history and test results

Subject	Time of symptom onset	Symptoms by history	Suspected fish	SPT	RAST	Western blot
1	Immediate	OIS, A, W, SOB, F, Ax	Hake	+++	12.6	Strong +
			Yellowtail	++	42.6	Strong +
			Salmon	+++	1.0	Strong +
			Mackerel	–	2.4	ND
2	Immediate	OI, FS	Hake	++	1.7	Strong +
			Salmon	+	3.7	Strong +
			Mackerel	+	2.0	ND
3	*Immediate*	*OIS, D, W, F*	*Mackerel*	+	0.3	*ND*
4	Immediate	OIS, E, U, D, W, SOB, Ax	Hake	+++	22.2	Strong +
			Yellowtail	+++	71.7	Strong +
5	Within 30 minutes	OIS, U, SOB, W, N, V, H	Hake	+++	0.3	Weak +
			Yellowtail	+++	3.1	Weak +
			Mackerel	–	0.3	ND
6	12 hours	swelling and pain all over	Hake	–	0.3	–
			Yellowtail	–	1.4	–
7	1 hour	OIS, U, A, SOB W, F, Ax, Dz	Hake	+	0.3	–
			Yellowtail	–	0.5	–
8	Within 30 minutes	OIS, E, A, N, V, F, Ax, Dx	Hake	+++	6.6	Strong +
			Yellowtail	+++	2.9	Strong +
			Salmon	+++	0.8	Strong +
			Mackerel	+++	0.3	ND
9	*Within a few hours*	*OIS, SOB, W*	*Hake*	–	0.3	–
			Yellowtail	–	1.3	Weak +
			Salmon	–	0.3	Weak +
			Mackerel	–	0.3	ND
10	Within 15 minutes	N, V, D, A, H	Yellowtail	+	2.7	Strong +
11	(*i*) Within a few minutes (*ii*) Within a few hours	OIS, N, V, SOB	Yellowtail	+	2.7	Strong +
12	Immediate	OIS, U, N, V, SOB, W	Hake	–	0.3	–
			Yellowtail	+	3.1	–
			Salmon	+	0.3	–
			Mackerel	–	0.3	ND
13	6 hours	OIS, U, A, N, V, D, W, SOB, F, Dz	Hake	–	0.3	–
			Yellowtail	–	0.8	Weak +
14	Within a few hours	U, E, N, V, W, SOB	Yellowtail	–	0.6	–
			Salmon	–	0.3	–
15	3 - 12 hours	OIS, U, E, H, F	Hake	–	0.3	–
			Yellowtail	–	0.8	–
			Salmon	–	0.3	–
16	30 minutes	OI, D, H, F	Yellowtail	–	0.7	–
17	1½ hours	N, V, F	Yellowtail	–	0.7	–
18	1 - 12 hours	U, A, N, V, D, H, Ax	Yellowtail	–	0.6	–
19	Within 1 hour	OIS, A, N, V, SOB, W, H, Ax	Hake	–	0.3	–
			Yellowtail	–	2.7	–
20	*Immediate*	*OIS, U*	Hake	–	0.3	–
21	?	SOB, W, D, F, Ax, Dz	Snoek	–	ND	ND
22	2 hours	A, V, D, N	Hake	–	–	+

ND = not done; SPT = skin-prick test; OI = oral itching; OIS = oropharyngeal itching and swelling; E = eczema; U = urticaria; W = wheezing; V = vomiting; SOB = shortness of breath; A = abdominal pain; N = nausea; D = diarrhoea; F = flushing; Dz = dizziness; H = headache; Ax = anxiety.

Of the 17 subjects who reported allergy to yellowtail, 29% had all positive test results, 47% had all negative test results and 24% had equivocal results (Fig. 3).

Of the subjects who reported allergy to salmon, 42% showed all positive test results, 29% had all negative results and 29% had equivocal results.

Only 1 subject had all positive test results for mackerel (14%), 42% had all negative results and 43% had equivocal results.

The results of subjects 16 - 22 (the 7 subjects who underwent food challenges) are shown in Table III.

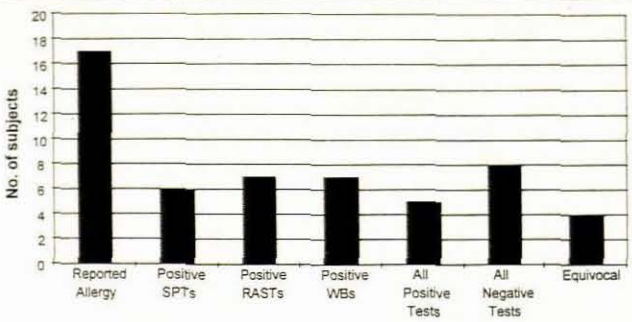

Fig. 3. Distribution of subjects with reported allergy to yellowtail, showing positive and negative *in vivo* and *in vitro* tests for yellowtail allergy.

Table III. Test results for subjects 16 - 22

Subject	Suspected fish	SPT	RAST	Western blot	Challenge
16	Yellowtail	–	0.7%	–	–
17	Yellowtail	–	0.7%	–	–
18	Yellowtail	–	0.6%	–	+
	Placebo				+
19	Hake	–	0,3%	–	–
	Yellowtail	–	2.7%	–	+
20	Hake	–	0.3	–	–
21	Snoek	–	ND	ND	–
22	Hake	–	0.3	weak +	–

We did not consider it appropriate to challenge those subjects who had a clear history of fish sensitivity supported by *in vitro* and skin-prick test evidence of specific IgE to the fish in question.

Seven DBPCFCs were performed on 5 subjects and 2 open challenges were performed on 2 subjects with equivocal results. There were 3 positive outcomes. Only in subject 19 was a positive diagnosis clinically confirmed by DBPCFC. He reacted rapidly (within minutes) to each of the yellowtail drinks and experienced no reaction to the placebo drinks. Oropharyngeal itching and swelling were experienced immediately after fish consumption. These symptoms were similar to those that had occurred in previous reactions reported in the history. They were, however, less severe and resolved more rapidly. This may be attributed to the challenge procedure in which the smallest amount of fish necessary to produce an observable reaction was selected.

Subject 18 experienced adverse reactions of a different nature to both the yellowtail and the placebo challenges. These reactions only occurred about 1.5 hours into the challenge. The symptoms she experienced were abdominal cramps, bloating and dizziness. Her blood pressure dropped and she experienced blurred vision and slurred speech on both challenges. There were no symptoms typical of a type I allergy.

The remaining four DBPCFCs were considered negative, as in each case the maximum dose of 15 g fish produced no reaction. Two open challenges, performed by choice at home by 2 subjects when they knew that their skin-prick tests were negative, were also negative.

All 8 skin-prick tests performed on these subjects were negative (Table III). A snoek RAST was not developed and Western blots were not performed on subject 21 because of the unavailability of snoek at the time. The yellowtail RASTs performed were negative, except in the case of subject 19, whose reading was 2.7%. In addition, the Western blot results were negative on these patients except for a weakly positive result for subject 22.

Overall, the skin-prick test produced 1 false-negative result and the Western blot test produced 1 false-negative and 1 false-positive result. The in-house RAST had the best correlation with the results of the challenges (100%).

Discussion

This study has, for the first time, reported the spectrum of seafood allergy in the Western Cape and has demonstrated the importance of DBPCFC in assessing some of these subjects.

Prawns and crayfish are most frequently reported to cause adverse reactions; hake and yellowtail are the commonest of the bony fish. These seafoods are commonly served at many restaurants and fast food outlets. Reports of adverse reactions to seafoods such as limpet, alikreukel, scallop, carp and maasbanker are uncommon. These seafoods are not as readily obtainable as the more popular varieties, and the lower the exposure of a population to a certain seafood species, the lower the incidence of adverse reactions will be. However, it is noteworthy that some of the subjects' reactions to the more uncommon species were very severe. The high frequency of positive reactions to perlemoen was an unexpected finding and is the subject of a separate communication (Lopata *et al.* — unpublished data).

The nature of the symptoms experienced and their time of onset for the different types of seafood were compared and, as shown in other studies, the symptoms experienced were almost identical for crustaceans, molluscs and bony fish.[16,17] One important difference between the two seafood types was that shellfish was associated with a higher incidence of anaphylaxis. Two subjects in the study had a history of anaphylaxis. They both reported shellfish as the causative factor. This finding is consistent with those of O'Neil *et al.*[16] and Daul *et al.*[17]

The most common symptom was nausea/vomiting (57%), followed by oropharyngeal itching and swelling (53%). A proportion of our subjects had symptoms suggestive of food intolerance and not an IgE-mediated allergy. The symptoms associated with food intolerance are predominantly gastro-intestinal.

Although DBPCFCs have not been performed on the first 15 of these subjects, it was possible to demonstrate *in vivo* and *in vitro* sensitivity to fish based on the information obtained from the history of the subjects and their test results. All the subjects who had strong positive test results experienced reactions either immediately or within 30 minutes of fish ingestion. Because of the severity of their skin test reactions and blood results, it may have been dangerous to perform DBPCFCs on these subjects. In 1966, Aas[7] undertook studies on hypersensitivity to fish. He stated that in cases such as those mentioned above, the demonstration of strong positive skin reactions, in addition to an unmistakable history of a type I allergic reaction, was accepted as confirmatory evidence of clinical allergy.

In the group of subjects with all negative test results to each fish species, the diagnosis was unsure. There is a chance that all 3 types of test produced false-negative

results in each subject and since the sensitivity of *in vitro* and skin tests is less than 100%, one would be reluctant to allow these subjects to eat fish without a DBPCFC's being performed. In our study, subjects who had negative results for all three tests for salmon allergy were found to have a history characteristic of an intolerance reaction.

There were 3 subjects with equivocal results in respect of hake. One had a conflicting skin-prick test result (subject 7) and another had a conflicting RAST result (compared with the other 2 tests). Although subject 7 had an extremely good history of type I allergy (including being atopic and having a family history of food allergy), her skin prick test result was not strongly positive and the other two tests were both negative. This set of data is inconclusive. A proper diagnosis can therefore not be made without a food challenge.

Subject 5 had a very good history of a type I reaction, a strong positive skin-prick test result, a positive Western blot result, but a negative RAST result. One could assume that the RAST result obtained was likely to be a false-negative result, but once again a proper diagnosis could not be made without a food challenge.

In the cases of equivocal results for yellowtail, salmon and mackerel, the same trends were noted as in respect of hake. Because of the occurrence of false-negative and false-positive results produced by all these tests, as well as conflicting opinions in the literature, it was difficult to formulate any conclusions or make any diagnosis in these subjects without performing a DBPCFC.

Fish challenges confirmed the presence of IgE-mediated allergy in 1 subject and refuted it in 6. The adverse reactions experienced by these 6 subjects were attributed to food intolerance. Three subjects in this study therefore experienced the toxic reactions typical of SFP, i.e. nausea, vomiting, flushing and an oral burning sensation within 1.5 - 2 hours of fish ingestion. Once considered uncommon, SFP accounted for 4.5% of cases of food poisoning reported to the Centers for Disease Control in the USA between 1978 and 1982.[20] A number of incidents of SFP, some involving quite large groups of individuals, have been reported in the literature over the last 20 years.[21-24]

In each of the 10 incidents reported to Tygerberg Hospital Pharmacology and Toxicology Consultation Centre in South Africa in 1990, a number of common symptoms were reported by affected individuals. These included nausea, diarrhoea, flushing, headache, abdominal cramps, an oral burning sensation, erythema and urticaria of the skin.[10] The symptoms began within 1.5 hours in all cases. In our study, 3 of the subjects who experienced adverse reactions to yellowtail developed symptoms consistent with those of SFP. In 2 of the subjects, reactions took place within 30 minutes and 1.5 hours, respectively. When fish is improperly refrigerated or when refrigeration is delayed, histidine is converted to histamine by certain bacteria which contain the enzyme, histidine decarboxylase. Enterobacteriaceae, such as *Proteus morganii* and *Klebsiella pneumoniae*, contain this enzyme and are often implicated in SFP. The results of the various tests, as well as the negative outcomes of the DBPCFCs show quite conclusively that SFP must have been the cause of the original adverse reactions.

A definite diagnosis of type I allergy cannot be made for subject 18. Although both of her challenges were positive (yellowtail and placebo), all 3 tests performed were negative and her history did not suggest an IgE-mediated hypersensitivity. The conclusion to be drawn from this is that there is a very low probability of her being truly allergic to yellowtail. The blackcurrant juice used in this study did not contain preservatives or added sugar. It was made from a natural grape husk base and imported blackcurrants. The subject stated that she 'reacts' to very sweet food products. Grapes contain a large amount of the monosaccharide, fructose. Her positive reaction to the placebo could be due to the abundance of fructose in the juice. With regard to yellowtail, a further challenge should be performed using a different masking agent.

The results of subject 21 clearly indicate that he did not have an IgE-mediated allergy to snoek. The open challenge confirmed that the fish itself was not the causative agent of this adverse reaction. He also reported on his questionnaire that he had previously had marked sensitivity to sulphur dioxide, which triggered asthma attacks almost immediately. The symptoms he experienced upon eating his meal correlated well with those documented in sulphite-sensitive asthmatics. He stated that the snoek was consumed in a restaurant, but did not state what other foods and beverages he ingested at that time. Legislation states that packaged foods containing more than 10 ppm total sulphur dioxide should be labelled. The primary manifestation of sulphite sensitivity is asthma and is well documented in the literature.[25-29]

The negative predictive accuracy of the skin-prick test, i.e. the number of negative skin tests truly representing absence of clinical fish hypersensitivity, was 6/7 (86%). Only one false-negative reaction was obtained. This occurred in subject 19. The Western blot for the same subject also produced a false-negative result. Although this was the only subject proven to have IgE-mediated hypersensitivity to fish on DBPCFC, he demonstrated false-negative laboratory and skin test results. This indicates that for a correct diagnosis, DBPCFC has to be applied. Although the number of false-positives obtained was small, it still indicates that these tests are not completely reliable. The negative predictive accuracy of the skin-prick tests and the RASTs (i.e. the accuracy of the test in determining the proportion of subjects who test negative that truly are negative) were very similar to those reported by Sampson and Albergo[14] in 1984. In their study, they were 82% and 100% respectively, whereas in our study, they were 86% and 100% respectively. From our study, one can conclude that our tests are extremely useful in ascertaining the absence of an immediate hypersensitivity to fish.

The varied opinions of past researchers on the accuracy and reliability of the other diagnostic tests indicate that none of them has proved adequate to confirm an IgE-mediated allergy.[30] We have confirmed the value of the DBPCFC in diagnosing seafood allergy in our study.

It can be concluded from this study that some people who claim to be allergic to fish may, in fact, not be truly allergic. Intolerance reactions are abundant, be they due to additives or toxins, e.g. SFP. Symptoms experienced as a result of intolerance reactions are similar to those experienced in hypersensitivity reactions. Misdiagnoses can be avoided by means of a series of tests such as those used in this study. The DBPCFC should be used to verify a definite clinical allergy.

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