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Clinical Utility of IgE Antibodies to ω-5 Gliadin in the Diagnosis of Wheat Allergy: A Pediatric Multicenter Challenge Study

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Key Words
Allergy tests · Food challenge · IgE · ω-5 gliadin · Pediatric allergy · Wheat

Abstract
Background: There are contradictory results regarding the clinical usefulness of the determination of IgE antibodies to ω-5 gliadin in children with a suspicion of wheat allergy (WA). ***Methods:*** The study comprised 311 children and young adults with suspected wheat intolerance treated at three separate pediatric clinics and, with the exception of 25, were found to be positive in specific IgE antibody determinations to wheat. Their ages ranged from 6 months to 20.4 years (median age, 2.3 years). Possible relationships between IgE antibodies to ω-5 gliadin and a physician's diagnosis of WA and challenge symptoms were studied. ***Results:*** The mean concentration of IgE antibodies to ω-5 gliadin was 1.2 kU_A/l in WA patients and <0.35 kU_A/l in patients without WA ($p < 0.0001$). Seventy-two percent of the WA patients had positive ω-5 gliadin levels and 75% of the patients without WA had negative levels. Logistic regression showed a significant relationship between the probability of WA and the concentration of IgE antibodies to ω-5-gliadin with a 2.6-fold (95% CI: 2.0–3.3) increased risk. Age was an important factor to consider as the risk of WA increased 5.4-fold (95% CI: 1.4–21) for children ≤1 year of age and 2.5-fold (95% CI: 2.0–3.2) for children >1 year of age with increasing levels of IgE. ***Conclusion:*** Detection of IgE to ω-5 gliadin seems to be associated with responsiveness to the challenge test and is particularly useful in infants with a suspicion of WA.

Introduction

Wheat is one of the six most common foods causing allergy in children and the third most common food allergen in Japanese children [1]. IgE antibodies to egg, cow's milk and peanut have been useful in predicting clinical reactivity [2–4]. Furthermore, the correlation between the outcome of oral food challenges and levels of IgE antibodies to wheat was established in Japanese children with suspected wheat allergy (WA) [5]. ω-5 gliadin has been identified as the major antigen in children with wheat-dependent, exercised-induced anaphylaxis [6]. Furthermore, IgE antibodies to ω-5 gliadin have been found in children with immediate reactions to ingested wheat [7], and recently published results show that increased levels of IgE antibodies to ω-5 gliadin correlate with the outcome of oral

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wheat challenge [8]. The level of antibodies to ω-5 gliadin has thus been suggested to serve as a marker for clinical reactivity and an aid for the decision for or against wheat challenge. Contradictory results have been reported from two populations of German and American children where no correlation between ω-5 gliadin antibody levels and the outcome of oral food challenge could be demonstrated [9].

The objective of this survey was to evaluate the possible clinical usefulness of IgE antibody concentrations to ω-5 gliadin in relation to WA in a large cohort of food-challenged children.

Patients and Methods

This retrospective study was performed in 311 children and young adults with suspected wheat intolerance treated at three different clinics in Japan. The clinics were the Fukuoka National Hospital (n = 88, site 1), Fukuoka, the Aichi Children's Hospital (n = 114, site 2), and the Ohbu and Sagamihara National Hospital (n = 109, site 3), Sagamihara. The three participating departments were representative for pediatric allergology in Japan. Inclusion criteria were suspicion of WA based either on clinical history and/or serology. All individuals, except for 25, had specific IgE antibody to wheat. The children had been referred from primary care physicians or enrolled at the outpatient clinic due to immediate hypersensitivity reactions following wheat ingestion. Clinical history comprised skin, gastrointestinal tract and/or respiratory tract symptoms following wheat ingestion. The age of the patients ranged from 6 months to 20.4 years (median age, 2.3 years), and 215 of the individuals were males. Informed consent was given by the child or child's parents prior to enrolment.

Clinically, each patient was subjected to a detailed medical examination and medical history data were collected. In order to confirm or exclude WA, the diagnosis was based on either oral food challenges or case history or, in most cases, a combination of both. Blood was sampled for baseline determination of IgE antibodies to wheat and ω-5 gliadin. Serum samples were analyzed for IgE antibodies to wheat and ω-5 gliadin using the ImmunoCAP® System FEIA (Phadia AB, Uppsala, Sweden). The detection limit of the assays was 0.35 kU_A/l.

All wheat-food challenges were open challenges performed in a hospital setting and supervised by physicians in accordance with the guidelines for the diagnosis and management of pediatric food allergy in Japan [10, 11]. In children with a strong convincing history for high-risk responses, including severe symptoms on challenge, the challenge procedure was not carried out (n = 36). When a child had no objective WA symptoms and/or was eating wheat (n = 60), a challenge was not carried out and the child was classified as no WA (NoWA). Based on case history, physical examination and, in most cases, challenge outcome, each child was classified as having an immediate hypersensitivity reaction to ingested wheat or NoWA.

Statistical Methods

The Mann-Whitney non-parametric test was used to test differences between the groups. A p value of 0.05 was regarded as significant. Performance characteristics, i.e. sensitivity and specificity, were calculated for various cutoff values, including the optimal cutoff values proposed by the receiver-operating characteristic (ROC) plots. For quantitative evaluation, a logistic regression model was formulated as the probability of receiving a positive clinical diagnosis as a function of the logarithm of the specific IgE concentration:

$$\text{logit}(Pr[Y = 1/\ln \text{IgE (kU/l)}]) = \alpha + \beta \ln \text{IgE (kU/l)}$$

This quantitative model describes the relationship between sensitization and clinical diagnosis of WA. Statistical analysis was carried out using SAS System V9.1.

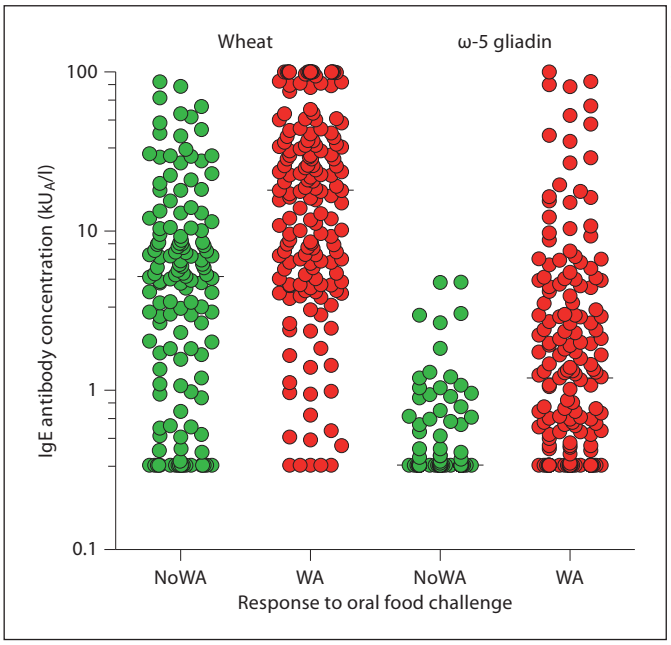

Fig. 1. Allergen-specific IgE titers for wheat and ω-5 gliadin for WA and NoWA patients.

Results

The diagnosis of WA was confirmed in 173 children by symptoms following oral wheat challenge or a convincing case history of anaphylaxis in relation to wheat intake. Five of these children had specific IgE to wheat <0.35 kU_A/l. The remaining 138 children were classified as NoWA. The demographic characteristics and outcome of oral wheat challenges are presented in table 1 for both WA and NoWA patients. The median concentrations of IgE antibodies to wheat and ω-5 gliadin in children with confirmed WA were 18.1 (range <0.35 to >100) and 1.2 (range <0.35–100) kU_A/l, respectively. The corresponding values

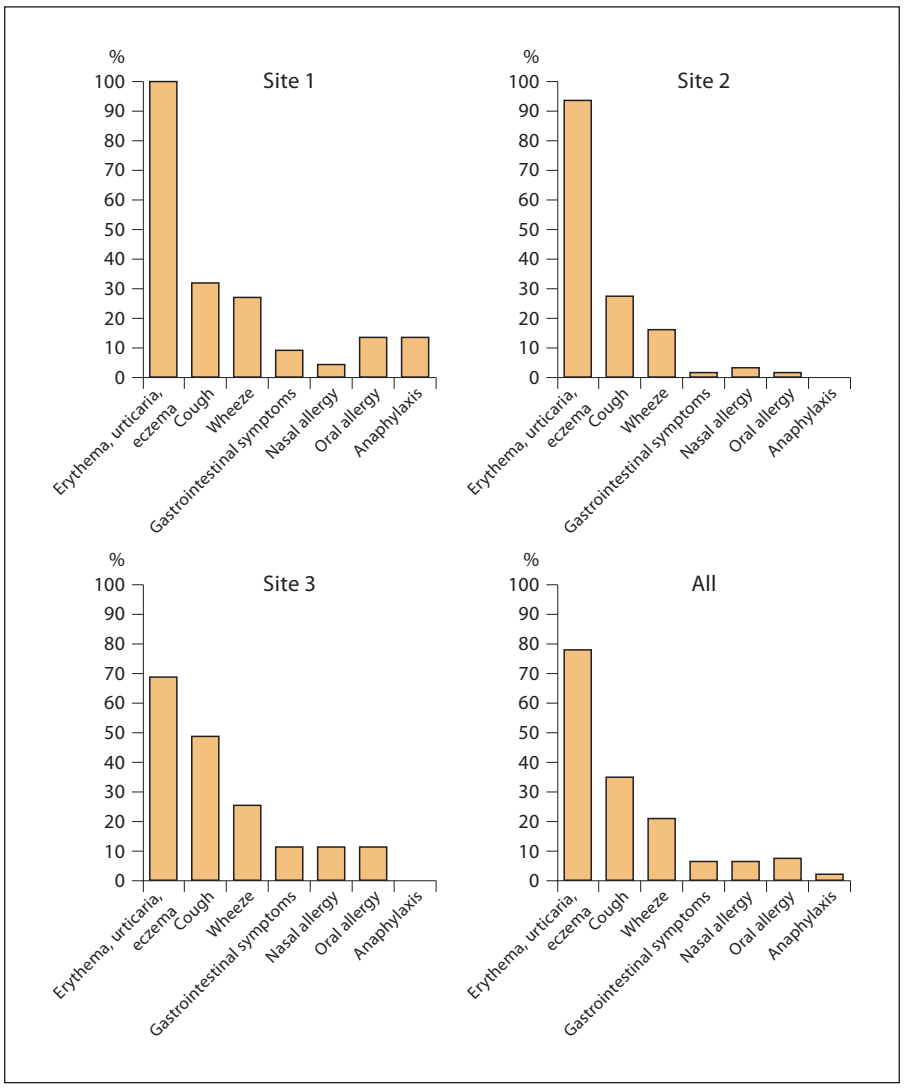

Fig. 2. Symptom frequencies in WA patients at food challenge. Numbers of patients are given in table 1.

for the children classified as NoWA were 5.2 (range <0.35–86.8) and <0.35 (range <0.35–4.8) kU_A/l, respectively (fig. 1). This difference in allergen-specific IgE concentrations between the two groups was significant ($p < 0.0001$). Seventy-two percent (125 of 173) of the WA patients had positive ω-5 gliadin levels and 75% (104 of 138) of the NoWA patients had negative ω-5 gliadin levels. In total, 137 of the 173 WA patients were challenged, and symptom responses following challenge are presented in figure 2 for each of the clinics separately and for all three combined. Skin reactions (erythema, urticaria and eczema) were predominating, amounting to >75%. As shown for site 1, >10% of the patients experienced an anaphylactic reaction during the challenge. In the remaining WA patients that were not challenged but had a convincing history (n = 36), skin reactions (94%), cough (17%), wheezing (14%) and anaphylaxis (5%) were the most frequent symptoms.

ROC analyses were performed to evaluate the diagnostic ability of the in vitro tests. The area under the curve (AUC) for ω-5 gliadin was 78.5% (fig. 3). At an estimated cutoff of 0.41 kU_A/l, values of 72% (sensitivity), 79% (specificity), 81% (PPV), 69% (NPV), 3.4 (positive likelihood ratio) and 0.5 (negative likelihood ratio) were obtained for the assay. The corresponding figures for wheat were: AUC 73.0%, 61% (sensitivity), 74% (specificity), 75% (PPV), 60% (NPV), 2.4 (positive likelihood ratio) and 0.5 (negative likelihood ratio) at a cutoff of 10.1 kU_A/l. The concentration difference between the two pediatric groups was further investigated using a logistic regression model. A significant relationship between the probability of WA and

Table 1. Demographic and background characteristics of the patients (numbers, medians and ranges)

		Wheat allergy			No wheat allergy		
		sex	age, years	challenge/ convincing history	sex	age, years	challenge/ convincing history
Site 1	Male (n = 79)	31	2.4 (1.0–8.7)		48	3.9 (1.0–20.4)	
	Female (n = 35)	14	3.5 (1.0–7.1)	22/23	21	4.5 (1.4–15.4)	
	Total (n = 114)						24/45
Site 2	Male (n = 62)	48	1.6 (0.6–7.1)		14	1.9 (0.8–7.6)	
	Female (n = 26)	19	2.1 (0.6–8.8)		7	3.0 (0.9–6.9)	
	Total (n = 88)			63/4			21/0
Site 3	Male (n = 71)	38	2.8 (1.1–12.0)		33	1.8 (0.6–14.8)	
	Female (n = 38)	23	2.3 (0.8–8.6)		15	2.1 (0.5–8.2)	
	Total (n = 109)			52/9			33/15
All sites	Male (n = 212)	117	2.0 (0.6–12.0)		95	2.8 (0.6–20.4)	
	Female (n = 99)	56	2.2 (0.6–8.8)		43	3.3 (0.5–15.4)	
	Total (n = 311)			137/36			78/60

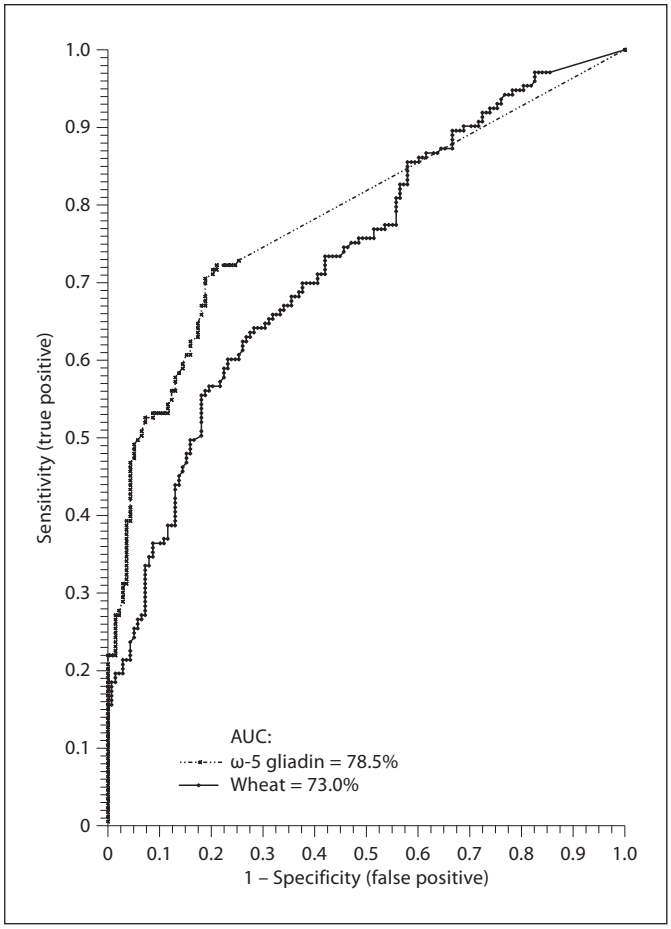

Fig. 3. ROC curve based on all patients.

the concentration of IgE antibodies to ω-5 gliadin was thus found. The risk increased 2.6-fold (95% CI: 2.0–3.3) with increasing levels of IgE (fig. 4a). Furthermore, when grouping the children into different age groups, there was a significant difference between ≤1 and >1 year of age in the probability of WA for the concentration of IgE antibodies to ω-5 gliadin. The risk of WA increased for children ≤1 year of age 5.4-fold (95% CI: 1.4–21) and 2.5-fold (95% CI: 2.0–3.2) for children >1 year of age with increasing levels of IgE, as illustrated in figure 4a. The relationship between the concentration of IgE antibodies to wheat and ω-5 gliadin was also investigated in a logistic regression model. A significant association to WA was found for ω-5 gliadin with a 2.1-fold increased risk (95% CI: 1.9–3.6). Figure 4b shows the probability of WA at nine different values of ω-5 gliadin increased with increasing antibody concentrations of specific IgE to wheat.

Discussion

Our results confirmed a difference in the IgE levels of ω-5 gliadin between WA and NoWA children in this multicenter challenge study. Further, we demonstrate that IgE antibodies to ω-5 gliadin are particularly useful in predicting food challenge outcome in children <1 year of age.

Our findings based on 311 Japanese children are not in agreement with the recent findings of Beyer et al. [9], who could not find a correlation between ω-5 gliadin lev-

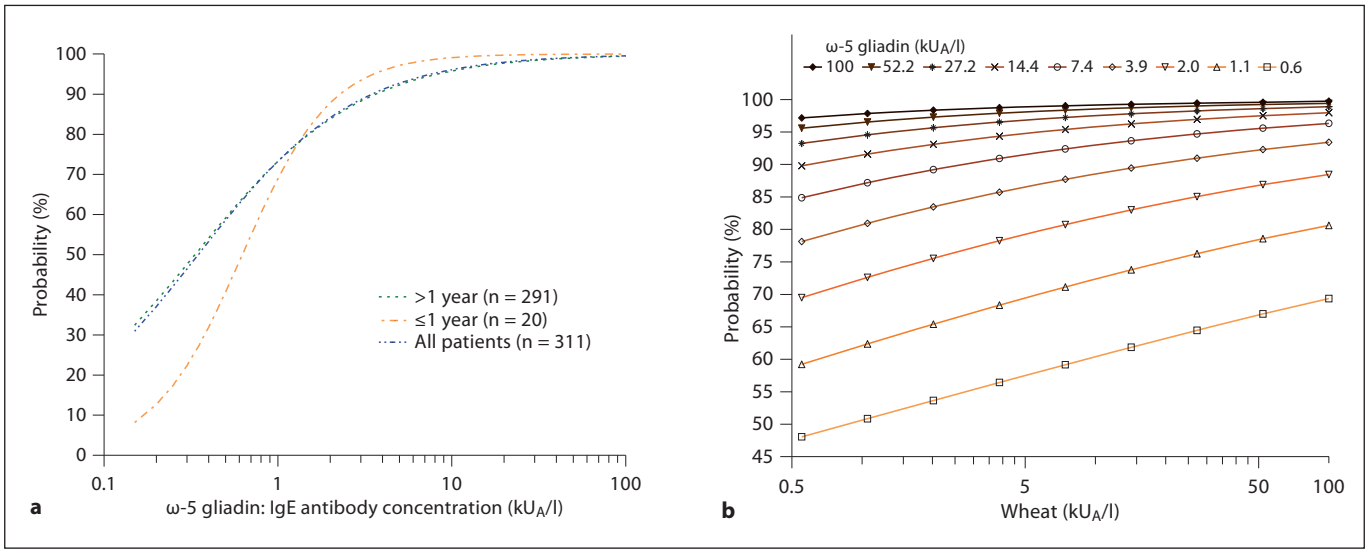

Fig. 4. Fitted predicted probability curves for the outcome of WA at a given IgE value for ω-5 gliadin for all children and for children ≤1 and >1 years of age (**a**) and for nine concentrations of ω-5 gliadin in relation to specific IgE to wheat (**b**).

els and the outcome of oral wheat challenges in a group of 57 German and 29 American children. One explanation could be the sample size, as our study contains 5 and 10 times more children, respectively. Another explanation could be that the inclusion criteria of the study population differed and the study participants had different phenotypes. With regard to the German group, almost half of the children (9 of 19) reacted to wheat challenge but were not sensitized to wheat. In our study, only 5 of 137 challenge-positive children were not sensitized to wheat. The German study population thus included more individuals with non-IgE-mediated WA with delayed symptoms than our study.

Further, no child had ω-5 gliadin levels >20 kU_A/l in their study compared to 11 individuals in our study. A third explanation as to why we arrived at a different conclusion could be the age factor. WA, which usually begins in early childhood, is outgrown in most cases by 3–5 years of age [12], whereas 35% show a persistent WA into adolescence [13]. The children in our study had a median age of 2.3 years and they were representative of typical pediatric cases of immediate allergy to wheat in our opinion.

We speculate that ω-5 gliadin may differ among populations in Asia and Europe due to dietary habits and the genetic background. Our study is however in agreement with the Finnish study, which demonstrated earlier that IgE to ω-5 gliadin is highly predictive of immediate allergy to ingested wheat in children [7]. Further studies are needed to clarify the impact of different races, food habits and genetic variations on immediate allergy to wheat.

Measuring IgE to ω-5 gliadin is useful in the diagnostic workup when investigating immediate-type WA in children and young adults. In Japan, both IgE to wheat and ω-5 gliadin are now routinely assessed when investigating these patients. Patients sensitized to ω-5 gliadin are not challenged with wheat as it is most likely to fail. Patients responsive to the test are asked to strictly avoid wheat. The serology of these patient is then followed prospectively in order to have an indication that tolerance had developed and wheat challenge should be performed. The other scenario is the patient sensitized to wheat but not to ω-5 gliadin during the initial investigation. A wheat challenge is performed as soon as possible in order to confirm or exclude a diagnosis of WA.

In conclusion, the detection of IgE to ω-5 gliadin seems to be associated with responsiveness to the challenge test and is particularly useful in infants with a suspicion of WA.

Acknowledgments

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