ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

The Features of Anaphylaxis Cases Followed in the Pediatric Allergy Clinic

Çocuk Alerji Kliniği'nde İzlenen Anafilaksili Olguların Özellikleri

Mahmut Doğru, İlknur Bostancı*, Serap Özmen*, Tayfur Giniş*, Handan Duman Şenol*

Zeynep Kamil Woman and Children's Disease Training and Research Hospital, Clinic of Child Health and Diseases, İstanbul, Turkey
*Dr. Sami Ulus Maternity and Children's Disease Training and Research Hospital, Clinic of Child Health and Diseases, Ankara, Turkey

Abstract

Introduction: Anaphylaxis is a severe hypersensitivity reaction that can be life-threatening. The frequency of anaphylaxis varies among the societies. In this study, the demographic characteristics, clinical course, triggering agents and treatment approaches of the patients who were diagnosed with anaphylaxis in our pediatric allergy clinic were evaluated.

Materials and Methods: The medical records of children who received a diagnosis of anaphylaxis between 2010 and 2012 were retrospectively evaluated.

Results: Between 2010 and 2012, 39.371 patients were admitted to our outpatient clinic. Sixty-six patients (49 male, 17 female) with a mean age of 8.9±5.3 years were evaluated as anaphylaxis. In 37 of the cases, anaphylactic attack occurred at home. Dermatological symptoms were the most frequent complaints. A probable cause of anaphylaxis was identified in all the patients except for five of them (92.4%). Food was the cause of anaphylaxis in 25 of the cases, followed by hymenoptera sting in 22 patients and drugs in 14 patients. The most common causes of anaphylaxis according to age groups were food, hymenoptera sting and drugs (0-3 years, 4-14 years and over the age of 14, respectively). Antihistamines were applied to all patients. The other medications that were applied were corticosteroid, oxygen, intravenous fluids, adrenaline (21/66), and salbutamol.

Conclusions: The common cause of anaphylaxis in children is food allergens. However, the frequency decreases by age and other causes are more common than food. In our country, usage of adrenaline for the treatment of anaphylaxis is low.

Keywords
Anaphylaxis, child, foods, adrenaline, tryptase

Öz

Giriş: Anafilaksi hayatı tehdit edebilen, ciddi bir hipersensitivite reaksiyonudur. Anafilaksi sıklığı toplumlara göre değişmektedir. Bu çalışmada çocuk alerji kliniğimizde anafilaksi tanısı konulan hastaların demografik özellikleri, klinik seyirleri, tetikleyici ajanlar ve tedavi yaklaşımları değerlendirilmiştir.

Gereç ve Yöntem: 2010-2012 yılları arasında anafilaksi tanısı konulan çocukların tıbbi kayıtları retrospektif olarak değerlendirildi.

Bulgular: Polikliniğimize 2010-2012 yılları arasında 39,371 hasta başvurdu. Yaş ortalaması 8,9±5,3 yıl olan 66 çocuk (49 erkek, 17 kız) anafilaksi olarak değerlendirildi. Olguların 37'sinde anafilaksi ev ortamında gerçekleşmişti. Dermatolojik semptomlar en sık başvuru şikayetleriydi. Beş hasta dışındaki tüm hastalarda (%92,4) olası anafilaksi nedeni tanımlandı. Besinler olguların 25'inde anafilaksi nedeniydi. Bunu takiben, olguların 22'sinde arı sokması, 14'ünde ilaçlar anafilaksi nedeniydi. Yaşlara göre en sık anafilaksi nedenleri besinler, arı sokması ve ilaçlardı (sırasıyla 0-3 yaş, 4-14 yaş ve 14 yaş üstü). Tüm hastalara antihistaminik uygulanmıştı. Uygulanan diğer ilaçlar kortikosteroid, oksijen, intravenöz sıvı, adrenalin (21/66) ve nebülize salbutamol idi.

Anahtar kelimeler
Anafilaksi, çocuk, besinler, adrenalin, triptaz

Received/Geliş Tarihi : 06.05.2016
Accepted/Kabul Tarihi : 19.10.2016

DOI:10.4274/jcp.58070

Address for Correspondence/Yazışma Adresi: Mahmut Doğru MD, Zeynep Kamil Woman and Children's Training and Research Hospital, Clinic of Child Health and Diseases, İstanbul, Turkey
Phone: +90 505 270 35 14
E-mail: mdmahmut@yahoo.com

Sonuç: Çocuklardaki anafilaksinin sık nedeni besin alerjenleridir. Fakat bu sıklık yaşla azalmaktadır ve diğer nedenler besinlerden daha sıktır. Ülkemizde anafilaksi tedavisinde adrenalin kullanımı düşüktür.

Introduction

Anaphylaxis is a term used to describe the sudden onset of a potentially fatal, severe systemic hypersensitivity reaction (1). The actual frequency of this disorder remains unknown. However, it is widely believed to be higher than previously reported, particularly since anaphylaxis is associated with a spectrum of manifestations ranging from mild symptoms, which are underreported, to very severe and fatal presentations. The prevalence of anaphylaxis in the general population, regardless of triggering agent, is estimated to be between 0.05-2%, with a higher reported frequency in children (2,3). Results of recent studies point to an increase in the frequency of anaphylaxis over the years, particularly in the young (4). Data on the characteristics of anaphylaxis in Turkey is sparse (5-8). The aim of this study was to share our experience as a tertiary pediatric center with anaphylaxis, with reference to demographic characteristics, clinical course, triggering agents and approach to treatment.

Materials and Methods

We used ICD-10 diagnostic codes to identify all children (under 18) presenting to the our outpatient clinic between 01.01.2010 and 31.12.2012, with an anaphylaxis. These codes included T78.2 (anaphylactic shock, undefined), T78.0 (anaphylactic shock due to adverse food reactions), T80.5 (anaphylactic shock due to serum), T88.6 (anaphylactic shock due to drugs). A diagnosis of anaphylaxis was made based on criteria put forth by the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (Table 1) (9). Details regarding patient demographics, presenting symptoms (dermatological, respiratory, cardiovascular, gastrointestinal, neurological, etc.), their onset and duration, triggering agent, underlying allergies, clinical course, presence of a biphasic reaction, recurrence rates and laboratory tests utilized were recorded. Patients with an identifiable trigger were subject to a skin prick test and/or specific immunoglobulin E (IgE) measurements after at least 6 weeks from an anaphylactic attack. Provocation tests were not performed due to ethical concerns.

The study was approved by the Local Ethics Committee of the Zeynep Kamil Woman and Children's Diseases Training and Research Hospital (Date: 07.06.2013, No: 59) and adhered to the principles of Helsinki Declaration. Oral informed consent was obtained from all subjects and their parents.

Skin Prick Test

The Quantitest used for the skin tests (Stallergenes SA, 92160, Antony, France) consisted of common aeroallergens (house dust, grass and tree pollen, molds, danders, and cockroaches) as well as suspected food allergens. In the event of a borderline result with any of the food allergens, a prick-to-prick test was performed directly from the suspected food. For patients with a

Table 1. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, and swollen lips-tongue-uvula) and at least 1 of the following;
a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia),
b. Reduced blood pressure or associated symptoms of end-organ dysfunction [eg, hypotonia (collapse), syncope, incontinence].
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours);
a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula),
b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia),
c. Reduced blood pressure or associated symptoms [eg, hypotonia (collapse), syncope, incontinence],
d. Persistent gastrointestinal symptoms (eg, cramping abdominal pain, vomiting).
3. Reduced blood pressure after exposure to a known allergen for that patient (minutes to several hours);
a. Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure*,
b. Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline.

Adapted from reference 6. *Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than [70 mmHg + (2x age)] from 1 to 10 years, and less than 90 mmHg from 11 to 17 years, Normal heart rate ranges from 80 to 140 beats/min at age 1 to 2 years, from 80 to 120 beats/min at age 3 years, and from 70 to 115 beats/min after age 3 years

suspicion of a drug allergy, intradermal testing was performed using custom-made solutions containing the offending drug. All skin prick tests were applied on the anterior surface of the forearm. Histamine (10 mg/mL) and physiologic saline were used as positive and negative references, respectively. Skin reactions were evaluated 20 minutes after application of the skin test, and an induration of ≥3 mm was considered indicative of a positive reaction.

Blood Sampling and Measurement of Serum Specific Immunoglobulin E and Tryptase Levels

Measurements of specific IgE were made using a immunoCAP system (Pharmacia Diagnostic AB, Uppsala, Sweden). A value greater than class 0 (<0.35 kU/L) was considered significant. Serum tryptase level was measured when the onset of symptoms was less than 3 hours. Serum tryptase levels were estimated by UniCAP (System ImmunoCAP Tryptase®, Pharmacia & Upjohn). According to the manufacturer, the interassay variability for tryptase levels between <1 and 100 mg/L is <5% and the upper 95th percentile for healthy nonallergic subjects is 11.4 kU/L. Levels above 11.4 kU/L was considered high.

Statistical Analysis

Data analysis was performed using the Statistical Package for Social Sciences for Windows 11.0 (Chicago, USA) packet program. Values for continuous variables were given as either mean ± standard deviation or as median, based on normality of distribution. The chi-square and Mann Whitney U tests were used to compare means, where applicable. A p-value of <0.05 was considered indicative of statistical significance.

Results

Out of the 39.371 children who presented to our outpatient clinic between 2010 and 2012, we reviewed the medical records for 241 children which were entered the above mentioned ICD-10 codes. Sixty-six (49 male, 17 female) of these cases met criteria for anaphylaxis, with a mean age of 8.9±5.3 years (0.9-18). The frequency of anaphylaxis in our clinic is thus 66/39.371 for two years. In 37 of our patients (56.1%) the anaphylactic attack occurred at home, with 6 patients (9.1%) developing anaphylaxis in the hospital. In the remaining 23 patients (33.8%), anaphylaxis occurred in outdoors. The mean age of onset of anaphylaxis was 81.9±63.7 (2-208) months. Twenty-seven patients (40.9%) had a previous history of an atopic disorder (12 of the patients with asthma, 11 of the patients with allergic rhinitis, 9 of the patients with atopic dermatitis) while a family history was present in 25 patients (37.9%).

Dermatological symptoms were the most commonly reported presenting complaints in our patient population (65/66, 98.5%), followed by respiratory symptoms (55/66, 83.3%), cardiovascular symptoms (21/66, 31.8%), gastrointestinal symptoms (16/66, 24.2%) and neurological symptoms (11/66, 16.7%). A summary of presenting findings is provided in Table 2.

Table 2. Presenting symptoms of anaphylaxis in our study population

Symptom	n	%
Dermatological	**65**	**98.5**
Angioedema	64	94.0
Urticaria	59	89.4
Pruritus	32	48.5
Respiratory	**55**	**83.3**
Cough	41	62.1
Shortness of breath	41	62.1
Wheezing	22	33.3
Hoarseness	12	18.2
Cyanosis	6	9.1
Nasal discharge	4	6.1
Nasal blockage	1	1.5
Feeling of choking	1	1.5
Stridor	1	1.5
Cardiovascular	**21**	**31.8**
Syncope	12	18.2
Hypotension	9	13.6
Cyanosis	6	9.1
Palpitation	1	1.5
Gastrointestinal	**16**	**24.2**
Vomiting	13	19.7
Abdominal pain	6	9.1
Nausea	5	7.6
Neurological	**11**	**16.7**
Confusion	11	16.7

A probable cause of anaphylaxis could be identified in all patients except for five (61/66, 92.4%). Food allergens were the recognized cause of anaphylaxis in 25 (37.9%) of the patients, followed by a hymenoptera sting in 22 (33.3%) patients and drugs in 14 (21.2%) patients. Beta-lactam antibiotics were the most common cause of drug-related anaphylaxis, whereas milk and dairy products were the most frequently encountered food allergens. Vespula spp were responsible for anaphylaxis in 20 (90.9%) of the patients who developed a reaction due to a hymenoptera. About half of the cases of drug-related anaphylaxis occurred in the hospital. A summary of triggers of anaphylaxis is shown in Table 3. The most common causes of anaphylaxis according to age groups are foods, hymenoptera sting and drugs (respectively 0-3 years, 4-14 years and over the age of 14) (Figure 1).

Table 3. Triggers of anaphylaxis in our study population and diagnostic evaluation

Triggers	n	%	Skin test	Spesific IgE	Clinical history
Foods	**25**	**37.9**			
Cow's milk	11	16.7	+	+	+
Hazelnut	2	3	+	+	+
Egg	2	3	+	+	+
Lentil	2	3	+	-	+
Wheat	2	3	+	+	+
Goat's milk	1	1.5	+	-	+
Peach	1	1.5	+	-	+
Walnut	1	1.5	+	-	+
Almond	1	1.5	+	-	+
Kiwi	1	1.5	+	-	+
Banana	1	1.5	+	-	+
Insect venom	**22**	**33.3**			
Vespula spp	20	30.3	+	+	+
Honeybee	2	3	+	+	+
Drugs	**14**	**21.2**			
Betalactam antibiotics	6	9.1	+	-	+
Nonsteroidal anti-inflammatory drugs	2	3	-	-	+
Anesthetics	2	3	+	-	+
Vaccines	2	3	+	-	+
Esomeprazole	1	1.5	+	-	+
Paracetamol	1	1.5	+	-	+
İdiopatic	**5**	**7.6**	**-**	**-**	**+**

IgE: Immunoglobulin E

Twenty-nine of our patients (43.9%) had a previous history of anaphylaxis with the identified allergen (15 of the patients with a food-related anaphylaxis-milk is the most common, 8 of the patients with venom-associated anaphylaxis, and 6 of the patients with drug-related anaphylaxis).

The mean time between the manifestation of symptoms and exposure to the allergen was 28.6±27.9 minutes (2-120, median: 20). A biphasic reaction was observed in four of the patients, whose symptoms recurred hours (most within 10 hours) after resolution of the initial phase. All patients received an antihistamine (mostly pheniramine maleate IM), followed by a corticosteroid (mostly Methyl prednisolone IM, Dexamethasone IM) in 64 (97.0%) patients, oxygen in 42 patients (63.6%), intravenous fluids in 29 patients (43.9%), epinephrine in 21 patients (31.8%), and a nebulized salbutamol in 17 patients (25.8%).

Thirty of the patients (45.5%) required hospitalization, with a mean duration of stay of 33.2±26.4 hours (8-120). Only seven patients required observation for more than 24 hours. Overall, it took anaphylactic symptoms an average of 87.2±69.8 minutes (10-480) to resolve. Tryptase measurement was made in 9 patients, and an elevated level of

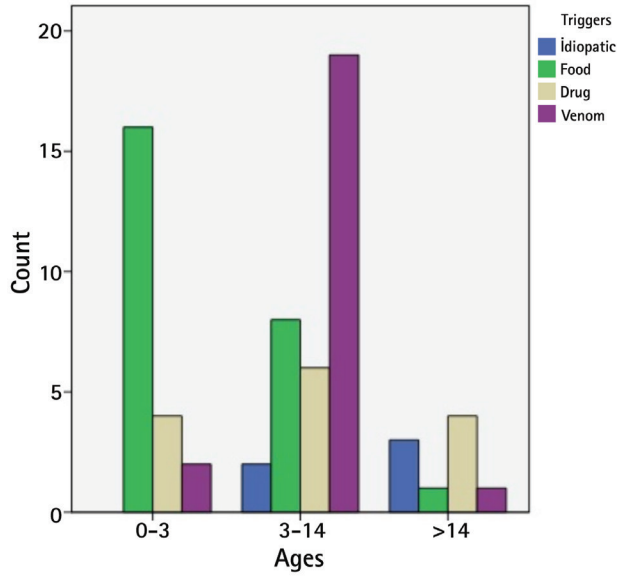

Figure 1. Causes of anaphylaxis according to age groups

11.4 kU/L was observed in only two of them (due to anesthetic and hymenoptera). An epinephrine auto-injector had been prescribed for all patients.

Discussion

Anaphylaxis is defined as a potentially fatal serious hypersensitivity reaction of sudden onset (1). It is the most serious clinical consequence of allergy, which can cause death when diagnosis and treatment of anaphylaxis is delayed. Anaphylaxis is an underdiagnosed condition since some of its features are shared by other clinical conditions. There are very few studies from Turkey on anaphylaxis (5-8).

Most of our cases (74.2%) were male, with particular prominence in patients under the age of 15 years, while in older patients, females were more prominent (10). A similar male predominance was reported in other studies (5,6,8,11,12). Annual frequency of anaphylaxis for our outpatient pediatric allergy clinic was 0.084%. Previously, the prevalence of anaphylaxis in the general population, regardless of the trigger, was estimated to be between 0.05-2% (2). However, in a more recent study it has been reported that all-cause anaphylaxis affects 6.7-70/100000 individuals annually (13). In a recent study, the frequency of anaphylaxis in patients admitted to the emergency room was found as 3.3/100000/year (14). Anaphylaxis is known to occur more commonly in children (3). In a study by Decker et al. (3), the reported annual prevalence of anaphylaxis for all ages was 49.8/100000 individuals, compared to 70/100000 individuals in patients under the age of 19 years. Recent studies have shown an increasing trend in the frequency of anaphylaxis, particularly in the very young (4). In two studies by the same work group, an increase in the annual frequency of anaphylaxis from 21/100000 individuals between 1983-1987 to 49/100000 individuals between 1990-2000 was observed (3,15).

More than half of our cases with anaphylaxis occurred at home, which is an expected result considering young children tend to spend most of their time indoors. This is similar with the results of other studies (11,16,17).

An allergic disorder was present in 40.9% of our patients with anaphylaxis, similar to the rate of 40.3% reported by Thong et al. (18), and lower than the 58.8% rate reported by Decker et al. (3).

In our patient group, dermatological, respiratory, cardiovascular, gastrointestinal and neurological symptoms occurred with decreasing frequency, a result was consistent with findings of other studies in the literature, with reported rates of 80-90%, 70%, 45%, 30-45% and 15%, respectively. Urticaria and angioedema were the most common presenting symptoms (13,19).

Food allergens were the most commonly identified cause of anaphylaxis in our patient population, with milk and dairy products at the forefront, followed by hazelnuts, eggs, lentils and wheat. Numerous other studies have also reported food as being the most common cause of anaphylaxis (3,5,11,12,15,17-21). Triggering food allergens differ according to the dietary habits of the population studied. For example, while De Swert et al. (11) reported peanuts to be the most common cause of anaphylaxis in their study population, in another study by Thong et al. (18) crustacean shellfish was the most frequently identified triggers. On the other hand, milk and fish were mainly implicated in a study by Novembre et al. (17).

Hymenoptera stings were the second most frequent cause of anaphylaxis in our study. In two studies by Decker et al. (3) and Orhan et al. (5), hymenoptera stings were the most common cause of anaphylaxis. Drugs were the third most frequent cause of anaphylaxis in our study, with beta lactam antibiotics at the top of the list, followed by nonsteroidal anti-inflammatory drugs (NSAID), anesthetics, and vaccines. Unlike in children, drugs are the leading cause of anaphylaxis in adults, occurring mainly in middle-aged individuals and the elderly. Similarly in our study, drugs are the most common cause of anaphylaxis over the age of 14. Antibiotics, particularly beta-lactams, along with NSAIDs are the main allergens implicated as a cause of anaphylaxis (13). While some studies in the literature list drugs as the second most frequent cause of anaphylaxis (11,17,20), other investigators like Pumphrey and Roberts (22) and Cianferoni et al. (23) reported drugs to be the leading cause in patients with fatal anaphylaxis or those hospitalized for anaphylaxis. Half of the drug related anaphylaxis in our study required hospitalization due to anaphylaxis.

About half of our patients gave a previous history of anaphylaxis, particularly in those for whom a food allergen was the identified cause of the reaction. De Swert et al. (11) also reported on similar findings in

their study, where they stressed on the importance of patient education with regard to the avoidance of the offending allergen.

The times between the development of anaphylaxis symptoms and exposure to the offending allergen observed in our study (2-120 minutes) is consistent with those reported in the literature (11,17,22). Symptoms of anaphylaxis usually manifest within 5-30 minutes of parenteral introduction of an allergen, however this period may sometimes extend beyond 1 hour. With oral exposure, symptoms usually develop within the first two hours (21).

Anaphylactic symptoms may recur hours after apparent resolution of initial symptoms. This is defined as a biphasic reaction, which has been reported to mostly occur within 10 hours of the initial attack. The reported incidence of biphasic reactions is between 1-23% (24). In our study, such a reaction was observed in 6.1% of patients.

Antihistamines were the most commonly used drugs for the treatment of anaphylaxis, a result similar to findings from previous studies (2,5,6,11,14). Even though antihistamines are considered a second line treatment option for the management of anaphylaxis, this group of drugs are still widely used as the first treatment of choice in our country (5,6). Adrenalin was used in nearly third of our patients. Adrenalin was reported to have been used in 32.3% of patients studied by Orhan et al. (5) and 44.4% of patients in a study by Vezir et al. (7). Epinephrine was mainly used to treat drug-related anaphylaxis, or in attacks that developed in the hospital. Failure to inject epinephrine promptly in patients with anaphylaxis occurs because of a lack of recognition of signs and symptoms, delayed diagnosis, perception that the episode is mild, preference for using an oral H1-antihistamine, and fear of side effects. Epinephrine should be administered as soon as the diagnosis of anaphylaxis is suspected.

Due to the lack of controlled studies how long patients with anaphylaxis will be observed, is undefined. The duration of follow-up differs with every patient, and a decision should be made taking into consideration the patient's general condition and the proximity of his/her place of residence to a healthcare facility. Some authors suggest that patients with moderate-severe anaphylaxis, those with active asthma, a history of a biphasic reaction and/or continuing risk of drug absorption should be followed up for 8-24 hours (21). While 45.5% of our patients required hospitalization, duration of stay was longer than 24 hours in only 7 patients.

Recently a multicenter study containing twelve centers with a number of 137 patients, two hundred and twenty-four anaphylactic events was reported. They reported 43.8% of the episode occurred at home. The symptoms, triggers and treatment of the patients of the study were similar to our patients. The difference with our study was occurrence of death (5).

Laboratory tests may be useful to confirm a diagnosis of anaphylaxis or to exclude the presence of other disorders that may mimic anaphylaxis. Measurement of serum tryptase, which should ideally be performed within moments of an anaphylactic attack, was performed in only 9 of our patients, and elevations were observed in only two patients. This may be attributed to inadequate blood sampling technique, as specimens needed to be centrifuged and extracted serum samples to be frozen almost immediately to obtain accurate measurements. On the other hand, serum tryptase levels are seldom increased when anaphylaxis is triggered by food or when hypotension or shock is absent (13).

Conclusions

Food allergens are the most common cause of childhood anaphylaxis in our study, with most cases occurring at home. But this frequency decreases with age and other factors (i.e drugs, venoms) become more common than food allergens. The usage of epinephrine rates for the treatment of anaphylaxis are quite low in Turkey, highlighting the need for doctor-oriented education aimed at raising awareness.

Ethics

Ethics Committee Approval: Zeynep Kamil Woman and Children's Diseases Training and Research Hospital (Date: 07.06.2013, No: 59), Informed Consent: It was taken.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Mahmut Doğru, Handan Duman Şenol, Tayfur Giniş, Concept: Mahmut Doğru, İlknur Bostancı, Serap Özmen, Design: Mahmut

Doğru, İlknur Bostancı, Serap Özmen, Data Collection or Processing: Mahmut Doğru, Handan Duman Şenol, Tayfur Giniş, Analysis or Interpretation: Mahmut Doğru, İlknur Bostancı, Serap Özmen, Handan Duman Şenol, Tayfur Giniş, Literature Search: Mahmut Doğru, İlknur Bostancı, Serap Özmen, Writing: Mahmut Doğru, İlknur Bostancı, Serap Özmen, Handan Duman Şenol, Tayfur Giniş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Simons FE, Ardusso LR, Bilò MB, Dimov V, Ebisawa M, El-Gamal YM, et al; World Allergy Organization. 2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis. Curr Opin Allergy Clin Immunol 2012;12:389-99.
2. Lieberman P, Camargo CA Jr, Bohlke K, Lieberman P, Camargo CA Jr, Bohlke K, 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.
3. Decker WW, Campbell RL, Manivannan V, Luke A, St Sauver JL, Weaver A, et al. The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project. J Allergy Clin Immunol 2008;122:1161-5.
4. Shen Y, Li L, Grant J, Rubio A, Zhao Z, Zhang X, et al. Anaphylactic deaths in Maryland (US) and Shanghai: a review of forensic autopsy cases from 2004 to 2006. Forensic Sci Int 2009;186:1-5.
5. 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;41:1767-76.
6. Serbes M, Can D, Atlihan F, Günay I, Asilsoy S, Altinöz S. Common features of anaphylaxis in children. Allergol Immunopathol (Madr) 2013;41:255-60.
7. Vezir E, Erkoçoğlu M, Kaya A, Toyran M, Özcan C, Akan A, et al. Characteristics of anaphylaxis in children referred to a tertiary care center. Allergy Asthma Proc 2013;34:239-46.
8. Topal E, Bakirtas A, Yilmaz O, Ertoy Karagol IH, Arga M, Demirsoy MS, et al. Anaphylaxis in infancy compared with older children. Allergy Asthma Proc 2013;34:233-8.
9. 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. Ann Emerg Med 2006;47:373-80.
10. Simons FER, Peterson S, Black C. Epinephrine dispensing for out-of-hospital treatment of anaphylaxis in infants and children: a population-based study. Ann Allergy Asthma Immunol 2001;86:622-6.
11. De Swert LF, Bullens D, Raes M, Dermaux AM. Anaphylaxis in referred pediatric patients: demographic and clinical features, triggers, and therapeutic approach. Eur J Pediatr 2008;167:1251-61.
12. Sheehan WJ, Graham D, Ma L, Baxi S, Phipatanakul W. Higher incidence of pediatric anaphylaxis in northern areas of the United States. J Allergy Clin Immunol 2009;124:850-2.
13. Simons FE. Anaphylaxis. J Allergy Clin Immunol 2010;125 (Suppl 2):161-81.
14. Harduar-Morano L, Simon MR, Watkins S, Blackmore C. Algorithm for the diagnosis of anaphylaxis and its validation using population-based data on emergency department visits for anaphylaxis in Florida. J Allergy Clin Immunol 2010;126:98-104.
15. Yocum MW, Butterfield JH, Klein JS, Volcheck GW, Schroeder DR, Silverstein MD. Epidemiology of anaphylaxis in Olmsted County: a population-based study. J Allergy Clin Immunol 1999;104:452-6.
16. Mehl A, Wahn U, Niggeman B. Anaphylactic reactions in children-a questionnaire-based survey in Germany. Allergy 2005;60:1440-5.
17. Novembre E, Cianferoni A, Bernardini R, Mugnaini L, Caffarelli C, Cavagni G, et al. Anaphylaxis in children: clinical and allergologic features. Pediatrics 1998;101:E8.
18. Thong BY, Cheng YK, Leong KP, Tang CY, Chng HH. Anaphylaxis in adults referred to a clinical immunology/allergy centre in Singapore. Singapore Med J 2005;46:529-34.
19. Ben-Shoshan M, Clarke AE. Anaphylaxis: past, present and future. Allergy 2011;66:1-14.
20. Pastorello EA, Rivolta F, Bianchi M, Mauro M, Pravettoni V. Incidence of anaphylaxis in the emergency department of a general hospital in Milan. J Chromatogr B Biomed Sci Appl 2001;756:11-7.
21. Lieberman PL. Anaphylaxis. In: Adkinson NF Jr, Bochner BS, Busse WW, Holgate ST, Lemanske RF Jr, Simons FER, editors. Middleton's allergy: principles and practice. 7th ed. China, Elsevier; 2009. p.1027-49.
22. Pumphrey RS, Roberts IS. Postmortem findings after fatal anaphylactic reactions. J Clin Pathol 2000;53:273-6.
23. Cianferoni A, Novembre E, Mugnaini L, Lombardi E, Bernardini R, Pucci N, et al. Clinical features of acute anaphylaxis in patients admitted to a university hospital: an 11-year retrospective review (1985-1996). Ann Allergy Asthma Immunol 2001;87:27-32.
24. Lieberman P. Biphasic anaphylactic reactions. Ann Allergy Asthma Immunol 2005;95:217-26.