

Management of Food Allergy to Fish with Oral Immunotherapy: A Pediatric Case Report

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Fish allergy represents a persistent allergic disorder that usually does not improve spontaneously. Because neither fully effective therapeutic strategy nor truly curative approaches are currently available for food allergy, we report herein a case of fish allergy in a 11-year-old male patient treated with Oral Immunotherapy (OIT). The patient at the age of 4 years, for the first time, experienced immediate urticaria and angioedema, rhinitis, cough, and dyspnea after ingestion of both salmon and codfish. Skin prick test, specific IgE, and oral food challenge (OFC) were positive for both salmon and codfish. Therefore, positive allergy tests and challenge confirmed allergy to fish. The patient underwent oral administration of increasing doses of the offending food. He was initially treated by OIT using dehydrated codfish. When the dosage of 1 g was achieved and tolerated by the patient, a desensitization regimen was continued through the administration of cooked codfish. At the end of the protocol, the patient achieved desensitization also confirmed by negative OFC with fish. This case suggests that OIT could be used for treatment of food allergy caused by fish with successful results.

Background

FOOD ALLERGY REPRESENTS an allergic disorder that affects up to 6% of children and up to 3% of adults in Europe.¹ Supportive management of food allergy, consisting of avoidance of offending foods and early recognition and treatment of symptoms, is currently the standard of care for affected individuals. Avoidance of food allergen(s) is a significant burden for allergic patients and their families. Therefore, oral immunotherapy (OIT), administration of incremental doses of the offending food, has been proposed in an attempt to achieve a transient (desensitization) or sustained (tolerance) immunologic nonresponse.²

Very few reports describe fish allergy successfully treated with OIT in children³ and adults.⁴ We report the case of a Caucasian male patient affected by cod and salmon allergy successfully treated with OIT.

Case Presentation

A 11-year-old Caucasian male was admitted to our allergy unit with a clinical history of allergy to fish. He had never eaten fish in the first 4 years of life because he didn't like it. He presented immediate urticaria and rhinitis after ingestion of salmon and swelling of the tongue-lips and dyspnea within 2 hours of ingestion of codfish at the age of 4

years. Since then, he underwent a strict avoidance of fish in the diet for 7 years for fear of a potential severe allergic reaction. His family history was positive for father's allergic rhinoconjunctivitis, but no food allergy was reported.

Diagnosis of IgE-mediated allergy to codfish (*Gadus morhua*: Atlantic cod) and salmon (*Salmo salar*: Atlantic salmon) was made based on the clinical history and an allergological workup. The skin prick test (SPT) performed with commercial extract (Lofarma, Milan, Italy) was applied on the forearm skin, and the size of the wheal was of 6 mm for cod fish and 5 mm for salmon and parvalbumin. Specific IgE were measured by fluorescence enzyme immunoassay (ImmunoCAP; Phadia, Uppsala, Sweden) whose lower detection limit was 0.35 KU/L: the patient had specific IgE for codfish equal to 4.72 KU/L, specific IgE for salmon equal to 3.20 KU/L, and specific IgE for parvalbumin equal to 6 KU/L (Table 1). The open oral food challenge (OFC) was carried out by administering cooked cod and salmon on 2 different days; in particular, our protocol consisted in the administration of increasing doses (50 mg, 100 mg, 300 mg, 1 g, 2 g, 4 g, and 10 g) every 30 min. It resulted in swelling of the lips, rhinitis, dyspnea, and generalized urticaria after 15 min of ingestion of 1 g of cod or salmon.

Because the natural history of fish allergy is often life-long, given the persistence of moderate fish sensitization at 11 years of age that suggested the unlikely spontaneous

TABLE 1. TOTAL IgE, SPT, AND IgES AT BASELINE AND AFTER CONCLUSION OF ORAL IMMUNOTHERAPY

	<i>At baseline</i>	<i>After oral immunotherapy</i>
Total IgE	618 UI/mL	452 UI/mL
Codfish SPT	5 mm with pseudopods	3 mm
Codfish IgE	4.72 KU/L	2.85 KU/L
Salmon SPT	5 mm with pseudopods	3 mm
Salmon IgE	3.2 KU/L	1.5 KU/L
Parvalbumin SPT	5 mm	3 mm
Parvalbumin IgE	6 KU/L	4 KU/L

SPT, skin prick test.

resolution of allergy, we proposed specific OIT treatment after the acquisition of parental written informed consent.

Ten days after the OFC was performed, the patient underwent OIT with codfish that was performed in the Pediatric Allergy Unit of Policlinico Hospital–University of Messina (Italy) under medical and nursing supervision. Emergency department was available for the treatment of severe adverse reactions.

The protocol was designed to achieve a total amount of 100 g of codfish in 24 weeks.

In particular, during the induction stage, we administered codfish using a dehydrated extract (Lofarma) for 16 week and during the second stage, cooked cod at progressively increasing doses. The starting dilutions of the protocol were prepared with 65 mg of dehydrated cod extract and the addition of 50 mL of water, obtaining a solution containing 1.3 mg/mL of cod (equal to 0.072 mg per drop).

The first 8 doses of the protocol were administered through the sublingual route and then swallowed after 2 min; when higher doses were reached, from the ninth dose of reconstituted solution, the patient swallowed the dose immediately (Table 2).

The consecutive updosing protocol involved increased weekly doses of cooked fish carried out at the outpatient clinic. The doses were weighed in our laboratory with the Mettler Toledo PL303 balance and obtained after boiling the fish.

Finally, a maintenance regimen was carried out with a weekly intake of 100 g dose of fish at the patient's home to preserve the desensitized state (Table 2).

Written instructions were given and the parents were trained to recognize any reaction that might occur during home administration of OIT. They also received rigorous instructions for the use of autoinjectable epinephrine, betamethasone, and chlorpheniramine as per need. Parents were also advised to call our center in case of appearance of adverse events.

During the first 8 sessions of the induction phase, the patient experienced only temporary itchy throat at the dosage of 4 drops (0.288 mg), 8 drops (0.576 mg), 16 drops (1.152 mg), 3.5 mL (4.608 mg), and 7.1 mL (9.216 mg) of the reconstituted solution. In addition, itchy throat, running nose, and cough appeared when the dosage of 65 mg was reached. The monitoring of vital signs and the cardiopulmonary functions were normal and symptoms improved spontaneously without rescue medication. Similar symptoms occurred during the updosing in the 14th (260 mg), 15th (390 mg), and 16th (585 mg) weeks.

On one occasion, the patient was treated with oral antihistamine (5 mg of cetirizine dihydrochloride) and nasal

TABLE 2. INDUCTION PHASE WITH DILUTED COD EXTRACT (A) AND BAKED COD (B)

<i>(a)</i>				
<i>Days/weeks</i>	<i>Drops^a</i>	<i>mL</i>	<i>Capsules (65 mg)</i>	<i>mg</i>
1/1	1	—	—	0.072
07/2	2	—	—	0.144
14/3	4	—	—	0.288
21/4	8	—	—	0.576
28/5	16	—	—	1.152
35/6	32	1.8	—	2.304
42/7	64	3.5	—	4.608
49/8	128	7.1	—	9.216
56/9	256	14.2	—	18.432
63/10	—	28.4	—	36.864
70/11	—	—	1	65
77/12	—	—	2	130
84/13	—	—	3	195
91/14	—	—	4	260
98/15	—	—	6	390
105/16	—	—	9	585

<i>(b)</i>	
<i>Days/weeks</i>	<i>G</i>
112/17	1
119/18	2
126/19	4
133/20	8
140/21	16
147/22	32
154/23	64
161/24	100

^aSolution of 65 mg dehydrated cod extract in 50 mL water.

inhaled steroid (100 mcg per nostril of budesonide) for the appearance of urticaria and sneezing when the dosage of 4 g of cooked codfish was achieved. He was referred home for 1 week with the previous tolerated dose (2 g), and a second attempt with 4 g of food was performed later and it was successful without symptoms.

No other adverse reactions were reported during the remaining induction phase and once 100 g of cod was achieved in the hospital or during a weekly home administration of the same dosage, which was maintained for 3 months. Finally, the patient started a free diet with both codfish and salmon. Because he liked these fishes, he consumed regularly about 100–150 g of cooked fish twice or thrice a week. OFC performed after 3 months of regular fish consumption was negative and the results of SPT and specific IgE had declined (Table 1).

Discussion

In this article, we have described a standardized protocol for oral desensitization in a patient affected by codfish and salmon allergy in a day-hospital regimen. Fish allergy was suggested by personal clinical history, SPT, and specific IgE for tested fishes and confirmed by positive OFC. The patient underwent an oral desensitizing treatment with codfish during which he experienced only mild side effects. He completed successfully desensitization in 25 weeks until a dosage of 100 g was consumed without symptoms and continued eating the same dosage of fish for another 3 months without problems. The acquired state of tolerance was confirmed with a second OFC, a repeat SPT, and specific IgE after 3 months of

regular fish consumption. So, even though some mild side effects occur, OIT should be considered for children suffering from fish allergy, since it is unlikely to resolve spontaneously.⁵

Fish and shellfish commonly cause adverse allergic reactions such as urticaria, angioedema, asthma, and anaphylaxis.⁶

The prevalence of seafood allergy is usually highest in communities where fish or shellfish are commonly used in the diet such as China, Japan, and the United States.⁷ In Europe, Iceland, Faroe Islands, Portugal, Norway, and Spain are the countries where the higher consumption of seafood is recorded.⁸ The European prevalence of food challenge-defined allergy to fish and shellfish is estimated about 0.1% (0.02–0.2%) and 0.1% (0.06–0.3%), respectively.⁹ Cod, tuna, salmon, trout, and plaice are the commonest fishes involved in allergic reactions,¹⁰ while shrimp, mussel, crab, and octopus are most frequently reported as responsible for allergic reaction among shellfish.⁹

In childhood, the prevalence of fish allergy is low (0.2%), although the prevalence of shellfish allergy is higher than fish allergy (0.5%).¹¹

Fish adverse reactions may also be caused by food contamination (parasite *Anisakis*) or newly formed toxic products (histamine, ciguatoxins, tetrodotoxin, saxitoxins, brevetoxins, domoic acid, okadaic acid, dinophysistoxins, pectenotoxins, and yessotoxin).⁶ However, in the majority of patients, allergy to fish is IgE mediated (acute urticaria, angioedema, respiratory or gastrointestinal symptoms, and anaphylaxis) or due to the non-IgE-mediated food protein-induced enterocolitis syndrome. The route of sensitization to fish may be through the gastrointestinal tract or by skin contact or inhalation of cooking vapors of seafood.¹⁰ Because of its large distribution in many fish species, Gad c I parvalbumin is considered a pan-allergen for fish, although other allergens like Gad m 2.0101 (enolase) and Gad m 3.0101 (aldolase) have recently been characterized.¹² Tropomyosin is considered the principal allergen of shellfish.¹³

People who are allergic to fish usually tolerate shellfish and vice versa. In contrast, cross-reactivity often occurs within fish or shellfish species, for example, most people who are allergic to cod would react to halibut and most people who are allergic to shrimp would react to crab.⁶

The present standard of care of fish allergy is strict dietary avoidance. However, despite patient and parents vigilance, accidental ingestion of offending foods may occur, resulting in clinical symptoms and emergency medication.

Several clinical studies on OIT are available, and some trials are currently underway to better define indications, contraindications, and practical aspects. However, few studies have described standardized protocols for oral desensitization in children and adults affected by fish allergy.

Patriarca et al. published 2 articles, in which oral desensitization to fish was conducted and successfully completed in 5–10 months in 10 patients of which 9 were children.^{3–4}

In our case, clinical allergy to fish was supported by the suggestive clinical history for fish allergy and a positive of diagnostic allergological workup. As suggested for other food allergies,¹⁴ the relatively low levels of specific IgE were felt to predict a favorable outcome to fish desensitization. In addition, patient and his family were highly motivated to overcome this limiting food allergy so adherence to the protocol was excellent and contributed to the success of the study.

Currently, the patient continues to eat fish regularly and weekly, so it's too early to say that he has acquired sustained unresponsiveness to the culprit food. Although clinical desensitization and immune modulation have been demonstrated with OIT,¹⁵ it is still unclear whether oral desensitization represents the first step toward permanent oral tolerance. Assuming that the duration of desensitization could be crucial for achieving tolerance, given also the natural history of fish allergy that is often lifelong, we suggest regular consumption of offending food for at least 2 years followed by fish avoidance for 3 months, when the food challenge is repeated to determine the maintained tolerance.

In conclusion, we demonstrate that OIT may be an effective option for the treatment of mild to moderate fish allergy. The particularity of our protocol is the short duration compared with other studies, in which the desensitization period ranged from 5 to 10 months. Nevertheless, we are aware of the limitation of our study as it describes a single case. Because still few reports describe fish allergy successfully treated with OIT, further studies are needed to reinforce our conclusions and consolidate this therapeutic approach.

Consent

Due to the experimental treatment, we obtained the approval of the ethics committee who requested the informed consent that was obtained from the parents.

Author Disclosure Statement

No competing financial interests exist.

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