

ORIGINAL ARTICLE

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Clinical cross-reactivity of wheat and barley in children with wheat allergy

Noriyuki Yanagida^{1,2}  | Mari Takei¹  | Akemi Saito¹ | Sakura Sato¹  | Motohiro Ebisawa¹ 

¹Department of Allergy, Clinical Research Center for Allergy and Rheumatology, National Hospital Organization, Sagami National Hospital, Sagami, Japan

²Department of Pediatrics, National Hospital Organization, Sagami National Hospital, Sagami, Japan

Correspondence

Noriyuki Yanagida, Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagami National Hospital, 8-1 Sakurada, Minami-ku, Sagami, Kanagawa 252-0392, Japan.
Email: sagami@foodallergy.jp

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Abstract

Background: Several studies have reported in vitro cross-reactivity between wheat and barley. However, evidence regarding the clinical cross-reactivity of wheat and barley is limited. This study examined the clinical cross-reactivity of barley and wheat among children with immediate-type wheat allergies.

Methods: We examined the threshold dose of a wheat oral food challenge for wheat-allergic children. We examined the reactivity of barley, and the oral food challenges of barley tea and barley rice were implemented as needed. We measured the specific immunoglobulin E (sIgE) levels in wheat, ω -5 gliadin, and barley.

Results: We evaluated 53 children (39 [74%] boys) with a median age of 6.6 years. Among them, 39 (74%) patients had a history of anaphylaxis to wheat. The median wheat-, barley-, and ω -5 gliadin-sIgE levels were 57.3, 12.1, and 3.2 kU_A/L, respectively. Twelve patients reacted to barley tea (1.8 mg), 14 reacted to barley rice (220–440 mg), and 27 were tolerant to barley tea and barley rice. Barley-allergic patients had significantly higher wheat- and ω -5 gliadin- and barley-sIgE levels and significantly lower threshold doses of wheat than barley-tolerant patients. Omega-5 gliadin-sIgE was the most useful predictor of barley allergy among wheat-allergic patients; the ω -5 gliadin-sIgE 95% positive predictive value for barley allergy was 4.6 kU_A/L.

Conclusions: Half of wheat-allergic children reacted to barley. A lower threshold dose of wheat is related to cross-reactive barley allergies. Omega-5 gliadin-sIgE predicts cross-reactive barley allergy in children allergic to wheat. Clinical cross-reactivity to barley should be considered in the management of wheat-allergic children.

KEYWORDS

barley, children, cross-reactivity, food allergy, gliadin, threshold, wheat

1 | INTRODUCTION

Barley is a cereal grain commonly consumed as a healthy food (i.e., soup, cereals) and in beverages (i.e., beer and barley tea). Barley tea is the most frequently consumed beverage among children in Japan at home and in schools.¹

Wheat (*Triticum aestivum*) and barley (*Hordeum vulgare*) belong to the tribe Triticeae of the Poaceae family.² The cross-reactivity between wheat and barley is an important issue in managing wheat allergies.² Some in vitro studies have evaluated cross-reactivity between wheat and barley.^{3–5} Immunoglobulin E (IgE) from patients sensitized to wheat cross-reacts with γ 3-hordein of barley owing to sequence homology with wheat allergens.³

However, limited information is available regarding the clinical cross-reactivity of wheat and barley to immediate-type wheat allergy.⁶ Therefore, we examined the clinical cross-reactivity between wheat and barley.

2 | METHODS

2.1 | Study design

We retrospectively collected children's data from a clinical chart review. We prospectively collected data on barley consumption. We also prospectively collected data on the additional oral food challenge (OFC) of barley for patients who had never consumed barley. We have prospectively collected data of all food allergic patients at the outpatient clinic in the study period (UMIN000013561).

2.2 | Eligibility criteria

The eligibility criteria were as follows: (1) patients reactive to the wheat OFC, (2) wheat-specific IgE ≥ 0.35 kU_A/L, (3) aged 1–15 years, and (4) provided consent to participate in this study. The exclusion criteria were poorly controlled bronchial asthma (defined according to the Global Initiative for Asthma 2019), exacerbation of atopic dermatitis (diagnosed using the UK Working Party Criteria), and treatment with oral immunotherapy for wheat. Patients with missing laboratory or clinical data were excluded from the study. We excluded children with wheat-dependent exercise-induced anaphylaxis and did not exclude those with a history of wheat-induced anaphylaxis.

2.3 | Clinical outcomes

The primary outcome was clinical reactivity to barley. Secondary outcomes included reactivity to barley tea and barley rice, wheat, barley, ω -5 gliadin-sIgE levels, and the threshold dose of wheat OFC.

Key Message

Half of the wheat-allergic children in this study reacted to barley owing to clinical cross-reactivity. Omega-5 gliadin predicts barley allergy in children allergic to wheat. Clinical cross-reactivity to barley should be considered in the management of wheat-allergic children.

2.4 | OFC of wheat and barley

As described in previous studies,⁷ an OFC using boiled udon noodles (Japanese wheat noodles commonly consumed by children) was administered.⁸ Stepwise, wheat OFC was implemented to determine the threshold dose (Figure S1).⁹ After first passing the 52mg OFC, the 390mg OFC and 1300mg OFC were administered. If patients could consume barley tea (1.8 mg), an OFC using barley rice (220–440mg) was administered. Patients who had not consumed barley tea within 1 year received an OFC using barley tea. Patients with a recent history of immediate reaction to barley tea within 1 year avoided OFC and were regarded as barley-reactive. In both stepwise OFCs, two portions of the challenge food were administered, starting with one-fourth of the total load, followed by the remainder at 1 h after starting OFC.⁸ These protein data were similar to those reported by the Ministry of Education, Culture, Sports, Science, and Technology of Japan (2020; <https://fooddb.mext.go.jp/>). The severity of symptoms was assessed according to Japanese anaphylaxis guidelines.¹⁰ Anaphylaxis was defined according to the World Allergy Organization anaphylaxis guidelines.¹¹ The threshold dose was defined as the cumulative dose at which the participant developed objective symptoms.^{12,13}

2.5 | Immunological parameters

We measured wheat, barley, and ω -5 gliadin-sIgE levels using an ImmunoCAP assay (Thermo Fisher Scientific/Phadia AB). Sensitization was defined as IgE level ≥ 0.10 kU_A/L.

2.6 | Sample size

Based on a previous study,¹⁴ we hypothesized that the expected cross-reactive barley allergy would be 40%, and the width of the confidence interval would be 20% ($\alpha = .05$, $\beta = .8$). The required sample size was calculated to be 46.

2.7 | Statistical analyses

Data were analyzed using SPSS version 25 (IBM Corp.). Data are expressed as *n* (%) or median values, with 25%–75% interquartile

range (IQRs). Mann–Whitney U tests were performed for continuous variables. Spearman's correlation coefficient was used to determine relationships among continuous variables. Fisher's exact test was used to compare the proportions. Statistical significance was set at a two-tailed p -value $< .05$.

2.8 | Ethical consideration

This study was performed per the tenets of the Declaration of Helsinki. Written informed consent was obtained from all the participants or their guardians. This study was approved by the Ethics Committee of the National Hospital Organization Sagami-hara National Hospital (approval no. 160106).

3 | RESULTS

3.1 | Enrollment

Informed consent was obtained from 124 patients between October 2015 and June 2016. Of these, we obtained the threshold dose for wheat OFC for 107 patients. We excluded seven patients without consumption and OFC of barley tea and 47 without consumption and OFC of barley rice. Finally, we included 53 patients with a history of barley consumption or oral food challenge (Figure 1). No patients had barley allergies without wheat allergies throughout the study period.

3.2 | Patients' characteristics

Among the 53 patients, 39 (74%) were boys, and 39 (74%) had a history of anaphylaxis (Table 1). The median age was 6.6 years. Among 53 participants, 52 had previous consumption of barley

(with/without symptoms), including barley tea. Among 26 patients with barley allergy, 23 had previous reactions to barley. Of these, five had confirmed reactions to barley after more than 1 year of avoidance. Three were new reactions confirmed by OFC. Regarding allergic complications, 66% of the patients had food allergies other than wheat and barley, 53% had atopic dermatitis, and 30% had bronchial asthma. The threshold dose of wheat protein by the wheat OFC was 104 mg. The median wheat-, barley-, and ω -5 gliadin-sIgE levels were 57.3, 12.1, and 3.2 kU_A/L, respectively.

3.3 | Clinical outcomes

Among the 53 patients, 26 reacted to barley. Twelve reacted to barley tea (1.8 mg), and 14 reacted to barley rice (220–440 mg). Among the 12 patients allergic to barley tea, four patients received OFC of barley rice, and all four patients reacted to the barley rice OFC. The median time interval between OFC to wheat and that to barley was 6 (range: 1–18) months. No differences were observed in the clinical background between patients with barley allergy and those with barley tolerance (Table S1).

3.4 | Threshold dose of wheat

The threshold doses assessed by wheat OFC for barley-allergic patients, and barley-tolerant patients were 71.5 (26–159.9) mg and 161.2 (104–780) mg, respectively (Figure 2D). Patients allergic to barley had lower threshold doses of wheat OFCs than barley-tolerant patients ($p = .004$). Among barley-allergic patients, the threshold doses assessed by wheat OFC for barley tea allergic patients, and barley rice-allergic patients were 26 (26–513.5) mg and 104 (26–159.9) mg, respectively (Figure S2). No significant differences were observed in the threshold dose of wheat between patients allergic to barley tea and barley rice ($p = .322$).

FIGURE 1 Patient enrollment. Among the 124 patients who agreed to participate in this study, 17 did not respond to stepwise wheat OFC. All patients consumed wheat and barley rice. We also excluded seven patients who did not consume barley tea and 47 who did not consume barley rice. Finally, 53 patients were included in the analyses: 26 barley-allergic and 27 barley-tolerant patients.

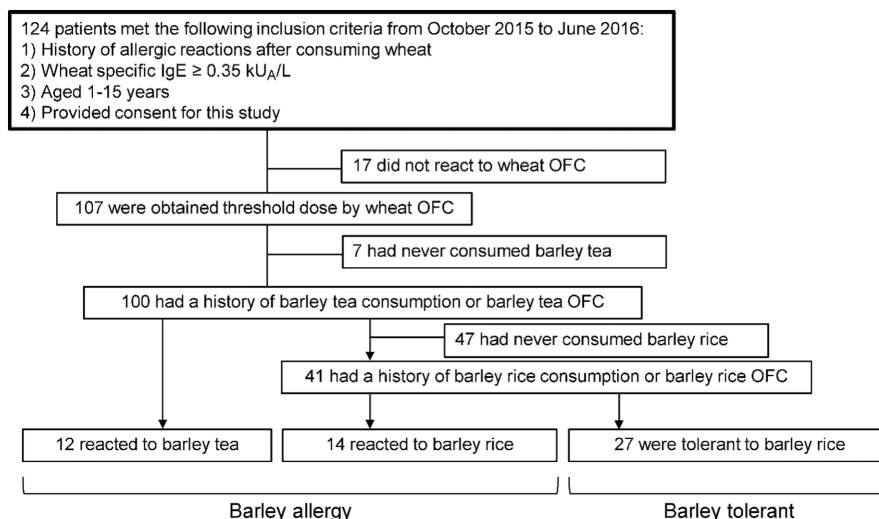


TABLE 1 Patient backgrounds

	All patients (n = 53)
Sex (male)	39 (74%)
Age at the time of enrollment (years)	6.6 (4.8–9.0)
Allergic complications	
Food allergy (other than wheat and barley)	35 (66%)
Bronchial asthma	16 (30%)
Atopic dermatitis	28 (53%)
History of wheat-induced anaphylaxis	39 (74%)
History of immediate reaction to barley	23 (43%)
Eliciting dose during wheat OFC (mg)	104 (26–455)
Total IgE level (IU/L)	656 (275–1380)
Allergen sIgE level (kU _A /L)	
Wheat	57.3 (11.9–236.9)
Barley	12.1 (3.8–55.5)
Gluten	65.6 (11.4–308)
ω -5 gliadin	3.2 (1.0–13.2)

Note: Data are expressed as *n* (%) or median values, with 25%–75% interquartile ranges provided in parentheses. All participants were positive to barley and gluten; 94% (50/53) were positive to ω -5 gliadin. Abbreviations: IgE, immunoglobulin E; OFC, oral food challenge; sIgE, specific immunoglobulin E.

3.5 | Laboratory data

There was a strong correlation between barley and wheat ($r = .944$) and ω -5 gliadin ($r = .771$; Figure S3). There were significant differences in wheat-, barley-, and ω -5 gliadin-sIgE levels between barley-allergic patients and barley-tolerant patients (Figure 2A–C), and the probability curve for barley allergy is shown in Figure 3. The area under the curve for wheat, barley, and ω -5 gliadin-sIgE was 0.763 (0.630–0.895), 0.751 (0.618–0.883), and 0.797 (0.678–0.916; Figure S4), respectively. The 95% positive predictive values of barley allergy for wheat, barley, and ω -5 gliadin-sIgE were 18948.3, 14.5, and 4.6 kU_A/L, respectively (Table S2). The probability curve for barley tea allergy is shown in Figure S5.

3.6 | Symptoms induced by barley

The symptoms induced by barley tea and barley rice are shown in Table S3. The symptoms induced by barley tea were milder than those induced by barley rice ($p = .046$). The most common symptoms of barley tea were oral mucosal symptoms (50%), and those of barley rice were respiratory symptoms (64%; Table S3).

4 | DISCUSSION

This study revealed the clinical cross-reactivity of wheat and barley among children with immediate-type wheat allergies. Similar to previous studies,^{6,14,15} we confirmed that half of the wheat-allergic patients reacted to barley.

All the subjects were sensitized to barley. This study showed a strong correlation between sIgE levels in wheat and barley. These results suggest in vitro cross-reactivity between wheat and barley, similar to the results of previous studies.^{3,4}

Comparing barley-reactive and -tolerant subjects, reactivity to barley was associated with a lower wheat threshold dose and higher wheat-specific IgE levels. These results strongly suggest the clinical cross-reactivity of barley and wheat. An in vitro study showed that wheat is the primary source of sensitization.¹⁶ Similarly, we considered wheat a primary source of sensitization; barley results in secondary sensitization due to cross-reactivity to wheat. None of the patients tolerated wheat and reacted only to barley. Sensitization to barley is caused by cross-reactivity.

In our study, the most useful predictor of barley allergy among wheat-allergic patients was ω -5 gliadin. The γ 3-hordein of barley is combined with an antibody against ω -5 gliadin due to sequence homology with wheat allergens.^{3,17} Omega-5 gliadin is the most useful predictor of wheat allergies. Due to its sequence homology with wheat allergens, ω -5 gliadin may also be the most useful predictor of barley allergy. Clinically, the ω -5 gliadin sIgE value of the 95% positive predictive values for barley allergy was 4.6 kU_A/L. Therefore, wheat-allergic patients with ω -5 gliadin-sIgE ≥ 4.6 kU_A/L should avoid barley.

Reactions with barley tea were milder than reactions with barley rice. Barley tea contains fewer proteins than barley rice. This difference in protein content in foods may contribute to the severity of induced symptoms. Most patients with wheat allergy consume barley tea. Moreover, all symptoms induced by barley tea were mild. Barley tea is the most frequently consumed beverage among children in Japan at home and in schools,¹ and consumption of barley tea may improve quality of life in schools. However, no patients developed tolerance to barley rice by continued daily consumption of barley protein. Therefore, in other countries except Asian countries, improvement of the quality of life by the consumption of barley tea may be limited.

This study had some limitations. First, the patients included in this single-center study may have selection bias. Most patients had a history of anaphylaxis to wheat. They had high sIgE levels in wheat and ω -5 gliadins. All participants were positive to wheat and barley. Therefore, the findings are restricted to children sensitized to both foods. Although, all symptoms induced by barley tea were mild, the number in this study were limited. Further studies are required to confirm these results in the general population. Second, we excluded 47 patients who could consume barley tea without barley rice OFCs. However, no significant background difference was observed between the included and excluded patients who consumed barley tea (Table S4). Finally, this study did not examine double-blind

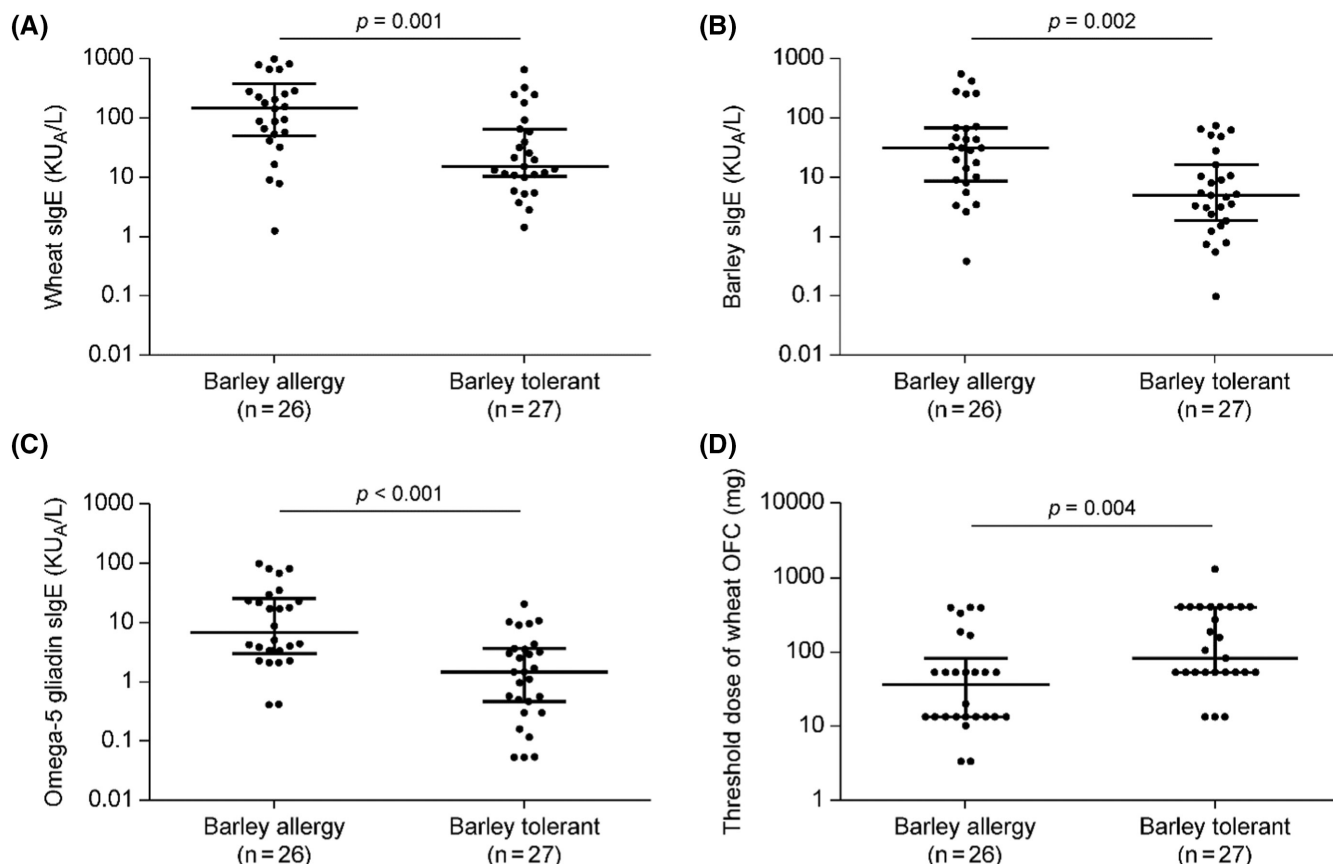


FIGURE 2 Differences of specific IgE to wheat, barley, ω -5 gliadin, and the threshold dose of wheat OFC with and without barley allergy. There were significant differences in the wheat-, barley-, and ω -5 gliadin-sIgE levels between barley-allergic patients and barley-tolerant patients (A–C). The threshold doses assessed by wheat OFC for barley-allergic patients and barley-tolerant patients (D). IgE, immunoglobulin E; OFC, oral food challenge; sIgE, specific immunoglobulin E

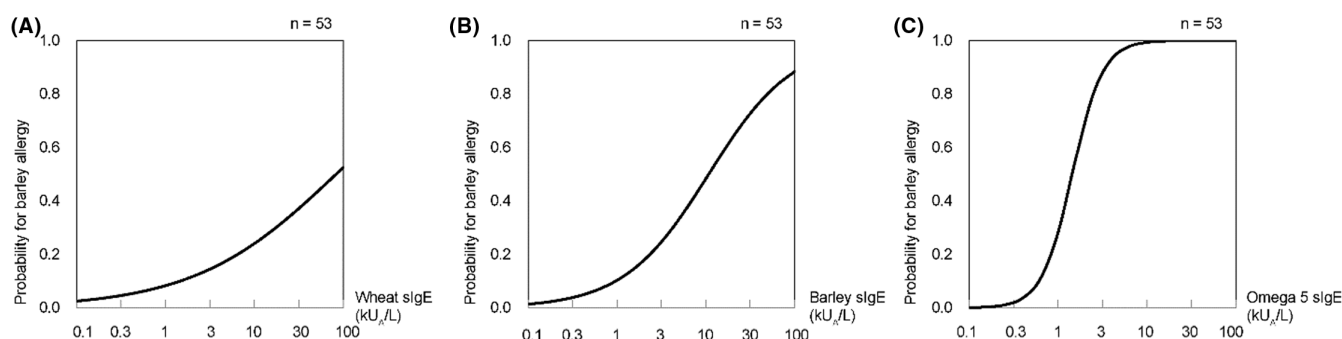


FIGURE 3 Probability of barley allergy. The probability of barley allergy was calculated using (A) wheat sIgE, (B) barley-sIgE and (C) ω -5 gliadin-sIgE. IgE, immunoglobulin E; sIgE, specific immunoglobulin E

placebo-controlled food challenges, and further studies regarding these are needed.

5 | CONCLUSIONS

This study revealed clinical cross-reactivity between wheat and barley. Half of the children allergic to wheat reacted to barley. Omega-5

gliadin predicts barley allergy in children allergic to wheat. Clinical cross-reactivity to barley should be considered in the management of wheat-allergic children.

AUTHOR CONTRIBUTIONS

NY and MT designed the study. NY drafted and designed the manuscript. NY generated figures. NY analyzed and interpreted the data. MT collected data. AS examined the serum samples. NY, MT,

SS, AS, and ME critically read the paper. All authors discussed the results of this study. NY and MT should be considered joint first authors.

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CONFLICT OF INTEREST

Motohiro Ebisawa received lecture fees from Mylan EPD. Sakura Sato received lecture fees from Mylan EPD. All other authors declare that they have no relevant conflicts of interest.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/pai.13878>.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Noriyuki Yanagida  <https://orcid.org/0000-0001-9643-744X>

Mari Takei  <https://orcid.org/0000-0002-5948-4957>

Sakura Sato  <https://orcid.org/0000-0003-3674-0759>

Motohiro Ebisawa  <https://orcid.org/0000-0003-4117-558X>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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