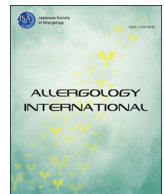




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Original Article

Skin prick test is more useful than specific IgE for diagnosis of buckwheat allergy: A retrospective cross-sectional study

Noriyuki Yanagida^{a,*}, Sakura Sato^b, Kyohei Takahashi^a, Ken-ichi Nagakura^a, Kiyotake Ogura^a, Tomoyuki Asami^a, Motohiro Ebisawa^b^a Department of Pediatrics, Sagami National Hospital, Kanagawa, Japan^b Department of Allergy, Clinical Research Center for Allergy and Rheumatology, Sagami National Hospital, Kanagawa, Japan

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BW, Buckwheat; BW-sIgE, Buckwheat-specific immunoglobulin E; CI, Confidence interval; EAACI, European Academy of Allergy and Clinical Immunology; OFC, oral food challenge; SPT, Skin prick test

ABSTRACT

Background: Buckwheat (BW) is a potentially life-threatening allergen. Usefulness of BW-specific immunoglobulin-E (BW-sIgE) level for diagnosis of BW allergy is controversial, while the skin prick test (SPT) is widely used because of its less invasive procedure and immediate results. However, there are no data comparing usefulness of the SPT and BW-sIgE level. Therefore, our study aimed to clarify efficacy of the SPT for diagnosis of BW allergy.

Methods: This retrospective cross-sectional study evaluated patients who underwent an oral food challenge (OFC) for diagnosis or confirmation of acquired tolerance using 3072 mg of BW protein between July 2006 and April 2014. We then compared the diagnostic performance of BW sIgE and SPT to predict positive OFC results.

Results: We analyzed 126 patients aged 2–16 years (median, 7.7 years), 18 (14%) of whom showed positive OFC results. Between patients with positive and negative OFC results, there was no significant difference in BW-sIgE level. However, patients with positive OFC results had a larger SPT wheal diameter. Area under the curve for positive OFC results for BW-sIgE level and SPT wheal diameter were 0.583 and 0.791, respectively. The 5%, 10%, 50%, and 90% positive predictive values of SPT wheal diameter were 2.0 mm, 5.2 mm, 14.7 mm, and 24.1 mm, respectively.

Conclusions: Our study revealed that the SPT was more useful than BW-sIgE level for diagnosis of BW allergy. Thus, an OFC may be avoided if the patient's SPT wheal diameter is at least 24.1 mm.

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Introduction

Buckwheat (BW) is widely consumed in Asian countries¹ and has become increasingly popular in the United States, Canada, and Europe.² However, BW can be a potent allergen and may cause life-threatening anaphylaxis.³ Prevalence of BW allergy in school children in Japan is approximately 0.22%.⁴ In fact, in Japan, BW allergy is the sixth most common food allergy⁵ and the fourth most common cause of food-induced anaphylaxis.⁶ For diagnosis of BW allergy, usefulness of BW-specific immunoglobulin E (BW-sIgE) level is controversial.^{7,8} However, application of more useful components, such as Fag e 3, has been limited to research purposes

only.⁷ Currently, the most accurate diagnostic method is still the oral food challenge (OFC).⁵

The skin prick test (SPT) and sIgE level can be used to examine sensitization.⁹ The SPT is useful for diagnosis of IgE-mediated allergy with high sensitivity¹⁰ and is widely used because of its less invasive procedure and immediate results compared with sIgE level.⁹ However, usefulness of the SPT for BW allergy is unknown. Therefore, this study aimed to clarify efficacy of the SPT for diagnosis of BW allergy.

Methods

Study population

This retrospective cross-sectional study analyzed patients who underwent an OFC with BW between July 2006 and April 2014 at Sagami National Hospital. We analyzed patients who

* Corresponding author. Department of Pediatrics, Sagami National Hospital, 18-1 Sakuradai, Minami-ku, Sagami, Kanagawa 252-0392, Japan.

E-mail address: n-yanagida@sagami-hosp.gr.jp (N. Yanagida).

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underwent a first BW OFC and did not have missing clinical or laboratory data (Fig. 1). We enrolled patients suspected of having BW allergy with a positive BW-sIgE level as well as BW-allergic patients with past immediate reactions to BW in order to diagnose tolerance acquisition.

OFC

In total, 64 g of BW noodles, containing 3072 mg of BW protein, were used for the OFCs. Patients were encouraged to consume a bite at 15-min intervals, as described in Japanese guidelines,⁵ under two days of hospitalization. The OFCs were openly observed by a physician throughout according to European Academy of Allergy and Clinical Immunology (EAACI) food allergy and anaphylaxis guidelines.⁹ As described in anaphylaxis guidelines in Japan,¹¹ the OFC was regarded as positive when objective symptoms or persistent moderate subjective symptoms were observed. Anaphylaxis was defined according to World Allergy Organization Anaphylaxis Guidelines.¹² For cases in which a provoked reaction occurred, the treatments administered were determined based on EAACI food allergy and anaphylaxis guidelines.⁹

Laboratory data

Blood samples were drawn within 180 days of the OFC because blood examinations are recommended annually for school children.⁵ BW-sIgE level was assessed using the ImmunoCAP assay system (Thermo Fisher Scientific/Phadia, Uppsala, Sweden), which can detect levels of at least 0.1 kU_A/L. If BW-sIgE level measured less than 0.1 kU_A/L, we regarded the measurement as 0.05 kU_A/L, as previously described.¹³

SPT

The SPT was performed using a sterile bifurcated needle (Precision Medical Products, Denver, PA, USA), commercial BW extract (1:10 ratio; Torii Pharmaceutical, Tokyo, Japan), negative control of glycerin with saline, and positive control of histamine (10 mg/mL).¹⁴ The SPT was performed by an allergist during the hospitalization for the OFC. In the SPT, maximum wheal size was evaluated 15 min after the skin prick.¹⁵

Table 1
Patient characteristics.

Characteristic	Total (n = 126)	Positive (n = 18)	Negative (n = 108)	P value
Male	86 (68.3)	11 (61.1)	75 (69.4)	0.585
Age, median (range), y	7.6 (2.4–16.8)	8.0 (2.7–14.5)	7.6 (2.4–16.8)	0.832
Food allergy other than BW	107 (84.9)	15 (83.3)	92 (85.2)	0.735
Atopic dermatitis, current	30 (23.8)	5 (27.8)	25 (23.1)	0.766
Bronchial asthma, current	17 (13.5)	2 (11.1)	15 (13.9)	>0.999
Allergic rhinitis, current	13 (10.3)	3 (16.7)	10 (9.3)	0.397
History of immediate reaction to BW	18 (14.3)	7 (29.2)	11 (10.8)	0.045
History of anaphylaxis due to BW	9 (7.1)	3 (16.7)	6 (5.6)	0.119
Total IgE, median (range), IU/mL	1115.0 (5.0–17,100)	700.5 (26–5050)	1470.0 (5.0–17,100)	0.026

Data are expressed as n (%) unless otherwise noted.
BW, buckwheat; IgE, immunoglobulin E.

Statistical analysis

Data were expressed as medians and ranges. To analyze differences between groups, the Mann–Whitney *U* test or Fisher's exact test was used for statistical comparison, with *p* values of <0.05 considered to be statistically significant. Uni- and multivariate analyses were performed by logistic regression. In order to create probability curves with 95% confidence intervals (CIs), regression analysis of BW-sIgE levels with logarithmic transformation and of SPT wheal diameters without logarithmic transformation was performed as previously described.¹⁶ SPSS version 24.0 (IBM Corporation, Armonk, NY, USA) was used for all statistical analyses.

Ethical considerations

The study design was in accordance with the Declaration of Helsinki. The risk of symptoms following the OFC was fully explained both orally and in writing to the patients and their guardians. Written informed consent was obtained from all participants and study approval was obtained from the Institutional

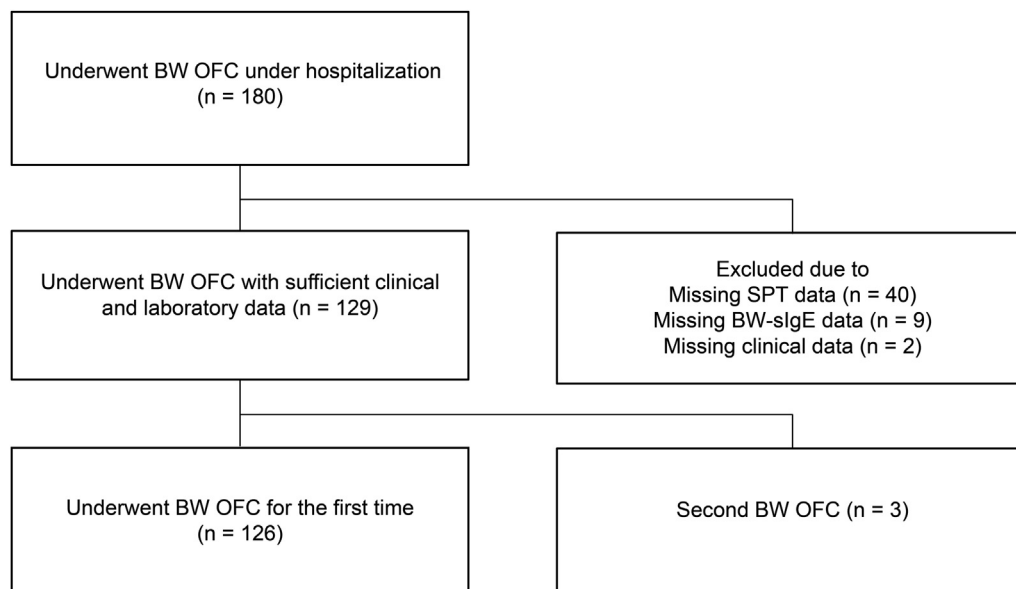


Fig. 1. Flowchart of study participation. BW, buckwheat; BW-sIgE, buckwheat-specific immunoglobulin E; OFC, oral food challenge; SPT, skin prick test.

Review Board of Sagami Hospital. Patient anonymity was preserved using methods approved by the Ethics Committee.

Results

Patient characteristics

In total, 180 patients underwent an OFC (Fig. 1). Forty patients were excluded from analysis due to lack of SPT data, 2 patients due to lack of clinical information, 9 patients due to missing laboratory data, and 3 patients due to having a second BW OFC. Thus, 126 patients with suspected or definitive BW allergy, aged 2.4–16.8 years (median, 7.6 years), were evaluated (Table 1). Median BW-sIgE level was 3.3 kU_A/L. Among the 126 patients, 18 had history of reaction to BW, and 9 had history of anaphylaxis due to BW (Supplementary Table 1).

OFC results and induced symptoms

During the BW OFCs, 18 patients (14.3%) showed a positive reaction, and all presented objective symptoms. Skin symptoms were most common (14 patients, 77.8%) followed by respiratory (11 patients, 61.1%) and gastrointestinal (10 patients, 55.6%) symptoms (Table 2). Among patients with positive OFC results, there were no differences in BW-sIgE level or SPT wheal diameter between anaphylactic and non-anaphylactic patients (Supplementary Fig. 1). Among 9 patients with history of anaphylaxis due to BW, 6 passed the BW OFC (Supplementary Table 1).

Moderate and severe symptoms occurred in 12 (66.7%) and 3 (16.7%) patients, respectively. Of those, 8 patients with moderate symptoms and all patients with severe symptoms experienced anaphylactic reactions. Thus, anaphylactic reactions were observed in 11 patients (61.1%).

Oral antihistamines were the most frequent treatment, which were administered in 9 patients (50.0%). Intramuscular adrenaline injections were administered in 2 patients (11.1%). Median threshold dose was 2496 mg (range, 192–3072 mg).

Comparison of positive and negative OFC results

Patient characteristics were compared according to positive or negative OFC results (Table 1). Patients with positive OFC results

more frequently had history of reaction to BW ($p = 0.045$), lower total IgE level ($p = 0.026$), higher ratio of BW-sIgE to total IgE ($p = 0.005$), and larger SPT wheal diameter ($p < 0.001$) (Fig. 2). Median SPT wheal diameter of patients with positive OFC results was 12 mm (range, 0–25 mm), while that of patients with negative OFC results was 3 mm (range, 0–20 mm).

Risk factors for positive OFC results

Risk factors for positive OFC results were analyzed by performing uni- and multivariate analyses (Table 3). In multivariate analysis adjusted for presence of immediate reaction, total IgE level was found to be an insignificant factor (per 10-fold increase; adjusted odds ratio [OR], 2.349; 95% CI, 0.973–5.669; $p = 0.058$), as was ratio of BW-sIgE to total IgE (per 10-fold increase; adjusted OR, 3.653; 95% CI, 0.469–9.085; $p = 0.065$). On the other hand, SPT wheal diameter remained a significant factor (per 1-mm increase; adjusted OR, 1.251; 95% CI, 1.123–1.394; $p < 0.001$).

Comparison of diagnostic performance of BW-sIgE and SPT

Diagnostic performance of BW-IgE and the SPT were compared (Fig. 3, Table 4). Area under the curve (AUC) for positive OFC results for BW-sIgE level and SPT wheal diameter were 0.583 and 0.791, respectively. Thus, SPT wheal diameter was the most effective parameter (95% CI, 0.646–0.941). Optimal cut-off value of SPT wheal diameter was 6.5 mm, which produced a sensitivity and specificity of 77.8% and 84.3%, respectively.

Among 95 patients with an SPT wheal diameter ≤ 6.5 mm, 4 patients (4.2%) showed positive OFC results. In contrast, among 31 patients with an SPT wheal diameter > 6.5 mm, 14 patients (45.2%) showed positive OFC results.

Fitted predicted probability curves derived from the OFC results at a given BW-sIgE level and SPT wheal diameter are presented in Figure 4. We could not calculate the 95% positive predictive value of BW-sIgE level and SPT wheal diameter. However, the 5%, 10%, 50%, and 90% positive predictive values of SPT wheal diameter were 2.0 mm, 5.2 mm, 14.7 mm, and 24.1 mm, respectively.

Discussion

Usefulness of BW-sIgE level for diagnosis of BW allergy is controversial.^{7,8} To the best of our knowledge, our study is the first to reveal that the SPT is more useful than BW-sIgE level for diagnosis of BW allergy.

Almost three-fourths of all patients had an SPT wheal diameter ≤ 6.5 mm. Among those patients, only 4.2% showed positive OFC results. Generally, with a positive predictive value of less than 5%, patients can consume causative foods safely.⁵ Thus, the SPT could effectively predict most non-BW-allergic patients. Generally, many patients avoid BW without undergoing an OFC because the OFC is time consuming and frequently induce anaphylaxis especially in BW OFC. Therefore, the SPT would be beneficial to such patients to safely introduce BW OFC with low rate of positive OFC results and consequently introduce BW in their daily diet after undergoing an OFC. In our study, anaphylaxis was observed in 11 out of 18 patients. This high incidence may originate from the fact that all patients in our study were high-risk patients who received an OFC under hospitalization and not in an outpatient clinic. Nevertheless, anaphylaxis due to BW is known to be more frequent than that by other antigens.⁵ This is compatible with a previous report.¹⁷

Adjusted ORs are useful to compare diagnostic performances of examinations.¹⁸ In multivariate analysis, the SPT was the only significant risk factor for positive OFC results. The SPT is more effective than BW-sIgE level and improves the efficacy of diagnosis of BW

Table 2
Induced reactions and severity of positive OFC results.

Symptom	Positive OFC results (n = 18)
Skin	14 (77.8)
Respiratory	11 (61.1)
Gastrointestinal	10 (55.6)
Neurologic	1 (5.6)
Cardiovascular	1 (5.6)
Anaphylaxis	11 (61.1)
Severity	
Mild	3 (16.7)
Moderate	12 (66.7)
Severe	3 (16.7)
Treatment	
Antihistamine (IV or IM)	9 (50.0)
Antihistamine (oral)	8 (44.4)
β_2 stimulant inhalation	6 (33.3)
Steroid (IV)	6 (33.3)
Steroid (oral)	4 (22.2)
Drip infusion	5 (27.8)
Adrenaline (IM)	2 (11.1)
None	3 (16.7)

Data are expressed as n (%).

IM, intramuscular; IV, intravenous; OFC, oral food challenge.

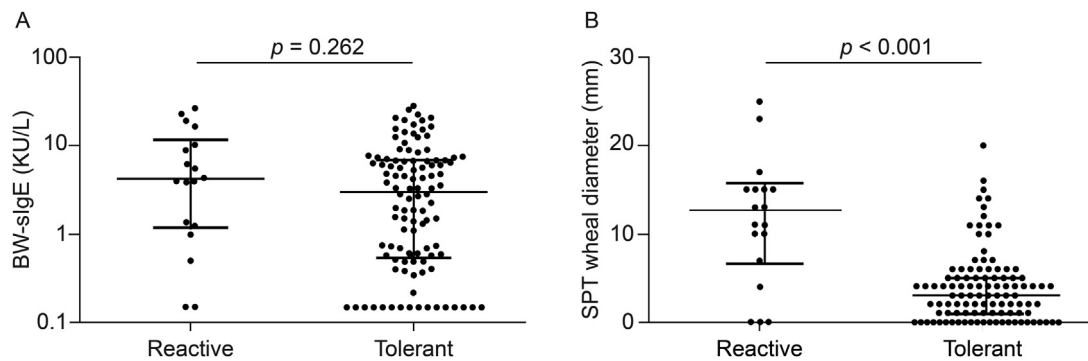


Fig. 2. Differences in BW-sIgE level (A) and SPT wheal diameter (B) were analyzed between reactive (n = 18) and tolerant patients (n = 108). BW-sIgE, buckwheat-specific immunoglobulin E; SPT, skin prick test.

Table 3

Uni- and multivariate analyses of factors related to positive OFC results.

Risk factor for positive OFC results (n = 126)	Crude OR (95% CI)	P value	Adjusted OR [†] (95% CI)	P value
BW-sIgE (10-fold increments)	1.602 (0.739–3.471)	0.233	1.647 (0.746–3.639)	0.217
Total IgE (10-fold increments)	0.437 (0.187–1.022)	0.056	0.426 (0.176–1.029)	0.058
Ratio of BW-sIgE to total IgE (10-fold increments)	4.026 (1.599–10.132)	0.003	3.653 (0.469–9.085)	0.065
SPT wheal diameter (1-mm increase)	1.263 (1.139–1.400)	<0.001	1.251 (1.123–1.394)	<0.001
History of immediate reaction to BW	3.406 (1.157–10.030)	0.026	–	–

BW, buckwheat; BW-sIgE, buckwheat-specific immunoglobulin E; CI, confidence interval; OFC, oral food challenge; OR, odds ratio; SPT, skin prick test.

[†] OR was adjusted by history of immediate reaction to BW.

allergy. We calculated the 90% positive predictive value of SPT wheal diameter as 24.1 mm. Therefore, an OFC may be avoided if the patient's SPT wheal diameter is 24.1 mm, similar to reports of egg or milk.¹⁹ Alternatively, in the future, we might consider use of another method simultaneously, such as component Fag e 3, to diagnose BW allergy more effectively.⁷ Verstege *et al.* reported a correlation between SPT and OFC results with regard to cow's milk, hen's egg, wheat, and soy.¹⁹ Their data indicate that foods seem to be different in terms of their diagnostic accessibility.

With wheat and soy, the correlations between IgE methods (SPT and sIgE) and OFC outcomes did not show satisfactory results.²⁰ Therefore, they hypothesized that animal proteins, such as cow's milk and hen's egg, reflected their IgE sensitization. However, for

plant proteins, such as wheat and soy, this correlation may be less valid. In fact, non-IgE-mediated clinical reactions were more common following an OFC with plant proteins compared with animal proteins.²¹ BW is also a plant. However, this does not fully explain the reason for the discrepancy in diagnostic efficacy between the SPT and BW-sIgE level. In some fruit allergy, prick to prick test is more useful than antigen sIgE.⁵ In this context, the allergen extract in SPT will greatly affect diagnostic efficacy. So, the difference in diagnostic efficacy of BW allergy may also originate from the difference in BW extract used in the SPT and BW-sIgE level; however, we do not know the compositions of ingredients due to trade secrets. Therefore, further research is needed to reveal the mechanism.

There are some limitations to our study. First, the OFCs were not double-blind, placebo-controlled challenges. However, all patients with positive OFC results had objective symptoms, including anaphylaxis. Therefore, we believe this limitation did not affect our conclusions. Second, we included only 126 patients under hospitalization, which may be fewer than previous study.²² Patients with history of life-threatening anaphylaxis or high BW-sIgE level may avoid an OFC. Therefore, we should consider potential selection

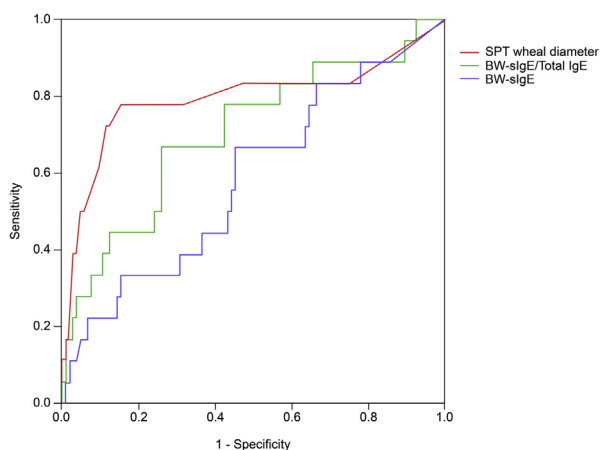


Fig. 3. Receiver operating characteristic curve for positive oral food challenge results. BW-sIgE, buckwheat-specific immunoglobulin E; SPT, skin prick test.

Table 4

Diagnostic performance of BW-sIgE and SPT.

	BW-sIgE	BW-sIgE/total IgE	SPT wheal diameter
AUC	0.585	0.706	0.791
95% CI	0.439–0.732	0.565–0.846	0.646–0.941
Optimal cut-off value	3.71 kU _A /L	0.038	6.5 mm
Sensitivity, %	66.7	66.7	77.8
Specificity, %	54.6	74.0	84.3

AUC, area under the curve; BW, buckwheat; BW-sIgE, buckwheat-specific immunoglobulin E; CI, confidence interval; SPT, skin prick test.

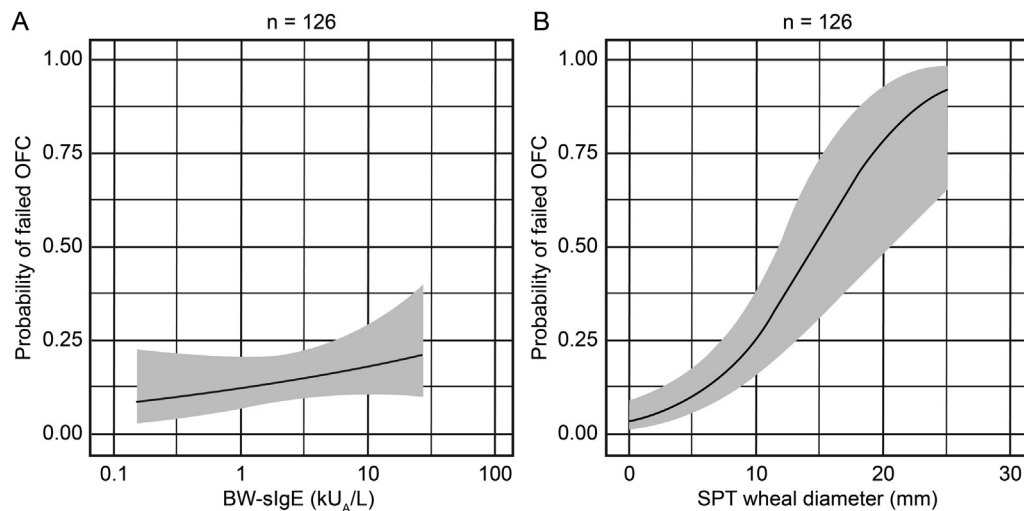


Fig. 4. Fitted predicted probability curves with 95% confidence intervals for OFC results at a given BW-sIgE level (A) and SPT wheal diameter (B). BW-sIgE, buckwheat-specific immunoglobulin E; OFC, oral food challenge; SPT, skin prick test.

bias in this study. Third, we could not examine additional components, such as Fag e 2²³ and Fag e 3,⁷ which may be candidates for improving diagnosis. Thus, larger prospective studies are needed to confirm whether the SPT can effectively diagnose BW allergy.

In conclusion, our study clearly revealed that the SPT is more useful than BW-sIgE level for diagnosis of BW allergy. An OFC may be avoided if the patient's SPT wheal diameter is at least 24.1 mm.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.alit.2017.04.005>.

Conflicts of interest

ME received lecture fees from Pfizer and Siemens. ME is on scientific advisory board of DBV Technologies. The rest of the authors have no conflict of interest.

Authors' contributions

NY conceived of this study and wrote this manuscript. SS revised this manuscript and figures critically. SS, KT, KN, KO, TA and ME collected data. KT contributed in the data analysis and generated figure. ME advised study design and helped to draft the manuscript. All authors read and approved the final manuscript.

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