

Clinical and Laboratory Features, and Quality of Life Assessment in Wheat Dependent Exercise-induced Anaphylaxis Patients from Central China

Hao CHEN (陈浩), Nan HUANG (黄南), Wen-jing LI (李文静), Xiang DONG (董翔), Shan-shan QI (祁姗姗), You-na WANG (王有娜), Guang-hui LIU (刘光辉), Rong-fei ZHU (祝戎飞)[#]
Department of Allergy, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

© Huazhong University of Science and Technology and Springer-Verlag Berlin Heidelberg 2016

Summary: Wheat dependent exercise-induced anaphylaxis (WDEIA) is a rare but potentially severe food allergy caused by the combination of wheat ingestion and physical exercise. The impact of WDEIA on quality of life (QOL) is unclear. This study characterized the clinical and laboratory features and investigated the QOL in WDEIA patients from Central China. Twenty-eight WDEIA patients were analyzed, and QOL was measured by validated Chinese version Food Allergy Quality of Life Questionnaire-Adult Form (FAQLQ-AF) and Food Allergy Independent Measure (FAIM) after obtaining the diagnosis. The results showed that half of the patients were females. The median onset age was 37 years old. The symptoms occurred within 1 h after wheat ingestion (26/28). Symptoms of anaphylaxis included cutaneous (26/28), respiratory (11/28), gastro-intestinal (5/28) and cardiovascular manifestations (27/28). Skin prick tests were positive to salt soluble (89.3%) and salt insoluble wheat allergen extracts (100%). Positive rate to wheat, gluten and omega-5 gliadin specific IgE was 64.3%, 92.9% and 92.9% respectively. Specific IgE to omega-5 gliadin with a cut-off value 0.83 KU/L offered highly efficient diagnostic criterion for WDEIA (sensitivity: 89.3%; and specificity: 88.9%). The mean scores of FAQLQ-AF and FAIM were 4.70 and 4.98 respectively and level of anti-omega-5 gliadin IgE had positive correlations with FAQLQ scores. Thereby, WDEIA is commonly found in mid-age adults. In most cases, multi-organs especially skin and cardiovascular systems are involved. Salt insoluble wheat allergen skin test and serum specific IgE to gluten and omega-5 gliadin help to diagnose WDEIA. QOL in WDEIA patients is severely impaired.

Key words: wheat allergy; anaphylaxis; IgE; quality of life; Central China

Wheat-dependent exercise-induced anaphylaxis (WDEIA) is a clinical phenotype of exercise-induced anaphylaxis where ingestion of wheat together with exercise triggers an anaphylactic reaction. The clinical manifestations of WDEIA are varied, often contingent on the amount of wheat intake and intensity of physical activity^[1]. In addition, multiple underlying cofactors such as aspirin, alcohol intake, infections, stress or female sex hormones/menstruation can substitute for or synergize with exercise to elicit the anaphylactic reaction after wheat ingestion in sensitized patients^[2], which might lead to the inter-regional differences of clinical features in WDEIA patients. In China, few WDEIA patients were reported^[3, 4]. Nowadays, there remains no current, approved curative treatment for food allergy; therefore, the mainstay of therapy is food avoidance and emergency treatments in the event of an accidental ingestion. Thus, patients must be vigilant about food allergen avoidance in multiple settings, which can lead to reduced health-related quality of life (QOL)^[5]. Wheat is one of the staple foods in China, which makes it rather difficult to avoid, and auto-injection epinephrine equipment is not available in China. This burden and fear of accidental ingestion may have a strong negative

impact on patients' QOL. However, there are no published reports of QOL in WDEIA patients in China. Our study aimed at characterizing the clinical and laboratory findings and investigating the QOL in WDEIA patients from Central China.

1 MATERIALS AND METHODS

1.1 Study Population

All patients presented to Tongji Hospital from September 2010 to July 2014 with the final diagnosis of WDEIA were retrospectively reviewed. Our database includes 100% of our food allergy outpatients allowing such studies. The study had been approved by the Independent Ethical Committee of Tongji Hospital. All patients had provided their general consent to participation and subsequent anonymous reporting of the collected data. Patients were considered to have WDEIA if they fulfilled both of the following criteria: (1) had experienced anaphylaxis as defined by the latest World Allergy Organization criteria in the context of wheat ingestion and exercising within 6 h^[6]; (2) could eat wheat safely in the absence of the exercise and exercise safely in the absence of wheat ingestion within 6 h. Individuals with anaphylaxis symptoms occurring more than 6 h, and up to 24 h, after wheat ingestion were also included.

Eighteen allergic patients with abnormal specific

Hao CHEN, E-mail: chen hao1019@126.com

[#]Corresponding author, E-mail: zrf13092@163.com

IgE to wheat but without experience of anaphylactic reactions after ingestion of wheat products were also enrolled in our study and served as controls. The serum specific IgE to wheat, gluten and omega-5 gliadin was tested with ImmunoCAP (Thermo Fisher, Uppsala, Sweden).

1.2 Information Obtained

The case records were reviewed and the information presented included the demographics data (sex, age, height, weight, education degree, inhabitation place, etc), case history (personal and family history of allergic diseases, number of episodes, symptom onset time, organ involved, challenge result, etc), vital signs and physical examination signs.

1.3 Allergen Tests

All the patients had received 30 inhalant and food allergen tests, including dust mites, cockroach, pet danders, pollens, fungi, egg, milk, shrimp, crab and fruits. The positive reaction to skin prick test was defined as the maximum wheal diameter ≥ 3 mm^[7], and the positive specific IgE was defined as the serum level ≥ 0.35 KU/L.

Wheat salt soluble (2 g wheat flour extracted with 2 mL 0.9% sodium chloride) and insoluble allergen extracts (2 g wheat flour extracted with 2 mL 70% ethanol) prick to prick skin tests and specific IgE to wheat, gluten and omega-5 gliadin (Thermo Fisher, Uppsala, Sweden) were routinely performed for all WDEIA suspicions.

1.4 Quality of Life Assessment

Food Allergy Quality of Life Questionnaire for Adults (FAQLQ-AF) and Food Allergy Independent Measure (FAIM) were utilized to assess the QOL of WDEIA patients. The FAQLQ-AF, FAIM and questions concerning participant characteristics were translated from English into Chinese, then this Chinese-language questionnaire package was back translated as requested by the World Health Organization (available at http://who.int/substance_abuse/research_tools/translation/en/index.html). The FAQLQ-AF consists of 29 items that are answered using a 7-point response scale (1=minimal impairment; 7=maximal impairment). The total FAQLQ-AF score is the average score of all individual items of the FAQLQ-AF.

The FAQLQ-AF is divided into 4 domains: allergen avoidance and dietary restrictions (AADR), emotional impact (EI), risk of accidental exposure (RAE) and food allergy related health (FAH). The construct validity and internal consistency of the Chinese version of the FAQLQ-AF were evaluated by computing the correlation between the FAQLQ-AF and the FAIM (individual FAQLQ-AF questions and total FAIM score; individual FAQLQ-AF questions and individual FAIM questions; total FAQLQ-AF score and total FAIM score). Moderate correlation coefficients (0.40–0.60) were expected. Subsequently, the internal consistency of the FAQLQ-AF was measured using Cronbach's Alpha. An $\alpha \geq 0.70$ indicates good internal consistency^[8].

All the WDEIA patients were requested to complete the FAQLQ-AF, FAIM after the diagnosis was made, either in paper version or electronic version from internet.

1.5 Statistical Analyses

Continuous measures were expressed as $\bar{x} \pm s$ for normally distributed data, and median with interquartile

range (25th percentile–75th percentile) for non-normally distributed data. Descriptive statistics was used to describe the demographic data. Descriptive statistics and percentiles were performed. Paired *t* test was utilized to compare the serum specific IgE levels and different domain scores of FAQLQ-AF. A comparison was made between the Pearson correlation coefficients and the Spearman rank correlation coefficients. The linear regression and correlation coefficients were evaluated for statistical significance. A *P* value of less than 0.05 was considered significant.

The ROC curves were prepared and analyzed using data from WDEIA patients and control group. In addition, an optimization of cut-off value was made by plotting sensitivity and specificity for wheat specific IgE values and choosing the cut off value as the point where both measures gave the best results.

2 RESULTS

The clinical symptoms, investigations, laboratory findings and management of the WDEIA patients were depicted in table 1.

2.1 Demographics

Twenty-eight cases were enrolled. Fourteen (50%) were female, ranging in age from 18 to 66 years old at initial clinical evaluation. Thirteen (46.4%) had other possible allergically-mediated diseases, mainly urticaria (11/28, 39.3%) and 5 (17.9%) had a family history of atopy (table 1).

2.2 Clinical Symptoms

The episode onset ages were 17 to 65 years old (median 37 years old). The majority of the episodes happened within 1 h after wheat ingestion and the reactions were delayed up to 10 to 24 h in one case having a history of chronic gastroenteritis and superior mesenteric artery syndrome. The clinical manifestations included skin symptoms such as urticaria (92.9%, 26/28), respiratory symptoms such as dyspnea and wheeze (39.3%, 11/28), gastrointestinal symptoms such as abdominal pain and vomiting (17.9%, 5/28) and cardiovascular manifestations such as hypotension, dizziness even syncope (96.4%, 27/28). Seven (25.0%) cases had recurrent symptoms because of accidental wheat ingestion and exercise after obtaining a diagnosis. The remaining 21 (75.0%) cases had no further symptoms with strict wheat avoidance (table 1).

2.3 Skin Prick and Specific IgE Tests

Skin prick tests showed positive results in 25 (89.3%) individuals to salt soluble wheat allergen extract and 100% (28/28) positive to salt insoluble wheat protein extracts. 64.3% (18/28) had positive wheat IgE results [median (interquartile range): 0.44 (0.28–0.72) KU/L], 92.3% (26/28) had positive gluten IgE results [median (interquartile range): 3.33 (1.72–6.62) KU/L], and 92.3% had positive omega-5 gliadin IgE results [median (interquartile range): 6.31 (3.36–16.53) KU/L]. The levels of serum specific IgE to omega-5 gliadin were higher than those to gluten and wheat ($P < 0.05$). There were 10 (35.7%) individuals with positive results to other aeroallergen and food allergen extracts (skin prick test and/or specific IgE).

Table 1 Characteristics and clinical manifestations of WDEIA patients

No.	Sex	Age (years)	BMI	Education level	Inhabitant area	Allergy history	Family allergy history	Episode times	First episode age (years)	Latent period after food ingestion (min)	Other concomitant diseases/condition	Clinical symptoms			
												Respi-ratory	Der-mal	Diges-tive	Cardiov-ascular
1	M	62	23.7	USS	City	N	N	4	56	20-30	Chronic sinusitis, DM	N	Y	N	Y
2	F	41	23.1	Bachelor	City	N	N	3	40	30-45	None	Y	Y	N	Y
3	M	55	26.8	USS	City	CU	Y	3	55	10	None	N	Y	N	Y
4	M	51	18.0	USS	City	N	N	5	50	30-2400	Chronic gastroenteritis	Y	Y	N	Y
5	F	28	21.6	Bachelor	City	CU	N	3	27	20-30	None	N	Y	N	Y
6	F	48	20.8	USS	Suburbs	N	Y	10	46	10-30	None	Y	Y	N	Y
7	M	29	27.6	Bachelor	City	CU	N	3	28	15	None	N	Y	N	Y
8	M	32	23.7	Bachelor	City	N	N	2	31	20	None	N	Y	N	Y
9	F	29	20.0	Post-graduate	City	N	Y	2	29	15	None	Y	Y	Y	Y
10	M	51	23.3	USS	City	N	N	2	48	10	None	Y	Y	N	Y
11	M	44	22.5	Bachelor	City	N	N	1	41	30	None	Y	Y	Y	N
12	F	44	19.8	USS	City	N	N	2	41	20	None	N	Y	N	Y
13	F	28	21.3	Bachelor	City	N	N	1	28	30	None	N	N	N	Y
14	M	63	23.7	USS	City	CU	N	2	62	45	Alcohol intake	N	Y	N	Y
15	F	21	19.3	Bachelor	City	N	N	1	21	30	None	N	Y	Y	Y
16	F	44	21.2	USS	Suburbs	N	N	2	43	30	None	N	N	N	Y
17	M	41	29.7	USS	Suburbs	CU	N	1	41	60	Alcohol intake	N	Y	Y	Y
18	M	44	25.1	Bachelor	City	AR, AS	N	5	42	30	None	Y	Y	N	Y
19	F	66	22.1	USS	City	CU	N	2	65	30-45	None	N	Y	N	Y
20	F	25	21.3	Bachelor	City	N	N	10	22	20	None	Y	Y	N	Y
21	F	40	19.9	Bachelor	City	CU	N	4	37	30-45	None	N	Y	N	Y
22	F	33	21.2	Bachelor	City	CU, AR, AS	N	1	32	45	None	Y	Y	N	Y
23	F	20	19.7	Bachelor	City	N	N	2	20	60-120	None	N	Y	Y	Y
24	M	42	20.1	USS	City	N	N	2	41	30-60	None	N	Y	N	Y
25	F	19	18.0	Bachelor	City	CU	N	1	19	30	None	Y	Y	N	Y
26	M	39	23.7	USS	City	CU, AR	N	3	37	30	None	N	Y	N	Y
27	M	18	20.9	Bachelor	City	AR, AS	Y	8	17	60	None	N	Y	N	Y
28	M	64	20.3	USS	Suburbs	CU	Y	1	64	60	None	Y	Y	N	Y

M: male; F: female; CU: chronic urticaria; AR: allergic rhinitis; AS: asthma; DM: diabetes mellitus; N: no; ND: not done; Y: yes; USS: up to secondary school; EI: emotional impact; TS: total score

2.4 ROC Curves for Wheat Specific IgE Tests

ROC analysis was performed to evaluate the diagnostic ability of the different *in vitro* tests in the diagnosis of WDEIA. Median (interquartile range) of the specific IgE to wheat, gluten and omega-5 gliadin in control group was 0.77 (0.47–0.98), 0.50 (0.12–0.44) and 0.06 (0.02–0.16) KU/L respectively. The area under the curve (AUC) derived from the ROC analysis, for each test showed the highest value was 0.918 for omega-5 gliadin, compared to 0.858 for gluten and 0.282 for wheat. This procedure was also used to obtain a maximum efficiency cut-off value of 0.83 KU/L for the anti-omega-5 gliadin IgE test with a sensitivity of 89.3% and a specificity of 88.9%. For the anti-gluten IgE test the maximum efficiency cut-off value of 1.66 KU/L gave a sensitivity of 78.6% and a specificity of 83.3% (fig. 1).

2.5 Quality of Life Assessment

A strong positive correlation between the FAQLQ-AF and FAIM was found ($r=0.808$, $P<0.001$), supporting the construct validity of the Chinese version FAQLQ-AF.

The mean scores of FAQLQ-AF and FAIM in our patients were 4.70 ± 1.26 and 4.98 ± 1.10 respectively. The

domain scores for AADR, EI, RAE and FAH were 4.59 ± 1.36 , 4.91 ± 1.16 , 4.62 ± 1.41 and 5.21 ± 1.47 respectively. Interestingly, the serum level of anti-omega-5 IgE had a positive correlation with FAQLQ ($r=0.3985$, $P=0.04$) (table 2). Sex, age, education level, inhabitant area and episode times had no correlations with FAQLQ (table 2).

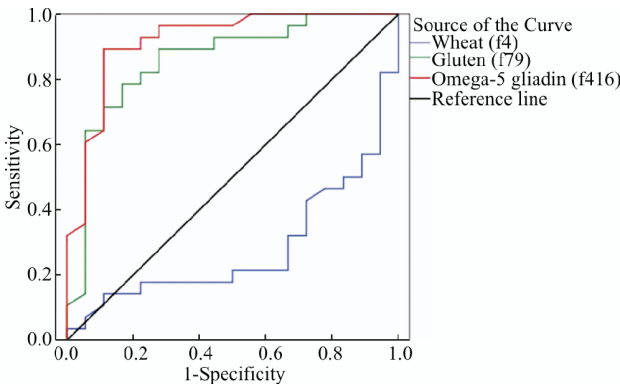


Fig. 1 The ROC curves for wheat specific IgE tests

Table 2 The *P* value of Pearson's and Spearman's correlation coefficients among the various variables

	Sex	Age	BMI	Education level	Inhabitant area	Family allergy history	Episode times	First age	Wheat	Gluten	Omega-5 gliadin	FAIM	TS
Sex	NA												
Age	0.044	NA											
BMI	0.004	0.211	NA										
Education level	0.045	0	0.330	NA									
Inhabitant area	1	0.164	0.486	0.028186	NA								
Family allergy history	0.636	0.639	0.777	0.904772	0.074293	NA							
Episode number	0.883	0.680	0.718	0.98516	0.719439	0.089183	NA						
First age	0.047	0	0.209	0	0.125875	0.538643	0.54543	NA					
Wheat	0.317	0.609	0.770	0.39899	0.687412	0.583097	0.452078	0.614	NA				
Gluten	0.548	0.903	0.562	0.86695	0.110674	0.491243	0.001113	0.976	0.953	NA			
Omega-5 gliadin	0.932	0.921	0.832	0.87546	0.685996	0.824455	0.004594	0.933	0.415	0	NA		
FAIM	0.518	0.157	0.158	0.990822	0.176938	0.53567	0.549556	0.206	0.172	0.2515	0.213154	NA	
TS	0.712	0.820	0.683	0.50802	0.219726	0.496527	0.051963	0.974	0.371	0.0520	0.035699	0	NA

3 DISCUSSION

FDEIA is a rare and potentially fatal food allergy characterized by the onset of exercise related anaphylaxis during or soon after food ingestion. Precise data on prevalence of FDEIA are lacking in many countries. A questionnaire-based study on Japanese high school students reported the prevalence of FDEIA was 0.017% and the most common association was with wheat^[8]. In the Asian region, WDEIA has been reported in Japan, Korea, Thailand, Singapore and China^[3, 9–12]. However, the diagnosis of WDEIA is often delayed and this is likely related to lack of awareness of the condition among patients as well as doctors^[13]. Until recently, there have been very few allergy centers and allergists in China. It is a big challenge for the general practitioners to evaluate a large panel of potential allergens before incriminating a specific culprit, which may lead to an under-diagnosis of WDEIA. The combination of wheat ingestion and physical exercise and the existence of cofactors may elicit different clinical manifestations among different regions. We have characterized the clinical manifestations and laboratory findings and firstly assessed the QOL in our WDEIA patients, which may help to increase awareness of this rare disease.

Our study showed that WDEIA was more common in mid-age adults (median 37 years old) and occurred equally in males and females. This is similar to a report from Northern China^[3]. This result was not consistent with a previous study from Japan where young males were more prone to WDEIA^[14]. Genetic factors, wheat cooking methods, levels of alcohol intake, and other cofactors may contribute to the differences seen. The typical time to symptoms onset after wheat ingestion was 10 min to 2 h, mostly within 1 h. One outlier case, with underlying chronic gastroenteritis and superior mesenteric artery syndrome, had symptoms delayed as much as 10 to 24 h, after wheat ingestion, which may be attributed to the fact that the underlying gastrointestinal pathology

delayed wheat protein absorption. In our study, skin and cardiovascular systems were mostly involved during anaphylaxis, followed by respiratory and gastrointestinal symptoms, which was similar to other studies^[15]. An interesting observation of our study was that almost half of our WDEIA patients also had chronic urticaria. We suspect the chronic urticaria may actually have been a mild form of wheat allergy, because some patients' urticaria symptoms resolved dramatically after strict wheat avoidance in our study. Although the exact mechanism of WDEIA is unclear, blood flow redistribution and increased gastrointestinal permeability induced by exercise may facilitate wheat allergen absorbed to blood and result in subsequent allergic reaction^[16]. However, we cannot explain why some WDEIA patients had no acute symptoms during wheat ingestion even with a high level of specific IgE to wheat allergens. Further studies are needed to elucidate the mechanism.

The gold standard for the diagnosis of WDEIA is a double-blind placebo-controlled food exercise challenge. However, the challenge test is time-consuming and potentially unsafe. Brochow *et al* reported challenge test results with wheat and exercise often were negative in patients with WDEIA despite a clear history^[17]. For the above reasons, we did not perform challenge test in our study, however, 7 cases mistakenly ingested wheat containing foods, exercised and experienced anaphylaxis after WDEIA was diagnosed. Thus, an easy laboratory diagnostic test for predicting severe systemic reactions is desirable.

Nowadays, skin prick tests and *in vitro* IgE assays are first level diagnostics for wheat allergy. However, commercial wheat allergen extract prick solution is not available in many countries including China. Therefore, it would be desirable to offer *in vitro* tests to specific wheat proteins that could predict clinical risk severity. A previous study reported that only 41% of WDEIA patients had wheat-specific IgE on ImmunoCAP testing^[18], and omega-5 gliadin had a sensitivity of 80% in adults

with WDEIA, with good specificity of 96% at a cut-off of 0.89 KU/L^[19]. According to previous studies, wheat contained approximately 20% soluble allergens and 80% insoluble allergens. The soluble allergens, implicated in Baker's asthma, were mainly albumins (about 75%) and globulins (about 25%), while the insoluble allergens, implicated in WDEIA, were composed of glutenins (about 50%) and gliadins (about 50%)^[20]. In our study, we performed skin prick tests to salt insoluble wheat extracts obtained in our lab and got positivity in 100% of the patients, which seemed to be an easy way to diagnose wheat allergy. We also found the positive rate of specific IgE to gluten and omega-5 gliadin was 92.3% and 92.3% respectively. ROC analysis showed both the AUCs of omega-5 gliadin and gluten were high, confirming the role of these two tests in the diagnosis of WDEIA, while omega-5 gliadin had the higher value and a cut-off concentration of 0.83 KU/L giving the maximum efficiency, which was very similar to previous study^[19]. Negative omega-5 gliadin IgE cannot exclude WDEIA, since patients might be allergic to other wheat components such as high molecular weight (HMW) glutenin^[18], which might explain the salt insoluble skin prick test had a higher positive rate than omega-5 gliadin IgE test in our WDEIA patients. However, one should be aware that the wheat skin test extracts we used have not been standardized, which might lead to inconsistent results in different situations.

Avoidance of the offending food is currently the only available treatment for food allergy. Food-allergic individuals at risk for anaphylaxis should always carry an epinephrine auto-injector for emergency treatment^[21]. However, wheat containing foods are very difficult to avoid since it is one of the staple foods in daily life, and epinephrine auto-injector is not available in all countries, including China. This burden and fear of accidental ingestion may have a strong adverse impact on patient's QOL. Previous studies have shown that the health-related QOL is impaired in individuals with confirmed and perceived food allergy^[22]. As a disease specific QOL questionnaire, FAQLQ-AF is especially useful in anaphylactic disorders, in which no objective measurement of the extent or severity of disease exists^[23]. Our study showed that the mean score of FAQLQ-AF in WDEIA patients was 4.70 out of 7. van der Velde *et al* reported the mean FAQLQ-AF score in food allergy patients, including food related anaphylaxis patients was 4.35^[24], which implied the QOL of WDEIA patients was more severely impaired than other food allergy patients. We also found the FAQLQ-AF score had positive correlations with level of anti-omega-5 gliadin IgE, which implied anti-omega-5 gliadin as potential surrogate indicator to evaluate the clinical severity of WDEIA patients.

In conclusion, WDEIA has become an important condition in Central China and is found in mid-age adults. Clinical manifestations vary. In most cases, multi-organ especially skin and cardiovascular systems were involved. Salt insoluble wheat allergen extract skin test and serum specific IgE to gluten and omega-5 gliadin tests help to diagnose WDEIA. The QOL is more severely impaired in WDEIA patients than other food allergy patients. Further studies are needed to better profile and understand the pathophysiological mechanisms for WDEIA patients.

Conflict of Interest Statement

The authors declared no potential conflicts of interest.

REFERENCES

- Morita E, Kunie K, Matsuo H. Food-dependent exercise-induced anaphylaxis. *J Dermatol Sci*, 2007,47(2):109-117
- Fisher J, Schuck E, Biedermann T. Wheat-dependent exercise-induced anaphylaxis exclusively during menstruation. *Allergy*, 2010, 65(10):1347-1348
- Cai PP, Yin J. Association between single nucleotide polymorphisms and wheat-dependent exercise-induced anaphylaxis in Chinese population. *Chin Med J*, 2013,126(6):1159-1165
- Rongfei Z, Wenjing L, Nan H, *et al*. Wheat-dependent exercise-induced anaphylaxis occurred with a delayed onset of 10 to 24 hours after wheat ingestion: A case report. *Allergy Asthma Immunol Res*, 2014,6(4):370-372
- King RM, Knibb RC, Hourihane JO. Impact of peanut allergy on quality of life, stress and anxiety in the family. *Allergy*, 2009,64(3):461-468
- Simons FE, Arduzzo LR, Bilò MB, *et al*. 2012 Update: World Allergy Organization guidelines for the assessment and management of anaphylaxis. *Curr Opin Allergy Clin Immunol*, 2012,12(4):389-399
- Konstantinou GN, Bousquet PJ, Zuberbier T, *et al*. The longest wheal diameter is the optimal measurement for the evaluation of skin prick tests. *Int Arch Allergy Immunol*, 2010,151(4):343-345
- Bullinger M, Anderson R, Cella D, *et al*. Developing and evaluating cross-culture instruments from minimum requirements to optimal models. *Qual Life Res*, 1993,2(6):451-459
- Aihara Y, Takahashi Y, Kotoyori T, *et al*. Frequency of food-dependent exercise-induced anaphylaxis in Japanese junior-high-school students. *J Allergy Clin Immunol*, 2001,108(6):1035-1039
- Yang MS, Lee SH, Kim TW, *et al*. Epidemiologic and clinical features of anaphylaxis in Korea. *Ann Allergy Asthma Immunol*, 2008,100(1):31-36
- Thalayasingam M, Allameen NA, Soh JY, *et al*. Wheat-dependent exercise-induced anaphylaxis: a retrospective case review from a tertiary hospital. *Postgrad Med J*, 2014,90(1067):488-492
- Pacharn P, Jirapongsananuruk O, Daengsuwan T, *et al*. Wheat-dependent exercise-induced anaphylaxis in Thai children: a report of 5 cases. *Asian Pac J Allergy Immunol*, 2009,27(2-3):115-120
- Wong GK, Huissoon AP, Goddard S, *et al*. Wheat dependent exercise induced anaphylaxis: is this an appropriate terminology? *J Clin Pathol*, 2010,63(9):814-817
- Inomata N. Wheat allergy. *Curr Opin Allergy Clin Immunol*, 2009,9(3):238-243
- Sheffer AL, Tong AK, Murphy GF, *et al*. Exercise-induced anaphylaxis: a serious form of physical allergy associated with mast cell degranulation. *J Allergy Clin Immunol*, 1985,75(4):479-484
- Barg W, Medrala W, Wolanczyk-Medrala A. Exercise-induced anaphylaxis: an update on diagnosis and treatment. *Curr Allergy Asthma Rep*, 2011,11(1):45-51
- Brockow K, Kneissl D, Valentini L, *et al*. Using a gluten oral food challenge protocol to improve diagnosis of wheat-dependent exercise-induced anaphylaxis. *J Allergy*

- Clin Immunol, 2015,135(4):977-984
- 18 Morita E, Matsuo H, Chinuki Y, *et al.* Food-dependent exercise-induced anaphylaxis--importance of omega-5 gliadin and HMW-glutenin as causative antigens for wheat-dependent exercise-induced anaphylaxis. *Allergol Int*, 2009,58(4):493-498
- 19 Matsuo H, Dahlström J, Tanaka A, *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(2):233-236
- 20 Tripathi A, Commins SP, Heymann PW, *et al.* Diagnostic and experimental food challenges in patients with nonimmediate reactions to food. *J Allergy Clin Immunol*, 2015,135(4):985-987
- 21 Sicherer SH. Food allergy. *Lancet*, 2002,360(9334):701-710
- 22 Marklund B, Ahlstedt S, Nordstrom G. Health-related quality of life in food hypersensitive schoolchildren and their families: parents' perceptions. *Health Qual Life Outcomes*, 2006,4:48
- 23 Oude Elberink JN. Significance and rationale of studies of health-related quality of life in anaphylactic disorders. *Curr Opin Allergy Clin Immunol*, 2006,6(4):298-302
- 24 van der Velde JL, Flokstra-de Blok BM, de Groot H, *et al.* Food allergy-related quality of life after double-blind, placebo-controlled food challenges in adults, adolescents, and children. *J Allergy Clin Immunol*, 2012,130(5):1136-1143.e2

(Received July 3, 2015; revised July 3, 2016)