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Letter to the Editor

Long-term outcomes after sustained unresponsiveness in patients who underwent oral immunotherapy for egg, cow's milk, or wheat allergy

Dear Editor,

Oral immunotherapy (OIT) is effective for treating persistent food allergies.¹ However, treatment interruption for several days could cause allergic symptoms on re-exposure to allergens. Therefore, sustained unresponsiveness (SU) through oral food challenge after weeks/months of food avoidance needs to be evaluated.^{1–4}

Several studies have reported the long-term outcomes of OIT for cow's milk or eggs; however, the long-term outcomes after achieving SU are not well described.^{4–6}

We aimed to clarify the outcomes after achieving a 2-week period of SU (2-week SU) in patients who underwent OIT for egg, cow's milk, or wheat allergy. The study was approved by the ethical review board of the National Hospital Organization, Sagami National Hospital. Parent/guardian signatures on the questionnaires were considered consent for study participation.

This study included children aged ≥ 6 years who achieved a 2-week SU within 2 years after starting OIT for egg, cow's milk, or wheat allergy and were followed up for at least 1 year after a 2-week SU.

OIT was performed from April 2009 according to the study protocol published previously² (Supplementary Methods).

In September 2015, we mailed survey questionnaires to participants. We evaluated the frequency and severity of symptoms that required medication after achieving a 2-week SU by analyzing questionnaire responses and retrospectively reviewing medical records. Those who did not require medication were defined as having "no symptoms" (Supplementary Methods, Supplementary Table 1). For statistical analysis, Mann–Whitney test, and Fisher's exact or the χ^2 test were conducted for comparisons of continuous variables and categorical variables, respectively. $P < 0.05$ was considered statistically significant. SPSS version 20 (IBM, Armonk, NY, USA) was used for all analyses.

Of 130 children meeting the inclusion criteria, responses were received for 108 (83%) (Supplementary Fig. 1, Supplementary Table 2). Overall, 61 children were allergic to egg, 30 to cow's milk, and 17 to wheat. The median interval since achieving a 2-week SU was 3.6 years.

During the period, 44 (41%) of 108 patients experienced symptoms: 17 (28%) patients with egg allergy, 17 (57%) with cow's milk allergy, and 10 (59%) with wheat allergy. Twenty-four (22%) patients experienced moderate or severe symptoms (Table 1,

Supplementary Table 3, 4). Adrenaline auto-injectors were used to treat symptoms of two patients (one, egg allergy that developed after ingesting a lightly cooked egg and one, wheat allergy that developed when playing tag).

Twenty-two (59%) of 37 patients (of the 44 patients, 7 patient's answers were unclear) experienced their first symptoms ≥ 2 years after a 2-week SU. A similar trend was observed in patients with moderate or severe symptoms, 11 (52%) of 21 (of the 24 patients, 3 patient's answers were unclear) experienced their first symptoms ≥ 2 years after a 2-week SU (Fig. 1).

Symptoms of 32 (73%) patients that developed after a 2-week SU were attributed to co-factors such as exercise, fatigue, and illness. Exercise was the most common contributor occurring in 16 (67%) patients with moderate or severe symptoms and contributed more to those than mild symptoms ($P = 0.002$; Supplementary Table 5).

Moreover, exercise was considerably a common co-factor in patients with cow's milk allergy and wheat allergy than those with egg allergy ($P = 0.048$ and $P = 0.003$ respectively; Supplementary Table 6).

After OIT, most patients with egg, cow's milk, or wheat allergy had regularly consumed processed foods containing the antigen (Supplementary Table 7).

Thus, our results revealed that allergic symptoms persisted long term, even after achieving a 2-week-SU and moderate or severe symptoms were associated with exercise.

In a previous report of patients with cow's milk allergy after OIT, 44% of patients had symptoms other than oral/pharyngeal symptoms assessed at the 3–5-year follow-up after achieving a desensitization status (unevaluated SU),⁵ which were similar to our evaluations after a 2-week SU. The duration of elimination of food allergens to evaluate SU in our study was shorter than that in other reports;^{1,3,4} therefore, the duration of our study may be insufficient. However, in a previous report, most patients experienced induced symptoms only by ingestion after achieving a desensitization status;⁵ conversely, in our study, 73% of patients who experienced symptoms developed them in the presence of co-factors such as exercise after a 2-week SU. Patients who acquired less reactivity to antigen were possibly selected by performing oral food challenge after 2 weeks of avoidance. This may explain that symptoms in patients in the present study were induced not only with ingestion of the causative foods but also due to the presence of a co-factor. Evaluating a 2-week SU may help assess the onset risk of symptoms in the absence of co-factors.

Peer review under responsibility of Japanese Society of Allergy.

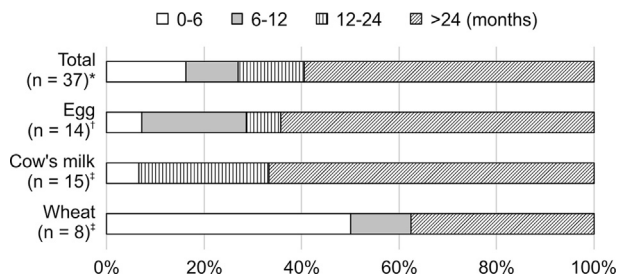
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Table 1
Severity of symptoms after 2 weeks of sustained unresponsiveness.

Symptoms	Total Food allergen (n = 108)	Food allergen		
		Egg (n = 61)	Cow's milk (n = 30)	Wheat (n = 17)
None	64 (59)	44 (72)	13 (43)	7 (41)
Mild	20 (19)	10 (16)	5 (17)	5 (29)
Moderate	15 (14)	4 (7)	8 (27)	3 (18)
Severe	9 (8)	3 (5)	4 (13)	2 (12)

Data are expressed as n (%).

**Fig. 1.** Time between the first onset of symptoms and achieving a 2-week period of sustained unresponsiveness. The proportion of patients and the interval until the first onset of symptoms are shown. *Seven patients' answers were unclear. [†]Three patients' answers were unclear. [‡]Two patients' answers were unclear.

Additionally, eggs, cow's milk, and wheat occur in many food products, so eliminating these allergens for >2 weeks is unlikely in the real-world settings.

Hsiao *et al.*⁷ reported that 4 of 24 subjects with peanut allergies experienced allergic symptoms 11 times after achieving SU, with 9 (82%) of those induced 1–5 years after achieving SU. Their findings were similar to those of our study that symptoms may be induced in the long term even after SU.

Exercise-triggered symptoms after SU had two features. First, exercise was accompanied by moderate or severe symptoms. An analysis from the European anaphylaxis registry showed similar results of physical exercise being a factor associated with development of severe anaphylaxis.⁸ Second, exercise-triggered symptoms were seen mainly in patients with cow's milk allergy or wheat allergy. The reports of anaphylaxis triggered by exercise after OIT and limited to patients with cow's milk allergy or wheat allergy support our results.^{5,9,10}

This study had some limitations, including recall bias due to questionnaire use, and that the analyzed patients who experienced induced symptoms were limited to those requiring medication. This suggested a greater number of patients with induced symptoms. Nevertheless, we believe that our results accurately reflected the induction of moderate or severe symptoms.

In conclusion, children who underwent OIT for egg, cow's milk, or wheat allergy experienced symptoms in the long term even after a 2-week SU, and exercise was the most common trigger of moderate or severe symptoms. Therefore, long-term follow-up and preparation for management of allergic symptoms are required.

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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.2019.02.012>.

Conflict of interest

ME serves on the DBV Technologies Scientific Advisory Board. The rest of the authors have no conflict of interest.

Tetsuharu Manabe ^a, Sakura Sato ^b, Noriyuki Yanagida ^a, Noriko Hayashi ^b, Makoto Nishino ^a, Kyohei Takahashi ^a, Ken-ichi Nagakura ^a, Tomoyuki Asaumi ^a, Kiyotake Ogura ^a, Motohiro Ebisawa ^{b,*}

^a Department of Pediatrics, National Hospital Organization, Sagamihara National Hospital, Kanagawa, Japan

^b Department of Allergy, Clinical Research Center for Allergy and Rheumatology, National Hospital Organization, Sagamihara National Hospital, Kanagawa, Japan

* Corresponding author. Department of Allergy, Clinical Research Center for Allergy and Rheumatology, National Hospital Organization, Sagamihara National Hospital, 18-1, Sakuradai, Minami-ku, Sagamihara, Kanagawa 252-0392, Japan.
E-mail address: mebisawa@foodallergy.jp (M. Ebisawa).

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Supplementary Methods

Rush Oral Immunotherapy (from April 2009).

We included patients who developed anaphylaxis after eating either <30 g of egg (3,672 mg of egg protein), <50 ml of cow's milk (1,603 mg of milk protein), or <50 g of udon noodles (1,300 mg of wheat protein) during the double-blind placebo-controlled food challenge (DBPCFC), prior to oral immunotherapy (OIT). We excluded patients with poorly controlled bronchial asthma or atopic dermatitis, and any other forms of current immunotherapy. An initial introduction of food allergens was conducted in the hospital for 5-9 days. After discharge, the amount of antigen ingested was increased slowly, aiming at full dose (a whole egg, 200 mL of cow's milk, and 200 g of udon noodles).

Patients were strictly restricted from ingesting antigen within an hour before exercise and during an illness such as fever or diarrhea.

As allergic reaction was not induced within 3 months after the full dose was achieved, an oral food challenge (OFC) was conducted 2 weeks after food avoidance (unresponsiveness challenge). We determined the avoidance period based on the assumption that periods when patients could not consume causative food, due to factors such as an illness, lasted at most 2 weeks.

Patients who failed unresponsiveness challenge were asked to consume the full dose of antigen every day and the unresponsiveness challenge was re-conducted in patients who were symptom-free for three months (until October 2011). After October 2011, the intake frequency was gradually decreased from every day to every other day, followed by twice a week, and finally to once a week. The clinical course was confirmed asymptomatic for a month at each stage. The unresponsiveness challenge was re-conducted in patients without symptoms for more than a month after a once-a-week ingestion of food allergens (tapering protocol). The patients freely consumed processed foods with an upper limit of 1/8th of the full dose.

Slow Oral Immunotherapy (from April 2009)

We included patients who developed allergic reactions immediately after eating either <one whole egg (7,344 mg of egg protein), <200 mL of cow's milk (6,412 mg of milk protein), or <100-200 g of udon noodles (2,600–5,200 mg of wheat protein) prior to DBPCFC or open food challenge. We excluded patients who had experienced anaphylaxis during oral food challenge before the study prior to OIT. The starting dose of OIT was 1/4th or less than the symptom-inducing threshold at OFC, and the patient's home dose was gradually increased for 4 weeks up to 10 weeks, on a case-by-case basis,

aiming at full dose (a whole egg, 200 mL of cow's milk, and 200 g of udon noodles).

Patients were strictly restricted from ingesting antigen within an hour before exercise and during an illness such as fever or diarrhea.

If an allergic reaction was not induced within 3 months after the full dose was achieved, the unresponsiveness challenge was conducted until August 2011. After this time, if patients did not experience allergic reaction within a month after reaching the full dose, the intake frequency was gradually decreased from every day, to every other day, and then to twice a week on the condition that the clinical course at each stage was confirmed asymptomatic for a month. We conducted the unresponsiveness challenge in patients without allergic symptoms for more than a month after a twice-a-week ingestion of allergens.

Patients who failed the unresponsiveness challenge were asked to consume a full dose of antigen every day and the unresponsiveness challenge was re-conducted in patients who were symptom-free for three months (until August 2011).

After August 2011, we implemented a tapering protocol similar to rush OIT. The subjects consumed processed foods freely with an upper limit of 1/8th of the full dose.

After achieving a 2-week sustained unresponsiveness

After achieving a 2-week period of SU, patients were asked to consume the target amount of food allergens more than once a week; processed foods could be consumed freely within the target dose. The patients' clinical course was followed for at least 2 years.

Content of the Questionnaire (For Egg Allergy)

Q1. Have you experienced any allergic reactions requiring medication (oral, inhalation, intravenous) after a 2-week sustained unresponsiveness?

Q2. a) When did the allergic reaction appear?

b) What did you eat? How much did you eat?

c) What symptoms did you experience? How was the severity of symptoms graded? [The patients were instructed to refer to online suppl. Table S1.]

d) What kind of medication did you use?

Q3. Please select the circumstances that triggered your allergic reaction. (Multiple responses allowed).

- during exercise • had a cold • feeling tired • Hay fever
- took medicine (antipyretic analgesic)
- scar in the oral cavity (e.g., dental treatment)
- during or after bathing • ate more than usual
- premenstrual • nothing in particular

Q4. How often did you eat processed eggs in the last 3 months? (Mark one that applies).

1) three or more times a week

2) at least once a week

3) less than once a week

Q5. How often have you eaten eggs in an unprocessed form (1/4th or more of a whole egg) in the last three months? (Mark one that applies).

1) three or more times a week

2) once or twice a week

3) less than once a week

Supplementary Table 1. Grading of symptoms.

	1 (mild)	2 (moderate)	3 (severe)
Skin	Localized urticaria,	Generalized urticaria,	
	exanthema, wheal,	exanthema, wheal,	-
	pruritus	pruritus	
	Swollen eyelid or lip	Swollen face	-
Gastrointestinal tract	Pruritus of the throat		
	or oral cavity	Throat pain	-
	Mild abdominal pain	Moderate abdominal pain	Cramps
	Nausea, emesis,	Recurrent emesis,	Continuous
	diarrhea	diarrhea	emesis, loss of bowel control
Respiratory tract	Intermittent cough,		Persistent cough,
	nasal congestion,	Repetitive cough	hoarseness,
	sneezing, rhinorrhea		“barky” cough

			Audible wheezing, dyspnea, cyanosis, oxygen saturation of <92%, swallowing or speaking difficulties, throat tightness, respiratory arrest
	-	Chest tightness, wheezing through a stethoscope	
Cardiovascular	-	Pale face, mild hypotension, tachycardia (increase of >15 beats/min)	Hypotension, dysrhythmia, severe bradycardia, cardiac arrest
Neurological	Change in activity level, tiredness	“Light-headedness,” feelings of “impending doom,” somnolence, headache	Confusion, loss of consciousness, incontinence

The severity score should be based on the most affected organ system. To help patients accurately describe their symptoms, the questionnaire was accompanied by a revised version.

Supplementary Table 2. Baseline profile of patients.

	Total	Egg	Cow's milk	Wheat
	n = 108	n = 61	n = 30	n = 17
Age at study (years)	12.9	12.9	13.4	12.9
	(12-16)	(11-15)	(12-16)	(11-16)
Age at OIT start (years)	8.4	8.0	8.5	8.9
	(7-10)	(7-10)	(7-10)	(7-11)
Sex (male:female)	69:39	40:21	18:12	11:6
Rush/slow OIT	71/37	39/22	19/11	13/4
Time from OIT start to a	0.8	0.7	0.9	1.2
2-week SU (years)	(0.5-1.4)	(0.5-1.0)	(0.6-1.4)	(0.5-1.7)
Time from a 2-week SU	3.6	3.8	3.7	2.9
to study (years)	(2.9-4.6)	(3.0-4.6)	(3.2-4.8)	(2.3-3.9)
Total IgE at baseline	1015	941	1056	1200
OFC (kU _A /L)	(437-2070)	(455-1700)	(414-2233)	(651-3465)
Antigen-specific IgE at		18.8	18.1	70.0
baseline OFC (kU _A /L)		(9-31)	(8-38)	(18-101 [†])
Threshold dose at		918	202	83

baseline	OFC	(mg of	(306-1995)	(93-467)	(70-359)
protein)					

† Values >100 were expressed as 10¹.

Data are expressed as median values, with 25%-75% interquartile range provided in parentheses. OIT, oral immunotherapy; SU, sustained unresponsiveness; IgE, immunoglobulin E; OFC, oral food challenge; kU_A/L, kilounits per liter.

Supplementary Table 3. Comparison between the characteristics of patients who experienced symptoms after a 2-week SU and those who did not.

		Symptoms	No symptoms	<i>P</i>
Egg		n=44	n=17	
	AD	5 (11)	2 (12)	0.637
	BA	5 (11)	3 (18)	0.393
Baseline	Total IgE (kU _A /L)	1060 (441-1625)	887 (487-1690)	0.962
	Egg White sIgE (kU _A /L)	18.6 (7-32)	18.8 (9-30)	0.723
	Ovomucoid sIgE (kU _A /L)	17.2 (3-33)	16.5 (7-26)	0.838
	Total IgE (kU _A /L)	740 (430-1525)	789 (512-2060)	0.506
After				
SU [†]	Egg White sIgE (kU _A /L)	9.8 (3-20)	7.5 (3-16)	0.743
	Ovomucoid sIgE (kU _A /L)	5.3 (1-14)	5.5 (3-15)	0.470
Cow's milk		n=17	n=13	
	AD	12 (71)	4 (31)	0.035

	BA	10 (59)	6 (46)	0.374
Baseline	Total IgE (kU _A /L)	1140	1415	0.621
		(403-2055)	(338-2495)	
	Cow's milk sIgE (kU _A /L)	19.4 (11-53)	12.4 (5-25)	0.133
After	Total IgE (kU _A /L)	1230	1680	0.744
SU		(598-2335)	(249-2602)	
	Cow's milk sIgE (kU _A /L) [‡]	10.4 (6-14)	6.3 (3-20)	0.419
	Wheat	n=10	n=7	
	AD	1 (10)	2 (29)	0.360
	BA	2 (20)	1 (14)	0.640
Baseline	Total IgE (kU _A /L)	1495	2230	0.696
		(709-3002)	(1018-6895)	
	Wheat sIgE (kU _A /L)	60.2 (17-101)	61 (18-101 [†])	0.489
	ω5 sIgE (kU _A /L) [§]	2.6 (1-13)	7.1 (3-12)	0.522
After	Total IgE (kU _A /L)	1294	2080	0.845
SU		(638-4492)	(970-6010)	
	Wheat sIgE (kU _A /L)	42.1 (22-51)	14 (10-101)	0.283

		††	
ω5 sIgE (kU _A /L) [¶]	0.5 (0.3-3)	1.4 (0.8-5)	0.957

† data of 1 patient was missing.

‡ data of 1 patient was missing.

§ data of 6 patients was missing.

¶ data of 1 patient was missing.

†† Values >100 were expressed as 101.

Values are reported as n (%) or medians (IQRs)

The Mann-Whitney test was applied for data expressed as medians (IQRs) and chi-square or Fisher's exact test were applied for data express as n (%).

Statistically significant *p* values (<0.05) are in bold.

SU, sustained unresponsiveness; AD, atopic dermatitis; BA, bronchial asthma; sIgE, specific immunoglobulin E; kU_A/L, kilounits per liter.

Total IgE and antigen specific IgE at baseline and after a 2-week SU of each antigen showed no significant difference between patients who experienced symptoms after a 2-week SU and those who did not. The morbidity of AD in patients with cow's milk allergy was significantly higher in patients who experienced symptoms after a 2-week SU than those who did not. (71% vs 31%, *P*=0.035). It is unknown whether atopic

dermatitis influenced the outcome after a 2-week SU, because information about the condition of atopic dermatitis upon induction of symptoms were not included in the questionnaire.

Supplementary Table 4. Comparisons of symptoms after a 2-week SU between patients who underwent slow OIT and patients who underwent rush OIT.

	Rush OIT	Slow OIT	<i>P</i>
Egg	n=39	n=22	
Experienced symptoms	10 (26)	7 (32)	0.605
Number of symptoms	0 (0-1)	0 (0-1)	0.551
Moderate or severe symptoms	4 (10)	3 (14)	0.495
Cow's milk	n=19	n=11	
Experienced symptoms	10 (53)	7 (64)	0.421
Number of symptoms	0 (0-1)	1 (0-1)	0.672
Moderate or severe symptoms	6 (32)	6 (55)	0.216
Wheat	n=13	n=4	
Experienced symptoms	9	1	0.162
Number of symptoms	1 (0-1.5)	0 (0-0.75)	0.178
Moderate or severe symptoms	5 (38)	0 (0)	0.208

Values are reported as n (%) or medians (IQRs)

The Mann-Whitney test was applied for data expressed as medians (IQRs) and chi-square or Fisher's exact test were applied for data expressed as n (%).

OIT, oral immunotherapy

Co-factors with induced symptoms (exercise, illness, fatigue, hay fever, ate more than usual) for each antigen showed no significant difference between patients who underwent slow OIT and patients who underwent rush OIT.

Supplementary Table 5. Circumstances at the onset of symptoms.

	Mild symptoms (n=20)	Moderate or severe symptoms (n=24)	<i>P</i>
During exercise	4 (20) [§]	16 (67) [¶]	0.002
Feeling tired	8 (40)	6 (25)	0.287
Ate more than usual	5 (25)	5 (21)	0.743
Hay fever	4 (20)	3 (13)	0.498
Had a cold	2 (10)	4 (17)	0.521
Bathing	0 (0)	1 (4)	0.356
Premenstrual	0 (0)	1 (4)	0.356
Nothing in particular	6 (30)	6 (25)	0.711

χ^2 test or Fisher's exact test were conducted for comparing co-factors in each antigen between mild symptoms and moderate or severe symptoms.

§Marathon or running in 2 patients, playing tag and jumping rope in 1 patient each.

¶Marathon or running in 7 patients, playing tag and dodge ball in 2 patients each, jumping rope, basketball, soccer, walking, and cycling in 1 patient each.

Thirty-two (73%) of the patients who experienced symptoms had co-factors.

Some patients experienced symptoms under multiple situations, e.g., exercise and feeling tired. Therefore, the sum for each situation exceeded 44. No one answered “took medicine” or “scar in the oral cavity.”

All of the patients who experienced exercised-triggered symptoms after a 2-week SU did not experience them during oral immunotherapy.

Supplementary Table 6. Co-factors in patients who experienced symptoms after a 2-week SU.

Co-factor	Egg (n=17)	Cow's milk (n=17)	Wheat (n=10)
Exercise	3 (18)	10 (59)	7 (70)
Illness	2 (12)	2 (12)	8 (80)
Fatigue	6 (35)	6 (35)	2 (20)
Hay fever	4 (24)	2 (12)	2 (20)
Ate more than usual	2 (12)	4 (24)	6 (60)

Values are reported as n (%)

SU, sustained unresponsiveness.

χ^2 test or Fisher's exact test were conducted for comparing co-factors of symptoms for each antigen. *P* value on multiple comparisons was expressed with Bonferroni corrected significance level.

Exercise was a considerably common co-factor in patients with cow's milk allergy

(59%) and wheat allergy (70%) than those with egg allergy (18%) ($P=0.048$ and

P=0.003 respectively), and illness was more common in patients with wheat allergy (80%) than in patients with egg allergy (12%) and patients with cow's milk allergy (12%) (p=0.003, respectively). Fatigue, hay fever and "ate more than usual" co-factors showed no significant differences between each antigen.

Supplementary Table 7. Frequency of ingesting food allergens of interest during the 3 months before the survey.

Form of the food allergen	Frequency of ingestion	Food allergen		
		Egg	Milk	Wheat
		(n = 61)	(n = 30)	(n = 17)[†]
Processed	≥3 times per week	11 (18)	16 (53)	11 (65)
	1–2 times per week	12 (20)	4 (13)	3 (18)
	<1 time per week	38 (62)	10 (33)	2 (12)
Unprocessed‡	≥3 times per week	48 (79)	23 (77)	15 (88)
	1–2 times per week	9 (15)	5 (17)	1 (6)
	<1 time per week	4 (7)	2 (7)	1 (6)

[†]The details of one patient with wheat allergy are unknown.

‡Ingesting unprocessed forms was defined as eating ≥25% of the target dose.

362 patients ≥ 6 years of age (145 with egg allergy, 159 with cow's milk allergy, and 58 with wheat allergy) received OIT aimed at full dose



111 continued OIT

79 withdrew from OIT

25 had an unclear clinical course

147 patients acquired a 2-week SU

15 needed >2 years for acquiring a 2-week SU

2 were within 1 year from a 2-week SU

130 patients (75 with egg allergy, 35 with cow's milk allergy, and 20 with wheat allergy) were mailed a questionnaire

108 patients who answered the questionnaire were analyzed: 61 (81%) with egg allergy, 30 (86%) with cow's milk allergy, and 17 (85%) with wheat allergy