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Letter to the Editor

Low-dose oral immunotherapy for walnut allergy with anaphylaxis: Three case reports

Dear Editor,

Tree nut allergy is one of the most common food allergies. Recently, its prevalence has been increasing globally and is estimated to be 0.05–4.9%.¹ In Japan, walnut allergy is rapidly increasing and is the fourth most common causative food; the frequency of anaphylactic shock is 16.7%.² The rate of tolerance acquisition for tree nuts is approximately 10%.³

There are a few reports on oral immunotherapy (OIT) for walnut allergy. OIT with a maintenance dose of 1200 mg walnut protein often causes adverse reactions that require intramuscular adrenaline.⁴ Recently, low-dose OIT has been used to treat anaphylactic reactions in children to egg, milk, wheat, and peanuts,^{5–9} enabling them to ingest low doses of allergens with a reduced risk of developing symptoms. However, no study has investigated low-dose OIT in children with walnut allergy. Therefore, we examined the safety and efficacy of low-dose OIT for walnut anaphylaxis.

The study subjects were children over 5 years old and positive for oral food challenge (OFC) with 75 mg walnut protein. OIT was performed between March 2016 and August 2019 using a study protocol similar to that published previously^{5–8} (Supplementary Fig. 1, Supplementary Methods, and Supplementary Table 1). Ethical approval was obtained from the institutional review boards of Sagami National Hospital (Approval number: 151014).

The home starting dose, which was safely administered during 3 days of hospitalization, was continued for 1 month and gradually increased to 75 mg/day (maintenance dose) administered once daily during the maintenance phase at home (Supplementary Table 2). Patients received antihistamines from the start of OIT until there was no symptom for 1 month after desensitization. Thereafter, at least 1 year after the subjects started OIT, it was discontinued for 2 weeks, thus stopping walnut exposure. Next, they underwent OFC with 450 mg walnut protein, equivalent to 3 g whole walnut. If they passed this OFC, they were considered to have achieved “short-term unresponsiveness (STU).”

Three children with a history of anaphylaxis to walnut participated in this study. Cases 1, 2, and 3 were 7-, 8-, and 7-year-old children, respectively; their characteristics are shown in Table 1.

Cases 1, 2, and 3 received a home starting dose set at 30, 18, and 18 mg, after hospitalization; they achieved desensitization to 75 mg after 3, 4, and 3 months, respectively. All subjects achieved STU to 450 mg. In case 1, the subject experienced pharyngeal discomfort and cough after exposure to 450 mg walnut during the OFC, which

was conducted 12 months after starting OIT. The subject continued OIT and passed the OFC at 450 mg in 24 months. In cases 2 and 3, the subjects achieved STU at 14 and 12 months, respectively (Table 1). After achieving STU, we instructed them to ingest 150–450 mg twice weekly at home.

Regarding adverse reactions (Table 1, Supplementary Table 3), two subjects required treatment on day 1 of OIT during hospitalization. During the home dose, the adverse reaction rate per intake was 3.1% in all cases. In case 1, the subject developed two anaphylactic reactions which were immediately improved by oral histamine and inhalant medications 1 and 16 months after commencing OIT, and there were no severe adverse reactions. The other subjects did not develop anaphylaxis during the OIT period (Table 1).

Regarding immunological changes, walnut-specific IgE (sIgE) levels increased after 1 month and decreased gradually until 12 months in all cases; Jug r 1-sIgE levels showed similar changes. Walnut-specific IgG₄ (sIgG₄) levels tended to increase after starting OIT in all cases (Fig. 1).

This study reports that the three children who had walnut allergy with anaphylaxis could undergo OIT effectively. In Japan, walnut allergy has rapidly increased in recent years, and there are many cases of anaphylaxis.² Because the rate of spontaneous tolerance acquisition for walnut allergy is low² and there is a risk of anaphylaxis due to accidental ingestion in children with a history of anaphylaxis, OIT may be a candidate for treating walnut anaphylaxis. Elizur *et al.*⁴ reported OIT for walnut allergy with 49/55 subjects (89%) achieving desensitization using 4000 mg walnut protein; however, they did not assess sustained unresponsiveness. Therefore, if children consumed walnuts on consecutive days without achieving sustained unresponsiveness, it may be an increasing burden. Here, the continuous intake of 75 mg walnut effectively facilitated the consumption of 450 mg walnut. Furthermore, we assessed STU after 2 weeks of discontinuation and instructed the subjects to resume ingestion of 150–450 mg walnut twice weekly after achieving STU. Consequently, after achieving STU, none of the subjects developed anaphylaxis for 1 year, which could reduce the burden associated with frequent intake. A similar result of reduced symptoms of accidental ingestion with low-dose OIT has been reported for peanut allergy.^{8,9} Low-dose OIT for walnut allergy may also reduce the symptoms of accidental ingestion and enable anaphylactic children to consume 450 mg walnut. Therefore, low-dose OIT would be a better option for severe walnut allergy.

In a previous study,⁴ eight subjects (15%) developed adverse reactions that required intramuscular adrenaline at home. Here,

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Table 1
Characteristics of the three subjects before starting OIT for walnut allergy and clinical outcomes.

		Case 1	Case 2	Case 3
Age (years)		7	8	7
Sex		Male	Female	Female
Number of anaphylaxis reactions		3	2	1
Threshold of baseline OFC (mg)		75	75	18
Symptoms during baseline OFC		Generalized urticaria Dyspnea Decrease in activity level	Moderate abdominal pain	Throat pain Emesis
Total IgE (IU/mL)		388	1240	201
Specific IgE (kU _A /L)	Walnut	145	21.7	75.2
	Jug r 1	126	17.2	69.1
	Pecan	59.2	10.6	16.4
Specific IgG ₄ (mg _A /L)	Walnut	1.3	0.6	1.3
Allergic complications		BA, AR, hazelnut allergy	AD, AR, hazelnut allergy	AD, AR, pecan allergy
Time to achieve desensitization to 75 mg		3 months	4 months	2 months
Time to achieve STU to 450 mg		24 months	14 months	12 months
Adverse reaction				
Total number of intakes of OIT	In hospital	3	3	3
	At home	584	345	209
Number of adverse symptoms	In hospital	1 (33%)	2 (66%)	1 (33%)
	At home	14 (2.4%)	4 (1.2%)	18 (8.6%)
Severity (Mild/Moderate/Severe)	In hospital	0 (0%)/1 (33%)/0 (0%)	1 (33%)/1 (11%)/0 (0%)	1 (33%)/0 (0%)/0 (0%)
	At home	9 (1.5%)/5 (0.9%)/0 (0%)	4 (1.2%)/0 (0%)/0 (0%)	18 (8.6%)/0 (0%)/0 (0%)

OIT, oral immunotherapy; OFC, oral food challenge; BA, bronchial asthma; AD, atopic dermatitis; AR, allergic rhinitis; STU, short-term unresponsiveness.

All subjects were sensitized to tree nuts: cashews, hazelnuts, and almonds. The nuts except those listed above on allergic complications could be ingested and were not assessed as food allergens.

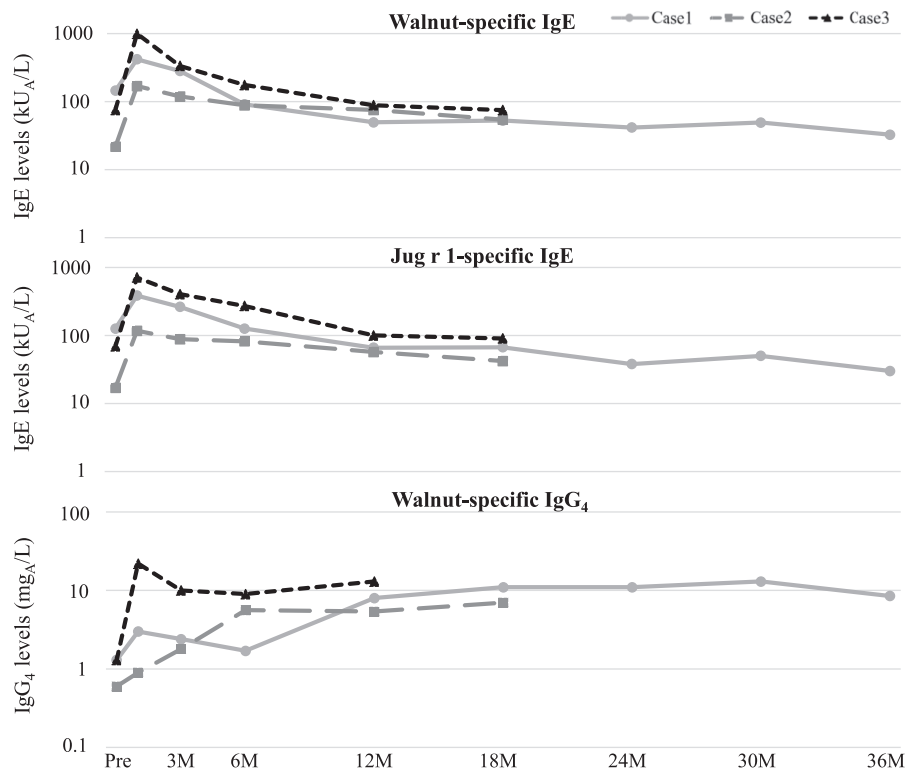


Fig. 1. Changes in walnut-specific IgE and IgG₄ over time. M, month(s); Pre, at baseline.

adrenaline was not required. Because anaphylaxis occurs twice, safety should be investigated with more cases. Additionally, the OIT should be performed in a specialized facility for allergy.¹⁰

Regarding immunological changes, during low-dose OIT for peanuts and wheat, the sIgE level temporarily increases and then decreases^{7–9} whereas the sIgG₄ level quickly increases.^{5–9} We confirmed immunological changes during low-dose walnut OIT similar to other antigens.

Limitations of this study include the absence of a control group. However, a child with a high walnut-sIgE level and history of anaphylaxis is unlikely to acquire tolerance naturally. Additionally, 2-week avoidance of walnut may be too short a period to assess sustained unresponsiveness. However, none of the subjects developed anaphylaxis for 1 year with the ingestion of walnut twice weekly.

In conclusion, this is the first report on low-dose OIT for walnut allergy with anaphylaxis. Low-dose OIT of walnuts was effective and feasible, achieving STU to 450 mg walnut protein in all cases.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2021.01.007>.

Conflict of interest

ME serves on the clinical medical advisory board of DBV Technologies and has received lecturing fees from Mylan EPD. SS received speaker honoraria from Mylan EPD. The rest of the authors have no conflict of interest.

Koki Sasamoto^{a,b}, Ken-ichi Nagakura^a, Sakura Sato^c,
Noriyuki Yanagida^{a,*}, Motohiro Ebisawa^c

^a Department of Pediatrics, National Hospital Organization, Sagami-hara National Hospital, Kanagawa, Japan

^b Department of Pediatrics, Toho University Ohashi Medical Center, Tokyo, Japan

^c Clinical Research Center for Allergy and Rheumatology, National Hospital Organization, Sagami-hara National Hospital, Kanagawa, Japan

* Corresponding author. Department of Pediatrics, National Hospital Organization, Sagami-hara National Hospital, 18-1 Sakuradai, Minami-ku, Sagami-hara, Kanagawa, 252-0392, Japan.

E-mail address: sagami@foodallergy.jp (N. Yanagida).

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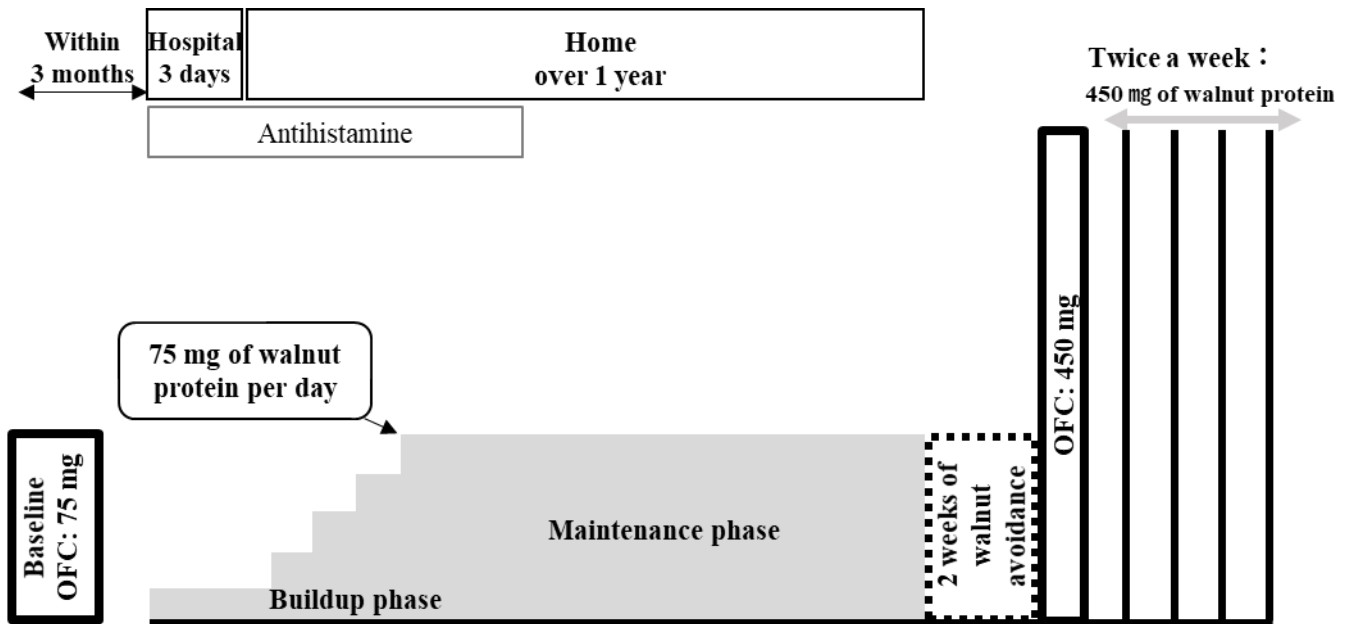
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Supplementary Fig. 1. Walnut OIT protocol.

OFC, oral food challenge; OIT, oral immunotherapy.

Supplementary Table 1. Classification of severity according to clinical symptoms

	1 (Mild)	2 (Moderate)	3 (Severe)
Skin	Localized urticaria, exanthema, wheal, pruritus	Generalized urticaria, exanthema, wheal, pruritus	-
	Swollen eyelid or lip	Swollen whole face	-
Gastrointestinal tract	Pruritus of the throat or oral cavity	Throat pain	-
	Mild abdominal pain	Moderate abdominal pain	Cramps
	Nausea, emesis, diarrhea	Recurrent emesis, diarrhea	Continuous emesis, loss of bowel control
Respiratory tract	Intermittent cough, nasal congestion, sneezing, rhinorrhea	Repetitive cough	Persistent cough, hoarseness, “barking” cough
	-	Chest tightness, mild wheezing	Apparent wheezing, dyspnea, cyanosis, saturation < 92%, swallowing or speaking difficulties, throat tightness, respiratory arrest
Cardiovascular	-	Pale face, mild hypotension [※] , tachycardia (increase > 15 beats/min)	Hypotension ^{※※} , dysrhythmia, severe bradycardia, cardiac arrest
Neurological	Change in activity level, tiredness	“Light-headedness,” feeling of “impending doom,” somnolence	Confusion, loss of consciousness, incontinence

※Mild hypotension: $< 80 + (2 \times \text{age})$ mmHg in age of 1–10.

※※Hypotension: $< 70 + (2 \times \text{age})$ mmHg in age of 1–10.

Supplementary Table 2. Dosing schedule for walnut protein in OIT

STEP		1	2	3	4	5	6	7	8
Case 1	Walnut protein (mg)	9	14	21	30	45	75		
Cases 2 and 3		5	9	13	18	26	38	53	75

OIT: oral immunotherapy.

When grade 1 symptoms appeared, dosing for the next day did not change. When grade 2 or 3 symptoms appeared, the dose was decreased by 1 or 2 steps, respectively.

Supplementary Table 3. Detail of adverse reactions during walnut OIT

	Case 1		Case 2		Case 3	
	In hospital	At home	In hospital	At home	In hospital	At home
Total number of intakes	3	584	3	345	3	209
Number of adverse symptoms	1 (33.3%)	14 (2.4%)	2 (66.6%)	4 (1.2%)	1 (33.3%)	18 (18.6%)
Organ system of symptoms						
Skin	1 (33.3%)	5 (0.9%)	1 (33.3%)	1 (0.3%)	0 (0%)	0 (0%)
Mucosal	0 (0%)	1 (0.2%)	1 (33.3%)	0 (0%)	1 (33.3%)	11 (5.3%)
Respiratory	1 (33.3%)	10 (1.7%)	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)
Gastrointestinal	0 (0%)	8 (1.4%)	2 (66.6%)	3 (0.9%)	1 (33.3%)	18 (8.6%)
Cardiovascular	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neurological	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Treatment						
Total number of treatments	1 (33.3%)	11 (1.8%)	1 (33.3%)	2 (0.6%)	0 (0%)	0 (0%)
Antihistamine	1 (33.3%)	10 (1.7%)	1 (33.3%)	2 (0.6%)	0 (0%)	0 (0%)
Corticosteroid	1 (33.3%)	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
β_2 inhalation	1 (33.3%)	11 (1.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Adrenaline	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

OIT, oral immunotherapy.

Supplementary Methods

Protocol for walnut oral immunotherapy (OIT)

The OIT protocol is illustrated in Supplementary Fig. 1. This OIT was performed in a combination of hospitalization and outpatient visits. Patients received antihistamine as a pre-medication and were hospitalized for 3 days to determine the home starting dose. Patients continued to take walnuts at the home starting dose of walnuts determined at discharge until 1 month after discharge. After 1 month, if asymptomatic intake continued for 5 consecutive days, the dose was increased by 1 step according to the dosing schedule table (Supplementary Table 2). Patients increased the dose of walnuts in stages up to 75 mg/day (maintenance dose). Patients received the maintenance dose daily after the buildup phase and visited our hospital every 1–3 months. Once the patients were asymptomatic for 1 month and were able to consume 75 mg, the pre-medication was discontinued. For patients who had been on OIT for more than 1 year and had been asymptomatic to walnut protein intake for more than 3 months, walnut intake was temporarily discontinued for 2 weeks, and then received 450 mg of OFC. The patients who passed these OFCs were considered to have achieved "short-term unresponsiveness (STU)" and instructed to ingest 150–450 mg walnut protein twice a week. If the patients did not achieve STU, they were instructed to ingest 75 mg walnut daily.

Definition

We defined desensitization as the absence of symptoms after ingesting 75 mg walnut on consecutive days, and STU as passing the OFC with 450 mg after 2 weeks of avoidance of walnuts.

Managing adverse reactions

Patients and their legal guardians were informed about treatment options if symptoms developed. All patients were

prescribed antihistamines, steroids, inhaled β_2 agonists, and auto-injectable adrenaline (EpiPen), and were appropriately managed according to the severity of their symptoms in accordance with the Japanese Food Allergy Treatment Guidelines (Supplementary Table 1)^{1,2}. Their parents recorded the presence or absence of symptoms daily. The emergency care system included a 24-hour phone call from our medical allergy specialist staff. Patients living away from our hospital were prepared for emergency care at an appropriate emergency location in advance.

Immunological parameters

We measured both walnut- and Jug r 1-specific IgE and IgG₄ levels (ImmunoCAP Assay System, Thermo Fisher Scientific, Uppsala, Sweden) at 0, 1, 3, 6, and 12 months and then every 6 months.

Ethical considerations

This single-center study was performed at the Sagamihara National Hospital between March 2016 and August 2019 (UMIN Registry UMIN000040531). We obtained approval from the institutional review board of the Sagamihara National Hospital (Approval number: 151014). The study was conducted in accordance with the Declaration of Helsinki. Informed consent and assent were obtained from subjects and their guardians.

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