Selective allergy to wedge sole fish (*Dicologlossa cuneata*) due to Beta Parvalbumin

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Fish allergy is one of the most relevant food allergies worldwide. It affects between 0.3-1% of the general population [1-4], being more prevalent in infants than in adults [4-6]. Fish consumption is growing up quickly as it is considered a major source of macro and micronutrients [5-7], thus fish allergy rates are also expected to increase [4,7]. Most fish allergic patients show a cross-reacting pattern, affecting common fish species consumed, due to great homology among their parvalbumins [2-4,8-10]. Interestingly, the main edible fish species and eating habits varies between geographic areas, which sometimes results in specific fish allergy patterns [1,4,6,10].

The *Soleidae* fish family is made up by flatfishes, which are bottom-dwelling fishes feeding on small crustaceans and other invertebrates [11]. Among them, the wedge sole fish (*Dicologlossa cuneata*) is present in East Atlantic and Mediterranean Sea, and it is highly consumed in Southern Spain [11]. We report a case of selective allergy to this fish, identifying the implicated allergen.

A 51-year-old man, with no previous history of either respiratory or food allergies, was attended in our outpatient clinic. In 2018, while being on holidays in Cádiz (Southern Spain), he developed chest oppression and cold sweat immediately after the ingestion of a small piece of fried wedge sole fish. Symptoms improved in 30 minutes without treatment. This

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was the third time that a similar event happened to him. Thereafter, our patient had tolerated other types of fish, including: cod, tuna, hake, sea bass, halibut, salmon and anchovies. Since then, he had avoided only the flatfishes (fish order *Pleuronectiformes*), showing no new reactions.

Skin prick-test (SPT) were performed with a standard battery of commercially available fish extracts, being positive only to sole (8 mm mean wheal diameter) and Anisakis (5 mm). Then, prick-by-prick tests were done with wedge sole fish and turbot, being positive to both of them (12 mm and 7 mm, respectively). In addition, serum specific IgE (sIgE) to different fish species was determined using ImmunoCAP, which showed a low level of specific IgE (kU/L) to *Lepidorhombus* (a genus of turbots native to the northeastern Atlantic Ocean) (0.29) and *Solea* (0.58) (Supplementary File 1). The patient was diagnosed with suspected allergy to pleuronectiform fishes, and a flatfish-free diet was recommended.

In order to identify the culprit allergens, raw and cooked extracts from *Dicologlossa spp., Solea spp., Lepidorhombus spp., Scophthalmus spp., Merluccius spp., Salmo spp., and Gadus spp.* were elaborated. SDS-PAGE and IgE Western-Blot were performed with them (Supplementary File 2, Supplementary Figures 1-2), showing a weak recognition of low molecular weight (MW) bands (10-14kDa) both in *Dicologlossa* and *Solea* extracts, which did not appear in the other lanes. Furthermore, a slightly weaker 15-25 kDa band was also identified in the *Dicologlossa* extract. High MW bands (37-50 kDa) were clearly recognized in all the extracts but with a higher intensity in lane 1 *Dicologlossa spp.* A western blot inhibition with our patient serum, using *Dicologlossa* spp. in solid phase was also done (Supplementary Figure 3), showing low MW bands (10-14kDa) present in *Dicologlossa*

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extracts inhibited by *Sole spp*. at all concentrations tested. Subsequently, we performed an IgE Western-Blot with extracts of cooked fishes, showing a strong detection of the band of around 12-14kDa in cooked *Dicologlossa* spp., a weaker band in cooked *Solea* spp. but with no equivalent band in the other cooked pleuronectiformes fishes tested (Figure). Mass spectrometry sequencing revealed the identity of this protein, a parvalbumin beta-2-like, with a protein sequence coverage similar to another parvalbumin beta-2-like of *Hippoglossus stenolepis*, subspecies of *Solea*, included in the order pleuronectiformes (Supplementary Figure 4). In addition, a second low MW band (15-25kDa) was also seen (Figure). Moreover, high MW bands (37-50 kDa) were recognized by our patient serum in all raw pleuronectiformes fish extracts, but disappeared when these extracts were cooked (Figure).

Wedge sole fish belongs to the subclass *Actinopterygii*, order *Pleuronectiformes*, together with flounders, soles, turbot, plaice, and halibut. There are two clinically relevant families in pleuronectiformes, *Soleidae* (sole and wedge sole) and *Bothidae* (*Lepidorhombus* and turbot). The wedge sole species that is mostly consumed is *Dicologlossa cuneata* [12].

Wedge sole has a high commercial value, especially in the South Atlantic coast, being gastronomically appreciated for its flavor and few thorns, and consumed fried or cooked [3,5,6,8]. To our knowledge, allergy to wedge sole has not been previously reported. Here we report a patient allergic to wedge sole, but tolerant to common allergenic fishes, thus suggesting IgE sensitization to a species-specific fish allergen.

Parvalbumins are classified into two different families, namely α and β, and they can be found not only in fishes but also in other species, such as birds, reptiles, amphibians and

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mammals [3,5,8]. The β-parvalbumin from bony fish have a high sequence identity with α-parvalbumin from other species, specifically 63-76% with amphibians (implicated in patients with symptoms after ingestion of frog 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].

β-parvalbumin are the major fish allergens, being recognized by 90-95% of fish allergic patients [2-4,6,7]. Furthermore, β-parvalbumin are considered to be highly cross-reactive among most fish species [3,4,8,9]. However, some patients show isolated clinical allergy to a single fish species [2-5,8,9]. We believe that the β-parvalbumin described in our report is probably a selective allergen of pleuronectiforme *Soleidas*, since our patient serum has not recognized similar protein bands in the other fish extract tested, other than sole and wedge sole fish, and our patient tolerated most usually allergenic fish species.

With respect to the slightly weaker 15-25 kDa band recognized by our patient serum, it could be either a triosephosphate isomerase β, previously identified in common sole (5), or perhaps just a β-parvalbumin dimer.

Regarding the 37-50 kDa proteins recognized by our patient serum, we believe that they might be enolases or aldolases. These proteins are considered to be the second most frequent fish allergens [3,8], being recognized by around 63-50% of patients, and characterized to be thermolabile proteins with controversial clinical relevance [1,3,8]. In addition, our patient did not recognized them when fishes were cooked, thus it is likely that in our case they are not clinically significant.

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In conclusion, we report the first case of selective allergy to wedge sole fish. We also describe a new β-parvalbumin as the responsible allergen, which seems to be selective for the group pleuronectiformes soleidae (Sole and *Dicologlossa*).

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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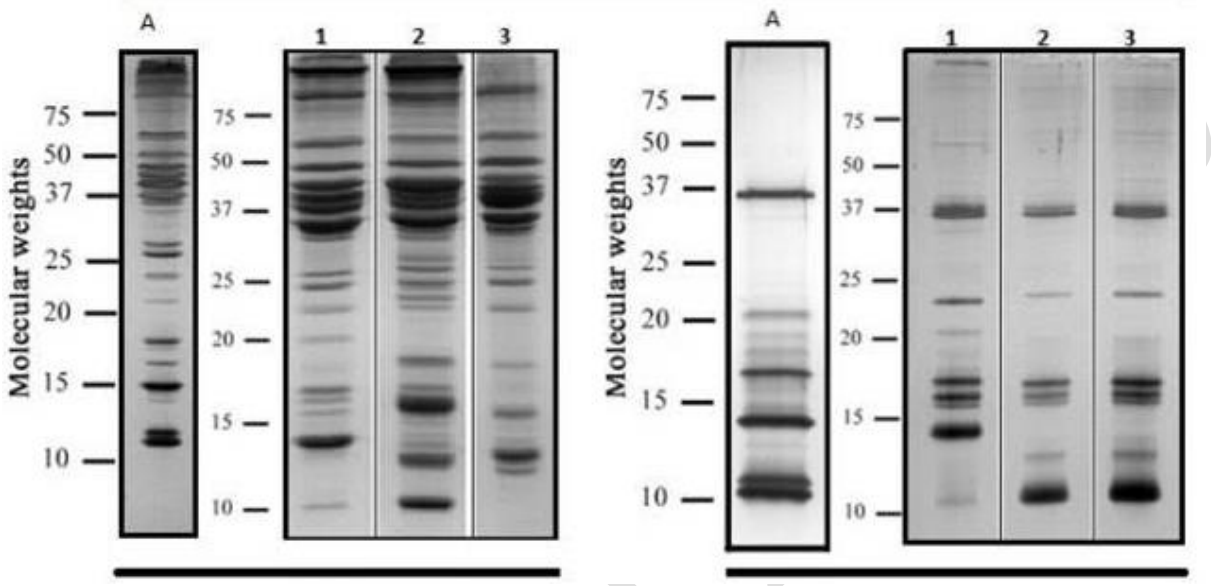
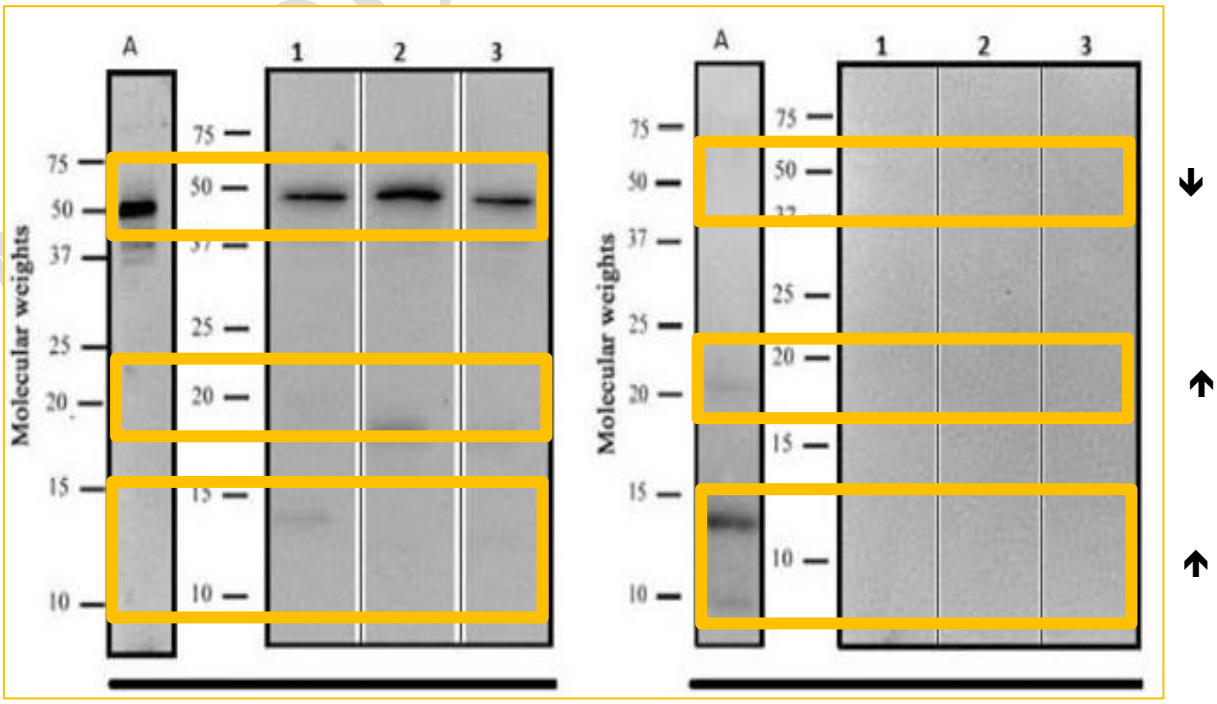
FIGURES

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



(RAW) **(COOKED)**

Figure 2. IgE-immunodetection performed under reducing conditions with the patient serum and the following extracts: lane A, *Dicologlossa spp.*; 1, *Solea spp.*; 2, *Lepidorhombus spp.*; 3, *Scophthalmus spp.*.



(RAW) **(COOKED)**

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