

Cows Milk-Dependent Exercise-Induced Anaphylaxis under the Condition of a Premenstrual or Ovulatory Phase Following Skin Sensitization

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ABSTRACT

Background: A 24 year-old woman with atopic dermatitis occasionally developed symptoms, including dyspnea and generalized urticaria, following ingestion of food containing cows milk. Similar episodes had continued, and had been treated empirically since the age of 16 years.

Case Summary: Although a skin test and IgE RAST showed positive reactions to cows milk, a provocation test with cows milk alone did not induce any symptoms. Therefore, food-dependent exercise-induced anaphylaxis (FDEIA) was suspected, but examination using various combinations of cows milk, aspirin and exercise failed to elicit any symptoms. Finally, a provocation test during the ovulatory phase with cows milk followed by aspirin and exercise evoked systemic urticaria, dyspnea and hypotension.

Discussion: The symptoms against cows milk began when she took baths with bath salts containing cows milk as its main ingredient for one year at the age 15 years. Sensitization to cows milk through eczematous skin is indicated from this history. Hormonal change during a premenstrual or ovulatory phase is also an important factor for the development of FDEIA in this case.

KEY WORDS

atopic dermatitis, cows milk, cows milk allergy, FDEIA, menstrual cycle

INTRODUCTION

Food-dependent exercise-induced anaphylaxis (FDEIA) is a unique disorder caused by exercise after ingestion of food. Case reports of FDEIA were first reported by Maulitz *et al.*,¹ and are rapidly increasing in number since its definition by Kidd *et al.*² Many kinds of food have been identified as causes of FDEIA in past reports.³ Although any kind of food appears to be responsible for FDEIA, a recent study performed in Japan indicates that the type of food responsible has been comparatively limited.⁴ FDEIA caused by milk is very rare, and only one case has been found so far in the literature. Allergy to cows

milk is most frequently seen in the first year of life, which has been speculated to result from the fact that potential allergens such as β -lactoglobulin can pass through the immature gut mucosa of babies, but not through the mature gut mucosa of adults. Therefore, cows milk allergy is rare in adults. A retrospective study of 34 adult cows milk allergy cases revealed that cows milk allergy mainly occurs in females, and suggested that a sex-hormonal factor is involved as a trigger in adult cases of cows milk allergy.⁵ On the other hand, triggers for FDEIA (besides food and exercise) include multiple factors such as fatigue, sleep deficit, common cold, high humidity, low temperature or aspirin, but there have been few reports of a

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Table 1 Results of aspirin, cows milk, exercise-challenge tests

	At non-premenstrual or ovulatory phase	At ovulatory phase
Aspirin + Exercise	–	–
Aspirin + Cows milk + Exercise	–	+

– : No symptoms, + : Wheal and general symptoms such as systemic urticaria, dyspnea and hypotension

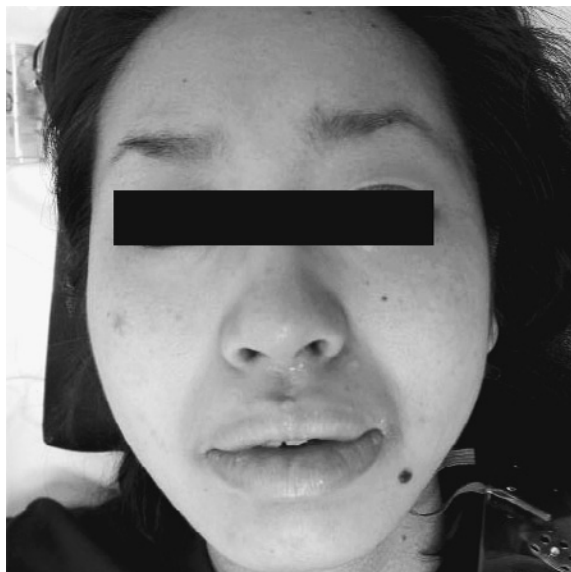


Fig. 1 The provocation test at the ovulatory phase with cows milk followed by aspirin and exercise evoked systemic urticaria, dyspnea and hypotension. The figure shows swelling of her eyelids and lips, lacrimation, and facial pallor.

sex-hormonal factor as a trigger for FDEIA. The development of cows milk allergy or FDEIA caused by cows milk appears to require some special conditions. We report a case of FDEIA caused by cows milk in an adult woman, which indicates a possible mechanism for FDEIA and a sensitization route for adult cows milk allergy.

CLINICAL SUMMARY

A 24-year-old woman consulted our hospital due to recurrent urticaria followed by anaphylaxis. She had developed generalized urticaria since the age of 16 years. Occasionally the urticaria was followed by systemic reactions such as hypotension, dyspnea or syncope. Following a carefully taken history, it became clear that the episodes repeated while she was exercising after ingesting foods containing cows milk. She had a history of mild atopic dermatitis since her teens, while the family history was unremarkable. FDEIA caused by cows milk was suspected.

PATHOLOGICAL FINDINGS

Laboratory findings, including full blood count, liver-

and renal-function tests, serum electrolytes and total serum IgE, were all normal. RAST for specific IgE showed a slightly positive reaction for whole cows milk (0.41 IU/ml), but was negative for wheat, gluten, shrimp, latex, α -lactalbumin, β -lactoglobulin and casein.

Skin prick tests with either cold or boiled cows milk resulted in positive reactions, while skin prick tests with various FDEIA-causing foods, such as wheat, gluten, shrimp or buckwheat, resulted in negative reactions. Neither casein nor lactalbumin showed a positive skin reaction. To clarify the diagnosis, specific challenge tests were undertaken with informed consent. Ingestion of a half cup of milk (approximately 100 ml) was challenged. The exercise challenge was performed on a treadmill for 10 minutes at a speed of 8 km/h. Provocation tests with cows milk, aspirin (500 mg) or exercise alone did not induce any symptoms. Consequently, combined tests with cows milk, aspirin and/or exercise were performed, and the results are described in Table 1. All tests were preceded by the intake of 500 mg of aspirin. The combined test with aspirin, cows milk and exercise did not elicit any symptoms. Thus, another factor appeared to be required to induce her symptoms. According to her past history, the symptoms had developed during a premenstrual or ovulatory phase. The same challenge tests were then performed around the day of ovulation (Table 1). The ovulatory phase was presumed based on her basal body temperature. The combination of aspirin, cows milk and exercise then elicited general urticaria, followed by anaphylactoid reactions around the day of ovulation (Fig. 1). She was immediately treated with epinephrine and corticosteroids by intravenous infusion, and she recovered from the symptoms 1 hour after onset.

DISCUSSION

Cows milk allergy is less frequent in adults and tends to persist longer when compared with cows milk allergy in children.⁵ A recent investigation reported that cows milk allergy/intolerance in children recovered 87% at 3 years of age.⁶ Symptoms relating to cows milk allergy in the present case started when she was 16 years of age and had persisted for more than 7 years. We performed a careful history, which revealed a candidate route for her sensitization to cows milk. She had atopic dermatitis when she first

developed her symptoms to cows milk. She had had a habit at that time of taking baths with bath salts which contained cows milk as its main ingredient one year prior to the onset of the cows milk allergy. This sequence strongly suggests that her sensitization to cows milk may have occurred through her eczematous skin. In fact, she had temporarily developed severe eczematous lesions mainly on her cubital fossa and popliteal fossa at that time. It is well known that latex sensitization frequently occurs in those with hand dermatitis, suggesting that the eczematous lesions in this patient might be involved in the sensitization following bathing in milk.

Previously, adult-onset sensitization to casein *via* the respiratory tract after occupational exposure has been reported.⁷ That case and our case indicate that cows milk allergy may occur through the mucoepidermis or an eroded epidermis in adults, but not through the gut mucosa. In addition, an interesting study by Stöger P *et al.*⁵ showed that women represented 91.2% of the 34 adult cows milk allergy patients investigated and that 39% of them suffered their first symptoms during or soon after a pregnancy, and some also experienced a worsening of symptoms in their premenstrual phase. Those authors suggested that a sex-hormonal factor might be a trigger for the cows milk allergy. In our case, the symptoms had developed during the premenstrual or ovulatory phase, suggesting the involvement of a sex-hormonal factor in the development of her symptoms. Although the patient may belong to the wide category of cows milk allergy, she could be further categorized as FDEIA. The facts further indicate that a sex-hormonal factor also acts as a trigger for FDEIA. Especially, female sex-hormonal factors such as estradiol are suggested to be involved in mast cell activation. The direct activation of mast cell by estradiol or estrogens through the estrogen-receptor or calcium influx has been observed in recent studies.^{8,9} Evidence supports the enhanced sensitivity to allergic reaction in females, while increases of interleukin-1 (IL-1) activity in human plasma has been observed after exercise or ovulation.^{10,11} IL-1 might lower the threshold of FDEIA due to its potent activity as a histamine releaser.

Two possible hypotheses concerning the mechanism for FDEIA have been proposed in the literature.^{12,13} One is that FDEIA could be a subtype of exercise-induced anaphylaxis,¹² while the other is that an IgE-mediated type I allergic reaction to food is the essential part of FDEIA and that exercise is just a triggering factor.¹³ Although the exact mechanism underlying the development of FDEIA is still under discussion, various triggers have been found. Fatigue, sleeplessness, common cold, low temperature and aspirin are well-known factors.⁴ A sex-hormonal

factor could also be a trigger for the FDEIA described in this study. Considering these findings, the latter hypothesis is more easily acceptable as an explanation for the mechanism in our case. We conclude that an IgE-mediated weak allergy to cows milk causes systemic symptoms under stressed conditions combined with exercise and ovulation. A sex-hormonal factor is required for the development of the FDEIA caused by cows milk allergy. But after sensitization, how a patient is distinguished into immediate allergy or FDEIA remains to be clarified. One simple hypothesis would be that the patient does not elicit symptoms due to a weak sensitization to cows milk (IgE RAST 0.41 IU/ml), while a stronger sensitization induces an immediate allergic reaction without any additional conditions.

We believe that the case presented here provides clues to achieve a better understanding of the mechanism of FDEIA.

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