INTRODUCTION

Anaphylaxis is a severe, systemic allergic reaction typically caused by food, drugs, or insect venom. The lifetime prevalence...
of anaphylaxis from all triggers is estimated to be 0.05%-2%. Although anaphylaxis is predominantly a childhood condition, most studies reporting on the clinical features and causes have focused on adult or combined adult and pediatric populations. Therefore, the prevalence and triggers of anaphylaxis in childhood cannot be assessed accurately because there are minimal pediatric data.

To date, drugs and insect stings are the most common anaphylaxis triggers in adults. By comparison, food is the most common cause in children. For example, a retrospective review of 5 years of Australian emergency department charts revealed that food (85%), unknown (9%), drugs (6%), and insect stings (3%) were the principal agents responsible for anaphylaxis in children. A separate study in the United States reported similar patterns. While drugs and insect stings are more prevalent triggers for adolescents than for infants and young children, insect stings are more likely to trigger large local reactions or urticaria than anaphylaxis in infants.

Few reports have investigated how the causes of anaphylaxis change throughout childhood. Therefore, we sought to better understand anaphylaxis triggers among different age groups of Korean children.

MATERIALS AND METHODS

Study design and participants

Data were collected retrospectively on patients under 18 years of age who were diagnosed with anaphylaxis between January 2009 and December 2013 in 23 secondary or tertiary pediatric allergy hospitals covering most major cities in South Korea. Using the International Statistical Classification of Diseases, 10th Revision (ICD-10) as a reference, T78.0 (anaphylactic reaction due to food), T78.2 (anaphylactic shock, unspecified), T80.5 (anaphylactic reaction due to serum), T63.4 (toxic effect of venom of other arthropods, labeled insect sting anaphylaxis for this study), and T88.6 (anaphylactic reaction due to adverse effect of correct drug or medication properly administered) were selected as anaphylaxis-associated codes. Medical record reviews ensured that each anaphylaxis category met 2005 Anaphylaxis Symposium (AS) criteria.

Demographic data, including age, sex, and personal and family histories of allergies, were collected. Laboratory results were examined (when available) to determine the anaphylaxis causes. Clinical manifestations of anaphylaxis were classified into 5 groups: cutaneous, respiratory, cardiovascular, gastrointestinal, and general. All symptoms were documented and investigated.

Laboratory data included the total and specific serum immunoglobulin E levels directed against trigger agents and skin prick and oral provocation test results. For patients who were simultaneously exposed to a variety of possible triggers and for whom no laboratory data were available, triggers were coded as “unknown.”

All data were recorded in case report form and entered into a customized Microsoft Access database by a single pediatric allergist. The study was approved by the Institutional Review Board of each participating hospital.

Triggers

The anaphylaxis triggers in this study were classified as food, drugs and radiocontrast media (RCM), exercise, insect stings, or idiopathic factors. Where possible, foods were also characterized more specifically as major food allergens based on the Food Allergen Labeling and Consumer Protection Act of 2004 (e.g., peanuts, tree nuts, fish, eggs, soy, and shellfish, including crustacean or molluscan) or “other food” category included items that were few in number and did not have a common category (e.g., red ginseng, Cacao).

Multiple component food items typically served hot (e.g., pizza, hamburger, and ramen) were coded as “unspecified foods.” “Idiopathic factor” is generally diagnosed when no trigger can be identified despite a detailed history of the episode and a comprehensive evaluation. When more than 1 food item was reported or a specific food was not listed, the “idiopathic factor” category was also used. Taking a combination of medications was recorded as “unspecified drugs.”

Comparisons by age group

Because anaphylaxis triggers differ between young children and adolescents, we analyzed them by 4 age groups based on developmental milestones: infants, ≤2 years; preschoolers, 3 to 6 years; school age children, 7 to 12 years; and adolescents, 13 to 18 years.

Statistical analysis

Statistical analyses were performed using version 19.0 of SPSS for Windows (SPSS, Chicago, IL, USA). Taking a cross-sectional approach, this report is limited to raw, stratified descriptions of variables. Missing data were reduced by queries to the study centers. Sex, date of birth, and date of reaction formed the minimum set of information used as an inclusion criterion. Other data missing from a medical record were coded as missing variables.

RESULTS

Demographics

During the 5 years of the study period, a total of 991 pediatric anaphylaxis events occurred in the 23 South Korean secondary and tertiary pediatric allergy hospitals in this study. A high proportion of these events (66.0%) affected male patients. The mean age of the study subjects was 5.89 years (± 5.24). Of the 991 study subjects, 363 (24.6%) were infants, 270 (27.2%) were...
In 740 food-induced anaphylaxis cases, milk (210 cases, 28.4%), egg white (101 cases, 13.6%), walnuts (59 cases, 8.0%), and wheat (53 cases, 7.2%) were the most frequent single food causes (Table 2). Tree nuts (13.2%) were the third most common food trigger group, which includes walnuts as the most common tree nut trigger, followed by pine nuts, cashews, and almonds. Food items reported <3 times in the study are not listed in detail, including other tree nuts (pecans, hazelnuts, sunflower seeds, macadamias, pistachios, and chestnuts), fruit (kiwi, peaches, apples, cherries, melon, jack fruit, and pineapples), cereals (sweet corn, oats, red beans, barley, and potato...
toes), and others (perilla, sesame, pumpkins, cacao, red ginseng, garlic, and goat milk). Pupa (0.8%) and Chinese yams (0.5%) were ranked among the least common triggers.

Food triggers differed by age group, with milk and seafood as the top triggers in age groups less than 6 years and greater than 7 years, respectively (Fig. 2). In patients less than 6 years of age, the most common triggers are milk, egg whites, walnuts, and wheat. In age groups with ages greater than 7 years, the common anaphylaxis triggers are buckwheat and seafood.

Table 3 shows the changes in specific food triggers over time. Frequencies of milk and tree nut-induced anaphylaxis showed a tendency to increase over time.

### Drug triggers of anaphylaxis by age

The drug triggers were antibiotics (37 cases, 34.9%), nonsteroidal anti-inflammatory drugs (NSAIDs, 19 cases, 17.9%), vaccines (10 cases, 9.4%), and drugs and RCM (7 cases, 6.6%) (Table 4). Muscle relaxants, idursulfase, anticonvulsants, and lidocaine were each indicated <3 times in the study. Cephalosporins (24 cases, 22.6%) and the influenza vaccine (7 cases, 6.6%) were the most frequent causes of antibiotics and vaccine-in-
Triggers of Anaphylaxis in Korean Children

To our knowledge, this is the first nationwide study to investigate common triggers of anaphylaxis by age in children in Korea and throughout the rest of Asia. The pattern of allergens reported as triggers for anaphylaxis was rather different between age groups. Although food was the most common cause of anaphylaxis in childhood, the frequency of drugs as triggers increased with age. Among the food triggers, milk, egg white, walnut, and wheat were the most common causes of anaphylaxis in young children. In older children, seafood and buckwheat were the most likely triggers.

In the present study, the main causes of anaphylaxis were food (74.7%), drugs and RCM (10.7%), idiopathic factors (9.2%), exercise (3.6%), and insect stings (1.8%). These results are quite different from those of a recent study of anaphylaxis epidemiology in Korean adults, wherein most cases were induced by drugs (46.6%), food (24.2%), insect stings (16.5%), and exercise (5.9%). As in this study, common anaphylaxis triggers for adults differed by age groups and geographical area. In Korean adults younger than 30 years old, food was the most common trigger, whereas drugs were the prime cause in patients older than 31 years. Seafood was the most common cause of food-induced anaphylaxis in Korean adults, and we found similar results in adolescents. Therefore, we suggest that seafood-induced anaphylaxis starts in adolescents and persists in young adulthood. This may partly reflect the fact that young children probably eat less seafood than adults in Korea.

In Western countries, milk and egg whites are described a frequent triggers of anaphylaxis in young children, while in school-age children, peanuts and tree nuts frequently trigger anaphylaxis. In this study, milk and egg white were the most common triggers of food-induced anaphylaxis only in young children, while seafood and buckwheat were found to be triggers more often in adolescents. This may be explained by a natural desensitization that occurs in many infants and children with clinical reactivity to milk and egg whites. For example, in a Danish study, 87% of subjects had recovered by 3 years of age and could tolerate. Food-induced anaphylaxis is a severe reaction of food allergy. Therefore, change with prevalence of milk- and egg white-induced anaphylaxis in children might be associated with natural history of milk and egg white allergies.

Although milk and egg white allergies are common worldwide in early childhood, the emergence of other, common food allergens varies in different countries, reflecting diet habits, genetic background, and exposure to food allergens early in life. In this study, tree nuts (13.2%) were one of the most common foods causing anaphylaxis. Among 5,149 participants in a U.S. registry that mainly included children with parent-reported peanut and/or tree nut allergies, the most commonly reported tree nut allergies were walnut (34%), followed by cashew (20%), almond (15%), pecan (9%), pistachio (7%), and the other tree nuts (<5% each). In a U.K. study, Brazil nuts was the most common tree nut allergen, followed by almonds, hazelnuts, and walnuts. Although these other data did not report on anaphylaxis triggers, tree nut allergies are one of the leading causes of fatal allergic reactions, and their prevalence appears to be increasing. The most likely tree nut to trigger allergic reactions may vary in different regions.

In this study, the most common tree nut triggers were walnuts, followed pine nuts, cashews, and almonds. Walnuts (8.0%) are a more prevalent cause of food-induced anaphylaxis than peanuts (6.2%) in this study. Although walnuts are one of the most frequent causes of food allergies and may induce fatal or near-fatal allergic reactions, it is rarely reported as a trigger in Asia. For example, in Singapore (another Asian country), peanuts are the most common anaphylaxis trigger in preschool children. In addition, our study demonstrated a higher prevalence of allergies to pupa, Chinese yam, and perilla compared to rates in Western countries. These findings suggest that more Korean children have been exposed to pupa, Chinese yam, and perilla than children in other countries.

We found that frequencies of milk- and tree nut-induced anaphylaxis increase over time, possibly following changes in children’s diets starting in early childhood. However, additional studies are needed to better understand connections between food triggers and diet patterns over time. For example, even among Asian children, common anaphylaxis food triggers vary by country. Some of these differences may be due to the availability of different types of food sources and variations in local dietary practice.

Drug triggers of anaphylaxis were caused by antibiotics,
NSAIDs, vaccines and drugs, and RCM. In Korean adults, NSAIDs are the most common drug allergens, followed by antibiotics and RCM.⁴ In the present study, drug triggers were more common in school children compared to infants and preschoolers. When antibiotics and NSAIDs are prescribed in school children, the potential for causing anaphylaxis should be taken into account.

There were several limitations to this study. First, the retrospective nature of the medical record review may have resulted in some inaccurate diagnostic coding. Secondly, selection bias may be a factor because only patients who visited secondary or tertiary pediatric allergy hospitals were chosen to participate. These patients may have sought further diagnosis or treatment based on personal choice, such as accessibility. Thirdly, our sample may not reflect the general population of young patients with anaphylaxis because participating organizations were selected because they are centers with pediatric allergy specialists. Nevertheless, because of the large number of participating centers and subjects in this study, these results may have a sentinel role.

To our knowledge, this is the largest study to investigate the change in anaphylaxis triggers by age group in childhood. Understanding these trigger patterns may help understand the pathophysiology of food allergies.

In conclusion, the most common anaphylaxis trigger in Korean children was food, which differed for Korean adults. In addition, the prevalence of drug triggers in children increased by age. These results should help improve the knowledge base and clinical outcomes for individuals at risk for anaphylaxis, particularly for children, as well as community awareness of anaphylaxis as a potentially fatal medical disorder.

REFERENCES

1. 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;97:596-602.
2. de Silva IL, Mehr SS, Tey D, Tang ML. Paediatric anaphylaxis: a 5 year retrospective review. Allergy 2008;63:1071-6.
3. Jirapongsananuruk O, Bunsawansong W, Phiyaphanee N, Visitsuntorn N, Thongngarm T, Vichyanond P. Features of patients with anaphylaxis admitted to a university hospital. Ann Allergy Asthma Immunol 2007;98:157-62.
4. Gaeta TJ, Clark S, Pelletier AJ, Camargo CA. National study of US emergency department visits for acute allergic reactions, 1993 to 2004. Ann Allergy Asthma Immunol 2007;98:360-5.
5. Liew WK, Chiang WC, Goh AE, Lim HH, Chay OM, Chang S, et al. Paediatric anaphylaxis in a Singaporean children cohort: changing food allergy triggers over time. Asia Pac Allergy 2013;3:29-34.
6. Ye YM, Kim HK, Kang HR, Kim TB, Sohn SW, Koh YI, et al. Predictors of the severity and serious outcomes of anaphylaxis in Korean adults: a multicenter retrospective case study. Allergy Asthma Immunol Res 2015;7:22-9.
7. Worm M, Eckermann O, Dölle S, Aberer W, Beyer K, Hawranek T, et al. Triggers and treatment of anaphylaxis: an analysis of 4,000 cases from Germany, Austria and Switzerland. Dtsch Arztebl Int 2014;111:367-75.
8. Huang E, Chawla K, Järvinen KM, Nowak-Wegrzyn A. Anaphylaxis in a New York City pediatric emergency department: triggers, treatments, and outcomes. J Clin Allergy Immunol 2012;129:162-168.e1-3.
9. Sampson HA, Muñoz-Furlong A, Aoki SA, Schmitt C, Bass R, Chowdhury BA, et al. Symposium on the definition and management of anaphylaxis: summary report. J Clin Allergy Immunol 2005;115:584-91.
10. Eder W, Ege MJ, von Mutius E. The asthma epidemic. N Engl J Med 2006;355:2226-35.
11. Wood RA, Sicherer SH, Vickery BP, Jones SM, Liu AH, Fleischer DM, et al. The natural history of milk allergy in an observational cohort. J Clin Allergy Immunol 2013;131:805-12.
12. Peters RL, Dharmage SC, Gurrin LC, Koplin JJ, Ponsonby AL, Lowe AJ, et al. The natural history and clinical predictors of egg allergy in the first 2 years of life: a prospective, population-based cohort study. J Allergy Clin Immunol 2014;134:485-91.
13. Hast A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. Clinical course in relation to clinical and immunological type of hypersensitivity reaction. Allergy 1990;45:587-96.
14. Sicherer SH, Furlong TJ, Muñoz-Furlong A, Burks AW, Sampson HA. A voluntary registry for peanut and tree nut allergy: characteristics of the first 5,149 registrants. J Allergy Clin Immunol 2001;108:128-32.
15. Ewan PW. Clinical study of peanut and nut allergy in 62 consecutive patients: new features and associations. BMJ 1996;312:1074-8.
16. Sicherer SH, Muñoz-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;125:1322-6.
17. Worm M, Moneret-Vautrin A, Scherer K, Lang R, Fernandez-Rivas M, Cardona V, et al. First European data from the network of severe allergic reactions (NORA). Allergy 2014;69:1397-404.

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