

Food-induced anaphylaxis in early childhood and factors associated with its severity

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ABSTRACT

Background: Several factors that increase the risk of severe food-induced anaphylaxis have been identified.

Objective: We aimed to determine the demographic, etiologic, and clinical features of food-induced anaphylaxis in early childhood and also any other factors associated with severe anaphylaxis.

Methods: We carried out a medical chart review of anaphylaxis cases from 16 pediatric allergy and immunology centers in Turkey.

Results: The data of 227 patients with 266 food-induced anaphylaxis episodes were included in the study. The median (interquartile range) age of the first anaphylaxis episode was 9 months (6–18 months); 160 of these patients were boys (70.5%). The anaphylaxis episodes were mild in 75 cases (28.2%), moderate in 154 cases (57.9%), and severe in 37 cases (13.9%). The most frequent food allergens involved were cow's milk (47.4%), nuts (16.7%), and hen's egg (15.8%). Epinephrine was administered in only 98 (36.8%) of these anaphylaxis episodes. A logistic regression analysis revealed two statistically significant factors that were independently associated with severe anaphylaxis: the presence of angioedema and hoarseness during the anaphylactic episode. Urticaria was observed less frequently in patients who developed hypotension. In addition, confusion and syncope were associated with 25.9- and 44.6-fold increases, respectively, in the risk of concomitant hypotension.

Conclusion: Cow's milk, nuts, and hen's egg caused the majority of mild and moderate-to-severe anaphylaxis episodes. The presence of angioedema and hoarseness in any patient who presents with a history of food-induced anaphylaxis should alert clinicians that the reaction may be severe. In addition, the presence of confusion, syncope, or stridor probably indicates concomitant hypotension.

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Food allergies affect children at a frequency of 6–8%, and foods are the main triggers of anaphylaxis in children, especially during early childhood.^{1–5} The etiologic factors of food-induced anaphylaxis differ in pediatric patients compared with adult patients. Although cow's milk, hen's egg, and peanut are the most common

allergens related to anaphylaxis in pediatric patients, peanut and seafood were found to be the most common allergens in an adult population. The clinical presentation (including the onset of symptoms, clinical severity, and sequence of symptom progression) may differ among individuals and also among distinct reactions in

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Table 1 Grading the severity of anaphylactic reactions*#

Grade	Skin	Gastrointestinal Tract	Respiratory	Cardiovascular	Neurologic
Mild	Sudden itching of eyes and nose, generalized pruritus, flushing, urticaria, angioedema	Oral pruritus, oral tingling, mild lip swelling, nausea or emesis, mild abdominal pain	Nasal congestion and/or sneezing, rhinorrhea, throat pruritus, throat tightness, mild wheezing	Tachycardia (increase > 15 beats/min)	Change in activity level plus anxiety
Moderate	Any of the above	Any of the above, crampy abdominal pain, diarrhea, recurrent vomiting	Any of above, hoarseness, barky cough, difficulty swallowing, stridor, dyspnea, moderate wheezing	As above	Light headedness feeling of pending doom
Severe	Any of the above	Any of the above, loss of bowel control	Any of the above, cyanosis or saturation < 92%, respiratory arrest	Hypotension and/or collapse, dysrhythmia, severe bradycardia and/or cardiac arrest§	Confusion, loss of consciousness

*From Ref. 13.

#The severity score should be based on the organ system most affected; the patient was considered as having severe anaphylaxis in the presence of one of the symptoms included in the severe group, among respiratory, cardiovascular, and neurologic systems.

§Hypotension defined as systolic blood pressure: 1 mo to 1 y <70 mm Hg; 1–10 y < [70 mm Hg + (2 × age)]; 11–17 y <90 mm Hg.

the same individual. Symptoms of food-induced anaphylaxis may also differ among different age groups of children.

Although urticaria and vomiting have been more commonly documented in infants, wheezing and stridor were found to be more frequent in preschool-age children.⁶ Most patients with food-induced anaphylaxis have a history of a reaction to food.^{7–9} The severity of allergic reactions to foods cannot be predicted by either the severity of previous reactions or by the results of allergy tests. In addition, in patients with a history of mild reactions, there is no way to know whether the next reaction to the same food will be life-threatening, near fatal, or fatal. Currently, several factors that increase the risk of severe food-induced anaphylaxis have been identified, including an atopic background, a preexisting food allergy, and co-existing asthma.^{8,10–12} However, few studies have investigated severe anaphylaxis in early childhood, so knowledge in this area is scarce. As a result, more studies are needed on this topic. The aim of this study was to determine the demographic, etiologic, and clinical features of food-induced anaphylaxis in early childhood and also the risk factors for severe anaphylaxis.

METHODS

Study Design and Population

We conducted a retrospective medical chart review of 16 pediatric allergy and immunology centers from

various cities in Turkey between January 2012 and March 2020. At these centers, the medical records of patients who visit the allergy clinic themselves or who are referred are maintained by pediatric allergists. This study included patients whose medical records were available for our review. [These medical records were retrospectively reviewed by pediatric allergists]. Children with a confirmed diagnosis of food-induced anaphylaxis were included in the final analysis. The severity of the anaphylaxis episode was determined according to the classification in the position paper of the European Academy of Allergy and Clinical Immunology (EAACI) on the management of anaphylaxis in childhood (Table 1).¹³ The severity was determined according to system involvement findings, whereas grading was assessed by using the information shown in Table 1.

Questionnaire

All the participants filled out a questionnaire that gathered their demographic data and clinical features. The data included the following: patient age, sex, and diet history; clinical manifestations; offending foods; the results of a diagnostic evaluation that included sensitization patterns to food allergens (by skin-prick testing [SPT] and/or measurement of serum food immunoglobulin E [IgE] levels); comorbid atopic diseases; other food allergies; any history of family atopic diseases and food allergies or previous urticaria in response to the same food; the interval between the time of exposure and the onset of anaphylaxis; the

number of previous anaphylaxis episodes and whether epinephrine was administered; and the need for intensive care unit treatment. Diagnostic testing was always based on the patient's history and was carried out by using SPTs and/or serum specific IgE levels.

The inclusion criteria of the study were as follows: patients (1) ages 0–6 years, (2) with complete medical records (including blood pressure measurements), (3) who met the criteria for anaphylaxis according to the Second Symposium on the Definition and Management of Anaphylaxis,¹⁴ and (4) whose diagnosis of food-induced anaphylaxis was proven by SPT and/or measurement of food-specific IgE levels. The exclusion criteria of the study were as follows: (1) anaphylaxis triggered by factors other than foods (*e.g.*, infections, drugs, venom), (2) incomplete medical records in terms of both the anaphylaxis diagnostic criteria and the severity grading findings, and (3) uncertainty in the diagnosis of anaphylaxis.

Definitions

Recurrent wheezing was defined as a history of two or more wheezing episodes. Rhinitis was defined as nasal symptoms, including anterior or posterior rhinorrhea, sneezing, nasal blockage, and/or itching of the nose; these symptoms must have occurred over two or more consecutive days for >1 hour on most days. Atopic eczema was defined as a chronic or recurrent inflammatory skin disease that is itchy and localized according to age. The complementary feeding period was defined as the period between 6 and 23 months of age. Hoarseness was defined as crying in a hoarse voice. Confusion was defined as apathy to the environment and/or a hypotonic appearance.

Laboratory Evaluation

The serum total IgE level, eosinophil count, and food-specific IgE level were measured. A specific IgE level > 0.35 kUA/L for any food allergen was considered positive. Those with a total percentage of eosinophils > 4% or an absolute eosinophil count > 350 cells/mm³ in a hemogram were described as having eosinophilia.

SPT

SPTs were performed by using the standard commercial extracts or, for nonavailable extracts, *via* the skin-prick-to-prick technique on the volar surface of the forearms or the back of the body with a 1-mm lancet according to the EAACI guidelines.¹⁵ A positive SPT result was defined as a mean wheal diameter of >3 mm than the negative control. Histamine (10 mg/mL) and saline solution were used as positive and negative controls, respectively. The commercial food allergen extracts (Abello-ALK, Madrid, Spain) used for the SPT were cow's milk, hen's egg (white and yolk), beef,

chicken, fish mix, wheat, rice, soybean, lentil, hazelnut, walnut, peanut, and pistachio.

Statistical Analysis

Statistical analysis was performed with SPSS Statistics (v.21.0; IBM Corp., Armonk, NY) and Microsoft Excel (Microsoft Corp., Redmond, WA). Normality was evaluated by the Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics were expressed as the frequency and percentage for categorical variables, whereas the median (interquartile range [IQR]) was used for non-normally distributed quantitative data. The categorical variables were compared by using the Pearson χ^2 test or the Fisher exact test, and the quantitative variables were compared with the Kruskal-Wallis test with a Bonferroni correction.

Binary and ordinal logistic regression was performed by including statistically significant and clinically important parameters to determine the factors that affect the severity of anaphylaxis. The total of the mild and moderate groups was assigned as a reference category in binary logistic regression and the mild group in ordinal logistic regression. Significant results were presented as odds ratio (OR) and 95% confidence interval (CI). A two-sided *p* value of <0.05 was considered statistically significant. The research protocol was approved by the ethical committee of Non-Invasive Clinical Research of Kocaeli University, Turkey (January 23, 2019, and December 2019). The families of the participants provided written informed consent.

RESULTS

Demographic and Diagnostic Workup

During the study period, 227 patients with 266 food-induced anaphylaxis episodes and with medical records were included in the study conducted at 16 pediatric allergy and asthma clinics. Of all the patients, 160 (70.5%) were boys, and median (IQR) age of anaphylaxis episodes of 9 months (6–18 months). Anaphylaxis was mild in 75 episodes (28.2%), moderate in 154 episodes (57.9%), and severe in 37 episodes (13.9%). In 202 of the 227 patients (88.9%), anaphylaxis occurred on the first known exposure to the triggering food. Recurrent anaphylaxis occurred in 25 patients (twice in 15 patients, three times in 8 patients, four times in 1 patient, and five times in 1 patient) before diagnosis. In 15 of these patients (6.6%), anaphylaxis occurred during the supplementary food period.

Among the recurrent anaphylaxis cases, the offending food was the same food allergen in 14 patients and different food allergens in 11 patients. In 100 episodes (37.6%), the patients had a history of food-induced urticaria previously with the same food before the anaphylaxis episode. Eight patients (3%) had multiple food allergies. Anaphylaxis episodes occurred at homes,

Table 2 Demographic characteristics according to the severity of anaphylaxis episode

	Severity of Anaphylaxis				<i>p</i>
	All (N = 266)	Mild (n = 75)	Moderate (n = 154)	Severe (n = 37)	
Age of the patients with an anaphylaxis episode, median (IQR), mo	9 (6–18)	7 (6–14)	9 (6–23)	9 (5–12)	0.467*
Boys, <i>n</i> (%)#	160 (70.5)	46 (66.7)	92 (71.3)	22 (75.9)	0.628§
Serum total IgE, median (min-max), kU/L	129.4 (54–410.5)	112.5 (42.6–243)	135 (53.1–447)	250 (69–799)	0.032*¶
Eosinophil count, median (min-max), cell/mm ³	460 (232.5–760)	471.5 (248–783.5)	380 (200–700)	500 (220–810)	0.258*
Allergy to multiple foods, <i>n</i> (%)#	41 (18.1)	12 (17.4)	25 (19.7)	4 (13.8)	0.742§
Atopy, <i>n</i> (%)					
Recurrent wheeze	85 (32)	20 (30.8)	52 (37.7)	13 (35.1)	0.630§
Rhinitis	87 (32.7)	23 (35.4)	50 (35.7)	14 (37.8)	0.966§
Atopic dermatitis	54 (20.3)	14 (18.7)	34 (22.1)	6 (16.2)	0.668§
History of same food-induced anaphylaxis, <i>n</i> (%)	26 (9.8)	7 (9.3)	14 (9.1)	5 (13.5)	0.607§
History of same food- induced urticaria, <i>n</i> (%)	100 (37.6)	29 (38.7)	57 (37.0)	14 (37.8)	0.802§
Family history of atopy, <i>n</i> (%)	109 (41)	31 (41.3)	65 (42.2)	13 (35.1)	0.733§
Location, <i>n</i> (%)					
Home	255 (95.9)	71 (92.2)	152 (98.2)	36 (96.7)	0.110
Allergy clinic	7 (2.6)	2 (3.9)	4 (3.6)	1 (3.3)	0.567
School	4 (1.5)	2 (2.7)	2 (1.3)	—	0.549
Kindergarten	2 (0.8)	1 (1.3)	1 (0.6)	—	0.667
Restaurant	—	—	—	—	—
IM epinephrine treatment, <i>n</i> (%)	98 (36.8)	28 (37.4)	51 (33.1)	19 (51.3)	0.277
IM epinephrine treatment ≥ 2 times, <i>n</i> (%)	22 (8.3)	3 (4)	12 (7.8)	7 (18.8)	0.037
Admitted to intensive care unit, <i>n</i> (%)	11 (4.1)	—	5 (3.2)	6 (16.2)	0.002

IQR = Interquartile range; IgE = immunoglobulin E; min = minimum; max = maximum; IM = intramuscular.

*Kruskal-Wallis test.

#A total of 227 patients with 266 episodes.

§ χ^2 test.

¶Mild and severe groups are different.

||Fisher Exact test.

allergy clinics, schools, and kindergartens in 255 (95.9%), 7 (2.6%), 4 (1.5%), and 2 patients (0.8%), respectively. In 243 episodes (91.4%), anaphylaxis occurred during the complementary feeding period. In 109 episodes, 41% of the parents had a history of atopic diseases. Eosinophilia and serum total IgE levels > 100 IU/L were detected in 147 (64.7%) and 151 patients (66.5%), respectively.

The demographic data of the patients are summarized in Table 2. SPT and/or food-specific IgE levels were used for diagnosis. The medians (IQRs) for positive SPT results and serum food-specific IgE levels are shown in Online Appendix 1. Intramuscular (IM) epinephrine treatment was given in 98 anaphylaxis episodes (36.8%).

Of the 37 severe episodes, 19 (51.3%) were treated with epinephrine. Twenty-two (8.3%) required repeated doses of epinephrine (20 anaphylaxis episodes treated with IM epinephrine twice and two treated three times with IM epinephrine). There were three patients with bradycardia and/or cardiac arrest. In these patients, adrenaline was administered three times in one patient and twice in two patients. Eleven anaphylaxis episodes (4.1%) were treated in an intensive care unit.

Trigger of Anaphylaxis and Severe Episodes

In the etiologic evaluation of food-induced anaphylaxis, 25 foods were detected as causative allergens. The most frequent food allergens involved were cow's

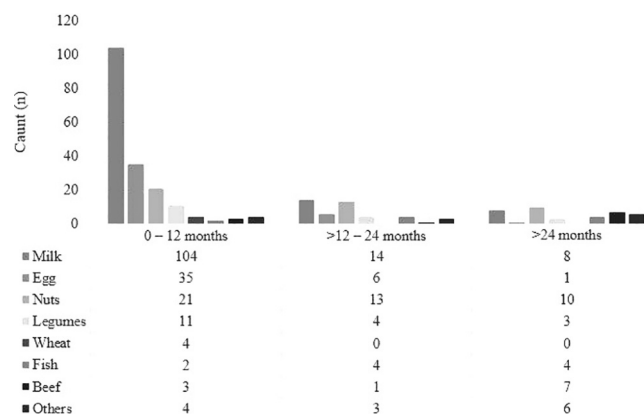


Figure 1. Frequency of food allergens according to age group.

milk (47.4%), nuts (16.7%), hen's egg (15.8%), lentils (4.5%), and fish (3.8%). The most common food allergens, according to age groups, were milk and egg in those < 12 months old, whereas milk and nuts were the most common allergens in those > 12 months (Fig. 1). In terms of the severity of reactions, cow's milk and hen's egg were found to be the major causative allergens in mild, moderate, and severe reactions. Also, it is worth noting that reactions due to chickpea were found to be severe in most of the patients (Table 3).

Clinical Manifestations

The skin and the respiratory system were most affected. Food proteins according to system involvement during index anaphylaxis episodes are presented in Online Appendix 2. With respect to the clinical manifestations, cutaneous symptoms were most frequently observed, with a proportion of 96.6%, and respiratory symptoms were 80.1%. With regard to system involvement, urticaria, dyspnea, vomiting, tachycardia, and syncope were the most common clinical manifestations, with a frequency of 83.8, 44.7, 45.9, 19.2, and 6.2%, respectively. In 262 episodes (98.4%), anaphylaxis developed within the first 2 hours. The symptoms and signs of food-induced anaphylaxis are summarized in Table 4.

Specificities of Severe Anaphylaxis

Severe anaphylaxis constituted 37 of all anaphylaxis episodes (13.9%) in our study. The median (IQR) age of anaphylaxis episodes was 9 months (5–12 months). Cutaneous manifestations (e.g., flushing), cardiovascular manifestations (e.g., hypotension), and respiratory system manifestations (e.g., hoarseness and dyspnea) were more common in severe anaphylaxis. The combination of manifestations, including hypotension, dyspnea, cyanosis, and angioedema, in severe anaphylaxis is shown in Fig. 2. In addition, the demographic characteristics of 37 severe anaphylaxis episodes are given in Online Appendix 3.

Similarities and Differences between Anaphylaxis Severities

The demographic characteristics of the patients, such as age, sex, presence of multiple food allergies, and presence of comorbid atopic diseases, did not differ according to the severity of anaphylaxis ($p > 0.05$) (Table 2). With respect to the etiology, anaphylaxis due to chickpea tended to be severe ($p = 0.007$) (Table 3). Cutaneous manifestations were more commonly observed in mild anaphylaxis ($p = 0.038$); respiratory system manifestations were common in moderate anaphylaxis ($p < 0.001$); and gastrointestinal ($p = 0.01$), cardiovascular ($p < 0.001$), and neurologic system ($p < 0.001$) manifestations were more common in severe anaphylaxis.

When evaluated based on symptoms and signs, flushing was more common in severe anaphylaxis ($p < 0.001$), and angioedema was less common in mild anaphylaxis ($p < 0.001$) among cutaneous manifestations. Among respiratory system manifestations, sneezing was more common in mild and moderate anaphylaxis ($p < 0.001$), whereas hoarseness ($p < 0.001$), dyspnea ($p < 0.001$), coughing ($p < 0.001$), and stridor ($p = 0.005$) were markedly more common in severe anaphylaxis. In contrast, recurrent vomiting was more common in severe anaphylaxis ($p = 0.017$), whereas nausea was more common in mild anaphylaxis ($p < 0.001$) among gastrointestinal manifestations. Also, cardiovascular findings (e.g., tachycardia) with neurologic findings (e.g., confusion) were more common in severe anaphylaxis ($p < 0.001$) (Table 4).

Independent Risk Factors Associated with Severe Anaphylaxis

Statistically significant signs and symptoms (presented in Table 4) were separately analyzed in an ordinal logistic regression. This analysis revealed two statistically significant factors that were independently associated with severe anaphylaxis: presence of angioedema (OR 3.29 [95% CI, 1.95–5.57]; $p < 0.001$) and hoarseness in anaphylaxis episodes (OR 4.16 [95% CI, 1.58–10.94]; $p = 0.005$) (Table 5). When the frequency of hypotension, syncope, and cyanosis, the three major symptoms of severe anaphylaxis, was evaluated together with other findings, the absence of urticaria was associated with a 5.814-fold (OR 0.172 [95% CI, 0.034–0.859]; $p < 0.032$) increase in the risk of concomitant hypotension. Confusion and syncope were associated with a 25.9-fold (OR 25.916 [95% CI, 3.742–179.477]; $p = 0.001$) and 44.6-fold (OR 44.686 [95% CI, 8.351–239.108]; $p < 0.001$) increase in the risk of concomitant hypotension, respectively. Multivariate logistic regression analysis of these three main symptoms of severe anaphylaxis is presented in Online Appendices 4 and 5.

Table 3 Distribution of triggers by severity of anaphylaxis in 266 episodes

Culprit Food or Ingredient	n (%)	Months of Age at Onset, median (IQR)	Severity of Anaphylaxis Episodes, n (%)			p
			Mild	Moderate	Severe	
Cow's milk	126 (47.4)	6 (5.5–12)	38 (50.7)	73 (48.3)	15 (40.5)	0.593*
Nuts	44 (16.7)	12.5 (9.3–24)	12 (16)	25 (16.6)	7 (18.9)	0.923*
Hazelnut	15 (5.6)	12.5 (9.8–24.5)	4 (5.3)	10 (6.6)	1 (2.7)	0.645#
Walnut	14 (5.3)	12 (6.8–21)	4 (5.3)	9 (6.0)	1 (2.7)	0.731#
Peanut	5 (1.9)	12 (9–24)	1 (1.3)	3 (2)	1 (2.7)	0.877#
Cashew	4 (1.5)	22 (12–60)	0	3 (2)	1 (2.7)	0.423#
Pistachio	4 (1.5)	12 (8.5–23)	2 (2.7)	1 (<1)	1 (2.7)	0.418#
Almond	3 (1.1)	9 (17.5–.)	0	1 (<1)	2 (5.4)	1.0
Hen's egg	42 (15.8)	6.3 (6–10)	12 (16)	25 (16.6)	5 (13.5)	0.903*
Lentil	12 (4.5)	12 (8–24)	6 (8)	5 (3.3)	1 (2.7)	0.263#
Beef	11 (4.1)	60 (6–126)	2 (2.7)	8 (5.2)	1 (2.7)	0.574#
Fish	10 (3.8)	24 (13.5–37.8)	1 (1.3)	9 (5.9)	0	0.103#
Chickpea	4 (1.5)	18 (7.5–29)	1 (1.3)	0	3 (8.1)	0.007#
Wheat	4 (1.5)	6 (5.6–6.8)	3 (4)	0	1 (2.7)	0.054#
Sesame	3 (1.1)	20 (1.5–.)	1 (1.3)	2 (1.3)	0	0.782#
Red fruit	2 (<1)	138 (108–.)	1 (1.3)	1 (<1)	0	0.727#
Pumpkin seed	1 (<1)	5 (5–5)	1 (1.3)	0	0	0.284#
Green pea	1 (<1)	9 (9–9)	0	0	1 (2.7)	0.138#
Bean	1 (<1)	10 (10–10)	0	0	1 (2.7)	0.140#
Peach	1 (<1)	7 (7–7)	0	1 (<1)	0	0.693#
Kiwi	1 (<1)	200 (200–200)	0	1 (<1)	0	0.693#
Honey	1 (<1)	181 (181–181)	1 (1.3)	0	0	0.282#
Chicken	1 (<1)	11 (11–11)	1 (1.3)	0	0	0.423#
Alfa-gal	1 (<1)	168 (168–168)	0	0	1 (2.7)	0.138#
Cinnamon	1 (<1)	9 (9–9)	0	0	1 (2.7)	0.138#
Poppy seed	1 (<1)	18 (18–18)	0	1 (<1)	0	0.693#

IQR = Interquartile range.

* χ^2 test.

#Fisher exact test.

DISCUSSION

In our study, with respect to the etiology of anaphylaxis severity, cow's milk, nuts, and hen's egg caused the majority of mild and moderate-to-severe anaphylaxis episodes during early childhood. One-third of the patients in food-induced anaphylaxis cases had a history of urticaria induced by the same food. The presence of angioedema and hoarseness in a patient diagnosed with food-induced anaphylaxis should suggest that the reaction can be severe. In addition, the absence of urticaria during a severe anaphylaxis episode increases the possibility of hypotension. The presence of confusion, syncope, or stridor probably indicates concomitant hypotension. In early childhood, it was reported in a few previous studies that milk, hen's egg, and nuts were the most common triggers in the etiology of food-induced anaphylaxis.^{15–18} Especially after the age of 12 months, the incidence of nuts increased in the etiology. In our study, although milk and egg were the most common

causes of food-induced anaphylaxis before 12 months of age, nuts and legumes were less involved in the etiology. After 12 months of age, an increase in the frequency of nut-induced anaphylaxis was observed. After 24 months, there was an increase in the rate of anaphylaxis because of fish and beef.

The symptoms of IgE-mediated food allergy can range from mild itching in the mouth and throat (oral allergy syndrome) to anaphylaxis.^{19–21} IgE-mediated food-induced mild reactions may progress to more severe forms in the following exposure. For example, reactions triggered by peanut may be mild in the first episode but may be severe and life-threatening in the following episode. This is why food-induced mild reactions to peanut were included in the relative epinephrine autoinjector indications in the guidelines.²² In our study, one-third of the patients in the food-induced anaphylaxis cases had a history of previous urticaria triggered by the same food. This result

Table 4 Clinical manifestations of patients based on anaphylaxis severity (N = 266)

Signs and Symptoms	All episodes, n (%)	Severity of Anaphylaxis Episodes, n (%)			p
		Mild (n = 75)	Moderate (n = 154)	Severe (n = 37)	
Skin	257 (96.6)	75 (100)	148 (96.7)	34 (91.9)	0.038*
Urticaria	223 (83.8)	64 (85.3)	132 (86.3)	27 (73)	0.131#
Flushing	145 (54.5)	45 (60)	74 (48.4)	26 (70.3)	0.031#
Pruritus	86 (32.3)	24 (32)	54 (35.3)	8 (21.6)	0.279#
Angioedema	130 (48.9)	17 (22.7)	88 (57.5)	25 (67.6)	<0.001#
Itchy in the eyes and/or nose	81 (30.5)	21 (28)	47 (30.7)	13 (35.1)	0.741#
Gastrointestinal system	150 (56.4)	43 (57.3)	78 (51)	29 (78.4)	0.010#
Nausea	61 (22.9)	37 (49.3)	19 (12.3)	5 (13.5)	<0.001#
Recurrent vomiting	122 (45.9)	37 (49.3)	61 (39.6)	24 (64.9)	0.017#
Abdominal pain	13 (4.9)	4 (5.3)	7 (4.5)	2 (5.4)	0.853*
Diarrhea	3 (1.1)	0	3 (1.9)	0	0.715*
Itchy in the mouth	13 (4.9)	5 (6.7)	7 (4.6)	1 (2.7)	0.715*
Tingling in the mouth	25 (9.4)	6 (8)	15 (9.8)	4 (10.8)	0.866#
Respiratory system	213 (80.1)	43 (57.3)	139 (90.3)	31 (83.8)	<0.001#
Sneezing	60 (22.6)	22 (29.3)	36 (23.4)	2 (5.4)	0.016#
Rhinorrhea	33 (12.4)	12 (16)	18 (11.7)	3 (8.1)	0.451#
Itchy throat	11 (4.1)	5 (6.7)	3 (1.9)	3 (8.1)	0.072*
Feeling stuck in the throat	31 (11.7)	7 (9.3)	18 (11.7)	6 (16.2)	0.565#
Wheezing	51 (19.2)	0	44 (28.6)	7 (18.9)	<0.001#
Dyspnea	119 (44.7)	0	90 (58.4)	29 (78.4)	<0.001#
Coughing	45 (16.9)	0	38 (24.7)	7 (18.9)	<0.001#
Stridor	19 (7.1)	0	13 (8.4)	6 (16)	0.005#
Cyanosis	18 (6.8)	0	0	18 (48.7)	<0.001#
Hoarseness	19 (7.1)	0	12 (7.8)	7 (18.9)	0.001#
Cardiovascular system	29 (10.9)	5 (6.7)	9 (5.8)	15 (40.5)	<0.001#
Tachycardia	51 (19.2)	5 (6.7)	9 (5.8)	37 (100)	<0.001#
Hypotension	14 (5.3)	0	0	14 (37.8)	<0.001*
Cardiac arrest and/or severe bradycardia	3 (1.1)	0	0	3	0.003*
Neurologic system	43 (16.2)	12 (16)	3 (1.9)	28 (75.7)	<0.001#
Syncope	17 (6.4)	0	0	17 (45.9)	<0.001*
Confusion	10 (3.8)	0	0	10 (27)	<0.001*
Dizziness	5 (1.9)	0	3 (1.9)	2 (5.4)	0.148*

*Fisher exact test.

χ^2 test.

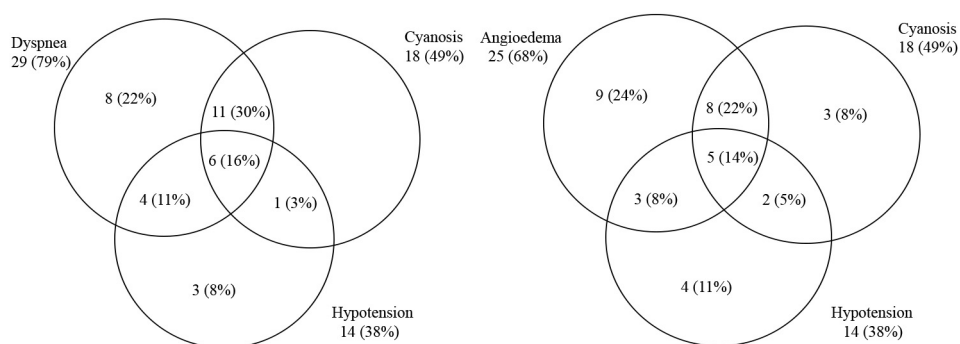


Figure 2. Overlap of the main clinical manifestations in 37 severe anaphylaxis episodes.

Table 5 Ordinal logistic regression analysis: Potential predictors that are associated with severe anaphylaxis

Variable	Odds Ratio	95 % Confidence Interval	<i>p</i>
Angioedema	3.29	1.95–5.57	<0.001
Hoarseness	4.16	1.58–10.94	0.005

suggested that patients who were diagnosed with food-induced mild allergic reactions, *e.g.*, urticaria, should be warned about anaphylaxis and should be prescribed epinephrine autoinjectors for a possible future reaction.

The frequency of severe anaphylaxis among all episodes in adolescents and adults varies between 11% and 25%.^{23,24} Drugs and insect venoms are the major triggers for severe anaphylaxis, whereas peanut is the major trigger for food-induced severe anaphylaxis in this age group. In our study, food-induced severe anaphylaxis in early childhood was at a considerable level that may be compared with adolescents and adults. It was found that the most common causes of severe food-induced anaphylaxis were cow's milk, nuts, and hen's egg. Also, in our study, the majority of anaphylactic reactions with chickpea were severe in early childhood. Therefore, one should be alert in terms of the development of severe anaphylaxis due to cow's milk, nuts, and hen's egg, which are the most frequent triggers for severe anaphylaxis in early childhood.

It should also be kept in mind that chickpea-induced anaphylaxis can be severe in early childhood. In addition, the severity of the reaction may be related to the amount of food intake.²⁵ Because our study was retrospective and almost all of the food-related anaphylaxis episodes developed outside the hospital, the relationship between the amount of food intake and the severity of anaphylaxis could not be evaluated in the file records. Although the relationship between the amount of food intake and the severity of anaphylaxis was not evaluated, the amount of food intake should be questioned for a patient diagnosed with anaphylaxis.

In anaphylaxis episodes, the skin is the most commonly involved system and urticaria is the most common presenting symptom.²² In terms of skin involvement, urticaria was less and flushing was most commonly seen in severe anaphylaxis episodes compared with mild-to-moderate episodes.²⁶ Hypotension without skin involvement has generally been observed in patients in severe drug-induced anaphylaxis cases.^{24,26} In our study, the absence of urticaria in food-induced severe anaphylaxis was associated with a 5.8-fold increase in the risk of concomitant hypotension. Therefore, a patient should be evaluated for the presence of hypotension in a food-induced

anaphylaxis episode that was not accompanied by urticaria.

The severity of anaphylaxis episodes is determined according to the EAACI position paper on the management of anaphylaxis in childhood.¹³ Cardiovascular findings (*e.g.*, hypotension) and respiratory system findings (*e.g.*, cyanosis) were observed in severe anaphylaxis. Although skin findings (*e.g.*, angioedema) and respiratory system findings (*e.g.*, hoarseness and barking cough) are seen in a mild-to-moderate anaphylaxis episode, in our study, the presence of angioedema and hoarseness were associated with 3.29- and 4.16-fold increases in the risk of severe food-induced anaphylaxis, respectively. In a review by Greenberger,²⁷ it was stated that one of the pathophysiologic changes in fetal anaphylaxis is massive angioedema of the tongue, oropharynx, or larynx. Therefore, clinically observed cutaneous angioedema and hoarseness may indicate the onset of massive angioedema in the respiratory tract. In supporting this idea, our study results showed that the presence of angioedema and hoarseness in any anaphylaxis episode may be clinical indicators of severe anaphylaxis.

Brown *et al.*²⁸ reported that, of 97 severe anaphylactic reactions, 45 (46%) were hypotensive, 23 (24%) were hypoxemic, and 29 (30%) were mixed. Delayed deteriorations were more common after hypotensive reactions and in patients with preexisting lung disease. In our study, the presence of syncope, confusion, and stridor were associated with an increase in the risk of concomitant hypotension. This result suggested that, especially if there is one of these findings, such as confusion, syncope, and stridor in infant period anaphylaxis, in which blood pressure measurement is neglected or difficult to measure, it should make us think that there may be accompanying hypotension and that the reaction is severe.

It is well known that the treatment of choice in anaphylaxis episodes is the administration of IM epinephrine.^{14,29,30} Various reports on food-induced anaphylaxis that occurred in the community identified underutilization of epinephrine. Epinephrine was found to be administered in 25–44% of severe reactions or anaphylaxis.^{9,31,32} In our study population, it is noted that the usage of epinephrine was not found to be as high as desired as a first-line treatment. Similar to previous study results, epinephrine was used in only 36.1% of the anaphylaxis episodes in our study. In our study, epinephrine was administered more to patients with severe anaphylaxis. Food-related mild anaphylaxis is mostly self-limited, and the symptoms improved when the patient visited the physician, which may cause the physician to mis-evaluate the reaction as mild. Although epinephrine was administered to only half of our patients with severe anaphylaxis, there were no deaths reported in our study. Although more than a decade has passed

since previous studies in Turkey, the usage of epinephrine is low. This may be attributed to a state of unawareness about the exact indications and dosages of epinephrine in this early age group. It is reasonable that the implementation of regular and intense education is essential for both the recognition and management of anaphylaxis.

Limitations

There were a few limitations of our study. First, the retrospective nature of the study was the main limitation, which is unfortunately a common problem for most anaphylaxis reports.^{6,33–35} Second, data were restricted to patients with complete medical records, which might have affected the results. Third, the relationship between the amount of food intake and the severity of anaphylaxis could not be evaluated. Fourth, because of the low number of patients in the severe anaphylaxis group, the 95% CI values determined for syncope and confusion, which were included in the logistic regression model, were found to be in a wide range.

CONCLUSION

Cow's milk, nuts, and hen's egg are the major responsible food allergens that cause mild, moderate, and severe food-induced anaphylaxis in early childhood. Food-induced urticaria may be a warning sign for a next anaphylactic reaction, which may be induced by the same triggering food. The presence of angioedema and hoarseness in a patient diagnosed with food-induced anaphylaxis may suggest that the reaction may be severe. In patients in severe anaphylaxis cases, hypotension is a prominent symptom in those who present without urticaria. In addition, the presence of confusion, syncope, or stridor probably indicates concomitant hypotension. There still are insufficiencies in the usage of IM epinephrine, which is the first-line treatment of anaphylaxis; therefore, physicians should be educated about the management of anaphylaxis and administration of epinephrine more regularly and intensely.

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