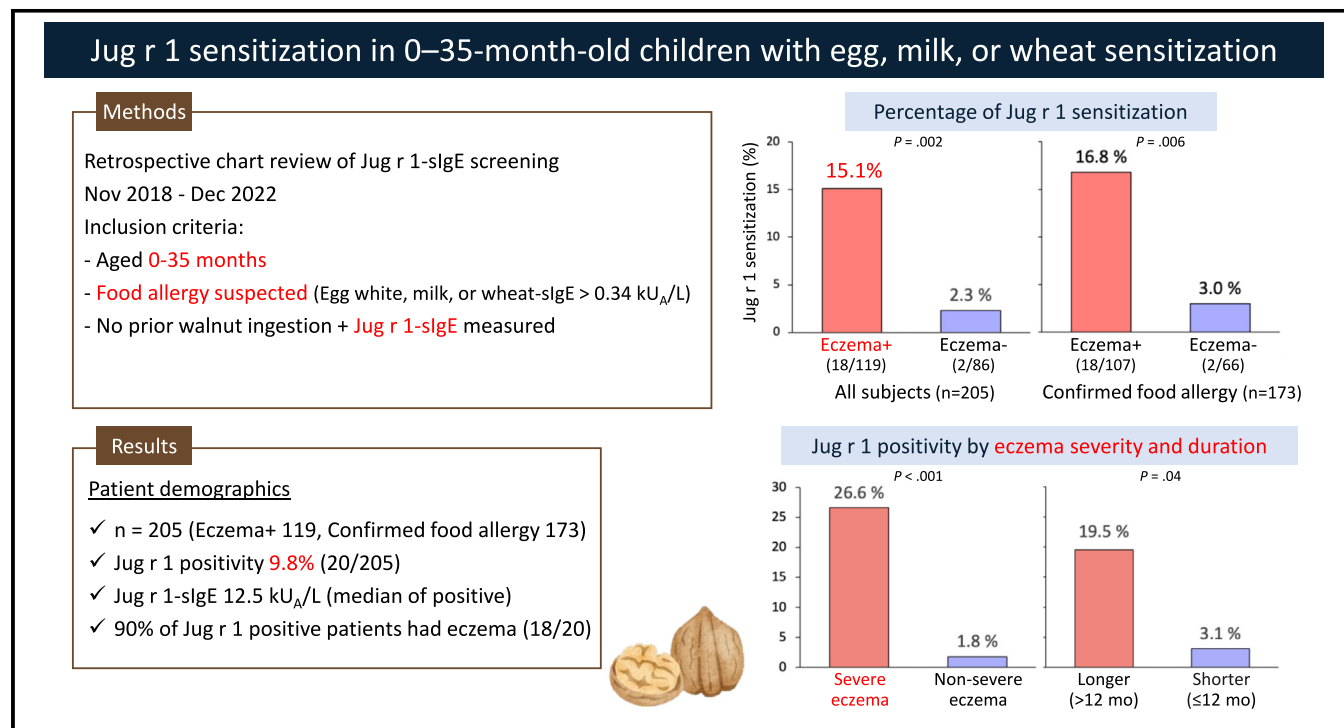


Jug r 1 sensitization in 0- to 35-month-old children with egg, milk, or wheat sensitization



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GRAPHICAL ABSTRACT



Background: The incidence of tree nut allergies in children is increasing, with walnut allergy being the most common in the United States and Japan. Allergic reactions, including anaphylaxis, frequently occur at the first intake of tree nuts, suggesting prior sensitization.

Objective: Our aim was to identify which children should be considered for workup for preexisting sensitization.

Methods: *Juglans regia* (Jug r) 1-specific IgE screening for 0- to 35-month-old children who had a positive specific IgE result for egg white, milk, or wheat and had never ingested walnuts was

conducted at a food allergy referral hospital between November 2018 and December 2022. Clinical data regarding age; sex; allergic disease complications; and egg, milk, or wheat allergy were examined retrospectively.

Results: The rate of Jug r 1-specific IgE positivity (level > 0.34 kU_A/L) of 205 children (125 of whom were boys) was 9.8%, with a median Jug r 1-specific IgE level of 12.5 kU_A/L in patients with a positive test result. Eczema was observed in 119 patients (58%). The rate of Jug r 1-specific IgE positivity was significantly higher in the eczema-positive group (15.1% [18 of 119]) than in the eczema-negative group (2.3% [2 of 86]) ($P = .002$). In the eczema-positive group, the rates of Jug r 1-specific IgE positivity per sensitized antigen were 13.7% for egg, 17.0% for milk, and 17.1% for wheat. The rate of Jug r 1-specific IgE positivity was significantly higher in the group with severe eczema (26.6% [17 of 64]) than in the group with nonsevere eczema (1.8% [1 of 55]) ($P < .001$).

Conclusion: Even in children younger than 3 years, 15% of children with eczema and egg, milk, or wheat sensitization were sensitized to Jug r 1. (*J Allergy Clin Immunol Global* 2023;2:100168.)

Key words: Tree nut allergy, food allergy, anaphylaxis, diagnosis, IgE, component-resolved diagnostics, walnut, eczema

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Abbreviations used

Jug r: *Juglans regia*
OFC: Oral food challenge
PPV: Positive predictive value

INTRODUCTION

The incidence of tree nut allergies in children is increasing, with walnut (*Juglans regia* [Jug r]) being the most common in the United States and Japan.¹⁻³ Walnut accounts for approximately 8% of allergy-causing foods in Japan.³ Allergic reactions, including anaphylaxis, in response to tree nuts are common in young children^{1,3,4} and frequently occur at the first tree nut intake, suggesting prior sensitization of these children.⁵

Which children should be considered for workup for preexisting sensitization to avoid such unexpected anaphylaxis is unclear. The first presentation in children with food allergies is often through reactions to eggs or milk in infancy. Infants with egg allergy are thought to be at increased risk of tree nut sensitization at age 1 year.⁶ To date, no study has explored the frequency of walnut allergy in infants and toddlers with other food allergies or assessed differences in the prevalence of childhood walnut allergy by the presence of eczema. Currently, what should be done about walnut allergy testing and advice on walnut introduction for those with other food allergies in infancy remain clinical dilemmas.⁶

Conversely, several studies have reported a high diagnostic performance of Jug r 1, the representative allergen component (2S albumin) of walnut.^{7,8} Prophylactic examination to detect Jug r 1-specific IgE in high-risk infants and toddlers may help avoid unexpected anaphylaxis at the first walnut intake. Thus, this study investigated Jug r 1-specific IgE positivity in young children with food allergies.

This study was conducted at Aichi Children's Health and Medical Center, a tertiary referral center for food allergies in Japan. A retrospective review of patients with food allergies between November 2018 and December 2022 was performed. Patients meeting the following criteria were included in the data analysis: patient age 0 to 35 months with measured Jug r 1-specific IgE values; either egg white-, milk-, or wheat-specific IgE values and at least 1 value greater than 0.34 kU_A/L; and no prior walnut ingestion before measurement of Jug r 1-specific IgE level. The following clinical data were examined: age; sex; complications of physician-diagnosed allergic diseases at measurement of Jug r 1-specific IgE level; egg, milk, or wheat allergy (diagnosed on the basis of oral food challenges [OFC] or history of objective reaction after definitive exposure to the food); and walnut consumption status as of December 2022. If a patient had multiple IgE measurements, the first measurement was considered. Early onset and severity of eczema were defined as previously reported.⁹ Eczema starting in the first 6 months of life was defined as "early" eczema. Eczema severity was diagnosed variably with the clinical tool SCORing Atopic Dermatitis or by ill-defined doctor-specific grading. Therefore, the requirement for continuous topical steroid therapy was adopted to define "severe" eczema. All significance tests were 2 sided, and *P* values less than .05 were considered statistically significant. All analyses were performed using EZR, a graphical user interface for R (version 3.5.1, R Foundation for Statistical Computing, Vienna,

Austria). This study was approved by the Aichi Children's Health and Medical Center Review Board (no. 2017001). Informed consent was obtained from the parents of all patients.

RESULTS AND DISCUSSION

In total, 205 children (of whom 125 were boys) had data regarding Jug r 1-specific IgE values and comprised the analytic sample. The Jug r 1-specific IgE positivity rate (>0.34 kU_A/L) was 9.8% (20 of 205), with a median Jug r 1-specific IgE level of 12.5 (range 0.41-508 kU_A/L) in patients with a positive test result (Table 1). Eczema was observed in 119 patients (58%). The rate of Jug r 1-specific IgE positivity was significantly higher in the eczema-positive group (15.1% [18 of 119]) than in the eczema-negative group (2.3% [2 of 86]) (*P* = .002) (Fig 1). The rate of Jug r 1-specific IgE positivity in the eczema-positive group was 16.8% in patients with confirmed food allergy.

The rate of Jug r 1-specific IgE positivity per sensitized antigen was 13.7% (14 of 102) for egg, 17.0% (8 of 47) for milk, and 17.1% (7 of 41) for wheat in the eczema-positive group, whereas the rates in the eczema-negative group were 2.9% (2 of 68), 3.4% (1 of 29), and 0% (0 of 13), respectively. Among patients with confirmed food allergy, the rates of Jug r 1-specific IgE positivity in the eczema-positive group were 14.5% (11 of 76) for egg, 17.8% (8 of 45) for milk, and 17.9% (5 of 28) for wheat, whereas in the eczema-negative group, the rates were 4.3% (2 of 46), 4.8% (1 of 21), and 0% (0 of 12), respectively. No significant differences were observed in rate of Jug r 1-specific IgE positivity according to the number of food sensitizations or allergies in all patients or patients with confirmed food allergy (data not shown).

The rates of Jug r 1-specific IgE positivity by age were 5.9% (1 of 17) at 0 to 11 months, 9.2% (9 of 98) at 12 to 23 months, and 11.1% (10 of 90) at 24 to 35 months in the eczema-negative group, and 10.0% (1 of 10), 14.8% (8 of 54), and 16.4% (9 of 55), respectively, in the eczema-positive group (see Fig E1 in the Online Repository at www.jaci-global.org). No significant difference was found in rate of Jug r 1-specific IgE positivity between age groups. Among the patients who tested positive for Jug r 1-specific IgE, 1 underwent oral food challenge (OFC) with a small amount of walnut (total dose 1.7 g), which yielded a negative result, and had no symptoms after consuming 1 g at home. The other patients had not ingested walnuts as of December 2022.

Fig 2 shows the correlation between Jug r 1 sensitization and severity, onset, and duration of eczema in the eczema-positive group. The rate of Jug r 1-specific IgE positivity was significantly higher in the group with severe eczema (26.6% [17 of 64]) than in the group with nonsevere eczema (1.8% [1 of 55]) (*P* < .001). There was no significant difference in Jug r 1-specific IgE positivity between the group with early onset and that with later onset; however, this may simply reflect the small number of patients with later onset. The rate of Jug r 1-specific IgE positivity was significantly higher in the group with an eczema duration longer than 12 months (19.5% [17 of 87]) than in the group with an eczema duration of 12 months or less (3.1% [1 of 32]) (*P* = .040).

To our knowledge, this is the first study to evaluate Jug r 1-specific IgE levels in a large number of children with suspected food allergies. We also report a particularly high rate of Jug r 1 positivity among patients with eczema and food sensitization. There was a significant correlation between Jug r 1 sensitization and eczema severity or duration, suggesting an involvement of percutaneous sensitization in the development of walnut allergy.

TABLE I. Demographic and clinical characteristics of patients positive for and negative for Jug r 1-specific IgE

Description	Jug r 1-positive	Jug r 1-negative	P value
Patients (no.)	20	185	
Sex, male/female	15/5	110/75	.18
Age (mo), median (min, max)	25 (9, 34)	21 (6, 35)	.10
Jug r 1-specific IgE level (U _A /mL), median (min, max)	12.5 (0.41, 508)	0.34 (0.34, 0.34)	<.001
Total IgE level (kU/L), median (min, max)	481 (93, 11,652)	145 (3, 4,029)	<.001
Atopic comorbidities, no. (%)			
Eczema	18 (90%)	101 (55%)	.002
Bronchial asthma	3 (15%)	14 (7.6%)	.25
Allergic rhinitis	2 (10%)	10 (5.4%)	.41

The Mann-Whitney *U*-test and Fisher exact test were used to compare continuous and categorical variables between groups, respectively.

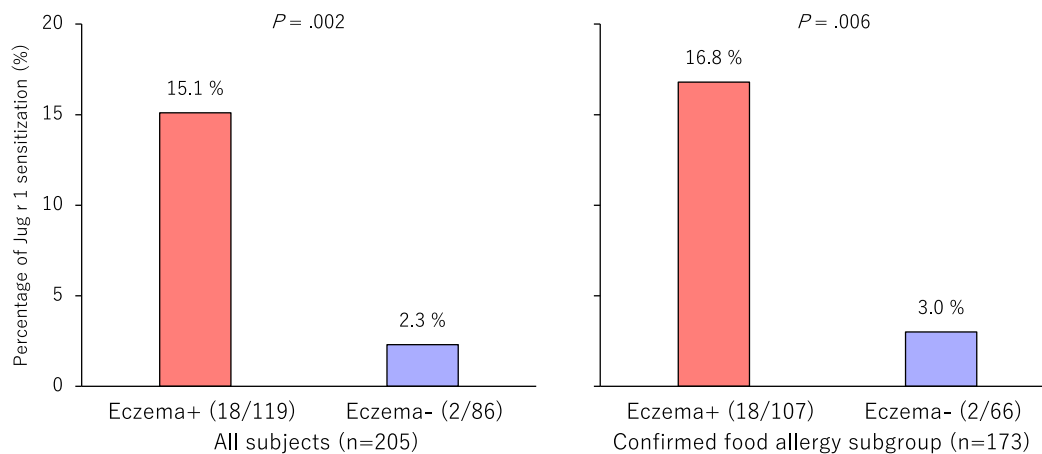


FIG 1. Percentage of Jug r 1 sensitization in 0- to 35-month-old children with egg, milk, or wheat sensitization. *Left*, All patients. *Right*, the subgroup with confirmed food allergy. The Fisher exact test was used to compare the categorical variables between groups.

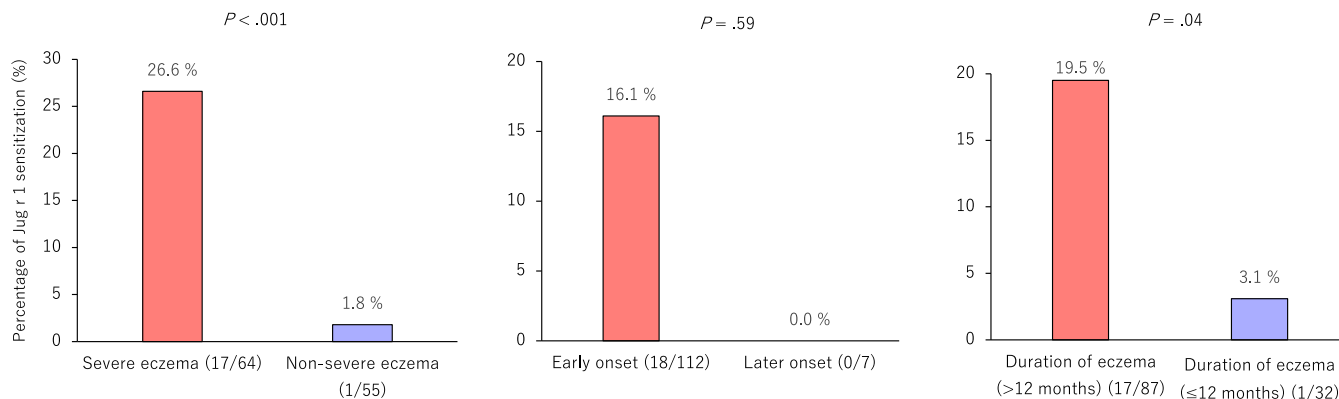


FIG 2. Percentage of Jug r 1 sensitization by severity, onset, and duration of eczema. Early onset was defined as eczema starting at or before age 6 months. Severe eczema was defined as eczema that required continuous use of topical steroid therapy. The Fisher exact test was used to compare the categorical variables between groups.

There have been several reports regarding the diagnostic accuracy of Jug r 1-specific IgE in children. In a study of 76 Israeli children (median age 8 years), a 95% positive predictive value (PPV) was obtained at a Jug r 1-specific IgE level of 0.21 UA/mL¹⁰; in 144 Japanese children (median age 6 years), a 95% PPV at a Jug r 1-specific IgE level of 0.98 UA/mL was reported.¹¹

However, even with high PPV, giving advice based solely on the result of Jug r 1-specific IgE testing could lead to unnecessary food restrictions and potentially increase the risk of development of walnut allergy. In this study, total IgE levels were significantly higher in the Jug r 1-sensitized group (Table I). Additional analysis showed significantly higher total IgE levels in the

eczema-positive group than in the eczema-negative group (data not shown), suggesting that eczema affected total IgE levels. Low levels of specific IgE in patients with high levels of total IgE may be a false-positive result,¹² and those patients should be considered for diagnostic OFCs.

The participants in this study were high-risk patients visiting a tertiary allergy center; thus, the results are not generalizable. Nor do we recommend Jug r 1 screening of the general population. Unnecessary screening tests are discouraged because they can lead to unnecessary food eliminations.¹³ However, we are concerned about advising patients in the eczema-positive group, who showed greater than 15% Jug r 1 positivity in a test high characterized by a PPV, to start consuming walnuts at home without screening because of a risk of anaphylaxis. Instead, it is necessary to alert selected high-risk patients with a screening test. Moreover, parents of children with food allergies are highly anxious¹⁴ and tend to avoid introducing foods with a high risk of anaphylaxis without screening. Therefore, ensuring Jug r 1 negativity through a screening test and reducing unnecessary food elimination through OFCs or careful home intake would be in the overall best interest of patients.

Data on early tree nut sensitization rates are limited. It has been reported that 19% to 33% of children with peanut or other food allergies were sensitized to 1 or more nuts according to the skin prick test.^{6,15} Although our results show a lower positivity rate than in previous reports, our data represent the sensitization rate in children aged 0 to 35 months who had never ingested walnuts.

Jug r 1 testing is also helpful in diagnosing coallergy to pecan nuts.¹⁰ Although pecan nuts are not commonly consumed in Japan and none of the participants in this study had a history of pecan consumption, the Jug r 1 testing results can also be used for patient instruction on pecan nut consumption.

The limitations of this study include its single-center retrospective design and its being conducted at a tertiary referral center. Additionally, measurement of specific IgE levels in patients with suspected food allergy is covered by the national health insurance in Japan; however, the system differs by country and region.

We observed that 15% of 0- to 35-month-old children with eczema and egg, milk, or wheat sensitization were sensitized to Jug r 1. In these high-risk children, efforts should be made to avoid anaphylaxis during their first walnut intake by considering Jug r 1 testing; in addition, the physician performing the test should be responsible for subsequent patient instruction or diagnostic OFC.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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Clinical implications: Measurement of Jug r 1-specific IgE may be an important tool to avoid unexpected anaphylaxis after first intake of walnut by 0- to 35-month-old children with eczema and egg, milk, or wheat sensitization.

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