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Usefulness of Wheat and Soybean Specific IgE Antibody Titer for the Diagnosis of Food Allergy

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ABSTRACT

Background: Since the first suggestion of threshold values for food specific IgE antibody levels in relation to clinical reactivity, several authors have proposed different threshold values for different allergens. We investigated the relationship between wheat/soybean specific IgE antibody levels and the outcome of wheat/soybean allergy diagnosis in children of different ages.

Methods: A retrospective study was conducted in 536 children admitted consecutively to our clinic with the suspicion of wheat and/or soybean allergy. The children underwent an oral food challenge and blood samples for specific IgE measurement were obtained.

Results: The children who reacted to the oral food challenge had higher specific IgE titers to the specific allergen compared to the non-reacting group. The risk for reaction increased 2.33-fold (95% CI 1.90-2.87) for wheat and 2.08-fold (95% CI 1.65-2.61) for soybean, with increasing levels of specific IgE. A significant difference between the ages of subjects pertained only to wheat.

Conclusions: We found a relationship between the probability of failed challenge and the concentration of IgE antibodies to both wheat and soybean. Age influences the relationship of allergen specific IgE levels to wheat and oral food challenge outcome. Younger children are more likely to react to low levels of specific IgE antibody concentration to wheat than older children.

KEY WORDS

food hypersensitivity, IgE, probability curve, soybean, wheat

ABBREVIATIONS

IgE, Immunoglobulin E; kUA/L, Kilounits of allergen-specific IgE per liter; DBPCFC, Double-blinded placebo-controlled food challenge; OFC, Oral food challenge; SPT, Skin prick test; WA, Child characterized with wheat allergy; NoWA, Child without wheat allergy; SA, Child characterized with soybean allergy; NoSA, Child without soybean allergy.

INTRODUCTION

The impact of food allergies extend beyond the affected individual and their immediate families. Feelings of anxiety are generated by the fear of a possible fatal food allergy and the practical problem of food avoidance. However, interpreting food allergy symp-

toms in children is complicated because of the dynamic nature of the allergic response which changes with time; the acquisition of food tolerance and amelioration of symptoms is reported in children with all types of food allergy.¹

In Japan, allergy to wheat and to soybean is the third and the fourth causative food allergen during in-

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fancy.² The majority of wheat and soy allergic children concomitantly suffer from moderate-to-severe atopic dermatitis and sensitization to other foods such as milk and egg. The high prevalence of wheat and soy allergy in Japan during infancy is most likely a reflection of the weaning tradition. Wheat is commonly introduced as udon noodles and soybeans as tofu as weaning food. Therefore, IgE sensitization to wheat occurs primarily in early infancy.

The various diagnostic errors and pitfalls in the management of food allergy suggest that we should utilize available tests more fully in the best interests of the patient.³ Sampson and Ho were first to publish a study on the relationship between food-specific IgE concentrations and the risk of positive food challenges. They also documented specific IgE threshold values to six common foods correlated to the outcome of DBPCFC.^{4,5} These threshold values were, in many cases, helpful in deciding if food challenge was necessary or potentially harmful to the patient.

Other research groups have since followed by describing the correlation between allergen specific IgE titers and food challenge. The focus has been primarily on food allergy towards hen eggs, cow milk and peanuts and also the significance of age.⁶⁻¹² For wheat and soybean, the association between allergen specific IgE antibody titers and food challenge procedures has not been clearly established.^{4,10}

Here, the primary objective was to study the relationship between the specific IgE antibody concentration to wheat and soybean and the outcome of food challenges for children suspected of suffering from wheat and soybean allergy. Our secondary objective was to investigate the influence of age in this relationship.

METHODS

STUDY POPULATION

In the period from 1997 to 2004, 536 children were referred to Sagamihara National Hospital for suspected wheat and/or soybean allergy of which 24 had previously documented wheat allergy and 17 subjects had a previously documented soybean allergy. The majority of patients were boys ($n = 384$), ages ranging between 6 months and 14.6 years (average age 1.3 years). Seventy three percent of patients had atopic dermatitis and 7% asthma; allergic rhinitis and allergic conjunctivitis were present in both 5% of patients.

Evaluation consisted of case history and physical examination. A blood sample was taken for the quantification of specific IgE antibodies to wheat and soybean on the first visit.

LABORATORY STUDIES

Allergen specific IgE antibody levels were measured using ImmunoCAP[®] System (Phadia AB, Sweden) towards wheat and/or soybean in these patients. The detection limit of the assay was 0.35 kUA/L.

ORAL FOOD CHALLENGE

Oral challenge is the standard procedure used for determining food allergy at Sagamihara National Hospital, when case history, physical evaluation and allergen-specific IgE indicate hypersensitivity to a particular food. Open challenges are routine at our clinic for very young children and follow the practice recommended by the EAACI.¹³ In children over 4 years of age or if the child claimed to have a subjective symptom, challenges were performed blinded. All open challenges were performed using the identical titration steps as for the double-blinded ones recommended by AAAAI.¹⁴ The time-interval between doses was 15 minutes. Food challenges were scored as positive by a pediatric specialist if one or more of the following objective clinical reactions were noted: urticaria, angioedema, skin rash, cough, wheeze, breathing difficulties, vomit, diarrhea, shock or exacerbation of eczema. Full emergency equipment was at hand. The provocation test was terminated when clinical symptoms were observed or when the highest allergen dose was reached. Subsequently, subjects were carefully monitored for 24 hours. For provocation of wheat allergy 100 g udon noodle was used, and for soybean allergy 100 g tofu. For toddler age half the dose was used. When a child had a very convincing positive history with a high risk of reacting strongly to a challenge, the challenge procedure was not carried out.

Based on case history, physical examination and, in most cases, challenge outcome, each child was classified as having an immediate hypersensitivity to ingested wheat (designated as wheat allergy, i.e. WA) or not (designated as no wheat allergy, i.e. NoWA). Respectively, children were investigated for immediate hypersensitivity to soybean (designated as soybean allergy, i.e. SA) or not (designated as no soybean allergy, i.e. NoSA). This study was approved by the Institutional Review Board at the Sagamihara National Hospital, and all patients gave written informed consent to participate.

STATISTICAL METHODS

The primary outcome measure was clinical reactivity, determined by food challenge or confirmed clinical history. A Kruskal-Wallis test was used to assess differences between groups.

The relationship between sensitization status and outcome measure was analyzed using logistic regression. Fitted, predicted probability curves were plotted using the results from the logistic regression. A p -value of less than 0.05 was considered to indicate a statistically significant difference. Computerized statistical analysis was carried out using SAS System V8.2.

RESULTS

Overall, 590 conclusive remarks were made regard-

Table 1 Symptoms provoked by oral food challenge

	Total (n = 62) No. (%)	Wheat (n = 41) No. (%)	Soybean (n = 21) No. (%)
Cutaneous	60 (97)	40 (98)	20 (95)
Mucous membrane	1 (2)	1 (2)	0 (0)
Lower respiratory	11 (18)	6 (15)	5 (24)
Gastrointestinal	2 (3)	1 (2)	1 (5)
Anaphylaxis	4 (6)	3 (7)	1 (5)

ing food allergy for the 536 patients during the period between 1997 and 2004. All 590 conclusive remarks were based on either oral food challenges or through a strong convincing history. Oral challenges were performed in 277 subjects for wheat and 272 for soybean for a total of 549 oral food challenges. With the exception of 5 challenges which were single-blinded, the rest of the 544 food challenges were performed openly. Twenty four wheat allergy patients and 17 soybean allergy patients already had definitive symptoms within 3 months of the examination. Among the 277 wheat challenges, 41 or 51% of the performed wheat challenges were assessed as positive. Among 272 soybean challenges, 21 or 8% were assessed as positive. Symptoms provoked by the oral food challenge are listed in Table 1.

The levels of wheat and soybean specific IgE were significantly higher in the group that failed the challenge (Table 2). This indicated a relationship between the levels of specific IgE and the outcome of challenge. This relationship was further investigated using a logistic regression model. A significant relationship between the probability of failed challenge and the concentration of IgE antibodies to both wheat and soybean was found. For wheat, the risk increased 2.33-fold per logarithmic increase (95% CI 1.90-2.87) and for soybean the risk increased 2.08-fold per logarithmic increase (95% CI 1.65-2.64), of specific IgE. Fitted probability curves for the relationships are presented in Figure 1.

A post-stratification of the children challenged for wheat gave 2 significant age groups, under 1 year of age with an 4.09-fold risk increase (95% CI 2.60-6.45) and 1 year or older with a slightly lower risk, a 2.18-fold increase (95% CI 1.62-2.93), with increasing levels of wheat-specific IgE (Fig.2). For soybean, a stratification in relation to age was not possible.

DISCUSSION

We set out to determine the relationship between wheat/soybean specific IgE antibody levels and the outcome of wheat/soybean allergy diagnosis in children of different ages. Our retrospective study shows that there is a relationship between the probability of

Table 2 Specific IgE levels for wheat and soybean, for children with or without wheat allergy (WA & NoWA) and soybean allergy (SA & NoSA) respectively

	Wheat		Soybean	
	NoWA	WA	NoSA	SA
Arit. Mean	1.88	19.29	1.98	14.87
Geo Mean	0.48	5.27	0.54	3.97
Median	< 0.35	4.31	< 0.35	3.89
N	236	65	251	38

failed challenge and the concentration of IgE antibodies to both wheat and soybean, also that the relationship for wheat was modified by the age of the children. Younger children were more likely to react to low levels of specific IgE antibody concentration to wheat than older children.

We have previously indicated that IgE levels serve as useful predictors of challenge outcomes for hen egg allergy and cow milk allergy and that the prediction was influenced by age.¹² However, in the present study only wheat showed a similar age-dependent relationship.

The relation between wheat and soybean IgE levels and the likelihood of reaction has previously been reported in 2 European studies. In a study by Celik-Bilgili *et al.*¹⁰ based on oral challenges performed on a patient-based material, the association for both wheat and soybean was rather poor, whereas in a study by Östblom *et al.*¹⁵ based on questionnaire data, the relationship for soybean was almost identical as the German study although the relationship between wheat IgE levels and reported hypersensitivity was better. Our results show a stronger association between the IgE results and challenge outcome for wheat and soybean compared to the 2 European studies. For soybean, one reason might be that it is common in Japan to give infants soybean products as baby food in infancy, whereas in Europe, exposure to soybean during infancy is low and consequently IgE sensitization to soybean is relatively uncommon. In Europe, soybean allergy also manifest as oral allergy syndrome in patients allergic to birch due to cross-reactivity of Bet v 1- specific IgE to the PR-10 soy protein.¹⁶ Therefore, it is estimated that the difference in early exposure to soybean may create a relatively frequent opportunity for Japanese infants to receive soybean antigen stimulation through intestinal immune system in digestive organs compared to European infants.

We found a relationship between wheat IgE antibody concentrations and reactivity to wheat and that age influenced the outcome, as the association between the concentrations of serum-specific IgE and the outcome of challenge was stronger for younger children than older children.

Many questions remain unsolved questions in food

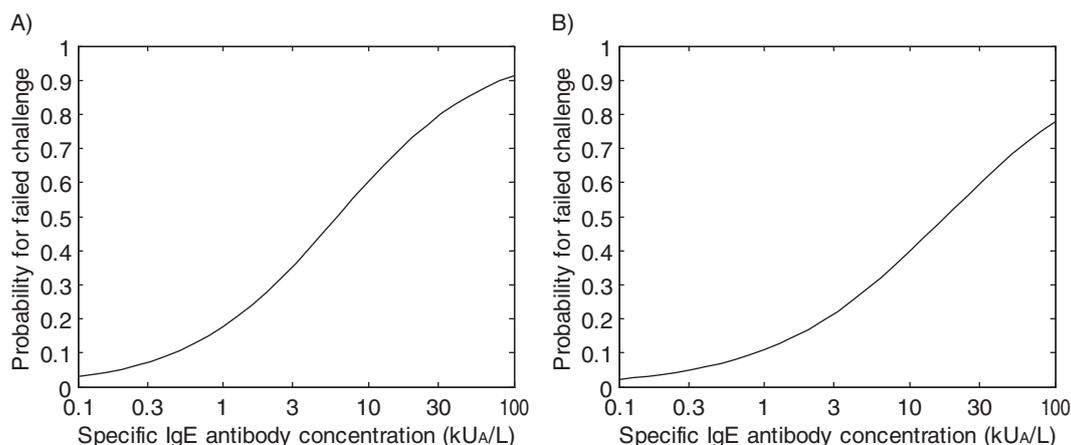


Fig. 1 Fitted predicted probability curves for the outcome of challenge at a given IgE value for **A)** wheat and **B)** soybean.

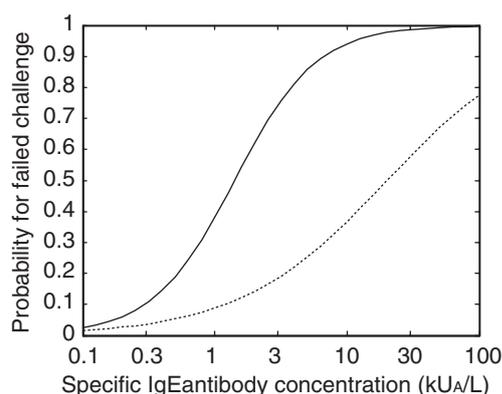


Fig. 2 Fitted predicted probability curves for the outcome of challenge at a given IgE value for different age groups of wheat, where the solid curve represents children younger than 1 year and the dotted curve for children 1 year or older.

allergy, and the issues of cross-reacting proteins and botanically-related foods, and the significance of positive tests for IgE, all play a role in the dilemma of wheat or soybean allergy. Our study, together with many others, do support the concept that IgE levels can be a useful laboratory measure in determining when a food challenge should be considered. As a consequence to this, it appears now that challenges are being used less often to confirm a clinical diagnosis and more often to test for clinical resolution of allergy, which is the norm in cow milk allergy and hen egg allergy, but less common in allergy to wheat and soybean.

We conclude that the levels of specific IgE to wheat and soybean are related to oral food challenge outcome when investigating children suspected of having food allergy. Age was found to influence this relationship in wheat allergy but not in soybean allergy.

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