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World Allergy Organization Journal

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Wheat allergy in patients with recurrent urticaria

Ying-Yang Xu^{a,b,1}, Nan-Nan Jiang^{a,1}, Li-Ping Wen^{a,b}, Hong Li^{a,b}, Jia Yin^{a,b,*}^a Department of Allergy, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, China^b Beijing Key Laboratory of Precision Medicine for Diagnosis and Treatment on Allergic Diseases, China

ARTICLE INFO

Keywords:

Recurrent urticaria
Wheat allergy
Wheat-dependent exercise-induced anaphylaxis
Wheat-induced anaphylaxis
ω-5 gliadin

ABSTRACT

Background: Clinical observation revealed that most of wheat-induced anaphylaxis (WIA)/wheat-dependent exercise-induced anaphylaxis (WDEIA) patients showed a history of recurrent urticaria. We aim to determine the association between recurrent urticaria and anaphylaxis in wheat allergy.

Methods: Population-based cohort study involved patients with WIA (n = 193, including WDEIA n = 104), recurrent urticaria (n = 177), non-wheat-related anaphylaxis (n = 584), atopic disease (excluding anaphylaxis, n = 221) and healthy control (n = 95) from 2009 to 2016. Detailed course of urticaria and anaphylaxis were obtained from medical records and following-up questionnaire. Serum IgE specific to wheat, gluten and ω-5 gliadin and skin prick test to wheat were examined. Clinical and laboratory data were statistically analyzed.

Results: In recurrent urticaria patients, wheat allergy was not rare, and 6.8% (n = 12) was diagnosed as wheat-induced urticaria. Patients with WIA/WDEIA had higher prevalence of recurrent urticaria history than those with non-wheat-related anaphylaxis (164/193, 84.9% vs 85/584, 14.5%), and 70.4% of them (136/193) had recurrent urticaria prior to their first anaphylactic attack. Among patients with WIA/WDEIA and previous urticaria, 46.3% experienced an exacerbation of urticaria. The value of serum specific IgE to ω-5 gliadin was significantly higher in patients with WIA/WDEIA than those with wheat-induced urticaria.

Conclusions: We recommend screening wheat allergy in recurrent urticaria to identify patients who have a potential risk to develop severe reactions earlier.

Background

Wheat is widely consumed in China, although it can trigger a variety of allergic reactions that are mediated by IgE or T-cells.¹ Dependent on the route of wheat exposure, IgE-mediated wheat allergy can manifest as Baker's asthma and rhinitis, or as a traditional food allergy.^{1,2} The severity of allergic reactions to wheat varies from pruritus, urticaria, and angioedema to dyspnea, hypotension, collapse, and shock. Previous reports have shown that the prevalence of wheat allergy is 0.4% among American adults and 0.2% among Japanese adults.^{3,4} Although the prevalence of wheat allergy in China is unknown, wheat is considered the causative allergen in approximately 37% of Chinese cases of food-induced anaphylaxis.⁵

Wheat-induced anaphylaxis (WIA) is a severe type of wheat allergy, including a distinct form which is known as wheat-dependent exercise-

induced anaphylaxis (WDEIA). In China, WDEIA was first described in 2010, and that report found 13 of the 15 enrolled patients also had a history of recurrent urticaria.⁶ Interestingly, recurrence of anaphylaxis and urticaria was not detected after elimination of wheat from the patients' diet, which indicates that their recurrent urticaria may be related to wheat ingestion and that it is a part of wheat allergic reaction. Thus, we hypothesized that recurrent urticaria might be a prodrome or early stage of anaphylaxis resulting from wheat allergy, and it can develop into anaphylaxis with or without certain exacerbating factors, such as physical activity, acetylsalicylic acid (aspirin), or other nonsteroidal anti-inflammatory drugs (NSAIDs).⁷ Moreover, so far, little is known regarding the clinical features of WIA/WDEIA among Chinese patients, and there are no predictable indicators that can be utilized for such potentially fatal allergic reactions. Therefore, we analyzed a large number of cases with recurrent urticaria and WIA/WDEIA. We aim to explore the

Abbreviations: WDEIA, wheat-dependent exercise-induced anaphylaxis; WIA, wheat-induced anaphylaxis; WIU, wheat-induced urticaria.

* Corresponding author. Department of Allergy, Peking Union Medical College Hospital, #1 Shuaifuyuan, Wangfujing, Beijing, 100730, China.

E-mail addresses: carlxy@126.com (Y.-Y. Xu), jiangnanonly@163.com (N.-N. Jiang), dr.wenliping@163.com (L.-P. Wen), lihong1228sec@163.com (H. Li), doctorjinyia@163.com (J. Yin).

¹ Both Ying-Yang Xu and Nan-Nan Jiang are the first authors.

<https://doi.org/10.1016/j.waojou.2019.100013>

Received 3 July 2018; Received in revised form 3 December 2018; Accepted 8 January 2019

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potential association between recurrent urticaria and WIA/WDEIA and evaluate the role of wheat allergy among patients with recurrent urticaria.

Materials

Patients and controls

This study recruited 193 patients with a diagnosis of WIA (including 104 with WDEIA), 177 with recurrent urticaria (including 12 wheat-induced urticaria, WIU) who were treated at the Department of Allergy, Peking Union Medical College Hospital between 2009 and 2016. The diagnostic criteria for WIA, WDEIA, and wheat-induced urticaria are illustrated in Fig. 1. Anaphylaxis is determined according to the world allergy organization (WAO) systemic allergic reaction grading system (Grades 4 and 5).⁸ Recurrent urticaria is defined as the occurrence of urticaria resolves quickly, generally within several hours, but either the frequency or the duration fail to fulfill the standard of chronic urticaria (on most days in a week and more than 6 weeks). During the same period, three other groups were enrolled as comparison: 584 patients with non-wheat-related anaphylaxis, 221 atopic patients who were diagnosed as having atopic disease (i.e. allergic rhinitis, allergic asthma, atopic dermatitis, food allergy, etc) but never experienced symptoms after wheat ingestion, and 95 healthy individuals. All the clinical data were from medical records and following-up questionnaire. The study was approved by the ethics committee of Peking Union Medical College Hospital.

Skin prick test

Skin prick test was performed by using extracts of wheat flour (Allergen Manufacturing and Research Center, Peking Union Medical

College Hospital, Beijing, China). The response was read as positive when the wheal diameter was greater than one third of the positive control.

Specific IgE measurements

Serum levels of specific IgE to wheat, gluten, and ω -5 gliadin and common food allergens were tested by the ImmunoCAP system (Phadia AB, Uppsala, Sweden). The detection limit was defined as 0.35 kU_A/L, according to the manufacturer's recommendations. All the atopic and healthy control patients, patients with WIA/WDEIA, and nearly all the patients with recurrent urticaria were measured these three specific IgE to wheat.

Statistical analysis

The Chi-square test was used to compare the positive rate of specific IgE among recurrent urticaria, atopic and healthy controls and non-wheat-related anaphylaxis, and the rate of recurrent urticaria among patients with WIA/WDEIA or non-wheat-related anaphylaxis. The Mann-Whitney test and the Kruskal-Wallis test were used to evaluate onset age of urticaria and anaphylaxis, and the levels of IgE specific to wheat, gluten, and ω -5 gliadin in the different groups. Differences with a *P*-value of <0.05 were considered statistically significant. All analyses were performed using SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA).

Results

General characteristic of studied patients

This study included 193 patients with WIA (including 104 cases of WDEIA), 177 patients with recurrent urticaria (including 12 cases of WIU), and 584 patients with non-wheat-related anaphylaxis (Table 1). The median onset age of urticaria was 26.0, 30.5 and 26.0 years old in recurrent urticaria, WIA/WDEIA and non-wheat-related anaphylaxis group respectively, and no statistical difference was found among three groups (*p* = 0.81). The median onset age of anaphylaxis in WIA/WDEIA was significantly older than that in non-wheat-related anaphylaxis group (37.0 years vs 23.0 years, *p* < 0.001).

Of 112 patients with WIA/WDEIA who took skin prick test to wheat extract, 108 showed positive reaction (Supplementary Table). Besides wheat, specific IgE to other common food, such as milk, egg, peanut, soybean, buckwheat, oat, rice, maize, shrimp, crab and so on, were also measured in WIA/WDEIA patients. The results showed 38 patients had positive specific IgE to seafood, 28 to grain, 17 to nuts and seeds, 8 to vegetables and fruits, whereas 121 were negative to these common food (Supplementary Table).

Wheat allergy among patients with recurrent urticaria

Among the 177 patients with recurrent urticaria, 175 test results for IgE specific to wheat and gluten and 159 test results for ω -5 gliadin were available. The prevalence of wheat-, gluten-, and ω -5 gliadin-specific IgE was 13.1% (23/175), 13.1% (23/175), and 4.4% (7/159), respectively. The prevalence of these three parameters in atopic controls, healthy controls, non-wheat-related anaphylaxis patients and WIA/WDEIA patients were showed in Table 1. The positive rate of three specific IgE in recurrent urticaria group was higher than those in healthy controls (*p* = 0.003 for wheat, *p* = 0.001 for gluten and *p* = 0.048 for ω -5 gliadin). The positive rate of wheat specific IgE was higher in the atopic controls (*p* < 0.001) and in non-wheat-related anaphylaxis patients (*p* < 0.001) than that in recurrent urticaria group. There was no difference in prevalence of gluten-, and ω -5 gliadin-specific IgE between recurrent urticaria and atopic group or between recurrent urticaria and non-wheat-related anaphylaxis patients. According to the wheat allergy diagnostic criteria, 12 patients in the recurrent urticaria group (6.8%) were belonged to WIU. The prevalence of specific IgE against wheat, gluten, and ω -5 gliadin was 66.7% (8/12), 91.7% (11/12), and 50% (4/8)

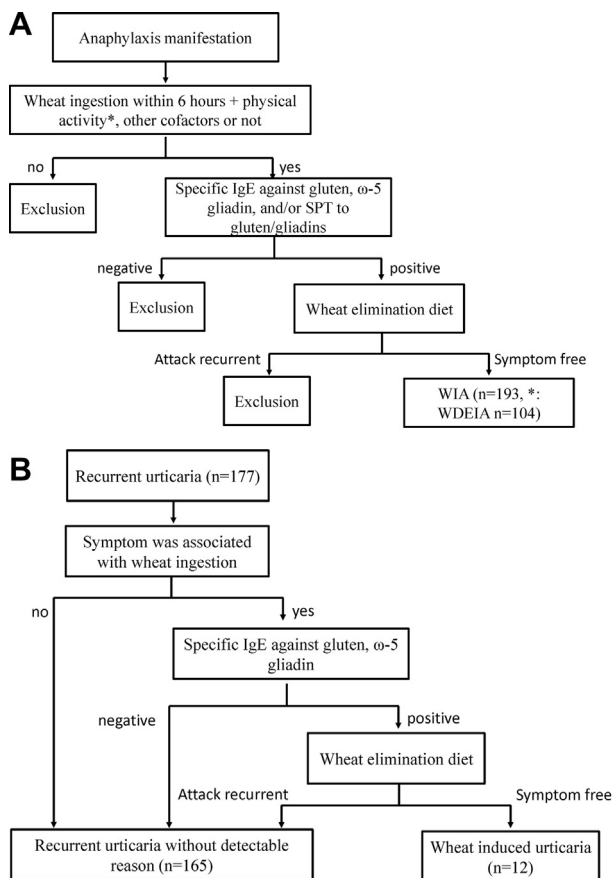


Fig. 1. Diagnostic criteria of WIA/WDEIA (a), wheat induce urticaria (b). WIA: wheat induced anaphylaxis; WDEIA: wheat dependent exercise induced anaphylaxis; SPT: skin prick test.

Table 1
The study groups.

		No. of Patients (male)	SPT	Specific IgE to wheat		Specific IgE to gluten		Specific IgE to ω-5 gliadin	
				Positive rate	Median (kU _A /L)	Positive rate	Median (kU _A /L)	Positive rate	Median (kU _A /L)
WIA	Total (including WDEIA)	193 (111)	96.4% (108/112)	62.7% (116/185)	0.59	96.2% (179/186)	2.2	87.8% (116/132)	6.87
	With recurrent urticaria	With previous urticaria: 136 (79) Subsequently developed urticaria: 28 (16)	96.5% (84/87)	63.6% (100/157)	0.59	96.8% (153/158)	2.39	89.8% (97/108)	7.16
	Without recurrent urticaria	29 (16)	96% (24/25)	57.1% (16/28)	0.55	92.8% (26/28)	1.35	79.1% (19/24)	5.79
Recurrent urticaria	Total	177 (68)	ND	13.1% (23/175)	0	13.1% (23/175)	0	4.4% (7/159)	0
	Wheat-induced urticaria	12 (8)		66.6% (8/12)	0.52	91.6% (11/12)	1.36	50% (4/8)	0.76
Non-wheat-related anaphylaxis	Total	584 (258)	ND	30.8% (50/162)	0	8.2% (13/157)	0	2% (3/150)	0
	Plus recurrent urticaria	85 (41)		46.3% (19/41)	0	10.2% (4/39)	0	2.6% (1/38)	0
Atopic controls		221 (111)	ND	66.0% (146/221)	0.68	13.5% (30/221)	0.07	2.2% (5/221)	0.01
Healthy controls		95 (44)	ND	2.1% (2/95)	-	1.0% (1/95)	-	0	-

WIA: wheat-induced anaphylaxis, WDEIA: wheat-dependent exercise-induced anaphylaxis.

respectively. In patients with WIU, the duration ranged from 4 months to 18 years. The frequency of urticaria was respectively more than once a month but equal or less than once a week in 9 patients, once a month in 1 patient, twice a year in 1 patient, and 1 patient developed urticaria every time when ingesting wheat products.

Recurrent urticaria among patients with WIA/WDEIA or non-wheat-related anaphylaxis

Among the 193 patients with WIA/WDEIA, 164 patients (84.9%) reported recurrent episodes of urticaria. The frequency of urticaria in these 164 patients were graded into 5 levels: (a) 2 patients had urticaria more than half a week; (b) 25 patients had urticaria from once to several times per week, but less than half of a week; (c) 37 patients from 1 to 3 times per month; (d) 42 patients from 7 to 11 times per year; (e) 58 patients from 1 to 6 times per year (Fig. 2). Of these patients, 136 patients had experienced recurrent urticaria before their first anaphylactic reaction (70.4% of the WIA/WDEIA group) and 28 patients developed recurrent urticaria after their first anaphylactic reaction. The history of

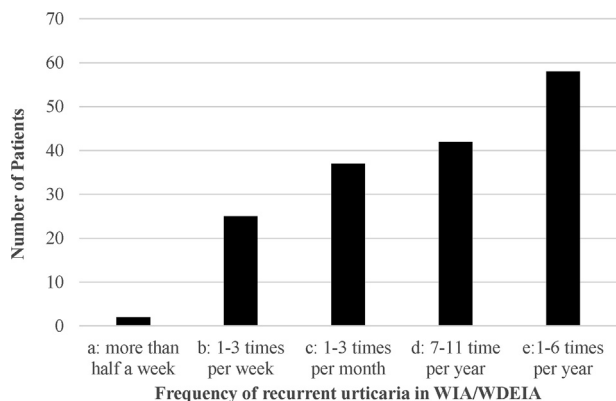


Fig. 2. Frequency of recurrent urticaria in WIA/WDEIA patients. (a) More than half a week, n = 2; (b) 1–3 times per week, n = 25; (c) 1–3 times per month, n = 37; (d) 7–11 times per year, n = 42; (e) 1–6 times per year, n = 58. WIA: wheat induced anaphylaxis; WDEIA: wheat dependent exercise induced anaphylaxis.

recurrent urticaria was not detected in 29 patients from the WIA/WDEIA group. To determine whether the high incidence of recurrent urticaria in WIA/WDEIA was distinctive, 584 patients with non-wheat-related anaphylaxis were reviewed for comparison, and only 85 patients had recurrent urticaria (14.5%), and 26 patients had experienced recurrent urticaria before their anaphylactic reaction (4.4%) (Fig. 3). The prevalence of recurrent urticaria history in WIA/WDEIA group was significantly higher than that in non-wheat-related anaphylaxis group (p < 0.001).

Interval between recurrent urticaria and WIA/WDEIA

Of the 136 patients in the WIA/WDEIA group with a previous history of recurrent urticaria, the median interval from the beginning of

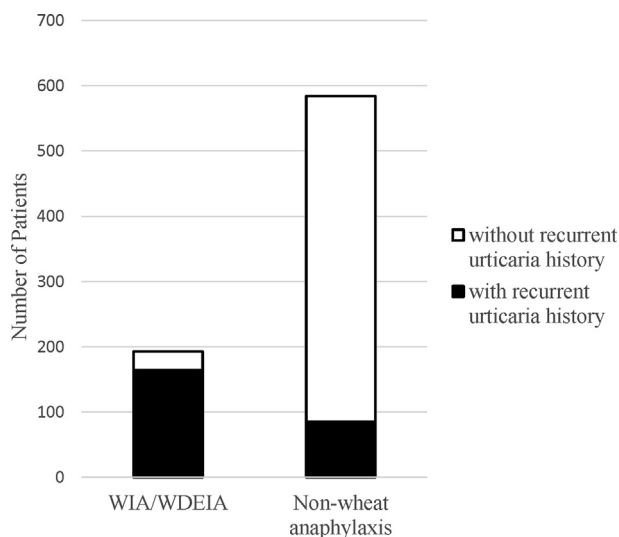


Fig. 3. Incidence of recurrent urticaria in WIA/WDEIA and non-wheat-related anaphylaxis patients. Compared with non-wheat-related anaphylaxis patients (85/584, 14.5%), more patients with WIA/WDEIA combined with recurrent urticaria (164/193, 84.9%), and 70.4% of them present with recurrent urticaria before the first anaphylactic episode. WIA: wheat induced anaphylaxis; WDEIA: wheat dependent exercise induced anaphylaxis.

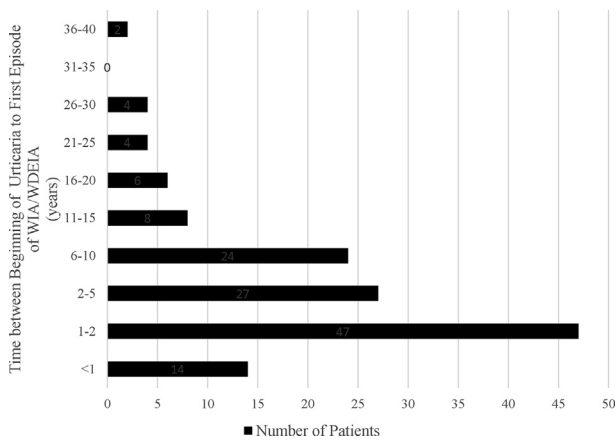


Fig. 4. Interval between onset of recurrent urticaria and WIA/WDEIA WIA: wheat induced anaphylaxis; WDEIA: wheat dependent exercise induced anaphylaxis.

recurrent urticaria to the first WIA/WDEIA episode was 3.00 years, with an interquartile range of 1.06–8.75 years (range: 0.1–40 years). The distribution of interval between recurrent urticaria to WIA/WDEIA was showed in Fig. 4.

Clinical pattern from recurrent urticaria to WIA/WDEIA

Of the 136 WIA/WDEIA patients with previous recurrent urticaria, 63 patients experienced intensified attacks of urticaria before the first anaphylactic episode. Specifically, 56 patients (41.1% of the 136 patients) had an increased frequency of urticaria, and all 63 patients (46.3% of the 136 patients) exhibited exacerbation in terms of the involved area, duration, and required treatment. Seventy-one of 136 patients (52.2%) did not report noticeable changes in recurrent urticaria, and only 2

patients reported noticeable relief from urticaria before they developed anaphylaxis.

Levels of IgE among patients with WIA/WDEIA and with/without recurrent urticaria and WIU

The patients were classified according to whether they had WIA/WDEIA (n = 193) or WIU (n = 12), and were then subdivided into group 1 (WIA/WDEIA plus recurrent urticaria), group 2 (WIA/WDEIA without recurrent urticaria), and group 3 (only WIU). IgE test results were analyzed for wheat (n = 196), gluten (n = 198), and ω-5 gliadin (n = 140) in all patients with wheat allergy. Specific IgE against ω-5 gliadin in group 3 was lower than that in group 1 (p = 0.0018) and group 2 (p = 0.0423). Furthermore, ω-5 gliadin-specific IgE in patients with WIA/WDEIA was higher than that in patients with WIU (p = 0.0027). There was no significant difference in wheat- or gluten-specific IgE among group 1, 2 and 3. The statistic results were illustrated in Fig. 5.

Discussion

Wheat is one of the six most common allergens among children,⁹ and is the most common cause of food-induced anaphylaxis in China, as well as the most common cause of food-related exercise-induced anaphylaxis.⁵ Similar results have been reported in Japan and Korea.^{10,11} Unfortunately, WIA/WDEIA are life-threatening diseases and there are no indicators or methods that can be used to identify such patients in early stage. We have noticed that many patients with WIA/WDEIA present to our clinic with a history of recurrent urticaria, which motivated us to evaluate the potential association between recurrent urticaria and anaphylaxis in patients with wheat allergy.

The present study collected 177 recurrent urticaria patients serving as comparison. It revealed that 6.8% of recurrent urticaria cases were due to wheat allergy. The positive rates for wheat-, gluten-, and ω-5 gliadin-specific IgE in recurrent urticaria patients were higher than those in

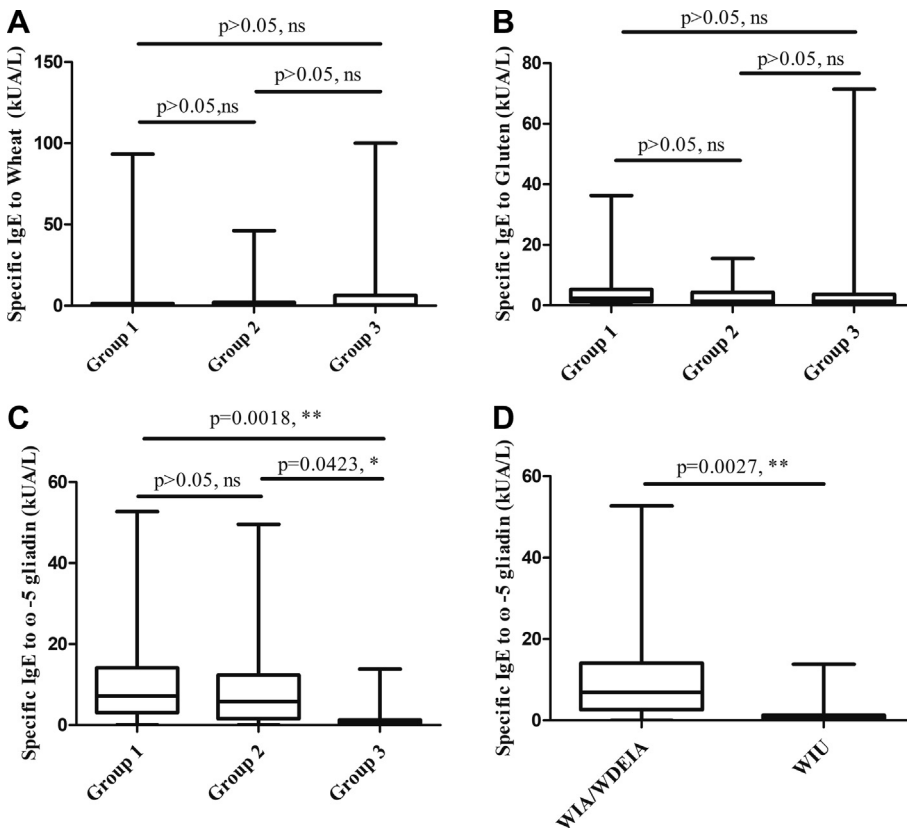


Fig. 5. Specific IgE against wheat, gluten and ω-5 gliadin among patients with WIA/WDEIA and with/without recurrent urticaria and WIU. A significant difference of ω-5 gliadin-specific IgE was found between Group 1 and 3, Group 2 and 3, and also WIA/WDEIA and WIU. Group 1: WIA/WDEIA with recurrent urticaria; Group 2: WIA/WDEIA without recurrent urticaria; Group 3: WIU. ns: not significant; WIU: wheat induced urticaria; WIA: wheat induced anaphylaxis; WDEIA: wheat dependent exercise induced anaphylaxis.

healthy controls. More patients in the atopic group and patients with non-wheat-related anaphylaxis showed positive specific IgE to wheat than recurrent urticaria. One possible reason was that the majority of these patients were allergic to weed pollen or other plant-food allergens and there might be cross-reaction between wheat and weed pollen or some plant-food. However, none of the atopic control or non-wheat-related anaphylaxis patients developed allergic manifestation after ingestion of wheat products. Compared to this high prevalence of wheat allergy in recurrent urticaria patients, none of the atopic controls or healthy controls were determined as wheat allergy. Another finding was that 84.9% of the 193 patients with WIA/WDEIA had a history of recurrent urticaria, and 70.4% of them (136/193) had recurrent urticaria before their first anaphylaxis episode. After the diagnosis of WIA/WDEIA, a wheat-free diet was recommended to these patients and a following-up questionnaire for one year was completed. Most patients subsequently experienced no episodes of urticaria or anaphylaxis during the follow-up. Only two patients reported relapsing 1 or 2 urticaria attacks during a year, which occurred after outdoor exercise but without ingestion of wheat. Interestingly, only 14.5% presented with recurrent urticaria as a complication in patients with non-wheat-relating anaphylaxis. The incidence of combined recurrent urticaria was much higher in WIA/WDEIA patients than in those with non-wheat-related anaphylaxis, which indicates recurrent urticaria may be clinically meaningful in cases of WIA/WDEIA, but not in other types of anaphylaxis.

As stated in the Mueller grading system allergic reaction was classified into 4 grades, I to IV, from generalized urticaria, to hypotension, collapse, and losing of consciousness (i.e. anaphylaxis).¹² It has been published that WDEIA could manifest as mild reaction, such as urticaria and angioedema.^{13,14} Thus, for our patients described above, recurrent urticaria and anaphylaxis may be two different degrees or phases of wheat allergy. Based on the present evidence, in WIA/WDEIA patients with previous recurrent urticaria, urticaria could develop to anaphylaxis within a broad interval range (0.1–40 years), although most cases (54%) involved progression within 1–5 years. Knowledge of this information is essential for both the physician and patient. Nevertheless, these patients have a long-term risk of anaphylaxis if they continue to have wheat allergy, especially when potentially exacerbating co-factors exist. Certain co-factors are well-documented to aggravate or precipitate WIA/WDEIA, for instance physical activity, use of aspirin and nonsteroidal anti-inflammatory drugs, and alcohol consumption.⁷ It has been generally accepted that sufficient exercise intensity can provoke anaphylaxis in patients with wheat allergy (i.e. WDEIA). Aspirin and other nonsteroidal anti-inflammatory drugs are independent risk factors for WIA/WDEIA. A retrospective study showed, on a per episode basis, 12% of anaphylactic reaction due to aspirin alone, rather than exercise.¹⁵ Corresponding to previous studies, we observed that 104 of the 193 patients with WIA got severe attacks during exercise, and 15 cases involved aspirin-related anaphylaxis. Among patients with WIA/WDEIA and a previous history of recurrent urticaria before the first anaphylactic attack, 46.3% of patients reported that their urticaria worsened concerning the involved area, duration, and treatment, while 41.1% reported an increasing frequency of urticaria attacks. Hence, the clinical progression of recurrent urticaria may be relevant for evaluating the risk of anaphylaxis among patients with wheat allergy.

Since 1999, ω -5 gliadin has been considered the major allergen in cases of WDEIA,¹⁶ and several studies have indicated that ω -5 gliadin-specific IgE can predict food challenge outcomes and facilitate the diagnosis of WIA/WDEIA.^{17–21} Here, we observed the level of specific IgE to ω -5 gliadin was remarkably higher in patients with WIA/WDEIA (median 6.87kU_A/L) than those with WIU (median 0.76kU_A/L, Fig. 5d), which may be useful for evaluating the risk of anaphylaxis in patients with wheat allergy.

According to the EAACI/GA2LEN/EDF/WAO guidelines, routine testing is not recommended for acute urticaria.²² However, for patients with recurrent episodes of acute urticaria, and those whose duration are more than 6 weeks but occurrence less than most days a week, the possible cause may be necessary to explore to some degree. Based on the findings of our study, we recommend screening wheat allergy in patients with recurrent

urticaria by a test for specific IgE to gluten and ω -5 gliadin which is useful to distinguish patients with a potential risk of WIA/WDEIA before severe reaction occurs. If there is evidence of wheat allergy, clinicians should pay attention to the potential anaphylaxis, and should focus on educating patients regarding their food diary, the symptoms of anaphylaxis, avoiding excise for 4–6 hours after wheat ingestion, and carefully consider administration of aspirin and other nonsteroidal anti-inflammatory drugs. Even emergency medicine should be prescribed to such patients in case of anaphylaxis. It may be helpful to prevent the adverse event of WIA/WDEIA.

Conclusion

In conclusion, we analyzed data from patients with WIA/WDEIA, recurrent urticaria and non-wheat-related anaphylaxis. The results indicate that 6.8% of patients with recurrent urticaria were allergic to wheat, and they had a potential risk of WIA/WDEIA. This highlights the importance of examining patients with recurrent urticaria for wheat allergy. Identifying wheat allergy patients when they manifest as recurrent urticaria and giving appropriate education is helpful to prevent severe allergic attacks. Furthermore, monitoring the clinical course of recurrent urticaria, especially regarding any changes in severity, and testing for ω -5 gliadin-specific IgE may be valuable for identifying patients with a high risk of severe reactions.

Ethics approval and consent to participate

All the patients have signed a written informed consent form before they were recruited. This study was approved by the ethics committee of Peking Union Medical College Hospital.

Consent for publication

All the participants enrolled have signed informed consent form, in which consent for publication of their clinical and laboratory data without name were included.

Availability of data and methods

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

All the authors have no conflicts of interest or financial disclosure.

Authors contributions

Ying-Yang Xu analyzed and interpreted the data, and drafted the article.

Nan-Nan Jiang made substantial contributions to acquisition of the cases.

Li-Ping Wen made substantial contributions to acquisition of the cases.

Hong Li made substantial contributions to acquisition of the cases.

Jia Yin made substantial contributions to conception and design, made major contributions to acquisition of the cases, and gave final approval of the version to be published.

Acknowledgement

We are appreciated all the patients who participated in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.waojou.2019.100013>.

Funding

This study was supported by two foundations: CAMS Innovation Fund for Medical Sciences (CIFMS, NO. 2016-I2M-1-003), National Natural Science Foundation of China (NO. 81273277) and National Epidemiology Study of Asthma and Allergies in China (NO. 200802001).

References

- Inomata N. Wheat allergy. *Curr Opin Allergy Clin Immunol*. 2009;9:238–243.
- Houba R, Doekes G, Heederik D. Occupational respiratory allergy in bakery workers: a review of the literature. *Am J Ind Med*. 1998;34:529–546.
- Vierk KA, Koehler KM, Fein SB, Street DA. Prevalence of self-reported food allergy in American adults and use of food labels. *J Allergy Clin Immunol*. 2007;119:1504–1510.
- Morita E, Chinuki Y, Takahashi H, Nabika T, Yamasaki M, Shiwaku K. Prevalence of wheat allergy in Japanese adults. *Allergol Int*. 2012;61:101–105.
- 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;8:353–361.
- Yin J, Wen L. Wheat-dependent exercise-induced anaphylaxis clinical and laboratory findings in 15 cases. *Chin J Allergy Clin Immunol*. 2010;4:26–32.
- Scherf KA, Brockow K, Biedermann T, Koehler P, Wieser H. Wheat-dependent exercise-induced anaphylaxis. *Clin Exp Allergy*. 2016;46:10–20.
- Cox LS, Sanchez-Borges M, Lockey RF. World allergy organization systemic allergic reaction grading system: is a modification needed? *J Allergy Clin Immunol Pract*. 2017;5:58–62.
- Majamaa H, Moisiö P, Holm K, Turjanmaa K. Wheat allergy: diagnostic accuracy of skin prick and patch tests and specific IgE. *Allergy*. 1999;54:851–856.
- Morita E, Kunie K, Matsuo H. Food-dependent exercise-induced anaphylaxis. *J Dermatol Sci*. 2007;47:109–117.
- Yang MS, Lee SH, Kim TW, et al. Epidemiologic and clinical features of anaphylaxis in Korea. *Ann Allergy Asthma Immunol*. 2008;100:31–36.
- Mueller U, ed. *Insect Sting Allergy: Clinical Picture, Diagnosis and Treatment Stuttgart*. New York: Gustav Fischer Verlag; 1990.
- Tanaka S. An epidemiological survey on food dependent exercise-induced anaphylaxis in kindergartners, school children and junior high school students. *Asia Pac J Public Health*. 1994;7:26–30.
- Wong GK, Huissoon AP, Goddard S, Collins DM, Krishna MT. Wheat dependent exercise induced anaphylaxis: is this an appropriate terminology? *J Clin Pathol*. 2010;63:814–817.
- Jiang N, Yin J, Wen L-P. Aspirin related wheat dependent excise induced anaphylaxis: a retrospective analysis of 20 cases. *Chin J Allergy Immunol*. 2014;8:181–187.
- Palosuo K, Alenius H, Varjonen E, et al. A novel wheat gliadin as a cause of exercise-induced anaphylaxis. *J Allergy Clin Immunol*. 1999;103:912–917.
- Ebisawa M, Shibata R, Sato S, Borres MP, Ito K. Clinical utility of IgE antibodies to ω -5 gliadin in the diagnosis of wheat allergy: a pediatric multicenter challenge study. *Int Arch Allergy Immunol*. 2012;158:71–76.
- Matsuo H, Dahlström J, Tanaka A, et al. Sensitivity and specificity of recombinant ω -5 gliadin-specific IgE measurement for the diagnosis of wheat-dependent exercise-induced anaphylaxis. *Allergy*. 2008;63:233–236.
- Park HJ, Kim JH, Kim JE, et al. Diagnostic value of the serum-specific IgE ratio of ω -5 gliadin to wheat in adult patients with wheat-induced anaphylaxis. *Int Arch Allergy Immunol*. 2012;157:147–150.
- Palosuo K, Varjonen E, Kekki OM, et al. Wheat ω -gliadin is a major allergen in children with immediate allergy to ingested wheat. *J Allergy Clin Immunol*. 2001;108:634–638.
- Christensen MJ, Eller E, Mortz CG, Brockow K, Bindslev-Jensen C. Exercise lowers threshold and increases severity, but wheat-dependent, exercise-induced anaphylaxis can be elicited at rest. *J Allergy Clin Immunol Pract*. 2018;6:514–520.
- Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73:1393–1414.