Anaphylaxis in adults referred to a clinical immunology/allergy centre in Singapore

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ABSTRACT

Introduction: To study the clinical features and causes of anaphylaxis in consecutive adult patients referred to a clinical immunology/allergy centre in Singapore.

Methods: A retrospective review of 67 consecutive adults with anaphylaxis who presented from July 1, 1998 to February 28, 2002 was performed. Anaphylaxis was defined as a severe life-threatening systemic IgE-mediated hypersensitivity reaction. Non-steroidal anti-inflammatory drug-induced idiosyncratic reactions and other non-IgE mediated reactions were excluded. Hypotension and bronchospasm were not required to make a diagnosis. The aetiology was determined from clinical history followed by measurement of allergen-specific IgE levels, skin prick test with commercially-available allergen extracts or prick-prick test with the fresh/cooked/canned food products.

Results: The mean age of patients was 32.9 ± 10.9 (range 19-57) years. There were 44 (65.7 percent) males and 23 (34.3 percent) females. The main causes were food (44.8 percent), insect stings (32.8 percent) and idiopathic (22.4 percent). There were no cases due to drugs or natural rubber latex. Seafood (crustaceans and molluscs) comprised 66.7 percent of food-induced anaphylaxis. Honeybee and wasp stings together comprised 45 percent of insect venom anaphylaxis. The most common manifestations were dyspnoea (59.7 percent), urticaria (58.2 percent), angioedema (44.8 percent), and syncope (43.3 percent). Hypotension was documented in only 28.4 percent of cases.

Conclusion: Food (crustaceans and molluscs) was the most common cause followed by insect stings or bites. The inability to identify the causative insect in 50 percent of cases with insect venom anaphylaxis limited the role of specific immunotherapy. Compared to other reported series, there were no cases of drug or latex anaphylaxis.

Keywords: hypersensitivity, radioallergosorbent test, skin tests, immunotherapy

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INTRODUCTION

Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction. The nomenclature proposed in the October 2003 report of the Nomenclature Review Committee of the World Allergy Organisation proposed that anaphylactic-type reactions be reclassified as allergic or nonallergic anaphylaxis[1]. Allergic anaphylaxis is further classified as IgE- or non-IgE-mediated reactions. However, the terms *anaphylactoid* and *anaphylactic* remain commonly used in differentiating non-IgE-mediated (including other immunologically mediated mechanisms) and IgE-mediated reactions, respectively. Hypotension and severe bronchospasm do not have to be present for a reaction to be classified as anaphylactic. There have been no studies to date from South-east Asia on the epidemiology of the causes of anaphylaxis. We describe 67 consecutive adults managed in our clinical immunology/allergy centre in Singapore over a 44-month period.

METHODS

A retrospective review of 67 consecutive adults (age ≥18 years) with anaphylaxis who presented from July 1, 1998 to February 28, 2002 was carried out. Anaphylaxis was defined as a severe life-threatening systemic IgE-mediated hypersensitivity reaction. Non-steroidal anti-inflammatory drug (NSAID)-induced idiosyncratic reactions and other non-IgE mediated reactions were excluded. Hypotension and bronchospasm were not required to make a diagnosis of anaphylaxis. The aetiology of anaphylaxis was determined from clinical history, followed by measurement of allergen specific IgE levels using the Pharmacia CAP system (Pharmacia, Peapack, NJ, USA), skin prick test (SPT) using allergen extracts (Greer Laboratories, Lenoir, NC, USA) or prick-prick test with the fresh, cooked, or canned food products.

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Table I. Foods implicated in 30 cases of food-induced anaphylaxis.

	Number	Percentage	Type(s)
Molluscs	11	36.7	Limpet, abalone
Crustaceans	9	30.0	Prawn, crab, lobster
Tree nut	2	6.7	Almond, walnut
Fruit	2	6.7	Rambutan, longan, rock-melon
Bird's nest	1	3.3	
Peanut	1	3.3	
Fish	1	3.3	
Alga (as health supplement)	1	3.3	Chlorella
Others	3	10.0	Additives

Positive tests were defined as CAP specific IgE ≥0.7kU/L, and mean SPT wheal diameter 3 mm greater than the negative control.

The data was analysed using EXCEL (Microsoft) and SPSS version 10.0 (SPSS Inc, Chicago, IL, USA). Statistical significance of the differences was assessed using chi-square test for proportions. The Fisher exact test was used when the expected frequency for any cell was less than five. The one-way analysis of variance (ANOVA) was used to assess differences for means. P-value less than 0.05 was considered to be statistically significant.

RESULTS

The mean age was 32.9 ± 10.9 (range 19-57) years. There were 44 (65.7%) males and 23 (34.3%) females. The racial distribution was 43 (64.2%) Chinese, seven (10.4%) Malays, five (7.5%) Indians, and 12 (17.9%) from other racial denominations. The main causes of anaphylaxis were food (30, 44.8%) and insect stings (22, 32.8%). 15 cases (22.4%) were idiopathic. None were attributed to drugs or natural rubber latex. Seafood crustaceans and molluscs, comprised 66.7% of food-induced anaphylaxis. The other putative food allergens are summarised in Table I. One patient had food-dependent exercise-induced anaphylaxis (FDEIA) following a meal, although this could not be reproduced upon food and exercise provocation testing. Honeybee and wasp stings together comprised 45% of insect sting anaphylaxis.

A median of one (range one to ten) episode of anaphylaxis occurred before the patients were referred to the clinic. No patient experienced recurrent (biphasic, recurring eight to 12 hours after the initial attack) or persistent (lasting from five to 32 hours) anaphylaxis. The most common manifestations of anaphylaxis were dyspnoea (59.7%), urticaria (58.2%), angioedema (44.8%) and syncope (43.3%). Hypotension was documented in only 19 (28.4%) cases. A history of atopy was present in 27 (40.3%) patients including asthma in 14 (20.9%).

A comparison of the clinical characteristics among the three different aetiologies of anaphylaxis is summarised in Table II. There were statistically

Table II. Clinical profile of patients.

	Food (n=30)	%	Insect venom (n=22)	%	Idiopathic (n=15)	%	p-value
Age (years)							
(mean ± sd)	36.4 ± 10.8		29.6 ± 11.0		30.9 ± 9.5		0.059 (ns)
(range)	19-57		19-57		19-47		
Sex							
Male	14	46.7	21	95.5	9	60.0	0.001 (s)
Female	16	53.3	1	4.5	6	40.0	
Race							
Chinese	19	63.3	14	63.6	10	66.7	0.638 (ns)
Malay	2	6.7	3	13.6	2	13.3	
Indian	4	13.3	0	0.0	1	6.7	
Others	5	16.7	5	22.7	2	13.3	
Atopy							
Present	18	60.0	5	22.7	4	26.7	0.012 (s)
Absent	12	40.0	17	77.3	11	73.3	
Personal history							
Allergic rhinoconjunctivitis	15	50.0	4	18.2	4	26.7	0.045 (s)
Asthma	11	36.7	2	9.1	1	6.7	0.017 (s)
Atopic eczema	3	10.0	0	0.0	0	0.0	0.144 (ns)
Family history							
Allergic rhinoconjunctivitis	6	20.0	2	9.1	1	6.7	0.357 (ns)
Asthma	6	20.0	3	13.6	2	13.3	0.775 (ns)
Atopic eczema	3	10.0	1	4.5	1	6.7	0.754 (ns)
Food allergy	2	6.7	0	0.0	0	0.0	0.280 (ns)

ns: not statistically significant, s: statistically significant

Table III. Epidemiology of all causes of anaphylaxis.

Year	Author	Type of study	Period of study	Country	No. of cases	Age (range)	Sex F:M	Atopy (%)	Causes	Outcomes measures
1994	Yocum, et al.[3]	Retrospective allergy clinic	3 years 6 months	United States	179	Mean 36 years	1.9:1	37%	Food (33%) Idiopathic (19%) Insect venom (14%) Drugs (13%) Exercise (7%)	Nil
1995	Kemp, et al.[4]	Retrospective allergy clinic	14 years	United States	266	Paediatric and adult Mean 38 years (12-75)	1.4:1	37%	Idiopathic (37%) Food (34%): crustacean, peanut Drugs (20%): NSAID Exercise (7%) Latex (0.8%)	Nil
1996	Pumphrey, et al.[5]	Retrospective allergy clinic	Unknown	United Kingdom	172	Paediatric and adult 5 months - 69 years	1:1	59% - Food (59.9%) - Idiopathic (11.6%) - Venom (16.3%) - Drug (8.7%) - Latex (3.5%)	Peanut (42) Tree nut (23) Other food (20) FDEIA (5) Venom (6Bee, 22 Wasp) NMRB (7) NRL (6) Idiopathic (20)	Nil
1998	International Collaborative Study of Severe Anaphylaxis[6]	Prospective multi-centre	3 years	Hungary, Spain, India, Sweden	123	Unknown	Unknown	Unknown	Unknown	Mortality 2%
1998	Novembre, et al.[7]	Retrospective paediatric allergy clinic	2 years	Italy	76	Unknown	0.5:1	82%	Food (57%): seafood, milk Drugs (11%) Venom (12%) Exercise (9%) Additives (1%) Specific immunotherapy (1%) NRL (1%) Vaccines (2%) Idiopathic (6%)	Nil
2000	Pumphrey, et al.[8]	Retrospective fatal anaphylaxis registry	8 years	United Kingdom	56	Adult and paediatric Median 52 years (7-85)	1.5:1	Unknown	Drugs (38%) Venom (34%) Food (28%)	Nil
2001	Pastorello, et al.[9]	Retrospective emergency room attendances	2 years	Italy	140	Unknown	Female	Atopic	Food (39%) Drugs (36%) Idiopathic (21%) Venom (2%) Others (2%)	Incidence 4%
2001	Cianferoni, et al.[10]	Retrospective inpatient hospitalisations	11 years	Italy	107	Adult Mean 48 ± 18 years	0.8:1	51%	Drugs (49%) Venom (29%) Food (8%) Specific immunotherapy (6%) Idiopathic (6%) Exercise (2%)	Nil
2001	Brown, et al.[11]	Retrospective emergency room attendances	1 year	Australia	142	Paediatric and adult ≥13 years Mean 37.3 ± 15.8 years (14-86)	1.5:1	23.2% asthma	Drugs } Venom } 73% Food } Idiopathic (27%)	Incidence 1:439 Mortality 0.7%
2004	Helbling, et al.[12]	Retrospective case review from hospitals/ allergy clinics	3 years	Switzerland	226	Paediatric and adult Mean 41 years (5-74)	0.9:1	39.5% - Venom(47.1%) - Drug (17.7%) - Food (14.1%) - Idiopathic (10.6%)	Venom (59%) Drugs (18%) Food (10%) Idiopathic (5.3%)	Annual incidence 7.9 - 9.6/ 100,000 inhabitants Mortality 1.3%
2004	Peng, et al.[13]	Observational follow-up (UK General Practice Research Database)	6 years	United Kingdom	675	Unknown	Unknown	Unknown	Venom Drugs	Incidence 8.4/100,000 person-years Mortality 0.1%
2004	Bohlke, et al.[14]	Retrospective study from health maintenance organisation diagnosis codes	6 years	United States	67	Paediatric Median age 12 years (7 months -17 years)	0.7:1	60% - Food (72%) - Idiopathic (70%) - Venom (44%) - Drugs (30%)	Unknown	Incidence 10.5/ 100,000 person-years
2004	Cianferoni, et al.[15]	Prospective follow-up study	7 years	Italy	76	Paediatric	Unknown	Unknown	Unknown	Nil
2005	Thong, et al.	Retrospective allergy clinic	3 years 8 months	Singapore	67	Adult	0.5:1	40.3%	Food (44.8%) Insect sting (32.8%) Idiopathic (22.4%)	Nil

significantly more males than females among patients with insect venom and idiopathic anaphylaxis (p=0.001). The number of males and females among those with food-induced anaphylaxis were similar. A personal history of atopy was more common among adults with food-induced anaphylaxis (p=0.012) than the other two groups with significantly more adults with allergic rhinoconjunctivitis (p=0.045) and asthma (p=0.017). There was no difference in the mean age (p=0.059) or racial distribution (p=0.638) among the three groups.

DISCUSSION

The epidemiology of all causes of anaphylaxis in the United States, United Kingdom, Europe and Australia has been described in several studies (Table III)[2-15]. In these studies, the common causes of IgE-mediated anaphylaxis included drugs (penicillin, anaesthetic agents given during the perioperative period), insect stings, food and natural rubber latex. NSAID and radiocontrast media were common causes of non-allergic anaphylaxis. Exercise may precipitate anaphylaxis in certain food- and medication-dependent events. The cause of anaphylaxis remains unidentified in up to two-thirds of patients presenting to a clinical immunologist/allergist for evaluation. However, as most of these were retrospective, adult cohorts from specialty centres, with differences in methodology and inclusion criteria, the true incidence and prevalence of anaphylaxis worldwide remain unknown.

Published studies on the epidemiology of all causes of anaphylaxis in the Asia-Pacific region are lacking, although the overall incidence of anaphylaxis appears to be low. However, the epidemiology of anaphylaxis from specific causes has been reported from Australia, Japan, Korea and Singapore[16]. Our study is similar to previous larger studies because food is found to be the commonest cause, there is a predominance of males among those with insect venom anaphylaxis[17], and there is an association of atopy with food-induced anaphylaxis[18].

However, there are several notable differences. There were no cases of drug-induced allergic anaphylaxis, in particular from beta-lactam antibiotics. This is consistent with our study on inpatients with drug allergy verified by an allergist-immunologist where no cases were reported prospectively over a two-year period[19]. Firstly, this may be because the putative drug is often stopped early enough when patients first develop mild cutaneous manifestations in the form of urticaria or angioedema, hence leading to subsequent avoidance of the drug. This may also explain the absence of drug-induced anaphylaxis in our inpatient series which comprised notifications from all the various specialties in our hospital. A second reason may be that patients with drug-induced anaphylaxis may not have required long-term follow-up since the cause had been identified and thus subsequently easily avoided. This is in contrast to other causes of anaphylaxis where patients need to be followed-up to assess the success of their avoidance measures, reasons for any further anaphylactic episodes and yearly renewal of their epinephrine autoinjector. The epinephrine autoinjector is available only in certain hospitals with allergy/immunology services in Singapore and on a "named-patient" basis.

There were no cases of natural rubber latex (NRL) allergy causing anaphylaxis, in contrast to Caucasian studies. Powdered and non-powdered NRL gloves are used in most hospitals in Singapore. A review of 90 cases of occupational asthma in Singapore from 1983 to 1999 revealed no instances of occupational asthma from NRL[20]. Similarly, a review of 965 patients with occupational skin diseases from 1989 to 1998 in Singapore showed that although rubber chemicals were a common allergen in 18.7% of cases, especially in the electrical and electronics industry, NRL was the implicated allergen in only one of 23 (4.3%) cases of contact urticaria[21]. Thus, our local experience differs from that in North America and Europe where pooled rates of latex sensitisation in health-care workers is estimated to be 8%, latex-induced rhinoconjunctivitis 7.8%, latex-induced asthma 1.4%[22], and the prevalence of latex-induced anaphylaxis 10% – 17% of 1:5,000 to 1:10,000 medical or surgical procedures[23]. In the Asia-Pacific region, sensitisation rates are reported to vary from 6.8% in clinic populations[24] to 10.2% in atopic children[25]. The prevalence of clinical immediate hypersensitivity is reported to range from 3.3%[24] to 4.6%[26], although anaphylaxis appears to be rare.

The pattern of food-induced anaphylaxis was different from Caucasian studies. Limpet, a gastropod mollusc, was a common food allergen. This has also been reported in Spain[27] and Japan[28], where the putative limpets were of different genera. Another unusual allergen was bird's nest. In a local paediatric study, bird's nest was found to be the most common cause of IgE-mediated FA[29]. Although not a common cause of food-induced anaphylaxis, bird's nest was the third most common food allergen among adults with IgE-mediated food allergy in our centre, causing mild cutaneous reactions like urticaria and angioedema. IgE-mediated FA to peanut, tree nuts,

fruits and vegetables were not as prevalent as in studies from other adult western populations[30]. This may be due to differences in food preparation (thus affecting the allergenicity of food allergens like peanut) and regional dietary habits[31].

Food-dependent exercise-induced anaphylaxis (FDEIA) is an unusual entity where the pathogenesis remains unknown[32]. Foods that have been associated include shellfish, tree nuts, legumes, fruits, vegetables, grains and diary. Prevention of acute attacks includes avoiding putative foods up to 4 hours before exercise and modification of the individual's intensity and duration of exertion during exercise[33]. We had only one patient with FDEIA which could not be reproduced upon exercise following the ingestion of various suspected foods. The inability to reproduce symptoms of FEDIA using provocation tests followed by exercise has been well described in previous studies, with postulated reasons including failure to reach the same threshold of intensity or duration of exercise as during the initial acute episode.

Insect venom anaphylaxis occurred predominantly in personnel from the uniformed services. There were limitations in the use of specific immunotherapy (SIT), which is one of the definitive therapies for insect venom anaphylaxis[34], because honeybee and wasp stings, for which SIT vaccines are commercially available, together only accounted for 45% of insect sting anaphylactic reactions. Although ant bite anaphylaxis is becoming an increasingly common problem in the region[35], for which SIT may be effective[36], most of the vaccines (apart from fire ant) are currently not commercially available. SIT may be considered on a case-by-case basis, especially if there is an occupational risk, avoidance is difficult or health-related quality of life is considerably impaired[37]. Military servicemen with insect venom anaphylaxis, who may otherwise not be fit to continue military duties, may benefit from SIT. However, the benefits of SIT have to be balanced with the inconvenience posed to servicemen in active duty, which has been found to be a major reason for non-compliance in a previous study of SIT in military servicemen[38].

In conclusion, in our series of 67 patients, food (crustaceans and molluscs) was the most common cause of anaphylaxis, followed by insect stings. The inability to identify the causative insect in 50% of those with venom anaphylaxis limited the role of specific immunotherapy. Compared to other reported series, there were no cases of drug or latex anaphylaxis.

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