

Prevalence of Wheat Allergy in Japanese Adults

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ABSTRACT

Background: Wheat is one of the most common causes of food allergies. The exact prevalence of wheat allergy has not been well delineated in Japanese adults.

Methods: We enrolled 935 adults in a cohort study established by Shimane University in order to examine the determinants of lifestyle-related diseases. A screening was conducted by a questionnaire-based examination and a detection of serum omega-5 gliadin-specific IgE. Subjects who tested positive in the questionnaire-based examination and/or the serum omega-5 gliadin-specific IgE test were further examined by detailed interviews and skin prick tests.

Results: A total of 22 subjects were picked up by the screening process, and 17 of these were further examined by secondary testing. Only two subjects were conclusively identified as having wheat allergy.

Conclusions: The prevalence of wheat allergy in Japanese adults was found to be 0.21% by using a combination of questionnaire-based examination, skin prick test and serum omega-5 gliadin-specific IgE test.

KEY WORDS

ImmunoCAP, omega-5 gliadin, skin prick test, wheat allergy

INTRODUCTION

Wheat allergy is one of the most widespread food allergies, because wheat is the most widely consumed food grain in the world. Acute IgE-mediated responses to wheat are common in children, whereas wheat-dependent exercise-induced anaphylaxis (WDEIA) is more common in adolescents and adults. Many studies have investigated the prevalence of wheat allergies in the European countries and the USA.¹⁻¹¹ The prevalence of wheat allergies was found to be 0.2-0.9% in adults and 0.4-1.3% in children, by using questionnaire-based studies.¹⁻⁶ Wheat sensitization was assessed by the detection of a serum IgE specific to wheat, which indicated non-specific binding of IgE in the IgE detection system; the prevalence was found to be fairly high in adults (0.4-4%).⁷⁻¹¹ A few surveys of wheat allergies have been reported from Asian countries.

Study of wheat allergens indicated that water/salt-insoluble gluten is responsible for WDEIA whereas acute IgE-mediated responses and atopic dermatitis

in children are related to a wide range of wheat proteins. Among the water/salt-insoluble proteins, omega-5 gliadin was identified as the major allergen in WDEIA.¹²⁻¹⁴ The detection of omega-5 gliadin-specific IgE was also found to be useful for identifying acute IgE-mediated wheat allergy and WDEIA in adolescents and adults.¹⁵ The aim of the present study was to determine the prevalence of wheat allergy in Japanese adults by using the omega-5 gliadin-specific IgE detection system.

METHODS

STUDY POPULATION

The study population comprised 935 adults (female : male, 523 : 412; median age, 68.6 years; age range, 24-93 years) who were enrolled in a cohort study established by Shimane University that was designed to examine the determinants of lifestyle-related diseases. This study was carried out from July 2009 to March 2010.

This study was approved by the ethics committee of the Shimane University Faculty of Medicine (ap-

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Table 1 Background of the subjects who were picked up by the screening, and the results of the secondary tests

case	age	gender	screening			second tests			
			history	Frequency of episode	ω -5 gliadin-ImmunoCAP	interview	prick test		
							wheat	bread	ω -5 gliadin
1	40	male	+	2	1.15	confirmed	+	+	+
2	72	female	-	0	0.46	excluded	-	-	-
3	74	male	-	0	0.59	excluded	-	-	-
4	74	female	-	0	0.51	nd	nd	nd	nd
5	75	male	-	0	2.07	excluded	-	-	-
6	77	male	-	0	0.91	excluded	-	-	-
7	82	male	-	0	2.35	excluded	-	-	-
8	67	male	+	>30	4.47	confirmed	+	+	+
9	78	male	-	0	0.97	nd	nd	nd	nd
10	72	female	-	0	0.77	excluded	-	-	-
11	69	female	-	0	0.92	nd	nd	nd	nd
12	85	male	-	0	9.53	excluded	-	-	-
13	73	male	-	0	0.45	excluded	-	-	-
14	77	male	+	10	<0.35	nd	nd	nd	nd
15	77	female	+	2	<0.35	excluded	-	-	-
16	73	female	+	unclear	<0.35	excluded	-	-	-
17	74	female	+	unclear	<0.35	nd	nd	nd	nd
18	67	female	+	unclear	<0.35	excluded	-	-	-
19	74	female	+	3	<0.35	excluded	-	-	-
20	67	male	+	4	<0.35	excluded	-	-	-
21	79	female	+	2	<0.35	excluded	-	-	-
22	75	female	+	1	<0.35	excluded	-	-	-

+, positive; -, negative; nd, not done.

proval No. 199), and written informed consent was obtained from all participants.

DIAGNOSTIC PROCEDURES

The subjects were screened for wheat allergy by a questionnaire-based examination and a serum omega-5 gliadin-specific IgE detection test. Unusual reactions that occurred within 4 h of ingestion of wheat products, including urticaria, angioedema of the face, discomfort sensation of mucosa, dyspnea, and unconsciousness, were recorded by the questionnaire-based examination. Serum omega-5 gliadin-specific IgE was detected using an enzymatic immunoassay system (ImmunoCAP; Phadia, Uppsala, Sweden), as described previously.¹⁶ A measurable specific IgE response was classified as a positive test result (i.e. CAP >0.35 kUA/L).

Wheat allergy was diagnosed using an in-depth interview to identify any allergic symptoms after ingesting wheat products, and a skin test. The skin prick tests were conducted with steel lancets by using purified omega-5 gliadin (1 mg/mL in saline) prepared as previously described,¹³ wheat extract (Torii Pharmaceutical Co., Tokyo, Japan) and bread extract (Torii).

Histamine dihydrochloride solution (10 mg/mL) was used as a positive control, and saline was used as a negative control. The wheals were evaluated after 15 min⁴; their sizes were measured using the formula, $(D + d)/2$, where D was the maximum diameter, and d, the perpendicular diameter. A positive test was defined as a wheal size of ≥ 3 mm greater than the negative control.¹⁷

WESTERN BLOTTING

Purified omega-5 gliadin (1 μ g/lane) was electrophoresed by SDS-PAGE and transferred to a polyvinylidene difluoride membrane (PVDF, Immobilon-P; Millipore Corp., Bedford, MA, USA). The PVDF membrane with sample from each patient was blocked with tris-buffered saline (TBS; pH 7.4), containing 5% skim milk, and was incubated with TBS containing 10% serum, at room temperature for 8 h. The membrane was washed 3 times with TBS containing 0.1% Tween 20 (TBST), and incubated at room temperature for 1 h with 20,000 $\times$ diluted horseradish peroxidase-labeled anti-human IgE polyclonal antibody (BioSource Int., Camarillo, CA, USA). The membrane was washed 3 times with TBST, and the IgE bound to

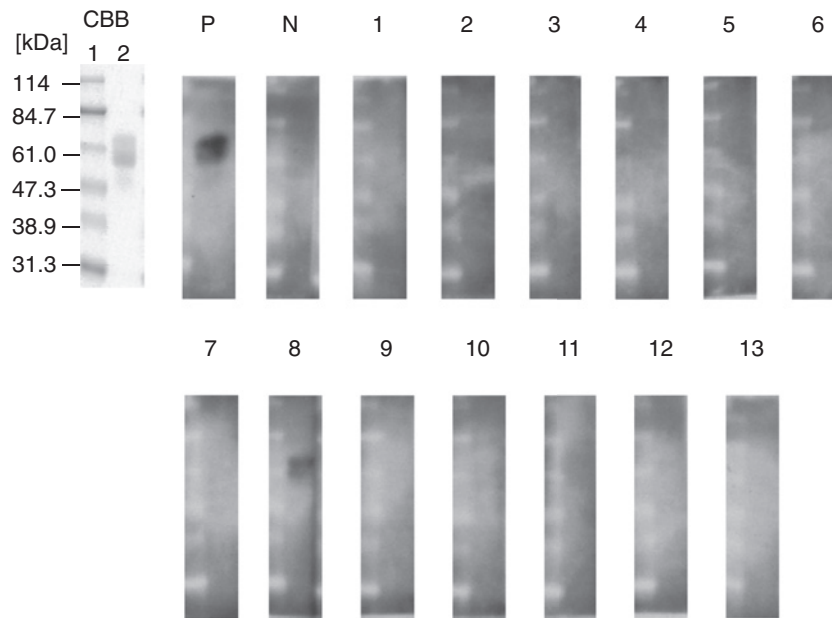


Fig. 1 Western Blotting of 13 subjects who were positive in the serum omega-5 gliadin-specific IgE test. P: positive control, N: negative control, 1-13: subjects who were positive in omega-5 gliadin-ImmunoCAP corresponding to Table 1.

the membrane was detected using an ECL-plus western blot detection reagent (GE Healthcare UK Ltd., Buckinghamshire, UK) and RX-U Fuji medical X-ray film (FUJIFILM Co., Tokyo, Japan).

RESULTS

The first screening using the questionnaire and the serum omega-5 gliadin-specific IgE test, identified 22 subjects (Table 1). The questionnaire showed that a history of unusual reactions after ingestion of wheat products was noted in 11 of the 935 subjects. Serum omega-5 gliadin-specific IgE screening detected 13 positive subjects, and 2 of these were positive in the questionnaire-based examination also, whereas the remaining 11 subjects were negative.

Of the 22 subjects, 17 (questionnaire-positive = 9; serum omega-5 gliadin-specific IgE test-positive = 10; both tests positive = 2) were accepted to enter secondary tests, namely, a detailed interview and skin prick tests. In the detailed interview, the responses to the questions regarding to the allergic symptoms after ingestion of wheat products confirmed that 2 of 17 subjects (cases 1 and 8) were allergic to wheat (Table 1). The skin prick test with wheat, bread, and omega-5 gliadin confirmed that both the subjects (cases 1 and 8) were sensitive to wheat products (Table 1). The remaining 15 subjects, who tested positive in the questionnaire-based examination and/or the omega-5 gliadin-specific IgE test were excluded after the detailed interview and the skin prick test.

Western blotting of the serum samples of the 13 subjects who tested positive in the omega-5 gliadin-

specific IgE test showed that the serum sample from only case 8 was positive, whereas the serum samples from the remaining 12 subjects showed no reaction (Fig. 1).

DISCUSSION

This study identified 2 adults with wheat allergy out of 935 adult subjects, which indicates that the prevalence of wheat allergy in the adults residing in Shimane Prefecture is 0.21%. The population tested in the present study was not large, but the diagnosis was reliable, because it was confirmed by the detailed interview conducted by the dermatologists, skin prick tests, and serum omega-5 gliadin-specific IgE tests, although a provocation test was not performed. This prevalence is comparable to that found in the European countries,¹⁻⁶ but it is remarkably higher than the prevalence of food-dependent exercise-induced anaphylaxis reported in Japanese children, in which case, the prevalence is 0.017%.¹⁸ The large difference may be attributed to the type of population being studied and the methods being used. This study screened adult subjects with questionnaire-based examination, skin prick test, and serum omega-5 gliadin-specific IgE test, whereas the previous study administered questionnaires to junior high school nurses. If the prevalence of 0.21% in the study population was to be generalized to estimate the prevalence of wheat allergy in all Japanese adults (approximately 100,000,000), then there could be 210,000 individuals with wheat allergy in Japan. The 2 subjects diagnosed with wheat allergy in this study had not been previ-

ously diagnosed; this indicates that the number of undiagnosed wheat allergy patients could be higher than that estimated by routine patient examinations.

We have previously demonstrated that detection of serum omega-5 gliadin-specific IgE is a highly useful method for identifying WDEIA patients and children with wheat allergy,^{13-16,19} and the omega-5 gliadin-ImmunoCAP system using recombinant omega-5 gliadin is now widely utilized in the diagnosis of wheat allergy. In the present study, 13 subjects were identified after screening 935 adults using the omega-5 gliadin-ImmunoCAP (class 1, 4; class 2, 7; class 3, 2); thus the proportion of Japanese adults testing positive in the omega-5 gliadin-ImmunoCAP test was 1.4%. The ImmunoCAP system usually considers class 2 as positive, so the positive percentage was calculated to be 0.96% (9 out of 935). This percentage is rather low compared with the levels previously determined in the adults in the European countries, by using methods for detecting serum IgE specific to wheat,⁷⁻¹¹ although approximately 80% of the positive reactions in our subjects are false-positives. The present study diagnosed wheat allergy in only 2 of 9 subjects, which indicates that the test yields false-positive results at a relatively high rate in healthy adults. This false-positive reaction was also confirmed by western blotting with native omega-5 gliadin, where only 1 subject (case 8) was found to have specific IgE (Fig. 1). The lack of reactivity of case 1 may be attributed to lower sensitivity of the western blotting.

On the other hand, 9 subjects were picked up by questionnaire-based examination, although omega-5 gliadin-ImmunoCAP test was negative in these subjects. Of these 9 subjects, 7 were excluded from wheat allergy by the detailed interview and skin prick testing. There remain 2 subjects (cases 14 and 17) who have not accepted the secondary tests. More recently, an increase of wheat allergy patients who were possibly sensitized with hydrolyzed wheat products have been reported.²⁰ These patients have been known to have low or negative score of omega-5 gliadin-ImmunoCAP test, thus these 2 subjects have still possibility to have wheat allergy. This might be a limitation of the study. Upon the questionnaire-based examination, none of these 9 subjects had angioedema of the face, which is a characteristic symptom of the patients sensitized with hydrolyzed wheat products, thus it is unlikely that these 9 subjects were sensitized with hydrolyzed wheat products.

The present cohort study was performed in Daitocho and Kamo-cho in Shimane Prefecture, both of which locate rural area. Since most subjects enrolled in the study were relatively aged, the result might not directly indicate a prevalence of wheat allergy in adults of whole Japan.

This study reports that the prevalence of wheat allergy is at least 0.21% in the Japanese adults, which was determined by using a combination of question-

naire-based examination, skin prick test, and serum omega-5 gliadin-specific IgE test.

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CONFLICT OF INTEREST

No potential conflict of interest was disclosed.

REFERENCES

1. Young E, Stoneham MD, Petrukevitch A, Barton J, Rona R. A population study of food intolerance. *Lancet* 1994; **343**:1127-30.
2. Altman DR, Chiaramonte LT. Public perception of food allergy. *J Allergy Clin Immunol* 1996; **97**:1247-51.
3. Emmett SE, Angus FJ, Fry JS, Lee PN. Perceived prevalence of peanut allergy in Great Britain and its association with other atopic conditions and with peanut allergy in other household members. *Allergy* 1999; **54**:380-5.
4. Woods RK, Stoney RM, Raven J, Walters EH, Abramson M, Thien FC. Reported adverse food reactions overestimate true food allergy in the community. *Eur J Clin Nutr* 2002; **56**:31-6.
5. Pereira B, Venter C, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of sensitization to food allergens, reported adverse reaction to foods, food avoidance, and food hypersensitivity among teenagers. *J Allergy Clin Immunol* 2005; **116**:884-92.
6. Venter C, Pereira B, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of sensitization reported and objectively assessed food hypersensitivity amongst six-year-old children: a population-based study. *Pediatr Allergy Immunol* 2006; **17**:356-63.
7. Gislason D, Björnsson E, Gislason T *et al.* Sensitization to airborne and food allergens in Reykjavik (Iceland) and Uppsala (Sweden)-a comparative study. *Allergy* 1999; **54**:1160-7.
8. Biagini RE, MacKenzie BA, Sammons DL *et al.* Evaluation of the prevalence of antiwheat, anti-flour dust, and anti-alpha-amylase specific IgE antibodies in US blood donors. *Ann Allergy Asthma Immunol* 2004; **92**:649-53.
9. Osterballe M, Hansen TK, Mortz CG, Bindslev-Jensen C. The clinical relevance of sensitization to pollen-related fruits and vegetables in unselected pollen-sensitized adults. *Allergy* 2005; **60**:218-25.
10. Ostblom E, Wickman M, van Hage M, Lilja G. Reported symptoms of food hypersensitivity and sensitization to common foods in 4-year-old children. *Acta Paediatr* 2008; **97**:85-90.
11. Ostblom E, Lilja G, Ahlstedt S, van Hage M, Wickman M. Patterns of quantitative food-specific IgE-antibodies and reported food hypersensitivity in 4-year-old children. *Allergy* 2008; **63**:418-24.
12. Palosuo K, Varjonen E, Kekki OM *et al.* Wheat omega-5 gliadin is a major allergen in children with immediate allergy to ingested wheat. *J Allergy Clin Immunol* 2001; **108**:634-8.
13. Morita E, Matsuo H, Mihara S, Morimoto K, Savage AW,

- Tatham AS. Fast omega-gliadin is a major allergen in wheat-dependent exercise-induced anaphylaxis. *J Dermatol Sci* 2003;**33**:99-104.
14. Matsuo H, Morita E, Tatham AS *et al*. Identification of the IgE-binding epitope in omega-5 gliadin, a major allergen in wheat-dependent exercise-induced anaphylaxis. *J Biol Chem* 2004;**279**:12135-40.
 15. Matsuo H, Kohno K, Niihara H, Morita E. Specific IgE determination to epitope peptides of omega-5 gliadin and high molecular weight glutenin subunit is a useful tool for diagnosis of wheat-dependent exercise-induced anaphylaxis. *J Immunol* 2005;**175**:8116-22.
 16. Morita E, Matsuo H, Chinuki Y, Takahashi H, Dahlström J, Tanaka A. Food-dependent exercise-induced anaphylaxis -Importance of omega-5 gliadin and HMW-glutenin as causative antigens for wheat-dependent exercise-induced anaphylaxis-. *Allergol Int* 2009;**58**:493-8.
 17. EAACI. Skin tests used in type I allergy testing. Position paper. Sub-Committee on Skin Tests of the European Academy of Allergology and Clinical Immunology. *Allergy* 1989;**44**(Suppl):1-59.
 18. Aihara Y, Takahashi Y, Kotoyori T *et al*. Frequency of food-dependent, exercise-induced anaphylaxis in Japanese junior-high-school students. *J Allergy Clin Immunol* 2001;**108**:1035-9.
 19. Ito K, Futamura M, Borres MP *et al*. IgE antibodies to omega-5 gliadin associate with immediate symptoms on oral wheat challenge in Japanese children. *Allergy* 2008;**63**:1536-42.
 20. Fukutomi Y, Itagaki Y, Taniguchi M *et al*. Rhinoconjunctival sensitization to hydrolyzed wheat protein in facial soap can induce wheat-dependent exercise-induced anaphylaxis. *J Allergy Clin Immunol* 2011;**127**:531-3.