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TITLE PAGE

Letter to the editor

TITLE:

Clinical relevance of IgE to rGly m 4 in diagnosis of adult soybean allergy

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Running title: Clinical relevance of IgE to rGly m 4

Abstract (249 words):

Background: Recent studies have shown that birch-pollen-related soybean allergy mediated by Gly m 4 is common in central Europe. However, the clinical relevance of measuring the level of the IgE antibody to Gly m 4 in the diagnosis of soybean allergy is still debated. Studies on soybean allergy outside Europe are limited.

Objective: The aims of this study were to elucidate the characteristics of soybean allergic adults in Japan and to evaluate the diagnostic efficiency of measuring the level of IgE-ab to rGly m 4.

Methods: Twenty-one soybean allergic patients were prospectively recruited, and their levels of IgE-ab to rGly m 4 were compared with those of 93 alder-pollen-sensitized control patients without soybean allergy.

Results: All the soybean allergic patients were sensitized to alder pollen and rGly m 4 whereas only one of them was sensitized to the soybean storage protein nGly m 5/6. The levels of IgE-ab to rGly m 4 in soybean-allergic patients were markedly higher than those in the alder-pollen-sensitized control patients. The area under the receiver-operating characteristic curve for the level of IgE-ab to rGly m 4 in the diagnosis of

soybean allergy was 0.87, which was significantly higher than that to the soybean extract (0.59, $p < 0.01$).

Conclusion: A strong relationship between adult soybean allergy and the level of IgE Ab to rGly m 4 was observed. Analysis of IgE-ab to rGly m 4 was an effective tool in discriminating patients with soybean allergy from alder-pollen-sensitized patients without soybean allergy.

Clinical Implications: Measuring the level of IgE-ab to rGly m 4 is an effective tool in discriminating adult patients with soybean allergy from Betulaceae-pollen-sensitized patients without soybean allergy.

Capsule summary: This study shows the clinical relevance of quantitative analysis of IgE-ab to rGly m 4, a pathogenesis-related class 10 protein in soybean, in the diagnosis of adult soybean allergy.

Key words: Soybean allergy, oral allergy syndrome, adults, Japan, pollen-food allergy syndrome, Gly m 4, Bet v 1, cross-reactivity, receiver-operating characteristics curve

Abbreviations:

AUC: area under the curve

IgE: Immunoglobulin E

kUA/l: kilo units of allergen-specific IgE per liter

OAS: oral allergy syndrome

PR-10: pathogenesis-related class 10

rGly m 4: recombinant Gly m 4

ROC: receiver-operating characteristics

SPT: skin prick test

To the editor:

Soybean is one of the most important foods causing food allergy in childhood¹. In addition, studies have shown that allergy to soybean can be caused by IgE cross-reactivity between Bet v 1, a major allergen of birch pollen, and its homologue pathogenesis-related class 10 (PR-10) protein in soybean, Gly m 4^{2, 3}. However, the clinical relevance of measuring the level of IgE-ab to rGly m 4 is still debated, considering that the concentration of Gly m 4 in soybean extract is quite low and that a considerable proportion of the birch-pollen allergic patients have IgE-ab to Gly m 4 without reporting any symptoms to soybean^{2, 4}. Sensitization to the soybean storage proteins Gly m 5 and Gly m 6 have been shown to contribute to more severe soybean allergy^{1, 5}. Data from studies on soybean allergy outside Europe, particularly in Asian populations, are still limited.

Japan has one of the largest soybean consuming populations in the world and tofu, miso, and natto are common soybean foods⁶. Soybean allergy is the fourth most common cause of food allergy in Japan among infants but, although reported, has been thought until recently to be rare in adults^{7, 8}.

The aim of this study was to elucidate the characteristics of soybean allergy among adults and the impact of sensitization to Gly m 4 on soybean allergy. Moreover, to analyze the diagnostic efficiency of measuring the level of IgE-ab to Gly m 4 in soybean allergy compared with Betulaceae-pollen-sensitized patients without soybean allergy.

We recruited 21 consecutive adult patients with soybean allergy who visited our clinic during 2009. Soybean allergy was diagnosed on the basis of a convincing case history and results of positive skin prick test (SPT) to soybean extract (extract named “edamame”, Torii, Tokyo, Japan) and/or soymilk (Luckme^R Yakult, Tokyo, Japan). The control group consisted of 93 alder-pollen-sensitized allergic rhinitis patients without soybean allergy recruited from the outpatient clinic during the same study period. Details of the criteria for both patient groups are shown in the Online Repository.

The IgE-ab levels to alder pollen, birch pollen, soybean extracts, rBet v 1, rGly m 4, nGly m 5 and nGly m 6 were determined using the commercially available ImmunoCAP[®] system (Phadia,, Uppsala, Sweden). IgE-ab level ≥ 0.35 kU_A/l was regarded as positive. The IgE-ab levels to nGly m 5 and nGly m 6 were measured in the soybean-allergic group only.

Statistical testing was performed using Fisher's exact test for the categorical and Mann-Whitney U test for the continuous variables. The receiver-operating characteristic (ROC) curves were plotted for the IgE-ab levels to rGly m 4 and soybean extract separately and the area under the ROC curve (AUC) was calculated and Student's t-test was conducted for the comparison (SPSS ver. 19.0 IBM, Japan). A p value <0.05 was considered significant.

The most frequent symptom among the soybean-allergic patients (Table E1, Online Repository) was oral allergy syndrome (17/21, 81%), followed by cough/ dyspnea (10/21, 48%) abdominal pain /diarrhea (8/21, 38%). Soymilk was the most provoking allergen in relation to exposure. Fifteen (71%) of the 21 patients reported reaction to any of the moderately heated soy product such as tofu and boiled edamame, and none to the fermented soy products such as natto, miso, and soy sauce (Table E2, Online Repository).

The frequency of sensitization to soybean in soybean-allergic patients was relatively low (48%), whereas all the soybean-allergic patients were sensitized to rGly m 4 (Table I). Only one patient was sensitized to the soybean storage proteins nGly m 5 and nGly m 6.

The IgE-ab levels to rGly m 4, as well as to alder pollen, birch pollen, and rBet v 1, were significantly higher in the soybean-allergic group than in the control group (median levels of IgE-ab to rGly m 4, 15.0 vs 0.68 kU_A/l; alder, 48.4 vs 4.77; birch, 42.4 vs 6.49; rBet v 1, 48.4 vs 3.85 kU_A/l, Fig. 1A). The ROC curve showed that AUC for the IgE-ab levels to rGly m 4 was 0.87 (Fig. 1B), which was significantly higher than that for soybean (0.59, $p < 0.01$). Applying a 4.0 kU_A/l cutoff level, the diagnostic efficiency of rGly m 4 reached 81% and 78% respectively, in terms of sensitivity and specificity.

This study revealed the characteristics of adult soybean allergy and the impact of sensitization to Gly m 4 in a Japanese population. In Japan, alder pollen (alder is part of the Betulaceae-family) is of minor clinical importance in terms of respiratory sensitization, compared to Japanese cedar pollen. However, although sensitization to alder pollen was not an inclusion criterion for the soybean-allergic patient group, all the patients were sensitized to alder pollen and rGly m 4. Moreover, the IgE-ab levels to rGly m 4 were markedly higher in the soybean-allergic patients than in the alder-pollen-sensitized control patients. These findings highlight the clinical impact of respiratory sensitization to pollen-derived PR-10 on the development of adult soybean allergy.

The most frequent symptom in the soybean-allergic patients was OAS. Soymilk was the allergen that most prevalently induced symptoms in those who had been exposed, whereas none of the soybean-allergic patients reacted to fermented soybean products. This finding was in agreement with that of Mittag et al². The explanation is that Gly m 4 is somewhat heat-labile but also apparently susceptible to degradation by fermentation.

This study was carried out in a population with high soybean consumption. Indeed, a study in Japan has shown that all the pediatric patients with soybean allergy were sensitized to Gly m 5 and Gly m 6, and sensitization to these allergens contributes to more severe soybean allergy⁵. However, only one of the 21 adult patients in our study was sensitized to Gly m 5 and Gly m 6, suggesting that primary sensitization to soybean (i.e., the oral route) was relatively rare. Therefore, we consider that sensitization to Gly m 4 is of more importance for adult patients with soybean allergy. Moreover, it is important to highlight the finding that some of these Gly m 4-mediated soybean-allergic adult patients experienced severe allergic symptoms including anaphylaxis.

One possible limitation of this study is related to the diagnosis of soybean allergy. Soybean allergy was diagnosed on the basis of a convincing case history and positive results of SPT. Double-blind placebo-control food challenge was not performed.

However, regarding oral symptoms, subjective symptoms are relatively reliable because they occur immediately after the ingestion of specific foods. Recently, Skypala et al. have shown the validity of self-completed structured questionnaire, namely, subjective allergic symptoms, as the basis of the diagnosis of oral allergy syndrome⁹.

We conclude that the discrimination between patients with pollen-related soybean allergy from Betulaceae-pollen-sensitized patients was effectively achieved in this Japanese adult population with a low prevalence of Betulaceae pollen allergy and high soybean consumption, by measuring the IgE-ab level to rGly m 4. A high level of IgE-ab to rGly m 4 was associated with adult soybean allergy.

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Table I. Demographics and frequencies of sensitization to allergens in study subjects.

	Soybean-allergic patients (n=21)	Alder-pollen-sensitized control patients (n=93)	p
Gender (=female), n (%)	17 (81%)	57 (61%)	0.128
Age, yrs (mean \pm SD)	41.4 \pm 16.1	44.5 \pm 16.6	0.438
Comorbidity, n (%)			
Allergic rhinitis	21 (100%)	93 (100%)	1.000
Asthma	3 (14%)	31 (33%)	0.449
Reported food allergy to soybean	21 (100%)	0 (0%)	<0.001
Reported OAS due to any other plant foods¶, n (%)	18 (86%)	17 (18%)	<0.001
Sensitization determined by CAP-FEIA (\geq 0.35 kUA/l), n (%)			
Alder pollen	21 (100%)	93 (100%)	1.000
Birch pollen	21 (100%)	93 (100%)	1.000
rBet v 1	21 (100%)	66 (71%)	0.003
Soybean	10 (48%)	30 (32%)	0.211
rGly m 4	21 (100%)	53 (57%)	<0.001
nGly m 5	1 (5%)	ND	
nGly m 6	1 (5%)	ND	

OAS, oral allergy syndrome; ND, not done

¶defined as reporting OAS due to any plant foods other than soybean in the structured questionnaire

Figure legend

Fig. 1. Levels of IgE-ab to alder pollen, birch pollen, rBet v 1, soybean, and rGly m 4 in sera from soybean-allergic patients and alder-pollen-sensitized control patients (A).

ROC curve for levels of IgE-ab to soybean and rGly m 4 in the diagnosis of soybean allergy (B). The number of negative test results in each set of measurement is indicated below the dotted cutoff line (0.35 kUA/l). *** $p < 0.001$.

