



Two-step egg introduction for prevention of egg allergy in high-risk infants with eczema (PETIT): a randomised, double-blind, placebo-controlled trial

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Summary

Background Evidence is accumulating that early consumption is more beneficial than is delayed introduction as a strategy for primary prevention of food allergy. However, allergic reactions caused by early introduction of such solid foods have been a problematic issue. We investigated whether or not early stepwise introduction of eggs to infants with eczema combined with optimal eczema treatment would prevent egg allergy at 1 year of age.

Methods In this randomised, double-blind, placebo-controlled trial, we enrolled infants 4–5 months of age with eczema from two centres in Japan. Exclusion criteria were being born before 37 weeks of gestational age, experience of ingestion of hen's eggs or egg products, history of immediate allergic reaction to hen's eggs, history of non-immediate allergic reaction to a particular type of food, and complications of any severe disease. Infants were randomly assigned (block size of four; stratified by institution and sex) to early introduction of egg or placebo (1:1). Participants in the egg group consumed orally 50 mg of heated egg powder per day from 6 months to 9 months of age and 250 mg per day thereafter until 12 months of age. We aggressively treated participants' eczema at entry and maintained control without exacerbations throughout the intervention period. Participants and physicians were masked to assignment, and allocation was concealed. The primary outcome was the proportion of participants with hen's egg allergy confirmed by open oral food challenges at 12 months of age, assessed blindly by standardised methods, in all randomly allocated participants who received the intervention. This trial is registered with the University Hospital Medical Information Network Clinical Trials Registry, number UMIN000008673.

Findings Between Sept 18, 2012, and Feb 13, 2015, we randomly allocated 147 participants (73 [50%] to the egg group and 74 [50%] to the placebo group). This trial was terminated on the basis of the results of the scheduled interim analysis of 100 participants, which showed a significant difference between the two groups (four [9%] of 47 participants had an egg allergy in the egg group vs 18 [38%] of 47 in the placebo group; risk ratio 0.222 [95% CI 0.081–0.607]; $p=0.0012$). In the primary analysis population, five (8%) of 60 participants had an egg allergy in the egg group compared with 23 (38%) of 61 in the placebo group (risk ratio 0.221 [0.090–0.543]; $p=0.0001$). The only difference in adverse events between groups was admissions to hospital (six [10%] of 60 in the egg group vs none in the placebo group; $p=0.022$). 19 acute events occurred in nine (15%) participants in the egg group versus 14 events in 11 (18%) participants in the placebo group after intake of the trial powder.

Interpretation Introduction of heated egg in a stepwise manner along with aggressive eczema treatment is a safe and efficacious way to prevent hen's egg allergy in high-risk infants. In this study, we developed a practical approach to overcome the second wave of the allergic epidemic caused by food allergy.

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Introduction

A second wave of the allergy epidemic, in the form of a rising prevalence of food allergies, has emerged in high-income countries following the first wave of increasing asthma and allergic rhinitis.¹ Food allergy often occurs in the early stage of the allergic march,² along with atopic dermatitis, and is associated with increased risks of anaphylaxis and asthma.³ Hen's egg allergy is one of the commonest forms of food allergy, with sensitisation to egg at 1 year of age strongly associated with sensitisation to aeroallergens at 3 years of age.⁴ Although food allergy and atopic dermatitis (and subsequent asthma) have been widely believed to be prevented by avoidance of

specific food during the perinatal and infancy periods,^{5,6} such an approach has not been supported by a Cochrane systematic review.⁷

Conversely, findings from observational studies^{8–11} have revealed that early introduction of solid food might decrease the incidence of food allergy compared with late introduction or avoidance. Several randomised controlled trials (RCTs) have been done to test the possible protective role of early introduction of solid foods. Investigators of the Learning Early About Peanut (LEAP) study¹² investigated the effect of introduction of peanuts in high-risk infants and found that early introduction reduced the prevalence of peanut allergy at 5 years of age (relative risk

Research in context

Evidence before this study

We searched PubMed and Embase between Jan 29, 2016, and March 31, 2016, in the English language, using the following search terms: "infant", "eczema", "prevention", "allergy", and "randomised controlled trial". The Food Allergy and Anaphylaxis Guidelines published by the European Academy of Allergy and Clinical Immunology reported that "the present evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic foods after the age of 4 months". The Consensus Communication on Early Peanut Introduction and the Prevention of Peanut Allergy in High-Risk Infants was released in 2015 on the basis of the Learning Early About Peanut Allergy trial data, which provided Level 1 evidence that early introduction of peanuts is safe and effective in selected high-risk infants at reduction of subsequent peanut allergy by up to 81%. The Enquiring About Tolerance study was a randomised controlled trial that recruited infants from the general population, assessing whether or not early exposure might reduce subsequent allergy. The per-protocol analysis suggested a possible protective effect of early introduction of peanuts and hen's eggs, but adherence to the study protocol was rather low and the results in the intention-to-treat analysis were negative. In addition to the Learning Early About Peanut Allergy and Enquiring About Tolerance studies, we identified only one trial published in 2013 describing the preventive effect of early introduction of eggs for high-risk infants with eczema. Investigators reported that a lower proportion of infants in the early egg introduction group (14 [33%] of 42) developed IgE-mediated egg allergy at

0.19; $p<0.0001$). Results of another RCT¹³ that investigated the effect of egg introduction at 4 months of age did not show any protection (relative risk of hen's egg allergy at 12 months 0.65; $p=0.11$) and highlighted a major problem of such an approach in infants with moderate-to-severe eczema because many might have sensitisation and clinical reactivity to egg by 4 months of age. In both RCTs, a considerable number of participants had allergic reactions to several types of food at first introduction. The Enquiring About Tolerance study¹⁴ assessed the possible preventive effect of early introduction of six types of food, including peanuts and hen's eggs, in infants from the general population. The complex protocol had rather low adherence and the results in the intention-to-treat analysis were negative. Findings of these RCTs suggest that a safe and practical approach for introduction of allergenic foods to high-risk infants with eczema is still very much needed.

Eczema in infancy is associated with an increased risk of percutaneous sensitisation to food allergens.^{15–17} Attentive and effective treatment of eczema might be needed before and during feeding of allergenic food, such as peanuts and eggs, to infants. Our experience of oral immunotherapy suggests that a very small amount of

12 months of age than in the placebo group (18 [51%] of 35); however, the difference did not reach statistical significance (relative risk 0.65 [95% CI 0.38–1.11]). Caution is needed when infants with moderate-to-severe eczema are first exposed to eggs because many have already developed sensitisation and clinical reactivity by 4 months of age.

Added value of this study

This trial is the first randomised, double-blind, placebo-controlled trial to produce results that show a safe and effective method of early introduction of hen's eggs to high-risk infants with eczema to prevent egg allergy. Our findings substantiate that early introduction of a small amount of heated egg in a stepwise manner combined with attentive treatment of eczema can reduce the prevalence of egg allergy in high-risk infants with eczema.

Implications of all the available evidence

Our results provide firm evidence that early introduction of potentially allergenic foods can be done safely by starting from a small dose and that prevention of food allergy can be achieved effectively in a stepwise manner. A small amount of solid food is safe, even for sensitised infants, and this stepwise approach is practical at a population level because infants do not need to be screened by skin prick, serum-specific IgE concentration, or challenge tests before introduction. Additional trials are needed to test this approach for prevention of other types of food allergies. Optimal control of eczema might be an integral part of the preventive programme to minimise the chance of percutaneous sensitisations.

solid food can be safely introduced even for patients who have already been sensitised at first introduction and that a stepwise increase in dose might be a safe approach. We did a randomised, double-blind, placebo-controlled trial, the Prevention of Egg Allergy with Tiny Amount Intake study, to investigate if the combination of stepwise introduction of egg with aggressive treatment of eczema reduces the risk of onset of hen's egg allergy at 12 months of age.

Methods

Study design and participants

In this randomised, double-blind, placebo-controlled trial, we recruited patients from the National Center for Child Health and Development (NCCHD) and Tachikawa Sougo General Hospital (TSGH) in Tokyo, Japan. Participants were eligible for enrolment if they were 4–5 months of age with atopic dermatitis meeting Hanifin-Rajka's diagnostic criteria.¹⁸ Exclusion criteria were being born before 37 weeks of gestational age, experience of ingestion of hen's eggs or egg products, history of immediate allergic reaction to hen's eggs, history of non-immediate allergic reaction to a particular

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