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Letter to the Editor

Fasting-associated urticaria and/or anaphylaxis: A case report

Dear Editor,

Anaphylaxis is a life-threatening systemic allergy with sudden onset. The prevalence is currently estimated at 0.05–2% in the USA and approximately 3% in Europe.¹ Frequent anaphylactic triggers include certain foods, venom, medications, natural rubber latex, and physical factors, including exercise, cold, heat, and sunlight. Anaphylaxis without an apparent trigger is classified as idiopathic anaphylaxis.² Here, we describe a case of a patient with fasting-associated urticaria and/or anaphylaxis.

A 6-year-old boy presented to our hospital with urticaria and other anaphylactic symptoms (Table 1, Episode number 2). He developed generalized urticaria and angioedema suddenly at 11:00 while attending class in school. Next, he had cough and nausea, which gradually worsened. Finally, he became drowsy and could not stand. His face became pale. In the hospital, he had tachycardia and slight hypotension. He was administered an intravenous drip injection of saline solution and hydrocortisone. He received antihistamine orally. His symptoms disappeared within several hours.

There was no history of food allergy, atopic dermatitis, bronchial asthma, mental disorder, or congenital metabolic disorder. There was also no family history of allergy. His physical and mental development was normal. His height, weight, and body mass index were 1.12 m, 21 kg, and 16.7 kg/m², respectively. Physical examination revealed no skin lesion, lymphadenopathy, or hepatosplenomegaly. White blood cell count, eosinophil count, basophil count, and total immunoglobulin E levels (IgE) were 15,000/μL, 240/μL, 15/μL, and 90 IU/mL, respectively. Allergen-specific IgE tests of ImmunoCAP fluorescent enzyme immunoassay (Thermo Fisher Scientific) were performed as per the manufacturer's instructions. The results were positive for ovomucoid, house dust, and house dust mites/*Dermatophagoides farinae* (0.57, 10.4, and 41.4 Ua/mL, respectively). Despite testing positive for ovomucoid, the patient consumed hen's eggs without any allergic reaction. The test was negative for all other suspected foods, including soybean, sesame, milk, wheat, rice, beef, peanuts, and latex. Moreover, he tested negative on the exercise challenge test, but it was performed without using aspirin. The C3 and C4 protein levels, C1 inactivator activity, and complement activities were normal; they were measured at rest not during urticaria or anaphylaxis. Thus, the patient was diagnosed with idiopathic urticaria and anaphylaxis. Treatment was initiated with standard daily doses of second-generation antihistamines, leading to a reduced number of urticaria and

anaphylaxis episodes. However, he occasionally developed urticaria and/or anaphylaxis symptoms during antihistaminic treatment. His mother had been noting the details. She eventually observed that his symptoms developed when he was hungry (Table 1).

After obtaining informed consent from the patient and his mother, a fasting challenge test was performed. It commenced after dinner, and the patient skipped breakfast the following day. After 16 h of fasting, at 11:00 on day 2, the patient developed urticaria, edema of the eyes and lips, and a swollen throat. He consumed bread and rice balls at 11:30 on day 2. The symptoms disappeared within 30 min without any medication. Whole blood histamine levels were 58.96, 14.18, and 40.51 ng/mL at 7:00, 11:00, and 13:00 on day 2, respectively. Levels of total ketone bodies, acetoacetic acid, and 3-hydroxybutyric acid were 56, 17, and 39 μmol/L, respectively, at 7:00 on day 2 and 935, 193, and 742 μmol/L, respectively, at 11:00 on day 2. At 13:00 on day 2, they recovered to 50, 30, and 20 μmol/L, respectively (Fig. 1). The patient consumed food more frequently and avoided fasting. This decreased the number of urticaria and/or anaphylactic episodes; antihistamine treatment was discontinued. When the patient began developing urticaria and/or anaphylactic symptoms, he consumed calorie-dense liquids or solids and the symptoms disappeared immediately.

To the best of our knowledge, this is the first case report of a patient with fasting-associated urticaria and/or anaphylaxis. This report highlighted two important points. First, fasting might be one of the factors triggering urticaria and/or anaphylaxis that was diagnosed as idiopathic thus far.

Second, whole blood histamine levels transiently decreased during the fasting challenge test. Yamaga *et al.* demonstrated a transient decrease of intracellular histamine in patients with anaphylaxis.³ Whole blood histamine levels correspond to intracellular histamine levels in basophils. Therefore, we considered that histamine levels in basophils transiently decreased. Yamaga *et al.* also demonstrated a reduced number of peripheral basophils in patients with anaphylaxis. It was speculated that the basophils migrate from the peripheral blood into the tissue.

Nevertheless, the mechanism through which fasting stimulates decrease of histamine in peripheral blood basophils is unknown. Misto *et al.* reported that the mast cells in mice contribute to fasting-induced ketogenesis control via a paracrine mechanism that involves secretion of histamine into the hepatic portal circulation.⁴ This article might be related to ours because urticaria and/or

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Table 1
Episodes with symptoms other than urticaria.

Episode #	Age	Skin and mucosal symptoms	Other symptoms	Treatment	Premedication	Hungry or not	Other
1	6 y 10 m	Generalized urticaria, angioedema	Nausea, cough	Antihistamine	No	Hungry	First anaphylaxis episode
2	6 y 11 m	Generalized urticaria, angioedema	Nausea, cough, difficult to maintain standing, drowsy, pale, tachycardia, slightly hypotension	Antihistamine, steroid	No	Hungry	First visit to our hospital
3	6 y 11 m	Generalized urticaria	Vomiting, fatigue	Antihistamine, steroid	Antihistamine	Hungry	
4	7 y 0 m	No skin symptoms	Nausea, fatigue, pale	Consuming foods	Antihistamine	Hungry	
5	7 y 1 m	Generalized urticaria	Tightness in throat, cough, drowsy	Antihistamine, steroid	No	Hungry	
6	7 y 6 m	Generalized urticaria	Drowsy, shivering	Antihistamine	Antihistamine	Hungry	
7	7 y 10 m	No skin symptoms	Nausea, fatigue, difficult to maintain standing	Consuming foods	No	Hungry	
8	7 y 10 m	Generalized urticaria, angioedema	Nausea, tightness in throat, fatigue, drowsy	Antihistamine, steroid	No	Hungry	
9	7 y 10 m	Generalized urticaria	Tightness in throat, cough, drowsy	Antihistamine	No	Hungry	
10	8 y 2 m	Generalized urticaria	Fatigue, pale	Consuming foods	No	Hungry	
11	8 y 3 m	Generalized urticaria, angioedema	Tightness in throat	Consuming foods	No	Hungry	Fasting challenge test
12	8 y 7 m	Generalized urticaria	Cough	Antihistamine, consuming foods	No	Hungry	
13	8 y 9 m	Generalized urticaria	Nausea, abdominal pain, tightness in throat, cough, fatigue, difficult to maintain standing, drowsy	Consuming foods	No	Hungry	
14	8 y 10 m	Generalized urticaria, angioedema	Tightness in throat, cough, chest tightness, fatigue, drowsy, tachycardia, slightly hypotension,	Consuming foods	No	Hungry	

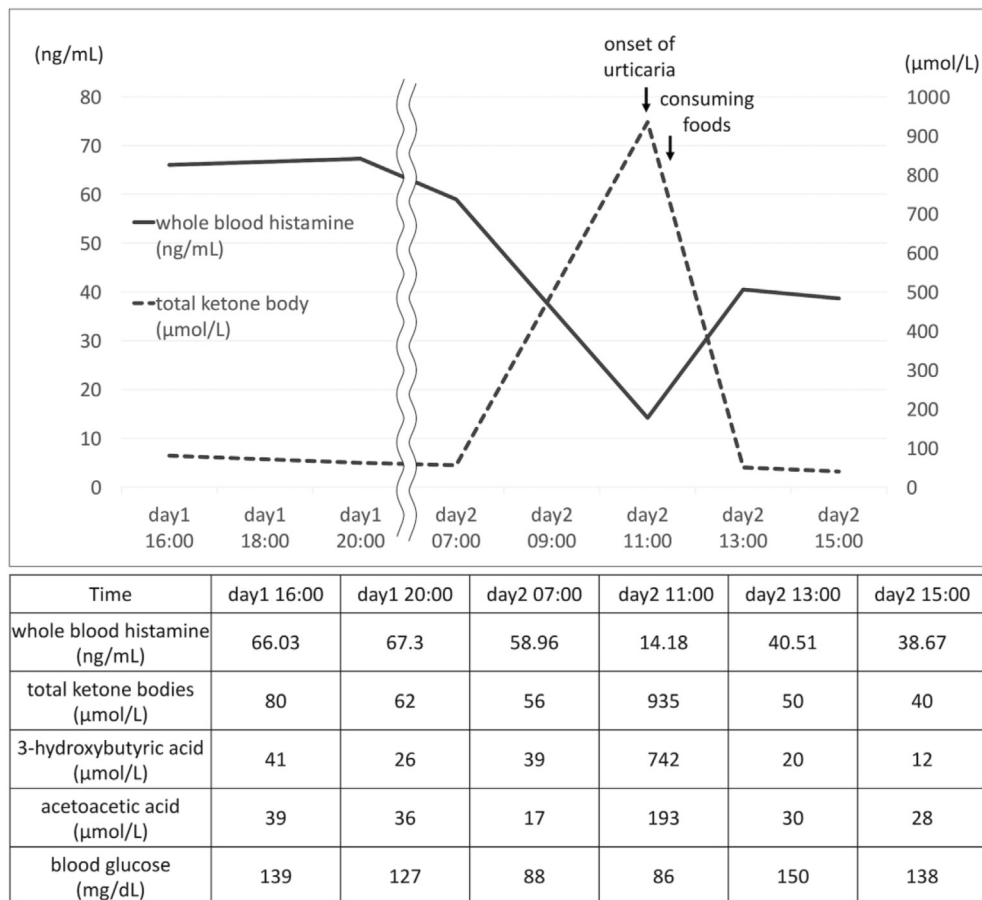


Fig. 1. This panel shows levels of whole blood histamine, ketone bodies, and blood glucose during the fasting challenge test. The normal range of whole blood histamine levels is unknown, but the median intracellular histamine level is 62.3 ng/mL [IQR, 46.0–85.1].³ The corresponding normal ranges of total ketone bodies, acetoacetic acid, and 3-hydroxybutyric acid are 0–131 μmol/L, 0–55 μmol/L, and 0–85 μmol/L, respectively. At 19:00 on day 1, the patient started fasting. At 11:00 on day 2, after 16 h of fasting, he developed urticaria. At 11:30 on day 2, he consumed foods, and his symptoms disappeared within 30 min.

anaphylaxis occurred only during the fasting condition, which generally stimulates hepatic ketogenesis. As shown in Figure 1, the development of urticaria coincided with the increase of ketone bodies. Thus, it is feasible that basophils release histamine and/or migrate into the skin when the rate of hepatic ketogenesis and levels of ketone bodies increase.

This report had some limitations. First, fasting provocation could not be blinded because of technical reason i.e., the patient was perhaps conscious of his hunger as he was made to fast. Second, some unknown factors could be the major causes triggering urticaria and/or anaphylaxis in this case. They might be present in basophils. Although most people fast for about 16 h, there has been no report of fasting-associated urticaria and/or anaphylaxis so far. Therefore, this case is quite rare. However, the factor triggering urticaria and/or anaphylaxis is common. Further studies are needed for understanding the role of basophils and the mechanism of the blood intracellular histamine level reduction because of fasting.

In conclusion, fasting might be one of the factors triggering urticaria and/or anaphylaxis; therefore, fasting-associated urticaria and/or anaphylaxis should be differentiated in the diagnosis of idiopathic urticaria and/or anaphylaxis.

Conflict of interest

The authors have no conflict of interest to declare.

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