Threshold and safe ingestion dose among infants sensitized to hen's egg

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i. Conflict of interest statement

Motohiro Ebisawa has received lecture fees from Mylan EPD. Sato Sakura has received lecture fees from Mylan EPD. The other authors declare that they have no conflicts of interest.

Ethical Approval and Trial Registration Statements

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Sagamihara National Hospital (approval number: 2013-20130318017). Written informed consent was obtained from the guardians of all patients before each oral food challenge.

ii. Financial support

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iii. Main text

To the Editor,

Generally, hen's egg is recommended to be introduced in infancy.[1] However, infants who have food allergies (FA) other than egg allergy (EA) or eczema are sometimes found to be sensitized to egg before introduction of egg, and these infants are often advised to completely avoid egg consumption. Since some infants do not have true EA, evaluating whether these patients can ingest eggs is crucial. To date, no method has been established for initiating egg consumption in sensitized infants. Oral food challenge (OFC) is the gold standard for the diagnosis of FA and is also critical for patient management.[2] The 2020 Japanese guidelines for food allergy recommend stepwise OFCs for the diagnosis and management of FA.[3] We have previously reported that stepwise OFCs are useful and safe for patients suspected with EA.[4,5]However, most patients in the study had a history of immediate reaction to eggs and were aged > 1 year. There have been no reports regarding stepwise OFCs in infants without a history of previous consumption of egg who were instructed to completely avoid egg consumption owing to sensitization (egg-sensitized infants). This study aimed to evaluate the usefulness of stepwise OFCs in egg-sensitized infants for introducing egg in order to determine the threshold and safe ingestion dose of egg.

We retrospectively examined infants who were found to be sensitized to egg after blood tests performed to assess eczema or FA other than EA who underwent stepwise OFCs between May 2016 and December 2018. Stepwise OFCs were performed starting with a low dose (containing 1/25 of a heated whole egg [HE], 250 mg of egg protein). After the low-dose OFC, we performed an OFC containing 1/8 of a HE (775–769 mg of egg protein, medium-dose OFC) and later 1/2 of a HE (3076–3100 mg of egg protein, high-dose OFC) if the results of each previous OFC were negative. Patients who passed the high-dose OFC received an OFC with scrambled egg containing a whole egg (6591.5 mg of egg protein, full-dose OFC) or were instructed to increase egg consumption up to one HE at home. If the result of the low-dose OFC was positive, the patients were advised to completely avoid egg consumption. The patients who failed medium-, high-, or full-dose OFCs were advised to consume the amount of egg that they could safely ingest (e.g., a seasoned powder, bread or processed meat, and a donut or slice of cake for positive medium-, high-, and full-dose OFC patients, respectively, Figure S1). The challenge foods used in this study are shown in Table S1. Serum specific immunoglobulin E to egg white (EW-sIgE) and ovomucoid (OVM-sIgE) levels were measured within 3 months of the low-dose OFC. Sensitization to egg was defined as an EW-sIgE level > 0.10 kU_A/L.

Of the 148 egg-sensitized infants who underwent low-dose OFC, 61 were excluded because they did not meet the eligibility criteria (Figure 1). The median OVM-sIgE level of the patients included in this study was significantly higher than that of those who were excluded (Table S2). The median age was 9.9 (interquartile range, 8.9–10.9) months, and the median EW-sIgE and OVM-sIgE levels were 18.0 and 0.99 kU_A/L, respectively.

Among 87 egg-sensitized infants, 12 failed the low-dose OFC and 9 and 8 failed medium- and high-dose OFC, respectively. Of the 58 patients who passed the high-dose OFC, 32 underwent full-dose OFC and 26 were instructed to increase egg consumption at home. Two patients failed the full-dose OFC and 56 were able to ingest a full dose (Figure 1). Thus, 64% (56/87) of egg-sensitized infants did not have an allergic reaction to egg. Of the 31 patients allergic to egg, the threshold dose was [?]1/25 of a HE for 39% (12/31), >1/25–1/8 for 29% (9/31), >1/8–1/2 for 26% (8/31), and >1/2–1 for 6% (2/31) (Figure 2). Therefore, 14% (12/87) of egg-sensitized infants needed to continue to completely avoid egg consumption. The median time between the low- and full-dose OFC was 10.8 months. The median time between the low-dose OFC and the date when the patients were able to ingest a full dose was 16.1 months. Probability curves based on the results of these OFCs are shown in Figure 3. The probability curves show that >50% of egg-sensitized infants would pass a low-dose OFC even if their EW-sIgE or OVM-sIgE levels exceeded 100 kU_A/L. The symptoms and treatment during OFCs are described in Table S3. There were no severe symptoms in the medium- and full-dose OFCs. However, one patient received intramuscular adrenaline during the low-dose OFC because of vomiting and appearance of a pale face. In the high-dose OFC, one patient developed a severe reaction (barking cough).

This study revealed that the rate of positive reactions to stepwise OFCs for egg-sensitized infants was not

high, and stepwise OFCs clarified the threshold and safe ingestion dose of eggs in these infants. Since the rate of positive reactions to low-dose and medium-dose OFCs was lower in egg-sensitized infants than in patients with a history of immediate reactions to egg[4] (14% vs. 21% and 12% vs. 14%, respectively), stepwise OFCs seem to be safer in egg-sensitized infants than in those with immediate reactions to egg. In addition, >50% of egg-sensitized infants passed low-dose OFCs even if their EW-sIgE or OVM-sIgE levels exceeded 100 kU_A/L. Therefore, even if infants have relatively high levels of EW-sIgE or OVM-sIgE, performing OFCs from a low initial dose may be considered.

Regarding the threshold dose in egg-sensitized infants, a previous study reported that 33% reacted to a boiled egg white OFC equivalent to one half of an egg.[6] In our study, the proportion of egg-sensitized infants who reacted to [?]1/2 of a HE was similar (33%, 29/87). However, by performing stepwise OFCs, 59% (17/29) could ingest [?]1/8 of a HE. For patients with EA, avoiding complete elimination of eggs may improve their prognosis[7,8] and quality of life (QOL).[9] Therefore, stepwise OFCs appear to be beneficial for egg-sensitized infants.

This study had some limitations. First, OFCs were not double-blind placebo-controlled. However, since most symptoms induced during OFCs were objective, the number of false-positive OFCs was considered to be low. Second, a few patients may have achieved tolerance during intervals between OFCs. However, since only 30% of Japanese EA patients achieve tolerance by 3 years of age,[10] the influence of intervals between OFCs is likely minimal. Third, approximately 40% of the egg-sensitized infants were excluded because of not undergoing stepwise OFCs, and the median OVM-sIgE level of these patients was significantly lower than that of those who were included. Therefore, our study may have overestimated the rate of positive reactions to stepwise OFCs for egg-sensitized infants.

In conclusion, stepwise OFCs appeared to be relatively safe for the introduction of egg in egg-sensitized infants. We found that only a small number of these infants required complete avoidance of eggs and that the majority of them were able to ingest a whole egg in the form of scrambled egg. We expect that stepwise OFCs will help improve the management of egg-sensitized infants who have completely avoided egg consumption.

iv. Keywords

threshold, oral food challenge, egg, food allergy, stepwise, sensitization, pediatric

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vi. Impact statement

Stepwise oral food challenges starting from a low dose are effective in determining the threshold and safe ingestion dose for infants who have completely avoided egg consumption owing to sensitization.

vii. References

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viii. Tables (each table complete with title and footnotes)

None

ix. Figure legends

Figure 1. Enrollment of subjects.

Stepwise oral food challenges (low-dose, medium-dose, high-dose, and full-dose) performed. After passing the high-dose OFC, 32 patients underwent full-dose OFC and 26 were instructed to increase egg consumption at home.

Abbreviation: OFC, oral food challenge

Figure 2. Percentage of egg-sensitized patients who had an allergic reaction to egg (A) and the threshold dose of egg in these patients (B).

Figure 3. Probability curve for failing the stepwise oral food challenge (OFC) at a given sIgE level against egg white (A) and ovomucoid (B).

The probability curves were constructed using results of multinomial logistic regression analysis.

Abbreviation: OFC, oral food challenge; sIgE, specific IgE

Author Contributions

Masatoshi Mitomori: Conceptualization (equal); data curation (lead); formal analysis (lead); investigation (lead); methodology (lead); project administration (lead); resources (lead); software (equal); supervision (equal); validation (supporting); visualization (supporting); writing-original draft (lead); writing-review and editing (equal). Noriyuki Yanagida: Conceptualization (lead); data curation (supporting); formal analysis (supporting); funding acquisition (lead);investigation (equal); methodology (equal); project administration (equal); resources (equal); software (equal); supervision (lead); validation (lead); visualization (lead); writing-original draft (equal); writing -review and editing (lead). Makoto Nishino: Conceptualization (supporting); data curation (supporting); formal analysis (supporting); investigation (equal); methodology (supporting);

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Key Message

This study showed that only a small number of the infants for whom egg consumption was completely avoided owing to sensitization needed complete avoidance of eggs, and the majority of them were able to ingest a whole egg in the form of scrambled egg. Stepwise oral food challenges starting from a low dose are relatively safe to introduce egg and effective in determining the threshold and safe ingestion dose for such infants.