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Exercise-induced Urticaria and Anaphylaxis

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Five patients with exercise-induced anaphylactoid reactions are reported. Because of a growing interest in physical exercise and the severity of the symptoms it is important to recognize this condition, even though rare. All of our 5 patients had a history of urticaria and anaphylaxis in association with physical stress, but it seems difficult to induce anaphylactoid reactions under laboratory conditions. Two different clinical patterns could be distinguished in these patients. Three had the anaphylactoid form with signs of alternative complement pathway activation, while 2 patients had the variant form presenting first as cholinergic urticaria and progressing to angioedema and vascular collapse. The latter patients had elevated plasma histamine levels during challenge, but no sign of complement activation was observed. Our findings suggest differing pathomechanisms for these two forms. ***Key words: Physical exercise; Anaphylactoid reactions; Complement activation; Histamine.***

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Exercise-induced anaphylaxis is regarded as a distinct though rare form of physical allergy (1–8). Atopic patients seem to be more predisposed as also are patients with food allergy (5, 6). The reaction begins with sensations of cutaneous warmth, pruritus and erythema and progresses subsequently to urticaria, angio-edema, often associated with respiratory distress and vascular collapse (3).

We report on 5 patients with exercise-induced reactions: 3 patients with exercise-induced anaphylaxis and 2 with exercise-induced cholinergic urticaria and angio-edema. All 5 patients underwent exercise challenge under laboratory conditions.

The purpose of this study was to further differentiate these two entities from each other by studying clinical manifestations, pulmonary function, plasma histamine levels and complement activation during appropriate provocation tests.

PATIENTS AND METHODS

The series constituted 5 patients, 4 men and one woman (Table I). Routine laboratory tests (white blood cell count, differential count, erythrocyte sedimentation rate, Cl inhibitor level and IgE level (Phadebas Ig-E test, Pharmacia AB, Uppsala, Sweden) all showed normal results. The patients underwent a controlled period of physical stress using bicycle-ergometer exercise in the Pulmonary Physiology Laboratory of the University of Helsinki. The load was gradually increased from 0 to 50, 100 and 120–150 to 200 W within periods of 4–6 min and during a total period of approximately 30 min. Before and once during the challenge, pulmonary function tests were performed including : forced expiratory vital capacity (FEVc), forced expiratory volume in one second (FEV 1), peak expiratory flow (PEF) and maximum expiratory flow volume (MEFV).

Blood samples were collected prior to and during the exercise at 5, 10, 15, 30, 45 and 60 min for following purposes: Histamine content was determined blind on frozen (−70°C) aliquots of plasma by radio-isotopic-enzymatic assay, as described by Dyer and co-workers, with a normal value of 0–7 nmol/l (9). Complement C3 and C4 levels were measured with a nephelometric assay using a Behring Laser Nephelometer (Behring Institute, West Germany). The quantitative level of complement factor B was measured from serum samples stores at −70°C using single radial immunodiffusion, as described earlier (10). The examination was performed blind at the same time from all samples from the same patient. The reference value for factor B was derived from 200 blood donors, giving a mean of 0.145 + 0.06 g/l. Controls were 2 healthy individuals exposed to physical stress in the open air by letting them run up and down the same hill and in the same way as described for Case no. 3. Both control subjects showed slightly increased plasma histamine values 5–10 min after starting the exercise (up to 10 nnmol/ml), but there was no change in the serum B factor levels.

CASE REPORTS

Case 1

A female student had a 2-year history of anaphylaxis which arose after jogging. Symptoms began after jogging for about 10–15 min, with pruritus and generalized urticaria followed by dizziness, respiratory distress and swelling of eyelids and lips. After her first attack she had an episode about twice a month, sometimes provoked by cold weather. The symptoms cleared up usually after 1 h. Angio-edema of the eyelids and lips persisted for several hours, sometimes 1–2 days.

The patient was challenged in the laboratory with bicycle

Table I. *Clinical symptoms in the 5 patients with exercise-induced anaphylaxis*

Cases... ...	No. 1		No. 2		No. 3		No. 4		No. 5	
Sex...	F		M		M		M		M	
Age at onset...	20		17		19		16		17	
Duration of symptoms, yrs	2		3		2		2		4	
Clinical symptoms	A	B	A	B	A	B	A	B	A	B
Warmth	+	+	+	−	−	−	+	+	+	+
Pruritus	−	−	+	+	+	−	+	+	+	−
Erythema	+	+	+	+	+	+	+	+	+	−
Urticaria	+	−	+	−	+	+	+	+	+	−
Angio-edema	+	−	+	−	+	−	+	−	+	−
Dizziness/vertigo	+	−	±	±	±	±	−	−	±	−
Gastrointest. pains	−	−	−	−	−	−	−	−	+	−
Nausea	−	−	−	+	+	+	−	−	−	−
Diarrhea	−	−	−	−	−	−	−	−	−	−
Respiratory distress	+	−	+	−	−	−	+	−	+	−
Larynx stridor	−	−	+	−	−	−	−	−	−	−
Hypotonia	?	−	?	−	+	+	+	+	−	−
Choking	−	−	−	−	+	+	−	−	+	−
Collapse	+	−	+	−	+	−	+	−	−	−
Tireness	+	+	+	+	+	−	+	−	−	−
Headache	+	+	+	+	−	−	−	−	−	−
Associate findings										
Atopy	−		+		−		+		−	
Seasonal variation	−		+		−		−		−	
Methacholine skin test	−		−		+		−		+	
Prick tests	−		−		−		+		+	
Change in										
Plasma histamine level	No		No		Increase		No		Increase	
Plasma factor B level	Decrease		Decrease		No		Decrease		No	

A = during spontaneous attacks.
B = during challenge with exercise bicycle in laboratory.

ergometer exercise. The strain was gradually increased from 10 to 120 W during 35 min. After 4 min at 120 W the test was interrupted because of weakness in her legs. She felt exhausted and experienced erythema and a burning sensation on her face. There was no urticaria but itching and erythema appeared also around her neck and upper chest about 40 min after starting the challenge. The response to physical strain was estimated to be 66% off the normal value for her age (she had avoided training for several months before the challenge). The pulmonary function tests were normal.

The plasma histamine level did not rise during the challenge. Serum B factor levels were found to be decreased 45–50 min after starting the challenge, whereas complement C3 and C4 levels were normal, indicating activation of the alternative complement pathway simultaneously with clinical symptoms. She was treated with antihistamines, without effect. Treatment with low doses of danazol was started and after that the patient reported that she had been able to walk briskly but had avoided jogging.

Case 3

A male student with a 2-year history of generalized urticaria with small punctate wheals following physical exercise and emotional stress. He has had episodes at least twice a month following physical exercise or sweating and by and by he began to experience dizziness and nausea in association with exercise. He was first challenged by dipping one arm in warm water. The test was started with + 37°C water, which gave a negative result until the temperature of the water raised to + 42°C. About 6 min after starting the test, erythema was noticed around the neck and upper chest and soon afterwards he became pale, cold-sweated and felt nausea. Small papular urticaria surrounded by erythema was seen over the whole body, progressing to angio-edema. His blood pressure fell and the pulse was over 100.

The provocation was stopped and adrenalin was administered. During the provokation there was no change in the serum B factor or complement C3 or C4 levels, but there was an increase in plasma histamine concentration, from 1 to 42 nmol/l in 5 min and to 64 nmol/l in 5 min after starting the provocation. A new increase up to 21 nmol/l was observed after 2 h, without clinical manifestations.

The patient was then tested with bicycle ergometer exercise in the laboratory. During the challenge he developed

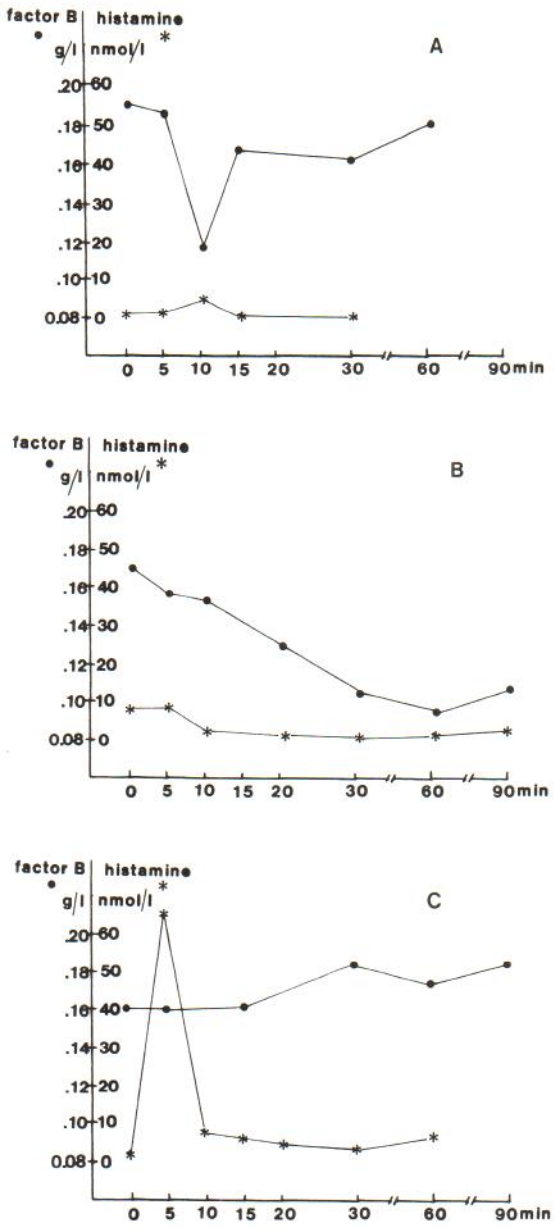

Fig. 1. Factor B (upper curves •–•–•) and histamine (lower curves ✳–✳–✳–) concentrations during challenge in 3 of the patients with exercise-induced anaphylaxis and urticaria: A and B with anaphylactoid form and C with variant form (A presents case no. 4; B, cases 1 and 2; C, cases 3 and 5).

only erythema and a few transient wheals on the upper trunk. The pulmonary function tests were normal. There was no significant change in the serum factor B level. The patient also had a history of generalized urticaria following emotional stress, for example before student examinations. The patient was subjected to emotional stress by applying certain psychological tests, performed by a psychologist. During the tests he developed generalized urticaria in about 15 min. He also developed urticaria during a deliberatedly unsuccessful attempt to place an indwelling catheter. About 30 min after beginning the operation he became pale, felt uneasy and complained of nausea and of stinging sensation in his skin. After 10 min he developed generalized urticaria. At the same time there was a rise in the plasma histamine concentration to 35 nmol/l. There was no change in complement C3, C4 or factor B levels.

Case 4

A schoolboy with an atopic background, but no previous history of collapse or urticaria. At the age of 16 he developed anaphylaxis after jogging for about 15 min. During the following year he had an episode about once a month, provoked by exercise, mostly after a meal or after sauna bathing. He had generalized urticaria, swelling of the eyelids, lips and fingers, associated with paleness, dizziness and palpitation. The symptoms developed usually within 15–20 min and cleared up after 2 h, except the swelling which could persist for up to 2 days.

He was exposed to physical stress with ergometer bicycle exercise. After the strain had been gradually increased from 50 to 100 W, he developed urticarial rash around the neck and upper chest in 3 min. The strain was increased to 150 W and further to 200 W. After 5 min at 200 W he complained of extreme tiredness and the test was interrupted and after 3 min the urticaria had disappeared and the patient felt well. His response to physical strain was regarded as normal and there was no significant change in the pulmonary function tests during the challenge.

Histamine and B factor levels were examined before and during the challenge. There was no change in the plasma histamine levels but about 10 min after starting the exercise there was a marked decrease in factor B level (Fig. 1A) in the serum. C4 or C3 levels were normal, indicating an activation of the alternative complement pathway. The patient was also challenged to physical stress in open air by letting him run up and down a hill. The test was first performed before taking a meal, with a negative result, and then soon after a meal. After running for about 6 min he complained of an odd feeling and 4 min later of itching and sudden generalized urticaria developed followed by swelling of the eyelids, lips and fingers. The blood pressure was very low and the pulse 110/min. Adrenalin and hydrocortisone were administered and he recovered in a few minutes. There was no change in the plasma histamine level but serum B factor level showed a smiliar decrease as shown in Fig. 1A.

RESULTS

The cinical findings in the 5 cases of exercise-induced anaphylaxis during spontaneous and induced attacks are presented in Table I. Symptoms developed after jogging for 10 to 15 and up to 30 min. The first symtomps were itching or a stinging sensation of the skin followed by erythema around the neck and upper chest, developing to generalized urticaria.

Subsequently angio-edema of the eyelids, lips and fingers developed. All 5 patients had a history of urticaria and anaphylaxis in association with physical stress but none of them developed an anaphylactoid reaction when they were challenged in the laboratory using a bicycle ergometer, increasing the load gradually over a period of 30–45 min. Serum C4, C3 and factor B levels and plasma histamine were determined before and at regular intervals during the exercise challenge. A depressed serum factor B level was recorded for 3 patients during the challenge tests, whereas their serum C3, C4 plasma histamine levels remained unchanged. In one patient there was a remarkable decrease in 10 min (Fig. 1A) and in the other 2 patients after 50 to 60 min (Fig. 1B). An elevated plasma histamine level (Fig. 1C) during challenge was found in 2 patients in whom serum factor B levels remained unchanged.

DISCUSSION

Interest in exercise-induced physical allergy, asthma and urticaria with anaphylactoid reactions has been growing, parallel to the recent interest in physical exercise. Anaphylactoid reactions are potentially life-threatening and it is therefore important for a physician to recognize them. Exercise-induced reactions with cutaneous manifestations have been classified in three different clinical patterns (1, 3).

1) Classic cholinergic urticaria is the most common form. It can be readily elicited by bicycle exercise, warm bath, shower or sauna, without evidence of vascular collapse (1). One-third of the patients display a positive reaction in the methacholine skin test (3).

2) A variant form in which exercise-induced attacks begin with punctate urticaria, progressing to angio-edema and vascular collapse (1, 2). Both classic cholinergic urticaria and the variant form are characterized by small wheals surrounded by erythema and are evoked by exercise or an increase in body temperature, elicited for instance by a warm bath or sauna (1, 3, 7, 8).

3) The anaphylactoid form is characterized by rather larger urticarial wheals than in cholinergic urticaria. The reactions could not be provoked by increasing the body temperature by warm bath or sauna (1). According to the diagnostic criteria proposed by Sheffer & Austen (1), 3 of our 5 patients had the anaphylactoid form and the other 2 had the variant form. One of these 2 was a young schoolboy (case no. 3) in whom we could induce urticaria and vascular collapse in three different ways, namely by dipping an arm in warm water, by bicycle-ergometer exercise and by causing emotional stress.

During the challenges, elevated plasma histamine concentrations were found, correlating to clinical symptoms. There were no signs of complement activation. Analogous to previous reports, we found it difficult to induce anaphylactoid symptoms under laboratory conditions (5). Interestingly, the 3 patients with the anaphylactoid form showed signs of alternative complement pathway activation when exposed to exercise. One of them showed a rapid decrease in serum B factor level in 10 min at the same time as the clinical symptoms appeared. The other 2 patients showed a decrease after 50–60 min, correlating to clinical symptoms such as feeling of sudden exhaustion, stinging sensation in the skin and erythema of the face, neck and upper chest persisting for several hours. Sheffer and co-workers found an elevated serum histamine level in their patients during an exercise challenge and there was a correlation with clinical symptoms such as itching, flushing erythema, headache and vertigo (1, 5). Complement activation was not studied in their patients. In contrast to their findings, none of our 3 patients with pure anaphylactoid form showed elevated plasma histamine levels during exercise challenge.

Our findings support the concept that there are at least two distinct forms of exercise-induced urticaria in which different pathomechanisms are involved. We have shown a decrease in the factor B level during exercise-induced anaphylaxis whereas the complement C4 and C3 levels remained normal, indicating the activation of the alternative complement pathway. Activation of the complement cascade leads to the emergence of complement split products C3a, C4a and C5a. It is known that especially the late complement protein C5a is a potent anaphylotoxin, causing increased vascular permeability and degranulation of mast cells (11) and consequently leading to anaphylaxis, as in the case of our 3 patients.

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