

Effect of Oral Sodium Cromoglycate in 2 Children With Food-Dependent Exercise-Induced Anaphylaxis (FDEIA)

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Food-dependent exercise-induced anaphylaxis (FDEIA) was prevented from recurring in 2 children by sodium cromoglycate (SCG) before intake of the causative food. *Case 1:* A 14-year-old girl who had suffered recurrent symptoms of anaphylaxis when she exercised after lunch. Radioallergosorbent test (RAST) was 1.49 UA/mL for wheat. She was advised to take SCG before lunch. In 2007, she ate bread at lunchtime without taking SCG and developed anaphylaxis. After this, she always took SCG and did not develop anaphylaxis. *Case 2:* A 9-year-old boy who had recurrent symptoms of anaphylaxis

when he exercised after lunch. RAST was 0.46 UA/mL for wheat. He started taking SCG before lunch. In June 2008, he forgot to take SCG and ate *fu* (a food made from wheat). He exercised after lunch and developed anaphylaxis. Since then, he has always taken SCG and has not developed anaphylaxis. *Conclusion:* Our findings suggest that SCG prevents FDEIA caused by wheat allergy.

Keywords: food-dependent exercise-induced anaphylaxis; sodium cromoglycate; children; wheat; gluten

Anaphylaxis induced by exercise after the intake of certain foods is referred to as food-dependent exercise-induced anaphylaxis (FDEIA). In 1979, Maulitz et al¹ reported the first case of anaphylaxis induced by exercise after the intake of seafood. In 1983, Kidd et al² reported a case of anaphylaxis after intake of celery and named this condition as FDEIA. There have been many similar reports from Japan. Harada et al^{3,4} and Aihara et al⁵⁻⁷ reported that the incidence of FDEIA increases when children become more active in their teens. The most common causative food is wheat.^{5,6,8} Studies on wheat antigens have been conducted, but the mechanism of FDEIA remains unclear.⁹⁻¹¹ For

prevention of FDEIA, it is important not to eat the causative food before exercise and to avoid exercise for 4 hours after the intake of such food.¹²⁻¹⁴ Oral prophylaxis for FDEIA by administration of antiallergy drugs has not yet been established. Here we report 2 children in whom sodium cromoglycate (SCG) prevented FDEIA when it was administered orally before intake of the causative food.

Case Reports

Case 1

The patient was a 14-year-old girl weighing 44 kg. There was nothing notable in her family history. She had developed allergic rhinitis at age 4 and allergic conjunctivitis at age 12. In November 2006 (when she was 12 years old), she developed generalized urticaria, coughing, vomiting, diarrhea, pale complexion, and malaise while playing *onigokkoasobi* (a chasing game) 1 hour after eating lunch at school. After she rested for approximately 2 hours in the sick room, her symptoms resolved. She had also

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Table 1. Examination of IgE RIST and IgE RAST in Case 1

IgE RIST	Value (IU/mL)	
	370	
IgE RAST	Value (UA/mL)	Score
Dermatophagoides pteronyssinus	≤0.34	0
House dust	≤0.34	0
Wheat	1.49	2
Rye	0.62	1
Barley	≤0.34	0
Egg white	≤0.34	0
Egg yolk	≤0.34	0
Milk	≤0.34	0
Soy bean	0.43	1
Sesame	1.12	2

Abbreviations: IgE RIST, serum IgE level radioimmunosorbent test; IgE RAST, serum allergen-specific IgE level radioallergo-sorbent test.

developed similar symptoms a few times before. In 2007 (when she was 13), she developed similar symptoms while playing soccer 2 hours after eating lunch. Her schoolteacher suggested that she should have the problem investigated before starting junior high school, so she visited our clinic in April 2007. We found that she had always eaten bread at lunchtime before she developed symptoms.

Allergy test (IgE assay). For radioimmunosorbent test (RIST), serum IgE levels were measured with a fluorescent immunoassay (FEIA; normal: <170 IU/mL; Phadia, , Uppsala, Sweden). For radioallergosorbent test (RAST), serum allergen-specific IgE levels were measured by using the CAP-FEIA system (detection range: 0.35 to 100 IU/mL; Phadia). When she first attended our clinic in April 2007, we measured IgE levels for the ingredients of the lunch she had eaten at school before the onset of anaphylaxis-like symptoms in the most recent episode. The results are shown in Table 1. RIST revealed that the serum IgE level was 370 IU/mL. RAST revealed that the serum allergen-specific IgE level was 1.49 UA/mL for wheat, 0.62 UA/mL for rye, 1.12 UA/mL for sesame seeds, and 0.43 UA/mL for soy beans. There was no reaction to barley, egg white, egg yolk, and milk.

Clinical course. FDEIA was diagnosed from her history. Performing strenuous exercise and sporting activities for 4 hours after lunch was prohibited until the cause of FDEIA could be determined. For

prevention, 100 mg of SCG was administered orally at 20 minutes before she ate lunch at school. In May 2007, she played dodge ball 30 minutes after eating lunch without taking SCG and developed generalized flushing 20 minutes later. Her symptoms resolved at 2 hours after the discontinuation of dodge ball. Exercise was prohibited for 4 hours after eating lunch, but she was allowed to exercise at her own discretion if she took SCG and did not develop any symptoms of anaphylaxis. In January 2008, she again forgot to take SCG, and played *onigokkoasobi* 20 minutes after eating lunch. As a result, she developed urticaria and flushing of the neck and face. She immediately took hydroxyzine pamoate (25 mg), the antihistamic drug she always carried, and her symptoms resolved after 30 minutes. Since then, she has always taken SCG at 20 minutes before lunch when she has exercise in the afternoon. No symptoms have occurred without exercise restrictions after eating lunch. She is currently a member of the track and field club at her junior high school and can exercise with the other pupils without dietary restrictions.

Case 2

The patient was a 9-year-old boy weighing 51 kg. There was no notable family history. He had suffered from asthma in early childhood, but has not had an attack since entering primary school. He was also suspected of having an allergy to dogs. When he was 7 years old, he was licked on the cheeks by a dog and subsequently developed facial flushing and conjunctival hyperemia. In April 2008, he did cleaning for 15 minutes after eating lunch at school and then played dodge ball. He complained of constriction in the throat 30 minutes later and developed rhinorrhea, sneezing, wheezing, and facial flushing/swelling. He was taken to a clinic near the school. By the time he arrived at the clinic (30 minutes after the onset of the symptom), his facial swelling had improved but wheezing persisted. A bronchodilator (procaterol hydrochloride), an antihistame (d-chlorpheniramine maleate), and an expectorant (ambroxol hydrochloride) were administered, and the wheezing resolved after 2 hours. He had suffered from similar symptoms several times in 2006 (when he was 7 years old) and IN 2007 (8 years old). In April 2008, he came to our clinic. Physical examination did not show any abnormalities. He had normal breathing sounds without any cough and there was no eczema.

Table 2. Examination of IgE RIST and IgE RAST in Case 2

IgE RIST	Value (IU/mL)	
	354	
IgE RAST	Value (UA/mL)	Score
Dermatophagoides pteronyssinus	≤0.34	0
House dust	0.73	2
Wheat	0.46	1
Gluten	0.85	2
Corn	0.38	1
Garlic	0.44	1
Egg white	≤0.34	0
Egg yolk	≤0.34	0
Milk	≤0.34	0
Soy bean	≤0.34	0
Kidney bean	≤0.34	0
Onion	≤0.34	0
Beef	≤0.34	0
Orange	≤0.34	0
Apple	≤0.34	0

Abbreviations: IgE RIST, serum IgE level radioimmunosorbent test; IgE RAST, serum allergen-specific IgE level radioallergosorbent test.

Allergy test (IgE assay). In April 2008, we investigated the levels of IgE for the ingredients of the lunch he had eaten at school before he developed anaphylaxis-like symptoms. The results are shown in Table 2. RIST revealed a serum IgE level of 354 IU/mL. RAST showed a serum allergen-specific IgE level of 0.46 UA/mL for wheat, 0.85 UA/mL for gluten, 0.38 UA/mL for corn, 0.44 UA/mL for garlic, and 0.73 UA/mL for house dust and *Dermatophagoides pteronyssinus*. It was negative for egg white, egg yolk, milk, soy beans, kidney beans, onion, beef, oranges, and apples.

Clinical course. He took 100 mg of SCG 20 minutes before eating lunch after attending our clinic in April 2008. In June 2008, he forgot to take SCG and had *miso* soup containing *fu* (a Japanese food that is made mainly from wheat and looks like small pieces of bread). After 30 minutes, he ran around with his friends and then developed wheezing, coughing, and urticaria. He immediately inhaled procaterol hydrochloride (10 µg) and took oxatomide (30 mg) and theophylline (100 mg) orally. He always carried these medications. The symptoms were relieved 1 hour later. Exercise after eating lunch was prohibited. No symptoms were observed after he started using SCG, so he was allowed to exercise at his own discretion

(like Case 1). After that, no symptoms of anaphylaxis occurred, even when he had miso soup containing fu at lunchtime and performed exercise. In August 2008, he again forgot to take SCG and ate fu. After 30 minutes, he played dodge ball and developed wheezing and coughing. He immediately stopped playing the game and rested in the sick room. After 1 hour, his symptoms resolved. He has taken SCG since then and no symptoms have occurred, even when he eats fu and exercises after lunch.

Discussion

FDEIA is a form of anaphylaxis caused by exercise after the intake of certain foods. Its major symptoms are generalized urticaria, angioedema (including facial swelling), respiratory impairment, hypotension, and disturbance of consciousness. In 1983, Kidd et al² reported a case of anaphylaxis after the intake of celery and named this condition food-dependent exercise-induced anaphylaxis.

The reported incidence of FDEIA varies between 0.0046% and 0.07%.^{5,6,8,15} Aihara and Ito⁶ conducted a large-scale survey of children from primary school, junior high school, and senior high school, and reported that the incidence of FDEIA was 0.008%. The most common causative food was wheat, and Aihara et al^{5,7} reported that 60% of FDEIA was wheat dependent. The incidence of FDEIA was reported to be highest among teenagers,^{4-7,13} suggesting that the incidence increases as children become more active.

The mechanism that underlies FDEIA remains unclear, but it is assumed that the release of transmitters, including histamine, causes anaphylaxis-like symptoms^{16,17} and that the autonomic nervous system is also involved.¹⁸

Studies of wheat, the most common causative food, have been conducted. ω-Gliadin and glutenin are the major antigens of wheat,^{9,10} and identification of their epitopes has made it possible to detect allergy more precisely than by conventional testing. It has been reported that blood gliadin levels are increased by exercise after wheat intake.¹⁹

Detection of Foods Causing FDEIA

Our 2 patients were diagnosed as having FDEIA from their history and the fact that anaphylaxis-like symptoms occurred during exercise after eating lunch

at school. Causative foods were identified from among a wide variety available at school lunch. Case 1 always ate bread before the occurrence of anaphylaxis-like symptoms and RAST was positive for IgE to wheat antigens, suggesting that the causative food was wheat. In case 2, exercise after eating bread did not lead to FDEIA. Anaphylaxis-like symptoms occurred several times during exercise after intake of fu for lunch, so fu was assumed to be the causative food. Fu is a very common Japanese food and is mainly used in soups. Its main ingredient is gluten, one of the wheat proteins that is produced from the precursors gliadin and glutenin in the presence of water. Gluten is a major sticky ingredient of fu. The causative proteins of wheat allergy are assumed to be ω -gliadin and glutenin,^{9,10} so the causative agent in case 2 was most likely to be gluten. The patient also developed FDEIA after eating a hamburger steak. Flour with high content of gluten was included in the hamburger steak and this was assumed to cause FDEIA.

For diagnosis of FDEIA, the history is most important. If anaphylaxis occurs during exercise within 2 hours of a meal, FDEIA can be suspected.^{7,13} Our 2 patients were diagnosed as having FDEIA caused by wheat from their history. Blood tests showed increased serum IgE levels (RIST), and IgE RAST was positive for wheat antigens. No prick tests or provocation tests were conducted.

Prevention of Anaphylaxis

If certain foods cause anaphylaxis regardless of whether the patient performs exercise, it can be prevented by not eating such causative foods.^{12,20,21} However, it is difficult to predict the occurrence of anaphylaxis if it is caused by a number of foods combined with exercise. For prevention of FDEIA, it is important not to eat causative foods before exercise and to avoid exercise after causative food intake.^{7,12-14,21,22} For complete prevention, exercise must be avoided for 4 hours after causative food intake.^{13,14} However, even if exercise is prohibited after causative food intake, children can forget such instructions and perform exercise because they do not have any symptoms in daily life. Fortunately, our 2 patients did not develop fatal anaphylaxis, but there have been some reports of death due to FDEIA,^{23,24} so prohibition of exercise alone is not sufficient. For prevention of FDEIA in children, it is important to

inform their guardians, teachers, and school nurses about this condition. For early treatment of anaphylaxis, it is also important for children to always carry epinephrine for intramuscular injection with them and to know how to inject it themselves.^{7,12,13,20,25}

Preventive Effect of SCG on FDEIA

Our 2 patients did not develop FDEIA when they took SCG, even if they exercised after lunch, but they developed FDEIA when they forgot to take SCG. These findings suggest that SCG is effective for the prevention of FDEIA.

There have been reports that intestinal permeability is altered by SCG as one of its pharmacological effects. When SCG was administered orally to food allergy patients before food intake, it reduced the symptoms of food allergy and prevented the blood antigen protein from increasing.^{26,27} SCG also inhibited immune complex formation associated with antigen-induced allergy.²⁸ SCG was reported to be effective for children who had atopic dermatitis associated with food allergy and those with food-induced asthma.^{29,30}

We advised our 2 patients not to exercise for four hours after lunch. If they forgot this advice and exercised after eating causative foods, they might have developed FDEIA. Therefore, we also advised them to take SCG, expecting that it would have the aforementioned effects²⁶⁻³⁰ and thus prevent FDEIA, although its influence on FDEIA was unknown at the time.

In a case similar to those of our 2 patients, Juji and Suko³¹ conducted a provocation test in an 18-year-old woman with FDEIA due to wheat allergy. When SCG was orally administered before wheat intake, it prevented a decrease of the forced expiratory volume in 1 second (FEV1.0; a respiratory function index) and prevented histamine release into the blood. Aihara et al³² also reported similar results in a 14-year-old boy with FDEIA caused by simultaneous intake of pickled plums and wheat. Ueno et al³³ recently reported the results of a provocation test performed in a 37-year-old man with FDEIA due to wheat, who showed a positive reaction to ω -5-gliadin (a causative antigen of wheat allergy). When SCG was administered orally before wheat intake, it prevented the blood gliadin concentration from increasing and also prevented symptoms from occurring. These reports agree with the results obtained in our 2 patients.

Limitations

We did not investigate respiratory function and blood histamine levels in a provocation test. Although provocation testing is important for the diagnosis of FDEIA, it has problems such as low sensitivity and the risk of severe anaphylactic shock in children. Thus, it is necessary to explain sufficiently to the patient and guardians about the risk of anaphylactic shock and to obtain informed consent. At our clinic we usually conduct an oral food challenge test in children who have atopic dermatitis associated with food allergy,³⁴ but considering the risk that a provocation test might cause anaphylactic shock, we did not do this in our 2 patients reported here. In Japan, guidelines for provocation testing to detect FDEIA have recently been published.¹⁵ In the future, we expect that allergy specialists will improve their diagnosis of FDEIA based on provocation testing and will conduct further research on the preventive effects of antiallergy drugs, including SCG.

Conclusion

Our report suggests that oral administration of SCG before meals can prevent FDEIA related to wheat. We expect that this report will contribute to research on the preventive effect of SCG for FDEIA.

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