

CASE REPORT

A case of cold-dependent exercise-induced anaphylaxis

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Summary

Exercise-induced anaphylaxis (EIA) is a form of physical urticaria that is induced by exercise. A 16-year-old Japanese boy had a 4-year history of recurrent wealing and dyspnoea after physical exercise such as jogging, playing handball or riding a bicycle in winter. The episodes were not associated with ingestion of foods including wheat or soya bean. A provocation test, with 15 min of exercise and 2 min of cold stimulation immediately before or immediately after the exercise, elicited a weal that was localized to the test area. A challenge test with ingestion of boiled soya beans and exercise did not elicit a weal. Therefore, in this case, cold exposure, but not food ingestion, was essential for inducing EIA. Cold-dependent EIA is different from cold urticaria, food-dependent EIA, cholinergic urticaria and cold-induced cholinergic urticaria, and may be a distinct entity.

Key words: cholinergic, cold, exercise-induced anaphylaxis, food-dependent exercise-induced anaphylaxis, urticaria

Exercise-induced anaphylaxis (EIA) is classified as a form of physical urticaria induced by exercise.¹ In EIA, as in other allergic diseases, mast cells may play an important role by releasing histamine, leukotrienes and prostaglandins.² However, its pathological mechanism is still not clear. Many factors, such as food ingestion, medication and the menstrual cycle, are reported to be associated with EIA.³ Of these, food ingestion is the most common predisposing factor for EIA (food-dependent EIA; FDEIA). We report a patient with EIA in whom a provocation test with cold stimuli and physical exercise elicited weals, whereas food ingestion was not associated with the EIA.

Case report

A 16-year-old Japanese boy was admitted to the Department of Dermatology, Ehime University School of Medicine (Ehime, Japan) with a history of recurrent generalized urticaria and dyspnoea. Since 12 years of age, he had suffered urticaria and dyspnoea after physical exercise such as jogging, playing handball or

riding a bicycle; these episodes only occurred between December and February. He bicycled to school between 07:00 and 08:00 h, when the temperature was 2–6 °C, according to local meteorological records; the temperature during the other exercise sessions was unknown. Exercise of more than 5 min induced a feeling of tingling or irritation that lasted 5–10 min. Itchy weals that often exceeded 3 cm in diameter then started to appear on the thigh and abdomen, and frequently spread over his entire body, in which case dyspnoea with wheezing occurred in about half of the episodes. The weals lasted 10–40 min. Hot baths and unpleasant emotional stimuli did not elicit wealing. He had taken no drugs known to be associated with anaphylactic reactions, such as non-steroidal anti-inflammatory drugs. He had no relevant past medical history, and his family history was unremarkable. At the age of 14 years, radioallergosorbent testing (RAST) for specific IgE antibodies had revealed a positive reaction for soya bean. Since then, he had not eaten food containing soya beans, except for soy sauce, and food ingestion was not associated with the occurrence of symptoms. Physical examination was normal. Laboratory findings included the following: white blood cell count $7.1 \times 10^9 \text{ L}^{-1}$ with 2.6% eosinophils; total serum IgE

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83 U mL⁻¹; normal serum electrolytes, liver function tests, creatinine, blood urea nitrogen, C3, C4 and CH50; negative cryoglobulin and cryofibrinogen.

Skin prick tests with various food allergens (Torii Pharmaceutical Co. Ltd, Tokyo, Japan) produced weal and flare reactions to soya bean and crab, but not to shrimp, rice, beef, wheat, egg white or buckwheat. RAST for specific IgE antibodies revealed class 3, 2, 1 and 1 reactivity for house dust mite, rye, shrimp and crab, respectively. RAST for soya bean, wheat, buckwheat, rice, egg white, egg yolk, milk and cod was negative.

A diagnosis of cold urticaria, EIA or FDEIA was suspected, so the challenge test described below was carried out.

Provocation test

Exercise challenge tests were undertaken on different days, after 6 h of fasting. Six tests were performed (Fig. 1).

- 1 Cold stimulation test: a plastic bag of frozen gel was placed on the flexor aspect of the forearm. After 2 min, the bag was removed, giving a local temperature on the forearm of -1°C , as measured by thermography.
- 2 Exercise challenge alone: bicycle ergometer at 150 W for 15 min.
- 3 Exercise challenge immediately after a 2-min cold stimulation test.

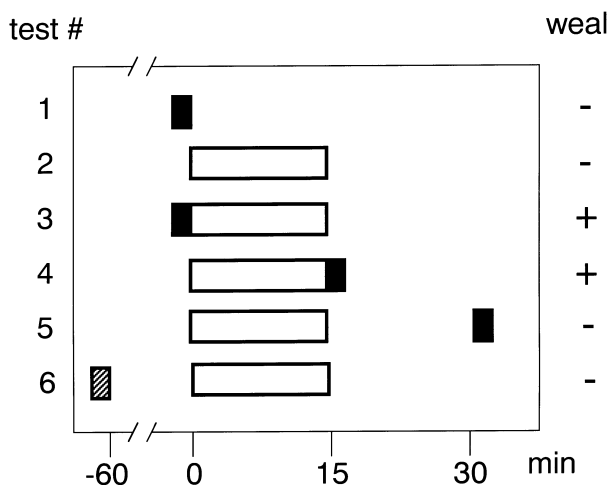


Figure 1. Provocation tests. Closed bar: cold stimulation test. Frozen gel in a plastic bag was placed on the flexor aspect of the forearm. After 2 min, the gel was removed, and the local temperature was -1°C . Open bar: exercise challenge test with bicycle ergometer at 150 W for 15 min. Hatched bar: ingestion of 50 g of boiled soya bean.

- 4 Exercise challenge immediately before a 2-min cold stimulation test.

- 5 The 2-min cold stimulation test was carried out after the 15-min exercise challenge and a subsequent 15 min rest.

- 6 The exercise challenge was carried out 1 h after ingesting 50 g of boiled soya bean without any additives except for soy sauce.

Only tests (3) and (4) provoked a giant weal, which was localized to the cold stimulation test area (Fig. 2). The weal lasted up to 10 min. To provoke a weal, cold stimulation was required immediately before or immediately after the exercise. Resting for 15 min decreased the responsiveness.

White blood cell count, percentage eosinophils, serum C3, C4, CH50 and plasma histamine levels were determined before and after the challenge tests; however, there were no significant changes with any of the challenges.

Discussion

In more than half of EIA patients, ingestion of an associated food precedes exercise by several hours.⁴ Various foods, such as shellfish, alcohol, tomato, cheese, celery, wheat and nuts, are reported to be associated with FDEIA.^{3,4} Wheat is the food that most frequently causes FDEIA in Japan.^{5,6} In our patient, however, episodes were not associated with ingestion of foods including wheat or soya bean, and the provocation test that combined soya bean ingestion and exercise did not elicit a weal. Only the combination of exercise and cold stimulation elicited a weal. This was reproducible, and no other factors were required.



Figure 2. A giant weal, provoked by test 3 in Figure 1. The weal was localized to the cold stimulated area.

Therefore, in our patient, cold exposure alone was a sufficient predisposing factor for EIA to elicit a weal.

EIA is generally related to heat,¹ although cold-related FDEIA has also been reported.⁷ In an epidemiological study of 199 patients with EIA, cold was a cofactor for EIA in 23% of the patients.⁸ Furthermore, in a questionnaire study of 279 patients with EIA, 44% reduced the incidence of attacks by avoiding exercise during extremely hot or cold weather,⁴ indicating that exposure to cold can be a cofactor for EIA. However, precise provocation tests, such as ours, have not previously been performed for these patients, and patients similar to ours may have been included in the previous reports.

Cholinergic urticaria is associated with sweating.¹ Although EIA used to be reported as a component of severe cholinergic urticaria,⁹ it appears to be a distinct entity.^{10,11} EIA can be distinguished from cholinergic urticaria by passive heat challenge.¹¹ After a passive heat challenge that increases core body temperature by more than 0.7 °C, only patients with cholinergic urticaria develop an anaphylactic reaction. We excluded cholinergic urticaria as a diagnosis because: (i) the weals rapidly developed into giant weals; (ii) warm stimuli alone, such as a hot Japanese-style bath, did not elicit weals; (iii) exercise alone did not induce weals; and (iv) sweating seemed to be irrelevant.

There is another unusual form of cholinergic urticaria, termed cold-induced cholinergic urticaria.^{12–14} In cold-induced cholinergic urticaria, cooling the body in a cold room at 4 °C provokes generalized urticaria that is indistinguishable from cholinergic urticaria,¹² while a local ice-cube test is negative. As the weal provoked in our patient was localized to the area of the cold stimulation test, he did not have cold-induced cholinergic urticaria.

In conclusion, we report a patient with cold-dependent EIA that was not cold urticaria, FDEIA, cholinergic

urticaria or cold-induced cholinergic urticaria, and may be a distinct entity. If cold exposure is suspected as a predisposing factor for EIA, a precise provocation test, such as the one that we used, may aid diagnosis.

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