Predictive factors of egg allergy clinical outcomes in infants and young children

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Abstract

Aim: The aim of the present study was to explore the tolerance march in children and establish probable factors that affect the prognosis of an egg allergy (EA). **Methods:** Two hundred children 6 months to 2.5 years old with atopic dermatitis (AD) were recruited into our study from 2018 to 2019. EA was diagnosed based on medical history, the skin prick test (SPT), and the oral food challenge test (OFC) ,EA was diagnosed in 78,among those, 7 were allergic only to egg yolk (OnlyEYA), 20 to egg white (OnlyEWA), and 51 to whole egg (WEA). Logistic regression analysis was used to detect the disease course and related risk factors of outcomes. The receiver operating characteristic curve was used to establish a predicting model. **Results:**The Scoring Atopic Dermatitis score in the WEA group was more severe and persistent than that in the other groups. Forty-three cases of EA developed clinical tolerance (average age, 32.3 ± 8.7 months). The tolerance rate of EYA was 75.9% and EWA was 56.3%. The SPT wheal diameter at initial diagnosis (SPT_{diag}) was the risk factor for persistent EA. The SPT wheal diameter after 6 months (SPT_{6mo})$in the tolerant group decreased markedly compared to that in the persistent EA group. Tolerance was higher when {}^{E}W-SPT_{6mo}$[?]39.5%$or {}^{E}Y SPT_{6mo}$[?]27%.**Conclusion:**$The initial SPT_{diag} and SPT_{6mo} values were significantly correlated with and can predict outcomes of EA.$**Key words:**$E$

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iii.Abstract and keywords

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Key words: Egg allergy, atopic dermatitis, outcome, related factors.

iv.Main text

Background

Egg allergy (EA) is one of most common food allergies that may occur very early in life [1,2]. In 2011, Koplin et al[3] and other studies reported that the prevalence of food allergies in 1-year-old children is as high as 11%, including 8.9% raw egg allergy,. A birth cohort study involving 12,049 infants in 9 European countries found that the highest incidence of egg allergy confirmed by the open food stimulation test was 2.18% in the UK[1]. In China, there cross-sectional studies[4] spanning 20 years (1999,2009 and 2019) on infants in the southeast city of Chongqing reported that the incidence of IgE- mediated food allergies has risen from 3.5% to 7.7% and 7.6%in 2019, and that egg and milk are the most common food allergies in childhood in China [5].

In 2012,a multicenter study showed that egg was the first allergen in the food allergy test of 0-2-year-old children in China, and its history and clinical manifestations were mainly skin symptoms (85-96.3%)[6].Immunoglobulin E (IgE)-mediated EA,aggravated AD symptoms in infancy that main manifestations are infantile eczema combined with digestive system and respiratory system issues, which affect the growth, development, and quality of the child's daily life,however, eggs are also one of the main sources of dietary protein for infants and young children, which drives EA with AD become a common skin complaint, and how to reduce blindly avoiding eggs also a challenge for pediatricians. Although natural tolerance occurs in 49.3% of infants with an average age of 3 years [7-9], Lack of relevant literature research in China,the exact age bracket of tolerance and predictive factors remain to be determined.

Mechanistically, five protein components in egg white (EW) have been found to bind with human serum IgE to induce an allergic reaction, including ovomucoid (OVM or Gal D 1), ovalbumin (OVA or Gal D 2), ovotransferrin (OVT or Gal D 3), lysozyme (Gal D 4), and ovomucin. In addition, egg yolk (EY) also contains antigens associated with allergies, namely yolk phosvitin,and yolk glycoprotein 42 (YGP42, Gal D 6) [10-11] . Because of the different antigenic components, clinical egg allergy is divided into three states—EW allergy (EWA), EY allergy (EYA), and whole egg allergy (WEA)[12].In this study, egg yolk and egg white oral food challenge test (OFC) were respectivd,identification of these three states and exploration of the probable factors that predict clinical outcomes may provide management strategies for EAs. **Methods**

Patients Selection

This study was approved by the Ethics Committee of Ruijin Hospital of Shanghai Jiao Tong University School of Medicine, and was conducted in accordance with the Declaration of Helsinki.All patients provided written informed consent before inclusion in the study.From the pediatric allergy clinic of Ruijin Hospital, China, 200 children with AD aged 6 months to 2.5 years old were included in the present study from 2018 to 2019.IgE-mediated EA was defined by OFC.,firetly,a positive skin prick test (SPT) to EW or EY [?] 3 mm and by keeping a diet diary,children whose AD symptoms(sleep status, itching, rash area and exudation) and digestive tract symptoms improved significantly with the elimination of the whole egg were further evaluated by OFC .The antigen used in the SPT included those fresh food obtained from egg yolk, egg white, cow's milk, wheat, fish, shrimp, peanut,soybean.

Oral Food Challenges

The child added egg yolk (boiled at 100degC for 15 min) in stepwise-increasing doses given every 30 min, if no reaction was observed with the previous dose.,OFC was performed in the hospital by a trained pediatrician, and the subjects were observed for at least 2 hours after the last dose before going home. Parents were asked to report any symptoms that occurred in the following at least 3 days. If any reactions suspicious of EA were reported, the children were to be brought to the hospital for appropriate manageent immediately inaccordance with the EAACI guidelines[13].And next,the egg white OFC was performed again after elimination of whole egg for 2 weeks..Any participant with an incomplete diagnostic process was considered a dropout.The symptoms were improved after avoidance, and the symptoms reappeared as OFC positive after re-intake, and the diagnosis of egg allergy was established. On the contrary, it is negative.

Groups

The children with AD who had negative results from both tests were recruited into the AD group(as control subjects).The Scoring Atopic Dermatitis (SCORAD) score and pruritus (itchy skin)/sleep Visual Analogue Scale (VAS) score were used to evaluate the clinical baseline skin conditions.The 78 children with EA were divided into three subgroups as follows: 7 with only EYA (OnlyEYA), 20 with only EWA (OnlyEWA), and 51 with whole egg allergy (WEA).At the end of follow-up, the patients with egg allergy were divided into tolerance group and persistent allergy group.

Follow up

Children with atopic dermatitis are given routine treatment, including skin moisturizing / or glucocorticoid ointment (topical application).Children diagnosed with egg ingredient allergy strictly avoid the corresponding ingredients, including oral food intake and family living environment contact avoidance.All patients were followed up at 3, 6, 12, and 18 months by recording the SCORAD score, itching/sleep VAS score, and respiratory symptoms (including nasal symptoms, chronic cough, wheezing, and asthma diagnosed by clinicians). SPT was concurrently conducted in the EA group. Tolerance is defined with negative in OFC: a wheal $<$ 3 mm and no allergic reaction after ingesting egg yolk or egg white for 3 consecutive days,OFC was also performed in the hospital by a trained pediatrician; otherwise, persistent allergy is considered.

Statistical analysis

SPSS v 25 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. The Mann–Whitney and χ^2 tests were used to compare the characteristics of the tolerant and persistent groups. Taking the egg tolerance as the dependent variable, univariate and multivariate logistic regression analyses were conducted, and the risk factors were used to plot the receiver operating characteristic (ROC) curves. Each cutoff value was calculated using the Youden index to obtain the prediction model. The survival analysis using the Kaplan–Meier curve was used to determine whether the predictor could effectively predict tolerance development.

Results

Among the 200 children with AD, 85 cases(42.5%) were positive for egg SPT, 78 cases(39%)egg allergy were diagnosed by OFC . EA group had no lost or withdrew from the study,56 had eaten eggs before diagnosis,29 had simultaneous milk allergies. Follow-up duration was 18 months in 43 children (55.13%) with egg tolerance

and 35 with persistent EA. In addition, 48 children in the EA group presented with respiratory symptoms, which revealed that EA was associated with an increased chance of asthma (26.9 vs 10.3%, P = 0.039) when compared to that in the AD group.

EA

In the present study, there was a 39% prevalence of EA in children with AD at 14.71 ± 7.9 months old after an EA diagnosis.According to AD severity classification, 24 cases (30.8%) were mild, 41 (52.6%) were moderate, and 13 (16.7%) were severe. The median score of the itchy skin/sleep VAS self-rating scale (0–10) was 5 (4–7). The SCORAD score (P = 0.012), severity grade (P = 0.003), and itchy skin/sleep VAS score (P = 0.012) in the EA group were higher than that in the AD group. No significant difference was observed in the distribution range of EOS% between the two groups.

In the WEA group, 12 patients (23.5%) had severe AD, and 27 (52.9%) had moderate AD. Meanwhile, in the OnlyEWA group, milder AD (40vs 57%) and moderate AD (60 vs 28%) were observed compared to that in the OnlyEWA group. In addition, we observed that the children in the WEA group had more skin damage (P = 0.045) and sleep impairment (P = 0.041) than those in the other groups.

Avoiding eggs and egg products greatly alleviated allergic symptoms in children with EA with a significant decrease.The changes of SCORAD and VAS scores in EA group were compared by Friedman-M method ,there were significant differences in different time periods(0, 3, 6, 12 and 18 months) .In addition, higher median SCORAD and VAS scores were observed at different follow-up time period in children in the WEA and OnlyEWA groups. Above all, a change in the scores was slower in children in the WEA and OnlyEWA groups than in other groups (P < 0.001).

Egg tolerance and persistent EA

No significant differences were found between the egg tolerance and persistent EA groups in age, sex, premature birth, cesarean section, exclusive breastfeeding, only child, and respiratory diseases. The EA-persistent group comprised more children from a smoking environment than the tolerant group (P < 0.05). There was no significant difference in the EA tolerance rate among children with different AD severity (i.e., mild, moderate, or severe).

Specifically, the average SPT wheal diameter at initial diagnosis (SPT_{diag}) in EY was 5 mm (3.25–6.875 mm) and in EW was 8.25 mm (6–10 mm) in the tolerance group.Additional follow-up results revealed that SPT_{diag} in the persistent group was 8 mm (6–9) in the EYA and 10.5 mm (9.25-15) in the EWA. Importantly, children om the persistent group had more persistent milk allergy (25.7 vs 9.3%), nasal symptoms (54.3 vs 30.2%), and asthma (40 vs 16.3%) than those in the tolerant group (Table 1).

Multivariate Logistic analysis was carried out again by using the factors of P < 0.1 in univariate logistic analysis, our results also showed that EW-SPT_{diag} (P = 0.031) and EY-SPT_{diag} (P = 0.023) were independent risk factors for persistent EA, with odds ratio (OR) values of 1.197 (95% confidence interval [CI]: 1.016–1.411) and 1.470 (95%CI: 1.055–2.049), respectively (Table 2). In addition, logistic analyses were conducted with persistent EA and persistent milk allergy as independent variables and respiratory disease symptoms (nasal congestion, asthma) as dependent variables. We observed that persistent EA was associated with nasal symptoms (P = 0.034) and asthma (P = 0.022), and that children with persistent EA were more likely to develop nasal congestion and asthma.

Tolerance to different egg ingredients

Egg tolerance was 86% in the OnlyEYA group, 60% in OnlyEWA group, and 49%in WEA group. The cumulative probability of allergic tolerance was calculated,there was a significant difference in the allergic tolerance rate among the three groups (P = 0.03). Specifically, patients in the OnlyEYA group were the earliest and the fastest to develop tolerance, followed by those in the OnlyEWA group and those in the WEA group (Fig. 1A).

In the WEA group, 38 children were tolerant to EY and 28 children were tolerant to EW. The tolerance rates of EY and EW were also compared. We found that patients with EYA developed a tolerance faster than those with EWA (P = 0.026) (Fig. 1B).

SPT_{diag} and $^{S}PT_{6mo} were significantly correlated with outcomes of EA$

We next analyzed the relationship between the size of SPT_{diag} and the development of EA tolerance. The children with EA were divided into the EWA group (n = 71) and EYA group (n = 58). The larger SPT_{diag} for EW or EY, the lower the probability of tolerance in the future. The SPT_{diag} for EY and EW ($P < 0.001$) decreased at 0, 3, 6, 12, and 18 months of follow-up (Fig. 2). The median SPT_{diag} in the persistent allergy group was higher than that in the tolerated group ($P < 0.05$).

To calibrate the SPT_{diag} conducted at irregular intervals, the reduction rate of the diameter was calculated at intervals of 6 months (ΔSPT_{6mo}), using the following formula:

$(\Delta SPT_{6mo})\% = [(V0{:}SPT\text{-}V2{:}SPT) / V0{:}SPT] * 100,$

where, V0:SPT is the first value of the mean perpendicular diameter of the SPT_{diag}, and V2:SPT is the value of the diameter of the SPT_{diag} in the second follow-up (6 months later).

Comparing the predictive power for tolerance acquisition in the EA group, ΔEY-SPT_{6mo} (area under the curve [AUC], 0.811; 95% CI, 0.692–0.929) was better than EY-SPT_{diag}(AUC, 0.787; 95%CI, 0.655–0.919). The cutoff values were 7.75 mm for EY-SPT_{diag} and 27% for ΔEY-SPT_{6mo}. The predictive power of using both ΔEY-SPT_{6mo} and EY-SPT_{diag} (AUC, 0.750; 95%CI, 0.628–0.872) was similar compared to using EY-SPT_{diag} or ΔEY-SPT_{6mo} alone (Table 3A). When the predictive power was compared in the EWA groups, ΔEW-SPT_{6mo} (AUC, 0.836; 95%CI, 0.746–0.926) was better than that in the EW-SPT_{diag} (AUC, 0.722; 95%CI, 0.598–0.847). The cutoff values were 10.25 mm for EW-SPT_{diag} and 39.5% for ΔEW-SPT_{6mo}. The predictive power of using both ΔEW-SPT_{6mo} and EW-SPT_{diag} (AUC, 0.798; 95%CI, 0.695–0.900) concurrently was similar to using EW-SPT_{diag} or ΔEW-SPT_{6mo} alone (Table 3B).

Patients were divided based on the cutoff ΔEY-SPT_{6mo} value of 27% and ΔEW-SPT_{6mo} value of 39.5% to perform additional analyses. Results showed that 42 patients had a ΔEY-SPT_{6mo} [?]27%, and 38 patients (90.5%) developed EY tolerance; Of the children with a ΔEW-SPT_{6mo} [?] 39.5%, 30 (83.3%) developed egg tolerance; The Kaplan–Meier curves showed more developed EYA tolerance in the group with ΔEY-SPT_{6mo} [?] 27% ($P < 0.001$) or ΔEW-SPT_{6mo} [?] 39.5% ($P < 0.001$) (Fig. 3).

Discussion

Relationship between AD and EA

There is a certain degree of overlap in the allergy march.Results from a population-based cohort[14] shown that > 50% of infants with AD have an FA, particularly in those with severe,persistent and early-onset eczema. Infants with eczema were 5.8 times more likely to develop egg allergy by 12 months than infants without eczema.Studies have shown that early introduction is effective in preventing the development of a food allergy in specific groups of high-risk infants [15,16].Mindlessly avoiding food can also increase the risk of malnutrition,it is important to know if you are allergic to eggs. The mechanisms by which a food allergy develops after the onset of atopic dermatitis may involve damaged skin barriers and inflammatory synergism [17]. The reason why egg was found to be more closely to related to AD is still unknown. One hypothesis is that the interaction between the microbial proteins and the skin and presence of homologous proteins between microbes and egg allergen may be related to the development of IgE sensitization and egg allergy[18].

Coinciding with this study, The results of the present study indicated that the prevalence of EA in children with AD was 39%, moderate and severe AD was strongly associated with EA, children with EA had more serious itching/sleep impairment, which resulted in a negative effect on daily life,and skin symptoms improved significantly after avoiding the foods containing the allergens. Although children with AD may have received routine treatment before entering this study.Some studies have mentioned that early onset AD (2 years old) is more easily relieved, and that moderate and severe AD are more likely to develop into persistent disease[19].

During the follow-up for 18 months the average tolerance age was 32.3 ± 8.7 months, which suggested that the age of 2–3 years was the peak period for development of EA tolerance,however,the severity of AD had no effect on the development of EA tolerance. So far, avoiding eggs is the most important method by which to reduce EA.

Risk factors for the outcome of EA

In their 2014 study, Sicherer et al. [20] have reported a cohort of children with EA aged 3 to 15 months who were followed up for a median of 74 months and have found a significant correlation between low specific-IgE levels; skin symptoms, such as urticaria or angioedema; and the EA outcome. To analyze the factors that influence EA tolerance, in the present study, no statistical differences were found in sex, exclusive breastfeeding, multiple food allergies, premature birth, cesarean section, family history of allergy, and early ingestion of eggs between the EA tolerance and persistent allergy groups.

EOSs are the main immune cells of a delayed type of food allergic reaction [21], and its number in peripheral blood is an easy index by which to determine an allergic status in the clinic. In the present study, we did not find that the using only the range of EOS% in infants and young children was of value in the diagnosis of rapid food allergy. In the clinic, for infants with only a slight increase in the proportion of EOSs, we must combine medical history, serum specific IgE value, and SPT to make a comprehensive judgment and a clear diagnosis before food avoidance.

Some studies have found that there is a strong correlation between EA in infancy and subsequent sensitivity to inhaled allergens, and persistent EA may be associated with the severity of asthma [17]. we found that the prevalence of asthma was higher in children with EA, and that 49% of the cases with wheezing and chronic cough appeared after 2 years.Persistent EA is a risk factor for nasal symptoms and asthma. In the allergy march, food allergy is a risk factor for asthma regardless of whether the suspected food is tolerated, and asthma risk at the age of 4 years is two to three times higher than that for those no history of food allergy [22]. Our results were consistent with reports from Rhodes et al [23], who have determined in their cohort of infants born to 100 groups of parents with a history of allergic disease that SPT is positive and EA and milk allergy are independent risk factors for adult asthma. In the present study, we found that children with persistent milk allergies were more likely to have persistent EAs, which, in part, coincided with study from Sicherer [20], which suggests that persistent milk allergy may be used as a time predictor of EA tolerance.

Kose et al. [24] have conducted a retrospective study and found that at the end of 6 months of consuming baked hen's egg (BE), the scrambled egg tolerance was negatively associated with EW-specific IgE levels, EW SPT, and the EW prick-to-prick test (PTP). EW PTP was the most significant parameter [22]. The study has found that the size and change rate of egg SPT wind mass is significantly related to the outcome of EA.SPT_{diag} was observed to be the risk factor for persisting EA, SPT_{diag} and $^{S}PT_{6mo}weresignificantlycorrelatedwithEAoutcomes.$

Tolerance of EA with different ingredients

Most of the children in the OnlyEWA group had moderate AD while, those in the OnlyEYA group had the least severe clinical symptoms that were relieved faster than that in the other groups. Children with EWA had more severe clinical symptoms and slower tolerance rates than children with EYA.Perez-Rodriguez et al. [25] have found that EW protein affects the integrity of the intestinal epithelial cell–barrier function. EY plays an important adjuvant role in the Th2-type response induced by EWA, and EY may promote the sensitization of EW protein by activating innate immune cells [25]. EW and EY have different antigenic components, and the tolerance rate for the different egg ingredients is also different.

During the 18-month follow-up, SPT decreased with time, which indicated that the size of the wheal is a predictor of egg tolerance. Specifically, the larger the diameter of the SPT_{diag}wheal, the less likely it is that egg tolerance will be developed, and the more serious and longer lasting the clinical symptoms. The cutoff value calculated by the ROC curve showed that EW-SPT_{diag}> 10.25 mm and EY-SPT_{diag} > 7.75 mm were associated with persistent EA. The decreasing rate of EW-SPT wheal [?] 40% and EY-SPT wheal [?] 27%

in 6 months suggested the development of egg tolerance. Regardless of whether it was EW or EY, the ability of ${}^{S}PT_{6\mathrm{mo}}$ $to predict the egg tolerance outcome was better than that of SPT_{\mathrm{diag}}$.

Conclusion

The diameter and change rate of the SPT wheal can well predict the outcome of tolerance to different egg ingredients.This detection method provides a method by which clinicians can guide the infants' families to scientifically avoid and reintroduce allergic foods, which would finally improve and strengthen health management and decrease their economic burden. It should be noted that in practice, the results of SPT for fresh food are also affected by various factors, including the individual specificity and immune status of the subjects, the ability of the operator, and the type of immune response, all of which should be considered to be able to make a judgment according to the actual situation of the children.

vi. References

1. Xepapadaki P, Fiocchi A, Grabenhenrich L, Roberts G, Grimshaw KE, Fiandor A, Larco JI, Sigurdardottir S, Clausen M, Papadopoulos NG, et al. Incidence and natural history of hen's egg allergy in the first 2 years of life-the EuroPrevall birth cohort study[J]. Allergy. 2016 Mar;71(3):350-357.

2. ThameH, LeungdyM. How Different Parts of the World Provide New Insights Into Food Allergy[J]. Allergy Asthma Immunology Res,2018,10(4):290-299.

3. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, Ponsonby AL, Wake M, Tang ML, Dharmage SC, et al.Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants[J]. J Allergy Clin Immunol. 2011 Mar;127(3):668-76.e1-2.

4. Ma Z, Chen L, Xian R, Fang H, Wang J, Hu Y. Time trends of childhood food allergy in China: Three cross-sectional surveys in 1999, 2009, and 2019[J]. Pediatr Allergy Immunol. 2021 Jul;32(5):1073-1079.

5. Zhang J, Shen Y, Li J, Li H, Si P. Component-Resolved Diagnostic Study of Egg Allergy in Northern Chinese Children[J]. Biomed Res Int. 2020 Mar 11;2020:3831087.

6.陈静,廖艳,张红忠,等.三城市两岁以下儿童食物过敏现状调查 [J].中华儿科杂志,2012, 50(1):5-9.

7. Sicherer SH, Sampson HA. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management [J]. J Allergy Clin Immunol, 2018, 141(1): 41-58.

8. Peters RL, Koplin JJ, Gurrin LC, Dharmage SC, Wake M, Ponsonby AL, Tang MLK, Lowe AJ, Matheson M, Dwyer T, et al. The prevalence of food allergy and other allergic diseases in early childhood in a population-based study: HealthNuts age 4-year follow-up [J]. J Allergy Clin Immunol. 2017 Jul;140(1):145-153.e8.

9. Samady W, Warren C, Wang J, Das R, Gupta RS. Egg Allergy in US Children [J]. J Allergy Clin Immunol Pract. 2020 Oct;8(9):3066-3073.e6.

10. Dona DW , Suphioglu C . Egg Allergy: Diagnosis and Immunotherapy[J]. International Journal of Molecular Sciences, 2020, 21(14):5010.

11. Lunhui H, Yanhong S, Shaoshen L, Huijing B, Yunde L, Huiqiang L. Component resolved diagnosis of egg yolk is an indispensable part of egg allergy [J]. Allergol Immunopathol (Madr). 2021 Mar 1;49(2):6-14.

12. Chokshi NY, Sicherer SH. Molecular diagnosis of egg allergy: an update [J]. Expert Rev Mol Diagn. 2015;15(7):895-906.

13.Eigenmann PA, Akdis C, Bousquet J, Grattan CE, Hoffmann- Sommergruber K, Jutel M. Food and drug allergy, and anaphylaxis in EAACI journals (2018) [J]. Pediatr Allergy Immunol. 2019;30(8):785-794

14. Martin PE, Eckert JK, Koplin JJ, Lowe AJ, Gurrin LC, Dharmage SC, Vuillermin P, Tang ML, Ponsonby AL, Matheson M,et al. HealthNuts Study Investigators. Which infants with eczema are at risk of food allergy? Results from a population-based cohort [J]. Clin Exp Allergy. 2015 Jan;45(1):255-64.

15. Natsume O, Kabashima S, Nakazato J, Yamamoto-Hanada K, Narita M, Kondo M, Saito M, Kishino A, Takimoto T, Inoue E, et al. PETIT Study Team. Two-step egg introduction for prevention of egg allergy in high-risk infants with eczema (PETIT): a randomised, double-blind, placebo-controlled trial[J]. Lancet.2017Jan 21;389(10066):276-286.

Perkin MR, Logan K, Bahnson HT, Marrs T, Radulovic S, Craven J, Flohr C, Mills EN, Versteeg SA, van Ree R, et al. Enquiring About Tolerance (EAT) study team. Efficacy of the Enquiring About Tolerance (EAT) study among infants at high risk of developing food allergy[J]. J Allergy Clin Immunol. 2019 Dec;144(6):1606-1614.e2.

17. Amat F, Soria A, Tallon P, Bourgoin-Heck M, Lambert N, Deschildre A, Just J. New insights into the phenotypes of atopic dermatitis linked with allergies and asthma in children: An overview[J]. Clin Exp Allergy. 2018 Aug;48(8):919-934.

18. Ong PY. The PATHOGENesis of Food Allergy[J]. Front Pediatr. 2019 Nov 21;7:484.

19. Kim JP, Chao LX, Simpson EL, Silverberg JI. Persistence of atopic dermatitis (AD): A systematic review and meta-analysis[J]. J Am Acad Dermatol. 2016 Oct;75(4):681-687.e11.

20.Sicherer SH, Wood RA, Vickery BP, Jones SM, Liu AH, Fleischer DM, Dawson P, Mayer L, Burks AW, Grishin A, et al. The natural history of egg allergy in an observational cohort[J]. J Allergy Clin Immunol. 2014 Feb;133(2):492-499.

21.Tan JW, Joshi P. Egg allergy: an update[J]. J Paediatr Child Health. 2014 Jan;50(1):11-5.

22. Vermeulen EM, Koplin JJ, Dharmage SC, Gurrin LC, Peters RL, McWilliam V, Ponsonby AL, Dwyer T, Lowe AJ, Tang MLK, et al. HealthNuts investigators. Food Allergy Is an Important Risk Factor for Childhood Asthma, Irrespective of Whether It Resolves [J]. J Allergy Clin Immunol Pract. 2018 Jul-Aug;6(4):1336-1341.e3.

23. Rhodes HL, Sporik R, Thomas P, Holgate ST, Cogswell JJ. Early life risk factors for adult asthma: a birth cohort study of subjects at risk [J]. J Allergy Clin Immunol. 2001 Nov;108(5):720-5.

24. Sirin Kose S, Asilsoy S, Uzuner N, Karaman O, Anal O. Outcomes of Baked Milk and Egg Challenge in Cow's Milk and Hen's Egg Allergy: Can Tolerance Be Predicted with Allergen-Specific IgE and Prick-to-Prick Test? [J]. Int Arch Allergy Immunol. 2019;180(4):264-273.

25.Lozano-Ojalvo D, Pérez-Rodríguez L, Pablos-Tanarro A, Molina E, López-Fandiño R. Hydrolysed ovalbumin offers more effective preventive and therapeutic protection against egg allergy than the intact protein [J]. Clin Exp Allergy. 2017 Oct;47(10):1342-1354.

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