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Food-induced anaphylaxis in children up to 3-years-old – preliminary study

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Abstract
Introduction and objectives: The aim of this study was to determine the frequency of food-induced anaphylaxis, analyze the symptoms, and triggering factors in a group of youngest children. Also, the study aims to estimate the frequency of anaphylaxis episodes in children in the Kuyavian-Pomeranian Voivodeship region.
Methods: Retrospective analysis of medical records of 29 children aged 0–3 years that presented symptoms of food-induced anaphylaxis. Medical charts were reviewed using a collection of documents with the clinical data.
Results: The frequency of anaphylaxis was determined to be 0.3% of all hospitalized children aged 0–3 years and 1.9% of children suspected of food allergy. The mean age of an anaphylactic reaction was 12±9 months. The most common symptom was mild-moderate urticaria. The respiratory symptoms were significantly more prevalent in toddlers than in infants ($p = 0.148$). Cardiac symptoms occurred only in the infant group, i.e., in two (11%) infants. As a possible cause of the symptoms, in 18 (62%) cases, parents most often indicated the consumption of milk or milk-rice porridge. Anaphylaxis as the first manifestation of food-allergy was significantly more prevalent in infants than in older children ($p = 0.0002$).
Conclusions: The incidence of anaphylactic reactions rated at 0.3% of all children hospitalized at this age. The most common symptoms of anaphylactic reaction were skin lesions. The primary cause of allergic reactions was cow's milk after the first exposure at home. Anaphylaxis has different patterns of symptoms depending on the age of the child.

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Introduction

By definition, anaphylaxis is a severe, potentially life-threatening systemic hypersensitivity reaction that is characterized by the rapid onset of life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes.[1]

Anaphylaxis can be triggered by a variety of agents, of which the most common cause is food.[2-7] More than 120 foods that can cause anaphylactic reaction have been described, although the most often sensitizing are: peanuts, tree nuts, cow's milk, eggs, fish, shellfish, wheat, and soya.[8] It is well documented that the triggers of anaphylaxis and the course of the disease in the pediatric population are different from the adult patients.[9]

The role of individual food allergens as causative agents of anaphylaxis depends on eating habits in different countries. For example, the most common food allergen in Asia is shellfish, while peanut allergy is extremely low compared to the Western countries.[10] However, according to data, worldwide the most common allergens in infants are hen's eggs and cow's milk.[10-13]

In some cases, the allergenic properties of food are affected by thermal processing. This is well documented in milk and egg allergens.[14] Most children reacting to unprocessed milk, tolerate it in baked form.[15] Regular intake of processed milk accelerates the acquisition of tolerance to unheated food.[16,17] Extensive heating also results in allergenicity changes in peanut proteins.

The clinical criteria for anaphylaxis are well defined.[1,9] In everyday medical practice, the diagnosis is based on the sudden onset, characteristic symptoms and typical signs such as urticaria, flushing, edema, cough, wheeze, stridor, abdominal pain, and vomiting.[1] Vital signs (heart rate, respiratory rate, blood pressure) need to be interpreted according to the age of the patient. The clinical presentation of anaphylaxis in infants and toddlers is different than in older children and adults. Small children cannot report subjective symptoms such as pruritus, throat tightness, nausea, or abdominal pain. On the other hand, some of the signs like irritability, inconsolable crying, or somnolence are difficult to interpret in infants.[4] Also, some other symptoms like regurgitation and irritabilitycan be observed in healthy infants.

The prevalence of food-induced anaphylaxis among the youngest children is unknown, although the increasing frequency is reported.[2] Worldwide the youngest children (age 0–4 years) have the highest hospital admission rates for food-induced anaphylaxis.[18-22]

The aim of the study was to assess the rate of hospitalization because of anaphylaxis and analyze the cause and course of the episodes of food-induced anaphylaxis in children aged 0–3 years.

Materials and methods

Food allergy was defined as an adverse reaction to food mediated by an immunological mechanism, involving specific IgE (IgE-mediated), cell-mediated mechanisms (non-IgE-mediated), or both IgE- and cell-mediated mechanisms (mixed IgE- and non-IgE-mediated).[1] Diagnosis of food allergy was made based on the clear medical history of the patient, sensitivity to a food allergen, and positive food challenge.

Anaphylaxis was diagnosed based on the criteria of EAACI Guidelines for Food Allergy and Anaphylaxis.[1] Food-related anaphylaxis was diagnosed in patients with symptoms of anaphylaxis triggered by food allergens. For the analysis of the personal and familial medical history of concomitant atopic diseases, the following criteria were adopted:

- Atopic dermatitis (AD) – the diagnosis was made using the Hannifin and Rajka criteria for atopic AD.[23]
- Asthma – was diagnosed based on the Global Initiative for Asthma (GINA) criteria. For the children below 5 years, the Modified Asthma Predictive Index was used to establish diagnosis.[24]
- Allergic rhinitis – the diagnosis was based on Allergic Rhinitis and its Impact on Asthma (ARIA) criteria.[25]

Anaphylaxis episode was graded using the World Allergy Organization criteria.[2] We conducted a retrospective analysis of medical records of 29 children aged 0–3 years that presented symptoms of food-induced anaphylaxis. The analysis is comprised of children hospitalized in the Department of Pediatrics, Allergology and Gastroenterology in the period from January 1, 2015 to December 31, 2018. During this period, 9667 children were hospitalized, aged 0–3 years, with infectious diseases and for allergy, gastroenterological, and nephrological diagnostics.

Among this group:

- Out of 1527 children who were admitted to the Department of Pediatrics, Allergology and Gastroenterology for food allergy diagnosis, 19 children met the criteria for food-induced anaphylaxis.
- Out of 22 children who were admitted to the Department of Pediatrics, Allergology and Gastroenterology due to suspected food-induced anaphylaxis, 10 children met the criteria for food-induced anaphylaxis.

All of the patients with episodes of food-induced anaphylaxis were examined by a doctor immediately after the onset of anaphylaxis – a full medical examination was performed. All of the patients underwent a diagnostic procedure in the next month after the episode of anaphylaxis. The results of the diagnostic workup were all obtained from chart review. All patients with anaphylaxis have a clear cause-effect relationship with food intake. During the period 2015–2018, none of the children aged 0–3 years was hospitalized because of the anaphylaxis triggered by factors other than food.

Medical charts were reviewed from a collection of documents with the following clinical data: demographic data, symptoms of anaphylaxis, exam findings and vital signs, past medical history, type of food triggering a reaction, the coexistence of allergic disease, family and perinatal history.

The diagnostic workup included specific IgE (sIgE), measured by using PolyCheck (Emma, Berlin). The concentration of sIgE was defined as positive for the results above

the detection limit (>0.15 kU/L). The tests were conducted at least 1 month after the occurrence of anaphylaxis, but not later than 3 months. The results of skin prick tests were not included in the study, because they were performed only in some patients – most of the children were receiving antihistamines and/or had skin lesions that made it impossible to perform the test.

When sIgE was positive and the history of the patient was compatible, the food was defined as susceptible to the anaphylactic reaction. In other cases, an open oral food challenge was performed in accordance with current guidelines.[1,2]

For the purpose of the study, the children were divided into two groups: infants from birth to 12 months of life and children from 13 months to 3 years of age. The study was approved by the appropriate IRB (Komisja Bioetyczna Collegium Medicum UMK).

Statistical analysis was performed using the Statistica 13.1 statistical package from Dell Inc. Evaluation of the correlation of qualitative variables was performed with the chi^2 test, and the Fisher exact test was used for 2×2 tables and the expected number n < 5. The value of the test probability p < 0.05 was considered statistically significant.

Results

In the period 2015–2018 years, 9383 children aged 0–3 years were hospitalized in the Department, including 1.527 (16.3%) because of suspected food allergy. Over the studied period, anaphylactic reactions after food intake were observed in 29 (0.3%) of all hospitalized patients; 1.9% of all children with suspected food allergy.

Demographic data

The mean age of the child at the time of an anaphylactic reaction was 12 ± 9 months. The characteristics of the study group are presented in Table 1.

Most reactions 27/29 (93%) occurred while at home. There was one episode of anaphylaxis reported in a coffee shop and one in the hospital.

Atopic personal and family history

Thirteen (45%) children had a positive family history of atopic diseases. None of the families of the patients had a history of anaphylaxis.

Sixteen (55%) children had a personal history of concurrent atopic disease (Figure 1). The most frequent symptom reported in the study group, independently of age, was AD (five infants and 11 toddlers). Asthma was reported in one infant and six toddlers. Anaphylaxis as the first manifestation of food allergy, without previous atopic history, was significantly more prevalent in infants than in older children (p = 0.0002).

Symptoms of anaphylaxis

Symptoms observed in children during the episodes of anaphylaxis are presented in Figure 2. Vital signs parameters were measured only in nine (31%) of the examined children.

In 11 (38%) patients, symptoms from skin/mucosal tissue and respiratory system were observed. Six (21%) patients had symptoms of skin/mucosal, respiratory, and gastrointestinal system. In next six children (21%), skin/mucosal and gastrointestinal symptoms were present. Two patients (7%) presented with skin, behavioral, and gastrointestinal symptoms. In another two patients (7%), skin, behavioral, and respiratory symptoms were observed. One (3.5%) child had symptoms of skin, respiratory, behavioral, and gastrointestinal system. One child (3.5%) was presented with respiratory, behavioral, and gastrointestinal symptoms.

The most common skin manifestation was urticaria: generalized in 10 (34%) patients and local in 19 (66%) patients. Other reported symptoms were pruritus and erythema/flush. Gastrointestinal symptoms were vomiting (n = 14, 48%), abdominal pain (n = 5, 17%), and diarrhea (n = 3, 10%).

Up to 62% (n = 18) of children reported symptoms from the respiratory tract, most commonly wheezing (n = 10, 34%) and cough (n = 9, 31%). The respiratory symptoms were significantly more prevalent in toddlers than in infants (p = 0.148).

In six patients (21%), behavioral symptoms like anxiety (n = 3, 10%), somnolence (n = 2, 7%), and irritability (n = 1, 3.5%) were observed.

Table 1 Patient characteristics.

Parameter	Total n = 29 (100%)	Infants n = 18 (62%)	Toddlers n = 11 (38%)	p
Male, n (%)	21 (72)	14 (78)	7 (64)	>0.05
First pregnancy, n (%)	11 (38)	7 (39)	4 (36)	>0.05
Birth on time, n (%)	26 (90)	18 (100)	8 (73)	>0.05
Birth weight, g mean ± SD	3436 ± 546	3524±323	3294±787	>0.05
Apgar scale, points				
Mean	9.65	9.9	9.27	>0.05
Min-max	6-10	9-10	6-10	
Way of birth, n (%)				
Natural	13 (45)	8 (45)	5 (45)	>0.05
Cesarean section	16 (55)	10 (55)	6 (55)	

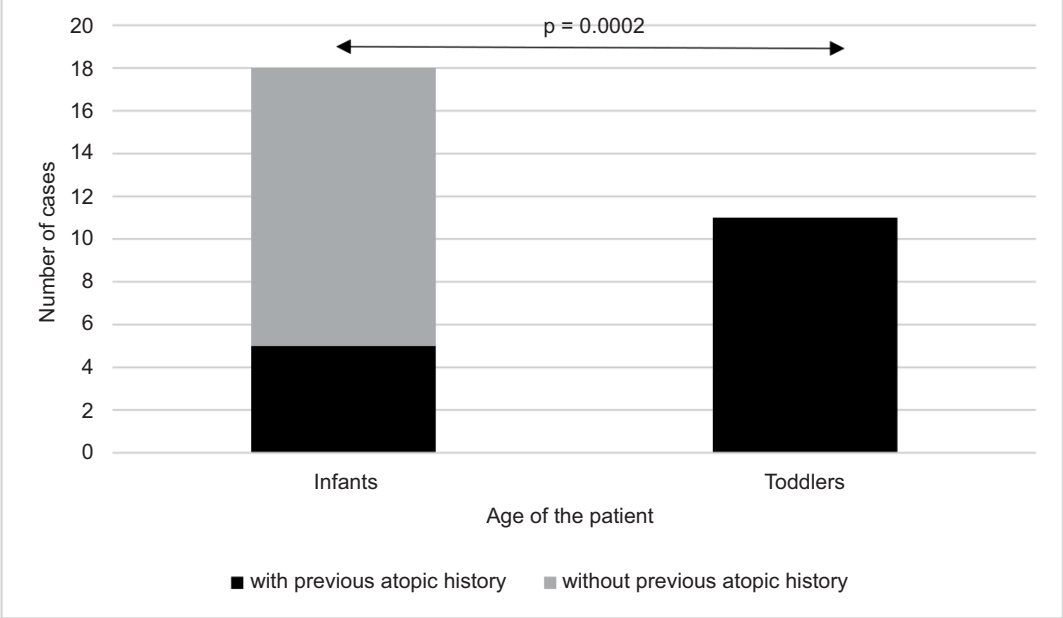

Figure 1 Personal atopic history in the infant and toddler group.

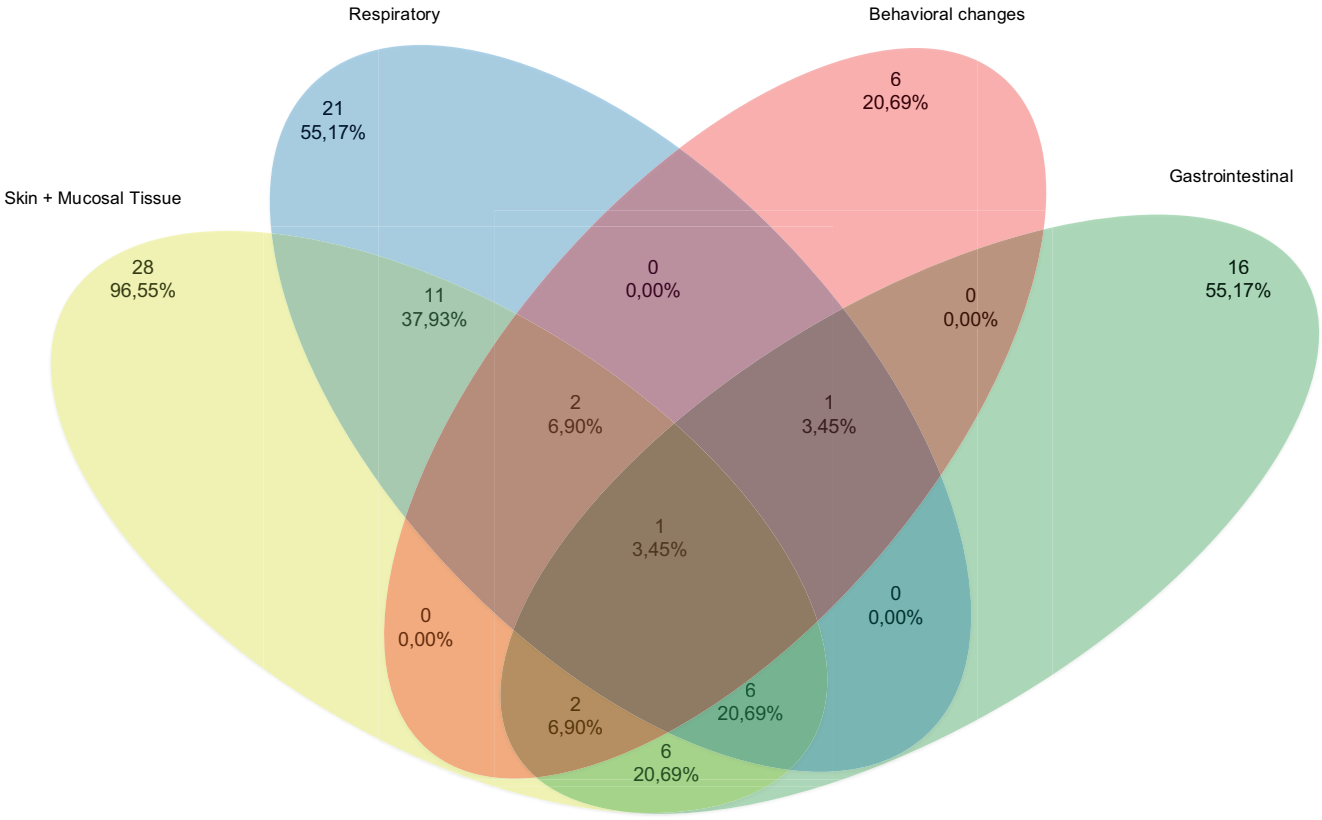

Figure 2 Symptoms observed in children during the episodes of anaphylaxis.

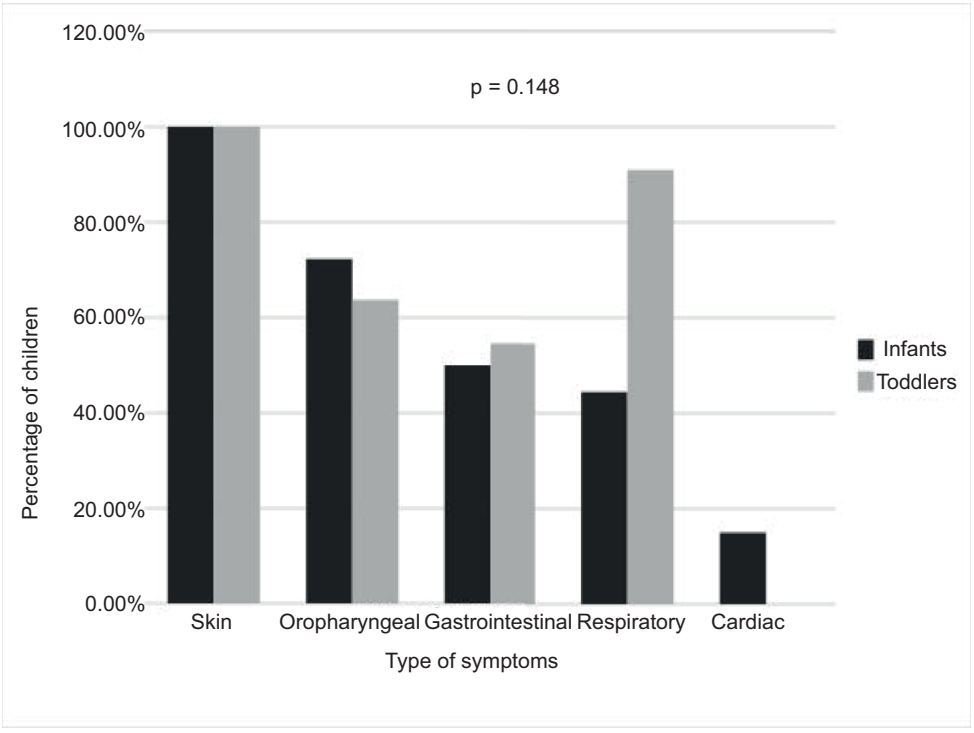

Figure 3 Anaphylaxis symptoms according to the age of studied children.

Cardiac symptoms occurred only in two (11%) infants. Both children presented with tachycardia and hypotension referring for the age, confirmed by physician examination.

The differences in the clinical manifestation of anaphylaxis between the group of infants and toddlers are presented in Figure 3.

All infants were classified as mild-moderate anaphylaxis. Two toddlers had severe type of reaction.

There were no differences between the course of mild and moderate anaphylaxis in infants and toddlers ($p > 0.05$). The performed statistical analysis did not show a statistically significant relationship between the severity of the reaction and the patient's age ($p = 1$). None of the children experienced a biphasic reaction.

Triggers of the episode of anaphylaxis

As a possible cause of the symptoms, in 18 (62%) cases, parents most often indicated the consumption of milk or milk-rice porridge, introduced as a new food to the child's diet or consumed in a random manner. The other possible reported triggers were: hen's eggs, wheat, peanuts, apple juice, and pumpkin seeds. In three children aged 2 years, there was an anaphylactic reaction after consumption of processed food possibly contaminated with trace amounts of milk, eggs, or nuts. In 11 (38%) cases, the anaphylaxis occurred after the first consumption of cow's milk-based formula. The trigger of the anaphylactic reaction was already known and had been previously diagnosed in 14 (48%) cases. In all of the children with previously diagnosed allergy, the allergic food was consumed accidentally or as a trace amount. More than 50% (n = 15) of the children had been breastfed when the incidence of anaphylaxis occurred. In all breastfed children, the occurrence of anaphylaxis was directly related to the introduction of the new food into the diet or feeding with milk-based formula. In 27 patients (93%), the time between exposure and onset of symptoms was less than 15 min; two (7%) patients reported a reaction with 1 h. Milk was consumed as a liquid food, egg in boiled form.

Sensitization – specific IgE in the blood

Sensitization has been demonstrated in all children. Most of the children were sensitized to cow's milk (n = 25, 86%). The majority of them (n = 20, 69%) were sensitized to casein.

The majority of patients (n = 24, 83%) had polysensitization, five (17%) of them had sensitization only to milk. All of the children with sensitization only to milk were infants up to 5 months. We found significantly higher sIgE concentration to milk and hazelnuts in toddlers than in infants (147 kU/L vs. 1.1 kU/L and 11 kU/L vs. 0.64 kU/L, respectively) (Table 2).

The statistical analysis did not show a significant difference between the mean concentrations of sIgE in the group of patients with mild, moderate, or severe reactions (Table 3). Also, anaphylaxis occurred in children with low concentration sIgE; in four (14%) children, sIgE was lower than 0.35 kU/L and in five (17%) children, sIgE was 0.35–0.7 kU/L.

Final diagnosis of causative food of anaphylaxis

The basis for identifying the allergen was a medical history taken from the caregivers. In 19 children (65%), the clear

medical history and clinical data made it possible to establish a diagnosis without oral food challenge (OFC).

In 10 (35%) children, OFC was performed to determine the causative factor. In total, 10 OFC were carried out – eight with milk, eight with rice, three with egg, and two with wheat. There were 10 positive OFC, including seven patients with milk, two patients with egg, and one patient with wheat. As an outcome of the OFC, anaphylaxis was observed in one patient, epinephrine was used.

Table 2 Sensitization to main allergens in the infants and toddlers group.

Food allergen	sIgE concentration, median, min–max, kU/L			p
	Total n = 29 (100%)	Infants n = 18 (62%)	Toddlers n = 11 (38%)	
Milk	2.1 0.18–693	1.1 0.18–448	147 2–693	0.012
Egg white	2.0 0.18–374	0.91 0.18–320	2.0 0.29–374	>0.05
Egg yolk	0.27 0.16–431	0.19 0.16–431	11.50 0.23–20	>0.05
Wheat	1.45 0.35–228	0.56 0.35–228	1.75 0.65–30	>0.05
Soya	0.42 0.17–150	0.39 0.17–45	1.0 0.18–150	>0.05
Peanuts	2.1 0.17–547	7.1 0.17–547	0.5 0.3–300	>0.05
Hazelnut	5.6 0.26–500	0.64 0.63–150	11 0.26–500	0.032
Sesame	3.00 0.18–200	0.43 0.18–189	3.0 0.18–200	>0.05
Almond	1.4 0.18–8.5	3.9 0.18–8.5	1.175 0.18–150	>0.05

Summarizing, milk was identified as a causative factor of the episodes of anaphylaxis in 19 (65%) children. Other elicitors of anaphylaxis were hen's eggs (n = 4, 14%), wheat (n = 1, 3%), peanuts (n = 1, 3%), and pumpkin seeds (n = 1, 3%). In three (10%) children with food polysensitization, who consumed food possibly contaminated with multiple allergens, until now the causative factor of anaphylaxis could not be determined.

Treatment of anaphylaxis

Most of children received treatment: antihistamine drug (n = 21, 72%), glucocorticoids (n = 13, 45%), salbutamol (n = 6, 21%), and epinephrine (n = 2, 7%). There were no significant differences between the treatment in infants and toddlers (p > 0.05). Part of the children (n = 8, 28%), after the episode, attended the hospital and received no treatment yet still fulfilled the criteria for anaphylaxis. None of the children required intensive care.

Discussion

Food-induced anaphylaxis is increasingly reported in all age groups, although the highest increase is observed in children and young adults. According to the epidemiologic data, a seven-fold increase in hospitalization in children due to food-induced anaphylaxis has been observed in Europe in the recent years.[26] According to the US data, the hospitalization of food-induced anaphylaxis in children has more than doubled from 2000 to 2009.[19] Also, in Australia, the anaphylaxis fatality rates have increased over the last 20 years by 6.2% per year.[22,24]

The true prevalence of anaphylaxis in infancy is unknown – the frequency is estimated with the variation from 0.19 to 30 cases per 100,000 children/year.[27] The incidence of anaphylaxis in children worldwide varied widely, ranging from 1 to 761 per 100,000 person-years for total

Table 3 Concentration of the milk, egg, and peanut sIgE according to the severity of anaphylaxis.*

Severity of anaphylaxis n = 29 (100%)	Type of sensitization	sIgE concentration, kU/L		
		Mean±SD	Median	Min-Max
Mild	Peanut	79.05 ± 158.5	0.31	0.03–547
n =16 (55.2%)	Cow's milk	110.81 ± 210.51	1.80	0–693
	Casein	32.31 ± 69.11	1.30	0–206
	Egg white	63.30 ± 133.89	0.04	0–374
Moderate	Peanut	1.79 ± 3.54	0.18	0–11.00
n =12 (41.3%)	Cow's milk	29.97 ± 59.39	58.67	0–164.00
	Casein	6.05 ± 10.04	9.86	0–25.00
	Egg white	4.65 ± 12.73	12.65	0–45.00
Severe	Peanut	0.08	0.08	0.08
n =1 (3.5%)	Cow's milk	13.00	13.00	13.00
	Casein	12.00	12.00	12.00
	Egg white	0.29	0.29	0.29

*p>0.05.

anaphylaxis and 1 to 77 per 100,000 person-years for food-induced anaphylaxis.[28] The epidemiology studies conducted in 2006 reported the lifetime prevalence of anaphylaxis as 0.05–2.0%.[6]

In our study, the frequency of episodes of anaphylaxis was determined to be 0.3% of all hospitalized children aged 0–3 years, during 3 years period and 1.9% of children suspected of food allergy among hospitalized patients. The estimated frequency of anaphylaxis is probably overstated due to the profile of the department.

Most of the children in the study were male (72%). The predominance of males with pediatric anaphylaxis cases is described in other studies.[8,29]

Our study found statistically significant differences in previous personal atopic history between the groups of infants and toddlers. All of the children >12 months had been diagnosed with at least one atopic disease (predominantly AD) whereas for over 70% of infants' anaphylaxis was the first manifestation of food allergy. Infants are frequently being introduced to new foods in their diet which can lead to developing anaphylactic reactions. However, the introduction of solid foods in infants is recommended. Few infants presented with symptoms of anaphylaxis after the first exposure to cow's milk formula. All of the reactions were self-limiting and occurred in private homes. Other researchers had similar observations.[29,30]

According to previous studies, the symptoms of anaphylaxis differ depending on the age of the children.[29,30] Samady et al.[30] found that the most common presentation of anaphylaxis in infants involved the skin and gastrointestinal system (i.e., vomiting). In the group of older children, similarly, other frequent symptoms were skin, oropharyngeal, gastrointestinal, and respiratory. Misirlioglu et al.[29] described cutaneous and respiratory system disorders in children <2 years old as the most frequent symptoms. The same conclusions were drawn by Jeon et al.[31]

Our data also support the observation that the main manifestation of anaphylaxis in infants are skin symptoms, regardless of the causative factor. Like in other studies, we found that respiratory symptoms were significantly more common in older children.[4] Comparing to other studies concerning children up to 18 years, we found cardiovascular symptoms to be rare (7% of all children with anaphylaxis).[32,33] One of the reasons could be due to the difficulty of recognizing cardiovascular symptoms in infants.

The measurement of blood pressure and interpretation of the results are usually underused and underreported in infants.[34] Like in other studies, we do not have complete data concerning vital signs measurements, including blood pressure, during anaphylaxis episodes. Conducted studies have shown that only 12.5% of children younger than the age of 3 years with anaphylaxis had a blood pressure measurement.[35] The ambiguity of symptoms makes it difficult to determine the final diagnosis of anaphylaxis, leading to underutilization of epinephrine, and a higher risk of death. In guidelines published in 2019, authors indicated that health care providers should be aware of the need to improve the recognition, diagnosis, and management of infants with anaphylaxis.[36]

The family history of allergic disease was observed in 45% of the patients in our study which is the same frequency estimated in other studies.[37]

Cow's milk is the most frequent trigger food in our group. That is similar to what is reported worldwide for that age group.[21,29] Some of the studies identify egg as the most common food trigger in infants.[30]

We found the concentration of sIgE for milk, casein, and hazelnut significantly higher for toddlers than infants. Most of the cases of anaphylaxis to cow's milk occurred with a low or very low concentration of sIgE, like in other studies.[16,30] The concentration of sIgE allows to estimate the risk of an allergic reaction after contact with the allergen but does not allow the assessment of its severity.[38] Long-term follow-up could indicate how sIgE concentration changes over time.

The main drug used in anaphylaxis is epinephrine. In our study, the commonly given group of drugs are antihistamines and steroids, even though according to the guidelines they are third-line drugs. Similar results are observed in other studies.[20,35] According to current knowledge, the lack of administration or delaying the administration of epinephrine is associated with an increased risk of death. Tsuang et al.[36] found that reactions triggered by milk are at higher risk for needing more than one dose of epinephrine. Although the guidelines strongly advise the use of epinephrine as the first-line drug in the treatment of anaphylaxis,[1] there is parental and doctor's uncertainty about the severity of the reaction, fear of side-effects, and difficulties deciding which drug to use.[37] Although usually associated with life-threatening anaphylaxis, none of the patients required ICU treatment.

There are some limitations to our study: the retrospective character of the analysis, bias (because of the profile of the department), only a small group of children, from one university hospital qualified for the study. The strength of the study is our material, i.e., a group of infants and toddlers with symptoms of anaphylaxis.

Conclusions

The incidence of anaphylactic reactions in children up to 3 years of age is rated at 0.3% of all children hospitalized at this age. The most common symptom of an anaphylactic reaction was urticaria. The primary cause of allergic reactions was cow's milk after the first exposure at home. Anaphylaxis has different patterns of symptoms depending on the age of the child. Anaphylaxis can occur even with a low concentration of sIgE.

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