

Short communication

Prediction of buckwheat allergy using specific IgE concentrations in children

Introduction: Buckwheat (BW) is considered to be one of the most important food allergens, and positive skin tests are found in about 5% of Koreans. We investigated the positive and negative predictive values of BW-specific IgE in subjects with a BW allergy in order to reduce the need for buckwheat challenge, which can be more riskier than other causes of food allergies.

Methods: Twenty-eight BW allergic subjects with symptoms after BW Open food challenge and 16 asymptomatic control subjects with positive skin test to BW were recruited. Serum samples from all patients were analyzed for BW-specific IgE antibodies using the Pharmacia CAP System.

Results: According to the receiver operator characteristic (ROC) analysis, the optimal cutoff level of BW-specific IgE, as the definitions of serum BW-specific IgE positive, was 1.26 kU_A/l. With this selected cutoff level, the sensitivity, specificity, positive and negative predictive values were 93.10, 93.33, 79.75 and 97.96%, respectively.

Conclusion: The use of the optimal cutoff level, 1.26 kU_A/l, that simultaneously maximizes sensitivity and specificity, would be helpful for avoiding unnecessary risky challenge in children with a strong clinical history and skin test responses.

M. H. Sohn¹, S. Y. Lee², K.-E. Kim¹

¹Department of Pediatrics and Institute of Allergy, Yonsei University College of Medicine, Seoul;

²Department of Pediatrics, Ajou University School of Medicine, Suwon, Korea

Key words: allergy; buckwheat; food allergy; open food challenge test; specific IgE.

Dr Kyu-Earn Kim
Department of Pediatrics
Yonsei University College of Medicine
Youngdong Severance Hospital
P.O. Box 1217
Seoul 135-270
Korea

Accepted for publication 30 June 2003

Buckwheat (*Fagopyrum esculentum*) is a broadleaf summer grown crop, which is used in making noodles, soups, cakes and biscuits in Europe and Asia. Buckwheat is known as a highly potent food allergen that is related to a IgE-mediated, type I immune reaction (1–3). Even when only a very small amount is ingested or inhaled, it can cause serious allergic reactions (4).

However, the lack of epidemiologic studies made it difficult to estimate the prevalence or incidence of a buckwheat allergy. Rowe (5) demonstrated a 5.4% positive skin prick reactions among 500 consecutive cases, but Horesh (6) published that 1% of his child patients were buckwheat-sensitive. In 1998 Takahashi et al. (2) performed the largest study on the buckwheat allergy, with a sample size of 92 680, in Yokohama. They reported that 0.22% of all children (140 boys and 54 girls) had a buckwheat allergy.

The double-blind, placebo-controlled food challenge (DBPCFC) has been the 'gold standard' for diagnosis of food hypersensitivity since its introduction by May in 1976 (7). DBPCFC is time-consuming and is not without risk. To reduce the need for DBPCFC, Sampson (8) showed the utility of food-specific IgE concentrations to milk, egg, peanut, fish, soybean, and wheat using the Pharmacia CAP system FEIA (Pharmacia and Upjohn Diagnostic, Uppsala, Sweden). Hill et al. (9) also reported that '100% diagnostic skin prick test (SPT) levels (SPT

wheel diameter > 6 mm)' compared with the *in vitro* measurement of the IgE antibody, reduces the need for food challenge.

With these considerations, we investigated the positive and negative predictive values of buckwheat specific IgE in the subjects with a buckwheat allergy in order to reduce the need for buckwheat challenge, which can be more riskier than other foods.

Material and methods

Subjects

Forty-four children who tested positive to buckwheat on an allergic skin test were enrolled. They were selected among patients who had been referred for evaluation of probable inhalant or food allergies. The subjects consisted of 29 males and 15 females, with a mean age of 8.34 ± 0.51 years, ranging from 4 to 14 years. The challenge test was performed in all subjects. The skin prick test was performed with buckwheat extract (Bencard, Brentford, UK) with a histamine positive control (1 mg/ml). If the wheal size of buckwheat was larger than the histamine positive control, we considered it positive. The subjects' sera were stored at -20°C until use.

Open food challenge

Open food challenges were performed after buckwheat was eliminated from the diet for 14 days. The use of antihistamines was

avoided for 7 days and the use of inhaled β -adrenergic agonists was avoided for 24 h before the challenge. Challenges were performed in the morning on an empty stomach. Initially, we administered 50 mg of BW flour and increased the dose by doubling it at 30-min intervals until the patients complained of symptoms. If the patients did not complain of symptoms after ingestion of 5 g of dried BW flour, the challenge with boiled BW was undertaken. The results were interpreted as positive when the characteristic symptoms such as urticaria, dyspnea, facial angioedema, vomiting, or abdominal pain occurred, or the peak expiratory flow rate was reduced by more than 15% of a pretest value.

CAP System FEIA

Serum samples from all patients were analyzed for buckwheat-specific IgE antibodies using the Pharmacia System CAP System FEIA, as detailed by the manufacturer.

Statistical methods

The levels of skin wheal diameters or serum BW-specific IgE between nonreactors and reactors were compared by a Student *t*-test. A level of $P = 0.05$ was considered as being statistically significant. The receiver operating characteristic (ROC) analysis was used to determine and calculate the single point that simultaneously maximizes 'true positives' (sensitivity) and minimizes 'false positives' (one specificity). Performance characteristics (sensitivity, specificity, positive and negative predictive values) for BW antigens were calculated at each cutoff point (10). For calculation, we also used 0.22% that Takahashi et al. (2) suggested as BW allergy prevalence.

Results

In 44 subjects with positive skin test to BW, 28 subjects showed characteristic symptoms after BW Open food challenge and 16 subjects were asymptomatic. Symptomatic BW-provocation reactors complained of cutaneous symptoms such as urticaria or facial angioedema (24/28, 85.7%), respiratory symptoms such as dyspnea or wheezing (21/28, 75.0%), and gastrointestinal symptoms vomiting or abdominal pain (14/28, 50.0%) during tests. In addition, one patient lost consciousness after BW ingestion. Five subjects of them experienced allergic symptoms after ingestion of BW-containing noodle or jelly and none had a known physician-diagnosed buckwheat allergy before provocation test. In the skin prick tests, symptomatic BW-provocation reactors had significantly longer levels of skin wheal diameter (wheal range 8–35 mm, mean 15.60 ± 7.67 mm) than nonreactors (wheal range 6–22 mm, mean 11.07 ± 4.81 mm, $P < 0.05$).

As shown in Fig. 1, the serum levels of BW-specific IgE were significantly higher in the BW-provocation reactors' sera (29.23 ± 6.21 kU_A/l) than in nonreactors' (0.35 ± 0.15 kU_A/l, $P < 0.01$). According to the receiver operator characteristic (ROC) analysis, the optimal cutoff level that simultaneously maximizes sensitivity and specificity, as the definitions of serum BW-specific IgE positive, was 1.26 kU_A/l. With this selected cutoff level, the

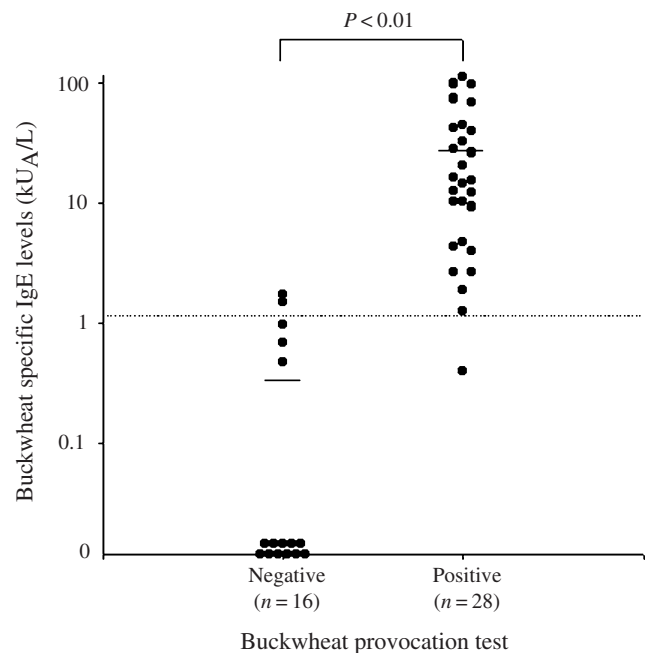


Figure 1. The serum levels of buckwheat (BW)-specific IgE antibodies in BW-allergic patients. The optimal cutoff level is drawn as a broken line. Horizontal lines represent geometric mean.

Table 1. Performance characteristics of the Pharmacia CAP System using buckwheat (BW)-specific IgE antibodies and BW open food challenge results in 44 children who tested positive to BW on an allergic skin test

Cutoff level (kU _A /l)	0.35	0.7	1.26	3.5	17.5	50
Open BW challenge						
Positive	33	31	29	23	12	5
Negative	11	13	15	21	32	39
Sensitivity (%)	84.85	87.10	93.10	100	100	100
Specificity (%)	100	92.31	93.33	76.19	50.00	41.03
Predictive value						
Positive (%)	100	76.16	79.75	54.22	36.07	32.35
Negative (%)	95.90	96.21	97.96	100	100	100

sensitivity, specificity, positive, and negative predictive values were 93.10, 93.33, 79.75, and 97.96%, respectively (Table 1) and confidence intervals for the sensitivity, specificity, positive, and negative predictive values were 85.61–100.59, 85.96–100.70, 67.87–91.62, and 93.78–102.14, respectively. According to the above definitions, the proportions of BW-specific IgE seropositivity in open food challenge positive and negative children were 96.4 (27 of 28) and 12.5% (two of 16), respectively. Additionally, the levels of BW-specific IgE below 0.40 kU_A/l had 100% positive predictive value and the levels above 1.77 kU_A/l had a 100% negative predictive value.

When we used ROC analysis for skin prick test results, the optimal skin wheal diameter was 7 mm and the sensitivity and specificity were 62.5 and 100%, respectively. However, there was no correlation between skin

prick test results and the serum levels of BW-specific IgE (data not shown).

Discussion

In Korea, buckwheat is considered to be one of the most important food allergens (11), and positive skin tests are found in about 5% of Koreans (12). Several cases of buckwheat hypersensitivity subjects have been reported, and recently Lee et al. (13) showed three cases of childhood nocturnal asthma due to a buckwheat allergy. Recent studies have identified different allergens, and verified that the 24-kDa buckwheat protein is the main allergen in common buckwheat (14), but other allergens (19, 16, and 9 kDa) may be of importance (15).

Matsumoto and Murakami (16) proposed problems with food hypersensitivity, including the buckwheat allergy. They showed that the RAST technique does not always recognize the food antigens digested during the absorption process *in vivo*, and recommend diagnosis with the oral Prausnitz-Küstner (P-K) test in combination with RAST. However, some recent reports using the CAP system FEIA have shown the possibility of accurate and safe diagnosis for food allergies (8, 9).

Our study also demonstrated a greater than 79.75% likelihood that a patient will experience an allergic reaction at the time of buckwheat ingestion, if they have an IgE antibody level to buckwheat of 1.26 kU_A/l or greater. When this 'optimal cutoff point' value was used, we

obtained a higher sensitivity and negative predictive value than the limits of detection of the assay (0.35 kU_A/l). Furthermore, compared with 0.7 kU_A/l that interpreted as 'positive' by manufacturer, this 'optimal cutoff point' value has also higher sensitivity, specificity, positive, and negative predictive values (Table 1). However, BW specific IgE results below this level does not always exclude the diagnosis, although oral food challenges may seem unnecessary in some patients with specific IgE above a defined cutoff point. Additionally, our study did not include the subjects with negative skin test results for necessary controlled challenge tests. This decision point would be helpful for the diagnosis of a buckwheat allergy in patients with a history and an allergic skin test.

In this study, we used open food challenges for the confirmation of a buckwheat allergy. When objective signs can be seen in infants and children, a positive challenge in an open fashion is acceptable, and does not necessarily need to be confirmed by a DBPCFC (17). Practically, open food challenges can be more helpful than DBPCFC in a clinical setting.

Buckwheat, even in small amounts, can provoke serious symptoms in a sensitized subject. Additionally, in a Japanese nationwide questionnaire screening for the buckwheat allergy only 14% of the participants were diagnosed with the allergy, and most of these were young children, or adults aged 20 years or over (18). Therefore the establishment of a more accurate and safe diagnostic method for the detection of sensitized children is important.

References

1. WIESLANDER G. Review on buckwheat allergy. *Allergy* 1996;**51**:661–665.
2. TAKAHASHI Y, ICHIKAWA S, AIHARA Y, YOKOTA S. Buckwheat allergy in 90,000 schoolchildren in Yokohama. *Arerugi* 1998;**47**:26–33 [in Japanese].
3. GÖTHE CJ, WIESLANDER G, ANCKER K, FORSBECK M. Buckwheat allergy: health food, an inhalation health risk. *Allergy* 1983;**38**:155–159.
4. SMITH HL. Buckwheat-poisoning with report of a case in a man. *Arch Int Med* 1909;**3**:350–359.
5. ROWE AH. Individual food and drug allergies and their control. In: ROWE AH, editor. *Clinical allergy: manifestations, diagnosis and treatment*. Philadelphia: Lea & Febiger, 1937:563.
6. HORESH AJ. Buckwheat sensitivity in children. *Ann Allergy* 1972;**30**:685–689.
7. MAY CD. Objective clinical and laboratory studies of immediate hypersensitivity reactions to foods in asthmatic children. *J Allergy Clin Immunol* 1976;**58**:500–515.
8. SAMPSON HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;**107**:891–896.
9. HILL DJ, HOSKING CS, REYES-BENITO LV. Reducing the need for food allergen challenges in young children: a comparison of *in vitro* with *in vivo* tests. *Clin Exp Allergy* 2001;**31**:1031–1035.
10. SAMPSON HA. Managing peanut allergy. *Br Med J* 1996;**312**:1050–1051.
11. LEE KY, KIM KE, JEONG BJ. Immediate type reaction of food allergy confirmed by open food challenge test: diagnostic value of history and skin test in food allergy. *Pediatr Allergy Respir Dis* 1997;**7**:173–186 [in Korean].
12. LEE KY, KIM KE. A study on the method of exclusion of unnecessary allergens from the vaccines for immunotherapy. *J Korean Soc Allergol* 1988;**8**:150–164 [in Korean].
13. LEE SY, LEE KS, HONG CH, LEE KY. Three cases of childhood nocturnal asthma due to buckwheat allergy. *Allergy* 2001;**56**:763–766.
14. URISU A, KONDO Y, MORITA Y, TSURUTA M, YASAKI T, YAMADA K et al. Identification of a major allergen of buckwheat seeds by immunoblotting methods. *Allergy Clin Immunol News* 1994;**6**:151–155.
15. PARK JW, KANG DB, KIM CW, KO SH, YUM HY, KIM KE et al. Identification and characterization of the major allergens of buckwheat. *Allergy* 2000;**55**:1035–1041.
16. MATSUMOTO T, MURAKAMI M. The oral Prausnitz-Kustner reaction in food allergies. *Arerugi* 1991;**40**:620–625 [in Japanese].
17. WATSON WT. Food allergy in children. *Clin Rev Allergy Immunol* 1995;**13**:347–359.
18. NAKAMURA S, YAMAGUCHI M. Studies on buckwheat allergosis. Report 2: clinical investigation of 169 cases with the buckwheat allergosis gathered from the whole country of Japan. *Allergy Immunol (Paris)* 1974;**5**:201:457–465.