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Original Article PEDIATRICS

A reference centre experience in central Anatolia in terms of causes, severity and treatment of childhood anaphylaxis

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ABSTRACT

OBJECTIVE: Anaphylaxis is a life-threatening reaction in every age groups. The causative factors, incidence, and severity of anaphylaxis differ between children and adults. Literature on anaphylaxis during childhood is insufficient. We believe that the data of this study will make important contributions to the literature.

METHODS: A retrospective analysis was conducted on patients aged 0–18 years who were admitted to the Pediatric Allergy Outpatient Clinic at Erciyes University between 2015 and 2021 and diagnosed with anaphylaxis.

RESULTS: The majority of the patients were male. Females, however, exhibited greater prevalence during adolescence ($p<0.001$). Of the total number of patients, 153 (86.9%) had atopy, whereas 25.56% had non-allergic chronic diseases. Food-induced anaphylaxis was identified in 49 (27.84%) patients, drug-induced anaphylaxis in 41 (23.29%), venom-induced anaphylaxis in 62 (35.22%) and idiopathic anaphylaxis in 19. The study observed that anaphylaxis affected several systems, including the skin/mucosa (91.47%), respiratory (72.15%), GI (40.34%), cardiovascular system (20.45%), and central nervous system (17.04%). It was also found that drug-induced anaphylaxis increased the severity of symptoms ($p=0.003$). Additionally, it was statistically significant that antibiotic-induced anaphylaxis ($p=0.002$) and wasp sting-induced anaphylaxis ($p=0.003$) developed within the first minute. Patients received intramuscular adrenaline in 95.46% of cases, while 4.54% did not receive appropriate treatment.

CONCLUSION: Anaphylaxis is a completely reversible reaction when diagnosed correctly and treated promptly. Therefore, it is essential to recognize the common triggers, know the risk factors, and provide patients with appropriate treatment. We believe that this study will contribute to better recognition of deficiencies in the management of anaphylaxis by highlighting important information for anaphylaxis.

Keywords: Adrenaline; anaphylaxis; childhood anaphylaxis; severity of anaphylaxis; trigger.

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Anaphylaxis is a rapidly developing, life-threatening and unpredictable reaction. If recognized early and treated properly, it's completely reversible [1].

Large-scale studies reveal an epidemiology of 50–112 cases per 100,000 people per year [2]. The incidence of anaphylaxis has shown a 4.3% increase annually between 2001–2010 [3]. While anaphylaxis can affect individuals of all ages, it's more prevalent in the 0–4 age group [4].

Cause of anaphylaxis varies based on age and country of residence. As anaphylaxis can have various causes, in certain cases, the triggering factor of the reaction cannot be identified. Hence, while anaphylaxis with un-

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known cause's rare in childhood, it has been found to be the most frequent trigger in some studies conducted with adults [5].

Allergic diseases, uncontrolled asthma, chronic conditions, medication usage can elevate the risk of anaphylaxis development [6].

The classical way for anaphylaxis to occur is IgE-mediated anaphylaxis. Mast cells and basophils plays important role in this pathway [7–9]. While there's evidence of anaphylaxis reactions involving IgG and immune complexes, non-allergic anaphylaxis can also occur in cases where the immune system isn't involved or the cause is unclear [7, 10].

There is no definitive laboratory test for diagnosing anaphylaxis. Diagnosis relies solely on clinical observations [11, 12]. If clinical findings indicate anaphylaxis, treatment should be initiated immediately, as this reaction can be mistaken for other diseases and can worsen rapidly [12]. The reaction typically occurs within 1 hour of exposure to the anaphylaxis agent. There are also potential difficulties in cases of biphasic anaphylaxis and late onset anaphylaxis [13].

While children typically experience skin/mucosal involvement the most, the respiratory, cardiovascular, gastrointestinal, and nervous systems may also be impacted. Urticaria is the most frequent symptom [14]. Reaction can be categorized as mild, moderate or severe, depending on symptom severity [15].

The indispensable administration in the treatment of anaphylaxis is always epinephrine to be administered intramuscularly without delay after diagnosis. The recommended dose of epinephrine is 0.01 mg/kg, administered into the vastus lateralis muscle [12].

The objective of the research is to ascertain the causative agents of anaphylaxis among children, the clinical manifestations, system participation, and the features of the observed reaction.

Highlight key points

- Atopy was detected in 86.9% of patients diagnosed with anaphylaxis.
- Skin reactions are the most common manifestation of anaphylaxis. The absence of skin involvement in 8.53% of patients should not delay the diagnosis of anaphylaxis.
- Drug-induced reactions are more severe.
- Reactions associated with antibiotic use and wasp stings occur more rapidly.
- The cause of anaphylaxis varies by age and gender. Among all patients, venom-associated anaphylaxis is the most common.

MATERIALS AND METHODS

Patiens

In this study, patients between the ages of 0–18 who were followed up with for anaphylaxis at Erciyes University Faculty of Medicine Pediatric Allergy Polyclinic between 2015–2021 were examined. Based on the data in the hospital information system and the hospital archive, an evaluation was made on the data of 176 patients who met the anaphylaxis diagnostic criteria. The study was conducted in accordance with the declaration Helsinki.

This single center retrospective cross-sectional study was conducted after the Erciyes University Clinical Research Ethics Committee with approval (approval number 2022/36, date 5/1/2022).

Prick Test

In the skin prick test, it was required that at least 4–6 weeks had passed since anaphylaxis before the test. Care was taken to ensure that the patients had not taken antihistamine medication in the last week. 23 parameters were evaluated in the prick test. Histamine was used as positive control. Physiological serum was used as negative control. Compared to negative control, those with an induration diameter of over 3 mm were considered positive.

Statistical Analysis

The data analysis was performed using the statistical software TURCOSA (Turcosa Analytics Ltd Co, Türkiye www.turcosa.com.tr). Numerical variables are presented as medians and quartiles, while categorical variables are presented as numbers and percentages. The data distribution was assessed using hypothesis tests (Shapiro Wilk, Kolmogorov-Smirnov normality test) and graphical methods (histogram, Q-Q plot, etc.). Objectivity and comprehensibility were prioritized in the presentation of the findings. The Mann-Whitney U test was employed to compare non-parametric data between groups, while categorical data was analyzed using the Pearson Chi-square and Fisher's exact tests. The level of significance was set at $p<0.05$.

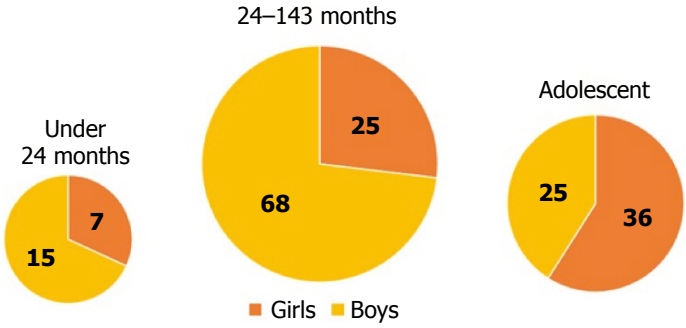


Figure 1. Number of the patients in the age groups.

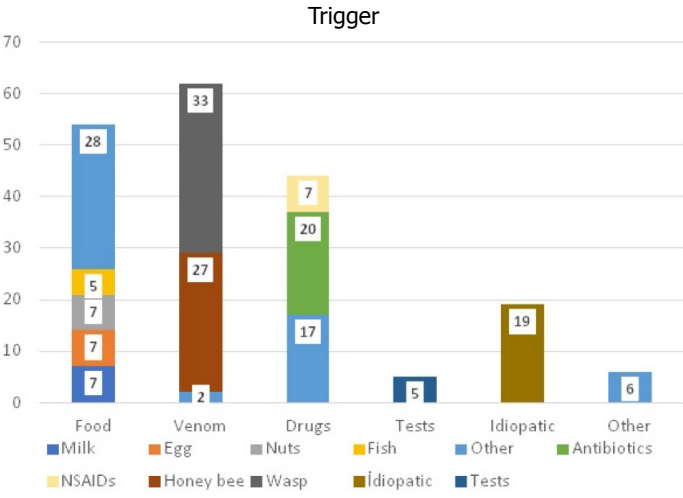


Figure 2. Trigger of the anaphylaxis reaction.

RESULTS

The mean age of 176 patients was 8.32±5.33 years. Of these patients, 108 (61.3%) were male, 68 (38.9%) were female. The patients were classified into three groups according to age-related risk factors, namely those under 24 months, those between 2–12 years, and adolescents (12 years and older). Of the patients under 24 months, 15 (68.18%) were male and 7 (31.81%) were female. Amongst the adolescent group, 25 (40.98%) were male and 36 (59.02%) were female. Among the two groups, boys accounted for 68 (73.11%) and girls 25 (26.88%). By age, the adolescent group was predominantly female ($p<0.001$) (Fig. 1).

Of the patients, 21 (11.93%) had obesity. There was no significant link between obesity and anaphylaxis severity ($p=0.49$) or recurrent anaphylaxis ($p=0.26$).

Atopy was present in 153 patients (86.9%), shown in Table 1.

Table 1. Atopy of the patients (n=176)

	%
Food allergy	31.81
Pollen allergy	23.29
Wasp venom allergy	18.75
Seasonal allergic rhinitis	17.61
Asthma	17.05
Honeybee venom allergy	15.3
Drug allergy	12.5
Cat allergy	7.38
House dust mites allergy	6.81
Atopic dermatitis	5.68
Mold allergy	3.4
Dog allergy	1.13

The rate of individuals with non-allergic chronic diseases was found 25.56%.

52 patients (29.54%) had recurrent anaphylaxis. There was no significant correlation between age groups and recurrent anaphylaxis ($p=0.21$).

In 49 patients (27.84%), anaphylaxis was triggered by food. Eggs, milk and nuts were triggered in 7 patients each (3.97%) and fish in 5 patients (2.84%).

41 patients (23.29%) presented drug-induced anaphylaxis. In 20 (11.36%) of these cases, antibiotics were the cause, while NSAIDs were responsible for 7 (3.97%) cases.

27 patients (15.34%) were diagnosed with anaphylaxis due to honeybee sting, whereas 33 patients (18.75%) had wasp sting-induced anaphylaxis.

Additionally, 19 patients (10.79%) were determined to have idiopathic anaphylaxis.

A total of 5 (2.84%) patients presented anaphylaxis following allergy test application. while rupture of hydatid cyst caused anaphylaxis in 1 patient (0.56%). In 5 patients (2.84%), anaphylaxis was associated with contact with cats (Fig. 2).

Patient's symptoms during anaphylaxis are listed in Table 2.

Affected systems were as follows: 161 patients (91.47%) had skin/mucous membrane involvement, while 127 (72.15%) presented with respiratory symptoms. 71 (40.34%) had GI symptoms, 30 (17.04%) suffered from

TABLE 2. Symptoms of anaphylaxis

	%
Urticaria	72.72
Shortness of breath	62.5
Angioedema	56.81
Vomiting	29.54
Hypotension	13.36
Nausea	9.09
Abdominal pain	7.38
Tachycardia	5.11
Cough	4.54
Cyanosis	4.54
Dizziness	4.54
Wheezing	4.54
Dysphagia	3.4
Sleepiness	2.84
Blackout	2.27
Throat itchiness.	2.27
Confusion	1.7
Sweating	1.7
Diarrhea	1.13
Itchy eyes	1.13
Seizure	1.13
Tingling in the mouth	1.13
Weakness	1.13
Arrest	0.56
Flushing	0.56
Shock	0.56
Sneezing	0.56

central nervous system (CNS) involvement, 36 (20.45%) reported cardiovascular system (CVS) symptoms (Fig. 3).

Mild, moderate and severe anaphylaxis were observed in 22 (12.5%), 105 (59.65%) and 49 (27.84%) patients. No statistically significant relationship was found between age-related risk factors and the severity of anaphylaxis or the presence of asthma (p=0.80, p=0.88).

The severity of anaphylaxis increased in cases of drug-induced anaphylaxis (p=0.003) (Table 3).

Biphasic anaphylaxis was observed in 7 patients (3.97%).

Upon retrospective analysis of anaphylaxis treatment, it was found that adrenaline was administered to 168 patients (95.46%), while 8 patients (4.54%) were given only pheniramine and dexamethasone.

TABLE 3. Drug induced anaphylaxis and severity of anaphylaxis (n=176)

	Drug induced anaphylaxis		
	No	Yes	Total
Anaphylaxis severity			
Mild	18	4	22
Moderate	88	17	105
Severe	29	20	49
Total	135	41	176

Pearson's Chi-Square. P=0.003.

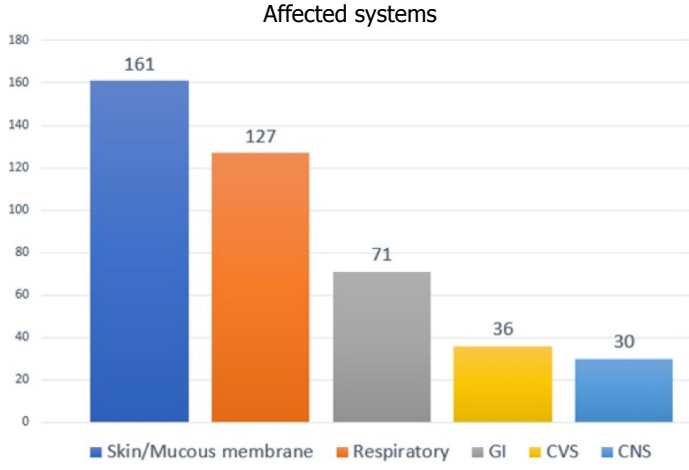


FIGURE 3. Affected systems.

When evaluating reactions within the first minute of exposure to the agent, it was significant that anaphylaxis induced by antibiotics (p=0.02) and wasp stings occurred within the first minute (p=0.03).

Eight patients (4.5%) who did not receive appropriate treatment were not treated with epinephrine and instead received glucocorticoids with antihistamines. All of these patients had multisystem involvement. One of these patients was classified as having severe anaphylaxis, one as having mild anaphylaxis, and the remaining six as having moderate anaphylaxis (Table 4).

DISCUSSION

Anaphylaxis is a potentially life-threatening reaction, and its prevalence is on the rise. Currently, there's a world-

Table 4. Patients who have not received appropriate treatment

Patient	Affected system	Severity of anaphylaxis	Treatment
1	Skin, respiratory	Moderate	Antihistamine + Glucocorticoid
2	Skin, gastrointestinal	Mild	Antihistamine + Glucocorticoid
3	Skin, respiratory	Moderate	Antihistamine + Glucocorticoid
4	Skin, respiratory	Moderate	Antihistamine + Glucocorticoid
5	Skin, respiratory	Moderate	Antihistamine + Glucocorticoid
6	Skin, respiratory, gastrointestinal	Moderate	Antihistamine + Glucocorticoid
7	Skin, CNS	Moderate	Antihistamine + Glucocorticoid
8	Skin, respiratory, CVS	Severe	Antihistamine + Glucocorticoid

CNS: Central nervous system; CVS: Cardiovascular system.

wide insufficiency of studies investigating anaphylaxis in pediatric populations, highlighting the need for a greater quantity and quality of research publications.

Anaphylaxis is more prevalent among women in adulthood, while in childhood, it's more prevalent in girls after puberty. 108 patients (61.3%) were male, 68 (38.9%) were female. Although males were more common in the study, the female gender was predominant in the adolescent period. In a comprehensive study including all age groups, 62% of 601 cases were females [16]. A study covering all age groups found that 62% of the 601 cases were female. A review comprehensively demonstrated that anaphylaxis was prevalent in males under the age of 10 years [17]. Another review indicated that girls experienced more anaphylaxis above 15 years of age [18]. Results aligned with the literature on the age and gender relationship.

The average age of the patients was 8.32±5.33 years. Categorized by age groups, 22 patients (12.5%) were below 24 months, 61 patients (34.65%) were adolescents, and 93 patients (52.84%) were between 2 and 12 years of age. The distribution was consistent with the multicenter study carried out in Türkiye [6].

Atopy was present in 86.9% of the patients. 17.61% of patients had seasonal allergic rhinitis, and 17% had asthma. Honey bee venom allergy was seen in 15.3% while wasp venom allergy was seen in 18.75%. The proportion of children with food allergy was 31.81%. Among food allergies, the most common allergy was to nuts with 16.47%. Drug allergy was present in 12.5% of patients and pollen allergy in 23.29%. In a large European study, asthma was associated with 22.9% of patients, seasonal allergic rhinitis was associated with 22.9% of patients and food allergy was the most common associated allergy in 55.43% of patients [19].

A history of atopy in first-degree relatives was present in 34.09% of the patients. In a study on pediatric anesthesia, family history was reported as a significant risk factor for anaphylaxis in such cases. However, many publications, including this study, had inadequate sharing of data regarding family history of anaphylaxis/atopy [20]. In a multicenter study conducted in Türkiye, the prevalence of family history of atopy was found to be 34.3%, which is similar [6].

The rate of individuals with non-allergic chronic diseases was 25.56%. Chronic diseases both activate inflammatory mechanisms and constitute a risk factor for anaphylaxis due to frequent drug use in the case of chronic disease. Unfortunately, the rates of non-allergic chronic diseases aren't reported in the literature.

Recurrent anaphylaxis was seen in 29.54% of patients. In a 2021 European review, recurrent anaphylaxis was seen in one in three patients [21].

A history of venom-induced anaphylaxis was present in 35.22% of patients.

Honeybee venom triggered anaphylaxis in 15.34% of patients, while wasp venom caused anaphylaxis in 18.75% of patients. 27.84% of patients experienced anaphylaxis due to food, with 3.97% developing it with eggs, milk, and nuts, respectively, and 2.84% with fish.

Drugs triggered anaphylaxis in 23.29% of patients, and 11.36% of all patients developed anaphylaxis after taking antibiotics.

The cause of anaphylaxis could not be identified in 10.79% of all patients.

In a study conducted in Türkiye, venom-induced anaphylaxis was the most frequently occurring factor, accounting for 32.3% of cases, followed by food-induced anaphylaxis at 31.3%, drug-induced anaphylaxis at 27.1%, and 8.3% of cases where the cause couldn't be determined. The study findings exhibit similarity [22]. In a study conducted in multiple centers in Türkiye, 38.4% of the participants experienced anaphylaxis due to food, 37.5% due to venom, and 21% due to drugs. 0.9% had idiopathic anaphylaxis [6]. Although foods and venoms were observed at similar rates, venom was found to be the most common trigger of anaphylaxis in some studies. The best example of how geographical structure affects anaphylaxis factors is a 5-year retrospective case review in Australia, in which 85% of patients had food-related anaphylaxis, drugs were the cause of anaphylaxis in 6% and insect stings in 3% [23]. In a study including both adult and pediatric data, idiopathic anaphylaxis was found to be the most frequent cause of anaphylaxis at 59%. This suggests that the causes of anaphylaxis vary according to age [16].

Skin/mucous membrane involvement was present in 91.47% of patients, respiratory system symptoms occurred in 72.15%, gastrointestinal system in 40.34%, cardiovascular system in 20.45% and CNS involvement in 17.04%. Similar results were obtained in previous studies conducted in Türkiye and Korea [22, 24].

Severe anaphylaxis was observed in 27.84%, mild in 12.5% and moderate in 59.65% of the patients. Although similar results have been observed in previous studies, mild anaphylaxis is expected to be the most common. This discrepancy between the data and the expectation is thought to be due to the fact that mild cases weren't admitted to the hospital or anaphylaxis wasn't recognized in these cases. In the study, no significant relationship was found between age groups and anaphylaxis severity. However, in a Korean study, it was reported that the severity of anaphylaxis increased with age. [24] This may be attributed to the different anaphylaxis triggers according to age. In the study, more severe reactions were seen in anaphylaxis triggered by drugs, especially antibiotics.

Biphasic anaphylaxis was seen in 3.97% of patients, and biphasic anaphylaxis was more common in NSAID-induced anaphylaxis. In a study including adult patients, the rate of biphasic anaphylaxis was 7.2% [13]. In another study, the rate of biphasic reactions was 11% and 75% of these reactions were food-related [25]. The incidence of biphasic reactions in adults reaches up to 20%, but 6% in children [26].

Patients diagnosed with anaphylaxis were evaluated, adrenaline was administered in 95.46% of the patients. In a multicentre study in Türkiye, adrenaline was administered to only 32.3% of patients, and it was noteworthy that 93.7% of patients received antihistamines and 83.5% received corticosteroids [6]. In another Turkish study, adrenaline was administered to 44.4% of patients [22]. In a Korean study, adrenaline was administered to 63.8% of patients [24]. In a Portuguese study, the rate of adrenaline administration was only 46% [27]. An analysis of 20 years of data from a center in Italy showed that intramuscular adrenaline was administered to only 18% of patients [28].

Although the skin is the most commonly involved system in anaphylaxis and all patients who did not receive appropriate treatment in this study had multiple system involvement including the skin, it was observed that adrenaline was not administered to these patients. Adrenaline administration should not be delayed after diagnosis.

Conclusion

Anaphylaxis is a serious reaction with sudden onset that can lead to death if not treated appropriately. Therefore, accurate diagnosis and treatment are essential. Although the frequency of the anaphylaxis is increasing, deficiencies of the diagnosis and treatment are noteworthy in the literature. It is imperative to increase the level of knowledge about anaphylaxis worldwide. We think the aim should be to recognize all patients in the early period, to manage cases appropriately and to administer intramuscular adrenaline, the most important treatment of anaphylaxis, in all patients. We believe that this study will contribute to better recognition of deficiencies in the management of anaphylaxis by giving important information for anaphylaxis.

Ethics Committee Approval: The Erciyes University Clinical Research Ethics Committee granted approval for this study (date: 05.01.2022, number: 2022/36).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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

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Authorship Contributions: Concept – TG, FT; Design – TG, FT; Supervision – FT; Data Collection and processing – TG, HE, SG; Analysis and interpretation – FT, HE, SG; Literature search – TG, HE, SG;Writing – TG, HE, SG; Critical review – FT, HE.

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