Exercise-Dependent Codfish Allergy due to Tropomyosin

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Food allergy dependent on augmentation factors (FALDA) is an IgE-mediated food allergy with allergic symptoms, ranging from intermittent urticaria to severe anaphylaxis, occurring only when an allergen is ingested in combination with augmentation factors such as exercise, nonsteroidal anti-inflammatory drugs, and alcohol. If anaphylaxis develops after food ingestion followed by exercise, this is called food-dependent exercise-induced anaphylaxis (FDEIA) [1]. In contrast to shellfish, which is a frequent allergen and the elicitor of the first published case of FDEIA [2], only exceptional cases of FALDA due to fish have been reported [3,4]. The causative allergens involved in fish FALDA have not been well determined to date. Tropomyosin is a panallergen in invertebrates such as shellfish, including crustaceans, although cross-reactivity to fish has been reported [5]. Here, we present the first case of FALDA to fish caused by cross-reactivity to tropomyosin, manifesting primarily as oral allergy syndrome induced by crustaceans. Both the patient and his parents gave their written informed consent for the publication of this case.

We report the case of a 12-year-old boy with bronchial asthma and allergic rhinitis caused by grass pollen and house dust mite (HDM) who reported 2 episodes of urticaria during exercise. The patient reported eating a whitefish-based meal at the school canteen about 30 minutes before playing soccer. During exercise, he experienced generalized urticaria, which resolved spontaneously thereafter. The patient reported another previous episode, likely with fish, and generalized urticaria while playing soccer. In the absence of fish, the patient exercised almost daily without developing symptoms, also after eating. Additionally, the patient reported intraoral itching when consuming mussels, shrimps, crabs, and tuna, which prompted him to abstain from eating seafood and all types of fish except salmon 2 months prior to the consultation.

Skin prick tests (SPTs, prick-to-prick) yielded positive results for cod, shrimp, and crab (Table). Serology testing (ImmunoCAP, Phadia) showed increased total serum IgE (640 kU/L) and specific IgE (sIgE) to HDM, multiple crustaceans and shellfish, and the shrimp tropomyosin Pen a 1 (Table). In association with the reported clinical symptoms, the patient was diagnosed with tropomyosin-mediated crustacean and shellfish allergy.

Additionally, sIgE levels ≥0.35 kU/L were found for tuna and cod, whereas no sIgE could be detected against the cod parvalbumins Gad c 1 and Gad m 1 (Table). However, sensitization to cod allergens was confirmed in a basophil activation test, which remained negative in a healthy control (Online repository, Figure E1, A).

In the next step, oral challenge tests were performed in line with current food allergy diagnostic guidelines [6]. On the first day, the patient tolerated cooked cod up to a cumulative dose of 124 g. On the second day, he tolerated 10 g and 15 g, although he developed pruritus and multiple wheals after 70 g of cod, with each intake followed by 15 minutes of anaerobic exercise on a treadmill. The symptoms subsided after intravenous antiallergic treatment with dimetindene maleate 4 mg and prednisolone 100 mg. Thus, the patient was diagnosed with FALDA due to cod.

As no sensitization was detected to parvalbumins, the main fish allergens [7] (Table), further molecular research was performed to identify the culprit allergen (Methods, see Online repository file). An enzyme-linked immunosorbent assay (ELISA) yielded negative results for cod enolase and aldolase (Gad m 2, Gad m 3), although the results were very weakly positive for cod extract and positive for shrimp extract, as well as natural and recombinant shrimp tropomyosin (Figure E1, B). In an inhibition ELISA, IgE binding to shrimp extract was dose-dependently inhibited by adding pure shrimp tropomyosin, confirming its predominant role in the sensitization profile. Further specific IgE determinations were performed using the ALEX2 (AllergyXplorer) test (Macroarray Diagnostics), and positive results were again recorded for multiple tropomyosins (Figure E1, C), including the fish tropomyosins Gad m 4 and Sal s 4 (Table). An IgE immunoblot assay with cod extract was then performed. Using patients' serum, the assay revealed an IgE-reactive band of approximately 35 kDa, which was also recognized by antitropomyosin antibodies, corroborating the identification of the causal allergen (Figure E1, D).

This is the first report of FALDA to fish caused by tropomyosin cross-reactivity. As proposed by Dijkema et al [5], tropomyosin cross-reactivity should be considered in patients who experience allergic reactions following fish

Table. Sensitization Profile of a Patient With FALDA due to Cod: Serum IgE and Skin Test Results.

Category	Allergen extracts	sIgE ImmunoCAP[a], kU/L	SPT[b], wheal/erythema, mm
Mites	HDM	30.4	0/0
Crustaceans	Shrimp	>100	10/12
	Crab	>100	5/8
	Lobster	>100	ND
	Langoustine	>100	ND
Mollusks	Mussel	72.2	ND
	Squid	25.1	ND
Fish	Tuna	2.92	ND
	Cod	0.35	3/4
	Salmon	0.30	ND

Category	Molecules		sIgE macroarray ALEX2[c], kU_A/L
	Allergen code	Protein identity	
Mites/insects	HDM, Der p 10	Tropomyosin	>50
	Storage mite, Blo t 10		>50
	Cockroach, Per a 7		>50
Crustacean	Shrimp, Pen a 1		>50
Fish parasite	Herring worm, Ani s 3		>50
Fish	Cod, Gad m 1	Parvalbumin	<0.1
	Cod, Gad m 2/Gad m 3	Enolase/aldolase	<0.1
	Cod, Gad m 4	Tropomyosin	0.79
	Salmon, Sal s 1	Parvalbumin	<0.1
	Salmon Sal s 2/Sal s 3	Enolase/aldolase	<0.1
	Salmon, Sal s 4	Tropomyosin	0.61

Abbreviations: FALDA, food allergy dependent on augmentation factors; HDM, house dust mite; ND, not done; sIgE, specific IgE; SPT, skin prick test.
[a]Phadia. IgE values <0.1 kU_A/L were considered negative.
[b]SPT were performed with allergen test solution for HDM (Leti Pharma S.L.U.) and as prick-to-prick skin tests for shrimp, crab, and cod.
[c]Macroarray Diagnostics. IgE values <0.1 kU_A/L were considered negative.

consumption with sIgE or positive SPT to at least 1 type of fish and a concomitant allergy to crustaceans and shellfish with sIgE to tropomyosin, but not to parvalbumin. Tropomyosin is a heat-stable panallergen found in invertebrates such as shellfish (including crustaceans), HDM, and the newly emerging food source of edible insects [8]. Although it was not originally thought to play a role as an allergen in vertebrates such as fish, cross-reactivity between tropomyosin from crustaceans and fish has recently been reported [5,9]. To date, tropomyosins from *Mozambique tilapia* (Ore m 4), striped catfish (Pan h 4), and Atlantic salmon (Sal s 4, positive in the case we report) have been included as food allergens in the WHO/IUIS Allergen Nomenclature Database (www.allergen.org, accessed on 21.12.2023). González-Fernandez et al [10] described recognition of cod tropomyosin with immunoblotting in several patients who reported symptoms after consumption of shellfish and fish.

Most fish allergies are not dependent on cofactors, and only exceptional cases of FALDA due to fish requiring exercise for elicitation have been published worldwide [3,4]. While vertebrate tropomyosins (eg, in meat) generally seem to be nonallergenic, this may not apply to fish tropomyosin for evolutionary reasons (eg, the ability to live in cold water), leading to a closer similarity to invertebrate tropomyosin [9]. However, this observation is thought to be related to weaker allergenicity than invertebrate tropomyosin [9], consistent with the sensitization profile in the case we report, which was overwhelmingly directed against invertebrate tropomyosins (Figure E1, C) and with clinical symptoms after ingestion of crustaceans independently of augmentation factors, albeit with the need for exercise to elicit symptoms after ingesting cod. Accordingly, we recommended total avoidance of crustaceans and shellfish, although the patient could continue eating whitefish in small amounts and separately from potential augmentation factors. Thus, we report the first case of FALDA to fish caused by tropomyosin cross-reactivity.

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Conflicts of Interest

BE reports nonfinancial support from Bühlmann Laboratories outside the submitted work. The remaining authors declare that they have no conflicts of interest.

Previous Presentation

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