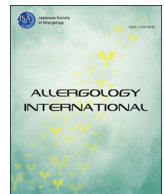




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Letter to the Editor

Probability curves for predicting symptom severity during an oral food challenge with wheat

Dear Editor,

Wheat allergy is the third most common food allergy among young children in Japan.¹ The most reliable examination for the definitive diagnosis of a food allergy is an oral food challenge (OFC); however, consuming wheat appears to be an independent risk factor for anaphylaxis during OFC.² As predictive factors for severe wheat OFC outcomes have not yet been identified, simple and easy indicators to predict induced symptom severity during wheat OFCs are needed. Omega-5 gliadin is a major allergen in young children with an immediate allergic reaction to wheat,³ and the serum ω -5 gliadin-specific IgE level was reported to be a useful parameter for predicting positive OFC outcomes.^{4,5} Conversely, we previously reported probability curves for predicting symptom severity during egg and milk OFCs based on allergen-specific IgE levels^{6,7} to add clinical usefulness to these that only predict positive outcomes.¹ Here we report probability curves for predicting symptom severity during a wheat OFC.

In this study, unified OFC protocols with a single database system were used to conduct a total of 1679 OFCs at 14 institutions between October 2012 and May 2014. The indication for OFC was decided according to the Japanese guidelines for food allergy with their clinical history of food allergy and related specific IgE levels.^{1,8} Of 173 wheat OFC cases, 117 OFCs with sufficient data for patients aged ≤ 6 years were included in the final analysis. We excluded 56 cases including 4 older patients, 16 cases of insufficient dosing, 3 inconclusive cases, and 33 cases without appropriate specific IgE data. Udon noodles were used for wheat exposure; children ingested 1, 2, 5, 10, and 20 (or 30) g of udon noodles in increasing order at intervals of 15–30 min. Considering that udon noodles contain 3.1% wheat protein,⁸ the maximal total consumed wheat proteins was 1488 mg during OFCs. An OFC was terminated once a distinct allergic symptom was induced following ingestion. Severity of induced allergic symptoms was graded from 1 to 5 using the grading system of the guideline,¹ which is based on Sampson's anaphylaxis severity score.⁹ In this study, a negative outcome was defined as the consumption of at least 38 g of udon noodles without any induced symptoms.⁸ Serum ω -5 gliadin- and wheat-specific IgE levels were monitored for 3 months prior to OFCs using the ImmunoCap test (Thermo Fisher Scientific, Uppsala, Sweden). The present study was approved by a local research ethics committee.

In statistical analyses, allergen-specific IgE levels, which were out of detection limits, were considered as 0.17 kUA/L for levels

<0.35 kUA/L and 100 kUA/L for levels ≥ 100 kUA/L. Allergen-specific IgE levels were used as linear parameters, and logistic regression analysis was used to assess the associations between allergen-specific IgE levels and OFC symptom severity. Probability curves were drawn using the results of logistic regression analysis, and all statistical analyses were performed using JMP[®] 11 statistical software (SAS Institute, Cary, NC, USA).

In our study population ($n = 117$; median age, 2 years), 66 patients (56.4%) had atopic eczema, 18 (15.4%) were taking asthma medication, and 10 (8.5%) had a history of anaphylaxis after wheat consumption. Thirty-four patients (29.0%) consumed wheat for the first time during OFC. The median ω -5 gliadin- and wheat-specific IgE levels were 0.37 kUA/L (range, 0.17–12.8 kUA/L) and 5.79 kUA/L (range, 0.17–100 kUA/L), respectively. During OFCs, 78 patients (66.7%) exhibited positive symptoms and were accordingly graded. Grade 1, 2, 3, 4, and 5 reactions were observed in 28 (23.9%), 27 (23.1%), 9 (7.7%), 13 (11.1%), and 1 patients (0.9%), respectively. Eleven patients (9.4%) were clinically diagnosed with anaphylaxis during OFCs. According to severity scores and related allergen-specific IgE levels, three different probability curves based on ω -5 gliadin-specific IgE (Fig. 1) and wheat-specific IgE (data not shown) were drawn to predict OFC outcomes. Because the distribution of our sample is relatively low, we restricted the range of X-axis and showed it linearly for ease of reference (Supplementary Fig. 1 is also shown with logarithmically transformed X-axis). As a result, an ω -5 gliadin-specific IgE level of 5.7 kUA/L had a 95% probability of predicting a positive outcome ($\geq$ grade 1), but we could not determine the wheat specific-IgE level that had a 95% probability of predicting a positive outcome. Fitness of the regression model assessed using the Hosmer–Lemeshow test for allergen-specific IgE levels showed no significant deviation between the hypothesized model and the actual observed event rate ($P > 0.05$).

We demonstrated that our strategy of using the allergen-specific IgE level as a useful indicator to predict severe allergic symptoms during OFCs^{6,7} could be applied for conducting a wheat OFC in Japanese children. In previous studies on egg and milk allergies, we reported the 5% probability level of allergen-specific IgE for predicting symptoms $\geq$ grade 3,^{6,7} which is currently used in clinical settings as one factor for OFC consideration. Although the ω -5 gliadin-specific IgE level of 17.2 kUA/L was estimated to have a 95% probability of predicting positive symptoms $\geq$ grade 3, we were not able to determine the ω -5 gliadin-specific IgE levels that had a 5% probability of predicting positive outcomes during wheat OFCs in this study population.

Peer review under responsibility of Japanese Society of Allergy.

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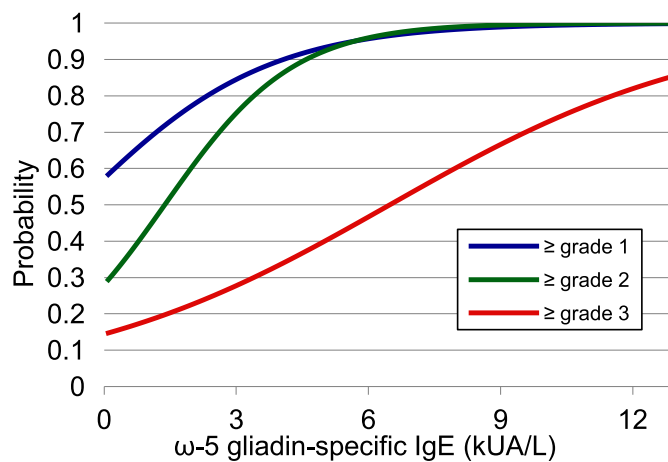


Fig. 1. Probability curves for ω -5 gliadin-specific IgE levels in patients aged 0–6 years ($n = 117$). Fitted predictive probability curves predicting the outcomes following an oral food challenge with wheat are shown.

As previously suggested,⁴ the symptom profile of a wheat allergy might be more distinctive than that of egg and milk allergies. In the present study, the ω -5 gliadin-specific IgE level was more useful than the wheat-specific IgE level for predicting a positive wheat OFC; this finding is consistent with previous reports.^{4,5} Furthermore, we were able to predict a risk for severe symptoms using the ω -5 gliadin-specific IgE level. In Japan, clinicians still prefer to administer OFCs to determine the dose of causative allergen, even for cases with an OFC predicted to be positive.¹ Assessment using OFCs allows for constructing an individualized treatment plan that includes the complete avoidance of the causative allergen, restriction of consumption, and/or implementation of oral immunotherapy as part of a clinical trial.¹⁰ Wheat OFCs might have a high risk of triggering severe symptoms.² Therefore, probability curves focused on symptom severity during OFCs are useful tools prior to testing, especially for wheat. Nevertheless, future prospective studies are needed to examine the validity of these probability curves.

Probability curves using the ω -5 gliadin-specific IgE level are simple and straightforward tools for assessing a risk for severe induced symptoms during wheat OFCs in young children with a wheat allergy.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.alit.2017.02.011>.

Conflict of interest

The authors have no conflict of interest to declare.

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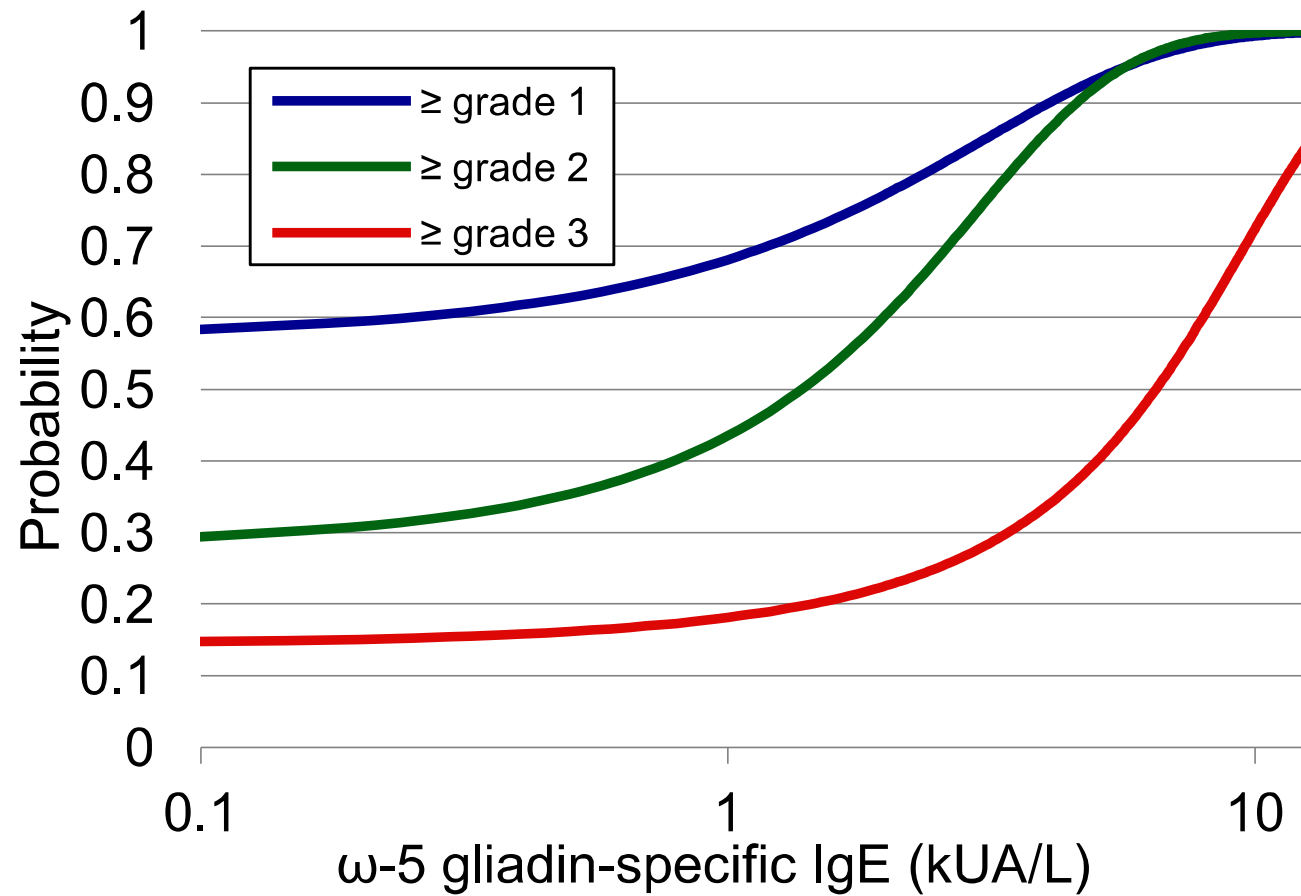
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Supplementary Fig. 1. Probability curves for ω -5 gliadin-specific IgE levels in patients aged 0–6 years ($n = 117$). Fitted predictive probability curves predicting the outcomes following an oral food challenge with wheat are shown. X-axis is logarithmically shown.