

Life-threatening, recurrent anaphylaxis caused by allergy to gliadin and exercise

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Summary

Background Exercise-induced urticaria or anaphylaxis is regarded as a distinct form of physical allergy. In some patients the symptoms occur only after ingestion of various food products in connection with exercise. We have come across patients with cereal dependent exercise-induced anaphylaxis.

Objectives The purpose of the present study was to analyse the allergens in cereals responsible for the severe anaphylactic symptoms and to verify the test methods suitable for screening the patients with cereal dependent exercise-induced anaphylaxis.

Methods The patients underwent skin-prick tests (SPT) with common inhalant and food allergens as well as with various cereal extracts. IgE-immunoblotting was used to identify the allergenic fractions.

Results Five patients found positive in SPT with NaCl wheat suspension had IgE antibodies to wheat, rye, barley and oats, especially directed against the ethanol-soluble protein fractions in immunoblotting. No IgE antibodies were detected against other cereals. The patients had been unaware of any cereal allergy since anaphylaxis occurred only in association with exercise postprandially. The patients were directed to follow a gluten-free diet and have been free from symptoms, being able to continue their outdoor physical activities.

Conclusion Wheat gliadin and the corresponding ethanol-soluble proteins of taxonomically closely related cereals were found to be the allergens in cereal-dependent exercise-induced anaphylaxis. Skin-prick testing with NaCl wheat suspension was a simple and practical test to screen patients with this kind of occult, possibly life-threatening, allergy to cereals.

Keywords: exercise-induced anaphylaxis, cereals, gliadin, skin-prick tests, SDS-PAGE, IgE-immunoblotting

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Introduction

Exercise alone can induce urticaria or anaphylaxis [1,2]. Exercise-induced anaphylaxis is characterized by hot flushing and pruritus followed by cutaneous erythema and urticaria. This often leads to vascular collapse, upper respiratory tract obstruction and shock after physical strain. Maulitz *et al.* [3] were the first to report a patient with postprandial exercise-induced anaphylaxis. Since then,

two subsets of exercise-induced anaphylaxis related to food ingestion have been reported: one related to a broad range of unspecified foods and the other dependent on specific food items such as celery [4], shrimp [5] shellfish, fruit [6,7] or hazelnut [8].

Cereals are common in our daily diet but, interestingly, only very few case reports of exercise-induced anaphylaxis caused by cereals have been published [6,9,10,12].

In the present study we report five patients with severe exercise-induced anaphylaxis following ingestion of cereals, implying that this condition is not as rare as previously thought.

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Table 1. Details of five patients with recurrent severe urticarial anaphylactic reactions

Sex	Female	Female	Male	Male	Male
Age (yr)	37	78	45	59	42
Tot. IgE kU/L	274	137	981	921	801
<i>Skin prick test</i>					
NaCl suspension (1:10 w/v)*					
Wheat	++++	++++	+++	++++	+++
Rye	—	++	—	+++	+++
Barley	++	++	++	+++	++
Oats	++	—	—	—	—
Neutral/acidic extract (10 mg/ml)					
Wheat	++	++	+++	++	++
Rye	—	—	—	—	+++
Barley	—	—	—	—	—
Oats	—	—	—	—	—
Gliadin (1 mg/ml)					
	+++	+++	++	+++	+++
RAST kU/L* (positive >0.3 kU/L)					
Gluten	6.9	1.1	17	3	31
Wheat	18	6.1	40	20	75
Rye	3.7	5.6	61	12	92
Barley	0.8	0	6.2	0	21
Oats	7.7	1.7	36	25	22

* Negative for rice, corn, millet and buckwheat.

Skin prick test: ++ wheal > 3 mm and half of the size, +++ equal to and ++++ twice as large as the wheal of the positive histamine control.

Materials and methods

Patients

During 1992–1993 altogether 112 urticaria/angiooedema patients were subjected to SPT including wheat NaCl suspension. Five patients (Table 1) with recurrent severe urticarial/anaphylactic reactions were positive to wheat. A detailed history revealed that all five patients had experienced one to three times annually an episode of generalized urticaria followed by anaphylaxis in association with exercise. The reactions were characteristically preceded by eating 1–3 h before the exercise. One female patient had used epinephrine autoinjections as first aid on eight occasions before she came to our attention. One male patient had severe anaphylaxis and lost consciousness while jogging. He was acutely admitted to a hospital where he recovered after treatment with oxygen, epinephrine and intravenous corticosteroids. The patients had no history of chronic or allergic diseases except for one patient, who was allergic to shrimps, which she had strictly avoided for several years. After diagnosing cereal allergy the patients were instructed to follow a gluten-free diet.

Twenty-seven adult atopic dermatitis (AD) patients without anaphylactic reactions were included as controls in the study.

Laboratory tests

The following laboratory tests were normal in all patients: RBC and WBC count, white cell differential count, serum IgA and IgG levels, complement components C₃ and C₄ and C₁ esterase inhibitor levels, anti-gliadin IgA and IgG antibodies, anti-endomysium and anti-reticulin antibodies.

Serum total IgE and specific IgE (RAST) levels (Pharmacia, Uppsala, Sweden) for cereals (Table 1), egg, milk, celery and shrimp were also measured.

In order to characterize the cereal allergens the following antigen extracts were made for SPT and immunoblotting.

NaCl suspensions

Commercial cereal grains were milled to produce the flour. Each cereal flour was suspended to 1:10 w/v with 0.9% NaCl overnight to get the SPT suspension (Table 1).

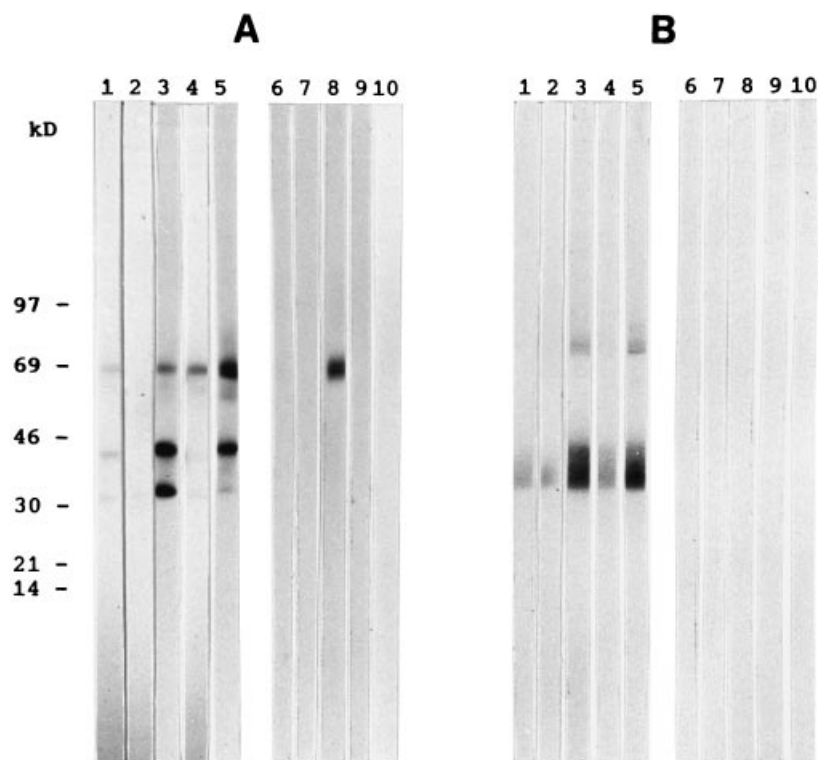


Fig. 1. IgE immunoblots with sera of the five patients. Molecular weights are given in kilodaltons (kDa). A. Wheat, B. Rye. Strips 1–5 alcohol-soluble extract and 6–10 neutral/acidic extract. IgE detection with ^{125}I -labelled anti-human IgE.

Neutral/acidic protein extracts

The flour samples of wheat, rye, barley and oats were extracted as previously described [12]. The protein content of each sample was determined [13] and the extracts were used in SPT and immunoblotting.

Purified gliadin

Commercial gliadin (BDH, British Drug Houses, Poole, UK) was dissolved in a mixture of equal volumes of 96% ethanol and albumin diluent and centrifuged at 10 000 rpm for 30 min. Then a sample of the supernatant was suspended with an equal amount of 85% glycerol and sterile filtrated through 0.22 μm Millipore filter to get the 1 mg/mL solution for SPT.

Ethanol-soluble protein extracts

The ethanol-soluble proteins (prolamins) of cereal flours, wheat, rye, barley and oats, were prepared as previously described [9]. The flours were defatted with water saturated butanol, air dried, extracted with 70% ethanol, centrifuged at 3000 rpm and then at 10 000 rpm. The supernatants were dialysed against 1% and 0.1% sodium chloride. The formed prolamins containing sediments were redissolved in 70% ethanol and the protein content was measured [13].

Skin-prick tests and tests for physical urticaria

SPTs were performed with a panel of commercial common inhalant allergens (ALK, Allergologisk Laboratorium, Copenhagen, Denmark), with foods including fresh vegetables, fruit, milk and egg and commercial fish, shrimp and nut allergens (1:20) (ALK, Copenhagen, Denmark). SPTs with the flour suspensions and gliadin were carried out also on the 27 control patients. Histamine chloride (10 mg/mL) served as the positive and the vehicle as negative control. All five patients were also tested for temperature-induced urticaria incubating an ice cube or +42°C warm water for 20 min on the forearm and for exercise-induced urticaria by performing an exercise test with a bicycle ergometer, in which the load was increased from 60 to 100 W within 30 min with pulse rate increase up to 120/min. Also intradermal skin testing with methacholine chloride 1 mg/mL was carried out. Dermographic urticaria was evaluated after application of firm pressure and friction to the skin.

Sodiumdodecylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotting

Pooled neutral and acidic extracts (0.75 mg/26 mm slot) and prolamins (0.32 mg/26 mm slot) of wheat, rye, barley and oats

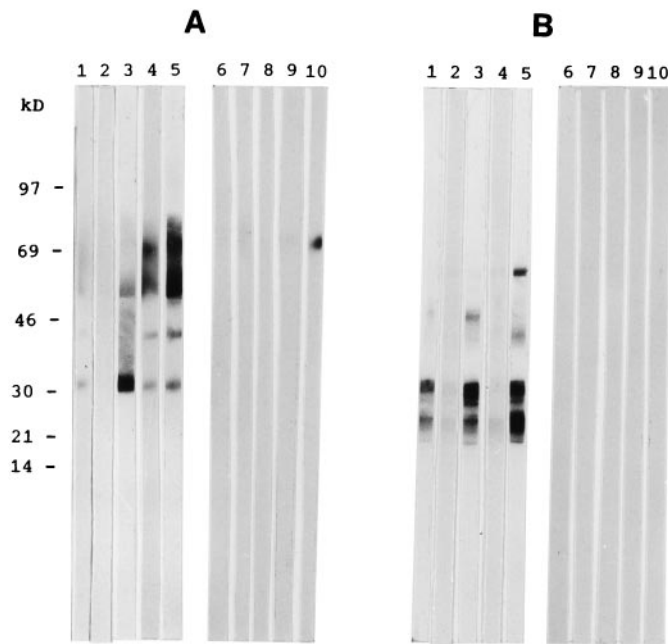


Fig. 2. IgE immunoblots with sera of the five patients. A. Barley. B. Oats. Strips 1–5 alcohol-soluble extract and 6–10 neutral/acidic extract. IgE detection with ^{125}I -labelled anti-human IgE.

and molecular weight markers (Rainbow, Amersham, UK) were separated by SDS-PAGE as described [14]. The proteins were transferred to nitrocellulose sheets (Schleicher & Schnell, $0.2\ \mu\text{m}$, Dassel, Germany) in a Transphor apparatus (LKB, Bromma, Sweden) as previously described [11].

Results

SPT and RAST

Table 1 shows the results from SPTs and the specific RAST values for cereals and gluten in the five patients. All SPT results with allergens other than cereals were negative, except for the one female patient who had a history of shrimp allergy. The vehicle controls were negative. The RASTs to foods, other than cereals, were negative. The SPTs with wheat were positive in 21 and with gliadin in three of the 27 AD control patients.

Tests for physical urticaria

Bicycle ergometry did not produce urticaria or anaphylaxis in any of the patients. However, all had positive ice cube test compatible with cold urticaria. One patient had positive methacholine chloride skin test suggesting cholinergic urticaria. The tests with warm water and for dermographic urticaria were negative.

Immunoblotting

Several ethanol-soluble cereal proteins (prolamins) bound IgE from the patient sera in immunoblotting (Figs 1 and 2).

In contrast, only two positive IgE-stained bands were seen in the neutral/acidic fractions.

Dietary treatment

The patients have now been followed for 3 years and none have experienced any severe reactions. Four of the five patients have adhered strictly to the gluten-free diet. One patient kept the diet for 6 months but then discontinued it. He was totally symptom-free during the diet but on resuming an ordinary diet he has had urticarial flares again. However, he has learned to avoid eating, especially cereal-containing food products, before exercise and has not experienced any severe exercise-associated anaphylactic reactions. One female patient experienced relief in unexplained abdominal pain when she started the gluten-free diet. One male patient decided initially not to follow the prescribed diet for 4 months and avoided exercise only. He, however, started to experience episodes of urticaria, which became more intense with time. Then he started a strict gluten-free diet and became symptom-free.

Discussion

Patients who have recurrent, unexplained, severe urticaria and anaphylaxis are at risk of a lethal outcome because of anaphylactic shock. The present patients had repeatedly visited general practitioners and emergency treatment units over several years but the underlying cause had remained unknown.

Cereals may give rise to hypersensitivity reactions if inhaled or ingested and may cause baker's asthma, coeliac disease and dermatitis herpetiformis [15,16]. Baker's asthma is mediated by IgE antibodies, which are mainly directed to albumins and globulins, proteins soluble in neutral solutions [15,17]; the main allergens are 12–15 kDa proteins found by IgE immunoblotting [18]. Wheat gliadin, the ethanol-soluble protein, has been mainly linked to dermatitis herpetiformis, a blistering skin disease, and to coeliac disease. In these diseases IgA antigliadin antibodies mark mucosal damage [16,19].

The present five patients with exercise-induced anaphylaxis reacted initially in SPT to a NaCl suspension of wheat. This suspension is a mixture of different allergens of wheat. Most of the AD patients had also a positive SPT with NaCl wheat suspension. However, in contrast to AD patients who typically have many positive SPT reactions against a variety of inhalant and food allergens, the patients with exercise-induced anaphylaxis in our study reacted exclusively to cereal allergens. We could confirm by the sensitive immunoblotting method that the IgE antibodies of these patients were directed against the ethanol-soluble fractions. Thus gliadin turned out to act as an allergen. Consequently, gliadin not only results in an IgA and IgG antibody response in dermatitis herpetiformis and coeliac disease, but can initiate an IgE response and cause life-threatening anaphylactic reactions in association with exercise. The patients also showed positive test results to the other taxonomically closely related cereals, rye, barley and oats. Rice, corn, millet and buckwheat are not such close relatives and they were negative in SPT and RAST and are allowed in the gluten-free diet.

Due to the severe history of our patients we did not carry out provocations with gluten or gliadin and exercise due to ethical reasons. The histories of exercise-induced anaphylaxis in association with eating, especially cereal flour-containing food products, the positive SPT, RAST and immunoblotting to cereals, the excellent response to a gluten-free diet, all confirmed the diagnosis of the present patients. Although cereal-dependent exercise-induced anaphylaxis has been described only rarely it may still not be a rarity. A simple SPT with a NaCl suspension of wheat flour and with gliadin identified easily the cereal allergy in the present patients. Therefore, we recommend including wheat suspension and gliadin to a SPT food panel when examining patients with a history of recurrent urticaria and anaphylaxis.

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