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# Age of resolution from IgE-mediated wheat allergy

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## Abstract

**Background:** Wheat allergy is common in children. The natural history of wheat allergies varies among different countries.

**Objective:** To study the age of resolution from IgE-mediated wheat allergy and to define the predictors of wheat tolerance.

**Method:** Patients with a history of immediate reactions after wheat ingestion were included in this study. Skin prick tests (SPTs) and measurement of serum-specific IgE (sIgE) to wheat and ω-5 gliadin was performed. An oral challenge to wheat was performed to determine wheat tolerance.

**Results:** Fifty-five patients aged between 6 months and 12 years were included in this study. The median age for development of wheat tolerance was found to be 76 months (range 37–114 months). The proportion of children with wheat tolerance was 14.7% by 2 years of age, 27% by 4 years, 45.7% by 5 years and 69% by 9 years of age. An independent predictor for wheat tolerance was sIgE levels against ω-5 gliadin of less than 0.35 kAU/L (adjusted hazard ratio 5.7; 95% CI 1.2–26.8).

**Conclusions:** Of the children with IgE-mediated wheat allergy included in this study, 45.7% developed tolerance by 5 years of age. The concentration of sIgE for ω-5 gliadin is helpful for predicting wheat tolerance.

**Keywords:** Age of resolution; IgE-mediated food allergy; Natural history; Wheat allergy; Outgrow

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## Introduction

Wheat (*Triticum* spp.) is usually introduced into the diet at an early stage of human life (approximately 4-6 months of age). Currently, the prevalence of wheat allergy (WA) is increasing,[1] and the principle recommendation for treatment is the avoidance of wheat-containing foods to prevent allergy symptoms.[2, 3] However, wheat can be hidden or mixed into a wide variety of foods. Therefore, it is difficult to achieve complete avoidance as per the standard worldwide recommendations. Although wheat is one of the most common food allergens in children, the natural history of IgE-mediated WA has been rarely reported.[4-7] A recent study showed that the median age of resolution for WA is 79 months.[4] Another study showed similar results, but used a smaller number of participants and did not report the number of patients that underwent an oral food challenge (OFC).[5]

In this study, we prospectively evaluated children with IgE-mediated WA to determine the age of resolution and to define the predictors of wheat tolerance.

## Methods

### *Patients*

Patients with a history of immediate allergic reactions within 2 hours of wheat ingestion were identified from the allergy clinic of the Department of Pediatrics, Siriraj Hospital between 2012 and 2014. Immediate reactions to wheat were defined by: (1) a positive OFC result; or (2) a recent history (no longer than 1 year) of an immediate reaction after wheat ingestion combined with a positive skin prick test (SPT) or level of specific IgE (sIgE) to wheat of greater than 0.35 kAU/L. An OFC was performed on patients that had avoided wheat ingestion and had no accidental exposure for more than 1 year in order to confirm the IgE-mediated WA diagnosis. We then followed up all patients every 3 months, in addition to determining their sIgE for wheat and ω-5 gliadin levels every 6 months. If the patients' sIgE levels to wheat were ≤ 26 kAU/L and ω-5 gliadin ≤ 1.06 kAU/L,[1,8] an OFC was performed to evaluate the resolution of IgE-mediated WA. Demographic data, clinical manifestations, the wheal size from the SPT, and the levels of

serum sIgE to wheat and ω-5 gliadin were collected prospectively. The Siriraj Institutional Review Board granted ethical approval. Patients with a history of cardiovascular disease, epilepsy or those with a delayed allergic reaction after wheat ingestion of greater than 2 hours were excluded from the study. Written informed consent from parents or guardians, and assent from children older than 7 years of age was obtained.

The patient data collected included the sex, age at enrollment, age at onset of wheat allergic reaction, duration of breastfeeding, age of solid food introduction, amount and type of food at first symptoms, symptoms for wheat hypersensitivity diagnosis, onset of symptoms after wheat ingestion, treatment, other atopic diseases and food allergies, and family history of atopic diseases.

The diagnosis of other atopic diseases and food allergies was performed by allergists. An allergy to other foods was defined as the patient having had clear symptomatic reactions to the specific food, combined with a positive SPT or sIgE to the food.

### *Skin prick test procedure*

The SPT was performed on each patients' back with a lancet, by using a commercial wheat extract (ALK Abello, Hørsholm, Denmark) and a crude wheat extract in Coca's solution with 10% alcohol (1:10 w/v), as described previously.[9] Histamine phosphate (10 mg/mL) and glycerinated saline were used as the positive and negative controls, respectively. The size of the wheal reaction was recorded as positive if it was ≥ 3 mm larger than the negative control.

### *Specific IgE for wheat and ω-5 gliadin*

The sIgE for wheat and ω-5 gliadin was measured every 6 months using the ImmunoCAP system (lower detection limit < 0.35 kAU/L; Phadia, Uppsala, Sweden).

### *Food challenge procedure*

Due to the severe symptoms of IgE-mediated WA, we followed a safety criteria to select patients for which an OFC could be performed. This criteria included: patients who had no symptomatic WA reactions for the 1 year prior; SPT for wheat ≤ 3 mm; and sIgE levels for wheat and ω-5 gliadin of ≤ 26 and 1.06 kAU/L, respectively. These sIgE cut-off levels had been determined previously,[1,8] and demonstrated the relationship between the sIgE levels and clinical reactivity. However, use of the size of the wheal induced by the wheat SPT for predicting clinical reactivity has not previously been reported.

The opened food challenge protocol began with 100 mg of wheat,[10,11] provided by sliced bread, which increased to 0.5, 1.0, 2.0, 4.0, 8.0 and 15.4 g at 30-minute intervals until a cumulative dose of 31 g of wheat (two slices of bread) was achieved, equivalent to 4.0 g of wheat protein. The challenges were terminated at the first sign of clinical reactivity.[12-14] The result of the challenge was defined as negative if the patient had no signs of an allergic reaction for at least 2 hours after completing the challenge. Wheat tolerance was diagnosed when the patients passed the OFC.

### *Statistical analysis*

All analyses was performed with SPSS Statistics version 18.0 (SPSS Inc., Chicago, IL, USA). Continuous data was presented as the median value and range, whereas categorical data was expressed as a number and percentage. Receiver operating characteristic (ROC) was used to calculate the best cut-point values, and the area under the curve (AUC) of the ROC was used for the comparison. The Kaplan-Meier method was used to generate the curves for the time taken to develop wheat tolerance, and the log-rank test was used to compare these curves among groups. Cox regression analysis was used to identify the predictors of wheat tolerance. Factors with a univariate p-value of < 0.1 were chosen for multiple Cox regression analysis. All tests were two-sided, and a *p*-value < 0.05 was considered statistically significant.

## Results

### *Baseline characteristics and food hypersensitivity*

Fifty-five patients were enrolled in this study, and the median age at enrollment was 34 months (range 6-144 months). The median age of symptom onset was 7 months (range 3-96 months). The mean age for solid food introduction was 6 months. The median duration of breastfeeding was 6 months (range 0-36 months), and out of 55 patients, 45 (81.8%) had been breastfed for more than 6 months. Patients were followed up until a median age of 40 months (range 10-139 months). The SPT for aeroallergens was performed in 37 patients, and 26 of them (70.2%) had a positive result. The baseline characteristics of the study population are shown in **Table 1**.

**Table 1. Baseline characteristics and food hypersensitivity symptoms of the study population (n = 55).**

| Baseline characteristics | Number of children (%) |
|---|---|
| Sex | |
| Male | 29 (52.7) |
| Female | 26 (47.3) |
| Severity of symptoms | |
| Urticaria/angioedema | 31 (56.4) |
| Anaphylaxis | 24 (43.6) |
| Organ involvement | |
| Skin | 55 (100) |
| Respiratory* | 24 (43.6) |
| Gastrointestinal* | 7 (12.7) |
| Cardiovascular* | 2 (3.6) |
| Neurologic* | 1 (1.8) |
| Other atopic conditions** | 34 (61.8) |
| Allergic rhinitis | 14 (25.5) |
| Asthma | 3 (5.5) |
| Atopic dermatitis | 20 (36.4) |
| Food allergy | 25 (45.5) |
| Cow's milk | 15 (27.3) |
| Egg | 20 (36.4) |
| Soybean | 5 (9.1) |
| Peanut | 5 (9.1) |
| Seafood | 9 (16.4) |
| Family history of atopic disease | 21 (38.2) |
| Maternal atopy | 11 (20.0) |
| Paternal atopy | 16 (29.1) |

* Only in anaphylaxis cases
**Diagnosed by allergists

From the allergy testing, the median wheal size from reactions to the commercial wheat and crude wheat extracts was 3.0 mm (IQR 0-6 mm) and 3.5 mm (IQR 0-10 mm), respectively. The median wheat and ω-5 gliadin sIgE levels were 3.78 kAU/L (range from 0.05 to >100 kAU/L) and 0.44 kAU/L (range 0-77.4 kAU/L), respectively. Of these patients, five had wheat sIgE levels between 50-99.9 kAU/L, and five had wheat sIgE levels ≥ 100 kAU/L.

### *Development of wheat tolerance*

Out of 55 patients, 25 (45.5%) met the safety criteria, and were subjected to the OFC. Of these patients, 18 (32.7%) passed the challenge. The median age for development of wheat tolerance was 76 months (range 37–114 months). The percentage of children with wheat tolerance was 14.7% by 2 years of age, 27% by 4 years, 45.7% by 5 years and 69% by 9 years of age (**Figure 1**). Among the 30 patients who were not suitable for OFC, 13 had a wheat sIgE > 26 kAU/L, 7 had ω-5 gliadin sIgE > 1.06 kAU/L, and 10 had a recent history of an allergic reaction to wheat.

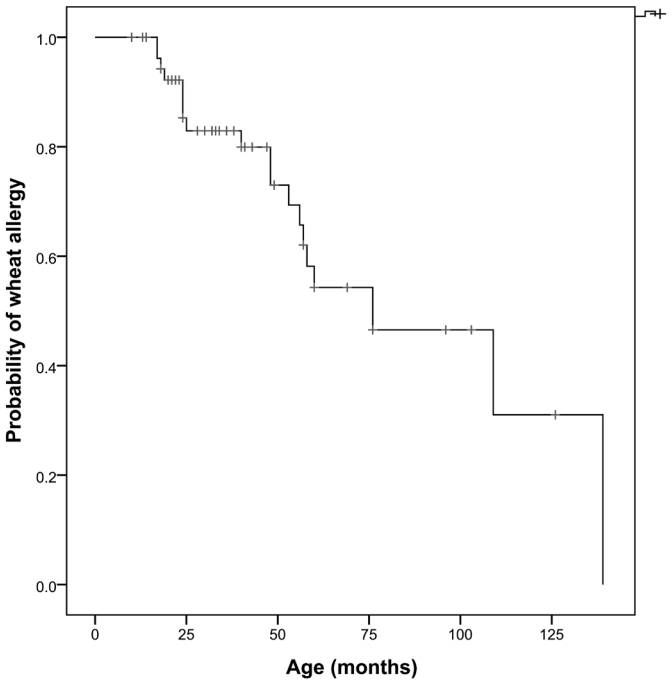


**Figure 1. Kaplan-Meier analysis of wheat tolerance after onset of IgE-mediated wheat allergy (N = 55).**

### *Predictors of wheat tolerance*

The factors found to be the best predictors for WA resolution or tolerance included the wheat SPT wheal size and the sIgE level for wheat and ω-5 gliadin before defining the tolerance of the patient (**Table 2**). However, the multiple Cox regression analysis showed that only the level of sIgE against ω-5 gliadin was an independent risk factor for predicting WA resolution (adjusted hazard ratio (aHR) 5.67, 95% CI 1.19–26.83; **Table 2**). However, the allergy type, family history of atopic disease, duration of breastfeeding, time of solid food introduction, and the amount of trigger food required to induce a reaction were not predictors of tolerance (data not shown).

**Table 2. Factors associated with wheat tolerance.**

| Factors | Crude HR (95%CI) | P-value | Adjusted HR* (95%CI) | P-value |
|---|---|---|---|---|
| Wheat sIgE level | | | | |
| < 0.35 kAU/L | 1.00 | | 1.00 | |
| ≥ 0.35 kAU/L | 4.33 (1.63-11.47) | 0.003 | 1.76 (0.63-4.95) | 0.285 |
| ω-5-gliadin sIgE level | | | | |
| < 0.35 kAU/L | 1.00 | | 1.00 | |
| ≥ 0.35 kAU/L | 8.64 (1.98-37.72) | 0.004 | 5.67 (1.19-26.83) | 0.029 |
| Wheat SPT wheal size | | | | |
| < 3 mm | 1.00 | | 1.00 | |
| ≥ 3 mm | 4.11 (1.18-14.37) | 0.027 | 2.28 (0.62-8.41) | 0.214 |

SPT = skin prick test; sIgE = serum specific IgE; HR = Hazard Ratio
*Adjusted for all factors listed

Different cut-off points for the ω-5 gliadin sIgE level were used to determine the greatest sensitivity, specificity, positive predictive value, negative predictive value, accuracy and the likelihood ratio (**Table 3**). We found that the best accuracy (83.6%) and the highest positive likelihood ratio (7.65) was observed when 0.35 kAU/L was used as the cut-off point. To evaluate the ability of the different tests for the diagnosis of tolerance from immediate wheat hypersensitivity, the AUC of the ROC for each test was performed. Among the three tests, the sIgE for ω-5 gliadin had the best diagnostic capacity for predicting WA resolution (AUC 0.90) compared to sIgE for wheat (AUC 0.84), and wheat SPT (AUC 0.81) in predicting wheat allergy resolution. (**Figure 2**).

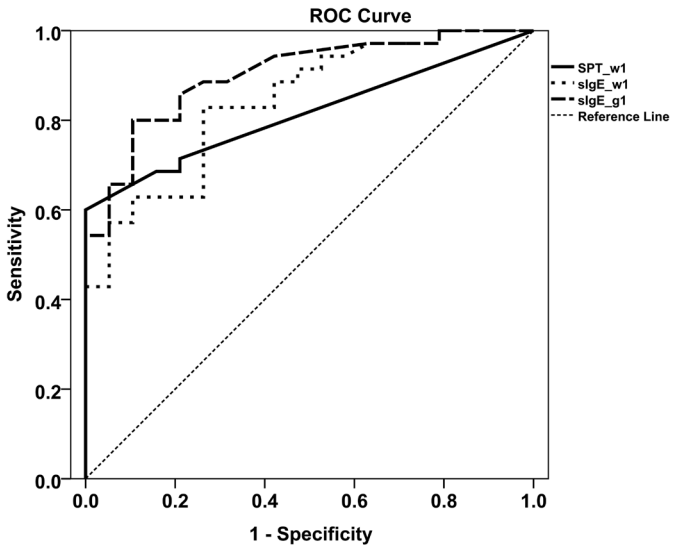


**Figure 2. Receiver operating characteristic curves for immediate wheat reactions in oral wheat challenge in comparison between wheat SPT wheal size, the sIgE level for wheat and ω-5 gliadin.**

In addition, a significant difference (P = 0.005) was observed for the rate of resolution when comparing children with levels of wheat sIgE < 0.5 kAU/L and 0.5 to 9.9 kAU/L (**Figure 3A**). The median age of resolution for these children was 48 and

**Table 3. Predictive capacity of ω-5-gliadin specific IgE for predicting wheat tolerance**

| Test | Sensitivity | Specificity | PPV | NPV | Accuracy | LR + | LR - |
|---|---|---|---|---|---|---|---|
| ω-5-gliadin sIgE | | | | | | | |
| < 0.20 kAU/L | 83.3% | 84.2 % | 90.9% | 72.7 % | 83.6% | 5.28 | 0.20 |
| < 0.35 kAU/L | 80.6% | 89.5% | 93.5% | 70.8% | 83.6% | 7.65 | 0.22 |
| < 1.00 kAU/L | 52.8% | 100% | 100% | 52.8 % | 69.1% | ∞ | 0.47 |

PPV = positive predictive value, NPV = negative predictive value, LR + = positive likelihood ratio; LR - = negative likelihood ratio

139 months, respectively. Significant differences (P = 0.006) in resolution were also able to be predicted by the level of ω-5 gliadin sIgE (**Figure 3B**), and the median age of resolution was 56 months for those with levels of ω-5 gliadin sIgE < 0.35 kAU/L. However, we were unable to determine the median age of children with ω-5 gliadin sIgE levels between 0.35 and 0.99 kAU/L because only two patients passed the OFC. Resolution was also associated with baseline SPT for wheat (**Figure 3C**). The median age of resolution was 57 months in children with a wheal size ≤ 3 mm, whereas none of the children with a wheal size > 3 mm underwent the OFC due to not meeting the safety criteria.

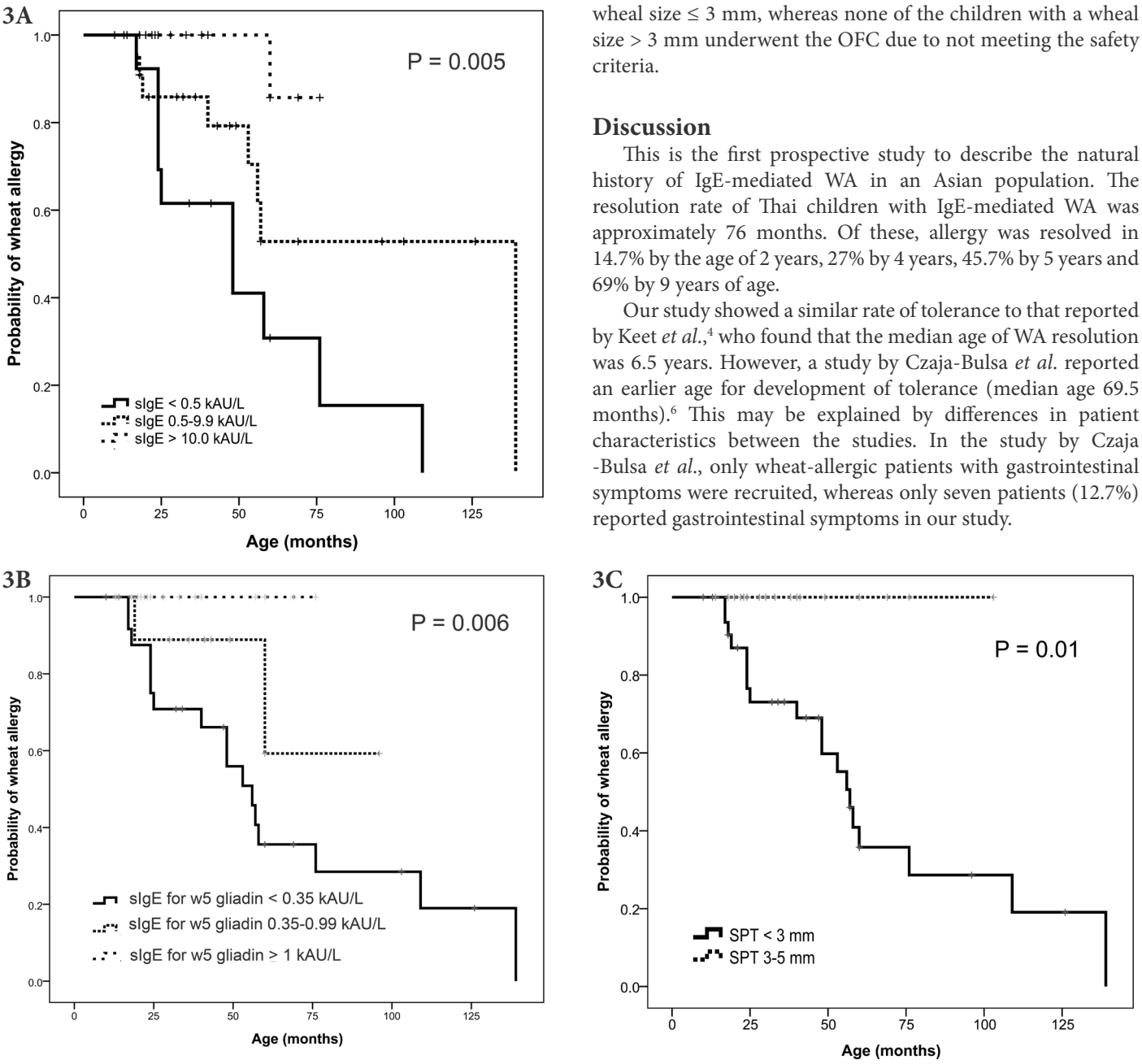


**Figure 3. Kaplan-Meier analysis represents time to develop wheat tolerance base on baseline wheat sIgE levels (A), baseline ω-5-gliadin sIgE levels (B) and baseline wheat SPT wheal size (C).**

## Discussion

This is the first prospective study to describe the natural history of IgE-mediated WA in an Asian population. The resolution rate of Thai children with IgE-mediated WA was approximately 76 months. Of these, allergy was resolved in 14.7% by the age of 2 years, 27% by 4 years, 45.7% by 5 years and 69% by 9 years of age.

Our study showed a similar rate of tolerance to that reported by Keet *et al.*,[4] who found that the median age of WA resolution was 6.5 years. However, a study by Czaja-Bulsa *et al.* reported an earlier age for development of tolerance (median age 69.5 months).[6] This may be explained by differences in patient characteristics between the studies. In the study by Czaja -Bulsa *et al.*, only wheat-allergic patients with gastrointestinal symptoms were recruited, whereas only seven patients (12.7%) reported gastrointestinal symptoms in our study.

The secondary goal of our study was to define the predictors of wheat tolerance. Although previous studies have shown a relationship between ω-5 gliadin levels and WA symptoms, they did not evaluate serum sIgE for ω-5 gliadin as a predictor of wheat tolerance. We found that serum sIgE for ω-5 gliadin lesser than 0.35 kAU/L was a strong predictor for wheat tolerance (HR 5.67, 95% CI 1.19–26.83, P < 0.029). This cut-off point is lower than the cut-off point established by Shibata *et al.*,[8] who reported that when 0.35 kAU/L was used as the cut-off point the specificity was only 48%, but this increased to 95% when 1.06 kAU/L was used as the cut-off point. This can be explained by the different inclusion criteria for the food challenges.

Similar to other food allergy studies,[15-17] the level of sIgE is an important factor for predicting the age of resolution. When the sIgE for wheat was less than 0.5 kAU/L, we found that the median age of resolution from WA was 48 months, compared to 139 months in patients who had an sIgE for wheat of between 0.5 and 9.9 kAU/L. In contrast, Perry *et al.*[18] demonstrated that 73, 33 and 56% of patients passed the challenge when wheat sIgE levels were 0.36–10 kAU/L, 10–20 kAU/L and greater than 20 kAU/L, respectively. However, most of their patients had atopic eczema, which could affect the sIgE levels and cause patients with high sIgE to pass the OFC.

In contrast to other studies that have investigated the natural history of food allergies,[7,19,20] we did not find that the presence of other food allergies, family history of atopic disease, duration of breastfeeding, time of introduction of solid food and amount of trigger food predicted the rate of wheat resolution. This finding may be explained by those patients having a higher rate of atopic eczema and/or multiple food sensitizations than those included in our study. Therefore, different factors might predict tolerance. However, some studies of the natural history of WA have yielded similar results to those obtained in the current study.[4,6]

The strengths of the present study included the large sample size of patients with wheat IgE-mediated reactions, the high anaphylactic reaction ratio (43.6%), low number of children suffering from atopic dermatitis, the prospective study design with re-evaluation at regular intervals, no losses during follow-up, and that all oral challenges were performed in the hospital. In addition, this is the first study to demonstrate predictors of wheat tolerance, as well as including a detailed analysis of wheat and ω-5 gliadin sIgE levels and baseline SPT for wheat.

Our study had some limitations, including a lack of serial SPTs for wheat and crude wheat extracts due to parental concern. Another limitation was the absence of a regular oral wheat challenge, due to the safety criteria cut-off values established from previous studies.[8,21-23] This limitation could result in underestimation of the proportion of children who developed wheat tolerance.

In conclusion, this is the first study to examine the natural history of wheat hypersensitivity in Thai children, in addition to providing practical guidelines for clinicians regarding the appropriate timing of food challenges. Of the children with wheat hypersensitivity included in this study, 45.7% developed tolerance by the age of 5 years. The levels of sIgE against ω-5 gliadin are helpful for predicting wheat tolerance.

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