Different tolerance of food protein-induced enterocolitis syndrome in fishes of the same family: A pediatric case report

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Fish is a common food allergen in children and adults [1], and the number of cases of food protein-induced enterocolitis syndrome (FPIES) due to fish intake has recently increased [2, 3]. Fish-related FPIES is common in Mediterranean countries, and fish are the second most common cause of FPIES in Spain following cow's milk, comprising 31% of cases [4]. Most patients with fish-related FPIES have varying degrees of tolerance to different fish species [2]. However, the contribution of the fish family to FPIES remains unclear. Therefore, patients with a history of fish-related FPIES should avoid eating fish from the same family as the fish that caused the illness. We herein report a pediatric case of fish-related FPIES with varying tolerance to fish within the same family.

A 3-year-old boy was referred to our department after several episodes of gastroenterocolitis associated with flatfish consumption. He had a history of recurrent vomiting at one year of age without skin or respiratory symptoms 2 h after ingesting flatfish. He experienced three similar episodes within the same year. Furthermore, he had no history of allergies and had not reacted to other species of fish he ingested. Therefore,

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only flatfish was eliminated from his diet.

At two years of age, an oral food challenge (OFC) in a different pediatric clinic with 6 g of flatfish (yellow striped flounder) induced no adverse symptoms. Accordingly, the patient was permitted to eat up to 6 g of flatfish, which he was able to eat several times, with only one reported episode of vomiting 90 min after eating. A detailed interview revealed that the patient was able to tolerate yellow striped flounder (*Pseudopleuronectes herzensteini*), dusky sole (*Lepidopsetta mochigarei*), and dark flounder (*Rhombosolea retiaria*) without symptoms at home. Gastroenterocolitis occurred only after consuming Greenland halibut (*Reinhardtius hippoglossoides*). The patient subsequently ingested increasing doses of all but Greenland halibut and had no adverse reactions.

At three years of age, the patient underwent OFC at our hospital, in which he ingested 6 g of Greenland halibut once. He experienced repeated vomiting, lethargy, and pallor 3.5 h after ingestion and was treated with intravenous acetated Ringer's solution. He recovered and was discharged 2 h after treatment. After returning home, the patient developed diarrhea for one day.

The flatfish-specific immunoglobulin E (IgE) test done prior to the aforementioned OFC was negative. We examined the lymphocyte transformation test (LTT) values of Greenland halibut and yellow striped flounder in patients with FPIES and healthy controls. Using a previously reported modified LTT [5], the patient reported in this study was examined for two different fish extracts. Subsequently, the patient's peripheral blood mononuclear cells (PBMCs) were extracted using a density gradient. The cells were suspended in RPMI 1640 media with 10% human AB serum at 1×10^6 cells/mL. Filter-sterilized dilutions of the test fish extracts (1/190, 1/570, 1/1,710, 1/5,130, 1/15,390, and

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1/46,170) were cultured using a concentration of 5×10^5 cells/mL. After 6 days, ^{3}H-thymidine or phytohemagglutinin was added and incubated for another 20–24 h. Phytohemagglutinin was used as positive control for mitogenesis, and the incorporation of ^{3}H-thymidine was used to determine the proliferative response. Liquid scintillation spectrometry (TopCount NXT^{TM}; Perkin-Elmer LAS [UK] Limited, Beaconsfield, Bucks, UK) was used to determine radioactivity in counts per minute (cpm). The stimulation index (SI) was calculated by dividing the allergen cpm by the negative control cpm. The cpm and SI of the Greenland halibut in our patient were higher than that of the yellow striped flounder. They were also higher compared to the cpm and SI of Greenland halibut in healthy controls (Figure 1).

The patient was able to eat other types of flatfish without experiencing adverse reactions. However, his symptoms and test results following Greenland halibut ingestion met one major and three minor diagnostic criteria for OFC interpretation according to the International Consensus Guidelines [6]. Thus, he was diagnosed with fish-related FPIES associated only with Greenland halibut, and his parents were advised to eliminate only one fish species from his diet rather than the entire Pleuronectidae family. When differentiated by subfamily, Pleuronectinae (Yellow striped flounder) and Rhombosoleinae (Dark flounder) could be ingested, but Hippoglossinae (Greenland halibut) induced symptoms. The OFC of the Kamchatka flounder in Hippoglossinae was proposed but not agreed upon and not performed.

The strong cross-reactivity of β-parvalbumin, the most common fish allergen, is found in various fish species. Hence, most patients with IgE-mediated fish allergies react to different fish species, and the current recommendation is to avoid all fish species [7].

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However, there have been rare reports of IgE-mediated hypersensitivity to specific fish species [8]. Furthermore, some studies have shown that most patients with fish-related FPIES reported varying levels of tolerance to fish species [2]. Flatfish is one of the most common triggers of fish-related FPIES [3]. However, there have been no reports of varying tolerance for different fish species within the Pleuronectidae family.

This report looked at the lymphocyte response as a whole but did not examine what cytokines were upregulated by it. In a previous study, TNF-α was elevated upon exposure to flatfish [9]. Thus, it may be recommended for future studies to examine the differences in cytokine production with exposure to different fish species within the same family. The LTT and OFC results were congruent in our study. However, other reports have reported discrepancies between both tests. In a case report on short-neck clam and squid-related FPIES, a comparison of LTT between healthy controls and a patient showed a difference in the former, but not in the latter [10]. Future studies may increase the number of cases and examine the precise corresponding SI cutoff values. The accuracy of LTT may also be examined further.

A limitation of this study was that OFC was not double-blinded and did not include the entire Pleuronectidae family.

In conclusion, this case suggests that individuals with fish-related FPIES may have varying tolerance to fish within the same family. A more detailed investigation should be considered if patients eating fish from the same family experience different symptoms.

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Patient consent

Written informed consent was given by the parents of this patient for participation in this study and publication of this report.

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Conflict of interest: None

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Figure 1. Comparison of LTT values between the patient and non-allergic healthy controls. A) Counts per minute; and B) stimulation index
LTT, lymphocyte transformation test.