

Long-term prognosis after low-dose peanut challenge for patients with history of anaphylaxis

Nobuko Akamatsu¹, Ken-ichi Nagakura¹, Sakura Sato¹, Noriyuki Yanagida¹, and Motohiro Ebisawa¹

¹Kokuritsu Byoin Kiko Sagamihara Byoin

March 31, 2023

Long-term prognosis after low-dose peanut challenge for patients with history of anaphylaxis

Nobuko Akamatsu, MD, PhD^{1,2}, Ken-ichi Nagakura, MD, PhD¹, Sakura Sato, MD³, Noriyuki Yanagida, MD, PhD^{1,3,*}, Motohiro Ebisawa, MD, PhD³

¹Department of Pediatrics, National Hospital Organization, Sagamihara National Hospital, Kanagawa, Japan

²Department of Pediatrics and Adolescent Medicine, Tokyo Medical University Hospital, Tokyo, Japan

³Clinical Research Center for Allergy and Rheumatology, National Hospital Organization, Sagamihara National Hospital, Kanagawa, Japan

Running title: Prognosis after low-dose peanut challenge

***Corresponding author:** Noriyuki Yanagida, MD, PhD

Department of Pediatrics, National Hospital Organization, Sagamihara National Hospital,
18-1, Sakuradai, Minami-ku, Sagamihara, Kanagawa 252-0392, Japan

E-mail: yana@foodallergy.jp

Word count: 1190

Number of figures: 2 **Number of tables:** 0

Conflict of interest: Motohiro Ebisawa and Sakura Sato have received speaker honoraria from Viatrix. All other authors declare that they have no conflicts of interest.

Financial support: This paper has not received any financial support.

Keywords : low-dose oral food challenge, peanut, food allergy, low-dose-tolerant, tolerant, pediatric, anaphylaxis

To the Editor,

Peanuts cause severe allergic reactions, and only 20% of peanut-allergic patients acquire tolerance.¹ Peanut oral food challenge (OFC) has a high risk of severe symptoms such as anaphylaxis, and OFC is avoided in children with an immediate history, especially with a history of anaphylaxis.¹ Peanut-allergic patients and their guardians have a lower quality of life because of worry that anaphylaxis may occur at any time.² Low-dose OFC may be useful to manage children with a history of anaphylaxis,³ but it has not been used

to evaluate prognosis. This study investigated long-term prognosis after low-dose peanut OFC for patients with a history of immediate reactions, including anaphylaxis.

We retrospectively analyzed participants with a history of immediate symptoms due to peanut ingestion, who received baseline low-dose OFC with 133 mg of peanut protein from August 2013–August 2017 at Sagami-hara National Hospital (Figure 1), and evaluated two-year tolerance acquisition.

We defined tolerance as passing an OFC with 795 mg protein (medium-dose OFC) and ingesting more than 795 mg protein without symptoms at home; consuming this dose enables cessation of strict avoidance in daily life. We defined baseline low-dose OFC negative patients as the low-dose-tolerant group and positive patients as the low-dose-reactive group. The low-dose-tolerant group was instructed to consume 133 mg at home twice a week. Then, based on guardians' preference, patients received a medium-dose OFC every 6 months or gradually increased peanut ingestion to 795 mg at home under a physician's direction. The low-dose-reactive group completely avoided peanuts and received low-dose OFC every 6 months. When the low-dose-reactive group passed low-dose OFC, they received medium-dose OFC (Supplementary Figure 1).

Anaphylaxis was defined according to the World Allergy Organization Guidelines.⁴ OFC protocol is described in the supplementary information.⁵ The percentage of patients who acquired tolerance within two years was estimated using Kaplan-Meier curves. The co-factors for tolerance acquisition were analyzed using Cox regression analysis. Multivariate analysis was performed on the results of low-dose OFC, total IgE, peanut-specific IgE (Pn-sIgE), and history of peanut-related anaphylaxis. SPSS (version 27.0; SPSS Inc., Chicago, IL) was used for all analyses; $p < 0.05$ was considered statistically significant. The Ethics Committee of The Sagami-hara National Hospital (2016-015) approved the study according to the Helsinki Declaration. Written informed consent was obtained from all patients' guardians.

Fifty-three patients (median age, 7.1 years) were enrolled; 43% had a history of anaphylaxis. The median Pn-sIgE level was 20.7 (interquartile range 7.0–57.5) kU_A/L . The median Ara h 2-specific IgE level was 10.4 (4.98–28.3) kU_A/L . The median thresholds of past immediate symptoms were 26.6 mg (13.3–133) (Supplementary Table 1).

Twenty-one patients (40%) passed the low-dose OFC and were defined as the low-dose-tolerant group, and 32 (60%) failed and were defined as the low-dose-reactive group (Supplementary Table 1); 35% of patients with a history of anaphylaxis passed the low-dose OFC. During low-dose OFC, oral mucosal symptoms were most common (72%), then gastrointestinal (63%) and respiratory symptoms (63%). Three patients required intramuscular adrenaline (Supplementary Table 2). When the low-dose-tolerant patients ingested low-dose peanuts at home, six (29%) had mild reactions like oral and throat discomfort; most reactions resolved naturally and did not require medical attention.

In the low-dose-tolerant group, 13 patients (62%) acquired tolerance within 2 years, including five patients with a history of anaphylaxis, whereas in the low-dose-reactive group, one patient (3%), with no history of anaphylaxis, acquired tolerance ($p < 0.001$) (Figure 2). In the low-dose-reactive group, 6% of patients passed low-dose OFC within two years.

The predictive factors of failure to acquire tolerance have been positive reactions to low-dose OFC (crude hazard ratios of total IgE, Pn-sIgE: 0.37 [95% confidence interval 0.15–0.94, $p = 0.04$], and log (Pn-sIgE) 2.23 [1.01–4.92], $p = 0.048$) (Supplementary Table 3). In 23 patients with a history of anaphylaxis, five (22%) acquired tolerance. In 30 patients with no history of anaphylaxis, nine (30%) acquired tolerance. History of anaphylaxis did not significantly affect tolerance acquisition (Supplementary Figure 2).

This is the first report showing that low-dose OFC can be undergone relatively safely with tolerance acquisition in some peanut-allergic patients, including patients with a history of anaphylaxis. Patients with a history of anaphylaxis have a lower quality of life because of worry that anaphylaxis may occur at any time.⁶ Therefore, these results are significant because if patients realize that low-dose peanuts can be ingested, complete avoidance becomes unnecessary, and tolerance acquisition could be assessed. The low-dose-reactive group was less likely to develop tolerance and required careful follow-up to prevent accidental ingestion.

Previous studies of long-term prognosis after peanut OFC excluded patients with a history of anaphylaxis,¹ therefore, their tolerance acquisition based on the results of OFC was unknown. In our current study, more than half of patients in low-dose-tolerant groups acquired tolerance within two years, even those with a history of anaphylaxis. Furthermore, one-fifth of patients with a history of anaphylaxis tolerated peanuts, and there was no significant difference between patients with and without a history of anaphylaxis in acquiring tolerance. Therefore, passing low-dose OFC could be considered to assess tolerance acquisition, regardless of the history of anaphylaxis.

It has been reported that peanut OFC is high risk because it often causes anaphylaxis and other serious symptoms.¹ In the previous studies of peanut OFC, subjects have no history of anaphylaxis or as few as 10%, while this study had 40%, but the occurrence of anaphylaxis in OFC was comparable.^{1,7} Furthermore, there is a report of a group of subjects, 83% of whom had a history of anaphylaxis, and all patients reacted with anaphylaxis in OFC.⁸ It has been reported that the incidence of anaphylaxis with OFC was higher with progression up to the total OFC ingested.⁷ Therefore this study suggests that low-dose OFC is relatively safe in patients with a history of anaphylaxis.

Recently, some trials of low-dose oral immunotherapy showed that ingesting low-dose peanuts (133-300 mg) could induce immunological changes and allow the intake of larger amounts.⁹ Similarly, daily ingestion of low-dose wheat is effective in increasing consumption dose and preventing accidental symptoms, even in patients with a history of anaphylaxis.¹⁰ Therefore, twice weekly ingestion of 133 mg in the low-dose-tolerant group may yield oral tolerance. In addition, few serious reactions were observed in the low-dose-tolerant group during the subsequent at-home dose escalation in this study.

This study has several limitations. First, 33 subjects were excluded because their two-year course could not be tracked. Although the excluded and included patients' backgrounds were similar (Supplementary Table 4), predictors of tolerance acquisition, such as anaphylaxis may be different with more subjects. Second, there was a lack of information on several points. Although at-home intake methods were unified, the frequency of home peanut intake and adherence was unknown. Additionally, we couldn't confirm thresholds of past immediate symptoms in 25% of subjects. However, the median thresholds were 26.6 mg in 75% of subjects who were able to assess the threshold. Therefore, we assume that thresholds in the remaining children were similar.

For peanut-allergic patients with a history of anaphylaxis, low-dose OFC is relatively safe and effective in the assessment of tolerance acquisition. Low-dose OFC results may effectively stratify peanut-allergic patients with anaphylaxis history with good and poor tolerance acquisition to select optimal management plans.

Nobuko Akamatsu, MD, PhD^{1,2}, Ken-ichi Nagakura, MD, PhD¹, Sakura Sato, MD³, Noriyuki Yanagida, MD, PhD^{1,3}, Motohiro Ebisawa, MD, PhD³,

¹Department of Pediatrics, National Hospital Organization, Sagamihara National Hospital, Kanagawa, Japan

²Department of Pediatrics and Adolescent Medicine, Tokyo Medical University Hospital, Tokyo, Japan

³Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, Kanagawa, Japan

Author Contributions:

Nobuko Akamatsu: Data curation (lead), Formal analysis (lead), Writing – original draft (lead); Ken-ichi Nagakura: Writing – original draft (lead), Writing - review & editing (lead); Sakura Sato: Methodology (lead), Writing – original draft (supporting), Writing - review & editing (supporting); Noriyuki Yanagida: Conceptualization (lead), Methodology (lead), Writing – original draft (supporting), Writing - review & editing (supporting); Motohiro Ebisawa: Conceptualization (lead), Supervision (lead), Project administration (lead), Methodology (equal), Writing - review & editing (lead)

Acknowledgments:

We thank all children and parents who participated in this study. We also thank all medical staff of the Sagamihara National Hospital.

Key Message:

Low-dose OFC can effective in assessment of tolerance acquisition in peanut-allergic patients, with or without a history of anaphylaxis. Low-dose OFC results can be used to select optimal management plans in peanut-allergic patients.

Ethical Approval:

The Ethics Committee of The National Sagamihara Hospital (2016-015) approved the study according to the Helsinki Declaration. Written informed consent was obtained from all patients' guardians.

Data Availability:

The data that support the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. Peters RL, Allen KJ, Dharmage SC, et al. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: A population-based assessment. *J Allergy Clin Immunol* 2015;135:1257–1266 e1-2.
2. Graham F, Caubet JC, Eigenmann PA. Can my child with IgE-mediated peanut allergy introduce foods labeled with “may contain traces”? *Pediatr Allergy Immunol* 2020;6:601-607.
3. Yanagida N, Okada Y, Sato S, Ebisawa M. New approach for food allergy management using low-dose oral food challenges and low-dose oral immunotherapies. *Allergol Int.* 2016;65:135-140.
4. Simons FER, Arduzzo LRF, Bilò MB, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J* 2011;4:13-37.
5. Ebisawa M, Ito K, Fujisawa T. Japanese guidelines for food allergy 2020. *Allergol Int* 2020;69:370-386.
6. Midun E, Radulovic S, Brough H, Caubet J.C Recent advances in the management of nut allergy. *World Allergy Organ J* 2021;14:100491.
7. Arkwright PD, MacMahon J, Koplin J, et al. Severity and threshold of peanut reactivity during hospital-based open oral food challenges: An international multicenter survey. *Pediatr Allergy Immunol* 2018;29:754-761.
8. Reier-Nilsen T, Michelsen MM, Lødrup Carlsen KC, et al. Predicting reactivity threshold in children with anaphylaxis to peanut. *Clin Exp Allergy* 2018 Apr; 48:415-423.
9. Nagakura KI, Yanagida N, Sato S, et al. Low-dose oral immunotherapy for children with anaphylactic peanut allergy in Japan. *Pediatr Allergy Immunol* 2018;29:512-518.
10. Nagakura KI, Yanagida N, Miura Y, et al. Long-term follow-up of fixed low-dose oral immunotherapy for children with wheat-induced anaphylaxis. *J Allergy Clin Immunol Pract* 2021;7:1117-1119.e2.

Figure legends

Figure 1. Study design and enrolled subjects.

Participants were patients with a history of immediate reactions due to peanut ingestion, who underwent baseline low-dose OFC. Participants without laboratory or clinical information after the baseline low-dose OFC were excluded. Tolerance acquisition for two years after baseline low-dose OFC was assessed. Twenty-one patients (40%) passed the low-dose OFC and were defined as the low-dose-tolerant group; thirty-two children (60%) failed the low-dose OFC and were defined as the low-dose-reactive group.

Abbreviations: OFC, oral food challenge

Figure 2. Tolerance acquisition rate based on the low-dose OFC result after two years.

The percentage of subjects who acquired 795 mg tolerance was estimated using Kaplan-Meier curves, and *p* -values were calculated using a log-rank test to compare the tolerance rate between low-dose-tolerant and low-dose-reactive groups; 62% of the low-dose-tolerant group took 795 mg of peanut protein, and 3% of the low-dose-reactive group took 795 mg peanut protein. The results of the low-dose OFC showed that there was a significant difference in the 795mg-tolerance (*p* -value <0.001).

Abbreviations: OFC, oral food challenge

