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Original article

Anaphylactic reactions in children – a questionnaire-based survey in Germany

Background: Severe anaphylactic reactions are medical emergencies requiring immediate recognition and treatment. Despite this, little is known on their clinical features, especially in infants and children.
Objective: To evaluate trigger factors, patterns of clinical reaction, site of occurrence and treatment modalities of reported reaction in infants and children below 12 years of age in Germany.
Methods: Paediatricians throughout Germany were asked by questionnaire to report accidental anaphylactic reactions over the previous 12 months. Severity of reported reactions was classified in grades I–IV according to reported symptoms.
Results: Hundred and three cases of anaphylaxis were evaluated. Median age was 5 years, 58% were boys. Site of occurrence was the child's home in the majority of cases (58%). Foods were the most common causative allergen (57%), followed by insect stings (13%) and immunotherapy (SIT) (12%); in 8% anaphylactic agent was unknown. Among foods, peanuts and tree nuts were the most frequent allergens (20% of food allergens in each case). Severe reactions with cardiovascular involvement occurred in 24% of cases. No fatal reaction was observed. Recurrent episodes of anaphylaxis were reported in 27% of cases, half of these caused by the same allergen again. For treatment, 20% of children received adrenaline, in 8% of cases intravenously. Thirty-six per cent of patients with grade-IV reactions received adrenaline, 24% intravenously. In 17% of all children an adrenaline self-injector was prescribed after the episode.
Conclusion: Our data: (i) shows an uncertainty of physicians in diagnosing anaphylaxis, (ii) reveals remarkable under-treatment of the majority of children with anaphylaxis, (iii) reflects the need for guidelines and training for physicians in managing children with anaphylaxis and (iv) should encourage the development of self-management programmes for patients and families.

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Key words: anaphylaxis; children; food allergy; immunotherapy; infants; insect sting allergy.

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Severe anaphylactic reactions are potentially life threatening (1–7). In the literature, foods, venom and drugs are the most commonly reported exogenous causative agents (8, 9). Symptoms vary widely and can involve multiple organ systems, with cutaneous, gastrointestinal, respiratory, cardiovascular and/or unspecific signs and symptoms (8, 10–12).

In the paediatric population, allergic disorders have reached epidemic proportions (12), and anaphylaxis is an increasingly common event (8, 13, 14). Although it is a medical emergency requiring immediate recognition and treatment, there is a lack of information on its prevalence and characteristics, particularly in infants and children. Data on epidemiology of anaphylactic reactions is generally available only for selected groups. An accurate profile of the epidemiology of anaphylaxis would increase awareness of anaphylactic reactions among physicians for the recognition and treatment. However, such data is difficult to obtain.

The purpose of this questionnaire-based investigation was to describe the most important trigger factors, the pattern of clinical reaction, site of occurrence and treatment of anaphylactic reactions in infants and children in Germany.

Methods

In a retrospective study between October 2002 and December 2003, German paediatricians (clinicians and GP's) were asked by circulars (sent out every 6 months) and by announcements in medical

Abbreviations: IgE, immunoglobulin E; i.v., intravenous; s.c., subcutaneous; SIT, specific immunotherapy.

Table 1. Classification of severity of reported anaphylactic reactions (grades I–IV) and frequency of occurrence

I Local reaction (no systemic reaction)	II Mild systemic reaction (systemic reaction without cardiovascular or pulmonary involvement)	III Severe systemic reaction (systemic reaction with pulmonary symptoms but cardiovascular system stable)	IV Shock (cardiovascular collapse)
Reddening	Urticaria	Wheezing	Dizziness*
Induration	Flush	Constriction in chest	Tachycardia*
Itching, etc.	Angioedema	Stridor	Fall in blood pressure
	Abdominal pain	Dyspnea, etc.	Collapse
	Nausea		Shock
	Vomiting		Cardiac/pulmonary arrest, etc.
Local	Diarrhea, etc.		
$n = 3$ (3%)	$n = 22$ (21%)	$n = 53$ (52%)	$n = 25$ (24%)

*Only in combination with other grade-IV symptoms.

journals to report accidental anaphylactic reactions occurring during the past 12 months in infants and children below 12 years of age. The physicians then received a two-page investigator-designed questionnaire about the episode.

This questionnaire covered demographic data, symptoms and physical findings of the episode, place of occurrence, suspected allergen, diagnostic tests, treatment modalities such as use of drugs, route of application, and drug administering person, hospitalization and prescribed emergency set after the episode. Reports were reviewed individually by two paediatric allergologists (AM, BN) and excluded if the reported episode was not accidental (e.g. occurred after diagnostic provocation) or if the patient was not under the age of 12. The severity was graded according to the investigator-defined criteria shown in Table 1, based on the reported symptoms and physical findings of the allergic episode.

Data processing and analysis was done with SPSS for Windows (Version 11.5). The Mann–Whitney *U*-test and chi-square analyses were used to test for statistical correlation. A $P < 0.05$ was considered significant.

Results

Study population

Hundred and three anaphylactic reactions reported from 93 paediatricians met the inclusion criteria and were evaluated. About 21/93 reporting physicians were from paediatric clinics, 72/93 were paediatric GP's. Patients' age ranged from 3 months to 12 years (median 5 years), 60/103 (58%), were boys and 43/103 (42%) girls. About 46 (45%) children suffered from bronchial asthma, 47 (46%) from atopic dermatitis, 34 (33%) from food allergies and 10 (10%) from allergic rhinoconjunctivitis.

Site of occurrence

The most common site of occurrence was in the child's home (58%) (Fig. 1). Ten per cent of all episodes occurred at school or kindergarten, and 10% on the street or other public places, while 14% happened in a medical setting like a practice or hospital (12% due to SIT, 1% due to a drug, and 1% due to a skin-prick test); 8% occurred elsewhere.

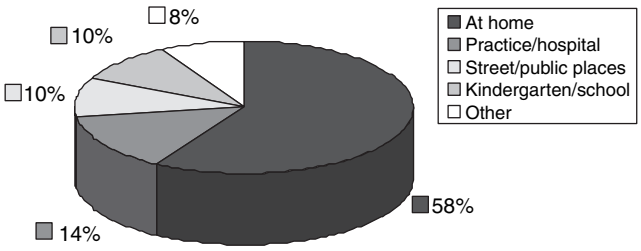

Figure 1. Site of occurrence of reported anaphylactic reactions.

Table 2. Frequency of reported causative allergens for anaphylaxis

Food	Insect sting	SIT	Medication	Other*	Unknown
All allergens ($n = 103$)					
59 (57%)	13 (13%)	12 (12%)	6 (6%)	4 (4%)	9 (8%)
Peanut	Tree nut	Cow's milk	Fish	Hen's egg	Other*
Foods ($n = 59/103$)					
12 (20%)	12 (20%)	8 (14%)	8 (14%)	4 (7%)	15 (25%)

*Lesser than or equal to two cases per allergen.

Triggering agents

In 92% of reported anaphylactic reactions a causative allergen was known or strongly suspected. For these, foods were the most common allergens (57% of all episodes), followed by insect stings with 13%, and specific immunotherapy (SIT) with 12% (Table 2). Medications were suspected to be responsible for 6% of anaphylaxes, and other agents in 4%. Considering foods in detail, the most commonly reported anaphylactic agents were peanuts (20% of all foods) and tree nuts (also 20%). In 14% of food-allergic anaphylaxes cow's milk was the suspected allergen; fish was also reported in 14% of cases, followed by hen's egg with 7%; 25% were various other food allergens. No significant difference was found for allergens looking only at severe reactions (grades III and IV).

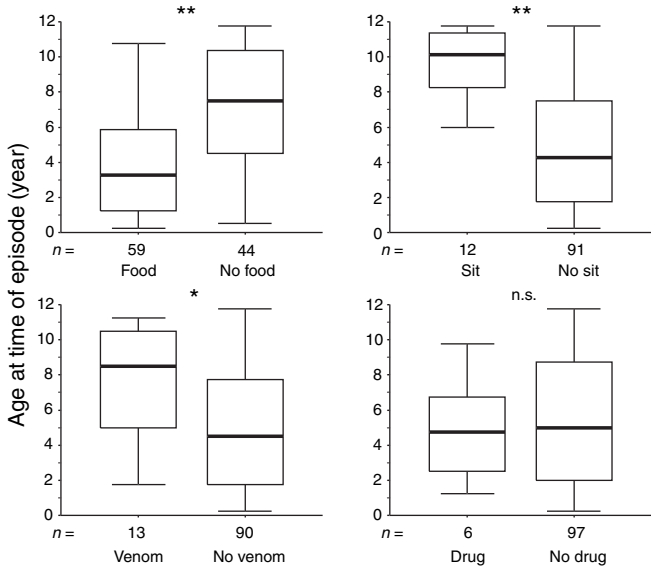

Figure 2. Age differences between food *vs* nonfood dependent, SIT *vs* nonSIT dependent, venom *vs* nonvenom dependent, and drug *vs* nondrug dependent clinical reactions. $*P < 0.05$, $**P < 0.001$.

There were significant age differences between the groups of children affected by the various causative agents. While children with reported food related anaphylaxis were significantly younger than the overall group (mean age, SD = 3.9 ± 3.0), those with SIT dependent and venom dependent anaphylaxis were significantly older (9.8 ± 1.9 and 7.6 ± 3.2, respectively) (Fig. 2).

Diagnostic tests

In 70 (68%) cases, allergy testing was performed to identify the anaphylactic agent, while in 26 (25%) cases no allergy testing was done at all. For the remaining 7/103 cases (7%) no information was provided. Specific Immunoglobulin E (IgE) concentrations in serum were determined in 63 children (45 positive, seven negative and 11 unknown results) and/or skin-prick tests were performed in 28 cases (19 positive, five negative and four unknown results). Ten children went through an allergen-provocation (in five cases with a positive result, three negative and two unknown) and four children underwent atopy-patch-testing (one positive, two negative and one unknown result).

Clinical symptoms

Independent of severity grading, 92% of all children showed cutaneous signs or symptoms. Respiratory involvement was found in 75% of the children and cardiovascular symptoms in 46%; the gastrointestinal tract was involved in 36% of all episodes. Graduating severity, in 3% of all cases reported symptoms were classified as local (grade-I reaction), and 21% as mild systemic reaction (grade II) (Table 1). Fifty-two per cent of all episodes were classified as severe systemic reaction (grade III). Twenty-four per cent of children experienced episodes with cardiovascular shock symptoms (grade IV). Considering only grades III and IV reactions, beside respiratory and/or cardiovascular symptoms an involvement of the skin was found in 91% of cases. One near-fatal reaction was reported, but there were no fatalities.

Recurrent reactions

In 28 cases (27%) the reported symptoms were already a recurrent episode. Twenty of these actual reactions (71%) were food-related, 2 (7%) occurred after an insect sting and two after SIT. In four children, the causative allergen was unknown. In 50% the recurrent episode was due to the same allergen as the anaphylactic episode(s) in medical history.

Treatment

Most of the children were treated with corticosteroids (80%), antihistamines (72%) and/or β2-agonists (72%). Adrenaline was used in 20% of all cases, 8% intravenous (i.v.), 1% subcutaneous (s.c.) and 12% by inhalation. No patient received intramuscular adrenaline. Seven per cent got i.v. fluids and 8% were not treated at all. Treatment in more detail and according to severity of reported anaphylaxis is shown in Table 3.

Drugs were administered to 32 children (30%) first by a nonhealth care professional, mostly by their parents (30 cases), two of them by a teacher. In these cases, oral antihistamines were used for treatment in 26 cases, rectal corticosteroids in 22 and inhaled steroids in two cases. Seven children received β2-agonists by inhalation and two of them inhaled adrenaline.

An epinephrine self-injector had already been prescribed in only 1 of the 28 patients with recurrent episodes of anaphylactic reactions, but it was not used in the reported severe systemic reaction (grade III). In all, 53 children (52%) were admitted to hospital: 15 out of 25 children with grade-IV reaction, 24/53 grade III, 11/22 of grade II and 3/3 grade-I reactions.

Emergency set

About 78 (77%) of the children were given 'emergency equipment' for first-aid treatment after the reported episode of anaphylaxis: 17 got an adrenaline-self-injector, one adrenaline for s.c. injection, and 19 adrenaline for inhalation. In all other cases antihistamines, steroids and/or β2-agonists were prescribed. Twenty-nine of the children were prescribed three different medications for intervention in the case of emergency, and two patients were given four different medications.

Table 3. Medical treatment according to grades I–IV anaphylaxis

	Grade				
	I (3)	II (22)	III (52)	IV (25)	Total (102)*
β2-Agonists	0	0	15 (28%)	6 (24%)	21 (21%)
Antihistamines	2 (67%)	15 (68%)	36 (68%)	20 (80%)	73 (72%)
Steroids	3 (100%)	13 (60%)	44 (83%)	22 (88%)	82 (80%)
Adrenaline (i.v./inhaled/s.c.)	1 (0/1/0) (33%)	3 (1/2/1)† (14%)	7 (1/6/0) (13%)	9 (6/3/0) (36%)	20 (8/12/1)† (20%)
Intravenous fluids	0	0	4 (8%)	3 (12%)	7 (7%)
No therapy	0	3 (6%)	3 (6%)	2 (8%)	8 (8%)

*In one reported case, the therapy was unknown.
†One patient was treated with both inhalant and subcutaneous adrenaline.

Discussion

Our survey confirms that anaphylaxis in childhood is mostly triggered by foods and occurs in an out-of-hospital setting in the majority of cases. Furthermore, it demonstrates that most of the children did not receive adequate treatment.

This is the first nation-wide investigation of anaphylaxis in infants and children in Germany. We aimed at performing a study in young children, and not in adolescents, which probably show a different pattern of clinical reactions, e.g. in terms of pollen-associated food allergies. Furthermore, the study was not designed as an epidemiological cross-sectional survey of the general paediatric population. It rather is a collection of cases seen by paediatricians in daily practice and hospital, without a selection of only hospitalized children or children seen in a specialist centre as published in other investigations of childhood anaphylaxis (12, 14, 15). Reactions as a result of allergen provocation were excluded.

In our retrospective design, we asked for the suspected etiologic agent of anaphylaxis. This was reported by the physicians in the questionnaire, and was not proven by allergy tests in the majority of cases. In a prospective study, *in vivo* or *in vitro* tests or provocation tests would be the method of choice to ensure a causing agent (16, 17). The fact of a retrospective survey may possibly bias towards reporting of more severe reactions. However, this is not likely since evaluation of the questionnaires revealed that one quarter (24%) was classified as grade I or II.

Remarkably, nine paediatricians volunteered information that they had not seen a case of anaphylaxis in a child, underlining the rare character of this medical emergency and the challenge for every medical career faced with such a situation.

Skin symptoms (92%) and respiratory (75%) symptoms were more frequent than gastrointestinal (36%) and cardiovascular ones (46%). This is in accordance with other investigations of anaphylaxis in children (8, 12, 14) where skin symptoms vary from 78 to 93%, respiratory involvement from 69 to 93% and gastrointestinal symptoms from 13 to 43%. Cardiovascular symptoms have been described in 8–26% of anaphylactic reactions.

The severity of reported reactions was graded by, the investigators according to reported symptoms (see Table 1). Gastro-intestinal symptoms are often associated with anaphylaxis. However, we graded severity solely according to potentially life-threatening symptoms and not to associated ones. In our view, the diagnosis of anaphylaxis should therefore be restricted to grades III and IV reactions, since grade-I reactions were not systemic and grade-II reactions were not considered to be life threatening. However, despite asking only for anaphylactic reactions, cases were reported with missing systemic signs or symptoms (grade I). This indicates the uncertainty many physicians might feel concerning anaphylactic reactions, as well as the problem of a clear definition of anaphylaxis.

According to the AAAAI, anaphylaxis is 'a collection of symptoms affecting multiple systems in the body. The most dangerous symptoms include breathing difficulties and a drop in blood pressure or shock, which are potentially fatal' (18). However, many of them include patients with systemic reactions without respiratory and/or cardiovascular symptoms (8, 9, 19), corresponding to our grade-II reactions. In accordance with our criteria, others demand respiratory and/or cardiovascular involvement (11, 12, 14). Detailed criteria for anaphylaxis vary considerably among all these authors. For our grades III and IV we chose the criteria of the EAACI-Position Paper defining anaphylaxis as a severe, life-threatening generalized or systemic allergic reaction (20).

In our study, foods were the most frequent supposed causative agents of reported anaphylactic reactions, and in particular peanuts and tree nuts. This is in accordance with other investigations (8, 14, 15), as is the frequent occurrence of insect stings, reported in 12% of cases in our study. In a surprising proportion of reported cases, however, immunotherapy (SIT) was suspected to be responsible for reported anaphylactic reactions. The SIT is of course known to be potentially anaphylactic, but despite its wide use, adverse events as severe as an anaphylactic reaction were not described, by others in such a high proportion in relation to other causes (14, 21,

22). As expected, the proportion of reported food-dependent reactions decreased with increasing age (8, 14), while immunotherapy-dependent reactions only occurred in children 6 years of age or older, as SIT is usually not applied in younger children (23).

Twenty-seven per cent of reported episodes were not the child's first experienced anaphylactic reaction. In 50% of these cases recurrent reaction was caused by the same allergen as in the previous episode. In this subgroup, foods were the large majority of agents (71%), higher than in the whole study population. This has also been described by, other investigators (15). Foods are commonly considered to be potentially avoidable. This high proportion of foods in recurrent episodes of anaphylaxis shows again that complete avoidance is a great challenge and requires the vigilance of the patients and adult carers. Especially in young children, surveillance is hardly feasible. Furthermore, in the case of peanut-allergy, accidental ingestion may occur quite often due to the wide distribution of peanut contents, Therefore, it is not only necessary to provide extensive instructions for avoidance, but a potent emergency drug should also be prescribed.

As expected (8, 12), most reported anaphylactic reactions occurred in the child's home (58%). Together with 10% of all reactions taking place at school or kindergarten, and another 10% on the street or other public places, the large majority of reported anaphylaxes happened in a nonmedical setting. Therefore, first-aid mostly has to be given by parents. In our study, 30% of all children were given medical treatment by a nonhealth care professional. Antihistamines and corticosteroids were used in the majority of cases. Only one child had an adrenaline self-injector, due to a previous anaphylactic reaction, but it was not used in the current episode (grade III). This demonstrates the difficulty facing patients and parents to in deciding whether it is appropriate to administer an adrenaline injection.

Regarding medical treatment for all children, only 8% were given adrenaline intravenously. Even of the patients with the most severe anaphylactic reactions (grade IV) only 24% were treated with adrenaline i.v. As adrenaline is considered to be the drug of choice for the treatment of anaphylaxis (1, 10, 24), this indicates a dramatic under treatment: at least 76% of these children did not get adequate treatment. In view that treating patients by SIT requires specially trained physicians, it was astonishing to realize that SIT patients were not diagnosed and treated better than other patients (only 1 out of 12 patients got i.v. adrenaline). Some of the patients got inhaled adrenaline; however, especially in usual dosages, this is by no way sufficient to treat other than local respiratory symptoms (24).

In our study, 8% of all children, and even 8% of the children with grade-IV reactions were given no treatment at all, showing that fortunately anaphylactic reactions might be self-limiting in many cases. However, this should never be a reason to delay or even inhibit adequate treatment in any case of anaphylaxis, which remains a potentially fatal emergency (1–6).

Fifty-two per cent of all children were admitted to hospital after the anaphylactic episode. Due to the possible recurrence of symptoms 8–10 h after the initial symptoms as well as after a complete remission of all signs and symptoms (11, 19, 25), surveillance for at least 24 h is suggested in any case of anaphylaxis.

In conclusion, our data demonstrates an uncertainty of physicians in diagnosing and treating anaphylaxis. Furthermore it proves a remarkable under-treatment of the majority of children with anaphylactic reactions. There is a need to train physicians in diagnosing and treating anaphylaxis and for guidelines. In addition, the establishment of self-management programmes, including the use of self-injectable adrenaline, for patients and their families should be encouraged (26).

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