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TITLE

IgE-mediated fish allergy in pediatric age: does canned tuna have a chance for tolerance?

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ABBREVIATIONS

oral food challenge (OFC)

skin prick test (SPT)

specific IgE (sIgE)

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CONFLICTS OF INTEREST

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To the editor

Consumption of fish has increased all over Europe, leading to a rise in reports of allergic reactions to fish,¹ including anaphylaxis.² Determining epidemiological data of IgE-mediated fish allergy is challenging because this type of allergy seems to vary with geographical eating habits, type of fish processing, and fish species exposure.¹ The diagnosis of IgE-mediated fish allergy is based on clinical history, skin tests and sIgE, followed by an oral food challenge (OFC) with the fish involved in the allergic reaction.¹ The evaluation through an OFC is not always possible in the clinical practice.¹ Specifically, in the pediatric age, children are often subjected to an allergic reaction to the first species of fish introduced in their diet before the consumption of another ones in their life. Furthermore, in the evolution of IgE-mediated-fish allergy, it is known that there is an important cross-reactivity between fish species; consequently, skin test and specific serum IgE are often positive for different species of fish.^{3,4} In these cases, to avoid severe reactions, the management of fish allergy relies on the elimination of all fish from the diet of the children.¹ On the other hand, it is known that some fish, such as tuna, are less allergenic and some industrial processes may induce changes in parvalbumin (the main fish protein) allergenicity.⁴⁻⁶ Parvalbumin is mostly in the white muscle of fish; in contrast, distinct species of fish, such as tuna and swordfish, contain a greater proportion of red muscle; consequently, they have a low parvalbumin content compared to other fish.⁴ Moreover, the canning process of tuna results in its cooking for up to 7 hours under pressure; it generates a conformational change in tuna allergens, rendering them less allergenic.⁵

Sletten et al investigated fresh and processed-IgE binding sera of children affected by fish allergy, using immunoblot and inhibition ELISA. Specifically, this study demonstrated that allergenicity in tuna was decreased after canning and, generally, the existence of trends to altered immunogenicity in some consumed fish species following a variety of traditional methods of processing.⁷

Recent studies regarding non-IgE-mediated fish allergy have analysed the possibility of an alternative dietary management, demonstrating the tolerance of some species of fish non-related to the culprit fish and avoiding unnecessary restricted diets.⁸ On the basis of these evidences, to avoid the elimination of all the fish from the diet of the children affected by IgE-mediated fish allergy, an OFC with some specific species of fish should be tried to confirm this tolerance. The

aim of this study is to contribute to the definition of a safe plan of re-evaluation of children affected by IgE-mediated fish allergy, evaluating canned tuna as the first type of fish introduced in the diet of these patients.

We performed a retrospective, observational study of all children with a known diagnosis of IgE-mediated fish allergy and an exclusion diet of all species of fish, who attended our tertiary pediatric allergy unit in Madrid, Spain, between 1 January 2018 and 31 October 2019. They underwent an oral food challenge (OFC) to canned tuna as first step of their therapeutic-diagnostic procedure. About OFC, it was performed offering the child a 90-gram can of tuna in progressively increasing quantities. Moreover, both tuna-SPT and tuna-sIgE were performed within 6 months of performing canned tuna-OFC. Exclusion criteria were represented by a home reintroduction of tuna or other fish, abnormalities in the medical evaluation and ongoing antihistamine therapy. STATA software (version 16) for Windows was used for statistical evaluation; specifically, Fisher's exact test was applied to study the correlation between anamnesis, diagnostic tests and OFC to canned tuna.

Twenty-five children (20 boys, 5 girls) with IgE-mediated fish allergy were selected and 26 OFC were performed. The median age during OFC was 75 months (range 26-214 months). Eighty percent suffered from co-existent atopic disease. Hake was the most commonly implicated fish (33%). Twenty-five children underwent tuna skin prick test (ALK, Madrid, Spain): it was positive (wheal size 3 mm or more) in 9 and negative in 14 cases. In 25 children tuna-sIgE (ImmunoCAP, Uppsala, Sweden) was determined and was positive (sIgE $\geq$ 0.35 kUA/l) in 15 and negative in 9 cases (*Table 1*). Twenty-four patients passed OFC to canned tuna on the first attempt. One patient failed OFC, but passed it after 697 days (*tab 2*, supplementary material). Consequently, 96% of OFC to canned tuna was passed and finally 100% of patients were able to tolerate the tuna in a canned form.

No statistically significant association has been found between tuna-SPT and the outcome of OFC to canned tuna ($p=0.462$) or between tuna-sIgE and OFC to canned tuna ($p=1,000$). Moreover, anamnesis regarding the length of time the patient was on tuna-exclusion diet (less than 2 years or more from the diagnosis of fish IgE-mediated allergy) was not statistically significant associate with the result of tuna-SPT and tuna-sIgE.

The absence of statistical significance between anamnesis and diagnostic tests is in line with the analysis of the data of the patient who failed OFC to canned tuna on the first attempt and passed it later. In fact, he shared anamnestic and diagnostic features of all other patients who passed OFC.

The possible explanation of this phenomenon could be explained both by the peculiarities of parvalbumin and by its conformational change, which takes place during the canned process.⁴⁻⁶ Consequently, it can be hypothesized that both anamnesis and diagnostic tests performed are related to a food, such as fresh tuna, with important differences in comparison with canned tuna. So, in other words, characteristics and processing make canned tuna a fish different from fresh tuna and other species.

This study has some limitations. First, the low sample size, due to the reduced incidence of this disease. Second, data were collected in a single pediatric allergy unit. Third, the anamnestic information about the exclusion criteria are self-reported by the parents of children, so some patients could be lost or misclassified. Finally, due to the small variability of allergenicity of some tuna species, it is possible that these results are not reproducible in all cases.

In conclusion, children affected by IgE-mediated fish allergy seems to show a high tolerance for the canned tuna. Both tuna-skin test and tuna-sIgE seem not to represent a prognostic factor for the challenge outcome. Since tuna-SPT and tuna-sIgE seem not related to the possibility that the patient tolerates canned tuna, the OFC to this type of processed fish represents the only procedure to verify its tolerance.

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TABLES

Characteristics	n (%)
Age at OFC (median, range), months	75 (26-214)
Gender	20 M, 5 F
% of patients suffering from co-existing atopic disease	20 (80%)
Tuna-exclusion diet < 2 years from the diagnosis of fish IgE-mediated allergy)	9 (36%)*
Tuna-exclusion diet > 2 years from the diagnosis of fish IgE-mediated allergy)	13 (52%)*
Patients with negative SPT	14 (56%)**
Patients with positive SPT	9 (36%)**
Patients with tuna-IgE < 0,35 kUA/l	9 (36%)***
Patients with tuna-IgE > 0,35 kUA/l	15 (60%)***
Culprit fish	- Hake 11 (33%)**** - Megrim 5 (15%)**** - Tuna 3 (9%)**** - Other 14 (42%)****
Patients with negative OFC to canned tuna at first attempt	24 (96%)
Patients with positive OFC to canned tuna at first attempt	1 (4%)
Patients with negative OFC to canned tuna at the end of allergy work-up	25 (100%)

*Table 1. Baseline patients characteristics and result (*not determined for 1 patients; ** not determined for 2 patients; *** not determined for 1 patient; ****percentage calculated on the basis of the total of species of fish referred in history)*

AUTHORSHIP

LP and AP designed the work, acquired, analyzed the data, drafted the initial manuscript and reviewed the manuscript. SI, VFA, PCF, NA analyzed the data and reviewed the manuscript. AP conceptualized, designed the work, acquired, analyzed the data, drafted the initial manuscript and reviewed the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Patient code	Sex	Comorbidities	Culprit fish	Anaphylaxis related to culprit fish	Duration of the diet without the culprit fish	Tuna-SPT	Tuna-sIGE (kUA/l)	Age of the child at OFC-time (years)	Canned tuna OFC- result
1	M	Yes	Other fish	No	≥ 2 years	Negative	0.03	11.53	Negative
2	M	No	Hake, tuna, other	No	≥ 2 years	Positive	8.73	6.86	Negative
3	M	Yes	Other fish	No	≥ 2 years	Negative	3.84	3.40	Negative
4	M	Yes	Other fish	Yes	≥ 2 years	Positive	6.02	14.32	Negative
5	M	Yes	Other fish	No	≥ 2 years	Positive	1.54	15.84	Negative
6	M	Yes	Other fish	No	≥ 2 years	Positive	1.58	17.81	Negative
7	M	Yes	Megrim	No	0-1.9 years	Negative	0.06	3.49	Negative
8	M	No	Megrim	No	≥ 2 years	Negative	0.02	4.26	Negative
9	M	Yes	Hake, megrim, Tuna, other fish	No	0-1.9 years	Negative	0.78	13.07	Negative
10	M	Yes	Other fish	Yes	≥ 2 years	Positive	5.77	17.24	Negative
11	M	Yes	Other fish	No	≥ 2 years	Negative	7.96	10.75	Negative
12	M	Yes	Tuna	No	Not known	Not known	0.03	16.98	Negative
13*	M	No	Hake	No	0-1.9 years	Negative	0.14	4.73	Negative (2nd attempt)
14	M	Yes	Hake	No	0-1.9 years	Negative	0.78	2.14	Negative
15	M	Yes	Hake	No	Not known	Negative	0.15	3.34	Negative
16	M	No	Other fish	No	0-1.9 years	Negative	0	6.27	Negative
17	M	Yes	Hake	Yes	≥ 2 years	Positive	2.36	7.19	Negative
18	F	Yes	Other fish	No	≥ 2 years	Positive	4.79	10.59	Negative
19	M	Yes	Hake, other fish	Yes	0-1.9 years	Not known	0.14	3.09	Negative
20	M	Yes	Hake	No	0-1.9 years	Positive	3.59	2.98	Negative
21	F	Yes	Megrim	Yes	Not known	Negative	9.19	2.54	Negative
22	F	No	Other fish	No	0-1.9 years	Negative	2.13	6.78	Negative
23	F	Yes	Hake	No	0-1.9 years	Positive	0.97	3.50	Negative
24	M	Yes	Hake	No	≥ 2 years	Negative	Not known	4.06	Negative
25	F	Yes	Hake, megrim, other fish	No	≥ 2 years	Negative	0	2.59	Negative

Table 2. Anamnestic data of children participating to the study. (*data referred to the second canned tuna-OFC performed)