

Case report

Occupational asthma caused by fish inhalation

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Occupational asthma (OA) due to fish inhalation, confirmed by specific bronchial challenge (SBC), has not been described as yet in medical literature, as far as we know. We describe two patients whose asthma was induced by occupational exposure to fish and confirmed by serial measurements of PEF and SBC. Two fish-processing workers reported asthma symptoms related to their workplace. They were skin tested with fish extracts and their sera assayed for IgE antibodies to various fish species. Nonspecific bronchial reactivity was assessed by methacholine challenge. The occupational relationship was confirmed by PEF monitoring in working and off-work periods. SBC with fish extracts was carried out to confirm the diagnosis of OA. Skin tests with raw and cooked plaice, salmon, hake, and tuna in patient 1 and anchovy, sardine, trout, salmon, Atlantic pomfret, and sole in patient 2 were positive. Specific IgE serum antibodies were found to salmon in patient 1 and to trout, anchovy, and salmon in patient 2. PEF measurements differed significantly ($P < 0.001$) between work and off-work periods for both patients. A bronchial challenge with methacholine was positive in patient 1. SBC with raw hake, salmon, plaice, and tuna extracts in patient 1 and raw salmon extract in patient 2 were all positive with an immediate response. SBC with *Dermatophagoides pteronyssinus* extract was entirely negative in both patients. In three asthmatic, non-fish-allergic controls, SBC with tuna, hake, salmon, and plaice were all negative. These results suggest that fish inhalation can elicit IgE-mediated occupational asthma.

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Occupational asthma is defined as a respiratory disease characterized by variable bronchial obstruction and bronchial hyperreactivity caused by specific agents inhaled at work. It has been documented after inhalation of various food substances, mainly dusts of vegetable origin including grain, wheat, and rye flour, castor bean, green coffee bean, soybean, garlic, and powdered gums (1). In addition, seafood-derived allergens have been reported to cause occupational asthma in snow-crab processors (2), prawn workers (3), deep-sea fishermen (4), and trout processors (5). In this paper, we report on two patients in whom asthma was induced by occupational exposure to fish, confirmed through specific bronchial challenges.

Material and methods

Case histories

A 19-year-old woman had worked at a fish-freezing factory for 2 years. During the last year of this employment, she developed daily asthmatic attacks with dry cough, dyspnea, and wheezes, 3 h after beginning her work. She had dry cough and chest tightness nightly after the end of her working day. She remained asymptomatic on weekends and after 1 month away from work, but, when she returned, severe asthma recurred within a few days. The patient did the cleaning, cutting, and packing of several fish species, including fresh plaice, tuna, salmon, and hake. At home, the patient cooked and ate the fish species she handled at work and others,

without any symptoms. Since she had begun her work, she presented also with dry cough and dyspnea when she was in contact with irritating environments. She had received inhaled budesonide and albuterol with slight improvement. There was no previous history of respiratory illness and no personal or familial history of atopy. She had smoked about 10 cigarettes per day for 3 years.

A 24-year-old man had worked at a fish-smoking factory for 5 years. A few weeks after taking this job, he had rhinoconjunctival symptoms minutes after beginning his daily work. He improved at home, on weekends, and on holidays. Two years later, he developed asthmatic attacks with dyspnea, chest tightness, and wheezing three or four days a week with nocturnal worsening, which required inhaled budesonide and albuterol. He remained without thoracic symptoms on weekends and holidays. During the fourth year, he developed perioral and lip itching and angioedema after eating trout, anchovy, salmon, and sardines. Two months later, he also noted rapid onset of dyspnea, chest tightness, and wheezing after sole ingestion. The patient was responsible for cleaning and processing fresh fish (trout, anchovy, salmon, Atlantic pomfret, and sardine) before they were smoked in another room of the factory. There was no previous history of respiratory illness and no personal or familial history of atopy. He was a nonsmoker.

Fish extracts

Extracts from raw and cooked fish species (plaice, salmon, tuna, hake, anchovy, sardine, trout, sole, and Atlantic pomfret) were prepared separately by blending 100 g of fish in 500 ml 0.01 M phosphate-buffered saline (PBS) (pH 7.2) in a commercial Waring blender (New Hartford, CT, USA) for 4 min at room temperature. Mixtures were extracted overnight at 4°C under constant stirring. Extracts were centrifuged (12 000 g) for 20 min at 4°C. The supernatant was subsequently dialyzed (Spectra/por, Spectrum Medical Industries, Los Angeles, CA, USA) (molecular mass cutoff >3500 Da) at 4°C against 2000 vol of 10 mM of glycine for 24 h, centrifuged at 30 000 g, and filtered through a 0.45-µm Millipore filter (Millipore Corp., Bedford, MA, USA). The material was stored at -20°C. For preparation of skin and specific bronchoprovocation tests, extracts were sterile filtered, and the filtrates were assessed for sterility. For skin prick testing, extracts were diluted 1 : 1 with sterile glycerol.

Immunologic studies

Skin prick tests (SPT) were performed with cooked and raw fish extracts (plaice, salmon, tuna, hake,

anchovy, sardine, trout, sole, and Atlantic pomfret) at 1 : 10 w/v concentration. For the purpose of this study, a positive skin test response was defined as a mean wheal diameter of 3 mm or greater to the test antigen in subjects who react to the positive control (10 mg/ml histamine hydrochloride), and who are negative to the diluent control (50% glycerol in PBS). Results were recorded 15 min after testing.

Fish-specific serum IgE levels were determined by CAP-FEIA (Pharmacia Diagnostic, Sweden) in patient 1 and by Phadezym RAST (Pharmacia Diagnostic, Sweden) in patient 2. The results were expressed by classes (0–6) and kU/l (0.35–17.5 PRU/ml), according to the manufacturer's instructions. CAP-FEIA or Phadezym RAST values equal to or greater than 0.35 kU/l or PRU/ml were considered positive. Total IgE was determined by CAP-FEIA (Pharmacia Diagnostic, Sweden) in patient 1 and by Phadezym PRIST (Pharmacia Diagnostic, Sweden) in patient 2. The results were expressed by U/ml.

Serial PEFR determinations

Serial peak-flow expiratory rates (PEFR) were obtained with a portable peak-flow monitor (Vitalograph Ltd, Buckingham, UK). The best result of three maneuvers at each determination was recorded. Determinations were carried out three times a day for periods of 2 weeks at work and away from work. Maximum and minimum daily values were kept for analysis of variability.

Bronchial challenge tests

Nonspecific bronchial reactivity was assessed by methacholine challenges. Specific bronchoprovocations (SBP) to several fish species and *D. pteronyssinus*, at weekly intervals, were performed according to the American Thoracic Society guidelines (6). For these challenges, the delivery system was identical, and pulmonary function was measured by assessment of FEV₁ (Sensor Medics, Anaheim, USA). Spirometric controls were carried out at 10-min intervals until a positive response was obtained and, from this moment, at 10-min intervals up to the first hour; after this moment, FEV₁ values were followed hourly for the next 12 h. Additionally, SBP with raw tuna, salmon, hake, and plaice were carried out in three allergic asthmatic control patients.

Methacholine and fish extracts were delivered with a De Vilbiss 646 nebulizer (De Vilbiss Co., Somerset, PA, USA), the measured output being (0.28–0.30 ml/min) with an intermittent aerosol generation. Each dose of aerosol consists of five

breaths, taken slowly from residual volume to total lung capacity with a 2–5-s breath-hold. SBPs were considered positive when a FEV₁ decrease of $\geq 20\%$ was obtained with a known quantity of the substance expressed as cumulative breath units (CBU). The upper limit for abnormal values in our laboratory is 333 CBU. Values over are considered irritative.

Oral challenge tests

Single-blind, placebo-controlled fish challenges were carried out in patient 1 with increasing quantities of salmon, tuna, plaice, and hake, up to 100 g. Lemon ice cream devoid of artificial coloring was employed as placebo. The different fish challenges were given at weekly intervals.

Results

Immunologic studies

In patient 1, SPT was positive to raw and cooked plaice, salmon, hake, and tuna fish. Specific IgE serum antibodies were positive to salmon (4.5 kU/l) and negative to plaice, tuna, and hake. SPT with fish extracts of anchovy, sardine, trout, salmon, Atlantic pomfret, and sole were all positive in patient 2. In this patient, specific IgE was positive to trout (10.6 PRU/ml), anchovy (2.1 PRU/ml), and salmon (1.4 PRU/ml). Total IgE was 408.5 U/ml in patient 1 and 517 U/ml in patient 2.

PEFR recordings

In patient 1, PEF measurements differed between period at work and away from work (Fig. 1). PEF variabilities were 15.9% at work and 0.5% away from work ($P < 0.001$). In patient 2, PEF variabilities were 12% and 3% at work and away from work, respectively.

Bronchial challenge tests

Challenge with methacholine, carried out only in patient 1, showed bronchial hyperresponsiveness (PD_{20} FEV₁ = 34 CBU). Bronchial challenges performed with raw hake, salmon, plaice, and tuna extracts in patient 1 and raw salmon extract in patient 2 were all positive with an immediate response (Fig. 2). The decrease in spirometric values was observed within 20 min and returned to baseline values within 2 h. Bronchodilator medication was required to reverse bronchoconstriction. In patient 2, the intradermal titration with trout, before the specific bronchial challenge, elicited an immediate severe anaphylactic reaction and a 22%

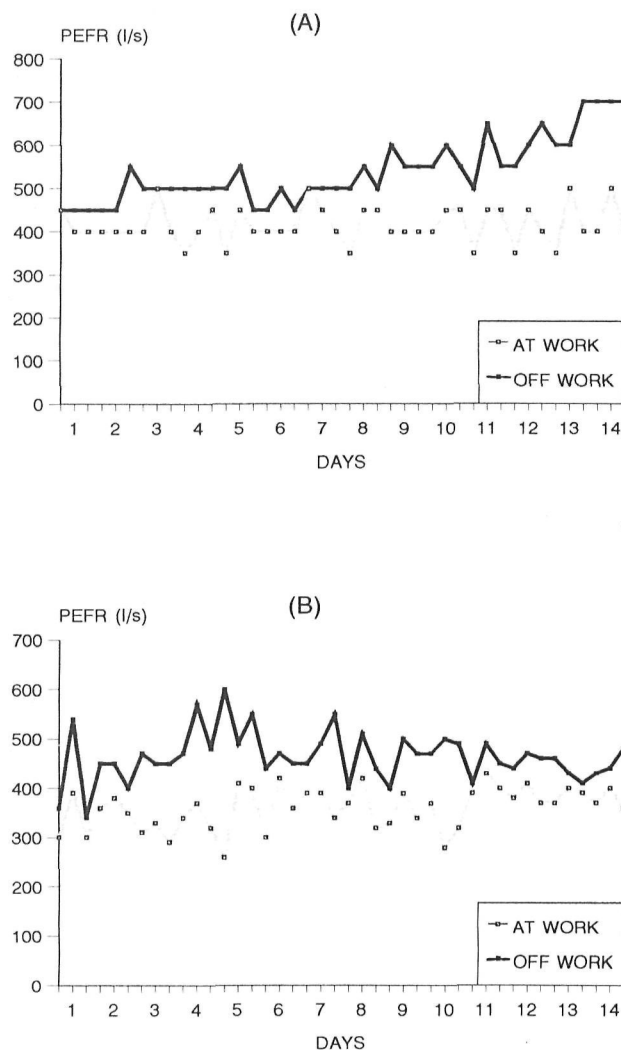


Fig. 1. Serial PEF recordings at work (gray line) and off work (black line) in patients 1 (A) and 2 (B).

FEV₁ fall, which precluded further challenges. Bronchial challenge with *D. pteronyssinus* extract was entirely negative in both patients. In three asthmatic non-fish-allergic controls, bronchial challenges with tuna, hake, salmon, and plaice were negative.

Oral challenges

Oral, single-blind, placebo-controlled challenges with increasing amounts of cooked tuna, plaice, salmon, and hake up to 100 g were negative in patient 1.

Discussion

Fish has been reported to be an important cause of IgE-mediated food hypersensitivity. In our area, fish has been implicated in 17.8% of allergic

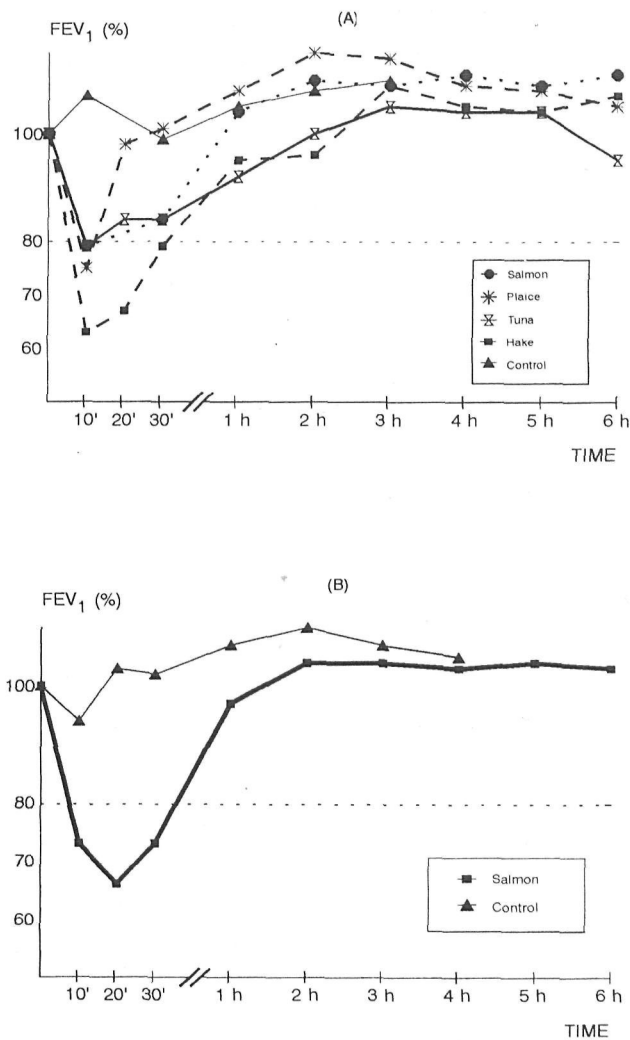


Fig. 2. Specific bronchial challenge tests with fish extracts and *D. pteronyssinus*, as negative control, in patients 1 (A) and 2 (B).

reactions to foods (7). The vast majority of IgE-mediated allergic reactions to fish result from ingestion. However, as described in 1937 by De Besche (8), fish may be an inhalant allergen that can trigger asthma.

Occupational asthma was demonstrated in two fish-processing workers who had positive skin test response and fish-specific IgE antibodies as well as work-related dyspnea with a fall in peak flow. In addition, specific inhalation challenges with fish extracts induced a fall in the FEV₁ of at least 20%. There is little information on this problem in the fish-processing industry. Droszcz et al. (9) found that only 2/51 fish-meal factory workers had allergic symptoms (both had rhinitis and skin changes) and positive skin tests to fish. In a study of health effects in the fish-processing industry, no mention of respiratory problems was made (10). Sherson

et al. (5) reported five trout-processing workers who had probably developed occupationally related asthma, but the specific role of fish was not determined.

In the nonoccupational setting, the incidental inhalation of steam from the cooking of fish has been related to allergic reactions in IgE-mediated fish-hypersensitive patients sensitized previously through the gastrointestinal route. Conversely, the two patients reported in our study became sensitized through the respiratory route, and both could, at least initially, tolerate fish ingestion. It is an intriguing question how fish allergenic particles could be inhaled into the lung. Fish allergens have been demonstrated in steam (collected by distillation) released by boiling fish (11), but our patients were exposed to raw fish. The possibility of fish airborne allergens coming through less common routes, such as natural moisture evaporation, has been poorly analyzed until now. However, as our patients had been exposed to raw fish, it is possible that some fish allergens may become airborne as aerosols from this source. At present, we are conducting studies to assess fish airborne particles by means of air samplers placed in fish markets, which could be a source of moisture evaporation.

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