

Characterization of children with IgE-mediated wheat allergy and risk factors that predict wheat anaphylaxis

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Abstract

Background: The number of children presenting with IgE-mediated wheat reactions to academic medical centers in Thailand continues to increase.

Objective: Improved knowledge about the clinical characteristic of wheat allergy is urgently needed to better understand the risk factors and to improve proper treatment in this patient population.

Methods: A cross-sectional study using questionnaire review of children who presented with IgE-mediated wheat allergy during 2001 to 2015 was performed. Patients were divided into the wheat anaphylaxis (WA) or the only skin symptoms (SO) group.

Results: One hundred children were enrolled. Fifty-one and 49 patients were allocated to the WA and SO group, respectively. The median age was 40.5 months (range: 6-200), and the median age of onset was 7 months (range: 3-96). The vast majority (90%) developed their first reaction after their first ingestion of wheat. Atopic dermatitis (AD) was found to be the only significant difference between groups and found more commonly in SO than in WA (59.2% vs. 35.3%, $p = 0.02$). Median mean wheal diameter (MWD) of skin prick test (SPT) and median sIgE level to wheat were higher in WA than in SO (8 vs. 3 mm, $p < 0.001$; and, 33.3 vs. 3.6 kU_A/l, $p < 0.001$).

Conclusion: Children with wheat allergy presented very early in life. AD was found in approximately half of the patients, and more commonly in SO. Median MWD of SPT and sIgE level to wheat were significantly higher in WA. These data will aid in further planning for a larger survey and intervention study in wheat allergy.

Key words: Clinical characteristic, IgE-mediated wheat allergy, children, risk factor, anaphylaxis

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Abbreviations:

SO only skin symptoms
WA wheat anaphylaxis

Introduction

An increase in the prevalence of food allergy has been globally observed in recent years.^{1,2} In addition to cow's milk, egg, peanut, soy, and seafood,³ wheat is one of the major causes of food allergy among children.^{4,5} Regarding IgE-mediated wheat allergy, the cutaneous system is responsible for the most common presenting symptom; however, anaphylaxis, which is the most severe form of all reactions, can be infrequently observed.^{6,7} The median age of tolerance from wheat allergy was reported to be approximately 6 years of age; however, a minority of patients will have wheat allergy that will persist into adolescence and adulthood.^{8,9} The prevalence of wheat allergy varied depending on the diagnostic methods used and the ethnicities studied.¹⁰

A study in conducted in Europe showed the prevalence of wheat allergy by oral challenge test to be 0.2-0.5%.¹¹ In Asia, the prevalence of wheat allergy varies significantly among countries. The highest prevalence of wheat allergy was found in Japan and Korea, with far lower rates of prevalence observed in other Asian countries.^{12,13} Over the last 2-3 decades in Thailand, wheat has developed into another leading food that causes allergic reactions in children.⁴ In addition, most of these patients were very young children. The cause of this disparity in the prevalence of wheat allergy among different countries and parts of the world is still not clearly understood. Moreover, few studies have set forth to determine the risk factors for developing wheat allergy. A systematic review concluded that early introduction of wheat might reduce the risk of wheat sensitization early in life, but that early introduction does not affect the risk of developing wheat allergy.¹⁴ In addition, the results of an investigation to elucidate the effect of breast feeding on wheat allergy development were inconclusive.¹⁴ Further studies about clinical characteristic of wheat-allergic patients might help us better understand the factors that influence the development of wheat allergy.

Accordingly, the aim of this study was to investigate the clinical characteristic of IgE-mediated wheat-allergic patients among Thai children, and to identify risk factors that are significantly associated with the severity of wheat allergy reactions.

Methods

A cross-sectional study using questionnaire review of children aged 0-18 years who presented with IgE-mediated wheat allergy was performed. Medical records from the Division of Allergy and Immunology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand and from the Samitivej Allergy Institute (SAI), Samitivej Thonburi Hospital, Bangkok, Thailand during 2001-2015 were reviewed to identify any eligible patients. Eligible patients were then invited to participate in the study by their physician during follow-up visits at the clinic of each participating center.

The diagnosis of IgE-mediated wheat allergy was made if patients met at least one of the following criteria: 1) a convincing clinical history of reactions within 4 hours after wheat ingestion combined with positive skin prick test (SPT) and/or a level of specific IgE (sIgE) to wheat that indicates a positive test within the previous year; or, 2) a positive oral food challenge (OFC) to wheat within the previous year. A mean wheal diameter (MWD) of SPT to crude wheat extract (1:10)¹⁵ of at least 3 mm greater than negative saline control and sIgE to wheat greater than 0.35 kU_A/l (ImmunoCAP, Uppsala, Sweden) were defined as positive. Patients with wheat anaphylaxis (WA) defined according to the clinical criteria published by the World Health Organization¹⁶ were assigned to the WA group, and those with only skin and mucosal involvement (SO) were allocated to the SO group. We excluded patients with delayed allergic reactions after wheat ingestion greater than 4 hours or patients that had wheat-dependent exercise-induced anaphylaxis. This study was approved by the Siriraj Institutional Review Board (SIRB)

(COA no. 250/2017). Written informed consent from parents or guardians and assent from children older than 7 years of age were obtained.

Demographic and clinical data, including gender, age at enrollment, age at onset of wheat allergy reaction, symptoms of the most severe wheat hypersensitivity reaction, onset of symptoms after wheat ingestion, duration of breast feeding, time to introduction of solid food, time to introduction to wheat, wheat ingestion during pregnancy (type of food was asked and then calculated into slices of bread equivalent of wheat protein), history of accidental exposure that lead to emergency department (ED) visit and/or hospitalization, received a prescription for adrenaline devices (adrenaline auto-injector and/or adrenaline prefilled-syringe), other allergic diseases, family history of allergic diseases, number of siblings, and socioeconomic status were collected, recorded, and analyzed. Allergy testing, including skin prick testing and/or level of sIgE to wheat, sIgE to omega-5 gliadin (ω 5G) and skin prick testing to grasses (Bermuda and Johnson) and other aeroallergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farina*, cat, dog, American cockroach, German cockroach, Carelessweed, Alternaria, Penicillium, Curvularia, and Cladosporium) were reviewed from medical records. Those tests were considered positive if the size of the MWD was at least 3 mm greater than that of the negative saline control. For patients who had SPT or sIgE to wheat, and sIgE to ω 5G performed more than once, the maximum size of the MWD and sIgE level were selected and included in our analysis.

Diagnosis of other allergic diseases and other food allergies were made by a group of board-certified allergists (Board of Pediatric Allergy, Royal College of Pediatrics of Thailand). Allergy to other foods was defined as having had a clear symptomatic reaction to food with a positive SPT and/or sIgE to specific foods, or with positive oral food challenge result.

Statistical analysis

All analyses were performed using SPSS Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). Categorical data are presented as number and percentage (%). Continuous data are expressed as mean \pm standard deviation (SD) for normally distributed data, and as median and range (minimum, maximum) for non-normally distributed data. The results of skin prick test or specific IgE are presented as median and interquartile range (IQR). Student's *t*-test was used to compare normally distributed continuous variables, Mann-Whitney U test was used to compare non-normally distributed continuous data, and chi-square test was used to compare categorical variables between groups. Parameters with *p*-value less than 0.1 was selected for multivariate logistic regression analysis to identify the risk factors, and predict the severity of wheat allergy reaction. A *p*-value less than 0.05 indicates statistical significance.

Receiver-operating characteristics (ROC) curves were used to establish the best cutoff value of the MWD of SPT to wheat, sIgE level to wheat, and sIgE level to ω 5G. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using the

best cutoff value according to a ROC curve analysis result, in order to distinguish WA, from SO group.

Results

One hundred eligible patients with wheat allergy were identified from medical record. All of them were asked and enrolled into the study. The demographic and clinical characteristics of patients are shown in **Table 1**. Forty-nine patients (49%) were classified as SO, and 51 patients (51%) were WA (**Figure 1**). The median age at enrollment was 40.5 months (range: 6-200), with a median age of onset of 7 months (range: 3-96). The majority of IgE-mediated wheat allergy patients developed their first reaction during the first year of life (48% during 0-6 months, and 46.0% during 7-12 months) (**Figure 2**). Reactions occurred during/after the first ingestion of wheat in 90 patients (90%). Solid food was introduced at the mean age of 5.7 ± 1.5 months, and wheat was introduced at the mean age of 7.4 ± 2.7 months. Median duration of breast feeding was 6 months (range: 0-36). The median estimated amount of wheat ingestion during pregnancy was 3 slices of bread per/week (range: 1-14 slices of bread/week).

Other food allergy was found in 54 patients (54%). Atopic dermatitis (AD) was found in 47 patients (47%), followed by allergic rhinitis (44%) and asthma (14%). Skin prick test to

grasses and other aeroallergens was performed in 81 patients, with positive result in 12 (14.8%) and 52 (64.2%) patients, respectively. Family history of any allergic diseases was reported in 45 (45%) patients.

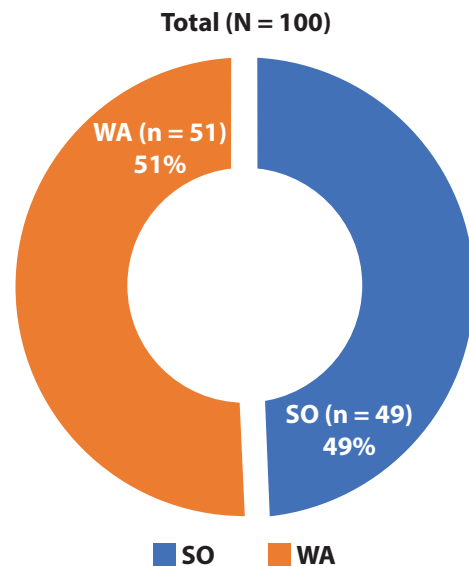


Figure 1. Number of patients with only skin symptoms (SO), and those with wheat anaphylaxis (WA)

Table 1. Demographic and clinical characteristic of patients compared between the skin symptoms (SO) and wheat anaphylaxis (WA) groups

Characteristics	Total (N = 100)	SO (n = 49)	WA (n = 51)	p
Male gender	49 (49%)	24 (49%)	25 (49%)	0.99
Age at enrollment (months)	40.5 (6-200)	38 (6-126)	43 (6-200)	0.16
Age of onset (months)	7 (3-96)	6 (3-96)	7 (3-84)	0.45
First time of wheat ingestion	90 (90%)	42 (85.7%)	48 (94.1%)	0.20
Duration of breast feeding (months)	6 (0-36)	6 (2-36)	6 (0-36)	0.25
Wheat ingestion during pregnancy (slices of bread/week)	3 (1-14)	2.5 (1-14)	3 (1-14)	0.84
Time to introduction of solid foods (months)	5.7 ± 1.5	5.4 ± 1.5	5.9 ± 1.5	0.10
Time to introduction of wheat (months)	7.4 ± 2.7	7.2 ± 2.8	7.5 ± 2.6	0.57
Other food allergy	54 (54.0%)	30 (61.2%)	24 (47.1%)	0.16
Allergic diseases				
AD	47 (47%)	29 (59.2%)	18 (35.3%)	0.02
AR	44 (44%)	21 (42.9%)	23 (45.1%)	0.82
AA	14 (14%)	5 (10.2%)	9 (17.6%)	0.28
Sensitization to grass [†]	12/81 (14.8%)	5/40 (12.5%)	7/41 (17.1%)	0.84
Sensitization to aeroallergen [†]	52/81 (64.2%)	29/40 (72.5%)	23/41 (56.1%)	0.30
Family history of any allergy	45 (45%)	22 (44.9%)	23 (45.1%)	0.98

Data presented as number and percentage, median and range (minimum, maximum), or mean \pm standard deviation

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; AA, atopic asthma

[†]Performed in 81/100 patients (n = 40 in SO, n = 41 in WA)

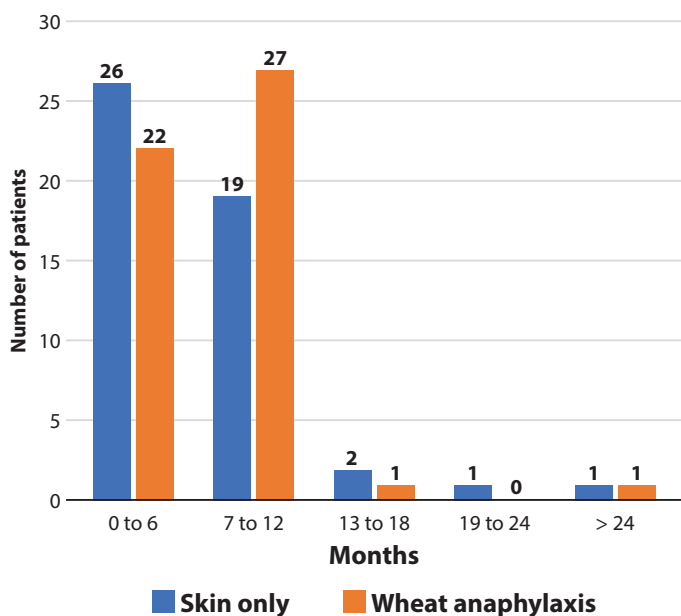


Figure 2. Onset of wheat allergy compared among patients with only skin symptoms (SO), and those with wheat anaphylaxis (WA)

Comparisons between groups (Tables 1 and 2) revealed history of AD to be the only statistically significant factor. AD was found to be significantly more common in SO than in WA (59.2% vs. 35.3%, $p = 0.02$) with an adjusted odds ratio (AOR) of 0.41 (95% CI: 0.18-0.93; $p = 0.03$). Introduction to solid food was delayed in the WA group compared to the SO group, but the difference between groups was not statistically significant (5.9 ± 1.5 vs. 5.4 ± 1.5 months, $p = 0.10$) (AOR: 1.22, 95% CI: 0.90-1.65, $p = 0.20$). There was no significant difference between groups relative to gender, age of onset, duration of breast feeding, wheat ingestion during pregnancy, time to introduction to wheat, having other food allergy,

allergic rhinitis, asthma, or positive family history of allergic diseases (Table 1). The number of siblings and socioeconomic status were also not significantly different between groups (data not shown).

Furthermore, patients with or without AD were compared, however there was no statistically significant difference between the groups, in terms of clinical characteristics and wheat allergy testing.

Number of children reported accidental exposure which required ED visit and/or hospitalization, and those whom received a prescription for adrenaline devices were significantly higher among WA compared to the SO group (35% vs. 12%, $p < 0.001$), and (40% vs. 10%, $p < 0.001$), respectively. However, among WA group, only 78.4% of them received a prescription for adrenaline devices.

The median MWD of the SPT to wheat was 4.5 mm (IQR: 2.6-10), whereas the median level of sIgE to wheat, and ω 5G were 9.9 kU_A/l (IQR: 1.6-65.2), and 1.3 kU_A/l (IQR: 0.1-11.7), respectively. The MWD of SPT to wheat was significantly larger, and the level of sIgE to wheat, and ω 5G were significantly higher in WA than in SO (Table 3).

ROC curves analysis showed a statistically significant to predict WA with area under the curve (AUC) of 0.718 (95% CI: 0.611-0.825; $p < 0.001$), 0.763 (95% CI: 0.669-0.856; $p < 0.001$), and 0.737 (95% CI: 0.627-0.848; $p < 0.001$) when using MWD of SPT to wheat, sIgE level to wheat, and sIgE level to ω 5G, respectively (Table 4a). The optimal cutoff values to predict anaphylaxis risk were found to be at 7.5 mm for MWD of SPT to wheat, 30.9 kU_A/l for sIgE level to wheat, and 3.1 kU_A/l for sIgE level to ω 5G.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) using the best cut-off value according to the ROC curves analysis of MWD of SPT to wheat, sIgE level to wheat, and sIgE level to ω 5G, in order to distinguish WA from SO were presented in Table 4b.

Table 2. Stepwise multivariate logistic regression analysis to identify factors that independently predict wheat anaphylaxis (WA) as compared to skin symptoms (SO) groups

Factors	WA (reference factor)	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
Atopic dermatitis	1	0.38 (0.17-0.85)	0.02	0.41 (0.18-0.93)	0.03
Time to introduction of solid food (months)	1	1.27 (0.95-1.71)	0.10	1.22 (0.90-1.65)	0.20

Table 3. Median size of mean wheal diameter (MWD) of skin prick test (SPT) to wheat, median level of specific IgE (sIgE) to wheat, and omega-5 gliadin (ω 5G) compared between the groups

Allergic testing	Total	SO	WA	p
MWD of SPT to wheat (IQR) [†]	4.5 mm (2.6-10)	3 mm (0-7)	8 mm (3.8-11)	< 0.001
sIgE to wheat (IQR) [‡]	9.9 kU_A/l (1.6-65.2)	3.6 kU_A/l (0.5-15.2)	33.3 kU_A/l (3.0-354)	< 0.001
sIgE to ω 5G (IQR) [§]	1.3 kU_A/l (0.1-11.7)	0.3 kU_A/l (0.1-13.8)	6.4 kU_A/l (0.5-22.1)	< 0.001

Data presented as median and interquartile range

[†]Performed in 88/100 patients (n = 46 in SO, n = 42 in WA)

[‡]Performed in 96/100 patients (n = 47 in SO, n = 49 in WA)

[§]Performed in 82/100 patients (n = 38 in SO, n = 44 in WA)

Table 4a. Area under the curve (AUC) of a receiver-operating characteristic (ROC) analysis using mean wheal diameter (MWD) of skin prick test (SPT) to wheat, level of specific IgE (sIgE) to wheat, and omega-5 gliadin (ω 5G), in order to distinguish wheat anaphylaxis (WA) as compared to skin only (SO) groups

Allergic testing	AUC	(95% CI)	<i>p</i>
MDW of SPT to wheat	0.718	0.611-0.825	< 0.001
sIgE to wheat	0.763	0.669-0.856	< 0.001
sIgE to ω 5G	0.737	0.627-0.848	< 0.001

Table 4b. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of mean wheal diameter (MWD) of skin prick test (SPT) to wheat, level of specific IgE (sIgE) to wheat, and omega-5 gliadin (ω 5G) using the best cutoff value according to a receiver-operating characteristics (ROC) curve analysis, in order to distinguish wheat anaphylaxis (WA) as compared to skin only (SO) groups

Cutoff	Sensitivity	Specificity	PPV	NPV
MWD of SPT to wheat \geq 7.5 mm	54.8%	80.4%	71.9%	66.1%
sIgE level to wheat \geq 30.9 kUA/l	51%	87.2%	80.6%	63.1%
sIgE level to ω 5G \geq 3.1 kUA/l	65.9%	84.2%	82.9%	68.1%

Discussion

This is the first study to date that fully elucidates the clinical characteristic of IgE-mediated wheat-allergic patients in children, particularly among Asian children. Our study suggests that the onset of wheat allergy begins very early in life, particularly during the first year of life (94% of our patients developed their first reactions within the first year of life). Moreover, their reactions occurred at their first introduction to wheat as a complementary food (90%). Age of onset of wheat allergy did not differ from other common foods that cause food allergy, such as egg and cow's milk.¹⁷ However, atopic dermatitis was found in only approximately half of our patients (47%). This finding indicates that the route of sensitization may be variable and may include the skin. Other prenatal, perinatal, and postnatal factors, microbial exposure, route of delivery, breast feeding, and diet factors may facilitate and promote the increasing incidence of this food allergy.¹⁸

In this study, we compared various factors that might predict disease severity in wheat allergy. Atopic dermatitis was found to be the only significant clinical preventive factor (AOR: 0.41, 95% CI: 0.18-0.93; *p* = 0.03) from WA, as compared to the SO group. Other studies of the natural history of cow's milk¹⁹ and egg allergy²⁰ in an observational cohort that found AD and AD severity to be significantly

associated with negative outcome of food allergy resolution; however, those studies did not compare between the severity of AD and anaphylaxis.

Approximately half of our patients, particularly among those in WA group experienced a severe reaction after accidentally consuming of wheat-containing food, even after the diagnosis has been made. Moreover, only three-quarter of WA children received adrenaline devices prescription. This result similar to the report by Ratanaprug C, *et al.*²¹ In that study, the rate of repeated anaphylaxis among children with history of food-induced anaphylaxis was approximately 40%, and only 85% of them carrying adrenaline devices.

We found that the larger size of the MWD of the SPT to wheat, and the higher level of sIgE to wheat, and ω 5G were addressed among WA. Anaphylaxis risk increased when the MWD size of SPT was 7.5 mm or larger than the normal saline control, when the level of sIgE to wheat was at least 30.9 kU_A/l or greater, and when the level of sIgE to ω 5G was at least 3.1 kU_A/l or greater, which suggests that these cut-offs of could be useful predictors for determining the severity of wheat allergy. Previous study from Keet CA, *et al.*⁸ reported peak wheat sIgE level to be a useful predictor of persistence/resolution of wheat allergy.

Diagnostic performance of SPT, and sIgE to wheat and ω 5G had been shown in several studies,²²⁻²⁴ in order to diagnose IgE-mediated wheat allergy. However, there has not been reported to distinguish WA, from those with SO symptoms before.

Grass sensitization was found in only 14.8% of patients in the present study. This result agreed with the study by Jones, *et al.*²⁵ that found no cross-reactivity between cereal grains and Bermuda grass; however, extensive cross-reactivity was observed between timothy and meadow fescue, both of which are in the same subfamily as wheat.

The strengths of the current study include the relatively large sample size. Furthermore, this is the first study to our knowledge that determine the cutoff value of wheat-allergic testing to distinguish WA, from those with SO symptoms. However, this study's most notable limitation is the lack of a control group that would have improved our ability to identify possible risk factors that might be associated with wheat allergy development, and the fact that some information was obtained from parental recall.

In conclusion, immediate reaction to wheat allergy among wheat allergy children from Thailand occurred very early in life, and at their first introduction to wheat. Since atopic dermatitis might not be the only route of sensitization, further investigation for other potential risk factors should be undertaken in a larger scale study.

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Conflict of interest declaration

All authors declare no personal or professional conflicts of interest relating to any aspect of this study.

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