

A New Diagnostic Criteria of Wheat-Dependent, Exercise-Induced Anaphylaxis in China

Nan-Nan Jiang, Li-Ping Wen, Hong Li, Jia Yin

Department of Allergy, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing Key Laboratory of Precise Diagnosis and Treatment on Allergic Diseases, Key Laboratory of Clinical Immunology, Chinese Academy of Medical Sciences, Beijing 100730, China

Abstract

Background: Wheat-dependent, exercise-induced anaphylaxis (WDEIA) is an allergic reaction induced by intense exercise combined with wheat ingestion. The gold standard for diagnosis of WDEIA is a food exercise challenge; however, this test is unacceptable for Chinese WDEIA patients and unable to be approved by the Ethics Committee of Chinese hospitals due to substantial risk. There are no diagnostic criteria for Chinese WDEIA patients. The aim of present study was to propose new practical diagnosis criteria for Chinese WDEIA patients.

Methods: We prospectively included 283 clinically diagnosed WDEIA patients from January 1, 2010 to June 30, 2014, and in the meanwhile, three groups were enrolled which included 133 patients with the history of anaphylaxis induced by food other than wheat, 186 recurrent urticaria patients, and 94 healthy participants. Clinical comprehensive evaluation by allergists used as the reference gold standard, receiver operator characteristic (ROC) curves were plotted, areas under curve (AUC) for specific immunoglobulin E (sIgE) were compared to evaluate the diagnostic value of IgE specific to wheat, gluten, and ω -5 gliadin. Patients were followed up by telephone questionnaire 1 year after diagnosis.

Results: We reviewed 567 anaphylactic reactions in 283 WDEIA patients. Of these anaphylactic reactions, 415 (73.3%) reactions were potentially life-threatening anaphylaxis. Among the 567 anaphylactic reactions, 75% (425/567) occurred during exercise. The highest AUC (0.910) was observed for sIgE for gluten, followed by omega-5 gliadin (AUC 0.879). Combined gluten- and ω -5 gliadin-specific IgE testing provided sensitivity and specificity of 73.1% and 99.0%, respectively. During the 1-year follow-up period, repeat anaphylaxis was rare when patients observed strict avoidance of wheat products combined with exercise or other triggering agents.

Conclusions: In this study, we proposed diagnostic criteria and management of WDEIA patients in China. Our present study suggested that confirmed anaphylactic reactions triggered by wheat with positive sIgE to gluten and omega-5-gliadin may provide supportive evidence for clinicians to make WDEIA diagnosis without performing a food exercise challenge.

Key words: Anaphylaxis; China; Gliadin; Oral Food Challenge; Wheat-Dependent Exercise-Induced Anaphylaxis

INTRODUCTION

Wheat-dependent, exercise-induced anaphylaxis (WDEIA), is a special form of wheat allergy. It is clinically characterized by anaphylactic reactions ranging from urticaria to respiratory, gastrointestinal (GI), and/or cardiovascular symptoms occurring 1–6 hours after wheat ingestion followed by physical exercise. Among wheat proteins, ω 5-gliadin and high-molecular-weight glutenin subunits have been reported to be the major allergens.^[1]

Besides exercise, cofactors such as aspirin, alcohol intake, infections, or stress can contribute to immediate-type hypersensitivity reaction after ingestion of wheat.^[2] Previously, we reported 20 patients who experienced their WDEIA after aspirin intake.^[3] The first report of WDEIA

in the Chinese population was reported by Yin and Wen in 2010,^[4] which proposed the first clinical diagnostic criteria in Chinese WDEIA patients mainly based on anaphylactic clinical manifestations following wheat ingestion combined exercise rather than food exercise challenge. Wheat allergy, especially WDEIA, seems underdiagnosed in China: our recent study revealed that wheat was the cause of anaphylaxis

Address for correspondence: Dr. Jia Yin,
Department of Allergy, Peking Union Medical College Hospital,
Chinese Academy of Medical Sciences and Peking Union Medical
College, Beijing 100730, China
E-Mail: doctoryinjia@163.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

© 2018 Chinese Medical Journal | Produced by Wolters Kluwer - Medknow

Received: 31-03-2018 **Edited by:** Qiang Shi

How to cite this article: Jiang NN, Wen LP, Li H, Yin J. A New Diagnostic Criteria of Wheat-Dependent, Exercise-Induced Anaphylaxis in China. *Chin Med J* 2018;131:2049-54.

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.4103/0366-6999.239304

in 20% of anaphylactic teenagers (10–17 years of age) and 42% of anaphylactic adults (18–50 years of age).^[5]

WDEIA is a multiple-factor allergic disease resulting from the interaction of environmental factors and genetic factors. Our previous study demonstrated that IL-4-C590T may be involved in the susceptibility to WDEIA, with the minor allele C being a possible risk factor for WDEIA.^[6] The gold standard for diagnosis of WDEIA has been a double-blinded, placebo-controlled food exercise challenge. However, such testing is not only time-consuming, but indeed may pose substantial risk to the patient. The amount of wheat and the degree of exercise required to trigger reaction varies among patients, and severe anaphylaxis during challenge may occur. Indeed the American Academy of Allergy, Asthma and Immunology reported that a 3-year-old boy died during a routine oral food challenge in August 2017. The application of such testing in routine clinical practice should be undertaken with some circumspection. Perhaps appropriately, because of these dangers, it is often difficult to gain Ethics Committee approval in China to use a combined food-exercise challenge in WDEIA patients. Recently, Kennard *et al.*^[7] reported 132 adult WDEIA patients in 4 UK centers diagnosed based on a clinical history compatible with allergic reactions after wheat consumption and with positive omega-5 gliadin specific IgE without performing food exercise challenge test. Therefore, we aimed to establish a new diagnosis criteria and management of this common but life-threatening disorder. We aimed to (1) characterize the clinical profile of WDEIA, (2) evaluate the diagnostic value of IgE specific to wheat, gluten, and ω -5 gliadin in WDEIA patients, and (3) propose practical diagnosis criteria for Chinese WDEIA patients.

METHODS

Ethical approval

This study was approved by the Ethics Committee of Peking Union Medical College Hospital of Chinese Academy of Medical Sciences. Informed written consent was obtained from patients before their enrollment in this study.

Study population

According to the early diagnostic criteria established by authors in 2010,^[4] which based on anaphylactic clinical manifestations following wheat ingestion combined exercise in 15 WDEIA Chinese patients, we prospectively included 283 clinically diagnosed WDEIA patients by three allergists who specialize in anaphylaxis in the Department of Allergy, Peking Union Medical College Hospital from January 1, 2010 to June 30, 2014. Moreover, in the meanwhile, we enrolled three groups which included 133 patients with the history of anaphylaxis induced by food other than wheat, 186 recurrent urticaria patients and 94 healthy participants with no past history of allergic diseases.

Patients were followed up by telephone questionnaire 1 year after diagnosis.

Inclusion criteria

Assessment of the outpatients with WDEIA was based on the criteria established by Yin and Wen^[4] in 2010. Group I (patient group) included 223 patients diagnosed with WDEIA according to the following diagnostic criteria and excluded the remaining 60 patients whose data were incomplete for statistical analysis:

1. Skin symptoms, respiratory manifestations, and cardiovascular system symptoms, plus/minus digestive symptoms
2. Symptoms onset during exercise occurring within 1–6 h after eating wheat products
3. No WDEIA occurred if they avoided eating wheat products entirely, or did not undertake exercise within 6 h after eating wheat-related foods
4. Food-dependent exercise-induced anaphylaxis FDEIA caused by other food rather than wheat related was excluded from the study.

Three control groups: Group II (control group) included 133 patients with the history of anaphylaxis induced by food other than wheat. Group III (control group) consisted of 186 recurrent urticaria patients. The 2018 new version of the EAACI/GA2LEN/EDF/WAO guidelines for urticaria was used to define recurrent urticaria.^[8] Group IV (control group) was composed of 94 healthy participants with no history of allergic diseases.

The specific immunoglobulin E antibody detection

All the prospectively recruited patients were screened with Immuno CAP (Thermo Fisher Scientific, Uppsala, Sweden) for wheat, gluten, and ω 5-gliadin, specific IgE levels >0.35 kUA/L were considered positive.

Statistical analysis

To evaluate the diagnostic value of serum IgE specific to wheat, gluten and ω -5 gliadin, receiver operator characteristic (ROC) curves were plotted. We used clinical comprehensive evaluation by allergists as the reference gold standard, which mainly depended on the confirmed anaphylactic reactions triggered by wheat. Sensitivity and specificity were calculated according to the identified optimal cutoff. Statistical analyses were performed using the SPSS software (ver. 16.0; SPSS, Inc., Chicago, IL, USA).

RESULTS

General characteristics of wheat-dependent, exercise-induced anaphylaxis patients

Fifty-four percent (153/283) of the patients were male. The average age of first anaphylactic reaction was 34.1 ± 13.5 years. The patients were divided into five age groups according to the age at onset of anaphylaxis [Figure 1]; 68% of the first anaphylaxis occurred at the 18–50 year age range. Moreover, 81.2% of patients came from Northern China. The geographic distribution of patients is shown in Table 1.

Clinical manifestation

We reviewed 567 anaphylactic reactions in 283 patients. Of these anaphylactic reactions, 415 (73.3%) reactions

were severe, potentially life-threatening anaphylaxis. The 334 (59.2%) reactions included collapse or loss of consciousness while 64 reactions (11.3%) manifested incontinence.

Recurrent anaphylaxis in wheat-dependent, exercise-induced anaphylaxis patients

Eighty-three (70%) patients had experienced more than two prior episodes. In total, the patients had an average of 3.5 ± 3.0 (range 1–30) anaphylaxis episodes, and 11 patients experienced more than 10 previous episodes. Table 2 shows the characteristics of the 11 patients with more than 10 anaphylactic reactions before their visits. The time duration from the first reaction to diagnosis ranged from 2 to 27 months.

Cofactors of wheat-dependent, exercise-induced anaphylaxis

Among the 567 anaphylactic reactions, 75% (425/567) occurred during exercise. Among those 425 reactions, 127 (30%) reactions occurred during relatively high

exercise intensity (such as badminton, basketball, running, mountaineering, and table tennis), and the remaining 298 (70%) reactions took place during lower exercise intensity (such as walking and doing housework). The length of time from initiation of exercise to anaphylaxis ranged from 15 to 60 min. A total of 48 reactions occurred after orally taking aspirin.

Diagnostic value of wheat/gluten/ ω -5 gliadin

Among 283 patients, 223 patients were detected with all three wheat components. We excluded the remaining 60 patients whose data were incomplete for statistics. The positive and negative number of three wheat allergen *in vitro* diagnostic tests in WDEIA and control patients are shown in Tables 3 and 4. We used clinical comprehensive evaluation by allergists as the reference gold standard, which mainly depended on the confirmed anaphylactic reactions triggered by wheat. In the patients with clinically diagnosed WDEIA, the sensitivities of the test for wheat-, gluten-, and ω -5 gliadin-specific immunoglobulin E (sIgE) were 61.9%, 85.2%, and 76.7%, respectively. The specificities calculated using the data from the control groups were 91.3%, 96.4%, and 98.5% for wheat, gluten, and ω -5 gliadin, respectively. In combination, the sensitivity and specificity of gluten- plus ω -5 gliadin sIgE were 73.1% and 99.0%, respectively.

Table 1: Geographic distribution of 283 WDEIA patients

Province/autonomous region	Number of patients	Province/autonomous region	Number of patients
Heilongjiang	10	Inner Mongolia	29
Jilin	14	Ningxia	1
Liaoning	19	Shanxi	3
Beijing	96	Gansu	3
Tianjin	10	Sichuan	2
Shanxi	12	Hubei	3
Hebei	32	Hunan	2
Shandong	12	Anhui	5
Henan	11	Shanghai	1
Jiangsu	1	Zhejiang	4
Fujian	2	Guangdong	1
Guangxi	4	Xinjiang	4
Hainan	1	Qinghai	1

WDEIA: Wheat-dependent, exercise-induced anaphylaxis.

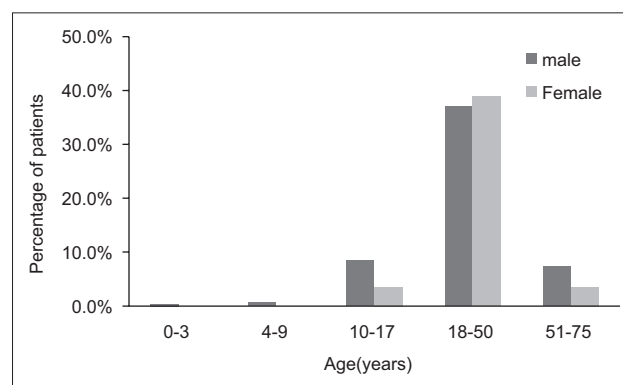


Figure 1: Age and sex distribution of 283 patients with WDEIA patients. WDEIA: Wheat-dependent, exercise-induced anaphylaxis.

Table 2: Characteristics of WDEIA patients with recurrent anaphylaxis (more than 10 episodes) before their visits

Case	Sex/age (years)	Time to diagnose* (months)	Episodes	sIgE (kUa/L)			Combined diseases	
				Wheat	Gluten	ω -5gliadin	CVD	RU
1	Male/35	7	>10	24.2	5.79	Negative	No	No
2	Male/28	2	>10	Negative	2.33	8.82	No	No
3	Female/46	15	10	3.90	24.4	41.1	Yes	Yes
4	Female/37	9	10	0.67	2.5	10.2	No	Yes
5	Male/56	8	10	Negative	3.73	Negative	No	Yes
6	Female/41	11	10	0.48	2.88	ND	No	No
7	Female/13	10	20	1.77	9.97	13.5	No	No
8	Male/25	27	10	2.38	13.0	15.8	No	Yes
9	Female/27	3	10	0.43	3.82	10.4	No	No
10	Male/37	2	12	Negative	1.63	UD	Yes	Yes
11	Male/35	9	>30	UD	1.99	5.17	No	No

*The length of time (in months) from the first clinical reaction to the diagnosis of WDEIA. CVD: Cardiovascular diseases; RU: Recurrent urticaria; ND: Not done; sIgE: Specific immunoglobulin E; WDEIA: Wheat-dependent, exercise-induced anaphylaxis; UD: Not done.

The highest positive predictive value was 97.6%, for the combination of gluten and ω -5 sIgE [Table 5].

To evaluate the diagnostic utility of the *in vitro* sIgE tests in WDEIA patients, ROC analyses for each diagnostic test were performed. The areas under the curve (AUCs) received from the ROC analysis for each test showed the highest value for the gluten test (0.910), 0.879 for ω -5 gliadin, and 0.794 for wheat.

Patient follow-up

During the follow-up period, almost all patients avoided further anaphylaxis by abiding to strict avoidance of wheat product in association with exercise or other cofactors. Moreover, 59% of the patients can eat wheat product without severe reactions, as long as they avoid exercise.

DISCUSSION

This is the largest investigation of pediatric and adult patients with WDEIA in China. Seventy percent of WDEIA patients experienced recurrent anaphylactic reactions before their clinic visits. Our previous study has suggested that wheat allergy was a potential risk factor for life-threatening and recurrent anaphylaxis.^[5] Mullins^[9] suggested that the highest risk of recurrent anaphylaxis was associated with sensitivity to wheat. Possible explanations for why recurrence is

so common are that WDEIA is difficult to diagnose and currently clinically underrecognized in China. Some patients were referred to our clinics with the previous diagnosis of “idiopathic anaphylaxis;” elderly patients were referred to cardiology for recurrent shock. Another reason is that unknowingly ingesting wheat products or wheat allergens hidden in other food may induce recurrent anaphylaxis. Our study documented that WDEIA becomes an important diagnostic consideration in patients presenting with recurrent anaphylaxis without an obvious allergenic trigger.

Our study showed that 64% of WDEIA patients also had a history of recurrent urticaria, which suggested that recurrent urticaria may be a mild presentation of wheat allergy. With the addition of cofactors, such as exercise or aspirin ingestion, severe systemic reactions occurred. In this regard, Wong *et al.*^[10] reported one WDEIA patient who presented with mild urticaria following wheat ingestion, who had exaggerated symptoms if ingestion when followed by physical activity.

The exercise intensity required to induce anaphylaxis varied among patients. In our study, the majority of reactions occurred following lower exercise intensity (such as walking and doing housework). Wong *et al.*^[10] showed that relatively low exercise intensity (walking <15 min) can provoke a reaction in WDEIA patients, so Wong *et al.* proposed that it

Table 3: sIgE response to wheat allergens in WDEIA and control patients

Groups	Wheat			Gluten			ω -5 gliadin		
	Positive	Negative	Total	Positive	Negative	Total	Positive	Negative	Total
WDEIA	138	85	223*	190	33	223	171	52	223
Control	36	377	413	15	398	413	6	407	413
Total	174	452	636	205	431	636	179	459	636

*Among 283 patients, 223 patients were detected with all three wheat components. We excluded the remaining 60 patients whose data were incomplete for statistics. WDEIA: Wheat-dependent, exercise-induced anaphylaxis; sIgE: Specific immunoglobulin E.

Table 4: sIgE response to 2 or more wheat allergens in WDEIA and control patients

Groups	Wheat + gluten			Gluten + ω -5			Wheat + gluten + ω -5 gliadin		
	Positive	Negative	Total	Positive	Negative	Total	Positive	Negative	Total
WDEIA	115	108	223*	163	60	223	91	132	223
Control	13	400	413	4	409	413	3	410	413
Total	128	508	636	167	469	636	94	541	636

*Among 283 patients, 223 patients were detected with all three wheat components. We excluded the remaining 60 patients whose data were incomplete for statistics. sIgE: Specific immunoglobulin E; WDEIA: Wheat-dependent, exercise-induced anaphylaxis.

Table 5: Sensitivity and specificity of *in vitro* diagnostic test in 223 WDEIA patients

sIgE	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Positive likelihood ratio	Negative likelihood ratio
Wheat	61.9	91.3	79.3	83.4	7.1	0.4
Gluten	85.2	96.4	92.7	93.8	23.6	0.3
ω -5 gliadin	76.7	98.5	95.5	88.7	51.1	0.2
Wheat and gluten	51.5	96.8	89.8	78.7	16.1	0.5
Gluten and ω -5 gliadin	73.1	99.0	97.6	87.2	73.1	0.3
Wheat/gluten/ ω -5 gliadin	40.8	99.3	96.8	75.8	58.2	0.6

sIgE: Specific immunoglobulin E; WDEIA: Wheat-dependent, exercise-induced anaphylaxis.

may also be worth considering an alternative terminology such as “activity-dependent wheat allergy” to describe WDEIA more accurately.

Besides exercise, our present study indicated that aspirin was an important cofactor of severe anaphylaxis reactions in WDEIA patients. We have reported 20 WDEIA cases in which life-threatening reactions were experienced after taking aspirin.^[3] Several WDEIA cases were previously reported^[11,12] where anaphylaxis was induced by aspirin but not by exercise after wheat ingestion. Aspirin is known to cause damage to the intracellular tight junction in the GI mucosa, which could lead to changes in GI permeability and increase skin testing reactions.^[13-15] It is thus speculated that the absorption of food allergens through the GI tract provokes and enhances anaphylactic symptoms in patients with food allergy.

Our study revealed that the gluten sIgE (f79) rather than omega-5 gliadin sIgE (f416) showed the best diagnostic value, based on ROC analysis. Gluten sIgE combined with omega-5 gliadin sIgE showed the best diagnostic value. Our findings were different from prior studies which suggested that omega-5 gliadin was the best marker for the diagnosis of WDEIA. Kennard *et al.*^[7] reported 132 WDEIA patients in four UK centers that the positive omega-5 gliadin sIgE was 100% and for wheat and gluten were 59% and 76%, respectively. Matsuo *et al.*^[16] documented that the highest AUC (0.850) was observed in the test for ω -5 gliadin, and the sensitivities of the allergen-specific IgE tests for wheat, gluten, and ω -5 gliadin were 48%, 56%, and 80%, respectively. Similar finding from Takahashi *et al.*'s study^[17] showed that the sensitivity and specificity of omega-5 gliadin were 81.3% and 100%, respectively, or 93.8% and 92.9% when combined with high-molecular-weight glutenin (HMW glutenin). In this regard, Matsuo *et al.*^[18] indicated that there is another minor subgroup of patients who have IgE antibodies that mainly reacts to an HMW glutenin subunit of gluten.

We propose new diagnostic criteria and new management of WDEIA patients based on the present data, alongside the anaphylaxis NIAID 2006 criteria^[19] and recently published diagnosis and management in FDEIA patients in the outpatient setting.^[20]

Clinical criteria for diagnosing wheat-dependent, exercise-induced anaphylaxis in China

WDEIA is highly likely when criteria 1, 2, 3, and 4 or 1, 2, 3, and 5 are fulfilled

1. Signs and symptoms consistent with anaphylaxis that occurred during exercise but only when exercise was preceded by wheat product ingestion were:
 - A. Acute onset (minutes to several hours) with involvement of the skin and/or mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, and swollen lips-tongue-uvula) and at least one of the following.
 - a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, and hypoxemia)

- b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypertonia, syncope, and incontinence).
 - B. Two or more of the following occurring rapidly after exposure to a wheat allergen (minutes to several hours):
 - a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, and swollen lips-tongue-uvula)
 - b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, and hypoxemia)
 - c. Reduced BP or associated symptoms (e.g., hypotonia, syncope, and incontinence)
 - d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, and vomiting).
2. Onset when patients undertook exercise within 6 hours after eating a wheat product.
3. Evidence of type I hypersensitivity to wheat: positive specific IgE to wheat extracts, especially to gluten and/or ω -5-gliadin, or positive skin testing to gluten and/or gliadins.
4. Successful avoidance of WDEIA when avoiding consumption of wheat products or when avoiding exercise within 6 hours after eating wheat related foods.
5. Symptoms may occur without exercise involvement; however, in the presence of other augmenting factors such as nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, and alcohol.

Clinical recommendations for patients with WDEIA and Management of WDEIA patients:

1. Avoid wheat products for 4–6 h before exercise
2. Avoid other possible augmenting factors when taking wheat products (such as NSAIDs, alcohol, infection)
3. Patients with cardiovascular diseases prescribed daily aspirin should strictly avoid wheat products or food containing gluten
4. Epinephrine injections and a mobile phone should always be available when exercising
5. Take first-generation H1 antihistamines (such as Cetirizine dihydrochloride oral drops) when early skin symptoms occur
6. Inhale short-acting β 2-adrenoceptor agonists (such as salbutamol) when asthmatic symptoms occur.

In conclusion, WDEIA is under-diagnosed and underestimated in China. WDEIA should be included in the differential diagnosis of patients presenting with idiopathic allergic reactions and recurrent urticaria. Alternative terminology such as “activity-dependent wheat allergy” might more accurately describe this condition. Confirmed anaphylactic reactions triggered by wheat with positive sIgE response to ω -5-gliadin or gluten can provide supporting evidence for clinicians to make the diagnosis with no food exercise challenge test. Efforts to raise clinical awareness, and use of these targeted sIgE tests, will be valuable for the diagnosis and management of this condition.

Financial support and sponsorship

This study was supported by grants from the CAMS Innovation Fund for Medical Sciences (No. 2016-I2M-1-003) and the Natural Science Foundation of China (No. 81273277).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Scherf KA, Brockow K, Biedermann T, Koehler P, Wieser H. Wheat-dependent exercise-induced anaphylaxis. *Clin Exp Allergy* 2016;46:10-20. doi: 10.1111/cea.12640.
2. Wölbing F, Fischer J, Köberle M, Kaesler S, Biedermann T. About the role and underlying mechanisms of cofactors in anaphylaxis. *Allergy* 2013;68:1085-92. doi: 10.1111/all.12193.
3. Jiang NN, Yin J, Wen LP. Aspirin related wheat dependent exercise induced anaphylaxis: A retrospective anaphylaxis of 20 cases (in Chinese). *Chin J Allergy Clin Immunol* 2014;3:181-7. doi: 10.3969/j.issn.1673-8705.2014.03.004.
4. Yin J, Wen LP. Wheat dependent exercise induced anaphylaxis: 15 cases review (in Chinese). *Chin J Allergy Clin Immunol* 2010;4:26-32. doi: 10.3969/j.issn.1673-8705.2010.01.006.
5. Jiang N, Yin J, Wen L, Li H. Characteristics of anaphylaxis in 907 Chinese patients referred to a tertiary allergy center: A retrospective study of 1,952 episodes. *Allergy Asthma Immunol Res* 2016;8:353-61. doi: 10.4168/air.2016.8.4.353.
6. Cai PP, Yin J. Association between single nucleotide polymorphisms and wheat-dependent exercise-induced anaphylaxis in Chinese population. *Chin Med J* 2013;126:1159-65. doi: 10.3760/cma.j.issn.0366-6999.20122439.
7. Kennard L, Thomas I, Rutkowski K, Azzu V, Yong PF, Kasternow B, *et al.* A multicenter evaluation of diagnosis and management of omega-5 gliadin allergy (Also known as wheat-dependent exercise-induced anaphylaxis) in 132 adults. *J Allergy Clin Immunol Pract* 2018 [Epub ahead of print]. doi: 10.1016/j.jaip.2018.02.013.
8. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, *et al.* The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. The 2017 revision and update. *Allergy* 2018;73:1393-414. doi: 10.1111/all.13397.
9. Mullins RJ. Anaphylaxis: Risk factors for recurrence. *Clin Exp Allergy* 2003;33:1033-40. doi: 10.1046/j.1365-2222.2003.x.
10. Wong GK, Huissoon AP, Goddard S, Collins DM, Krishna MT. Wheat dependent exercise induced anaphylaxis: Is this an appropriate terminology? *J Clin Pathol* 2010;63:814-7. doi: 10.1136/jcp.2010.078808.
11. Harada S, Horikawa T, Ashida M, Kamo T, Nishioka E, Ichihashi M, *et al.* Aspirin enhances the induction of type I allergic symptoms when combined with food and exercise in patients with food-dependent exercise-induced anaphylaxis. *Br J Dermatol* 2001;145:336-9. doi: 10.1046/j.1365-2133.2001.04329.x.
12. Matsukura S, Aihara M, Sugawara M, Kunimi Y, Matsuki M, Inoue Y, *et al.* Two cases of wheat-dependent anaphylaxis induced by aspirin administration but not by exercise. *Clin Exp Dermatol* 2010;35:233-7. doi: 10.1111/j.1365-2230.2009.03709.x.
13. Matsuo H, Morimoto K, Akaki T, Kaneko S, Kusatake K, Kuroda T, *et al.* Exercise and aspirin increase levels of circulating gliadin peptides in patients with wheat-dependent exercise-induced anaphylaxis. *Clin Exp Allergy* 2005;35:461-6. doi: 10.1111/j.1365-2222.2005.02213.x.
14. Aihara M, Miyazawa M, Osuna H, Tsubaki K, Ikebe T, Aihara Y, *et al.* Food-dependent exercise-induced anaphylaxis: Influence of concurrent aspirin administration on skin testing and provocation. *Br J Dermatol* 2002;146:466-72. doi: 10.1046/j.1365-2133.2002.04601.x.
15. Nakamura K, Inomata N, Ikezawa Z. Dramatic augmentation of wheat allergy by aspirin in a dose-dependent manner. *Ann Allergy Asthma Immunol* 2006;97:712-3. doi: 10.1016/s1081-1206(10)61107-6.
16. Matsuo H, Dahlström J, Tanaka A, Kohno K, Takahashi H, Furumura M, *et al.* Sensitivity and specificity of recombinant omega-5 gliadin-specific IgE measurement for the diagnosis of wheat-dependent exercise-induced anaphylaxis. *Allergy* 2008;63:233-6. doi: 10.1111/j.1398-9995.2007.01504.x.
17. Takahashi H, Matsuo H, Chinuki Y, Kohno K, Tanaka A, Maruyama N, *et al.* Recombinant high molecular weight-glutenin subunit-specific IgE detection is useful in identifying wheat-dependent exercise-induced anaphylaxis complementary to recombinant omega-5 gliadin-specific IgE test. *Clin Exp Allergy* 2012;42:1293-8. doi: 10.1111/j.1365-2222.2012.04039.x.
18. Matsuo H, Kohno K, Niihara H, Morita E. Specific IgE determination to epitope peptides of omega-5 gliadin and high molecular weight glutenin subunit is a useful tool for diagnosis of wheat-dependent exercise-induced anaphylaxis. *J Immunol* 2005;175:8116-22. doi: 10.1049/jimmunol.175.12.8116.
19. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr., Bock SA, Branum A, *et al.* Second symposium on the definition and management of anaphylaxis: Summary report – Second national institute of allergy and infectious disease/food allergy and anaphylaxis network symposium. *Ann Emerg Med* 2006;47:373-80. doi: 10.1016/j.annemergmed.2006.01.018.
20. Feldweg AM. Food-dependent, exercise-induced anaphylaxis: Diagnosis and management in the outpatient setting. *J Allergy Clin Immunol Pract* 2017;5:283-8. doi: 10.1016/j.jaip.2016.11.022.

中国小麦依赖运动诱发严重过敏反应新诊断标准的建立

摘要

背景：小麦依赖运动诱发严重过敏反应（wheat-dependent, exercise-induced anaphylaxis, WDEIA）是进食小麦制品后运动诱发的全身性过敏反应。诊断金标准为小麦联合运动激发试验，但激发试验存在较大风险，难以通过医院伦理委员会以及被中国WDEIA患者所接受，目前尚无适合中国WDEIA患者的诊断标准。本研究旨在探讨建立适合中国国情的WDEIA患者诊断标准。

方法：本研究前瞻性纳入283例WDEIA患者（2010年1月至2014年6月），同时纳入非小麦诱发的严重过敏反应患者133例，186例反复发作荨麻疹患者以及94例健康人群分别作为对照组I，对照组II，对照组III。以临床综合诊断作为相对金标准，采用受试者工作曲线下面积（AUC）比较小麦、面筋、 ω -5醇溶蛋白特异性IgE对WDEIA的诊断价值。诊断1年后对患者进行电话随访。

结果：本研究总结了283例WDEIA患者总计发生的567次严重过敏发作。415 (73.3%)为重度过敏反应。诊断WDEIA价值最高的为面筋sIgE（AUC 0.910），其次为 ω -5醇溶蛋白sIgE（AUC 0.873）。面筋sIgE联合 ω -5醇溶蛋白sIgE诊断灵敏度和特异度分别为73.1%，99.0%。随访结果显示经严格避食小麦制品及避免运动、阿司匹林等加重因素，大部分WDEIA患者未再次发生严重过敏反应。

结论：本研究建立了中国WDEIA患者的诊断标准及管理指南。临床病史结合面筋和 ω -5醇溶蛋白特异性IgE可临床诊断WDEIA而无需行食物运动激发试验。