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The etiology and clinical features of anaphylaxis in a developing country: A nationwide survey in Turkey

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Abstract

Background: Despite the increasing frequency of anaphylaxis, there is inadequate information on the etiology and clinical features in various countries, regions and age groups, especially in developing countries.

Objective: Our aim is to assess the etiology and clinical findings of anaphylaxis in Turkey. Gathering reliable data about the etiology and clinical findings of anaphylaxis in the general population will decrease the related morbidity and mortality.

Method: We obtained the names and phone numbers of individuals who had been prescribed an epinephrine auto-injector with a diagnosis of anaphylaxis from ministry of health. Demographic data, clinical history of the first episode of anaphylaxis including the triggering agent, clinical findings, course of hospitalization, and the management of anaphylaxis were obtained by phone survey.

Results: A total of 843 patients with a mean age of 21.4±17.3 years were evaluated. There was a significant male predominance among children younger than 10 years of age but a female predominance in older subjects. The most common causes of anaphylaxis were foods(40.1%) in children and bee venom(60.8%) in adults. The biphasic reaction rate was 4.3% and the median length of stay at an emergency department was 4.0 hours. Almost 60% of the patients had recurrent anaphylaxis episodes. Only 10.7% of the cases were prescribed an epinephrine auto-injector at their first anaphylaxis episode and only 59.2% of the patients were referred to an allergist during discharge from the emergency department.

Conclusions: In Turkey, bee venom was the most common cause of anaphylaxis, followed by food and drug. While more than a half of patients reported recurrent attacks; only 10% had been prescribed epinephrine auto-injector kit after their first episode. Strategies to improve the anaphyalxis management are therefore urgently required.

Keywords: Anaphylaxis, epidemiology, etiology, epinephrine autoinjector, food allergy, venom allergy, drug allergy

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Introduction

Anaphylaxis is a rare but life-threatening systemic reaction.[1] Its etiology and clinical features can vary according to the patient's age, the country and the region.[2-5] Despite the multiple published guidelines, the information on the diagnosis and treatment of anaphylaxis is still inadequate, even in developed countries.[1]

Anaphylaxis is a rare clinical condition. The level of knowledge and awareness of the physicians, the supply of healthcare services, and the development level of the country are variables that can influence the population's anaphylaxis awareness and therefore the anaphylaxis incidence.[6-8] It is therefore very difficult to conduct and compare population

-based studies on the incidence and clinical features of anaphylaxis from various countries on randomly selected samples of proper size. Most studies on the incidence, etiology and clinical features of anaphylaxis have therefore been conducted in developed western countries using hospital and regional healthcare records, ICD codes and follow-up of adrenalin auto-injector prescriptions.[4,5,9-11] There are very few studies with large patient groups from developing countries.[12-14]

Turkey, as a country with higher moderate income, has some features that are different than developed western countries as 48.8% of the population is younger than 30 years, and the mean educational duration is 7.6 years.[15,16] The aim of the study was to determine the etiology and clinical features of anaphylaxis by trying to reach all the patients prescribed adrenaline auto-injectors within a certain period. An increase in such data will enable comparison of countries and regions with different development levels, improvement of the clinical applications of physicians, and the development of methods for protection against anaphylaxis.

Methods

Epinephrine auto-injectors are not sold in pharmacies in Turkey. All prescribed epinephrine auto-injectors are provided and recorded by the Turkish Ministry of Health, from which we obtained the phone numbers of the patients who had been prescribed epinephrine auto-injectors. We obtained the names, surnames and phone numbers from the Turkish Ministery of Health, and then we conducted a cross-sectional phone survey with these subjects (or with their parents if they were under 18 years of age) between January 2008 and December 2011.

The phone survey was conducted by the pediatric allergy physicians. All the informations used in this study were obtained during phone survey. The participants were surveyed via a questionnaire composed of questions on demographic data, the indication for the epinephrine auto-injector prescription, the clinical history of first episode including the triggering agent, clinical findings, the location of the reaction, course of hospitalization, frequency of episodes, management plan for anaphylaxis, and the personal and family history for physician-diagnosed allergic disorders. We used the 2006 Second National Institute of Allergy and Infectious Disease/ Food Allergy and Anaphylaxis Network Symposium criteria for the definition and management of anaphylaxis.[1] Study subjects were divided into two groups according to their age at the first episode of anaphylaxis: Individuals younger than 18 years of age were grouped as children and older subjects were grouped as adults. The subject was listed as "unable to conducted" if the interview could not be carried out after three calls.

An individual was counted only once during the entire four-year period even if prescribed more than one epinephrine auto-injector.

The study was approved by the Ethics Committee of the Hacettepe University in Ankara, Turkey (Approval number: HET11/115-23). All the patients included in the study have received sufficient information and have given their verbal informed consent to participate in that study during phone survey.

Statistical analysis

Results were expressed as mean, median or percentages for the responses to each question. Student's t-test and the Mann-Whitney U-test were used for the analysis of normally distributed and skewed follow-up data, respectively. Categorical variables were compared with the Chi-square test. We analyzed the entire group and the two subgroups divided by age at the first anaphylaxis episode. A p-value ≤ 0.05 was considered indicative of statistical significance. The SPSS-15 statistical software package (SPSS, Inc., Chicago, IL) was used for the analyses.

Results

A total of 1802 patients were prescribed an epinephrine auto-injector in the relevant period. We were able to conduct the telephone survey in 1053 patients. An epinephrine auto -injector had been prescribed to 843 patients with a compatible history of anaphylaxis and 210 subjects who had a condition with a risk of anaphylaxis (such as food allergy, generalized cutaneous reactions due to bee venom or undergoing immunotherapy) but had never experienced it. We were unable to conduct the survey on 749 subjects (we could not reach 726 while 23 refused to take the survey) (**Figure 1**).

The age range of the 843 anaphylaxis patients was 1 to 79 years and 438 (52.0%) were male. The mean age was 27.5±19.1 years at present and 21.4±17.3 years at the time of the first anaphylactic episode. The demographic characteristics of the subjects are presented in **Table 1**.

Causes of Anaphylaxis

The most commonly reported causes of anaphylaxis were bee venom (49.6%), foods (25.0%), and drugs (12.0%) while 9.7% of the cases were idiopathic (**Table 1**). The most frequent cause of anaphylaxis among children was foods (40.1%), followed by bee venom (38.9%), idiopathic (8.8%), and drugs (8.1%). The causes in adults were bee venom (60.8%), drugs (16.1%), idiopathic (10.7%), and foods (9.2%) (**Table 1**).

The most common causes of food allergy were milk 15.5%), nuts (9.3%) and eggs (4.6%) in children, nuts and (2.7%) and fish (1.7%) in adults (**Table 1**). According to the age of the patient, milk was the leading cause of anaphylaxis in the first two years of life whereas nuts were the leading cause after this age (**Figure 2**). Food anaphylaxis appeared at earlier ages (9.5±14.3 years) compared to both bee venom and drug-induced anaphylaxis (25.6±16.4 and 26.7±16.5 years respectively, $p<0.001$) (**Figure 3a**).

The main causes of drug anaphylaxis were antibiotics and nonsteroidal anti-inflammatory drugs (NSAID) both in children and adults. Among antibiotics, penicillins were the most common allergens followed by cephalosporins both in children and adults (**Table 1**).

According to age at the time of anaphylaxis, there was a male predominance among children younger than 10 years of age and a female predominance in older subjects.

When compared according to gender, anaphylaxis due to bee venom was significantly more common in males than females, whereas anaphylaxis due to drugs was more frequent among females ($p<0.001$) (**Figure 3c**).

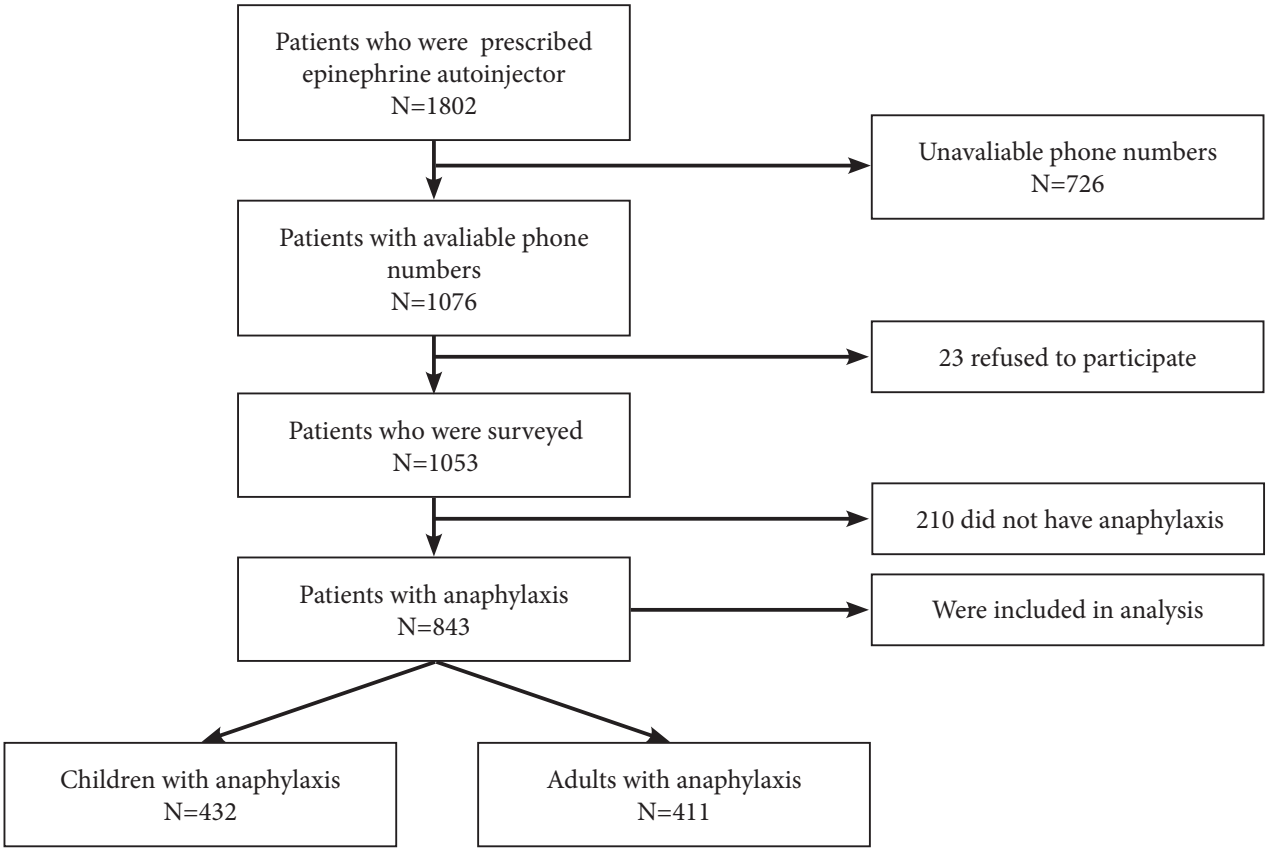

Figure 1. Study flow chart

Table 1. General characteristics and triggers in patients with anaphylaxis

	Total n=843	Children (<18 years) n=432	Adult (>18 years) n=411	P**
Age during survey, mean±SD	27.5±19.1	12.5±9.9	43.4±12.6	<0.001
Age at first episode, mean±SD	21.4±17.3	7.1±5.1	36.4±12.1	<0.001
Gender, male, n(%)	438(52.0)	267(61.8)	171(41.6)	<0.001
Type of trigger, n(%)				
Venom	418(49.6)	123(24.9)	250(60.8)	<0.001
Food	211(25.0)	173(40.1)	38(9.2)	<0.001
Milk	67(8.0)	67(15.5)	-	-
Nut	51(6.0)	40(9.3)	11(2.7)	-
Egg	23(2.7)	20(4.6)	3(0.7)	-
Fish	18(2.1)	11(2.5)	7(1.7)	-
Legume	10(1.2)	8(1.9)	2(0.5)	-
Others	42(5.0)	27(6.3)	15(3.6)	-
Drug	101(12.0)	35(8.1)	66(16.1)	<0.001
Penicillin	24(2.9)	11(2.5)	13(3.2)	-
Cephalosporin	7(0.8)	4(0.9)	3(0.7)	-
Other antibiotic	9(1.1)	3(0.7)	6(1.5)	-
NSAID	43(5.1)	12(2.8)	31(7.5)	-
Other medications	18(2.1)	5(1.2)	13(3.2)	-
İdiopathic	82(9.7)	38(8.8)	44(10.7)	0.350
Latex	9(1.1)	4(0.9)	5(1.2)	0.901
Others*	22(2.6)	14(3.2)	8(2.0)	-
Personal allergic disorders, n(%)				
Asthma	197(23.4)	117(27.1)	80(19.5)	0.013
Allergic rhinitis	148(17.6)	72(16.7)	76(18.5)	0.422
Atopic dermatitis	66(7.8)	61(14.1)	5(1.2)	<0.001

NSAID; nonsteroidal anti-inflammatory drugs; *cold urticaria (n=6), immunotherapy(n=2), inhalant allergy (n=12) and exercise induced anaphylaxis (n=2). ** P value between children and adult

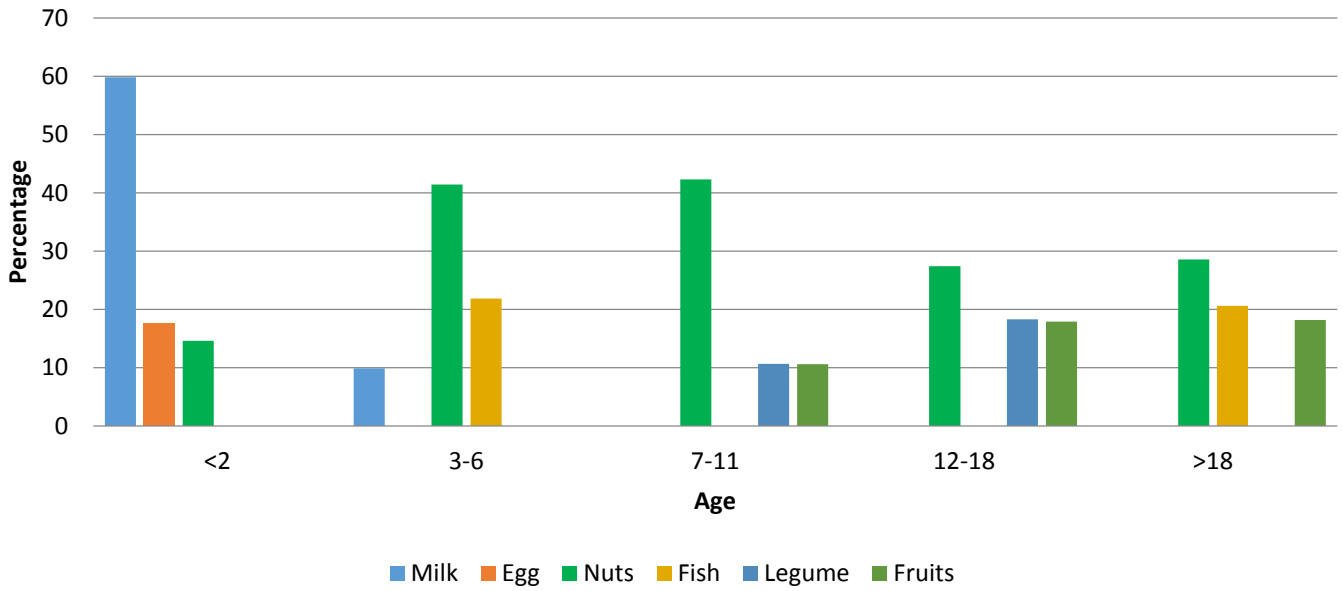

Figure 2. The three most common triggers of food-related anaphylaxis according to age groups

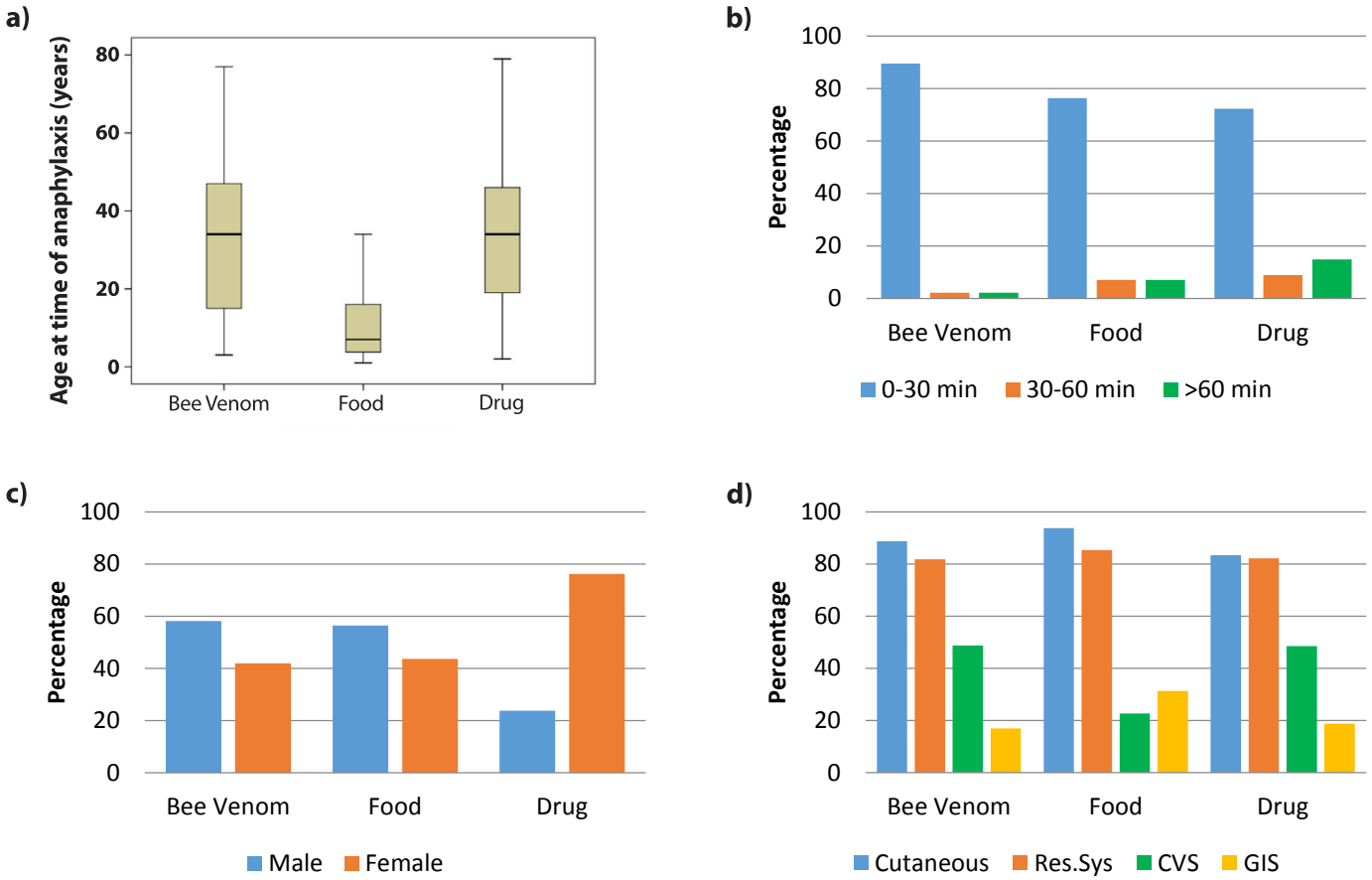

Figure 3. General features of anaphylactic episodes related to foods, drugs and bee venom: a) comparison of mean ages at the time of the first episode; b) comparison according to the duration between the trigger and onset of symptoms; c) comparison according to gender; d) comparison according to clinical findings

Clinical Manifestations in Anaphylaxis

Among the 843 individuals who had experienced anaphylaxis, mucocutaneous manifestations were the most commonly reported symptoms as seen in 91.7% of cases, followed by respiratory (83.7%), cardiovascular (40.0%) and gastrointestinal (21.0%) manifestations (**Table 2**).

Mucocutaneous and respiratory symptoms were more common in children ($p<0.001$) than adults, while adults presented

Table 2. General characteristics of first anaphylactic episodes

	Total n=843	Children (<18 years) n=432	Adult (>18 years) n=411	P*
Age at first episode, mean±SD	21.3±17.3	7.1±5.2	36.4±12.1	<0.001
Setting, n(%)				
Home	426(50.5)	260(60.2)	166(40.4)	<0.001
Outdoors	358(42.5)	140(32.4)	218(53.0)	<0.001
Hospital	37(4.4)	19(4.4)	18(4.4)	0.989
School/working office	22(2.6)	13(3.0)	9(2.2)	0.456
Time lapse between the trigger and onset of symptoms (min), n(%)				
<30	643(76.3)	331(76.6)	312(75.9)	0.809
30-60	34(4.0)	16(3.7)	18(4.4)	0.618
>60	43(5.1)	20(4.6)	23(5.6)	0.524
Could not remember	123(14.6)	65(15.1)	58(14.1)	0.809
Symptoms, n(%)				
Mucocutaneous symptoms	773(91.7)	411(95.1)	362(88.1)	<0.001
Respiratory tract symptoms	706(83.7)	378(87.5)	328(79.8)	<0.001
Cardiovascular system symptoms	337(40.0)	119(27.5)	218(53.0)	<0.001
Gastrointestinal tract symptoms	177(21.0)	95(22.0)	82(20.0)	0.467
Biphasic reaction, n(%)	36(4.3)	15(3.5)	21(5.1)	0.241
Epipen prescription in emergency, n(%)	90(10.7)	60(13.9)	30(7.3)	0.002
Referral to an allergist, n(%)	499(59.2)	278(64.3)	221(53.8)	0.002

* P value between children and adults

more frequently with cardiovascular symptoms than children (p<0.001). Food-induced anaphylaxis was more likely to cause gastrointestinal symptoms than drug- or venom-induced anaphylaxis (p<0.001 and p=0.021, respectively), while cardiovascular symptoms were more common in drug- and venom -induced anaphylaxis compared to cases due to foods (p<0.001) (**Figure 3d**).

Course of Anaphylaxis

The most common location of the anaphylaxis episode was the subject's home (50.5%) while 42.5% of the episodes cases. In case of bee venom, the rate of onset of symptoms within 30 minutes after contact with the trigger was higher than with food- and drug-induced anaphylaxis (p<0.001) (**Figure 3b**). A biphasic reaction was experienced by 36 subjects representing 4.3% of the anaphylactic reactions and did not differ between the two age groups and various triggers.

A total of 352 (41.7%) subjects had an anaphylactic episode once, while the rest had repeated episodes. Of the 843 patients, 191 (22.9%) had two episodes and 275 (33.0%) had at least three episodes of anaphylaxis.

Anaphylaxis management

Most of the patients (91.1%) were treated in an emergency setting during their first anaphylaxis episode. The median length of stay in the emergency department was 4.0 hours (range, 1-24 hours).

Although the epinephrine auto-injector prescription and referral to an allergist rates were higher in children, only 10.7% of the cases were prescribed an epinephrine auto-injector and only 59.2% of the patients were referred to an allergist during discharge from the emergency department (**Table 2**).

History of allergic diseases

Among the 843 patients, 343 of them had a personal history of one or more allergic diseases other than anaphylaxis. The most common was asthma (23.4%)while 17.6% had allergic rhinitis and 7.8% had atopic dermatitis. The frequencies of physician-diagnosed asthma and atopic dermatitis were higher in children than in adults (p=0.013 and p<0.001, respectively) (**Table 1**).

Discussion

This study described the etiology, clinical findings and management of Turkish patients with anaphylaxis. According to the result of the study, the most common causes of anaphylaxis were bee venom, foods and medications and there was a significant male predominance among children younger than 10 years of age, but a female predominance in older subjects. Mucocutaneous manifestations were the most commonly reported symptoms, while cardiovascular symptoms were more frequent in adults. The biphasic reaction rate was 4.3% and the median length of stay in the emergency department was 4.0 hours. Only 10.7% of the cases were prescribed an epinephrine auto-injector and only 59.2% of the patients were referred to an allergist during discharge from the emergency department.

Major causes of anaphylaxis may vary among different countries. In recent studies from China and Pakistan, medications were the leading cause of anaphylaxis in adults.[14,17] When we look at the childhood, results vary among studies. Hsin YC et al reposted that medication was the most common cause of anaphylaxis in children in Taiwan population,[18] while Orhan F et al showed that foods are the most common cause in children in Turkey.[12] Varitaion of

causes of anaphylaxis in different populations and also studies may be related to age, gender, cultural habbits, study population and geographic area. In our study, the most common cause of anaphylaxis was foods followed by bee venom in children while bee venom was the leading cause in adults in this study. Population-based studies estimate that the incidence of anaphylaxis due to bee venom ranges from 1.5 to 59.0%, most probably due to the variability in exposure to Hymenoptera venom.[19] Although there are a number of studies reporting relatively low frequencies,[3,20,21] a previous study from Turkey reported the rate of venom anaphylaxis as 37.5% during childhood which is similar to our results.[12] There may be several reasons for the high rate of venom anaphylaxis. Bee keeping is very common in almost all parts of our country and this might play a role by increasing the exposure rate. Besides, venom stings are usually painful, so most of the patients are aware that a sting has occurred. This may enable physicians to more easily diagnose Hymenoptera venom anaphylaxis compared to other causes. There may also be an actual increase in the rate of venom anaphylaxis since a three- to four-fold increase has been reported in patients seeking care for insect-related reactions.[22]

The order of allergenic foods that cause anaphylaxis varies between different ethnicities, cultures, eating habits, age groups and methods used. In accordance with the literature, we found that the most common reported cause of food-induced anaphylaxis was cow's milk followed by peanut and nuts in children, whereas peanuts and nuts were the most common causes followed by fish during adulthood.[2,3,21,23,24] In a previous study from Turkey, cow's milk was also reported as the most frequent cause of anaphylaxis during childhood similar to our results.[12]

We observed that the rate of anaphylaxis tended to be higher in males among patients younger than 10 years of age while there was a female predominance after this age, in accordance with the literature.[11,13,25] It is not clear why anaphylaxis is more common in females during adulthood and in males during childhood. However, studies in animal models have shown that estrogens enhance mast cell activation and allergen sensitization while progesterone increases target organ sensitivity to mediators.[26] Our results also revealed that anaphylactic episodes due to medications were significantly more common in girls than boys which supports the previous findings that the female gender has a higher risk for medication-induced anaphylaxis.[27]

Skin manifestations were the most common symptoms of anaphylaxis followed by respiratory system and cardiovascular system signs, similar to previous studies.[2-5,9,12] There was no mucocutaneous finding in about 10% of the episodes and also more than half of the episodes lacked cardiovascular symptoms. These findings supports that anaphylaxis may present with lack of skin findings and is not always related with cardiovascular collapse. Cardiovascular symptoms were more common in adults compared to children. This may be related to the high rate of and drug- and venom-induced anaphylaxis during adulthood as we also found that cardiovascular symptoms were more common in anaphylaxis induced by these substances than with food. Furthermore, the difficulty of recognizing cardiovascular symptoms in early ages may also have role in this finding. Cardiovascular system involvement (shock) and asphyxia are the major causes of mortality in anaphylaxis.[28,29] Studies from Australia and the United States have reported edications, insect stings and foods as the most common causes of anaphylaxis deaths.[30,31] The high mortality rate of drug- and venom-induced anaphylaxis could therefore be related to the more frequent involvement of the cardiovascular system with these triggers.

A retrospective study has reported the mean duration between exposure to the trigger and fatal cardiopulmonary arrest as 10-15 minutes for bee venom, 10-20 minutes for medications and 25-35 minutes for foods.[32] Bee venom-induced anaphylaxis was much more rapid in our study as well comparable with the findings of Orhan et al.[12] This is probably because anaphylaxis caused by ingested agents, including foods and drugs (for oral medications), is often slower to begin.

The prevalence of biphasic reactions is highly variable and ranges between 3% and 20% of the cases.[33-35] A total of 36 subjects (4.3%) experienced a biphasic reaction in our study and the median duration of observation was 4 hours. The significant frequency of biphasic reactions should be considered when deciding on the observation period after an initial event. The majority of the biphasic reactions occur within 8 hours, so an observation period of at least 8 hours after the initial manifestations have recovered is necessary.[33]

Current guidelines recommend that all patients suspected of having experienced an episode of anaphylaxis should be referred to an allergist and prescribed self-injectable epinephrine.[1] The fatal anaphylactic reaction risk has been reported to increase in patients who do not have epinephrine available at the time of the reaction.[29] Previous studies have demonstrated deficiencies in the management of anaphylactic patients with an epinephrine prescription rate of 16-43% and referral to an allergist rate of 12-31% at emergency department discharge.[36-38] In the current study, the epinephrine prescription rate on discharge was 10% and 59.2 % of the patients were referred to an allergist.

We also found that nearly 60% of patients had suffered an anaphylaxis episode more than once, indicating inadequate allergen avoidance among patients. Of the 843 patients, 191 (22.9%) had experienced a second event and 275 (33.0%) at least three episodes of anaphylaxis. Educational programs for physicians on the diagnosis and management of anaphylaxis prepared with the guidance of allergists are therefore needed to improve the standard of practice and ensure better management of anaphylaxis.

As expected, the most common causative agent responsible for anaphylactic episodes at home and outdoors and was foods (43.2%) and insect bite (86.3%), respectively. More than half of the reactions in children and nearly 40% of the reactions in adults had occurred at home in our study. All family members should therefore be adequately informed on medical treatment and the home administration of epinephrine should be encouraged. Besides, 3% of the reactions occurred at schools. This finding necessitates the presence of an anaphylaxis management policy at schools and the education of school staff.

Major limitation of our study is the underestimation that we could not avoid. Physician related factors including lack of recognition and diagnosis of anaphylaxis and subsequent

failure to prescribe epinephrine autoinjector might be a contributing factor for underestimation. Besides, in case of triggers such as medications, vaccines or biologic agents, physician might not prefer to prescribe epinephrine autoinjector or some of the physician might prescribe adrenaline flacon instead of an epinephrine autoinjector. Besides, we could not be able to survey with 749 cases which may be considered as a study bias.

We reported the etiologic and clinical characteristics of anaphylaxis in Turkey based on a survey of individuals throughout the country who were prescribed epinephrine auto-injectors in this study. This approach enabled capturing all the individuals who were prescribed an epinephrine auto -injector for anaphylaxis from all triggers, by all prescribing physicians, and from all parts of the country. Population -based anaphylaxis studies have used several methods including medical records,[2-4] international classification of diseases codes,[39,40] questionnaire[10] or epinephrine autoinjector dispending patterns.[11,41] Most of these studies were carried out in selected populations and mostly in Western countries. In two previous studies which used the epinephrine autoinjector dispending patterns, the data only included the demographic characteristics of the patients.[11,41] Our study is the first one which was carried out in our geographic region that includes a detailed data on etiology, clinical findings and management of anaphylaxis attacks in the general population.

In conclusion, bee venom was the most common cause of anaphylaxis, followed by food and drug in Turkey. While more than a half of patients reported recurrent attacks; only 10% had been prescribed epinephrine auto-injector kit after their first episode. Strategies to improve the anaphyalxis management are therefore urgently required.

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