

Wheat-dependent, Exercise-induced Anaphylaxis in Thai Children: A Report of 5 Cases

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SUMMARY Wheat is not an uncommon cause of food-dependent, exercise-induced anaphylaxis. This study aims to describe common clinical characteristics and laboratory manifestations of the disease. Five children, aged 8-14 years were evaluated. An atopic history was found in 20% of the patients. All patients had symptoms which involved the skin and three had hypotension. Serum specific IgE for wheat was measured and showed a positive result in 2 patients. A three-day challenge protocol with an open challenge for wheat on day 1, an exercise challenge test on day 2 and another exercise challenge test on day 3 after a meal containing wheat was performed. Four patients completed the three-day challenge protocol. Anaphylaxis occurred in 2 out of 4 patients who consumed more than 100 grams of wheat prior to the exercise. The three-day challenge protocol is a definitive diagnostic tool to confirm the diagnosis of WDEIA. However, the amount of wheat used for challenging should be at least 100 grams.

Abbreviations: WDEIA, wheat-dependent, exercise-induced anaphylaxis; FDEIA, food-dependent, exercise-induced anaphylaxis; SPT, skin prick test.

Exercise-induced anaphylaxis (EIA) is a severe form of physical allergy in which exercise precipitates anaphylaxis.¹ In 1979, Maulitz *et al.*² reported a case of an anaphylactic reaction triggered by food hypersensitivity in combination with exercise. Later on the term “food-dependent, exercised-induced anaphylaxis (FDEIA)” was used to describe a severe form of allergy for which ingestion of a specific food within 2 hours before or after exercise induces symptoms of anaphylaxis. Patients typically have IgE antibodies to the food that triggers the reactions, but they do not have allergic reactions after ingestion of the food without exercise afterward.³ Specific foods reported to have induced FDEIA in-

clude celery,³ shellfish,^{2, 4-6} wheat,^{5, 7-9} grapes,⁵ nut,¹⁰ peach,¹⁰ egg,¹¹ apple,¹² hazelnut,¹³ and cheese.¹⁴ Among these, wheat-dependent exercise induced anaphylaxis (WDEIA) is very common.^{5, 9}

In Thailand, wheat is found in various food-stuffs, such as bread, noodles, cake, doughnuts, etc. During 1998-2005, we collected data from 103 patients who had a history of food allergy at the Al-

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lergy Clinic, Department of Pediatrics, Siriraj Hospital, Mahidol University. The prevalence of wheat allergy was 4.85% (unpublished data). With the rising prevalence of wheat allergy and its life-threatening symptoms, WDEIA has become an important issue for pediatricians and general practitioners who need to become more aware of its dangers. WDEIA had never been reported in Thai children despite the fact that this condition was found in children in other countries.^{9,11} This study aimed to describe common clinical characteristics and laboratory manifestations of WDEIA in Thai children.

MATERIALS AND METHODS

Patients

The study was approved by the Institutional Ethics Board Committee, Siriraj Hospital, Mahidol University. Children with a history of WDEIA (recurrent episodes of anaphylaxis, using criteria from the Second Symposium on the Definition and Management of Anaphylaxis: Summary Report,¹⁵ after ingestion of a wheat-containing product together with exercise, but not after ingesting wheat or after exercise alone) were identified from the Pediatric Allergy Clinic, Siriraj Hospital, Bangkok, Thailand, during January 2002 to December 2006. Patients who had underlying diseases such as cardiovascular, hepatobiliary and renal diseases were excluded. Demographic data, clinical manifestations, the laboratory investigations and the results of a three-day challenge protocol (an open challenge for wheat, an exercise challenge test and the exercise challenge test after a meal containing wheat) of these patients were recorded after the patients' guardians had signed an informed consent.

A skin prick test (SPT) was performed with crude wheat extract (1:10 [w/v], in Coca's solution and 10% alcohol), wheat, egg yolk, cow's milk, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, American cockroach, German cockroach and Bermuda grass (ALK-Abello, New York, USA). Histamine dihydrochloride (10 mg/ml) was used as the positive and glycerin as the negative control. All SPTs were performed with steel lancets. Skin reactions were recorded 15 minutes after the test. The result was considered positive if the wheal size was 3 mm in diameter more than the negative control.

The specific IgE level for wheat was measured by an immunofluorometric method (FEIA RAST, CAP System, Pharmacia, Sweden) with a detection range of 0.35 to 100 IU/ml.

Three-day challenge protocol

The three-day challenge protocol is a standard method to diagnose FDEIA. The protocol consists of an open challenge for wheat on day 1, an exercise challenge test on day 2, and an exercise challenge test after a meal containing wheat on day 3. During the challenge, vital signs, peak expiratory flow rates, and clinical signs of anaphylaxis were recorded. At the presence of symptoms and signs of anaphylaxis, the challenge was discontinued and the patients were treated with an intramuscular injection of adrenaline (1:1,000; 0.01 ml/kg/dose).

Open challenge for wheat

The challenge protocol started with 1 gram of wheat. The amount was doubled every 30 minutes until a dose of 16 grams of wheat was reached (a cumulative dose of 31 grams).

Exercise challenge test

In a constant ambient environmental exercise laboratory, an exercise challenge was performed on a steady-state, motor-driven treadmill with slope and velocities adjusted to achieve 80 percent of the maximum predicted workload for the individual age of the patients. The exercise was then maintained at this level for 6 minutes.

A lung function test was performed before, immediately after and at 3, 5, 10, 15, 20, and 30 minutes after the exercise challenge, following the guidelines of The American Thoracic Society.¹⁶

Exercise challenge after a meal containing wheat

An exercise challenge test was performed within one hour after a meal containing at least 16 grams of wheat.

RESULTS

Five children (four boys, one girl) with a history of WDEIA were identified during January 2002

and December 2006. The clinical characteristics of the patients are shown in Table 1. The mean \pm SD of the patients' age at the onset of the symptoms was 11 ± 2.23 years (8-14 years). Four out of five patients had no personal or family history of atopy. Only patient #1 had a history of atopic dermatitis and asthma with an allergic mother. He also had a history of anaphylaxis after ingesting wheat only (without exercise) since 7 months of age. He then avoided wheat-containing food until the age of 5 years. After that he was able to consume wheat-containing food without symptoms. However, an anaphylactic episode reoccurred after eating wheat-containing food followed by exercise, at 8 years of age. The others had no history of food allergy before the onset of symptoms.

The type of wheat-containing foods, symptoms and their duration after food ingestion are presented in Table 2. The symptoms of anaphylaxis included skin manifestations, such as urticaria and angioedema (100%), respiratory symptoms such as dyspnea and wheezing (80%), gastrointestinal symp-

toms such as vomiting and abdominal cramps (40%), and hypotension (60%). No eye/nasal symptoms or convulsions were reported.

All patients had a positive wheat skin prick test (both commercial and crude extract) as shown in Table 3. In addition, neither of them had a history or positive results for skin prick tests for other food. Three out of five had positive skin prick tests for aeroallergens. The specific IgE for wheat was measured and showed positive results in two patients.

Four patients completed the open challenge for wheat and the exercise challenge test as shown in Table 4. The mother of patient #1 gave her informed consent only for the exercise challenge after a meal containing wheat.

The exercise challenge after a meal containing wheat was performed in all patients. Two patients (patients #3 and #4) developed anaphylaxis after the exercise challenge after a meal containing wheat but not after wheat ingestion or exercise alone.

Table 1 Clinical characteristics of the patients

Patient no.	Age (years)	Sex	Age at onset (years)	No. of attack/year	Atopic history	
					Personal	Family
1	8	Male	5	2	AD, AS	AR (M*)
2	14	Male	14	4	No	No
3	10	Male	9	4	No	No
4	12	Male	7	10	No	No
5	11	Female	10	1	No	No

M*, mother; AD, atopic dermatitis; AS, asthma; AR, allergic rhinitis.

Table 2 Causative food, symptoms and signs of anaphylaxis and onset of symptoms after food ingestion

Patient no.	Foods	Symptom and sign				Duration after food ingestion (minutes)
		Skin	Respiratory	GI	Hypotension	
1	Bread, Macaroni	Y	Y	N	N	15
2	Pizza	Y	Y	Y	N	30
3	Pizza, bread	Y	Y	N	Y	30
4	Cracker	Y	Y	N	Y	10-30
5	Bread	Y	N	Y	Y	30

Y, yes; N, no.

Patient #3 developed anaphylaxis on the second challenge with a higher dose of wheat (130 grams). Patients #2 and #5 developed urticaria when the exercise challenge was done after a meal containing wheat. Patient #1, who consumed only 25 grams of wheat followed by exercise, did not show any reactions.

The patients were followed for the duration of 1 year (patients #2 and #5), 3 years (patients #1, #3), and 5 years (patient #4). None of them outgrew the disease. Symptoms of WDEIA developed whenever they accidentally took wheat followed by exercise. However because of early treatment with an antihistamine after accidental exposure to a small amount of wheat, the symptoms were restrained to urticaria only and did not progress to anaphylaxis.

DISCUSSION

WDEIA has been previously reported in children^{9,17,18} and adults^{5,19} in several countries, in-

cluding Japan, Finland, France and Italy. This suggests that WDEIA is not a rare syndrome. In Thailand, however, WDEIA was previously reported only in 1 adult who ingested a taro-filled bun and a red bean-filled bun followed by exercise.²⁰ There was a report of 7 Thai children with wheat anaphylaxis but without relationship to exercise.²¹ Our study is the first report of WDEIA in Thai children. We report 5 cases of WDEIA in children over a period of 5 years, suggesting that WDEIA exists in Thai children.

WDEIA was reported to be more common in adult patients, male and in cases with atopic history, particularly those under 20 years of age.^{5,9} In our study, we found that 4 out of 5 patients were boys. Only 1 in 5 patients had an atopic disease (intermittent asthma and mild allergic rhinitis).

We found that skin and respiratory symptoms were the most prevalent which was confirmed by a previous study.⁹ Hypotension was observed in only 25% in that series. Another study reported that

Table 3 Results of skin prick tests and wheat specific IgE

Patient no.	Positive skin prick test		Wheat specific IgE (IU/ml)
	Food	Aeroallergen	
1	Wheat	Dust mites, cockroaches	10.4
2	Wheat	None	Not done
3	Wheat	Dust mites, <i>Alternaria</i>	Not done
4	Wheat	Dust mites	1.51
5	Wheat	None	Not done

Table 4 Results of wheat and exercise challenges

Patient no.	Wheat challenge	Exercise challenge	Wheat and exercise challenge	
			Amount of wheat before exercise (grams)	Symptoms
1*	Not done	Not done	25	None
2	Negative	Negative	40	Urticaria
3	Negative	Negative	16	None
			130	Anaphylaxis
4	Negative	Negative	100	Anaphylaxis
5	Negative	Negative	44	Urticaria

*Patient #1 was not challenged by wheat and exercise separately, however, he had a challenge by exercise after a meal containing wheat.

skin, respiratory symptoms and hypotension were found in 100%, 27.7% and 77.7% of cases respectively.²² The difference in the disease severity may be due to the difference in the age and race of the patients and also the amount of wheat consumed. The diagnosis of wheat allergy is based on the patients' clinical history, detection of wheat-specific IgE and on the results of elimination diets and oral challenges.²³ We found that the skin prick test was positive in all cases and wheat specific IgE was positive in 2 out of 2 patients, however the level was not high which could be explained by the fact that the commercial test reagent, which was a mixture of water/salt-soluble wheat proteins, perhaps lacked allergens containing the insoluble gliadin fraction.²⁴ In contrast, specific IgE to ω -5 gliadin corresponded well with the clinical diagnosis of WDEIA in previous studies.^{23, 25} Thus ω -5 gliadin specific IgE may perhaps be a better candidate for a diagnostic tool for WDEIA. Nevertheless, the skin prick test and specific IgE for ω -5 gliadin would not only be positive in WDEIA, but also in any wheat anaphylaxis so WDEIA should always be confirmed with a complete challenge program.

One of our patients (patient #3) had a positive result from exercise after a meal with 100 grams of wheat but not after 16 grams. From this result we suggest that patients should perform the exercise challenge after a meal containing at least 100 grams of wheat. This finding corresponded with a previous study²⁶ which reported a woman with a positive result by exercise challenge following an ingestion of 64 grams of bread, but not after 45 grams.

The limitation of this study is the low number of cases and the difficulty in obtaining the consent from the patients' parents. WDEIA is still under-diagnosed from both patients and doctors. Anaphylaxis is a severe condition therefore parents usually deny the challenge which could provoke anaphylactic symptoms. Specific IgE for wheat has 48% sensitivity while recombinant ω -5 gliadin has 80% sensitivity²⁷ but it is very expensive, which is why we could not use it.

In conclusion, this study showed that a three-day challenge protocol is a definitive diagnostic tool to confirm the diagnosis of WDEIA. However, the

amount of wheat used for challenging should be at least 100 grams.

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