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Incidence of food anaphylaxis in Piemonte region (Italy): data from registry of Center for Severe Allergic Reactions

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Abstract

There are wide differences in estimated incidence and prevalence of anaphylaxis because of the absence, until recently, of a universal consensus on the definition of anaphylaxis and the different source of collected data. We aimed to estimate the incidence of food anaphylaxis based on the database of Piemonte Region (Italy) Reference Center for Severe Allergic Reactions. All cases of severe food allergic reactions reported in 2010 were studied. Clinical data associated to the reports were evaluated according to National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network diagnostic criteria of anaphylaxis. 75 % of the 778 cases were classified as food anaphylaxis (incidence of 13/100,000 person-years, ranging from 9.9 in adults to 29/100,000 person-years in children). Nuts were the most frequent foods causing anaphylaxis. Milk and eggs were responsible for anaphylaxis more often in children, while peach, vegetables and crustaceans were in adults. Cardiovascular symptoms were more frequent in adults. Gastrointestinal involvement was more frequent in children. A high prevalence of respiratory allergic comorbidities was observed. Food is an important cause of anaphylaxis, particularly in subjects with respiratory allergic comorbidities. Children and adults differ in triggers and clinical presentation of anaphylaxis.

Keywords: Anaphylaxis, Food allergy, Epidemiology, Allergy

Introduction

Population-based studies estimate the incidence of anaphylaxis in western countries to be in the range of 4–50 per 100,000 person-years [1, 2], with a true lifetime prevalence in the range of 0.05–2 % [3]. Foods are reported to be the most important trigger of anaphylaxis, being responsible for 33.2–56 % of all anaphylaxis cases [4]. The other two principal triggers of anaphylaxis are insect stings and drugs [1, 5]. The relative contribution of each of these triggers to anaphylaxis may differ according to the study design, study population, or geographic area. The wide differences in the estimated incidences and prevalences of anaphylaxis are the direct result of the absence, until recently, of a universal consensus on the definition of anaphylaxis and the different source of collected data. For this reason in 2005 the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) developed a very useful preliminary definition, based on diagnostic criteria [6]. The symposium defined anaphylaxis as: “a serious allergic reaction that is rapid in onset and may cause death”. Clinically, involvement of at least two organs (skin or mucosal tissue, cardiovascular apparatus, breathing apparatus, gastrointestinal tract) is required, or a sudden reduced blood pressure along with a temporal relationship (generally minutes) to a potential causative agent. A problematic issue with this definition, which may explain the under-reporting or misreporting of anaphylaxis cases, is the failure to agree among health care providers on the severity threshold for classifying a reaction as anaphylactic reaction. According to two important studies [7, 8], only 1 % of the acute systemic allergic reactions evaluated in emergency departments had been diagnosed as anaphylaxis, as most of the systemic allergic reactions received a diagnosis of acute allergic or acute hypersensitivity reaction. In another study from hospital emergency departments in the United States, 57 % of very likely episodes of food anaphylaxis did not receive a diagnosis of anaphylaxis [9].

In 2007, to improve the quality of the diagnosis of the adverse events following immunization, the Brighton Collaboration proposed a case definition of anaphylaxis, based on a detailed check-list to assess the severity of signs and symptoms observed in patients. This procedure may help to decrease the variability of the assessment of severity of the reactions by health professionals. According to Brighton Collaboration's criteria, three levels of diagnostic probability are easily obtained by combining major and minor criteria [10, 11]. The clinical check-list of signs and symptoms related to the various organs potentially involved in anaphylaxis that was developed by Brighton Collaboration is much more detailed compared to the symptoms reported in the clinical criteria for diagnosing anaphylaxis by the NIAID/FAAN Symposium. We reasoned that Brighton Collaboration's check-list may help to graduate the severity of signs and symptoms, and may also be a useful tool for reviewing the medical chart records of patients who report severe allergic reactions, with the aim of identifying the anaphylaxis cases. In the present study we wished to report epidemiologic data of the incidence of food anaphylaxis in the Piemonte Region (Italy). Anaphylaxis was defined according to NIAID-FAAN definition, and the reported clinical manifestations were evaluated according to the Brighton Collaboration's clinical check-list and criteria for each patient. Data have been obtained by reviewing the database of the Reference Center for Severe Allergic Reactions of Piemonte Region (see "Methods"), focusing on allergic reactions triggered by foods as well on comorbidities.

Methods

Study design

In 2003 the Piemonte Region (Italy) activated the Reference Center for Severe Allergic Reactions, which monitors a population of 4,400,000 inhabitants and collects data mandatory for prescribing self-injectable epinephrine reimbursed by Regional Health System [12]. Patients reporting severe allergic reactions are referred to the nearest Allergy Clinic, where they receive accurate evaluation and a prescription for self-injected adrenaline, when appropriate. The Center allows the online connection of all the Allergy Clinics of the Region, with the purpose of recording the cases of severe allergic reactions in a registry. An Internet-based system, with restricted access only to authorized users, has been developed for the management of clinical data. The patients included in the registry are requested to provide their informed consent to the use and storage of their personal data for epidemiologic purpose [12]. In the present study, all the cases of severe food reactions and food anaphylaxis reported to the Regional Reference Center from 1 January to 31 December 2010, have been analyzed. The study has been approved by the Review Board of the Regional Center for Severe Allergic Reactions.

Identification of cases

The clinical data associated to the reports have been evaluated according to NIAID/FAAN criteria [6] and the case definition of Brighton Collaboration [10, 11].

We have assigned each case to one of three levels of decreasing probability using a clinical check-list based on recommendations of the Brighton Collaboration, thus obtaining two groups of patients: one group (anaphylaxis) with high, moderate and low probability of anaphylaxis and the other group (severe allergic reactions) that did not fulfill the criteria of anaphylaxis. We have separately analyzed children (<18 years) and adults (≥18 years).

In order to check the agreement between observers, 100 reports were analyzed independently by two allergists. Unanimity was observed in 93 cases, yielding an observed concordance of 93 % with a kappa index (κ) of agreement of 0.86.

Statistical analysis

The incidence per person year was calculated from the population of all children 0–17 years of age and adults ≥18 years of age living in Piemonte during 2010, in total 721,689 and 3,735,646, respectively [13]. Prevalence rates of eliciting foods, symptoms, and treatment are presented as proportions.

Data are also expressed in total numbers, but as mean or median when appropriate. Differences in proportions between groups were analyzed with either the Chi square analysis or Fisher's exact test. The one-sample Kolmogorov–Smirnov test was used for comparisons of distribution between variables. The data were analyzed with the statistical program PASW Statistics version 17.0 (SPSS Inc, Chicago, IL, USA). P value <0.05 was considered to be significant.

Results

Study population and demographic data

Among the 778 case reports of severe allergic food reaction, 582 could be classified as food anaphylaxis, respectively, with level 1 (n = 224, 38.5 %), level 2 (n = 343, 58.9 %) and level 3 (n = 15, 2.6 %) of probability. 221 patients were children (age 6 ± 5.4 years, range 0–17 years, M/F = 1.98), and 361 adults (age 34 ± 12.8 years, range 18–87 years, M/F = 0.51).

196 cases did not fulfill the criteria for the diagnosis of anaphylaxis, being classified as severe food allergic reactions, which consisted of urticaria or muco-cutaneous angioedema. 108 of these patients were children (age 5 ± 4.3 years, range 0–17 years, M/F = 1.57), and 88 adults (age 38 ± 13.9 years, range 18–85 years, M/F = 0.76). The incidence of food anaphylaxis in the general population of Piemonte Region was estimated to be 13 per 100,000 person-years, ranging from 9.9 in adults to 29 per 100,000 person-years in children.

Trigger foods

Table 1 shows the cases of anaphylaxis according to the triggering food in children and adults.

The specific food responsible for anaphylaxis was not identified in 49 patients, almost all of them were adults (43 cases). Nuts, particularly hazelnuts, were the most frequent foods causing anaphylaxis, both in children and in adults, respectively, in 31.7 and in 21.6 % of cases, with significantly higher prevalence in children compared to adults.

Milk and egg were responsible of anaphylaxis more often in children than in adults (respectively, 14.48 vs 3.88 % $p < 0.001$ and 15.38 vs 1.1 % $p < 0,001$), while peach, vegetables and crustaceans were implicated more frequently in adults than in children (respectively, 9.14 vs 4.52, $p = 0.039$, 5.54 vs 0.9 %, $p = 0.006$, and 9.69 vs 2.26 %, $p < 0.001$).

Clinical presentation of anaphylaxis

Figure 1 shows the prevalence of the symptoms in children and adults. Skin and respiratory symptoms were the most frequently reported symptoms both in children and adults (95.5 vs 93.9 % and 80.1 vs 82.8 %). Cardiovascular symptoms were reported more frequently in adults than in children (36.3 vs 15.8 %, $p < 0.001$), while gastrointestinal involvement was more frequent in children than in adults (43.4 vs 28.5 %, $p < 0.001$).

Table 2 shows the prevalence and severity of the involved systems (skin, respiratory, cardiovascular, and gastrointestinal) according to the triggering foods.

In 21 patients (6 children) anaphylaxis could be classified as food-dependent exercise-induced anaphylaxis (FDEIA). Triggering foods of FDEIA had been identified in 17 cases: nuts in 7, fresh fruits in 3, grain and flour, vegetables and crustaceans in 2 cases each, seeds in 1 case.

Comorbidities

Allergic rhinitis and oral allergic syndrome (pollen-food allergy) were more prevalent in adults than in children (respectively, 53.74 vs 36.2 %, $p < 0.001$ and 19.94 vs 8.15 %, $p < 0.001$), while atopic dermatitis was more prevalent in children than in adults (49.32 vs 3.6 %, $p < 0.001$). The prevalence of asthma was

similar (27.15 % in adults and 30.32 % in children) (Table 3). Table 4 shows the sensitization pattern to common inhalant allergens observed in 481 patients (183 children and 298 adults), with no significant difference between children and adults.

Discussion

According to our data, the incidence of food anaphylaxis in the general population of Piemonte Region appears to be similar to the incidence reported in the literature, which range from 10.5 per 100,000 person year to 32 per 100,000 person year [14–16]. We cannot exclude underestimation of the true incidence of food anaphylaxis, in particular, milder forms. First, due to selection bias, epidemiological studies based on the cases reported in allergy clinics are less accurate in providing the prevalence and the incidence of anaphylaxis in the general population. Nonetheless these studies provide the most accurate information regarding triggers and associated factors of anaphylaxis. Second, some anaphylactic episodes may have been treated by local healthcare providers and not referred. Third, mild episodes of anaphylaxis may resolve spontaneously. The primary limitation of this study is its retrospective design and our reliance on documentation in clinical records. The criteria used to define anaphylaxis will affect the results. In this study, we used the criteria of NIAID/FAAN and the case definition of Brighton Collaboration [10, 11]. However, since these criteria correspond to the criteria for anaphylaxis recently suggested by the World Allergy Organization [17], our results would not have been altered if the latter criteria had been used. A considerable strength of this study is that we had access to the patients' record, including the Emergency Department record and the diagnostic allergy work-up, which led to the identification of the culprit food in over 85 % of cases. This finding is significantly better compared to epidemiologic studies based on emergency department visits, where the specific eliciting food could not be identified in up to 26 % of cases [18]. In our study, most (88 %) of the cases where the specific food responsible for anaphylaxis was not identified were adults.

Among foods causing anaphylactic reactions, nuts were the dominating triggering foods, both in adults and in children, followed by milk and egg in children and peach, crustaceans and vegetables in adults. These findings confirm those of others [1, 18, 19] apart from peanut allergy, which was less common cause of anaphylaxis in Piemonte Region (7 %) as in other European surveys [20], compared to epidemiologic studies from the United States and the British Islands [21], where peanut anaphylaxis is particularly frequent. Fresh fruit was an important trigger of anaphylaxis, both in adults and in children, peach being the most frequent one, followed by apple. Plant-derived foods, due to lipid transfer protein (LTP) sensitization, are the most important cause of type 1 food allergy in Italy, according to a recent epidemiological survey [22] and in agreement with what is observed in the Mediterranean countries [23]. In our study, food anaphylaxis was more commonly observed in boys than in girls, but this gender preference reverses in adulthood, where it was more commonly observed in female than in male patients. In adults, anaphylaxis is more common in women potentially because of estrogens enhancing mast cell activation and allergic sensitization as was shown in an animal model [1, 24]. However, in studies estimating anaphylaxis incidence in children, males predominate [1]. Concerning presenting symptoms of anaphylaxis, cardiovascular symptoms are more frequent in adults compared to children, who report more gastrointestinal symptoms than adults, while muco-cutaneous involvement is as frequently reported in children as in adults. Other studies report that cardiovascular symptoms, such as hypotension and shock, are less common as manifestations of anaphylaxis in childhood [25, 26].

An important finding of our study is the high prevalence of respiratory allergic disease, rhinitis and asthma due to pollen, mites and pet dander (see Table 2). Particularly the prevalence of asthma appears quite higher in patients who report food anaphylaxis than in the general population of Torino, the most populous town of the same Region, according to a recent epidemiological study [27]. A history of asthma appears to

be a major risk factor for life-threatening anaphylactic reactions to food [28–30], but it is not particularly specific, as about a third of food allergic patients have asthma. Many of our patients (one-third of adults) had the oral allergic syndrome, mainly due to pollen-food allergy, as it is commonly observed in Northern Italy [22]. In conclusion, food is an important cause of anaphylaxis in the general population, particularly in subjects with respiratory allergic comorbidities (rhinitis and asthma).

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Food	**Children *n* = 221 (%)**	**Adults *n* = 361 (%)**	***p***
Nuts	70 (31.67)	78 (21.61)	0.007
Hazelnut	32 (14.48)	37 (10.25)	ns
Walnut	10 (4.52)	8 (2.22)	ns
Peanut	19 (8.6)	24 (6.65)	ns
Almond	7 (3.17)	4 (1.11)	ns
Chestnut	2 (0.9)	3 (0.83)	ns
Pine nut	–	2 (0.55)	ns
Fresh fruits	23 (10.41)	72 (19.94)	0.003
Peach	10 (4.52)	33 (9.14)	0.039
Apple	7 (3.17)	19 (5.26)	ns
Pear	4 (1.81)	3 (0.83)	ns
Banana	1 (0.45)	2 (0.55)	ns
Blueberry	1 (0.45)	–	ns
Plum	–	4 (1.11)	ns
Kiwifruit	–	4 (1.11)	ns
Melon	–	2 (0.55)	ns
Fig	–	2 (0.55)	ns
Avocado	–	2 (0.55)	ns
Cherry	–	1 (0.28)	ns
Milk and dairy foods	32 (14.48)	14 (3.88)	0.000
Crustaceans	5 (2.26)	35 (9.70)	0.001
Egg	34 (15.38)	4 (1.1)	0.000
Fish	17 (7.69)	20 (5.54)	ns
Seeds	14 (6.33)	18 (4.99)	ns
Grain and flour	7 (3.17)	15 (4.16)	ns
Vegetables	2 (0.90)	20 (5.54)	0.004
Legumes	3 (1.36)	16 (4.43)	ns
FDEIA	6 (2.71)	15 (4.16)	ns
Others	2 (0.90)	11 (3.05)	ns
Unidentified food	6 (2.71)	43 (11.91)	0.000

Table 1 Cases of anaphylaxis according to the triggering foods

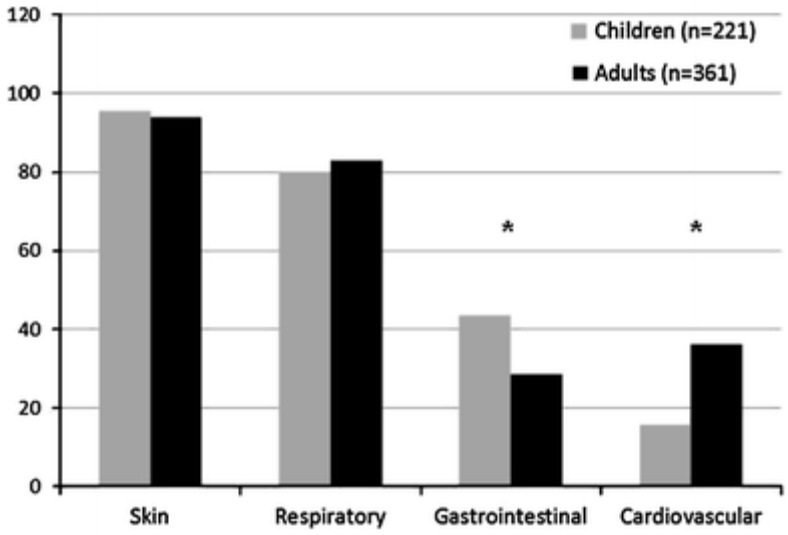

Fig. 1 Prevalence of the symptoms of anaphylaxis in children and adults. *p < 0.001

Triggering food	Total cases	Skin		Respiratory		Cardiovascular		Gastrointestinal
	(Count and %)	Involvement	Major	Involvement	Major	Involvement	Major	Involvement
Nuts	148	138	134	130	48	35	27	43
		93.24	90.54	87.84	32.43	23.65	18.24	29.05
Fresh fruits	95	93	90	79	26	28	18	28
		97.89	94.74	83.16	27.37	29.47	18.95	29.47
Milk and dairy foods	46	44	39	39	20	10	6	16
		95.65	84.78	84.78	43.48	21.74	13.04	34.78
Crustaceans	40	36	34	29	13	16	11	12
		90.00	85.00	72.50	32.50	40.00	27.50	30.00
Egg	38	37	36	27	12	6	3	21
		97.37	94.74	71.05	31.58	15.79	7.89	55.26
Fish	37	32	32	26	10	11	7	17
		86.49	86.49	70.27	27.03	29.73	18.92	45.95
Seeds	32	32	30	30	8	4	2	13
		100.00	93.75	93.75	25.00	12.50	6.25	40.63
Grain and flour	22	21	21	17	11	9	7	11
		95.45	95.45	77.27	50.00	40.91	31.82	50.00
Vegetables	22	19	19	15	3	8	5	7
		86.36	86.36	68.18	13.64	36.36	22.73	31.82
Legumes	19	18	15	17	6	4	3	7
		94.74	78.95	89.47	31.58	21.05	15.79	36.84
FDEIA	21	20	20	16	7	11	8	3
		95.24	95.24	76.19	33.33	52.38	38.10	14.29
Other	13	11	11	9	5	8	6	6
		84.62	84.62	69.23	38.46	61.54	46.15	46.15
Unidentified	49	49	45	42	18	16	10	15
		100.00	91.84	85.71	36.73	32.65	20.41	30.61
Total cases	582	550	526	476	187	166	113	199
		94.50	90.38	81.79	32.13	28.52	19.42	34.19

Table 2 Prevalence and severity (at least one diagnostic major criterion) of reaction in the involved systems, according to the triggering foods. Skin: generalized urticaria or generalized erythema; angioedema, localized or generalized; generalized pruritus with skin rash. Cardiovascular: measured hypotension, clinical diagnosis of uncompensated shock (at least 3 of the following: tachycardia, capillary refill time >3 s, reduced central pulse volume, decreased level of consciousness or loss of consciousness). Respiratory: bilateral wheeze (bronchospasm), stridor, upper airway swelling (lip, tongue, throat, uvula, or larynx), respiratory distress (at least 2 of the following: tachypnoea, increased use of accessory respiratory muscles, recession, cyanosis, grunting). Gastrointestinal symptoms are considered, by definition, minor criteria: diarrhea, abdominal pain, nausea, vomiting (see ref. [10])

Comorbidity	**Children *n* = 221 (%)**	**Adults *n* = 361 (%)**	***p***
Allergic rhinitis	80 (36.2)	194 (53.74)	<0.001
Oral allergic syndrome	18 (8.15)	72 (19.94)	<0.001
Atopic dermatitis	109 (49.32)	13 (3.6)	<0.001
Asthma	67 (30.32)	98 (27.15)	ns

Table 3 Prevalence of allergic comorbidities in children and adults

Sensitization	Children *n* = 183 (%)	Adults *n* = 298 (%)
Grass family	125 (68.30)	167 (56.04)
Asteraceae	60 (32.78)	130 (43.62)
Birch	68 (37.16)	116 (38.93)
Urticaceae	28 (15.30)	58 (19.46)
Dust mites	94 (51.37)	119 (39.93)
Animal epithelia	78 (42.62)	91 (30.54)

Table 4 Sensitization pattern to common inhalant allergens