Selective Allergy to Wedge Sole (*Dicologlossa cuneata*) due to ß-Parvalbumin

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Fish allergy is one of the most relevant food allergies worldwide. It affects 0.3%-1% of the general population [1-4] and is more prevalent in infants than in adults [4-6]. Fish consumption is growing quickly, as this food is considered a major source of macro- and micronutrients [5-7]; therefore, fish allergy rates are also expected to increase [4,7]. Most fish-allergic patients show a cross-reacting pattern, involving the most commonly consumed species, owing to marked homology between their parvalbumins [2-4,8-10]. Interestingly, the main edible fish species and eating habits vary with geographic area, sometimes resulting in specific fish allergy patterns [1,4,6,10].

The Soleidae family comprises flatfish, which are bottom-dwelling fish feeding on small crustaceans and other invertebrates [11]. One member of the family, the wedge sole (*Dicologlossa cuneata*), is common in the East Atlantic and Mediterranean and is widely consumed in southern Spain [11]. We report a case of selective allergy to this fish and identify the culprit allergen.

A 51-year-old man with no previous history of respiratory or food allergies came to our outpatient clinic. In 2018, while vacationing in Cádiz (southern Spain), he developed chest tightness and cold sweat immediately after the ingestion of a small piece of fried wedge sole. Symptoms improved in 30 minutes without treatment. This was the third such episode. Thereafter, he had tolerated other types of fish, including cod, tuna, hake, sea bass, halibut, salmon, and anchovies. Since then, he has avoided only flatfish (order Pleuronectiformes) and has experienced no new reactions.

Skin prick test (SPTs) were performed with a standard battery of commercially available fish extracts, yielding positive results only to sole (8 mm mean wheal diameter) and *Anisakis* (5 mm). Prick-by-prick tests performed with wedge sole and turbot yielded positive results to both species (12 mm and 7 mm, respectively). In addition, serum specific IgE (sIgE) to various fish species was determined using ImmunoCAP, which showed a low level of specific IgE (kU/L)

to *Lepidorhombus* (a genus of turbot native to the northeastern Atlantic Ocean) (0.29) and *Solea* (0.58) (Supplementary File 1). The patient was diagnosed with suspected allergy to Pleuronectiformes, and a flatfish-free diet was recommended.

In order to identify the culprit allergens, raw and cooked extracts were prepared from *Dicologlossa, Solea, Lepidorhombus, Scophthalmus, Merluccius, Salmo*, and *Gadus*. SDS-PAGE and IgE Western blot with the extracts (Supplementary File 2, Supplementary Figures 1-2) showed weak recognition of low molecular weight (MW) bands (10-14 kDa) in both the *Dicologlossa* and the *Solea* extracts, which did not appear in the other lanes. Furthermore, a slightly weaker 15- to 25-kDa band was also identified in the *Dicologlossa* extract. High-MW bands (37-50 kDa) were clearly recognized in all the extracts, albeit with a higher intensity in lane 1 (*Dicologlossa* species). A Western blot inhibition test with the patient's serum using *Dicologlossa* species in the solid phase (Supplementary Figure 3) showed low-MW bands (10-14 kDa) in *Dicologlossa* extracts inhibited by *Solea* species at all the concentrations tested. Subsequent IgE Western blot with extracts of cooked fish, showed strong detection of a band of around 12-14 kDa in cooked *Dicologlossa* species, a weaker band in cooked *Solea* species, but no equivalent band in the other cooked pleuronectiform species tested (Figure). Mass spectrometry sequencing revealed the identity of this protein, a parvalbumin ß-2–like protein, with a sequence coverage similar to that of another parvalbumin ß-2–like protein of *Hippoglossus stenolepis*, a subspecies of *Solea* included in the order Pleuronectiformes (Supplementary Figure 4). In addition, a second low-MW band (15-25 kDa) was also observed (Figure). Moreover, high-MW bands (37-50 kDa) recognized by the patient's serum in all raw pleuronectiform fish extracts disappeared when these extracts were cooked (Figure).

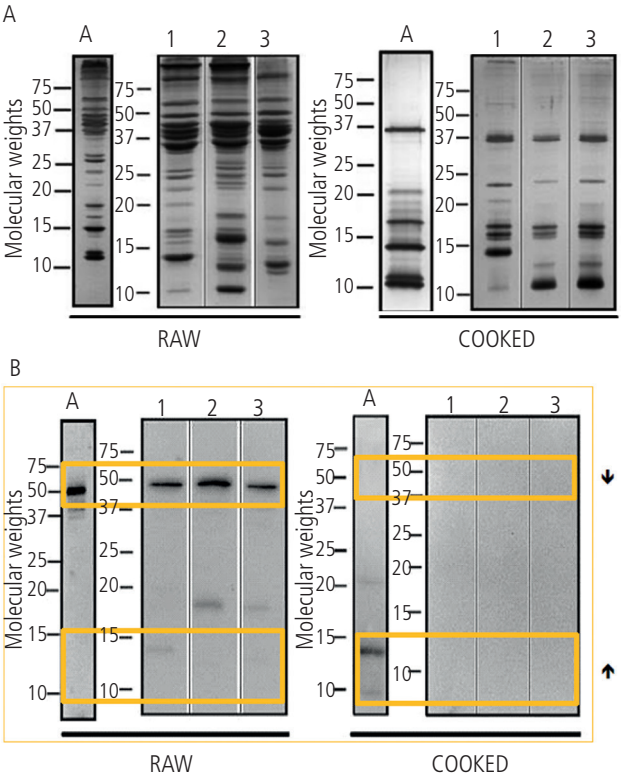

Figure. A, SDS-PAGE performed under reducing conditions with the following extracts, raw on the left and cooked on the right: lane A, *Dicologlossa* species; 1, *Sole* species; 2. *Lepidorhombus* species;3, *Scophthalmus* species. B, IgE-immunodetection performed under reducing conditions with the patient serum and the following extracts: lane A, *Dicologlossa* species; 1, *Solea* species; 2, *Lepidorhombus* species; 3, *Scophthalmus* species.

Wedge sole fish belongs to the subclass Actinopterygii, order Pleuronectiformes, together with flounder, sole, turbot, plaice, and halibut. There are two clinically relevant families in Pleuronectiformes, Soleidae (sole and wedge sole) and Bothidae (*Lepidorhombus* and turbot). *D cuneata* is the most commonly consumed wedge sole species [12].

Wedge sole has a high commercial value, especially on the South Atlantic coast, where it is appreciated for its flavor and lack of bones and consumed fried or cooked [3,5,6,8]. To our knowledge, allergy to wedge sole has not been previously reported. Here, we report the case of a patient allergic to wedge sole who tolerated common allergenic fish species, thus suggesting IgE sensitization to a species-specific fish allergen.

Parvalbumins are classified into 2 different families, namely, α and ß, and can be found not only in fish but also in other species, such as birds, reptiles, amphibians, and mammals [3,5,8]. The β-parvalbumins from bony fish have a high sequence identity with α-parvalbumins from other species, as follows: 63%-76% with amphibians (implicated in patients with symptoms after ingestion of frog's legs), 56%-69% with reptiles (allergy to crocodile meat has been described), and 54%-71% with birds (responsible for the fish-chicken allergy syndrome) [2,3,8].

ß-Parvalbumins are the major fish allergen, being recognized by 90%-95% of fish-allergic patients [2-4,6,7]. Furthermore, ß-parvalbumins are highly cross-reactive among most fish species [3,4,8,9], although some patients show isolated clinical allergy to a single fish species [2-5,8,9]. We believe that the ß-parvalbumin described in our report is probably a selective allergen of the pleuronectiform Soleidae family, since the patient's serum did not recognize similar protein bands in the other fish extracts tested, other than sole and wedge sole, and the patient tolerated most usually allergenic fish species.

The slightly weaker 15- to 25-kDa band recognized by the patient's serum could be either a triosephosphate isomerase ß, previously identified in common sole [5], or perhaps merely a ß-parvalbumin dimer.

We believe the 37- to 50-kDa proteins recognized by the patient's serum to be enolases or aldolases. These proteins are the second most frequent fish allergens [3,8]. They are thermolabile proteins with controversial clinical relevance and are recognized by around 63%-50% of patients [1,3,8]. Given that the patient in the present case did not recognize these proteins when the fish was cooked, it is likely that they are not clinically significant.

In conclusion, we report the first case of selective allergy to wedge sole. We also describe a new ß-parvalbumin as

the culprit allergen, which seems to be selective for the pleuronectiform Soleidae family (sole and *Dicologlossa*).

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Poulsen LK, Morisset M, Kuehn A. Allergy to Fish. In: Matricardi PM, Kleine-Tebbe J, Jürgen Hoffmann H, Valenta R, Ollert M, editors. EAACI Molecular Allergy User's Guide. Published by the European Academy of Allergy and Clinical Immunology, 2016;173-80.
2. Argiz L, Vega F, Castillo M, Pineda F, Blanco C. Selective Allergy to Conger Fish due to Parvalbumin. J Investig Allergol Clin Immunol. 2019;29:390-1.
3. Sharp MF, Lopata AL. Fish allergy: in review. Clin Rev Allergy Immunol. 2014;46:258-71.
4. Carvalho S, Marcelino J, Cabral Duarte MF, Costa C, Barbosa MA, Pereira Dos Santos MC. Role of Recombinant Parvalbumin Gad c 1 in the Diagnosis and Prognosis of Fish Allergy. J Investig Allergol Clin Immunol. 2020;30:340-5.
5. Pérez-Gordo M, Pastor Vargas C, Cases B, De Las Heras M, Sanz A, Vivanco F, et al. New allergen involved in a case of allergy to Solea solea, common sole. Ann Allergy Asthma Immunol. 2010;104:352-3.
6. Dasanayaka BP, Li Z, Pramod SN, Chen Y, Khan MU, Lin H. A review on food processing and preparation methods for altering fish allergenicity. Crit Rev Food Sci Nutr. 2020;1:1-20.
7. Perez-Gordo M, Cuesta-Herranz J, Maroto AS, Cases B, Ibáñez MD, Vivanco F, et al. Identification of sole parvalbumin as a major allergen: study of cross-reactivity between parvalbumins in a Spanish fish-allergic population. Clin Exp Allergy. 2011;41:750-8.
8. Kourani E, Corazza F, Michel O, Doyen V. What Do We Know About Fish Allergy at the End of the Decade? J Investig Allergol Clin Immunol. 2019;29:414-21.
9. Ebo DG, Kuehn A, Bridts CH, Hilger C, Hentges F, Stevens WJ. Monosensitivity to pangasius and tilapia caused by allergens other than parvalbumin. J Investig Allergol Clin Immunol. 2010;20:84-8.
10. Viñas M, Pineda F, Izquierdo-Domínguez A, Castillo M, Castillo MJ, Hernández N, et al. Allergy To Limanda aspera (Yellowfin Sole): Report of a Case of Food Allergy in a Child. J Investig Allergol Clin Immunol. 2018;28:137-8.
11. Infante C, Catanese G, Manchado M. Phylogenetic relationships among ten sole species (Soleidae, Pleuronectiformes) from the Gulf of Cadiz (Spain) based on mitochondrial DNA sequences. Mar Biotechnol (NY). 2004;6:612-24.
12. NCBI. Last accessed 11 April 2021. Available at: https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=30948.

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