Anaphylaxis Induced by Exercise or Cold Stimulation with Hyperleukotrieneuria During a Challenge Testing Not Containing Food Ingestion

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Case report

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Abstract

**Background:** Exercise-induced anaphylaxis (EIA) is rare and a potentially life-threatening disorder that can develop independently without food ingestion. Cold drinks can also trigger symptoms in some patients with cold-induced anaphylaxis. We present the case of a patient with exercise and cold-induced anaphylaxis that was diagnosed based on hyperleukotrieneuria in exercise loading and cold-drink challenge testing.

**Case presentation:** A 12-year-old girl presented with acute flushing, cyanosis, swollen eyelids, and dyspnea after an endurance run in winter or swimming in a cold-water pool. She also developed dyspnea after having a cold drink. She had no history of food allergies or atopy. No association was noted between anaphylaxis and food intake in her history. On the 1st day, she ingested 200 mL cold water at a temperature of 5°C in 30 s, which did not trigger any symptomatic responses, but urinary LTE4 level increased (pre-challenge test 295 pg/mg.cr, post-challenge test 400 pg/mg.cr). On the 2nd day, she underwent the exercise loading test according to the Bruce protocol by increasing the power of exercise every 2 min using an ergometer. She had been fasting for >15 h and did not have breakfast. Just after the exercise loading test, the plasma adrenaline and noradrenaline increased. At 15 min after the exercise loading test, the plasma adrenaline and histamine (pre-challenge test 0.7 ng/mL, 15 min post-challenge test 81 ng/mL) rised sharply with anaphylaxis symptom accompanied by increasing of urinary LTE4 (pre-challenge test 579 pg/mg.cr, post-challenge test 846 pg/mg.cr). After she was discharged, she was restricted from strenuous exercise especially in cold environments and prescribed an adrenaline autoinjector.

**Conclusion:** To our knowledge, cold stimulation becomes a co-effector for EIA. Measurements of urinary LTE4 levels during challenge testing are useful to diagnose anaphylaxis induced by exercise or cold stimulation.

**Background**

Exercise-induced anaphylaxis (EIA) is a potentially life-threatening disorder that can develop independently or in combination with food ingestion as food-dependent EIA (FDEIA). EIA without food ingestion is rare; few studies have reported positive challenge test results with elevated objective marker levels in patients with EIA [1]. Cold drinks can also trigger symptoms in some patients with cold-induced anaphylaxis.

Conversely, mast cells may play a role in cysteinyl leukotriene (CysLT) generation during anaphylactic reactions [2]. Urinary leukotriene E4 (LTE4) is the most reliable analytic parameter to monitor endogenous CysLT synthesis. We herein present the case of a patient with exercise and cold-induced anaphylaxis that was diagnosed based on hyperleukotrieneuria.

**Case Presentation**
A 12-year-old girl presented with acute flushing, cyanosis, swollen eyelids, and dyspnea after an endurance run in winter or swimming in a cold-water pool. She also developed dyspnea after having a cold drink. She had no history of food allergies or atopy. No association was noted between anaphylaxis and food intake in her history.

Laboratory assessment during the asymptomatic period revealed the absence of peripheral eosinophilia (white blood cell count, 5150/µL with 2% eosinophils) and total immunoglobulin (Ig) E level of 1255 IU/mL. Specific quantitative IgE testing with ImmunoCAP® revealed that she was above class 2 for house dust, dermatophagoides, cedar pollen, and cat dander and negative for wheat, shrimp, and crab. Furthermore, skin prick test was negative for wheat, shrimp, and crab. Based on the symptomatic episode, she underwent a 2-day challenge test to measure urinary LTE4 levels before and 3 h after the test. Urinary LTE4 was quantified using a commercial enzyme immunoassay kit (Cayman) after purification using high-performance liquid chromatography.

On the 1st day, she was asked to ingest 200 mL cold water at a temperature of 5 °C in 30 s, which did not trigger any symptomatic responses. After the challenge test, the plasma catecholamine (adrenaline, noradrenaline, and dopamine) and histamine levels did not significantly alter (Fig. 1a and 1b), but her urinary LTE4 level increased (Fig. 1c, pre-challenge test 295 pg/mg.cr, post-challenge test 400 pg/mg.cr). On the 2nd day, she underwent the exercise loading test according to the Bruce protocol [3] by increasing the power of exercise every 2 min using an ergometer. She had been fasting for > 15 h and did not have breakfast. She developed acute flushing, cyanosis, swollen eyelids, dyspnea, and hypotension when the maximum loading reached 80 watts. Just after the exercise loading test, the plasma adrenaline and noradrenaline increased (Fig. 2a). At 15 min. after the exercise loading test, the plasma adrenaline and histamine (Fig. 2b, pre-challenge test 0.7 ng/mL, 15 min.post-challenge test 81 ng/mL) rised sharply with anaphylaxis symptom accompaed by increasing of urinary LTE4 (Fig. 2c, pre-challenge test 579 pg/mg.cr, post-challenge test 846 pg/mg.cr).

The diagnosis of EIA had to be distinguished from systemic mastocytosis, exercise associated laryngoesophageal reflux, cardiovascular disorders, cholinergic urticarial, and hypoglycemia. The episode was confirmed to be exercise and cold-induced anaphylaxis that was diagnosed based on hyperleukotrieneuria in the challenge test. Her serum tryptase level was 1.3 µg/L, within the normal range when she was asymptomatic.

The patient was treated with anti-LT receptor antagonists. During hospitalization, to improve her QOL related to exercise, training by exercise prescription was conducted. Two weeks later, it was confirmed to increase the exercise intensity without anaphylaxis. After she was discharged, she was restricted from strenuous exercise especially in cold environments and prescribed an adrenaline autoinjector.

**Discussion And Conclusions**

In the present case, anaphylaxis with hypotension developed after exercise without food intake, and it was accompanied with elevated levels of plasma histamine and urinary LTE4, both of which are clinical
markers of mast cell activation [4]. Histamine is immediately released by mast cell degranulation that is activated by C3a and others. Plasma histamine levels were reported to be elevated in patients with FDEIA who had a positive challenge test [5]. Conversely, CysLT is derived from mast cell membranes within minutes, and urinary LTE4 levels increase after a positive challenge test in anaphylactic patients [2].

The mechanism underlying EIA, especially that which is not caused by specific food exposure, has not been completely elucidated; however, several hypotheses have been proposed. First, reduced cellular pH in lactic acidosis due to supramaximal exercise is proposed to promote mast cell degradation and increase the propensity toward anaphylaxis [6]. Second, mild-to-severe exercise alters blood flow distribution, with a greater percentage of cardiac output going to active tissues such as skeletal muscle accompanied with a reduction in the blood flow to the visceral organs, primarily the stomach and intestines. Functional heterogeneity has been demonstrated in human mast cells from different tissues. Therefore, the quantity and spectrum of mediators released may differ across different locations as well as under different situations [7]. These hypotheses warrant further investigation by comparison of patients with EIA with healthy controls.

Notably, urinary LTE4 levels were reported to not increase after exercise in healthy children [8]. The urinary LTE4 level in the present patient increased in both exercise loading and cold stimulation despite the negative result with cold-water intake; in the past, the patient had developed cold-induced anaphylaxis with urticaria in the swimming pool. Generally, both mast cell and recruited basophils release histamine and other inflammatory mediators (prostaglandins, leukotrienes, and cytokines), leading to the activation of urticarial lesions. The same mechanism occurs systemically during cold-induced anaphylaxis. Interestingly, a study reported two patients with FDEIA who developed symptoms induced by physical exercise at cold temperatures [9]. However, the rate of anaphylactic reactions induced by cold stimulation in patients with EIA or FDEIA is unknown.

The present patient may have developed anaphylaxis induced by both exercise and cold stimulation. We found that plasma histamine levels transiently increased after exercise loading in this patient; however, this increase was not observed after cold-water intake challenge test, with no symptoms. Stringent criteria in selecting subjects as well as the performance of several times of provocation tests might be needed for detecting the transiently increased histamine levels, even in FDEIA provocation tests [5]. As cold-water intake stimulation specifically to the throat mildly activates mast cells and basophils, we could not determine the elevated plasma histamine levels. There are some successful reports of anti-IgE to treat EIA [1] and cold-induced anaphylaxis [10]. The mechanism by which non-specific IgE-dependent mast cell activation can be provoked by exercise, cold stimulation, or both of them in such cases is unclear. The established efficacy of anti-IgE in the treatment of allergic asthma and allergic rhinitis putatively reflects the depletion of free IgE from serum and tissue, ultimately leading to reduced binding of IgE to its high-affinity surface receptor FcεRI. Because the occupancy of FcεRI by IgE determines the levels of surface FcεRI expression, this leads to a rapid depletion of both cell-bound IgE and surface FcεRI expression on blood basophils and a more gradual depletion of these proteins from skin and other organs’ mast cells [11].
To our knowledge, cold stimulation becomes a co-effector for EIA. Measurements of urinary LTE4 levels during challenge testing are useful to diagnose anaphylaxis induced by exercise or cold stimulation. In future, other reports may be explored to elucidate the mechanism of non-specific IgE-mediated activation of mast cells, which can drive allergic reactions in patients with anaphylaxis induced by both exercise and cold stimulation, as further understanding of these mechanisms will be beneficial in improving the management.

**List Of Abbreviations**

Exercise-induced anaphylaxis (EIA), food-dependent EIA (FDEIA), cysteinyl leukotriene (CysLT)

**Declarations**

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Not applicable

**Author’s contributions**

CM and KI assessed the patient and performed the provocation tests in hospital. AS and HO contributed to the reviewing of manuscript. CM was the major contributor in doing the literature review and writing the manuscript. Authors read and approved the final manuscript.

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**Ethics approval and consent to participate**

The report was approved by the Ethics Board of the National Hospital Organization Fukuoka National Hospital (No.F2-40).

**Consent for publication**

Consent obtained from patient.

**Competing interests**

The authors declare that they have no competing interests.

**References**


Figures
Figure 1

Changes in plasma catecholamine (a), histamine levels (b) and urinary LTE4 levels (c) by cold-drink challenge testing.
Figure 2

Changes in plasma catecholamine (a), histamine levels (b) and urinary LTE4 levels (c) by the exercise loading test.

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