

A good QoL is beneficial for outgrowing egg allergy

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Abstract

Background: Safely liberalizing the diet to include an allergenic food may accelerate resolution of food allergy. The outcome of liberalization, however, varies among patients. Methods: We conducted a prospective observational study to identify factors associated with outcome for egg allergy 1 year after oral food challenge (OFC). We enrolled children < 72 months-old who had egg allergy and underwent OFC for determination of the safe intake quantity of egg allergen. At enrollment, each child's clinical background was recorded. The Food Allergy Quality of Life Questionnaire–Parent Form (FAQLQ–PF) was administered to the caregivers to assess their children's QoL. Dietary advice based on the OFC result was then provided to support safe consumption of eggs. At 1 year after OFC, the quantity of egg each child safely consumed in daily life was surveyed. We classified the egg allergy outcome as Outgrowing (Group O) if the quantity increased during the 1 year, or as Non-outgrowing (Group N) if it did not. Factors associated with the outcome were investigated by multivariate logistic regression analysis. Results: A total of 93 children were enrolled, and after 1 year 57 finished in Group O and 36 in Group N. The mean FAQLQ–PF score at baseline was significantly lower (i.e., better QoL) in group O than in group N. Multivariate logistic regression analysis identified comorbid asthma, comorbid atopic dermatitis and a poor QoL as factors predicting an unfavorable outcome. Conclusion: QoL may affect food allergy outcome. Intervention focusing on QoL may promote outgrowing food allergies.

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Abstract

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Results : A total of 93 children were enrolled, and after 1 year 57 finished in Group O and 36 in Group N. The mean FAQLQ-PF score at baseline was significantly lower (i.e., better QoL) in group O than in group N. Multivariate logistic regression analysis identified comorbid asthma, comorbid atopic dermatitis and a poor QoL as factors predicting an unfavorable outcome.

Conclusion : QoL may affect food allergy outcome. Intervention focusing on QoL may promote outgrowing food allergies. (249 words)

Keywords

food hypersensitivity, egg hypersensitivity, quality of life

Key Message

Factors associated with natural outgrowing of food allergies are still to be clarified. In this study we investigated factors associated with the outcome of egg allergy 1 year after oral food challenge, focusing on the quality of life (QoL). The children's baseline QoL was evaluated using the Food Allergy QoL Questionnaire-Parent Form. Multivariate logistic regression analysis identified a good baseline QoL as a factor predicting increased intake of egg in daily life. Intervention focusing on children's baseline QoL may promote their outgrowing food allergies.

Introduction

Food allergies pose a significant public health concern due to their increasing incidence in infants and children in the last few decades worldwide, and particularly in industrialized countries.^{1,2} Emerging treatments, including oral and epicutaneous immunotherapy for food allergies, are still considered investigational because of safety concerns and uncertain long-term efficacy.³ Thus, the conventional management for patients with food allergies remains strict avoidance of the allergenic food and being prepared for any adverse reactions from unintended food ingestion.⁴ Since many children with a food allergy outgrow the disease,⁵ a practical strategy is to wait for "the day of resolution" by observing the current management principle.

Recently, however, observations that dietary inclusion of baked hen's egg or cow's milk accelerated resolution of egg or milk allergy have attracted attention.^{6–11} Although evidence for the potential of baked products to promote outgrowing the disease still awaits well-designed randomized controlled studies,¹² partial liberalization of a child's diet may be beneficial due to the improved quality of life and nutritional status.¹³

To ascertain the safety of implementing such diet liberalization, it is necessary to first perform oral food challenge (OFC) to determine the quantity of food that a patient can consume without triggering an allergic reaction. In the baked egg/milk diet, a patient must pass an OFC with baked egg containing 1 whole egg^{6,7} or baked milk containing 0.5–1.3 g of milk protein (equivalent to 15–40 mL of milk).^{8–11} The allergenicity of the baked products is assumed to be reduced, but children who nevertheless react to that quantity of allergen should completely avoid the food. However, they may safely consume a lesser amount of the allergen—such as 10 g of butter (equivalent to 2.9 mL of milk)—than that in the recommended baked diet.¹⁴ In Japan, the national health insurance covers OFC testing, and guidelines¹⁵ provide dietary guidance on how to consume a small, safe amount of an allergenic food based on the results of readily available OFC using a low dose of allergen. Dietary liberalization is now increasingly recommended and performed in pediatric practice in Japan.

This new approach to management of food allergy seems to be beneficial to the patients. The natural course of food allergy, however, varies widely from tolerance to persistence,⁵ which may affect results of the management. Reported predictors of persistence of a food allergy in the natural course include a history of anaphylaxis, the presence of another food allergy, comorbid allergic diseases such as asthma, reaction to even a low dose, elevated allergen-specific IgE (sIgE) levels, etc.^{5,16,17} In addition, it was reported that mothers with a high level of anxiety, even after a negative OFC for their child, were reluctant to reintroduce the offending food.¹⁸ Psychological factors may affect the natural history of food allergy.

We therefore designed and conducted the IQ-OFA (Impact of QoL on Outgrowing Food Allergy) study to identify factors that are associated with natural outgrowing of food allergies in children, with special focus on the QoL. In the current study, we aimed to investigate factors related to successful reintroduction of egg to the diet of egg-allergic children after OFC-based dietary advice. Our findings may contribute to children's ability to naturally outgrow food allergies.

Methods

Our IQ-OFA study enrolled children aged less than 13 years with food allergy who had undergone OFC at National Hospital Organization Mie National Hospital, a tertiary hospital for pediatric allergies. In our current study, we focused on children younger than 72 months of age who had egg allergy, since that is the most prevalent pediatric food allergy in Japan¹⁵ and most resolve by 72 months.¹⁶

OFCs were performed based on the Japanese Guideline for Food Allergy.¹⁵ The total challenge dose was decided for each child patient by pediatric allergy specialists based on the patient's history of food-induced reactions, sIgE level and other related factors. The low dose was at 1/32 of a cooked whole egg, the medium dose 1/8–1/2 of a cooked egg, and the high dose one cooked whole egg. Then a registered dietitian provided dietary advice for minimal avoidance of egg based on the OFC results. When the OFC was negative, a caregiver was advised to give the child egg at home in an amount not exceeding the total challenge dose. When the OFC was positive but the induced symptoms were mild, the advice was to consume egg in an amount not exceeding the threshold dose at home. When the OFC was positive, with moderate to severe induced symptoms, complete elimination of egg was advised.¹⁵

The amount of egg consumed at home was classified into 5 levels: level 0, complete elimination; level 1: cooked egg yolk without egg white (1/32 egg equivalent); level 2: a small roll or stick of bread (1/16–1/8 egg equivalent); level 3: a small donut or small cake (1/4–1/2 egg equivalent); level 4: 1/2–1 cooked egg; and level 5: >1 cooked egg. At 1 year after OFC, the amount of egg that each patient safely consumed in daily life was surveyed using a web-based questionnaire or by interview at an outpatient clinic and classified into the 6 levels described above. We classified the patient as "Outgrowing" (Group O) if the level was higher than the initial level, or as "Non-outgrowing" (Group N) if the level remained the same or had decreased.

The QoL of children was evaluated using the Japanese version¹⁹ of the Food Allergy QoL Questionnaire–Parent Form (FAQLQ–PF).²⁰ The FAQLQ–PF allows parents to report children’s health-related QoL from the child’s perspective. It consists of 3 domains: emotional impact (EI), food anxiety (FA) and social dietary limitations (SDL). The parents/caregivers of the patients answered each question on a 7–point Likert scale from “not at all” to “extremely”, in which a higher score indicates a worse QoL. The FAQLQ–PF was administered at OFC (baseline) and after 1 year.

Statistical analysis

The χ^2 or Fisher exact test was used to compare categorical variables, while the Mann–Whitney U test was used to compare continuous variables between the 2 groups. Multivariate logistic regression analysis was performed to evaluate factors related to increasing egg consumption (dependent variable). Independent variables were selected based on their clinical relevance. To dichotomize the FAQLQ–PF total score and specific IgE level, a cutoff value for the 1–year outcome was determined using a receiver operating characteristics (ROC) curve. All reported P values are 2-tailed, with a P value of $<.05$ considered to be statistically significant. Statistical analyses were performed with GraphPad Prism 8 (GraphPad Software; La Jolla, California) and SPSS (version 26; SPSS; Chicago, Illinois).

Results

Patient characteristics and outcome

A total of 316 food–allergy patients were enrolled in the IQ–OFA study, and 128 met the eligibility criteria of the present study. The OFC indicated that one patient had outgrown the egg allergy and was therefore excluded. The remaining 127 patients were followed up for 1 year after having received dietary advice, and 93 patients (73.2%) participated in the outcome survey (Figure 1). Fifty-seven patients (61.3%) were classified in the Outgrowing (Group O) and 36 (38.7%) in the Non-outgrowing (Group N). The distributions of the intake levels at entry (OFC) and at 1 year after OFC in Group N and Group O are shown in Figs. 2A and B. There was a significant leftward shift (toward lower levels) in the distribution in Group N (χ^2 test for trend: $P=0.0252$) and a significant rightward (toward higher levels) shift in Group O (χ^2 test for trend: $P<0.0001$).

Table 1 summarizes the clinical characteristics at the time of OFC. The subjects had a median age of 24 months and were predominantly boys, with comorbid and parental allergic diseases. One–fourth of the subjects had a history of anaphylaxis to some food, and most of them had multiple food allergies, with a median of 4 avoided foods (Table 1).

Comparing the 2 groups, patients in Group N were older and had higher prevalences of atopic dermatitis and asthma. Egg white (EW) and ovomucoid (OM) sIgE levels were also significantly higher in Group N. The groups showed no differences in the proportions of comorbid allergic rhinitis, family history of allergic diseases, food–induced anaphylaxis history or first–time OFC. There was no difference in the number of avoided foods (Table 1).

FAQLQ–PF

The total and subscale scores for the FAQLQ–PF at OFC were compared between Groups N and O. All the scores in Group N were significantly higher than those in Group O, indicating a better initial OOL in the outgrowing patients (Figure 3). At 1 year after OFC, the caregivers of 49 patients (17 in Group N and 32 in Group O) completed the FAQLQ–PF again. The scores remained the same in Group N. In contrast, both the total and subscale scores of SDL had decreased significantly in Group O, indicating improvement in the QoL (Table 2). Accordingly, after 1 year, Group N still showed statistically higher scores, i.e., a worse QoL, compared with Group O (Table S1).

Factors associated with increased egg intake after 1 year

Multivariate logistic regression was performed to identify factors associated with a favorable outcome, i.e., an increase in the intake level of egg at 1 year after OFC. The explanatory variables were age, EW–sIgE,

OFC results, number of avoided foods, history of anaphylaxis, parental allergic disease, comorbid asthma, comorbid atopic dermatitis, and the FAQLQ-PF total score. Continuous variables were dichotomized based on the optimal cut-off levels (for EW-sIgE and FAQLQ-PF) (Fig. S1) or clinical relevance (age, number of avoided foods). Although age >25 months and EW-sIgE >25 kU_A/L were negatively associated with a favorable outcome in univariate analysis, only comorbid asthma, comorbid atopic dermatitis and an FAQLQ-PF total score >3.8 were found to be independently associated with unfavorable outcome, with adjusted ORs of 0.246, 0.325 and 0.292, respectively (Table 3).

Discussion

In this study, we investigated factors associated with the clinical course of egg allergy, with special focus on the disease-specific QoL.¹⁹ The QoL was evaluated at the time of OFC, when a threshold of safe consumption was determined for dietary advice, and correlated with the 1-year outcome. We found that a better QoL at the OFC was an independent predictor of an increased intake level of egg at 1 year after OFC, indicating that outgrowing egg allergy was associated with the baseline QoL.

The mechanisms by which children naturally outgrow food allergy have yet to be elucidated.²¹⁻²³ Identification of clinical factors that accurately predict the prognosis of food allergy may help delineate the involved mechanisms.²⁴ We performed a systematic review of studies of the natural history of food allergy, focusing on predictive factors for outgrowing an allergy. We used “food allergy” AND “natural history” as keywords to conduct a Pubmed search of original research articles in English, published from January 1963 through April 2020. This search yielded a total of 358 studies. We excluded 263 studies dealing with irrelevant topics such as non-food allergy, anaphylaxis and eosinophilic esophagitis. We also excluded 25 studies that did not deal with prognostic factors. Finally, we selected 70 studies that investigated factors involved in the natural history of allergy to 3 food allergens (Figure S2).

Table S2 summarizes the factors that were reported to be negatively associated with outgrowing a food allergy: high specific IgE, large skin-prick-test reactions, systemic food-induced symptoms, history of anaphylaxis, comorbid asthma and atopic dermatitis, a family history of allergic disease, and multiple sensitizations (Table S2). Our present study found that comorbid asthma and atopic dermatitis were independently associated with not outgrowing egg allergy, which is in agreement with earlier studies. In addition, we identified disease-specific QoL as a predictive factor of food allergy outcome. Although it was reported that the QoL of patients improved after they underwent OFC, regardless of the OFC result,²⁵ no studies found an association between the QoL and the future food allergy outcome. We believe that this is the first study to find the disease-specific QoL to be a factor that may influence the natural history of food allergy.

Food allergy is a serious burden for affected patients and their caregivers because it requires strict performance of a variety of tasks, including careful cooking/eating to avoid the offending allergen, causes anxiety over the risk of anaphylaxis, and limits common social activities associated with eating. Thus, the parents of children with food allergy were reported to have a poorer general QoL than the parents of normal children.²⁶ The health-related QoL of children and adolescents with food allergy was shown to be worse than not only that of the general population but also that of type 1 diabetes patients.²⁷ Our present results indicate that a poor QoL is not only a consequence of the child’s food allergy but also a factor that possibly influences the future status of the child’s disease.

In fact, a prospective study that assessed the nutritional attitudes of children with food allergy before and after OFC in relation to their mothers’ anxiety showed a negative correlation between anxiety of mothers before OFC and degree of change in nutritional habits of their children after OFC.¹⁸ The authors stated that a positive attitude of mothers toward food before OFC promoted subsequent food reintroduction, which increased children’s interest in tasting new foods, and led to favorable changes in nutritional habits. A negative initial maternal attitude, on the other hand, led to an unfavorable attitude in the child.¹⁸ Likewise, in our present study, a better QoL—which is partly equivalent to less anxiety—may have led to the child having a positive attitude toward food and an increase in egg intake. This tendency was observed regardless of both the OFC results and the severity of egg allergy, represented by the specific IgE level. Since intake

of a small amount of an allergenic food after a negative low-dose OFC was reported to increase the intake threshold,^{28,29} a better initial QoL may promote outgrowing the allergy.

We also found that the initial QoL for the outgrowing patients further improved 1 year after the OFC, whereas the QoL for the non-outgrowing patients remained unchanged or became worse. The QoL of food allergy patients was reported to be worse in older children, probably because of a long period of food avoidance and an increasing demand for social activities involving food.^{30,31} Conversely, a negative OFC³² and oral immunotherapy³³ were associated with a better QoL. Our results are consistent with those earlier reports.

This study has at least 3 limitations. First, we used a questionnaire to determine the daily amount of egg consumed at 1 year after OFC, rather than repeat the OFC. However, the threshold determined by OFC does not always reflect a patient's actual eating habits. We believe that the caregiver-reported actual intake is more clinically relevant than an "experimental" OFC threshold. Second, the number of subjects was relatively small, and the statistical power to identify prognostic factors was thus not strong. Third, we followed up the patients for only 1 year and evaluated only the trend toward outgrowing egg allergy, not actual achievement of that goal. Further studies are needed to confirm our present findings.

In conclusion, we found that a better QoL at baseline was associated with a child's outgrowing egg allergy, while vice versa, a poorer QoL was associated with delayed resolution. A caregiver's psychological status, partly expressed as the disease-specific QoL, may have an impact on the child's food allergy outcomes. Intervention focusing on the child's baseline QoL may lead to better management of food allergies.

Author Contributions

Mizuho Nagao and Takao Fujisawa conceived the study. Kana Hamada, Mizuho Nagao, Ryo Imakiire, Kanae Furuya, Yumi Mizuno, Mayumi Matsunaga, Shingo Yamada, Kazutaka Nogami, Miyuki Hoshi, Taiga Kobori and Keigo Kainuma recruited the subjects and contributed to data collection. Kana Hamada, Takao Fujisawa and Mizuho Nagao conducted the analyses of the data. Yasunori Sato supervised the statistical analyses. Kana Hamada and Takao Fujisawa wrote the manuscript. Kazumoto Iijima made critical comments on the study design and manuscript. All the listed authors were involved in the review of the manuscript and approved the final content.

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Figure legends

Figure 1

Flow diagram of the subjects

Figure 2

Levels of egg intake at initial OFC (solid bar) and 1 year later (open bar) in Group N (A) and Group O (B).

Egg intake levels were classified as level 0: complete elimination; level 1: cooked egg yolk without egg white (1/32 egg equivalent); level 2: a small roll or stick of bread (1/16–1/8 egg equivalent); level 3: a donut or small cake (1/4–1/2 egg equivalent); level 4: 1/2–1 cooked egg; and level 5: >1 cooked egg.

Figure 3

Comparison of FAQLQ-PF scores between Group N and Group O.

Horizontal bars indicate the median score. The total and subscale scores (emotional impact, food anxiety and social dietary limitations) in Group N were significantly higher than in Group O. (P values; Mann–Whitney test)

Legends for supplemental figures

Figure S1 ROC curves of FAQLQ-PF (A) and EW-sIgE (B)

Receiver-operating characteristic (ROC) curves were constructed to identify cut-off values for predicting the egg allergy outcome 1 year after OFC. The optimal cut-off values determined by Youden index were 3.8 and 25 for FAQLQ-PF total score and EW-sIgE, respectively. AUCs (Area under the ROC curve) for the 2 factors were 0.70 (95%CI; 0.59-0.82) and 0.65 (95%CI; 0.53-0.78), respectively.

Figure S2. Flow diagram of the systematic review

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