

Occupational protein contact dermatitis from herring

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We present a case of occupational protein contact dermatitis caused by herring in a dolphinarium worker. The *in vivo* and *in vitro* tests results indicated a type I allergic mechanism. *In vivo* cross-reactivity among fish belonging to the Clupeiformes order was observed.

The term *protein contact dermatitis* (PCD) was introduced by Hjorth & Roed-Petersen (8) to describe patients with hand eczema who exhibited immediate symptoms when their skin was exposed to certain food proteins. The present report describes a case of occupational PCD caused by herring. Other fish species were also tested in the patient to determine whether a clinically relevant cross-reactivity was present.

Case report

The patient was a 22-year-old nonatopic woman who worked in a dolphinarium. She trained sea lions, seals, and dolphins. She fed them fish, mainly herring, which she had previously handled. After 4 months at work, she developed pruritic erythematous papules and subsequent excoriated papular eczema on the right forearm and fingers. The symptoms disappeared after she took a short sick leave and recurred on her return to work. On three occasions she developed angioedema of the lips and face after contact with seals, immediately after they had eaten herring. Previously she had been able to handle and eat raw and cooked fish without any adverse reaction. Clinical examination showed slight eczema on the fingers. Full blood count was normal.

Material and methods

Allergens

Extracts from herring, sardine, anchovy, salmon, cod, and tunny were prepared as follows: each fresh piece was triturated and fat was removed with acetone; then it was dried on filter paper. Ten grams of fish was dissolved in 100 ml of phosphate-buffered saline (PBS) and stored at 4°C for 24 h. After centrifugation (3000 g for 10 min), the supernatant was dialyzed at 4°C for 48 h and filtered through a 0.22-µm Millipore filter (Millipore Co., Bedford, MA, USA). The extract, at a final concentration of 1:10 w/v, was used for the *in vivo* and *in vitro* tests. A part of each extract was heated at 75°C for 30 min. Tenfold dilutions were made for skin tests.

Skin tests

Skin prick tests (SPT) were performed with all the above described extracts in duplicate on the patient's back. Furthermore, each raw and cooked fresh fish was tested by the prick-prick method. Skin prick tests were also performed with a fish commercial battery (herring (Bencard, Worthing, UK), sardine, anchovy, salmon, cod, and tunny (Aristegui, Bilbao, Spain). A battery of commercially available com-

mon inhalants (pollens, mites, animal danders, and fungal spores (Bencard, Worthing, UK) and food allergens (milk, egg, fish, nuts, and wheat (Bencard, Worthing, UK) were also tested.

Reactions were read after 15 min by measuring the two perpendicular diameters of the wheal; a wheal 3 mm larger than the negative control (0.9% normal saline) was considered to be positive. Histamine phosphate (10 mg/ml) was tested as positive control.

Rub tests were performed by rubbing with each raw and cooked fish for 30 s on the volar side of forearm and read at 15 min. Open and closed patch tests with raw and cooked fish were performed on the back. These tests were read after 20 min, 48 h, and 96 h.

Twenty subjects (10 atopics and 10 nonatopics) served as controls in all the previous skin tests.

Oral challenge tests

Open oral challenges with cooked herring were performed with clinical monitoring. The initial dose was 10 g, with twofold increases to a final dose of 160 g of fish or until the development of a reaction.

Total IgE

Total IgE was measured by the IgE EIA technique according to the manufacturer's instructions (Pharmacia, Uppsala, Sweden).

Histamine release test (HRT)

An HRT was performed by an automated fluorometric method according to Siraganian (16) with the modifications previously described (13). Two hundred microliters of whole blood was mixed with 20 μ l of serial four fivefold dilutions of the different fish extracts in 12 $\times$ 75-mm plastic tubes. After incubation for 30 min at 37°C, 400 μ l of PBS-10 mmol EDTA was added, and the tubes were centrifuged for 5 min at 400 g. The histamine content in the supernatant was measured by an autoanalyzer (Technicon Instruments, Inc., Tarrytown, NY, USA). At the same time, basal histamine (with no antigen) and total histamine (with addition of perchloric acid 10%) were measured in order to express the results of the test in percentages according to the following formula: histamine release (%) = $[(A-B)/(T-B)] \times 100$, where *A* is the peak produced by the sample stimulated by the antigen, *B* is the peak for basal histamine, and *T* is the peak for total histamine.

Results higher than 10% of histamine release were considered to be positive (17). The same test was performed on five atopics and five normal subjects who served as controls.

Specific IgE determination

A catabolite activator protein (CAP) assay was performed following manufacturer's instructions (Pharmacia, Uppsala, Sweden) for commercially available allergens: herring, cod, tunny, and salmon. For the present purpose, results equal to or above 0.70 kU/l were considered to be positive. In order to detect specific IgE antibodies against antigens not commercially available (sardine, anchovy), we coupled nitrocellulose paper disks (Hoeffer Scientific Instruments, San Francisco, CA, USA) with our own extracts by 24-h incubation at 24°C. The disks were washed three times in PBS 0.1% Tween 20 (PBS-Tw). Then 1% bovine serum albumin (BSA) in PBS was added, and the disks were incubated for 1 h at 24°C. After three more washes with PBS-Tw, the disks were ready to use. The RAST assay was performed according to the standard technique by ¹²⁵I-labeled anti-IgE (Pharmacia Diagnostic, Uppsala, Sweden). The RASTs were done in duplicate.

Results

The patient did not react to the commercial batteries of aeroallergens and food allergens tested. SPT results with raw and cooked herring and with our own raw and heated herring extracts were positive, as were those of the other fish extracts. SPT with commercial fish extracts were also positive, with the exception of tunny. SPT results are shown in Table 1.

Rub testing with raw and cooked herring, anchovy, and sardine, all belonging to the Clupeiformes order, evoked a positive reaction of erythema and wheals at the test site in 15 min. No late reactions were observed during the following 24 h. Rub tests with cod, salmon, and tunny were negative. Open and closed patch tests with all the fish spp. were negative. All skin tests were negative in the control subjects.

Oral provocation with 160 mg of herring resulted in a reaction of itching and angioedema of lips after 5 min which resolved spontaneously within 20 min.

Table 1. Skin prick tests results (mm)

Fish	Order	Raw fish	Cooked fish	Commercial fish extract	Raw fish extract	Heated fish extract
Herring	Clupeiformes	16 $\times$ 13	16 $\times$ 9	9 $\times$ 9	13 $\times$ 15	15 $\times$ 12
Sardine	Clupeiformes	9 $\times$ 6	9 $\times$ 5	3 $\times$ 3	13 $\times$ 10	14 $\times$ 9
Anchovy	Clupeiformes	13 $\times$ 9	13 $\times$ 9	6 $\times$ 5	14 $\times$ 7	11 $\times$ 9
Salmon	Salmoniformes	4 $\times$ 4	4 $\times$ 4	6 $\times$ 5	8 $\times$ 6	6 $\times$ 6
Cod	Gadiformes	11 $\times$ 7	8 $\times$ 6	7 $\times$ 8	19 $\times$ 11	20 $\times$ 9
Tunny	Perciformes	6 $\times$ 5	4 $\times$ 4	neg	5 $\times$ 4	6 $\times$ 5

Histamine 10 mg/ml 4 $\times$ 4.

Saline 0.9% negative.

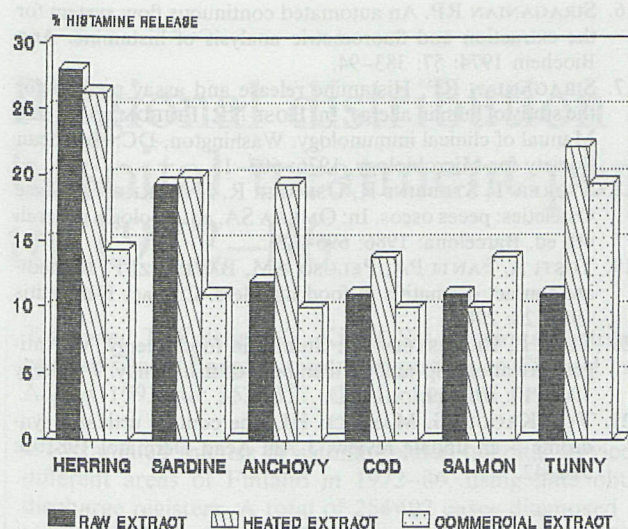


Fig. 1. Maximum HRT results.

HRT with herring extracts (raw, heated, and commercial) was positive, as it was with the other fish extracts. A dose-related histamine release was noted for each extract. Maximum histamine release results for each fish extract are shown in Fig. 1. Negative HRT results were obtained in control subjects.

Specific anti-herring IgE antibodies were found in the patient's serum (1.41 kU/l, class 2). RAST results were negative for the other fish spp. tested. Negative results were obtained in control subjects.

Discussion

Immediate contact skin reactions include a broad spectrum of skin symptoms (7, 10, 21). Contact urticaria is the prototypal skin reaction, but other types of dermatitis can occur. The term *PCD* was introduced by Hjorth & Roed-Petersen (8) for food handlers with hand eczema who exhibited immediate symptoms when their skin was exposed to certain food proteins to which they showed IgE-mediated sensitivity. Nonatopics were in a majority. Contact urticaria from fish is well known (1, 2, 6, 9, 11, 12), but PCD has attracted attention because it has been reported to be a problem among people working with fish (8, 9, 19).

The patient was a nonatopic woman who had developed chronic hand eczema, probably as a result of repeated, work-related exposure to herring. In this case, the positivity of immediate skin tests (prick and rub tests) and the HRT results, as well as the demonstration of herring-specific IgE antibodies by CAP assay, strongly suggest that the patient had developed type I hypersensitivity to herring. The positivity of the oral challenge test supports the clinical relevance of this sensitivity. Furthermore,

these oral symptoms are equivalent to oral allergy syndrome (OAS) (14) from fruits and vegetables. Therefore an association of a PCD with an OAS is reported.

The patient had positive SPT with all the fish tested. Previous papers (4, 5, 15, 20) have reported that this might be due to the presence of common allergens with little clinical expression among the different species, but limited information is available on fish cross-reaction patterns. This finding might also indicate nonspecific reactions, but all the control subjects had negative results.

When analyzing cross-reactivity, we found rub tests with taxonomically related fish (anchovy and sardine) to be positive, but negative with nonrelated fish. Like other authors (10), we believe that the rub test is a reliable test for the diagnosis of immediate contact reactions. We feel that this test might be of interest in the diagnosis protocol in immediate contact dermatitis, and it might confirm clinical cross-reactions among different fish spp., as occurred in our patient.

The negativity of open and closed patch tests might be related not only to the possibility that the procedure may not reproduce the conditions of exposure, but also to the fact that they were performed on the back and not on the site of the previous lesion.

Herring (*Clupea harengus*) belongs to the Clupeiformes order (18); it is the most abundant vertebrate species (3). Although herring has been mentioned as a cause of PCD (8), no particular studies with this fish have been reported, to our knowledge. In addition, we consider this case to be of interest in occupational allergy because our patient is an unusual kind of food handler.

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