Differences in Tolerance Among Patients With Food Protein–Induced Enterocolitis Syndrome in Fish From the Same Family: A Pediatric Case Report

Tsukahara A[1,2], Fujita M[1], Okamoto Y[3], Tsumagari S[1], Takamasu T[1], Inuo C[1]

[1]*Department of Allergy, Kanagawa Children's Medical Center, Kanagawa, Japan*

[2]*Department of Pediatrics, St. Marianna University School of Medicine, Kanagawa, Japan*

[3]*Kumanoko Kids Allergy Clinic, Kanagawa, Japan*

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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, accounting for 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 report the case of a child with fish-related FPIES and varying tolerance to fish within the same family. The patient's parents gave their written informed consent for participation in this study and publication of this report.

A 3-year-old boy was referred to our department after several episodes of gastroenterocolitis associated with flatfish consumption. At age 1 year he experienced recurrent vomiting without skin or respiratory symptoms 2 hours after ingesting flatfish. He experienced 3 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, only flatfish was eliminated from his diet.

At 2 years of age, an oral food challenge (OFC) with 6 g of flatfish (yellow striped flounder) at a different pediatric clinic induced no adverse symptoms. Accordingly, the patient was permitted to eat up to 6 g of flatfish, which he ingested several times, with only 1 reported episode of vomiting 90 minutes 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*). He subsequently ingested increasing doses of all these fish species except Greenland halibut and had no adverse reactions.

At 3 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 hours after ingestion and was treated with intravenous acetated Ringer solution. He recovered and was discharged 2 hours after treatment. After returning home, the patient developed diarrhea for 1 day.

The flatfish-specific immunoglobulin E (IgE) test performed 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], we tested 2 different fish extracts before extracting the patient's peripheral blood mononuclear cells using a density gradient. The cells were suspended in RPMI 1640 medium 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, 1/5130, 1/15 390, and 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 the solution was incubated for a further 20-24 hours. Phytohemagglutinin was used as a positive control for mitogenesis, and ^{3}H-thymidine was incorporated to determine the proliferative response. Liquid scintillation spectrometry (TopCount NXT; Perkin-Elmer LAS [UK] Limited) 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 for the patient were higher than that of the yellow striped flounder. They were also higher than the cpm and SI of Greenland halibut in healthy controls (Figure).

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 1 major and 3 minor diagnostic criteria for interpretation of OFC according to the International Consensus Guidelines of the American Academy of Allergy, Asthma & Immunology [6]. Therefore, he was diagnosed with fish-related FPIES associated only with Greenland halibut, and his parents were advised to eliminate only 1 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

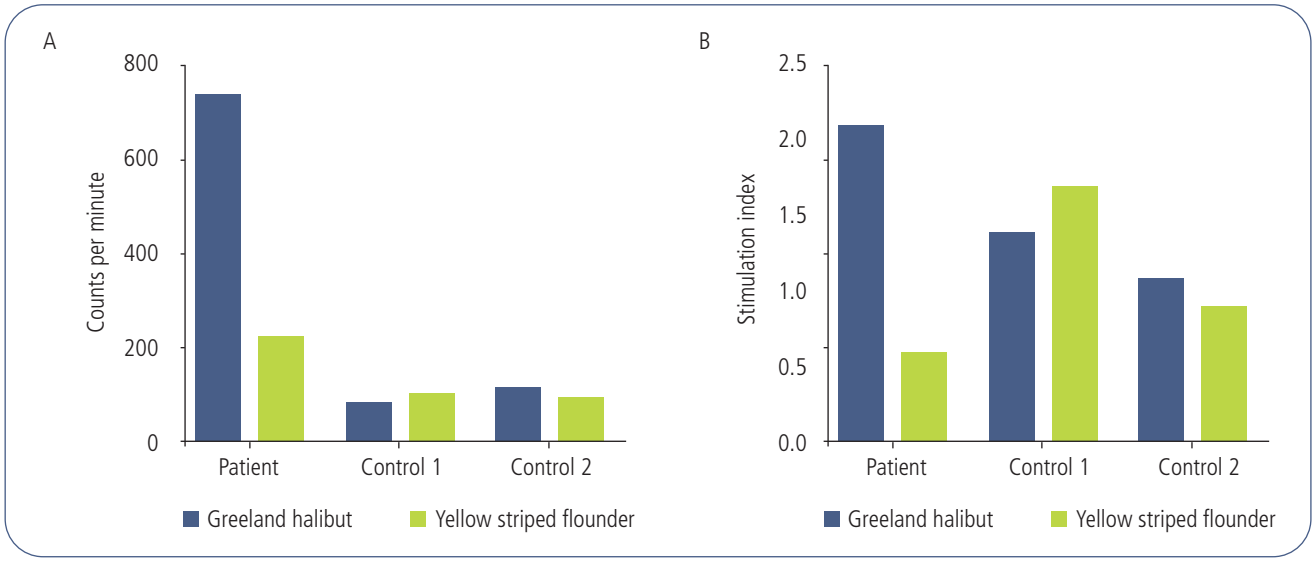

Figure. Comparison of lymphocyte transformation test results between the patient and nonallergic healthy controls. A, Counts per minute. B, Stimulation index.

OFC with Kamchatka flounder (Hippoglossinae) was proposed but not agreed upon and not performed.

Strong cross-reactivity with 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]. 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 which cytokines were upregulated by it. In a previous study, TNF-α was elevated upon exposure to flatfish [9]. Thus, future studies should examine differences in cytokine production on exposure to different fish species within the same family. We found the LTT and OFC results to be congruent. However, other authors have reported discrepancies between these tests. In a case report on FPIES associated with short-neck clam and squid, a comparison of LTT results 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 further examined.

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

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

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Ayumi Tsukahara
Department of Pediatrics
St. Marianna University School of medicine
2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan
E-mail: a2tsukahara@marianna-u.ac.jp

