What clinical factors are associated with biphasic anaphylaxis in Thai adult patients?

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Summary

***Background*: Anaphylaxis is an emergency condition and may be fatal. Approximately 20% of patients with anaphylaxis may develop recurrent episodes of anaphylaxis within 72 hours or biphasic anaphylaxis. The severity of biphasic anaphylaxis can be either more or less severe than the first episode. Knowledge of factors associated with biphasic anaphylaxis in particular in Asian populations is still limited.**

***Objectives*: To study predictors for biphasic anaphylaxis in Thai patients at the Emergency Department (ED).**

***Methods*: All consecutive patients diagnosed as anaphylaxis at the ED, Ramathibodi Hospital, Mahidol University, Bangkok were enrolled. The study was prospectively conducted from January to December 2011. Patients were divided into two groups; uniphasic and biphasic anaphylaxis. Multivariate logistic regression was used to identify factors associated with biphasic anaphylaxis.**

***Results*: During the study period, there were 63 patients diagnosed with anaphylaxis at the ED. Of those, 16 patients were excluded due to incomplete clinical data in regards of diagnosis or treatment of anaphylaxis, concomitant medications or pre hospital treatment. In total, there were 47 patients remaining in the study, including 10 patients with biphasic anaphylaxis (21.28%). The clinical characteristics of the uniphasic and biphasic anaphylaxis groups were comparable. In multivariate logistic regression analyses, only respiratory rate and abdominal pain were significantly associated with biphasic anaphylaxis. The adjusted ORs (95% CI) of both factors were 0.653 (0.457, 0.932) and 15.429 (1.395, 170.690), respectively.**

Conclusion*: Reduced respiratory rate and the presence of abdominal pain were two significant factors associated with biphasic anaphylaxis. *(Asian Pac J Allergy Immunol 2015;33:8-13)

Keywords: *anaphylaxis, biphasic, uniphasic, predictors, clinical factors*

Introduction

Anaphylaxis is a rapid immunological reaction that can be fatal.[1-3] Hypersensitivity reaction from allergens to human body via IgE antibodies causes mediators from mast cells and basophils to be released.[4-8] Variable prevalence rates are associated with different causes of anaphylaxis.[9] The lifetime prevalence rate of anaphylaxis is approximately 0.5-2%.[9] The most common manifestations are dermatological, respiratory, cardiovascular, and gastrointestinal symptoms, respectively.[10,11]

Biphasic anaphylaxis was first described by Popa and Lerner in 1984.[10] It was defined as recurrent anaphylaxis after complete improvement. The incidence rate of biphasic anaphylaxis varies from 3-20% and may occur from 1-72 hours after the first anaphylactic reaction.[12-16] In Thailand, the rates of anaphylaxis increased from 9.16/100,000 population in 1999 to 55.45/100,000 population in 2004.[17] Biphasic anaphylaxis may be fatal if physicians are unaware and as a result, the patients may develop this condition at home and receive delayed treatment.

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Submitted date: 26/12/2013
Accepted date: 2/6/2014

Information about the clinical factors associated with biphasic anaphylaxis in Thai or Asian populations is limited. Delayed diagnosis or epinephrine treatment may be factors associated with biphasic anaphylaxis in two studies from Hong Kong and Thailand,[18, 19] while the presence of a low respiratory rate, high body temperature, or having dyspnea at presentation increased the risk of biphasic anaphylaxis in the study from Hong Kong. This study aimed to find predictors for biphasic anaphylaxis development and also to remind physicians at the Emergency Department (ED) of individual risk factors for biphasic anaphylaxis.

Methods

The study was conducted prospectively at the ED, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. All consecutive patients (age ≥ 15 years) diagnosed as having anaphylaxis from January to December 2011 were enrolled. We excluded patients with pre-treatment of anaphylaxis, incomplete clinical data in regards to diagnosis or treatment of anaphylaxis from medical records, or no data of biphasic anaphylaxis occurrence. Patients who were taking beta blockers, immunosuppressants, corticosteroids, or antihistamines were also excluded because all these medications may modify clinical manifestations and treatment responses.

The diagnosis of anaphylaxis was defined by the Society of Allergy and Immunology of Thailand.[2] There are 3 diagnostic criteria for anaphylaxis and the diagnosis of anaphylaxis requires any one of these three following criteria to be met;

1. Acute dermatological or mucosal manifestations (minutes or hours), such as acute urticaria, angioedema and one of the following symptoms:
   a. Respiratory symptoms: rhinorrhea, hoarseness, dyspnea, wheezing, stridor, decreased peak expiratory flow (PEF), or hypoxemia
   b. Hypotension or organ failure such as hypotonia, collapse, fainting
2. Two or more symptoms following allergen exposure; symptoms should occur in minutes or hours
   a. Dermatological symptoms: urticaria, angioedema
   b. Respiratory symptoms: rhinorrhea, hoarseness, dyspnea, wheezing, stridor, decreased peak expiratory flow (PEF), or hypoxemia
   c. Cardiovascular symptoms: hypotension, collapse, fainting
   d. Gastrointestinal symptoms: abdominal pain, nausea, vomiting
3. Hypotension after allergen exposure; occur in minutes or hours
   a. Adults: systolic blood pressure less than 90 mmHg or a decrease of more than 30% of baseline systolic blood pressure
   b. Children: a systolic blood pressure decrease of more than 30% of baseline systolic blood pressure

Clinical data for all patients were collected including baseline characteristics, anaphylaxis symptoms, allergen exposure, laboratory investigations, treatment and outcomes. Patients were categorized as uniphasic and biphasic anaphylaxis. Those patients without recurrent anaphylaxis within 72 hours were defined as uniphasic anaphylaxis. Patients diagnosed as anaphylaxis were treated by attending ED physicians. The investigators were not involved in any treatment and were notified by the ED physicians to enroll the patients. In addition, the investigators called all patients to identify biphasic anaphylaxis after 72 hours of presentation. The study protocol was approved by the committee on human rights related to research involving human subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University.

Statistical analyses

Baseline and clinical characteristics of the uniphasic and biphasic groups were compared using descriptive statistics. Wilcoxon rank-sum or unpaired student t-test and Fisher's exact tests or Chi-square test were applied to compare the differences in numbers and proportions between the two groups, respectively.

Univariate logistic regression analyses were applied to calculate the crude odds ratios of individual variables for the development of biphasic anaphylaxis. All clinically significant variables were included in the subsequent multivariate logistical regression analyses. Analytical results were presented as crude odds ratios (OR), adjusted OR, and 95% confidence intervals (CI). All data analyses were performed with STATA software version 12 (College station, Texas, USA).

Table 1. Initial clinical manifestations of patients with anaphylaxis at the emergency department.

Clinical manifestations	Numbers (percentage)
Skin manifestations	44 (93.62)
Angioedema	20 (42.55)
Itchy	18 (38.30)
Urticaria	15 (31.91)
Maculopapular rash	16 (34.04)
Flushing	12 (25.53)
Respiratory manifestations	38 (80.85)
Dyspnea	23 (48.94)
Hypoxemia	14 (29.79)
Wheezing	14 (29.79)
Stridor	1 (2.13)
Decreased peak expiratory flow rate	2 (4.26)
Gastrointestinal manifestations	20 (42.55)
Nausea/vomiting	16 (34.04)
Diarrhea	5 (10.64)
Abdominal pain	4 (8.51)
Cardiovascular manifestations	12 (25.53)
Hypotension	6 (12.77)
Syncope	4 (8.51)
Palpitation	2 (4.26)

Results

During the study period, there were 63 patients diagnosed with anaphylaxis at the ED. Of those, 16 patients were excluded due to incomplete clinical data (2 patients), no data with regard to biphasic anaphylaxis (4 patients), having received pre-hospital treatment (5 patients), being on beta blockers (3 patients), and on antihistamine (2 patients). None of the 12 excluded patients had biphasic anaphylaxis. In total, there were 47 patients for analysis and the incidence rate of anaphylaxis in adult patients was 652/100,000 patient/year based on numbers of patients at the ED for the year 2011.

The initial presentations of anaphylaxis in all 47 patients are summarized in table 1. Skin manifestations were the most common presentation (93.62%), followed by respiratory (80.85%), gastrointestinal (42.55%), and cardiovascular presentations (25.53%). Dyspnea and angioedema were the most two common manifestations.

There were 10 patients who had biphasic anaphylaxis (21.28%). Nine patients had only one system involved and the most common system involved was the skin (5 patients). Another patient had cardiovascular and gastrointestinal symptoms of

Table 2. Clinical features of anaphylaxis patients categorized by type of anaphylaxis.

Factors	Biphasic group N = 10	Uniphasic group N = 37	p value
Mean age, year	38 ± 11.57	44 ± 19.80	0.354
Male gender, N (%)	3 (30)	16 (43.2)	0.718
Co-morbid diseases			
Allergic rhinitis	1 (10)	8 (21.62)	0.660
Asthma	0 (0)	6 (16.22)	0.317
Previous history of anaphylaxis	1 (10)	3 (8.11)	1.000
Duration, hours			
Allergen exposure to symptoms	1.5 (0 – 48)	0.58 (0 – 24)	0.790
Symptoms to emergency room	2.27 (0.47 – 15)	1.50 (0 – 20.18)	0.172
Waiting time at emergency room	0.33 (0 – 2.08)	0.18 (0 – 2.83)	0.368
Observation time at emergency room	10 (1.33 – 23.33)	7.25 (1.17 – 35)	0.649
Total time at emergency room	10.28 (1.33 – 23.33)	7.25 (1.17 – 35.17)	0.640
Total time at admittions ward	4.58 (4.58 – 4.58)	66.65 (26.65 – 305.17)	0.180
Types of allergens			
Unknown	0 (0)	3 (8.11)	1.000
Medications*	4 (40)	15 (40.54)	1.000
Foods**	4 (40)	15 (40.54)	0.317
Insects	2 (20)	3 (8.11)	0.317
Blood	0	1 (2.7)	0.999

Note. *indicated amoxicillin (2 patients), ciprofloxacin (2 patients), ibuprofen (2 patients), and others; **indicated fish (2 patients), shrimp (2 patients), chicken (2 patients), peanut (2 patients), and others.

Table 3. Clinical signs and serum tryptase levels of anaphylaxis patients at initial presentation, categorized by type of anaphylaxis.

Factors	Biphasic group N = 10	Uniphasic group N = 37	p value
Vital signs and oxygenation			
Body temperature (°C)	36.7 ± 0.56	36.7 ± 0.69	0.835
Heart rate, times/minute	98 ± 18.85	94 ± 19.24	0.561
Systolic blood pressure (mmHg)	123 ± 21.49	129 ± 42.14	0.646
Diastolic blood pressure (mmHg)	72 ± 10.71	73 ± 20.50	0.840
Respiratory rate (times/minute)	22 ± 2.27	26 ± 6.23	0.047
Oxygen saturation, %	98 ± 1.67	95 ± 5.16	0.121
Respiratory symptoms			
Hypoxemia	1 (10)	13 (35.14)	0.242
Dyspnea	2 (20)	21 (56.76)	0.072
Wheezing	2 (20)	12 (32.43)	0.700
Stridor	1 (10)	0 (0)	0.213
Decreased peak expiratory flow	1 (10)	1 (2.7)	0.384
Cardiovascular symptoms			
Syncope	2 (20)	2 (5.41)	0.194
Palpitation	0 (0)	2 (5.41)	1.000
Hypotension	0 (0)	6 (16.22)	0.317
Gastrointestinal symptoms			
Abdominal pain	3 (30)	1 (2.7)	0.026
Nausea/Vomiting	5 (50)	11 (29.73)	0.274
Diarrhea	1 (10)	4 (10.81)	1.000
Dermatological symptoms			
Edema	3 (30)	17 (45.95)	0.481
Itching	5 (50)	13 (35.14)	0.473
Urticaria	6 (60)	9 (24.32)	0.054
Maculopapular rash	4 (40)	12 (32.43)	0.716
Flushing	0 (0)	12 (32.43)	0.046
Median serum tryptase level (mg/ml)*	13.75 (3.96-55.60)	6.34 (1.57-38.20)	0.205

Note. *indicated 24 patients (50%); 6 patients in biphasic group and 18 patients in uniphasic group.

biphasic anaphylaxis. None of these patients required hospitalization. The median duration of biphasic anaphylaxis was 21.75 hours (range 4.5 to 47 hours). The incidence rate of biphasic anaphylaxis was 124/100,000 patient/year.

The clinical characteristics of the uniphasic and biphasic anaphylaxis groups were predominantly comparable (Table 2-4), in terms of clinical presentations, laboratory investigations, and treatment. A few factors were significantly different between the two groups, including respiratory rate, abdominal pain, and flushing. Patients in the biphasic group had a lower respiratory rate (22 vs 26 times/minutes; p value 0.047), a higher proportion had abdominal pain (30 vs 2.7%; p value 0.026); and a lower proportion of patients had flushing (0 vs 32.43%; p value 0.047), than the uniphasic group (Table 3). In multivariate logistic regression analyses, only respiratory rate and the presence of abdominal pain were significantly associated with biphasic anaphylaxis. The adjusted ORs (95% CI) of both factors were 0.653 (0.457, 0.932) and 15.429 (1.395, 170.690), respectively (Table 4).

Discussion

The incidence of biphasic anaphylaxis varies between 3 and 20%, and can occur as long as 72 hours after the diagnosis of anaphylaxis.[12-16] The incidence vary between countries; 5.3% in Hong Kong[18] and 6.3% to 15.4% in Thailand.[19,20] In this present study, we consecutively enrolled patients throughout a one year period and found an incidence rate of 21.28%, which was higher than that found in two previous reports from Asia. This information

Table 4. Treatments of anaphylaxis patients categorized by type of anaphylaxis.

Factors	Biphasic group N = 10	Uniphasic group N = 37	p value
Adrenaline			
Received, N (%)	9 (90)	33 (89.19)	0.999
0.3 mg	2 (20)	9 (24.32)	0.760
0.5 mg	7 (70)	24 (64.86)	
Median time to receive adrenaline, hr	2.67 (0 – 15.75)	1.67 (0 – 27.07)	0.115
Dexamethasone			
Received, N (%)	9 (90)	37 (100)	0.213
Median time to receive dexamethasone, hr	2.17 (0.67 – 15.75)	1.87 (0.08 – 27.07)	0.312
Salbutamol treatment, N (%)	3 (30)	17 (45.95)	0.481
Berodual treatment, N (%)	1 (10)	3 (8.11)	0.999
H1 blocker treatment, N (%)	10 (100)	37 (100)	0.564
Home medications			
Prednisolone	9 (90)	22 (59.46)	0.131
Chlorpheniramine	4 (40)	16 (23.24)	1.000
Hydroxyzine	5 (50)	7 (18.92)	0.096
Ranitidine	1 (10)	9 (24.32)	0.664
Cetirizine	5 (50)	7 (18.92)	0.096

should be available to physicians to inform them that biphasic anaphylaxis may have higher incidence rate than previously reported. Difficulty in diagnosis of biphasic anaphylaxis may lower the incidence rate.[1] Patients with dyspnea or shock may not be able to describe their symptoms. Patients may present with only one single system involvement which will not meet with the diagnostic criteria. In addition, in first time patients it may be difficult to identify trigger factors to ensure the diagnosis. The earliest biphasic anaphylaxis episode in the present study was 4.5 hours and latest one was 47 hours. Physicians should be made more aware of early recurrent anaphylaxis.

Biphasic anaphylaxis can be more severe, particularly with unstable vital signs.[10,12,18] In the present study, all patients with biphasic anaphylaxis were not severe and none required hospitalization. The tryptase level was not significantly higher than in those patients with uniphasic anaphylaxis. Previous reports have showed that the tryptase level is a marker for food induced anaphylaxis and anaphylactic deaths.[21,22] Because of the small numbers of patients who had the tryptase level measured in this study, there was no statistical significant difference in the tryptase level between those who had uniphasic and biphasic anaphylaxis. Only 50% of patients had the tryptase values for the analysis. Similarly, the small number of patients with flushing may result in it not being an independent factor in multivariate logistic analysis.

Clinical factors associated with biphasic anaphylaxis are still debatable. Some studies failed to demonstrate predictors for this condition.[15,18,23] This present study found that reduced respiratory rate and the presence of abdominal pain were associated with biphasic anaphylaxis. Similarly, Smit et al reported that initial abnormal respiratory features were negative related with biphasic anaphylaxis.[18] Other factors that were previously reported to be associated with biphasic anaphylaxis are delayed treatment[9] or delayed use of adrenaline[19], while patients with dyspnea, treated with salbutamol, or high body temperature were reported to have less biphasic anaphylaxis.[18] Treatment with adrenaline and dexamthasone were also found to be more often delayed in the biphasic group than in the uniphasic group in this present study, but this difference was not statistically significant.

Even though the numbers of patients in this prospective data collection study was small, all consecutive patients were studied. In addition, the results also showed significant factors associated with biphasic anaphylaxis. The underlying mechanisms to explain why both factors are associated with biphasic anaphylaxis are still unclear and need further investigation. Some factors also

need to be studied more in the Thai population, such as serum tryptase levels and the presence of flushing.

In conclusion, reduced respiratory rate and the presence of abdominal pain are two significant factors associated with biphasic anaphylaxis.

Acknowledgments

This study was supported by TRF grants from the Senior Research Scholar Grant, Thailand Research Fund grant number RTA5580004, and the Higher Education Research Promotion and National Research University Project of Thailand, Office of the Higher Education Commission, Thailand, through the Health Cluster (SHeP-GMS), Khon Kaen University.

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