Reactions of Buckwheat-Hypersensitive Patients during Oral Food Challenge Are Rare, but Often Anaphylactic

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Keywords

Buckwheat · Food allergy · Food hypersensitivity · IgE · Oral food challenge

Abstract

Background: Buckwheat (BW) is a common cause of life-threatening allergy in Asia. Few have examined oral food challenges (OFCs) using BW. We here describe the OFC outcomes for the diagnosis or confirmation of tolerance acquisition and clarify risk factors for positive OFCs. **Methods:** Between July 2005 and March 2014, we retrospectively reviewed data from children who underwent OFCs using 3,072 mg of BW protein at Sagami National Hospital. Children were suspected of having BW allergy because of positive results for BW-specific IgE or because they had been previously diagnosed with BW allergy owing to immediate reactions to BW. **Results:** Of 476 such patients, we analyzed 419 aged 1–17 years (median age 6.7 years). Forty-four (10.5%) reacted to the BW OFC and 24 (5.4%) experienced anaphylaxis. Among patients with suspected BW allergies ($n = 369$), 30 (8.1%) reacted to OFC. However, among patients with definitive BW allergies ($n = 50$) who underwent OFCs a median of

7.0 years after their last immediate reaction, 14 (28.0%) reacted to OFC. Among 12 patients with past anaphylactic reactions to BW, 8 exhibited tolerance to BW. A history of immediate reaction to BW and high BW-specific IgE levels were significant risk factors for a positive OFC. **Conclusions:** BW allergies are rare among children suspected of having BW allergies due to positivity for BW-specific IgE. Most children with definitive BW allergies can tolerate BW, even after anaphylactic reactions. Nevertheless, careful observation is needed when performing BW OFCs, considering the high incidence of anaphylactic reactions.

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Introduction

Buckwheat (BW) is a member of the Polygonaceae family that is consumed widely in East Asian countries and Russia [1]. Recently, the consumption of BW has increased as a healthy component of pizza and pasta in the USA and Europe, and this increased consumption has revealed BW as a hidden allergen [2, 3]. BW allergy has often been reported in Asia [4], and it is the sixth most com-

mon cause of food allergy in Japan [5]. The estimated prevalence of BW allergy in school children is 0.10% in Korea [6] and 0.22% in Japan [7]. Although BW allergy had been considered a rare food allergy in Europe and North America, recent studies revealed that substantial proportions of individuals were sensitized to BW in Italy (3.6%) [8], other European countries (1.0–9.7%), and the USA (2.5%) [9]. However, the actual prevalence of BW allergy is unknown among sensitized patients.

BW allergy can often cause life-threatening anaphylaxis [10]. BW is the fourth most frequent cause of food-related anaphylaxis in Japan [11] and fifth most frequent cause of food-related anaphylaxis in Korea [12]. In a recent examination of the draft genome of BW, Fag e 2 (a 16-kDa protein) [13, 14] was found to be an allergen, as were its homologues, identified by BLASTP searching in the BW genome database [15]. Targeting Fag e 3 was reported to improve the diagnosis of BW allergy [16]. Nevertheless, the most accurate diagnosis method is still oral food challenge (OFC).

A few previous reports have investigated OFCs with BW, but the sample size was limited to 12 [2] and 58 cases [16]. Maruyama et al. [16] reported that BW-specific IgE could not be used for BW allergy diagnosis, but their conclusion was limited as it was based on only 65 cases. Therefore, larger studies are needed. Furthermore, the prognosis of patients with a definitive BW allergy that was confirmed by immediate reaction remains unknown.

Our study aimed to reveal both the rate of definitive BW allergy among patients suspected of being allergic to BW based on positive BW-specific IgE findings, as well as the frequency of tolerance acquisition to BW allergy confirmed by OFC among patients with definitive allergies. Furthermore, we aimed to describe the symptoms induced during BW OFC and to clarify risk factors for a positive OFC.

Materials and Methods

Study Population and Enrollment

We retrospectively analyzed data from children who underwent OFCs with BW under hospitalization or at an outpatient clinic at Sagami National Hospital between July 2005 and March 2014. We analyzed the children who underwent a first BW OFC and who did not have missing clinical or laboratory data (online suppl. Fig. 1; see www.karger.com/doi/10.1159/000456008 for all online suppl. material). BW-hypersensitive patients underwent OFCs to confirm their BW allergy (group A). BW hypersensitivity was examined when screening tests for atopic dermatitis or other food allergy was indicated in the absence of suspicious events. Patients who had definitive BW allergies with past immediate reac-

tions to BW were also enrolled to diagnose tolerance acquisition (group B). Patients with high BW-specific IgE levels, history of anaphylaxis or a recent history of immediate reaction to BW were also enrolled.

Oral Food Challenge

OFCs were used to diagnose patients in group A or to confirm tolerance for patients in group B. In total, 64 g of BW noodles, containing 3,072 mg of BW protein, were used for the OFC (online suppl. Fig. 2). Patients were encouraged to consume a bite at 15-min intervals under hospitalization, or at 30-min intervals at an outpatient clinic, as described in the Japanese guidelines [5]. A physician openly observed the patients throughout the OFCs, and the method of OFC testing is detailed in online supplementary Figure 2. We regarded an OFC as positive when we observed objective symptoms or persistent moderate subjective symptoms, as described in online supplementary Table 1. Anaphylaxis was defined according to the World Allergy Organization Anaphylaxis Guidelines [17]. For cases in which a provoked reaction occurred, patients were administered treatments based on the European Academy of Allergy and Clinical Immunology's (EAACI) food allergy and anaphylaxis guidelines [18]. Here we present the OFC results, including the OFC-positive rates, symptoms, and treatments administered during OFC.

Laboratory Data

BW-specific IgE was assessed using the ImmunoCAP® assay system (Thermo Fisher Scientific/Phadia, Uppsala, Sweden). Laboratory data were collected within 180 days of OFC, because blood examinations are recommended once a year for school children [5]. ImmunoCAP® can detect levels of at least 0.1 kU_A/L. If BW-specific IgE measured less than 0.1 kU_A/L, we set the measurement to 0.05 kU_A/L.

Statistical Analysis

We expressed data in terms of median values and ranges. To analyze differences between the 2 groups, we used either the Mann-Whitney U test or Fisher exact test for statistical comparisons. We considered *p* values <0.05 as statistically significant. Logistic regression analysis was used for univariate and multivariate analyses. To determine risk factors for positive OFCs, we performed multivariate analyses using stepwise selection. In order to create probability curves with 95% confidence intervals (CI), we used regression analysis after logarithmic transformation of BW-specific IgE values [7]. We calculated the BW-specific IgE value for which approximately 95% of patients would have a clinical reaction. This so-called 95% predictive decision point (PPV) is generally used as the threshold value to decide whether an OFC should be performed [7]. We also calculated the 5, 10, and 50% PPVs. We used SPSS 20.0 (IBM Corporation, Armonk, NY, USA) to perform all statistical analyses.

Ethical Considerations

In accordance with the Declaration of Helsinki, the study design and risks of symptoms following OFC were fully explained to the patients and their guardians, both orally and in writing, and written informed consent was obtained from all participants for the OFC and for publication of the data. We also obtained approval from the institutional review board of Sagami Hospital.

Table 1. Patient background characteristics

Group	Total (<i>n</i> = 419)	Group A (<i>n</i> = 369)	Group B (<i>n</i> = 50)	<i>p</i> value
Male gender	293 (70.0)	261 (70.7)	32 (64.0)	0.329
Age, years	6.7 (1.3–17.9)	6.5 (1.3–17.9)	9.9 (6.4–11.5)	<0.001
Food allergy other than BW	354 (84.5)	324 (87.8)	30 (60.0)	<0.001
Current atopic dermatitis	179 (42.7)	166 (45.0)	13 (26.0)	0.014
Current bronchial asthma	93 (22.2)	84 (22.8)	9 (18.0)	0.586
Current allergic rhinitis	74 (17.7)	64 (17.3)	10 (20.0)	0.692
History of immediate reaction to BW	50 (11.9)	0 (0)	50 (100.0)	–
Age at first immediate reaction to BW, years	–	–	2.4 (1.0–9.0)	–
Duration from last immediate reaction to OFC, years	–	–	7.0 (0.2–15.6)	–
History of anaphylactic reaction to BW	12 (2.9)	–	12 (24.0)	–
Duration from last anaphylactic reaction to OFC, years	–	–	10.5 (1.9–15.6)	–
Total IgE, IU/mL	1,110 (<5–29,800)	2,103.4 (<5–29,800)	776 (5.0–6,740)	0.003
BW-specific IgE, kU _A /L	1.6 (0.05–441.0)	1.6 (0.05–441.0)	1.3 (0.11–26.9)	0.007
Number of positive OFCs	44 (10.5)	30 (8.1)	14 (28.0)	<0.001

Data are expressed as *n* (%) or median (range). BW, buckwheat; OFC, oral food challenge; group A, suspected of BW allergy; group B, definitive BW allergy with previous reaction to BW.

Results

Patient Enrollment and Background Characteristics

In total, 476 patients underwent OFCs (online suppl. Fig. 1). We excluded 17 patients from the analysis because of a lack of clinical information, 43 patients because of missing laboratory data, and 4 patients because of a previous history of BW OFC. We thus analyzed 419 patients with suspected or definitive BW allergies, who were 1.3–17.9 years old (median age 6.7 years; Table 1). The median BW-specific IgE level was 1.6 kU_A/L. Among the 419 patients, 50 had histories of reaction to BW (group B) and 12 patients had histories of anaphylaxis due to BW.

As compared with group B, group A contained more patients who experienced atopic dermatitis and had higher BW-specific IgE levels. The first immediate reaction in group B had occurred between the ages of 1.0 and 9.0 years (median age 2.4 years). The median duration between the last immediate reaction and OFC in group B was 7.0 years (range 0.2–15.6). For patients with histories of anaphylactic reactions, the median duration of complete elimination was 10.5 years (range 1.9–15.6).

Results of OFCs

During the BW OFCs, 44 patients (10.5%) reacted, all of whom presented objective symptoms. The clinical reactions and treatments during positive challenges are displayed in Table 2 and online supplementary Table 4. Moderate and severe symptoms were present in 24

Table 2. Data related to induced reactions and positive challenge severity

Symptoms	Positive BW OFC (<i>n</i> = 44)
Skin	36 (81.8)
Respiratory	28 (63.6)
Gastrointestinal	26 (59.1)
Neurological	5 (11.4)
Cardiovascular	3 (6.8)
Anaphylaxis	24 (54.5)
Severity	
Mild	10 (22.7)
Moderate	24 (54.5)
Severe	10 (22.7)

Data are expressed as *n* (%).

(54.5%) and 10 patients (22.7%), respectively. Fourteen of the patients with moderate symptoms, as described in online supplementary Table 1, and all of the patients with severe symptoms experienced anaphylactic reactions. Thus, we observed anaphylactic reactions in 24 patients (54.5%).

Oral antihistamine was the most frequently used treatment, and was administered to 28 patients (63.6%). Intramuscular adrenalin injections were administered to 9 patients (20.3%). The median threshold dose was 1,536 mg of BW protein (range 768–3,072 mg; online suppl. Fig. 3). The median times of the initial appearance of symptoms,

Table 3. Comparison of patients according to OFC results (positive vs. negative)

Results of challenge tests	Positive (n = 44)	Negative (n = 375)	p value
Male gender	29 (65.9)	264 (70.4)	0.394
Age, years	7.4 (2.2–14.5)	6.7 (1.3–17.9)	0.606
History of immediate reaction to BW	14 (31.8)	36 (9.6)	<0.001
History of anaphylaxis due to BW	4 (9.1)	8 (2.1)	0.028
Food allergy other than BW	36 (81.8)	318 (84.8)	0.659
Current atopic dermatitis	16 (36.4)	163 (43.5)	0.526
Current bronchial asthma	12 (27.3)	81 (21.6)	0.443
Current allergic rhinitis	6 (13.6)	68 (18.1)	0.537
Total IgE, IU/mL	826.5 (26.0–1,700)	1,150 (<5–29,800)	0.157
BW-specific IgE, kU _A /L	3.9 (0.15–441.0)	1.4 (0.05–32.6)	0.001

Data are expressed as n (%) or median (range).

maximal presentation of symptoms, and disappearance of symptoms after the start of OFC were 30 (range 1–660), 120 (range 5–740), and 180 min (range 30–780), respectively (online suppl. Fig. 4).

Tolerance Acquisition after Immediate Reaction to BW

Among the patients suspected of having BW allergies (group A, n = 369), 30 (8.1%) reacted to the OFC. On the other hand, among the patients with confirmed BW allergies, based on a convincing history (group B, n = 50), 14 (28.0%) reacted to the OFC, which was performed a median of 7.0 years after their last immediate reactions to BW. Among the 12 patients who had past anaphylactic reactions to BW, 8 patients had developed tolerance to BW.

Risk Factors for a Positive OFC

Patient characteristics were compared according to positive or negative OFC results (Table 3). The following factors were more frequent among patients with positive OFC results: histories of immediate reactions to BW ($p < 0.001$), histories of anaphylactic reactions ($p = 0.028$), and higher BW-specific IgE levels ($p = 0.001$). Higher BW-specific IgE levels were associated with a positive OFC result in group A and group B (online suppl. Tables 2 and 3).

The risk factors for positive challenge results were analyzed by multivariate regression after a stepwise selection of the variables in Table 1. A history of immediate reaction to BW (adjusted odds ratio 5.550, 95% CI 2.580–11.939, $p < 0.001$) and BW-specific IgE (per 10-fold increase; adjusted odds ratio 2.969, 95% CI 1.717–5.135, $p < 0.001$) were independent risk factors for a positive

OFC. When performing analyses within the 2 groups independently, a high BW-specific IgE level was the only significant risk factor for a positive OFC in both groups (online suppl. Table 5). Furthermore, among 44 patients who reacted to OFCs, no significant risk factor was found for severe reactions during the OFC.

Probability Curves

We developed probability curves from BW-specific IgE data using a logistic regression model (Fig. 1). Probability curves for group B were more robust than those for group A. We could not calculate a BW-specific IgE level indicative of a PPV exceeding 95% in either group. In group A, the BW-specific IgE levels indicative of PPVs exceeding 5 and 10% were 0.71 and 4.39 kU_A/L, respectively. In group B, we could not calculate a PPV exceeding 5%, but that exceeding 10% was 0.27 kU_A/L (online suppl. Table 6).

Discussion

In this study we showed that most patients suspected of having BW allergies rarely react to OFCs, and that most patients with a history of immediate reactions tolerate BW. The usefulness of BW-specific IgE levels remains controversial [16, 19]. We also applied a history of immediate reaction to BW and high BW-specific IgE levels to predict OFC results, and our study included the largest number of patients in such a study to date [16].

Probability curves that incorporate the presence or absence of immediate reactions to BW will provide considerable assistance in the management of patients who are

Fig. 1. Fitted predicted probability curves for the outcomes of the challenge at a given BW-specific IgE level. The probability curves represent the outcomes of the challenge at a given BW-specific IgE level. **a** The solid curve represents patients who were suspected of

having BW allergies, but without histories of immediate reactions to BW. **b** The solid curve represents patients who had histories of immediate reactions to BW. Each 95% CI is displayed by the shaded area around the line.

allergic to BW. Although severe reactions could not be predicted [20], a previous reaction to BW was a risk factor for positive reactions to a BW OFC in our study. Similarly, a history of a prior reaction was reported to be a risk factor for a multisystemic reaction in wheat OFC [21]. Because we could not predict severe reactions, further investigations with more OFC-positive participants will be needed to examine the risk factors for severe reactions. For example, the 10% PPVs for patients with and without a history of immediate reaction were 0.27 and 4.39 kU_A/L , respectively. This information will contribute greatly to risk assessments of patients before BW OFC.

The median age of patients who underwent OFC was 6.7 years, which is older than that for other common antigens, such as egg or milk [5, 18]. This is likely because most patients received OFCs around the time of their entry into elementary school, and because BW OFC does not have as high priority as other food allergies, since food labeling regulations in Japan make BW easy to avoid [11].

In group A, few patients reacted to BW OFC. In an Italian study, 61.3% of patients were atopic and a large number of patients demonstrated sensitization to BW. Likewise, in our study, group A had a higher prevalence

of atopic dermatitis than group B, which may have affected the total IgE and BW sIgE levels. Although a history of immediate reaction to BW was a risk factor for a positive OFC, more than two-thirds of group B had a negative OFC. Surprisingly, among the 12 patients with histories of anaphylaxis due to BW, 8 had developed tolerance to BW after a median of 10.5 years of dietary elimination. Therefore, the majority of infantile BW allergies seem to be tolerated later in childhood.

Even though most patients passed the OFC and few patients reacted during the OFC, most of the symptoms that did occur were not mild. Indeed, anaphylaxis was frequently observed. Severe reactions during OFC were seen in 6–10% of patients in response to cow's milk, chicken's eggs, wheat, and soy [22], as well as 24–36% of patients in response to peanuts [23, 24]. In our study, anaphylactic reactions were present in more than half of the patients who experienced positive reactions to the OFC, similar to the results of a previous report [2]. BW is known as an anaphylaxis-inducing food [12], as confirmed by our OFC data.

Moreover, our study was the first to suggest that most patients with reactions experienced symptoms within

30 min from the start of an OFC, and these symptoms mostly deteriorated around 90 min after their initial appearance. Provoked symptoms diminished within approximately 150 min, which is similar to the long duration seen for egg allergies [25]. These findings suggest that we should carefully observe patients for at least 2 h after the appearance of symptoms that arise in response to BW. Therefore, we should pay close attention to severe symptoms during a BW OFC and consider the risk factors prior to performing this challenge.

There were some limitations to our study. First, the OFCs were not double-blinded, placebo-controlled challenges. However, all OFC-positive patients had objective symptoms, including anaphylaxis, and therefore the lack of blinding and placebo control did not have a meaningful effect on our conclusions. Second, only 44 patients reacted positively to the BW OFC. This number may be too small to be representative. However, some of the patients who were definitely allergic or were suspected of being allergic to BW chose not to undergo the BW OFC, in order to avoid severe reactions to BW. Third, we could not examine the effectiveness of additional examinations, such as the skin prick test, or assessments to identify the component of BW or plant panallergens. BW components such as Fag e 2 [13] and Fag e 3 [16] may be candidates for improving diagnostic accuracy. Our study could not assess such components because it had a retrospective design, and we were unable to perform additional examinations using residual serum samples. Laboratory data were collected within 180 days of OFC; laboratory data

obtained closer to the day of the OFC may contribute to the prediction of the OFC result. Further studies that improve the accuracy of predicting positive challenges are necessary.

Our findings clearly revealed that true BW allergies are rare among children who are suspected of being allergic to BW based on detectable BW-specific IgE. Furthermore, our findings revealed that most children with definitive BW allergies can become tolerant to BW even after having anaphylactic reactions at younger ages. Prolonged and careful observations for frequent anaphylactic reactions are needed when performing a BW OFC. Risk factors for positive challenges should also be considered, including histories of an immediate reaction to BW and presence of high levels of BW-specific IgE.

Acknowledgments

All aspects of this study, including the study design, data collection, analysis, and the interpretation of data were supported by Health and Labor Sciences Research Grants for Research on Allergic Disease and Immunology from the Ministry of Health, Labor, and Welfare of Japan (Motohiro Ebisawa, grant No. 201414009A). We are particularly grateful to all of the pediatricians, nutritionists, and nurses who participated in patient recruitment and data collection at Sagamihara National Hospital.

Disclosure Statement

All authors have no conflicts of interest to declare.

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