
Case report

Severe reactions from roe without concomitant fish allergy

Soili Mäkinen-Kiljunen, PhD; Raija Kiistala, MD, PhD; and Elina Varjonen, MD, PhD

Background: Although fish allergy is common, no studies have been published on allergy to fish roe.

Objective: To describe 2 cases of IgE-mediated allergy to 2 roe species.

Methods: Two patients, one with local symptoms and the other with anaphylaxis following ingestion of roe, underwent skin prick testing (SPT) with 2 roe species, whitefish roe (WFR) and rainbow trout roe (RTR). Serum samples were taken for IgE measurement and immunoblotting to identify roe allergens. Inhibition studies were performed to scrutinize the cross-reactivity between the roes and to fish.

Results: The results of the SPTs with the roes were clearly positive in both patients but negative in control persons. The results of SPTs to all other foods were negative. Roe-specific IgE levels were elevated in the serum samples of both patients. Immunoblotting revealed different IgE-binding patterns of the extracts and different inhibition profiles with the serum samples. In WFR blotting, both serum samples detected a heavy IgE-binding band at approximately 20 kDa, which was not inhibited with fish. Cross-reactivity between the roes was demonstrated in the patient with local symptoms from RTR but not in the patient with anaphylaxis from WFR. The first serum sample also detected several IgE-binding bands in the RTR blot, the most intensive at 21 to 23 kDa and 30 kDa, which were partially inhibited by WFR and more completely with fish. The anaphylaxis patient did not detect allergens in the RTR blot. After the investigation, the patients have remained symptom free and able to consume all kinds of fish without problems.

Conclusions: IgE-mediated allergy to roe is possible without concomitant fish allergy. Roe allergy should be explored in patients who test negative to fish but are suspected of having seafood-related allergy.

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INTRODUCTION

IgE-mediated allergy to fish is a common problem, especially in countries where fish is frequently consumed.^{1–4} Most allergic reactions to fish are caused by ingestion, but some sensitive individuals experience symptoms after exposure to fish odors or vapors from cooking fish.^{5,6} Occupational sensitization may occur after handling and processing fish.⁷ IgE-mediated fish allergy is known to be due to fish proteins, but hypersensitivity reactions may also be provoked by contaminants such as toxins and parasites.⁸ Hidden allergens, such as milk casein in fish, have been reported to cause severe symptoms from fish in milk-allergic patients.⁹ IgE antibodies have been found in response to fish gelatin (type I collagen).¹⁰

Although fish allergy is common and there seem to be various routes of sensitization and antigens related to fish hypersensitivity, to our knowledge no studies have been published on allergy to fish roe. One short report on allergy to Russian caviar has been published.¹¹ We describe 2 patients with severe IgE-mediated allergy to roe but not to fish.

MATERIALS AND METHODS

Patients

Case 1. Patient 1 is a 17-year-old, female student who had experienced mild rhinoconjunctivitis from dry hay. Her father had hay fever and her sister had hay fever and asthma. The patient had not previously had any food allergy and she was not taking medication. She was admitted to our hospital for further investigations after she had experienced symptoms that suggested an immediate-type allergic reaction during Christmas dinner. Shortly after she had eaten rainbow trout roe (RTR) and shrimp, she felt itching of the lips and mouth, edema of the lips, followed by throat tightness and respiratory difficulties. She stopped eating and took antihistamines, which resulted in relief of the symptoms. She has been able to eat fish and shrimp symptom free after the reaction.

Case 2. A 30-year-old man without previous atopic symptoms traveled abroad and attended a dinner party where he was served whitefish roe (WFR). He had a severe allergic-type reaction immediately after swallowing roe expressed as an edema of the mouth and throat. Anaphylaxis was suspected, and he was immediately admitted to the hospital, where he received emergency treatment, including epinephrine, and was then followed up over night. He could eat fish before and after the reaction without any symptoms.

Helsinki University Central Hospital, Skin and Allergy Hospital, Helsinki, Finland.

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Skin Prick Tests

Skin prick tests (SPTs) were performed with 11 common inhalant allergens, including pollens (birch, timothy, meadow fescue, mugwort), animal dander (cat, dog, horse, cow), house dust mite (*Dermatophagoides pteronyssinus*), mold (*Cladosporium herbarum*) (Soluprick; ALK, Horsholm, Denmark), and natural rubber latex (Stallergenes S.A., Antony Cedex, France). In addition, 7 common food were tested with commercial SPT preparations (eg, milk, egg, soy, fish [cod and herring], wheat, and shrimp) (Soluprick). The prick-prick test was used to test sensitization to fresh vegetables, fruit, nuts, and spices with a series of 22 fresh foods and 9 cereal test solutions (1:10 wt/vol in 0.9% sodium chloride).

In addition, SPTs were performed with 2 roe samples, WFR and RTR as is, and the corresponding raw fish, whitefish (*Coregonus lavaretus*) and rainbow trout (*Oncorhynchus mykiss*), purchased from the local store. Histamine dihydrochloride (10 mg/mL) served as a positive control and saline diluent in 50% glycerol as a negative control. The largest wheal diameter was measured and the reaction was considered positive if the diameter was 3 mm or more over the negative control. All SPT results were read at 15 minutes. The SPTs with the roe extracts were performed also on 5 nonatopic controls.

Total and Specific IgE

The patients' serum total and fish-specific (cod and herring) IgE levels were measured by the commercial CAP system fluoroenzyme immunoassay (Pharmacia, Uppsala, Sweden). In-house radioallergosorbent assay testing (RAST) was used to measure serum specific IgE to roe (WFR and RTR) and raw fish and seafood, including whitefish, rainbow trout, pike (*Esox lucius*), saithe (*Pollacius virens*), shrimp, and oyster.¹² For this study, paper disks were coated with crushed roe and fish extracts containing 100 to 300 µg of total protein per disk as measured by the Bradford method and bovine IgG as the standard (Bio-Rad Laboratories, Richmond, CA).¹³ Values higher than 0.35 PRU/mL were considered positive according

to the Pharmacia reference system. A nonatopic serum was used as a control.

Immunoblotting was used to demonstrate individual allergens in the 2 roe extracts. Reduced extracts of WFR and RTR (6.5 mg and 13.6 mg of protein in 400 µL of sample buffer, respectively) and molecular weight markers (Caleidoscope; Bio-Rad) were separated by sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) in a 15% gel with a 4% stacking gel.¹⁴ The proteins were blotted to nitrocellulose paper (Bio-Rad) for staining with Coomassie brilliant blue and immunoblotting according to Towbin et al.¹⁵ IgE binding from the serum samples (diluted 1:2) was detected with radiolabeled anti-IgE (Pharmacia-Upjohn, Uppsala, Sweden).¹² A nonatopic serum and a pooled cod IgE-positive serum served as controls.

Cross-reactivity Studies

Immunoblot inhibition studies were used to evaluate allergen cross-reactivity between the roes and to fish. For this, the patients' serum samples were first incubated with 1:1 (wt/vol) roe extract (WFR or RTR) and with 1:2 (wt/vol) fish extract (whitefish or rainbow trout) before adding to roe blottings. Phosphate-buffered saline was used as control inhibitor. Serum from a nonatopic subject and a pooled fish IgE-positive serum served as controls.

RESULTS

SPTs and IgE Tests

Table 1 presents the SPT and serum IgE test (RAST) results with roe, fish, and seafood. Both patients tested SPT and IgE positive to roe but negative to fish and seafood. The results of SPTs with roe were negative in 5 control subjects. Also, roe RAST results were negative with the control serum.

Patient 1 also had a positive SPT result to grasses (timothy, 4 mm; meadow fescue, 3 mm) and dog (3 mm). The SPT result to histamine control was 5 mm. Patient 2 had a positive SPT result to birch (3 mm), timothy and meadow fescue (4 mm), and dog (5 mm). His SPT result to histamine control

Table 1. Skin Prick Test and Serum IgE Test Results to Roe, Fish, and Seafood

Allergen	Patient 1		Patient 2	
	SPT, mm	RAST, PRU/mL	SPT, mm	RAST, PRU/mL
Whitefish roe	10	1.3	18	2.6
Rainbow trout roe	8	4.6	12	0.9
Histamine control	6		5	
Rainbow trout	0	<0.35	0	<0.35
Whitefish	0	<0.35	0	<0.35
Cod*	0	<0.35	0	<0.35
Herring*	0	<0.35	0	<0.35
Pike	ND	<0.35	ND	<0.35
Coalfish	ND	<0.35	ND	<0.35
Shrimp	0	<0.35	0	<0.35
Oyster	ND	<0.35	ND	<0.35

Abbreviations: ND, not done; RAST, radioallergosorbent assay test; SPT, skin prick test.

* Commercial CAP values presented in kilounits per liter.

was 6 mm. Test results to all other foods, except fish roe, were negative. Total IgE levels for patients 1 and 2 were 28 and 42 kU/L, respectively.

Protein staining after SDS-PAGE revealed smear bands at approximately 20 and 40 kDa in both roe blots (not shown). In immunoblotting, a distinct binding of IgE from the patients' serum sample was demonstrated to a broad band at approximately 20 kDa (18–23 kDa) in WFR (Fig 1). In RTR blotting, patient 2 showed no or only a weak IgE binding, whereas patient 1 had IgE to several bands along the blotting area from less than 7 to greater than 100 kDa (Fig 2). Most intensive bands were demonstrated at approximately 21 to 23 kDa and 30 kDa. Far less and weaker bands were demonstrated with the fish-positive serum, one weak band at 20 kDa in WFR and one faint band at 23 kDa in RTR (not shown). No binding was demonstrated from the nonatopic serum.

Cross-reactivity in Immunoblot Inhibition

In immunoblot inhibition studies, different IgE profiles were achieved in the 2 roe blottings with the 2 serum samples. A complete inhibition of the IgE binding to WFR blot was achieved by RTR with the first serum sample but not with the second serum sample (Fig 1). Preincubation with fish did not show any significant inhibition in WFR blotting with either of the 2 serum samples. The RTR immunoblotting with serum sample 1 was partly inhibited by preincubation with WFR; visible bands were mainly seen at approximately 21 kDa and higher, and one weak band was also seen below 7 kDa (Fig 2). The inhibition was more pronounced with fish; only one narrow band was visible at approximately 21 kDa after inhibition with whitefish and an additional band was also visible at more than 100 kDa after preincubation with rainbow trout. Patient 2 did not exhibit IgE binding to RTR immunoblotting. Inhibitions were complete with the homologous roe extract.

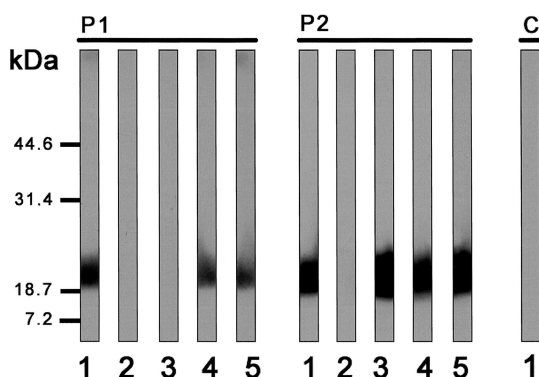


Figure 1. IgE immunoblot and immunoblot inhibition to whitefish roe (WFR) extract with serum samples from patient 1 (P1) and patient 2 (P2) with roe allergy. The WFR blot (lane 1) inhibited with WFR (lane 2), rainbow trout roe (lane 3), whitefish (lane 4), and rainbow trout (lane 5). Serum from a nonatopic individual (lane C) was used as a control. Molecular weight markers appear on the left.

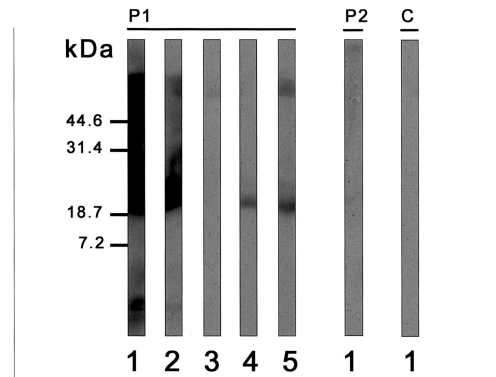


Figure 2. IgE immunoblot and immunoblot inhibition to rainbow trout roe (RTR) extract with serum samples from patient 1 (P1) and patient 2 (P2) with roe allergy. The RTR blot (lane 1) inhibited with whitefish roe (lane 2), RTR (lane 3), whitefish (lane 4), and rainbow trout (lane 5). Serum from a nonatopic individual (lane C) was used as a control. Molecular weight markers appear on the left.

DISCUSSION

An immediate-type allergy to fish and fish contaminants is well known.^{1–10} One case report exists on allergy to Russian Beluga caviar,¹¹ but we did not find any reports on allergy to “false caviar” or fish roe (fish eggs). We herein describe 2 patients who had severe allergic reactions from roe but who were not allergic to fish.

Roe consists of eggs of female fish enclosed in the ovarian membrane. Roes are available worldwide from several fish species and are often served as appetizers or used with blini pancakes as such. Roe is usually sieved, salted, and frozen before use in pastes, sauces, creamed soups, casseroles, and garnishes.

The color and size of roe eggs differ in different species. The RTR consists of big, orange-red eggs. Eggs of WFR are smaller and orange-yellow. Eggs are even smaller and orange-yellow in vendace (*Coregonus albula*) and light yellow in burbot (*Lota lota*). Roe is also available from cod, salmon (*Salmo salar*), Baltic herring (*Clupea harengus membras*), pike, smelt (*Osmerus eperlanus*), ruffe (*Gymnocephalus cernuus*), fourhorned sculpin (*Myoxocephalus quadricornis*), and lumpfish (*Cylopterus lumpus*). Lumpfish roe may be dyed black or red.

The name *caviar* may only be applied to the eggs of a sturgeon. The most delicate and expensive is the Russian caviar or black caviar from which 3 types exist: Beluga, Osetra, and Sevruga. Beluga caviar from sturgeon (*Huso huso*) from the Caspian Sea is considered the best, but sturgeons are also grown in Europe.

In addition to natural roes, artificial roe (Cavi-Art) has also been developed, which is made of seaweed and dyed black, yellow, or red. Soft or white roe is the milt or the sperm-containing fluid of a male fish, whereas the roe of crustacean and invertebrate is composed of the ovary and is called coral.

Crude fish extracts and caviar are perishable materials that may contain histamine and other mediators that can cause

allergy-like reactions and false-positive test results. In our case, the histamine effect was excluded, since all controls had negative SPT results. In addition, the fact that roe-specific IgE could be demonstrated in the patients' serum samples but not in the control serum samples excluded the possibility of a histamine effect.

The interesting aspect of the present study is the finding that fish roe may cause IgE-mediated sensitization without concomitant fish allergy. Furthermore, the 2 roe-sensitive individuals with distinct clinical manifestations showed a separate pattern of reactivity to the 2 roes in IgE immunoblotting and also disclosed different inhibition profiles.

Different fish species are considered to cross-react, mainly through the 12-kDa parvalbumin proteins.^{16–19} The most important allergens in Russian caviar have been at approximately 30, 84, 100, and 118 kDa.¹¹ Our studies with the 2 roe-specific serum samples demonstrated at least one IgE-binding band at approximately 20 kDa in both WFR and RTR, which was not inhibited by fish meat (Figures 1 and 2). Other bands not inhibited in RTR blot with serum sample 1 had molecular masses below 7 kDa and above 100 kDa. Cross-reaction between the 2 roes was demonstrated with the first serum only. IgE from the patient with more local symptoms was less specific and exhibited a crosswise inhibition between the roes, whereas IgE from the patient with anaphylaxis after WFR was more specific to WFR and was not inhibited with RTR.

Neither of our patients had symptoms from fish or showed an IgE-mediated sensitization to the 8 fish and seafood samples tested (Table 1). The first patient also tested negative to shrimp, which she had eaten with roe. Since roe is often served with other seafood, patients suspected of having allergic reactions on these occasions should be tested with roe. Tests with fish are not sufficient to detect roe sensitivity.

Challenge test is often performed to confirm food allergy. Because of the dramatic course of the reaction, our patients were not willing to undergo provocation test. However, both patients had convincing histories of allergic reactions following ingestion of roe, which was obviously IgE mediated as revealed by the clearcut immediate wheal reaction to roe and by the results of IgE-based assays. Allergy was specifically demonstrated to roe and not to fish or other food.

CONCLUSION

We describe 2 patients with severe allergic reaction from roe without concomitant fish allergy. The data clearly support the finding that roe may cause an IgE-mediated allergic reaction in sensitive individuals.

REFERENCES

- Bernhisel-Broadbent J, Scanlon SM, Sampson HA. Fish hypersensitivity, I: in vitro and oral challenge results in fish-allergic patients. *J Allergy Clin Immunol*. 1992;89:730–737.
- De Martino M, Peruzzi M, de Luca M, et al. Fish allergy in children. *Ann Allergy*. 1993;71:159–165.
- Hansen TK, Bindslev-Jensen C. Codfish allergy in adults: identification and diagnosis. *Allergy*. 1992;47:610–617.

- James JM, Helm RM, Burks AW, et al. Comparison of pediatric and adult IgE antibody binding to fish proteins. *Ann Allergy Asthma Immunol*. 1997;79:131–137.
- Crespo JF, Pascual C, Dominguez C, et al. Allergic reactions associated with airborne fish particles in IgE-mediated fish hypersensitive patients. *Allergy*. 1995;50:257–261.
- Taylor AV, Swanson MC, Jones RT, et al. Detection and quantitation of raw fish aeroallergens from an open-air fish market. *J Allergy Clin Immunol*. 2000;105:166–169.
- Douglas JD, McSharry C, Blaikie L, et al. Occupational asthma caused by automated salmon processing. *Lancet*. 1995;346:737–740.
- Audicana M, Fernández de Corres L, Munoz D, et al. Recurrent anaphylaxis due to *Anisakis simplex* parasitizing sea fish. *J Allergy Clin Immunol*. 1995;96:558–560.
- Koppelman SJ, Wensing M, de Jong GA, et al. Anaphylaxis caused by the unexpected presence of casein in salmon. *Lancet*. 1999;354:2136.
- Sakaguchi M, Masako T, Ebihara T, et al. IgE antibody to fish gelatin (type I collagen) in patients with fish allergy. *J Allergy Clin Immunol*. 2000;106:579–584.
- Untersmay E, Focke M, Kinaciyan T, et al. Anaphylaxis to Russian Beluga caviar. *J Allergy Clin Immunol*. 2002;109:1034–1035.
- Mäkinen-Kiljunen S. Banana allergy in patients with immediate-type hypersensitivity to natural rubber latex: characterization of cross-reacting antibodies and allergens. *J Allergy Clin Immunol*. 1994;93:990–996.
- Ceska M, Eriksson R, Varga JM. Radioimmunosorbent assay of allergens. *J Allergy Clin Immunol*. 1972;49:1–9.
- Laemmli UK. Cleavage of structural proteins during assembly of the head of bacteriophage T4. *Nature*. 1970;227:680–685.
- Towbin HT, Staehelin T, Gordon J. Electrophoretic transfer of proteins from polyacrylamide gels to nitrocellulose sheets: procedure and some applications. *Proc Natl Acad Sci USA*. 1979;76:4350–4354.
- Hansen TK, Bindslev-Jensen C, Skov P, et al. Codfish allergy in adults: IgE cross-reactivity among fish species. *Ann Allergy Asthma Immunol*. 1997;78:187–194.
- Bugajski-Schretter A, Elfman L, Fuchs T, et al. Parvalbumin, a cross-reactive fish allergen, contains IgE-binding epitopes sensitive to periodate treatment and Ca²⁺ depletion. *J Allergy Clin Immunol*. 1998;101:67–74.
- Helbling A, Haydel R, McCants ML, et al. Fish allergy: is cross-reactivity among fish species relevant? double-blind placebo-controlled food challenge studies of fish allergic adults. *Ann Allergy Asthma Immunol*. 1999;83:517–523.
- Porcel S, Leon F, Cumplido J, et al. Contact urticaria caused by heat-sensitive raw fish allergens. *Contact Dermatitis*. 2001;43:139–142.

Requests for reprints should be addressed to:

Soili Mäkinen-Kiljunen, PhD
Helsinki University Central Hospital
Skin and Allergy Hospital
PO Box 160
FIN-00029 HUS
Helsinki, Finland
E-mail: soili.makinen-kiljunen@hus.fi