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A Multi-Center Study on Anaphylaxis caused by Peanut, Tree Nuts and Seeds in Children and Adolescents

Short Title: Anaphylaxis to Peanut, Tree Nuts and Seeds in Children

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Peanut (PN) and tree nuts (TNs) are common causes of anaphylaxis in Western countries but no information is available in Korea. To feature clinical characteristics of anaphylaxis caused by PN, TNs, and seeds, a retrospective medical record review was performed in 14 university hospitals in Korea (2009-2013). One hundred and twenty-six cases were identified, with the mean age of 4.9 years. PN, walnut (WN), and pine nut accounted for 32.5%, 41.3%, and 7.1%, respectively. The median values of specific IgE (sIgE) to PN, WN and pine nut were 10.50 kUA/L, 8.74 kUA/L and 4.61 kUA/L, respectively. Among 50 cases managed in the emergency department, 52.0% were treated with epinephrine, 66.0% with steroid, 94.0% with antihistamines, 36.0% with oxygen, and 48.0% with bronchodilator. In conclusion, WN, PN and pine nut were the 3 most common triggers of anaphylaxis in Korean children and anaphylaxis could occur at remarkably low levels of sIgE.

Keywords

Anaphylaxis, peanut, tree nuts, seeds, Korean children

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Conflict of Interest Statement

The authors state that there are no conflicts of interest to declare.

Introduction

Anaphylaxis is a serious allergic reaction that is rapid in onset and might cause death (1) and the rate of occurrence is increasing worldwide (2). Lifetime prevalence of anaphylaxis is estimated at 0.05-2% (2), and is 0.10-0.13% in Korean schoolchildren from a population study (3).

There has been a considerable increase in the prevalence of peanut (PN) and tree nut (TN) allergy in Western populations (4), and it seems to be increasing in Asian children although the studies are limited (5, 6). They are potent allergens, accounting for a relatively high proportion of fatal food-induced anaphylaxis (7). Due to the paucity of reports about childhood anaphylaxis caused by PN, TNs and seeds, we carried out this study to better characterize the clinical features, therapeutic approach of anaphylaxis caused by PN, various TNs and seeds in Korean children and adolescents.

Methods

According to International Statistical Classification of Diseases, 10th Revision, T78.0 (anaphylactic shock due to adverse food reaction) and T78.2 (anaphylactic shock) were selected. Retrospective medical record review was performed by pediatricians trained in pediatric allergy to identify cases of anaphylaxis caused by PN, TNs and seeds under 19 years of age between January 2009 and December 2013 in 14 university hospitals in South Korea. Patients who fulfilled the diagnostic criteria published in 2006 by the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (1) were diagnosed as having anaphylaxis. The study was approved by the Institutional Review Board from all participating hospitals.

Data collection was done using a case report form developed by Food Allergy and Atopic Dermatitis Study Group in the Korean Academy of Pediatric Allergy and Respiratory Diseases. The severity of symptoms was assessed according to the method used by Sampson (8).

The sensitization to PN, TNs or seeds was evaluated by the levels of specific immunoglobulin E (sIgE) using the ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden) in 104 cases, and by skin prick test (SPT) in 11 cases. The median levels of sIgE were determined for PN, walnut (WN) and pine nut, while the individual sIgE levels were listed for other TNs and seeds due to the small number of cases. The result of SPT was considered as positive when the diameter of wheal was (i) greater than 3mm; or (ii) equal to or greater than a histamine control.

Statistical analysis was done using SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA).

Results

The total number of cases of all-cause anaphylaxis was 991, among which 126 cases were caused by PN, TNs and seeds. The mean age was 4.9 years (range 0.8-18.9 years), and 64.3% were male. More than 80% were under 7 years of age.

The triggers of anaphylaxis identified were PN, WN, almond, hazelnut, pine nut, cashew nut, pistachio, pecan, macadamia nut, perilla seed, sunflower seed, and sesame seed. WN, which accounted for 41.2%, was the most common trigger. The second and the third common triggers were PN (32.5%) and pine nut (7.1%), respectively (Table 1).

During the anaphylactic episodes, cutaneous symptoms dominated (96.0%), followed by respiratory (87.3%), gastrointestinal (26.2%), cardiovascular (7.9%) and neurologic (4.8%) symptoms (a detailed listing of all symptoms provided in Table S1). Cardiovascular symptoms were significantly higher in the older age group (Fig. S1A). According to the severity grading (8), 74.6% were classified as Grade 4 or 5, mainly with lower respiratory tract involvement or hypotension (Fig. S1B). Among 87 cases in which symptom onset time was identified, 27.6% experienced anaphylaxis immediately after ingestion of the trigger, 35.6% within 30 minutes, and 26.5% between 30 minutes and 2 hours. Overall, 89.7% experienced symptoms of anaphylaxis within 2 hours from contact with the trigger.

Among 104 cases in which serum sIgE levels were measured by ImmunoCAP, the median levels of sIgE to PN, WN and pine nut were 10.50 kU_A/L, 8.74 kU_A/L, and 4.61 kU_A/L, respectively (Table 2A). The individual levels of sIgE to other TNs and seeds are listed in Table 2B because the statistical analysis was not available due to the small number of cases.

Among 50 cases managed in the emergency department (ED), 94% were treated with antihistamines, 66% with systemic steroid, 52% with epinephrine, 48% with inhaled bronchodilators, and 36% with oxygen supply. The percentages of epinephrine administration in the ED each year is listed in Table S2. The epinephrine auto-injector (EAI) was prescribed to 41.3% in overall.

Discussion

To our knowledge, this is the first multi-center study to investigate the clinical features and laboratory results of anaphylaxis caused by PN, TNs and seeds in children.

In our study, the number of all-cause anaphylaxis, food-induced anaphylaxis, and anaphylaxis caused by PN, TNs and seeds increased by 4.2-fold, 4.6-fold and 6.3-fold respectively during the 5 years.

The number of anaphylactic episodes caused by PN, TNs and seeds was highest in 3-6 years. This finding correlated with an earlier report on food-induced anaphylaxis in which PN and TNs were most common triggers in the pre-school age group (9). The mean age of 4.9 years in our study was in between the peak ages of PN (24 months) and TN (62 months) allergy in an earlier study (10). As in most of the previous pediatric studies (11, 12), male predominance was noticed.

Even though PN has been known as a more common cause of anaphylaxis than other TNs in Western countries (10, 13), WN was a more common cause of anaphylaxis than PN in our study. As the distribution of food triggers reflects diverse eating habits in different countries, the relatively lower consumption of PN and progressively increasing use of WN as an ingredient of various cuisines in Korea may be an explanation for this. Another noticeable finding was that pine nut, which is widely used in Korean dishes, was the third most common cause of anaphylaxis. In Western countries, cashew nut, almond and pecan are more common TNs responsible for acute allergic reactions than pine nut (10, 11). Perilla seed was the most common trigger of anaphylaxis among seeds in this study. As far as we know, this is the first report of perilla seed-induced anaphylaxis in children. Sesame seed was not identified as a common trigger, despite the increasing prevalence of sesame allergy especially in developed countries (14).

Percentages of cutaneous, respiratory and gastrointestinal symptoms recorded were comparable with the findings of earlier studies on pediatric anaphylaxis in general (12, 15). As described in a previous review (13), the cardiovascular symptoms were significantly

higher in adolescents. The comparison with data on pediatric anaphylaxis specifically caused by PN, TNs and seeds was not available due to the lack of previous studies.

The median level of PN-sIgE (10.50 kU_A/L) was relatively lower than the levels presented in previous reports on PN allergy (16). Fifty-eight percent of PN anaphylaxis cases had PN-sIgE levels lower than 14.0 kU_A/L, the diagnostic decision point of symptomatic PN allergy suggested previously (17), and the minimum PN-sIgE level was as low as 0.39 kU_A/L. The WN-sIgE levels had an extremely wide range of 0.04 – 100 kU_A/L, with the median level of WN-sIgE (8.74 kU_A/L) slightly higher than the previously reported level in clinical WN allergy (16). There were 3 cases (WN, almond and hazelnut respectively) in which the sIgE level was even lower than the assay cutoff point of 0.35 kU_A/L. To confirm the causal relationship, an OFC should have been performed in such cases but it was not possible in this study due to the retrospective nature. In a recent study on correlations between allergic testing modalities and severity of oral food challenges on PN, TNs and/or sesame seed, skin prick test and sIgE showed only a weak correlation with severity scores (18). However, without a molecular characterization of the allergens, any conclusion is inadequate because of the possibility of presence of genuine allergenic proteins such as oleosin.

Previous studies have documented that epinephrine was not usually given as the first-line treatment (19). In our study as well, epinephrine was given only in 52% of cases of anaphylaxis treated in the ED, presumably due to under-awareness of healthcare professionals. However, with increasing awareness, the percentages of epinephrine administration escalated during our five-year study period, with the highest percentage of 75% in year 2013. The EAI was apparently under-prescribed even in older age groups, as noted in other studies (20).

There are some limitations. Firstly, the potential for inadequate or incomplete documentation exists because of the retrospective study design. The second limitation is that our findings might not be directly applicable to other populations due to geographical and cultural differences. Therefore caution is necessary for extrapolating our study findings to other ethnic groups.

Conclusions

This is the first multi-center study of childhood anaphylaxis focused on PN, TNs and seeds. New findings of our study are that (i) WN was a more common trigger of pediatric anaphylaxis than PN, at least in our area; (ii) pine nut was a surprisingly common trigger of anaphylaxis; and (iii) anaphylaxis to PN, TNs and seeds could occur even at very low levels of sIgE. A better knowledge on triggers and characteristics of anaphylaxis may contribute to a better management.

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Table 1. Triggers of anaphylaxis

Allergen		n (%)
Peanut		41 (32.5)
Tree nuts	Walnut	52 (41.3)
	Pine nut	9 (7.1)
	Cashew nut	6 (4.8)
	Almond	3 (2.4)
	Hazelnut	3 (2.4)
	Pecan	3 (2.4)
	Pistachio	1 (0.8)
	Macadamia nut	1 (0.8)
Seeds	Perilla	4 (3.2)
	Sunflower	2 (1.6)
	Sesame	1 (0.8)

Table 2. Specific IgE levels to PN, TNs and seeds

Cause	No of subjects*	<0.35 kU _A /L, n (%)	Minimum (kU _A /L)	Median (kU _A /L)	Maximum (kU _A /L)
(A)					
Peanut	41	0 (0.0)	0.39	10.50	>100
Walnut	42	1 (2.4)	0.04	8.74	>100
Pine nut	7	0 (0.0)	0.60	4.61	11.60
Cause	Case	Gender	Age	sIgE (kU _A /L)	
(B)					
Almond	1	F	6.5	0.18	
	2	M	2.8	1.39	
	3	F	1.8	18.00	
Hazelnut	1	M	5.4	0.24	
	2	M	3.3	0.82	
	3	M	4.6	36.10	
Cashew nut	1	F	5.3	0.59	
	2	F	5.8	0.72	
	3	M	4.8	11.20	

Pistachio	1	F	6.3	0.97
Pecan	1	M	1.8	20.00
Sesame seed	1	F	0.9	5.49

* Number of subjects in which sIgE levels were measured.

References

1. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;**117**(2):391-397.
2. Lieberman P, Camargo CA, Jr., Bohlke K, Jick H, Miller RL, Sheikh A, et al. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. *Ann Allergy Asthma Immunol* 2006;**97**(5):596-602.
3. Ahn K, Kim J, Hahm MI, Lee SY, Kim WK, Chae Y, et al. Prevalence of immediate-type food allergy in Korean schoolchildren: a population-based study. *Allergy Asthma Proc* 2012;**33**(6):481-487.
4. Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol* 2010;**125**(6):1322-1326.
5. Shek LP, Cabrera-Morales EA, Soh SE, Gerez I, Ng PZ, Yi FC, et al. A population-based questionnaire survey on the prevalence of peanut, tree nut, and shellfish allergy in 2 Asian populations. *J Allergy Clin Immunol* 2010;**126**(2):324-331, 331 e321-327.
6. Park M, Kim D, Ahn K, Kim J, Han Y. Prevalence of immediate-type food allergy in early childhood in seoul. *Allergy Asthma Immunol Res* 2014;**6**(2):131-136.
7. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;**107**(1):191-193.
8. Sampson HA. Anaphylaxis and emergency treatment. *Pediatrics* 2003;**111**(6 Pt 3):1601-1608.
9. Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Garcez T, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. *J Allergy Clin Immunol* 2015;**135**(4):956-963 e951.
10. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. *Pediatrics* 1998;**102**(1):e6.
11. de Silva IL, Mehr SS, Tey D, Tang ML. Paediatric anaphylaxis: a 5 year retrospective review. *Allergy* 2008;**63**(8):1071-1076.
12. Orhan F, Canitez Y, Bakirtas A, Yilmaz O, Boz AB, Can D, et al. Anaphylaxis in Turkish children: a multi-centre, retrospective, case study. *Clin Exp Allergy* 2011;**41**(12):1767-1776.
13. Chipps BE. Update in pediatric anaphylaxis: a systematic review. *Clin Pediatr (Phila)*

2013;**52**(5):451-461.

14. Dalal I, Goldberg M, Katz Y. Sesame seed food allergy. *Curr Allergy Asthma Rep* 2012;**12**(4):339-345.

15. Novembre E, Cianferoni A, Bernardini R, Mugnaini L, Caffarelli C, Cavagni G, et al. Anaphylaxis in children: clinical and allergologic features. *Pediatrics* 1998;**101**(4):E8.

16. Maloney JM, Rudengren M, Ahlstedt S, Bock SA, Sampson HA. The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. *J Allergy Clin Immunol* 2008;**122**(1):145-151.

17. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;**100**(4):444-451.

18. Song Y, Wang J, Leung N, Wang LX, Lisann L, Sicherer SH, et al. Correlations between basophil activation, allergen-specific IgE with outcome and severity of oral food challenges. *Ann Allergy Asthma Immunol* 2015;**114**(4):319-326.

19. Braganza SC, Acworth JP, McKinnon DR, Peake JE, Brown AF. Paediatric emergency department anaphylaxis: different patterns from adults. *Arch Dis Child* 2006;**91**(2):159-163.

20. Clark S, Bock SA, Gaeta TJ, Brenner BE, Cydulka RK, Camargo CA, et al. Multicenter study of emergency department visits for food allergies. *J Allergy Clin Immunol* 2004;**113**(2):347-352.