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ORIGINAL ARTICLE

IgE-mediated fish allergy in Singaporean children

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Abstract

Background: Fish is one of the common causes of food allergy and there is limited literature about fish allergy in Singapore.

Objective: We aimed to describe the demographics, clinical features, and natural history of children with IgE-mediated fish allergy.

Methods: A retrospective review was conducted for children diagnosed with fish allergy in a tertiary pediatric hospital in Singapore between 2015 and 2020.

Results: The diagnosis of fish allergy was made in 108 patients based on a convincing history of IgE-mediated allergic reaction and a positive skin prick test. The median age at first reaction was 12 months (range 6-168) with most reacting on first ingestion (62.0%). The most common fish causing reactions were threadfin (48.1%), salmon (33.3%) and cod (31.5%). Majority presented with cutaneous symptoms (97.2%). Anaphylaxis occurred in 6.5%. Five were mono-sensitized (4.6%), 77 were oligo-sensitized (71.3%) and 26 were polysensitized (24.1%). Most can tolerate another species of fish (75.9%), most commonly salmon (37.0%), tuna (24.1%) and cod (22.2%). Median duration of follow up was 24 months (range 0-176). Twenty-eight out of 108 children (25.9%) acquired natural tolerance to index fish at a median age of 60 months (range 18-159).

Conclusion: Most children with fish allergy can tolerate at least one other species of fish and resolution of fish allergy is possible. Thus, it is important to follow-up with an allergist to evaluate which fish species can be included in their diet to avoid unnecessary dietary restrictions.

Key words: fish allergy, IgE-mediated food allergy, anaphylaxis, natural history, Singaporean children

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Introduction

The prevalence of food allergy is on the rise globally, including in developing countries, with fish being one of the most common causes of food allergy.[1,2] The global consumption of fish has risen. Fish consumption per capita has increased from 9 kg in 1961 to 20.5 kg in 2018, with Asia having the highest fish consumption in the world.[3] In 2020, the population of Singapore consumed around 90 thousand metric tons of fish, with each person consuming approximately 16 kg of fish per year.[4,5] In 2012, the prevalence of fish allergy in late childhood in Singapore was 0.26% based on a convincing history derived using structured written questionnaires administered to 14- to 16-year-old children in randomly chosen secondary schools.[6] The onset of fish allergy occurs in early childhood and is often thought to persist until adulthood.[7] Fish-allergic patients are often advised to avoid all fish in view of the concerns of cross reactivity and potential severity of future reactions. However, complete dietary elimination of fish may be too restrictive

as some patients may be able to tolerate some species of fish, in particular tuna which is known to be less allergenic.[8]

Most studies focused on fish species more commonly consumed in the West and less is known about species consumed in Asia, with different species of fish consumed in different Asian countries. There is a paucity of data from Singapore, with only one study published in 2008 examining the allergenicity of tropical fish in 10 patients with fish allergy.[9] Hence this 5-year retrospective study aims to describe the demographic, clinical features, and natural history of Singaporean children with IgE-mediated fish allergy.

Methods

Children ≤ 18 years old who had a positive skin prick test (SPT) to commercial fish mix extract or prick-to-prick test (PPT) to fish between 2015 to 2020 were identified from our departmental electronic database at KK Women's and Children's Hospital, the largest tertiary pediatric hospital in Singapore. Clinical records were reviewed and data on demographics, age at first reaction, type of reaction, species of fish, pattern of cross-reactivity, concomitant food allergies, personal and family history of atopy were collected. Patients with incomplete or unclear history documented were contacted by the study team to clarify regarding the different species of fish that the child had reacted to or tolerated.

The diagnosis of fish allergy was made based on a convincing history of an immediate (onset within an hour) allergic reaction and a positive SPT or PPT. Children with fish allergy were classified into 3 groups: mono-sensitized, oligo-sensitized and polysensitized. Children who were mono-sensitized reacted to only one fish species and tolerated multiple other fish species. Children who were oligo-sensitized reacted to or were sensitized to more than one fish species but tolerated at least one other fish species. Children who were polysensitized reacted to or were sensitized to all fish species tested.[10] A resolved fish allergy is defined as patient-reported tolerance of a fish species that the child had previously reacted to. A persistent fish allergy is defined as no patient-reported tolerance to fish previously reacted to at the most recent visit.

SPT was performed using Stallergenes Greer Laboratories commercial extracts and Duotip-Test II disposable skin applicator. The commercial fish mix extract comprised of Atlantic cod, Southern flounder, Atlantic halibut, King/Atlantic mackerel, and Yellowfin tuna. Further evaluation of individual fish species was done by PPT to raw fish brought by patients. The selection of fish species for PPT is left to the parents as they are advised to bring fish that their family commonly consumes or wish to consider introducing into the child's diet. Serial skin prick test to fish was done. Positive SPT was defined as a mean wheal diameter ≥ 3 mm after 15 minutes in comparison to the negative control.

Open oral food challenges (OFC) were performed at the Allergy Outpatient Specialist Clinic in our unit following the recommendations set out by the PRACTALL Consensus Report. The diagnosis of anaphylaxis is in accordance with the World Allergy Organization Anaphylaxis Guidance 2020.[11]

Data were extracted for statistical analysis using IBM SPSS Statistics ver.19 (IBM Co. Armonk, NY, USA) and MedCalc. Demographic data was described using proportion, parametric continuous data was described as mean and standard deviation (SD) and nonparametric continuous data was described as median and interquartile range (IQR). Contingency tables were analyzed using Fisher's exact test. SPT levels between groups were compared using the Mann-Whitney test. A p-value < 0.05 was considered statistically significant.

The study was approved by Singhealth Centralized Institutional Review Board (reference number: 2022/2054). Informed consent was obtained from patients on active follow up, and waiver of informed consent was approved by the board for those no longer on follow up.

Results

A total of 108 patients were diagnosed with IgE-mediated fish allergy. Their demographics is shown in **Table 1**. Personal history of atopy was observed in 88.9% of the cohort and 84.3% had at least one other food allergy. The median age of fish introduction was 8 months (range 6-41) with threadfin (36.1%), salmon (15.7%) and cod (9.3%) being the 3 commonest fish first introduced. **Table 2** shows the fish consumed by our patients classified by class and order.

Table 1. Demographics of subjects in our study. (n = 108)

Age, years (median, range)	7.2 (2.4-21.3)
Gender, male	72 (66.7%)
Ethnicity	
Chinese	85 (78.7%)
Malay	11 (10.2%)
Indian	2 (1.9%)
Others	10 (9.3%)
Personal history of atopy	96 (88.9%)
Allergic rhinitis	51 (47.2%)
Atopic dermatitis	86 (79.6%)
Preschool wheeze	18 (16.7%)
Asthma	12 (11.1%)
Other food allergies	91 (84.3%)
Egg	61 (56.5%)
Peanut	40 (37.0%)
Shellfish	34 (31.5%)
Family history of atopy	56 (51.9%)

Table 2. Nomenclature of fish.

Class	Order	Common name	Examples of local names
Bony fish (Osteichthyes)	Anabantiformes	Snakehead	Sheng Yu (Mandarin), Ikan Toman (Malay)
	Anguilliformes	Eel	Unagi (Japanese)
	Carangiformes	Leather jacket	
		Ruhi	
		Scad	*Yellowstripe scad*: Jun Ling (Mandarin), Ikan Kuning (Malay) *Yellowtail scad*: Se La Yu (Mandarin), Ikan Selar (Malay)
	Carangaria	Threadfin	Wu Yu or Ma You Yu (Mandarin), Ikan Kurau (Malay)
	Cichliformes	Tilapia	
	Clupeiformes	Anchovy	Ikan bilis (Malay)
		Sardine	
		Whitebait	
	Cypriniformes	Barbel	
	Eupercaria	Seabream	
		Snapper	*Crimson snapper*: Hong Ji (Mandarin), Ikan Merah (Malay) *Emperor red snapper*: Hong Shi (Mandarin), Ikan Merah Coreng (Malay)
		Yellowtail fusilier	Huang Wei Yu or Dou Fu Yu (Mandarin), Ikan Delah (Malay)
	Gadiformes	Cod	Xue Yu (Mandarin), Ikan Kod (Malay)
		Haddock	
		Hake	
		Pollock	
	Gobiiformes	Marble goby	
	Gonorynchiformes	Milkfish	Niu Nai Yu (Mandarin), Ikan Su Su (Malay)
	Osmeriformes	Smelt	
	Perciformes	Barramundi	Asian sea bass (English), Jin Mu Lu (Mandarin), Ikan Siakap (Malay)
		Belt fish	
		Bonito	
		Grouper	*Red grouper*: Hong Shi Ban Yu (Mandarin), Ikan Kerapu Bara (Malay) *Greasy grouper*: Hua Shi Ban Yu (Mandarin), Ikan Kerapu Bintik Bulat (Malay)
		Mackerel	*Spanish mackerel*: Batang (English), Ma Jiao Yu (Mandarin), Ikan Tengirri (Malay) Indian mackerel: Gan Wang Yu (Mandarin), Ikan Kembong (Malay)
		Pomfret	*Chinese pomfret*: Dou Chang (Mandarin), Ikan Bawal Tambak (Malay) *White pomfret*: Bai Chang (Mandarin), Ikan Bawal Putih (Malay)
		Tuna	
	Pleuronectiformes	Flounder	
		Halibut	
		Sole	
	Salmoniformes	Salmon	San Wen Yu (Mandarin), Ikan Salmon (Malay)
	Zeiformes	Dory	Sutchi (English)
Cartilaginous fish (Chondrichthyes)	Carcharhiniformes	Shark	
	Myliobatiformes	Stingray	

Order chosen was based on fish base (https://www.fishbase.in/search.php)

Table 3. Clinical features of allergic reaction to fish. (n = 108)

Age at first reaction, months (median, range)	12 (6-168)	
Number who reacted on first ingestion	67 (62.0%)	
Commonest fish that children react to	Threadfin	52 (48.1%)
	Salmon	36 (33.3%)
	Cod	34 (31.5%)
	Anchovies	22 (20.4%)
	Grouper	17 (15.7%)
	Pomfret	17 (15.7%)
	Snapper	16 (14.8%)
	Mackerel	14 (13.0%)
	Barramundi	12 (11.1%)
	Dory	12 (11.1%)
Clinical manifestations	Anaphylaxis	7 (6.5%)
	Cutaneous	105 (97.2%)
	Gastrointestinal	6 (5.6%)
	Respiratory	4 (3.7%)
	Cardiovascular	0 (0.0%)
Skin prick test, mm (median, range)	Fish mix	5.0 (0.0-25.0)
	Threadfin	8.0 (0.0-27.0)
	Salmon	7.8 (0.0-30.0)
	Cod	4.0 (0.0-22.5)

Table 3 shows the clinical features of allergic reactions to fish. The median age at first reaction was 12 months (range 6-168) with most reacting on first exposure (62.0%). The most common fish causing index reactions were threadfin (48.1%), salmon (33.3%) and cod (31.5%). All but one reacted after ingestion of fish, with 1 patient reacting after inhalation of fish fumes. The majority presented with cutaneous features (97.2%). Seven children had anaphylaxis presenting with cutaneous and respiratory compromise. None had cardiovascular involvement.

Six open fish challenges were done for 5 patients. Four (2 salmon, 1 cod and 1 barramundi) were to assess for tolerance to another fish species and they all passed. Two (2 salmon) were done to assess for resolving fish allergy for which one failed. The child developed generalized hives, cough and running nose 2 hours after salmon ingestion.

Five children were mono-sensitized (4.6%), 77 were oligo-sensitized (71.3%) and 26 were polysensitized (24.1%). After their initial reaction to the index fish, 17 children (15.7%) reacted to another fish within the same order, but 26 (24.1%) could tolerate a fish from within the same order. The most common fish that these children could tolerate were salmon (37.0%), tuna (24.1%) and cod (22.2%). Median follow up was 24 months (range 0-176), with 13 patients lost to follow up after the first visit.

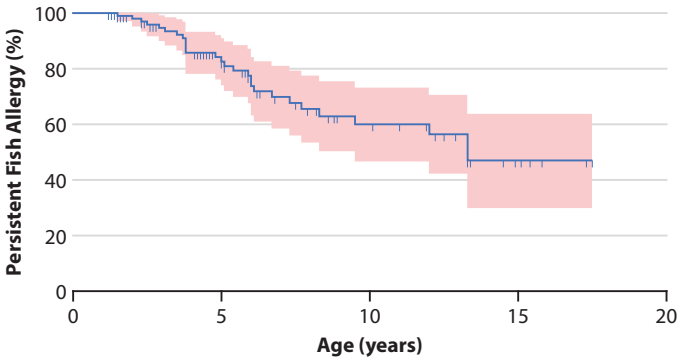

Figure 1. Graph representing the Kaplan-Meier survival curve of persistent fish allergy over time with the 95th confidence interval.

Figure 1 shows the natural history of fish allergy in our study. Resolution of fish allergy to the index fish was reported in 28 out of 108 children (25.9%) and occurred at a median age of 60 months (range 18-159). Median SPT at diagnosis in those with persistent allergy was 5.0, compared to 4.0 in those with resolved fish allergy (p = 0.013) (**Figure 2a**). Persistence of allergy was not significantly associated with other variables including gender, ethnicity, age at first reaction, concurrent food allergies, personal history of atopy and family history of atopy (**Table 4**). Sixty percent of the mono-sensitized group, 32.5% of the oligo-sensitized group and 0% of the polysensitized group outgrew their fish allergy (**Figure 2b**). Thirteen of the 28 patients with resolved fish allergy could tolerate all species of fish (46.4%), while 15/28 still reacted to other fish.

Data on exposure to fish oil supplements were known in 65 patients (60.2%). Of these patients, only 24 patients (36.9%) have tried fish oil supplements with 22/24 (91.7%) of them tolerating it. Seven of them tried a fish oil supplement which contained a fish causing prior reactions, 10 tried supplements derived from different fish species, and for the rest, there was no information on what type of fish was in the supplement. Of the 2 who reacted, one developed generalized urticaria and coughing and the other developed facial rash. The information on what type of fish was in the supplement was not known.

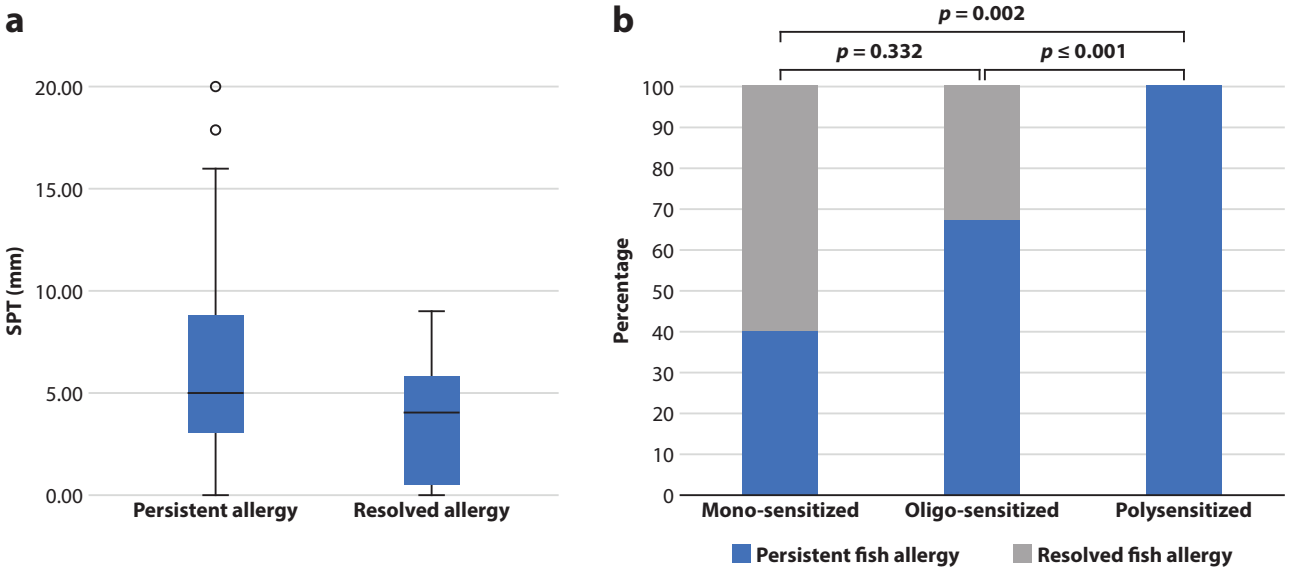

Figure 2.
a. Comparison of SPT at diagnosis and persistence of fish allergy.
b. Comparison of resolution of fish allergy in the 3 groups (mono-sensitized, oligo-sensitized and polysensitized.

Table 4. Comparison between persistent and resolved allergy.

Variable	Persistent allergy (n = 80)	Resolved allergy (n = 28)	*p* value
Gender, male	54 (67.5%)	18 (64.3%)	0.938
Ethnicity, Chinese	59 (73.8%)	26 (92.9%)	0.063
Age at first reaction, months (median, range)	12 (6-168)	12 (6-132)	0.938
Other food allergies	68 (85.0%)	23 (82.1%)	0.955
Personal history of atopy	70 (87.5%)	26 (92.9%)	0.669
Allergic rhinitis	34 (42.5%)	17 (60.7%)	0.149
Atopic dermatitis	63 (78.8%)	23 (82.1%)	0.912
Preschool wheeze	15 (18.8%)	3 (10.7%)	0.492
Asthma	9 (11.3%)	3 (10.7%)	1.000
Family history of atopy	40 (50.0%)	16 (57.1%)	0.804
Skin prick test, mm (median, range)	5.0 (0.0-20.0)	4.0 (0.0-9.0)	0.013

Discussion

Fish can be divided into two classes: bony fish (Osteichthyes) and cartilaginous fish (Chondrichthyes). Most edible fish are bony fish, while sharks and rays are cartilaginous fish.[12] There are more than 33,000 species of fish worldwide with different species consumed in different parts of the world.[13] The most consumed bony fish species belong to 7 orders (Salmoniformes, Gadiformes, Perciformes, Clupeiformes, Cypriniformes, Siluriformes and Pleuronectiformes).[12] Other orders seen in this study were Anabantiformes, Anguilliformes, Carangiformes, Cichliformes, Eupercaria, Gobiiformes, Gonorynchiformes, Osmeriformes and Zeiformes (**Table 2**).

Parvalbumin is the major fish allergen, with Gad c 1 being the first identified parvalbumin in Baltic cod in the early seventies.[14] To date (June 2022), the WHO/IUIS Allergen Nomenclature Sub-Committee (www.allergen.org) has registered parvalbumin from 17 fish species. It was also found to be the major fish allergen in 4 tropical fish (threadfin, Indian anchovy, pomfret and tenggiri) commonly consumed in Singapore.[9] Parvalbumin is a calcium-binding protein involved in muscle relaxation, which is highly stable and resistant to heat and digestion. It has 2 distinct isoforms– α-parvalbumin is found mostly in cartilaginous fish and β-parvalbumin is found in bony fish, with the former appearing to be less allergenic.[15] Parvalbumin content of different fish can vary greatly, ranging from in 0.234 mg/g in bigeye tuna to 11.2 mg/g in splendid alfonsino.[16] Fish with more white muscle and higher parvalbumin content such as cod (range 1.3-1.9 mg/g) seem more allergenic than fish with more dark muscle and lower parvalbumin content such as tuna, swordfish, mackerel and flounder (range 0.01-0.742 mg/g). The latter may be tolerated by many children with fish allergy.[17] Other fish allergens found in fish muscle include enolase and aldolase, which are heat labile.

Collagen was the second fish allergen identified in 2000, which is heat stable.[12] Other potential allergens include tropomyosin, creatinine kinase, triosephosphate isomerase, pyruvate kinase, lactate dehydrogenase, glucose-6-phoshate isomerase and glyceraldehyde-3-phospahte dehydrogenase.[10]

Singapore is a tropical island, and fish is a popular weaning food, thus it is not surprising that the median age of fish introduction was 8 months, before that of peanuts (mean age of 19 months) and egg white (mean age of 10.5 months).[18] Most of our patients reacted on first exposure with the majority presenting with cutaneous symptoms similar to previous studies.[9,19] However, our rate of anaphylaxis was low compared to other studies. Anaphylaxis occurred in 6.5% of our study cohort compared to 42.0% in a retrospective study from Portugal between 2005 to 2016.[19] A 2021 prospective study involving a series of food challenges to tuna, swordfish, and cod to look at the natural history of fish allergy found that 50.0% had anaphylaxis.[8,19] In our population, fish is the fifth cause (4 out of 191 patients) of food induced anaphylaxis in children, after shellfish, peanuts, tree nuts and milk.[20]

Cross-reactivity between fish species is due to the structural homology between parvalbumin of different species.[21] Also, mislabeling of fish/seafood is not uncommon with an average mislabeling rate of 8% according to a global meta-analysis published in 2019.[22] A 2022 study done in Singapore found a higher mislabeling rate of 26% with all occurring in samples bought from supermarkets. The most commonly mislabeled product was Patagonian toothfish, which was often sold as cod or seabass.[23] Thus, children with fish allergy are generally advised to avoid all species of fish in view of the concerns of cross-reactivity. However, our study has shown that most children are able to tolerate some fish species (75.9%). In the oligo-sensitized group, the majority (92.2%) could tolerate another fish species, with salmon, tuna, cod, anchovies, barramundi, mackerel, pomfret, sardine, white bait and snapper being the top 10 tolerated fish. However, 6 in the oligo-sensitized group could only tolerate canned tuna which is known to be less allergenic due to its low parvalbumin content and the canning process.[16,24] Still most of the children in the oligo-sensitized group were able to tolerate fish other than canned tuna. Tolerance to at least one fish species is important because of the beneficial effects of fish. The Ministry of Health in Singapore recommends consuming fish at least twice a week. Oily fish (e.g. salmon, tuna, sardines, mackerel etc.), in particular, are rich in omega-3 fatty acids, which has been associated with a lower risk of heart disease and could potentially prevent future development of atopic diseases.[1,25] Pattern of cross-reactivity is difficult to predict with some being able to tolerate a fish in an order but react to another in the same order. Thus, skin testing and oral food challenges would need to be done to ascertain safe options.

The major allergen for fish and shellfish is different, so cross-reactivity is not expected. In our study, 31.5% of fish allergic patients were also allergic or sensitized to shellfish. Cross-reactivity between fish and other vertebra meat (frog, crocodile, and chicken) has been described. This is due to cross-reactivity between parvalbumin for frog and crocodile, and between parvalbumin, enolase and aldolase in chicken.[26–28] Frog meat porridge is easily found in Singapore and 3 of our fish allergic patients reported prior reactions to it. One of our patients reacted to crocodile meat, and none have reacted to chicken.

Fish oil supplements are commonly consumed in Singapore for its perceived health benefits. However, little is known about tolerance of fish oil supplements in people with fish allergy. A small study in 2008 found that 6 patients with fish allergy were able tolerate 2 brands of fish oil supplements.[29] However, there are 2 case reports of patients who developed anaphylaxis after consumption of fish oil supplements.[30,31] In our study, although the majority had not tried fish oil supplements, most who did try had no reaction. The two patients who reacted to a fish oil supplement tried a brand where the information on the type of fish was unknown. Some of the patients (29.1%) could tolerate fish oil supplements containing fish they were known to be allergic to. There are alternative vegetarian omega-3 supplements made from algae oil for people with fish allergy.[32]

Fish allergy was thought to be a persistent allergy,[7] however recent studies are now suggesting that a significant portion can outgrow it. A retrospective study from 2005 to 2016 found that 74% of patients acquired tolerance to at least 1 fish species and 8% acquired tolerance to all fish species.[19] A prospective study published in 2021 involving a series of food challenges to tuna, swordfish and cod showed that fish tolerance increased from 3.4% in preschool children to over 45.5% in adolescents. Tolerance was defined by a negative food challenge to cod, as cod seemed to be more allergenic compared to other fish.[8] In our study, with a median follow up of 24 months, 25.9% acquired tolerance to a fish that they have reacted to previously. With a longer follow up time, we expect that more will outgrow their fish allergy. It also appears that those who are mono-sensitized or oligo-sensitized are more likely to outgrow their fish allergy compared to those who are polysensitized. We hypothesize that children who are polysensitized have a more severe phenotype compared to those who are mono- or oligo-sensitized and are thus less likely to outgrow their fish allergy.

Strengths of this study are: 1. This is the largest cohort of fish-allergic children described in Asia; 2. It provides insight to the type of local fish species that fish allergic children in Singapore commonly react to/ tolerate. Limitations of this study include its retrospective design, lack of OFC which is the gold standard for diagnosis of food allergy, missing data as patients are frequently not able to identify the species of fish that triggered the allergic reaction, and the lack of standardization for the types of fish brought for PPT. Thus, fish species brought for testing is heterogenous and limits comparison across the cohort. Moving forward, we plan to have a standardized fish panel for PPT. Other limitations in regard to interpreting our natural tolerance data include relatively short follow up duration and lack of regular OFC to assess for tolerance acquisition. Taxonomy of the fish was also based on our best knowledge but with potential for errors.

Conclusion

We have found that most children (75.9%) with fish allergy can tolerate at least one other species of fish and resolution of fish allergy is possible. Thus, it is important to follow-up with an allergist to evaluate which fish species can be included into the diets of these children to avoid unnecessary dietary restrictions.

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