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Master's Thesis in

Medical science

Clinical and laboratory findings of childhood

buckwheat allergy

in a single tertiary hospital

Ajou University Graduate School

Medical science Major

Kyujung Park

Clinical and laboratory findings of childhood buckwheat allergy in a single tertiary hospital

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I submit this thesis as the
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Ajou University Graduate School

Medical science

Kyujung Park

The Master's thesis of Kyujung Park in Medical science is hereby approved.

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ABSTRACT

Purpose

Although buckwheat allergy is one of the most severe food allergies in some countries, especially in children, few studies have investigated this condition. The aim of this study was to report clinical and laboratory findings of buckwheat allergy in Korean children.

Methods

Thirty-seven subjects, aged 1 to 14 years, were enrolled by retrospective medical record review from January 2000 through May 2015 at the Department of Pediatrics in Ajou University Hospital. Demographic profiles, previous exposure to buckwheat pillows, clinical symptoms, and laboratory findings were recorded.

Results

Twenty-six out of 37 children had immediate-type allergic symptoms to buckwheat, while 11 subjects were tolerant to buckwheat. Seventeen (65.4%) out of 26 buckwheat allergic children had anaphylaxis. The median buckwheat specific immunoglobulin E level in the buckwheat allergic group (7.71 kU_A/L) was significantly higher ($P<0.001$) than that in the buckwheat tolerant group (0.08 kU_A/L) with an optimal cut-off value of 1.27 kU_A/L (sensitivity 84.6%, specificity 100%). When adjusted for age between two groups, the difference showed borderline significance ($P=0.063$). In subjects who had anaphylaxis, buckwheat-specific immunoglobulin E levels ranged from 0.37 kU_A/L to 100 kU_A/L.
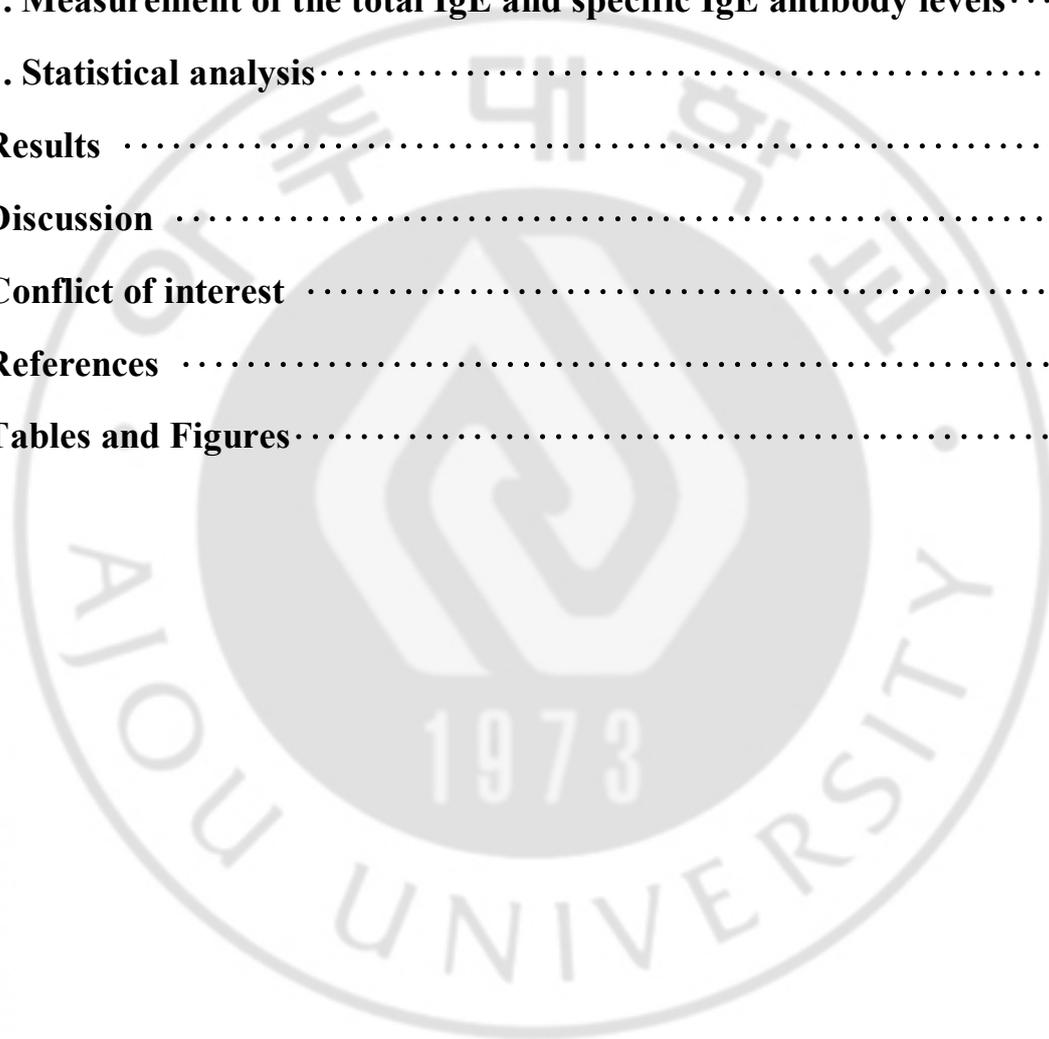
Conclusion

Almost two-thirds of buckwheat-allergic children had anaphylaxis. Amongst these children, a wide-range of buckwheat specific immunoglobulin E levels were observed. Anaphylaxis occurred in a subject with a remarkably low level of immunoglobulin E (0.37 kU_A/L).

Key words: Anaphylaxis, Hypersensitivity, Buckwheat, Child

Table of Contents

Introduction

Buckwheat (BW) (*Fagopyrum esculentum*), which belongs to the Polygonaceae family, is an important ingredient in various traditional Asian dishes. It is also used to make gluten-free flour that can be consumed by patients with celiac disease[1]. BW allergy is a typical IgE-mediated type 1 hypersensitivity, which is a major cause of anaphylaxis[1]. A 1998 Japanese study with 92,680 subjects reported that 0.21% (194 children) of school-aged children had a BW allergy[2]. In Korea, the prevalence of BW allergy was 0.1% (in elementary school students) and 0.13% (middle school), and BW was the fifth leading cause of anaphylaxis in children from a recent multi-center study at 23 tertiary hospitals[3,4]. In Europe, BW allergy caused food-related anaphylaxis in 4.5% of adults in France and 1.7% of adults in Italy who visited allergy clinics[5,6].

In Korea and Japan, BW husk pillows are commonly used, but studies investigating the relationship between exposure to BW husk pillows and BW allergy are rare. Two case reports document immune events related to using BW husk pillows. In 1 case report, 3 patients had chronic asthma due to exposure to BW husk pillows, and in another case report, 2 patients were sensitized to BW after using BW husk pillows[7,8].

The major allergens of BW are 8–10 kDa, 16 kDa, 19 kDa, and 24 kDa proteins; the 19 kDa protein is relatively specific for clinical reactions to BW[9]. More recently, the 40–50 kDa protein is implicated as an important allergen to predict moderate to severe clinical symptoms in Korean children with BW allergy[10]. BW is known to have cross-reactivity with latex, rice, poppy seeds, and quinoa[11-14].

The relationship between the level of buckwheat-specific IgE (BW-sIgE) and clinical symptoms to BW has not been substantially studied. A 2003 report demonstrated that a BW-sIgE level of 1.26 kU_A/L had a positive predictive value of 79.75% in predicting BW allergy in children[15]. The measurement of BW-sIgE has limitations in the diagnosis of a BW allergy, and is not a definitive predictor of symptom severity. The aim of this study was to report the clinical and laboratory findings of BW allergy in Korean children.

Materials and methods

1. Subjects

A retrospective medical record review was done for children who visited the Department of Pediatrics at Ajou University Hospital for suspicious food allergies from January 2000 through May 2015. Thirty-seven children who underwent BW-sIgE assay with history of ingestion of BW were enrolled. The BW-allergic group (n=26) comprised children who had immediate-type allergic reactions after ingesting BW, and the BW-tolerant group (n=11) comprised children who had no clinical reactions after ingesting BW. The BW-allergic group was further classified into 2 subgroups according to symptoms: anaphylaxis group and nonanaphylaxis group. The anaphylaxis group comprised children with a history of anaphylaxis after ingesting BW. Anaphylaxis was defined according to the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network[16]. The nonanaphylaxis group comprised children who experienced acute allergic reactions such as urticaria, but not anaphylaxis after ingesting BW. The study was approved by the Institutional Review Board of Ajou University Hospital (AJIRB-MED-MDB-15-171).

2. Measurement of the total IgE and specific IgE antibody levels

Serum concentrations of total IgE and BW-sIgE for all subjects were measured by means of ImmunoCAP, according to the manufacturer's instructions (Thermo Fisher Scientific, Uppsala, Sweden). The lower and upper limits of BW-sIgE were 0.05 and 100 kU_A/L, respectively.

3. Statistical analysis

The Mann-Whitney *U* test was used to compare characteristics and serologic parameters between study groups. Receiver operating characteristic (ROC) curves were constructed for total IgE and BW-sIgE.

Results

All 37 subjects were included in the study analysis. The BW-allergic group (n=26) consisted of 17 males and 9 females, with a median age of 7 years, ranging from 4 to 14 years. Seventeen subjects in the anaphylaxis group experienced anaphylaxis after ingesting BW, and 9 subjects in the nonanaphylaxis group had acute allergic reactions such as urticaria, angioedema, and/or vomiting after ingesting BW, but not anaphylaxis. Eleven subjects in the BW-tolerant group had no immediate-type allergic symptoms after ingesting BW. In the BW-allergic group, 9 (34.6%) had other previously known food allergies, mostly to plant foods such as wheat (Table 1).

In terms of clinical manifestations, 17 children (66%) in the BW-allergic group experienced anaphylaxis, 19% had respiratory symptoms only, and 15% had cutaneous symptoms only. None of the subjects had gastrointestinal or cardiovascular symptoms only (Fig. 1).

The median level of total IgE in the BW-allergic group was 390 kU_A/L, which was higher than that of the BW-tolerant group (187 kU_A/L) but this difference was not statistically significant (P=0.232) (Table 2). The median level of BW-sIgE in the BW-allergic group was 7.71 kU_A/L, which was significantly higher (P<0.001) than that of the BW-tolerant group (0.08 kU_A/L) before age adjustment. The difference in the levels of BW-sIgE between BW-allergic and BW-tolerant groups showed no statistical significance (P=0.063) when adjusted for age by linear regression analysis. The median level of BW-sIgE in the anaphylaxis group was 18.4 kU_A/L, which was higher than that of the nonanaphylaxis group (2.95 kU_A/L) but this difference was not statistically significant (P=0.125) (Table 3). In addition, the median BW-sIgE levels were compared between the BW-tolerant group and anaphylaxis group, the level was significantly higher in the anaphylaxis group even after age adjustment (P=0.021, data not shown).

To differentiate patients who experienced immediate-type allergic reactions after ingesting BW from those who were tolerant to BW, the optimal cutoff values for baseline concentrations of total IgE and BW-sIgE were obtained from the ROC curves (Fig. 2). To maximize both sensitivity and specificity at the same time, the optimal cutoff value of BW-sIgE to predict clinical reactivity to BW was >1.27 kU_A/L, with a sensitivity of 84.6% and a specificity of 100%.

Fourteen subjects had a history of exposure to BW husk pillows. However, the causal relationship between BW husk pillows and onset of symptoms after exposure to BW could not be identified due to the retrospective design of the study. The percentages of subjects with a history of exposure to BW husk pillows in the BW-allergic group and BW-tolerant group were 46.2% and 18.2%,

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respectively (Fig. 3). Additionally, half of patients who had respiratory symptoms after ingesting BW had a history of exposure to BW husk pillows, while only 28.6% of patients who had no respiratory symptoms after ingesting BW used BW husk pillows in the past.

The frequency of the type of BW exposure was the following: noodle ingestion in 18 subjects (69%), pancake ingestion in 2 subjects (8%), jelly (*muk*) ingestion in 2 subjects (8%), respiratory exposure in 1 subject (4%), and unknown in 3 subjects (11%) (Fig. 4).

Discussion

BW is a common cause of anaphylaxis in Asian countries. In one Japanese study, BW was the seventh leading cause of allergen-related anaphylaxis across all ages[17]. The prevalence of BW allergy among Korean and Japanese school-aged children was 0.36% and 0.21%, respectively[3,17]. BW allergy is a growing concern in Western countries as the consumption of BW increases, but few studies have been reported. We focused on the clinical details of childhood BW allergy and the relationship between BW-sIgE concentration in BW-allergic subjects.

In this study, the median age of BW-allergic children was 7 years, ranging from 4 to 14 years. This finding corresponds with an earlier report with a mean age of 8.34±0.51 years, ranging from 4 to 14 years[15]. In addition, as in previous pediatric study, a male predominance was observed in our study[15]. Nine out of 26 children in the BW-allergic group had other previously known food allergies, most of them being plant foods. From previous studies, BW is known to have cross-reactivity with latex, rice, poppy seeds, and quinoa[11-14]. However, our subjects who had previous plant food allergies were allergic to other plant sources, specifically, wheat (7 out of 8) and mung beans (1 out of 8) which are not known to have cross-reactivity with BW thus far.

The proportion of subjects who had a history of using BW husk pillows was higher in the BW-allergic group than in the BW-tolerant group. Subjects who had respiratory symptoms used BW husk pillows more often compared with those who did not have respiratory symptoms. One case report suggested that a small amount of BW flour attached to a BW husk pillow could induce sensitization and cause nocturnal asthma[7]. A case report in 2009 from the United States suggested that initial ingestion of BW food caused anaphylaxis after previous sensitization by BW husk pillow[8]. Our data suggests that some subjects have been sensitized by using BW husk pillows, but since the timing of pillow usage and ingestion of BW were not recorded, it is difficult to explain causal relationships.

In a previous analysis, 13% of patients who had anaphylaxis were counted among patients with food allergies in the United States, 23% in Japan, and 7.6% of patients below the age of 6 years in Korea[17-19]. From another study on pediatric peanut allergy in Canada, anaphylaxis was found in 36.7%[20]. Within patients who were sensitized to BW, 29.2% had anaphylaxis in Italy[21]. In the present study, 66% patients had anaphylaxis, which was remarkably higher than in previous studies. Patients with mild allergic reactions may go to local clinics, whereas patients with more severe symptoms may go to university hospitals. In this study, data were collected from a university

hospital, which may explain why we noted a higher proportion of anaphylaxis patients compared to previous studies. This may also contribute to bias. The frequencies of respiratory (19%) and cutaneous (15%) symptoms were comparable with findings of earlier studies in both adults and children, whereas frequencies of gastrointestinal symptoms were relatively lower in this study[15,19,21].

Reports on BW-sIgE levels in BW allergy are rare. In previous studies, mean BW-sIgE was 6.23 kU_A/L in patients with suspected BW allergy who were older than age 17, and median 29.23 kU_A/L in children[15,21]. However, the BW-sIgE levels between the allergic and nonallergic groups had no significant differences. In the present study, the BW-allergic group had a higher level of median BW-sIgE than in the BW-tolerant group but the difference showed no statistical significance when adjusted for age between the groups. From the ROC curves, the optimal cutoff value of BW-sIgE to differentiate the BW-allergic group from the BW-tolerant group in this study was 1.27 kU_A/L with a sensitivity of 84.6% and a specificity of 100%. A previous study reported the optimal cutoff level was 1.26 kU_A/L, with a sensitivity of 93.1% and a specificity of 93.33%, which coincides with the result of this study[15]. The median BW-sIgE level was higher in the anaphylaxis group than in the nonanaphylaxis group but this difference was not statistically significant (P=0.125). As the range of BW-sIgE levels in the Ana group was wide (0.37 to 100 kU_A/L), it may be suggested that severe allergic reactions to BW could be provoked even at a very low BW-sIgE levels. On the other hand, when the median BW-sIgE levels were compared between the BW-tolerant group and anaphylaxis group, the level was significantly higher in the anaphylaxis group even after age adjustment (P=0.021, data not shown).

There were several limitations in this study. First, the data from retrospective studies may be less complete compared to data from prospective studies because of partial or lack of documentation. In patients with very low levels of BW-sIgE, an oral food challenge test should have been performed to confirm the causal relationship but it was not possible in this study due to the retrospective nature. The amount and form of BW may have differed among each patient, and the timing of exposure to BW husk pillows and the first ingestion of BW could not be specified from the retrospective medical record review. Second, although the total number of subjects was relatively small, when compared to studies of other food allergies. However, it is compatible with previous studies of BW allergy considering low prevalence, especially in children. Finally, our findings are not representative for other populations due to geographical and cultural differences. In the future, it is necessary to do a prospective study with a larger population.

To conclude, the findings of this study suggests that BW caused a severe form of allergic reaction,

such as anaphylaxis, in almost two-thirds of BW-allergic children, and the optimal cut-off level of BW-sIgE to differentiate BW-allergic children from BW-tolerant children was 1.27 kU_A/L.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Table 1. Demographic profile of subjects

Variable	BW-allergic (n=26)	BW-tolerant (n=11)	Total (n=37)
Sex			
Female	9 (34.6)	2 (18.2)	11 (29.7)
Male	17 (65.4)	9 (81.8)	26 (70.3)
Age, median (range)[*]	7 (4–14)	4 (1–10)	6 (1–14)
Concurrent allergic diseases[†]			
Atopic dermatitis	9 (34.6)	5 (45.5)	14 (37.8)
Asthma	6 (23.1)	4 (36.4)	10 (27.0)
Allergic rhinitis	11 (42.3)	5 (45.5)	16 (43.2)
Urticaria	16 (61.5)	10 (90.9)	26 (70.3)
Angioedema	6 (23.1)	3 (27.3)	9 (24.3)
Known food allergy (other than BW)	9 (34.6)	9 (81.8)	18 (48.6)
Allergy to other plant foods	8 (30.8)	5 (45.5)	13 (35.1)
Lifelong exposure to BW husk pillow	12 (46.2)	2 (18.2)	14 (37.8)

Values are presented as number (%).

BW, buckwheat.

[*]P=0.002 (Mann-Whitney). [†]Most subjects had more than one concurrent allergic disease.

Table 2. Total IgE and BW-specific IgE levels in BW-allergic and BW-tolerant groups

Variable	BW-allergic (n=26)	BW-tolerant (n=11)	P value
Total IgE (kU$_A$/L)			0.232
Median	390	187	
Minimum	20	5	
Maximum	5,000	2,292	
BW-sIgE (kU$_A$/L)			<0.001[*]
Median	7.71	0.08	
Minimum	0.37	0.05	
Maximum	100	1.27	

BW, buckwheat; BW-sIgE, buckwheat-specific immunoglobulin E.

[*]P=0.063, adjusted for ages by generalized linear model.

Table 3. Total IgE and BW-specific IgE levels in anaphylactic and nonanaphylactic subjects

Variable	Anaphylactic (n=17)	Nonanaphylactic (n=9)	*P* value
Total IgE (kU$_A$/L)			0.095
Median	415	240	
Minimum	178	20	
Maximum	5,000	5,000	
BW-sIgE (kU$_A$/L)			0.125
Median	18.4	2.95	
Minimum	0.37	0.59	
Maximum	100	37.00	

BW, buckwheat; BW-sIgE, buckwheat-specific immunoglobulin E.
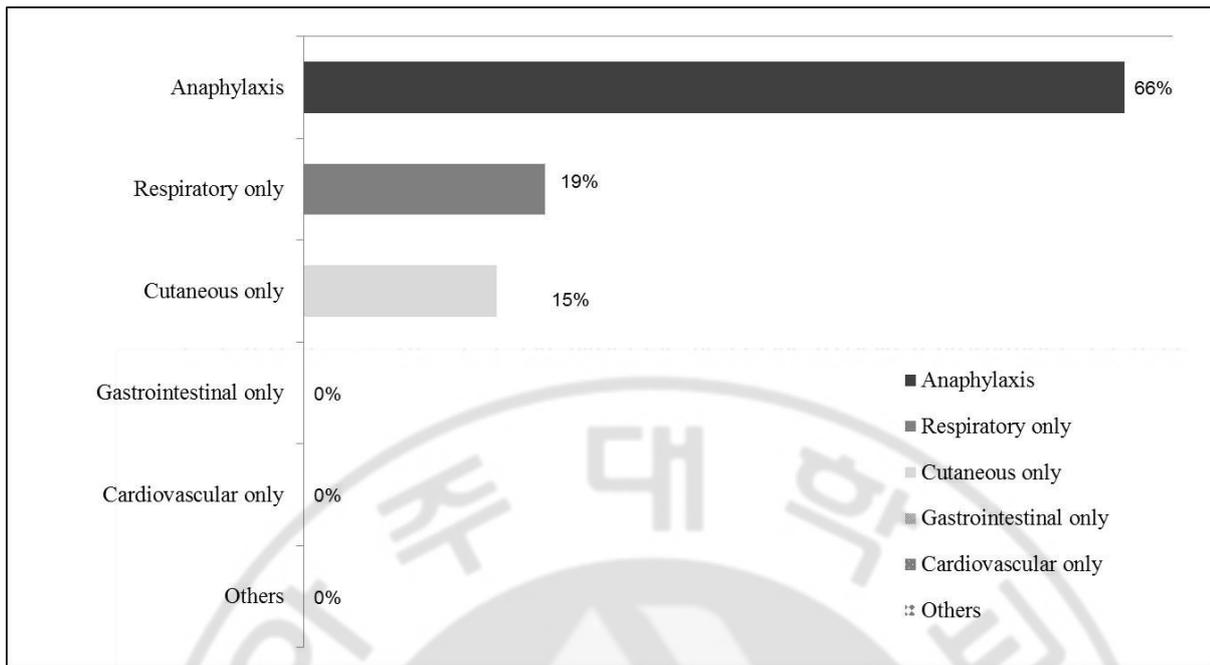
Figure 1. Clinical manifestations of buckwheat allergy

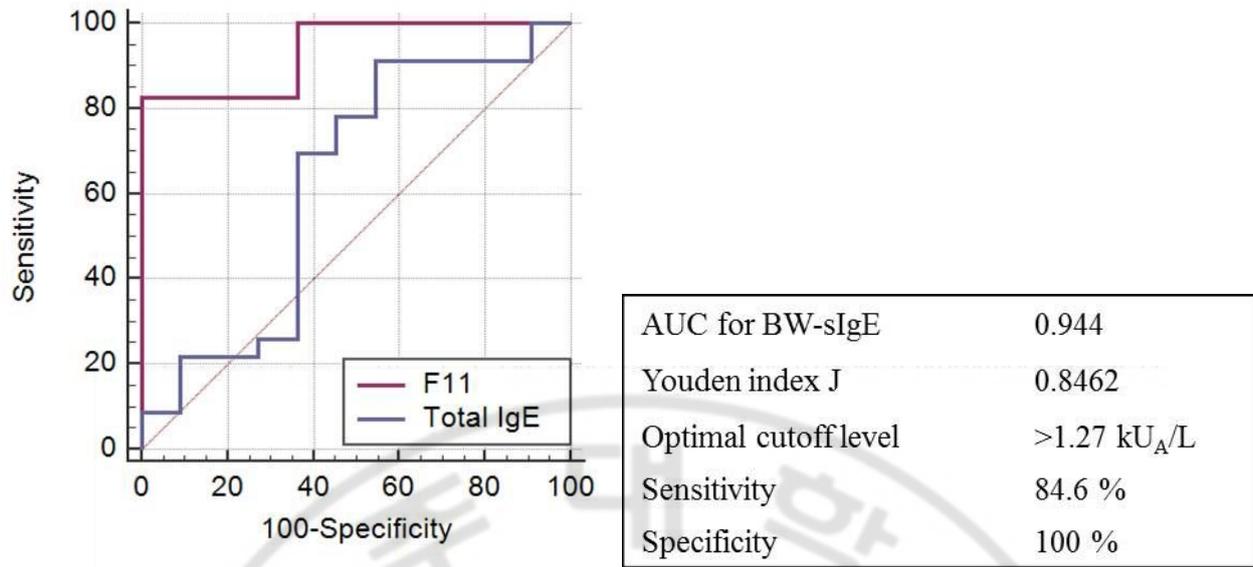| AUC for BW-sIgE | 0.944 |
Youden index J	0.8462
Optimal cutoff level	>1.27 kU$_A$/L
Sensitivity	84.6 %
Specificity	100 %
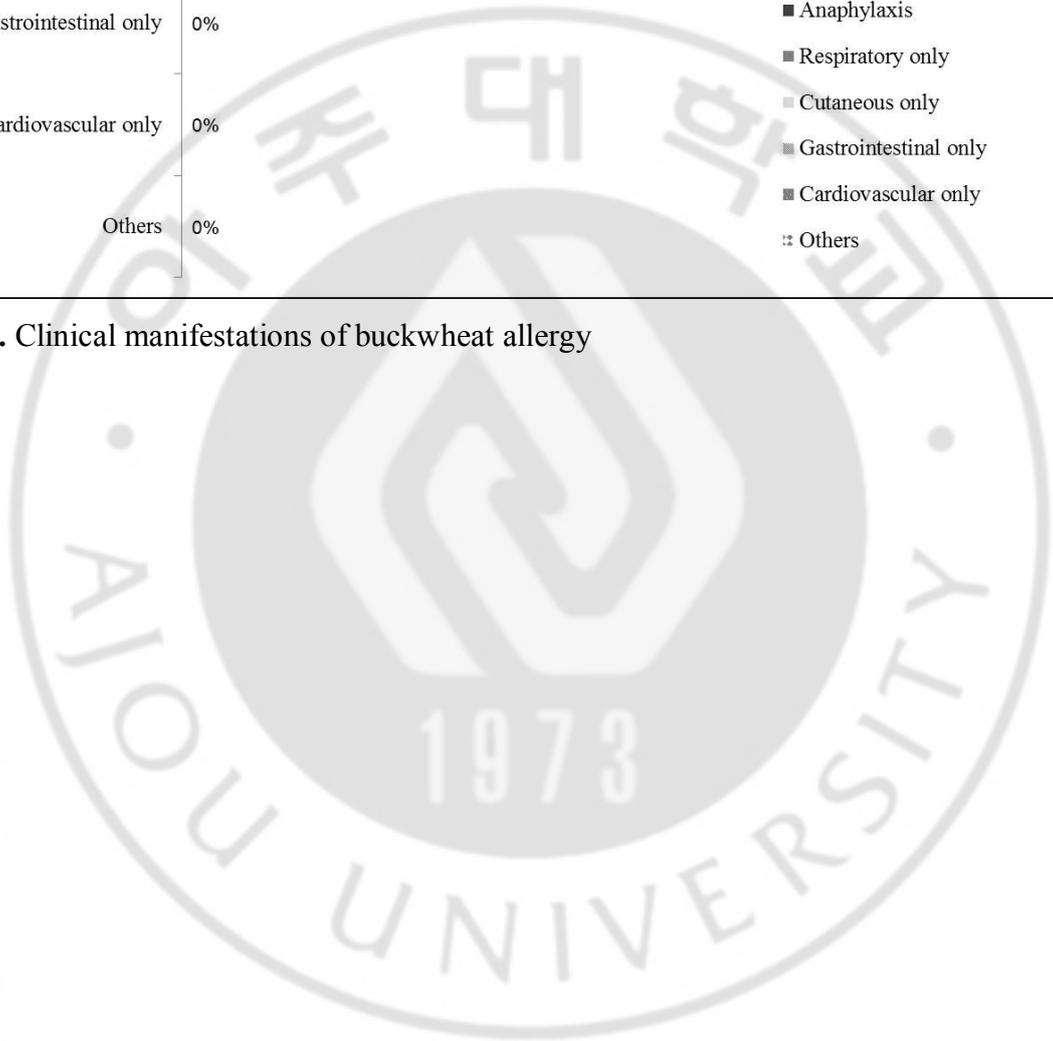
Figure 2. Receiver operating characteristic curve (BW-allergic vs. BW-tolerant). BW, buckwheat; BW-sIgE, buckwheat specific immunoglobulin E; AUC, area under the curve.
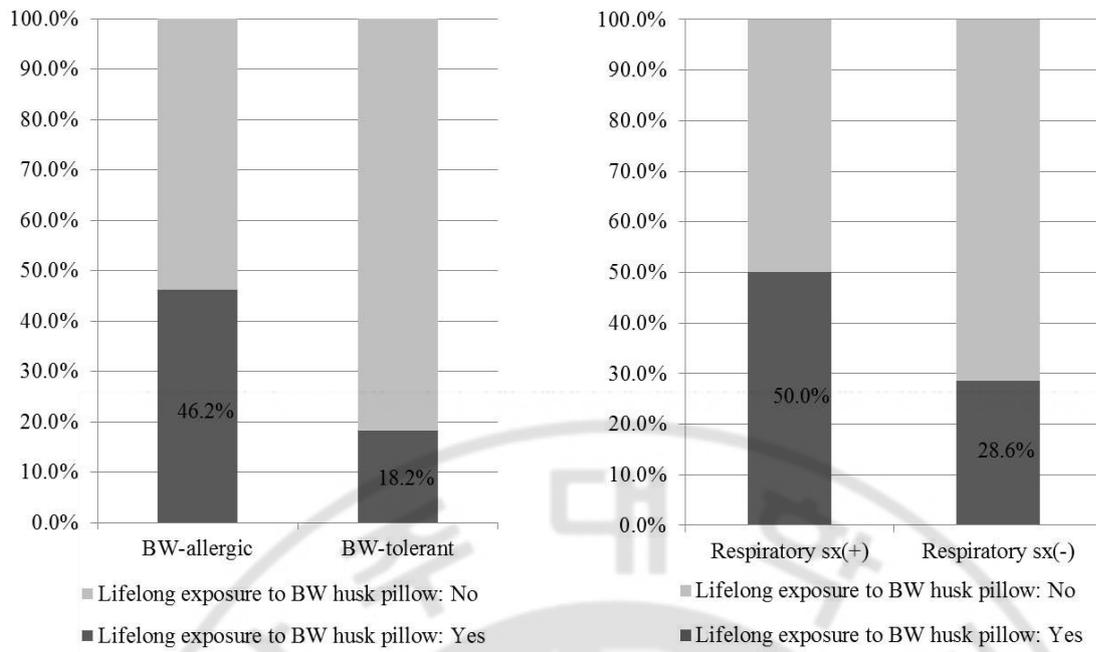
Figure 3. (A) BW allergy and lifelong exposure to BW husk pillows. (**B**) Respiratory symptoms after BW ingestion and lifelong exposure to BW husk pillows. BW, buckwheat; sx, symptom
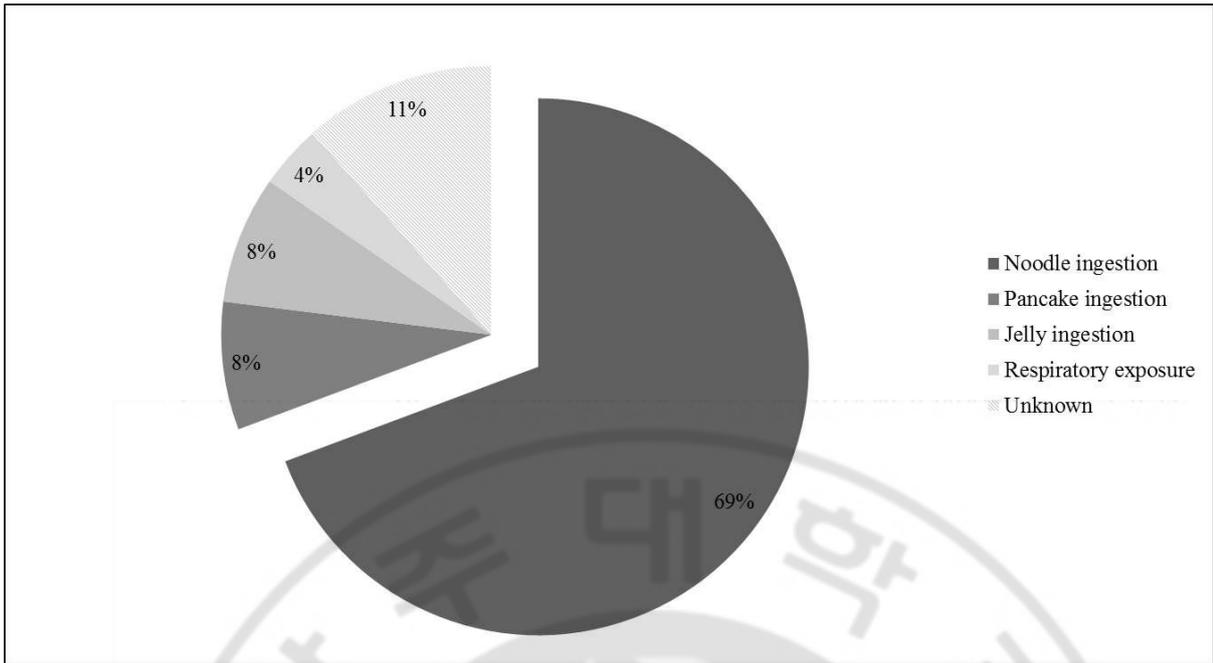
Figure 4. Form of buckwheat that induced the subject's clinical symptoms, as obtained from a detailed medical history.

논문요약

목적

메밀 알레르기는 소아에서 심한 증상을 유발하는 식품알레르기의 원인 중 하나이나, 연구가 많지 않다. 본 연구에서는 한국 소아청소년의 메밀 알레르기에 대한 임상적 증상과 메밀 특이항체와의 연관성을 알아보고자 한다.

방법

2000년 1월부터 2015년 5월까지 아주대학교병원 소아청소년과를 방문한 1세부터 14세까지의 소아청소년 중 메밀 특이항체 검사를 시행한 환아 37명을 대상으로 임상증상, 메밀 베개 사용 유무, 메밀 특이항체의 수치에 대하여 조사하였다.

결과

37명 중 26명은 메밀에 노출 후 즉시형 알레르기 반응을 경험(메밀 알레르기 군)하였고, 11명은 반응이 없었다(메밀 내성군). 26명 중 17명(65.4%)에서 아나필락시스 반응을 보였다. 메밀 알레르기 군의 메밀 특이항체 중간값은 7.71 kU_A/L로 메밀 내성군(0.08 kU_A/L)과 유의한 차이($P<0.001$)를 보였고 가장 최적의 절사값(optimal cut-off value)은 1.27 kU_A/L 였다(민감도 84.6%, 특이도 100%). 연령 보정 후에는 통계적으로 유의한 차이는 보이지 않았다($P=0.063$). 메밀에 노출 후 아나필락시스가 발생한 군은 특이항체의 범위가 0.37 kU_A/L부터 100 kU_A/L였다.

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결론

메밀 알레르기 군의 약 2/3에서 아나필락시스가 발생하였다. 아나필락시스가 발생한 군의 혈청 메밀 특이항체는 그 범위가 넓었고, 매우 낮은 농도(0.37 kU_A/L)에서도 아나필락시스가 유발되었다.

키워드: 아나필락시스(Anaphylaxis), 과민반응(Hypersensitivity), 메밀(Buckwheat), 소아(Child)