



Original Contribution

Factors associated with shock in anaphylaxis^{☆,☆☆}

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Abstract

Background: The aim of this study was to investigate the clinical characteristics of anaphylactic shock and the factors associated with anaphylactic shock in anaphylaxis.

Methods: Data were retrospectively collected from patients with anaphylaxis for 10 years. Study subjects were searched with broad disease codes including anaphyla-, adverse, angioedema, allergy, insect bite, bee, and hypersensitivity to prevent omission. All the 294 study subjects were divided into shock and nonshock groups.

Results: The mean age of the subjects was 43 years old, and males comprised 162 patients (55%). There were 119 patients (41%) in the shock group and 175 patients in the nonshock group. Age was older in the shock group than in the nonshock group; however, there was no difference in sex between 2 groups. Frequent causes of anaphylaxis were drugs in the shock group and food in the nonshock group. Nonsteroidal anti-inflammatory drugs and radiocontrast media were the most common cause of drug-induced anaphylaxis in the nonshock group and shock group, respectively. Cardiovascular symptoms were the most frequent symptoms in the shock group. Factors associated with the shock in cases with anaphylaxis were old age, emergency department (ED) arrival by emergency medical services use, radiocontrast material, symptoms with cyanosis, syncope, and dizziness.

Conclusion: Elderly anaphylactic patients with symptoms of cyanosis, syncope, and dizziness were at increased risk for the development of shock. Physicians in the ED have to be alert to the possibility of progression to shock in patients with anaphylaxis, and early recognition of anaphylactic shock is critical for adequate treatment.

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1. Introduction

Anaphylaxis is a serious allergic response for humans sensitized to a specific antigen by previous exposure. Many anaphylaxis cases are serious, and an immediate immunologic response can cause death [1].

The incidence of anaphylaxis might be more than previously reported, given the possibility of omission of

a precise diagnosis for anaphylaxis [2,3]. For many anaphylaxis patients, it is impossible to predict what has happened, and some die before adequate treatment commenced [3–11]. Thus, it is important to identify the progression to severe forms and development to shock to decide on the prognosis of anaphylaxis in the treatment for patients with anaphylaxis. Most of the previous studies investigated the characteristics of anaphylaxis based on classification of mild, moderate, and severe, with no study, to date, based on shock in anaphylaxis [1]. Therefore, we analyzed the characteristics of anaphylaxis in the absence and presence of shock and studied the factors associated with the occurrence of shock.

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2. Subjects and methods

Data were retrospectively collected based on chart review from January 2000 to December 2009 in patients admitted to the emergency department (ED) of 1 university hospital with a diagnosis of anaphylaxis. To search the patient database, broad diagnostic codes associated with anaphylaxis according to *International Statistical Classification of Diseases, 10th Revision*, were investigated. These codes were T78.0, T78.2, T78.2B, T78.2C, T80.5, and T88.6 of anaphylaxis; T78.1, T78.8, T78.9, and T88.7 of adverse; T78.3W1, T78.3W2, and T78.3W3 of angioedema; Z88 and Z88.0 to 88.9 of allergy; T00.9F, T14.0G, and T63.4A of insect bite; T14.1W1, X23, and X23.0 to 23.9 of bee; and T78.4B, T88.7D, and T88.7E of hypersensitivity.

Incomplete data on chart review or diagnosis was inconsistent with the criteria for anaphylaxis proposed by Sampson et al [1], although allergic reaction was excluded. Meeting 1 or more of the following criteria enabled a diagnosis of anaphylaxis: (1) acute skin reaction with respiratory or cardiovascular symptoms within minutes or hours; (2) associated symptoms with 2 or more involvement of skin, respiratory, cardiovascular, and gastrointestinal organs after exposure to allergen; and (3) reduced blood pressure after exposure to known allergen. Anaphylactic shock was judged to have occurred if systolic blood pressure was less than 90 mm Hg during patient treatment at the ED from admission to discharge [1].

General information including age, sex, elapsed time after exposure to allergen, route to ED by use of emergency medical services (EMS) or not, mental status, vital signs, history of allergy, comorbid chronic disorder, and smoking was collected. Causes of anaphylaxis were investigated in terms of involvement of drugs (nonsteroidal anti-inflammatory drugs [NSAIDs], antibiotics such as penicillin and cephalosporin; radiocontrast media, opioid analgesics, acetaminophen, etc), insects (bee, ant, etc), food (seafoods including Crustacea such as shrimp and crab; Pelecypoda of oyster, mussel, shell fish, etc; Cephalopoda of cuttlefish, octopus, etc; Osteichthyes of raw and cooked fish; wheat flour; buckwheat; apple; egg; pupa; etc), exercise induced, and idiopathic.

Exact causes of anaphylaxis were judged in cases involving patients who had an allergic history and who were exposed to the same allergen or common allergen known previously or who had been exposed to probable causative agents other than causes and who had been exposed to agents that might be strongly temporally associated with the development of anaphylaxis.

If it was difficult to know the exact causes because of exposure to multiple drugs and foods simultaneously, causes were not cleared [12]. Clinical features of anaphylaxis were classified into cutaneous, respiratory, cardiovascular, gastrointestinal, and neurologic symptoms. Cutaneous symptoms included urticaria, itching sense, rash, angioedema, and others; respiratory symptoms of dyspnea, hoarseness, cyanosis, laryngeal edema, cough, and wheezing; cardiovascular

symptoms of syncope, chest discomfort, palpitation, sweating, cardiac arrest, and others; gastrointestinal symptoms of nausea, vomiting, abdominal pain, and diarrhea; and neurologic symptoms of dizziness, headache, seizure, and others [11,13-15]. Patients were divided into 2 groups based on the development of shock at the ED: shock group and nonshock group. This study was approved by the institutional review board of our university hospital.

Frequency analyses were performed using SPSS for Windows 17.0 (SPSS, Chicago, IL), and χ^2 test, Fisher exact test, and the Student *t* test were used to compare the 2 groups. Potentially significant factors associated with shock in anaphylaxis of $P < .05$ from the univariate analysis were reanalyzed in the bivariate logistic regression with stepwise method. Model fitting test of logistic regression was carried out by Hosmer-Lemeshow test ($\chi^2 = 5.909$; $P = .657$). Statistical significance was defined as a *P* value less than .05.

3. Results

3.1. Clinical characteristics

Of the 294 study subjects, 162 were male (55%), and the average age was 43 years. The shock group was composed of

Table 1 Clinical characteristics of anaphylaxis

Characteristics	Nonshock (n = 175)	Shock (n = 119)	<i>P</i>
Age, y, mean $\pm$ SD	39.3 $\pm$ 16.3	48.5 $\pm$ 15.0	<.001
Male sex, n (%)	93 (53.1)	69 (58.0)	.413
Presentation via ambulance, n (%)	15 (8.6)	48 (40.3)	<.001
Decreased mentality at presentation, n (%)	2 (1.1)	19 (16.0)	<.001
Elapsed time from exposure to symptom onset, min	89.1 $\pm$ 207.7	44.1 $\pm$ 78.3	.010
Systolic blood pressure at presentation, mm Hg	120.9 $\pm$ 17.7	92.0 $\pm$ 32.0	<.001
Diastolic blood pressure at presentation, mm Hg	76.8 $\pm$ 11.3	57.5 $\pm$ 19.9	<.001
History of any allergy, n (%)	56 (32.0)	37 (31.1)	.870
Anaphylaxis	7 (4.0)	7 (5.9)	.457
Asthma	4 (2.3)	2 (1.7)	1.000
Drug	16 (9.1)	11 (9.2)	.977
Food	30 (17.1)	21 (17.6)	.911
History of chronic comorbid disease, n (%)	36 (20.6)	31 (26.1)	.272
Diabetes mellitus	6 (3.4)	7 (5.9)	.315
Hypertension	17 (9.7)	15 (12.6)	.435
Ischemic heart disease	6 (3.4)	6 (5.0)	.555
Chronic liver disease	5 (2.9)	3 (2.5)	1.000
Tumor	3 (1.7)	6 (5.0)	.165
Smoking, n (%)	51 (29.1)	47 (39.5)	.065

119 patients (40.5%), and the nonshock group was composed of 175 patients (59.5%). Age was older in the shock group than in the nonshock group. There was no difference in sex between the 2 groups. Emergency department presentation by ambulance was more prevalent in the shock group than the nonshock group. Elapsed time from exposure to causative allergen to symptom development was shorter in the shock group than in the nonshock group. Unclear mental status at the arrival to ED was more prevalent in the shock group. Overall allergic history was not different between the 2 groups, and food allergy was the most common allergy in both groups. History of chronic comorbid diseases had no difference, and smoking tended to be higher in the shock group (Table 1).

3.2. Causes of anaphylaxis

Common causes of anaphylaxis, in order of prevalence, were food, insect bite, and drugs in the nonshock group and drug, food, and insect bites in the shock group. Drugs were the most common cause in the shock group. Concerning drugs, NSAIDs and radiocontrast media were the most common cause in the nonshock group and shock group,

respectively. Antibiotic-induced anaphylaxis developed with the same frequency in the both groups. Bees were the most common cause of insect bites in both groups, with ant bites being detected in only 5 patients in the nonshock group.

Seafood was the most cause of food-induced anaphylaxis, especially in the nonshock group. Raw fish of the Osteichthyes induced anaphylaxis in many cases; however, there was no difference in both groups. Except unidentified food or seafood, wheat flour was most common in the nonshock group, and wheat flour and buckwheat were most common in the shock group. Exercise-induced anaphylaxis occurred in only patients in the shock group. Idiopathic anaphylaxis occurred in 10 patients in the nonshock group and in 3 in the shock group (Table 2).

3.3. Clinical symptoms or signs of anaphylaxis

Most frequent clinical symptoms of the anaphylaxis were cutaneous, followed by respiratory, gastrointestinal, cardiovascular, and neurologic in the nonshock group. However, the order was cardiovascular symptoms, followed by cutaneous, respiratory, neurologic, and gastrointestinal in the shock group. Overall, cutaneous and respiratory symptoms occurred with the same frequency in both groups;

Table 2 Causes of anaphylaxis

Cause, n (%)	Nonshock (n = 175)	Shock (n = 119)	P
Drugs	43 (24.6)	46 (38.7)	.010
NSAIDs	17 (9.7)	14 (11.8)	.574
Antibiotics	11 (6.4)	7 (5.9)	.887
Penicillin	5 (2.9)	2 (1.7)	.705
Cephalosporin	5 (2.9)	2 (1.7)	.705
Other antibiotics	1 (0.6)	3 (2.5)	.307
Radiocontrast media	9 (5.1)	21 (17.6)	.001
Opioid	2 (1.1)	1 (0.8)	1.000
Acetaminophen	3 (1.7)	2 (1.7)	1.000
Others	12 (6.9)	10 (8.4)	.621
Insect stings	54 (30.9)	27 (22.7)	.124
Bee	49 (28.0)	27 (22.7)	.307
Ant	5 (2.9)	0 (0.0)	.083
Foods	68 (38.9)	37 (31.1)	.173
Seafoods	38 (21.7)	14 (11.8)	.028
Crustacea	6 (3.4)	2 (1.7)	.480
Pelecypoda	11 (6.3)	2 (1.7)	.059
Cephalopoda	1 (0.6)	1 (0.8)	1.000
Osteichthyes			
Raw fish	12 (6.9)	8 (6.7)	.964
Cooked fish	8 (4.6)	1 (0.8)	.089
Wheat flour	7 (4.0)	2 (1.7)	.320
Buckwheat	0 (0.0)	2 (1.7)	.163
Apple	2 (1.1)	0 (0.0)	.516
Egg	2 (1.1)	0 (0.0)	.516
Pupa	2 (1.1)	0 (0.0)	.516
Others or unidentified	22 (12.6)	23 (19.3)	.114
Exercise-induced anaphylaxis	0 (0.0)	6 (5.0)	.004
Idiopathic	10 (5.7)	3 (2.5)	.191

Table 3 Clinical symptoms or signs of anaphylaxis

Symptom or sign, n (%)	Nonshock (n = 175)	Shock (n = 119)	P
Cutaneous	166 (94.9)	97 (81.5)	<.001
Urticaria	99 (56.6)	50 (42.0)	.014
Itching	69 (39.4)	61 (51.3)	.045
Flushing	41 (23.4)	32 (26.9)	.500
Angioedema	28 (16.0)	15 (12.6)	.419
Respiratory	100 (57.1)	68 (57.1)	1.000
Dyspnea	93 (53.1)	65 (54.6)	.803
Hoarseness	6 (3.4)	2 (1.7)	.480
Cyanosis	2 (1.1)	21 (17.6)	<.001
Laryngeal edema	5 (2.9)	1 (0.8)	.407
Cough	5 (2.9)	1 (0.8)	.407
Wheezing	5 (2.9)	5 (4.2)	.533
Cardiovascular	50 (28.6)	102 (85.7)	<.000
Syncope	3 (1.7)	45 (37.8)	<.001
Chest discomfort	40 (22.9)	16 (13.4)	.044
Palpitation	3 (1.7)	3 (2.5)	.689
Sweating	4 (2.3)	15 (12.6)	<.001
Cardiac arrest	0 (0.0)	1 (0.8)	.405
Gastrointestinal	56 (32.0)	34 (28.6)	.531
Nausea	22 (12.6)	21 (17.6)	.227
Vomiting	19 (10.9)	21 (17.6)	.096
Abdominal pain	25 (14.3)	10 (8.4)	.126
Diarrhea	19 (10.9)	4 (3.4)	.019
Neurologic	27 (15.4)	61 (51.3)	<.001
Dizziness	23 (13.1)	59 (49.6)	<.001
Headache	6 (3.4)	3 (2.5)	.743
Seizure	0 (0.0)	2 (1.7)	.163

Table 4 Factors associated with anaphylactic shock in anaphylaxis

	Odds ratio	95% confidence interval	<i>P</i>
Age	1.035	1.010-1.061	.007
Presentation via ambulance	8.106	3.349-19.621	<.001
Radiocontrast media	3.875	1.240-12.108	.020
Cyanosis	12.555	1.733-90.973	.012
Syncope	8.940	2.179-36.689	.002
Diarrhea	0.120	0.021-0.692	.018
Dizziness	9.486	4.354-20.670	<.001

however, itching sense and cyanosis were more frequent in the shock group. General cardiovascular symptoms, especially syncope and sweating, were more common in the shock group. Although general gastrointestinal symptoms were detected in the same frequency, diarrhea was more frequent in the nonshock group. Neurologic symptoms, particularly dizziness, were more frequent in the shock group (Table 3).

3.4. Factors associated with anaphylactic shock

Bivariate logistic regression analysis was performed to assess the factors associated with shock in anaphylaxis using the significant variables from the univariate analysis for clinical characteristics, causes, and clinical symptoms (Table 4). Factors associated with the shock development in the anaphylaxis were old age, EMS use, radiocontrast media induction, symptoms with cyanosis, syncope, and dizziness. Those who had symptom of diarrhea were at low risk.

4. Discussion

In the classification of the severity of anaphylaxis, 58.9% of patients display the severe form of anaphylaxis in Korea [16] compared with 12% to 40% in other countries [2,17,18]. Presently, the rate of severe anaphylaxis was 42.2% (124/294), and shock patients were 40.5% (119/224) of all the anaphylactic patients, based on the same classification in previous studies. It is reasonable that there are more patients classified with severe anaphylaxis than patients with shock because severe anaphylaxis was defined only from the criterion for severe anaphylaxis regardless of shock development. However, the reason that the frequency of severe anaphylaxis of all the anaphylaxis was lower than previous studies might reflect the method for searching of anaphylactic patients. Broad disease codes associated with anaphylaxis were searched to minimize the possibility for missing the diagnosis of anaphylaxis. There were

more patients with mild anaphylaxis than severe who were included as study subjects because of such a broad searching, the rate of severe of all the anaphylaxis was lower. For the precise analysis of the diagnosis and the prevalence of anaphylaxis, it is necessary to diagnose for anaphylaxis accurately and minimize the error or the omission of the diagnosis.

The causes of anaphylaxis, in order, were foods, drugs, and insects. This differs from the order of drugs, foods, and idiopathic reported in a previous Korean study and studies conducted elsewhere [16,17,19-22]. This result might be associated with the location of the study hospital and the dietary behavior of Koreans. The study hospital was located in southeast seaside in Korea; residents have a higher chance to eat seafood than the other areas. As for the characteristic diet life in Korea, many Korean people often eat some kind of Osteichthyes, especially sea fish; Cephalopoda; and Pelecypoda that are uncooked. Many cases of anaphylaxis occurred after exposure to raw seafoods. There was a lot of radiocontrast media-induced anaphylactic shock in the drug-related causes, like that in a previous Korean study [16].

Main causes of insect-induced anaphylaxis were red ant and bee in other countries [20,21,23-26] and bee in Korea [16] and in this study. Because western medicine and oriental medicine coexist in Korea, there were some cases of treatment with bee's stinger in oriental medicine and where a patient would prick the painful site with bee sting. Therefore, exposure for the purpose of treatment as well as exposure to bee sting in natural state made the bee the most common cause of insect-induced anaphylaxis in Korea.

Gastrointestinal symptoms associated with the hypotension were revealed in a previous study [17]. However, there were fewer gastrointestinal symptoms in the anaphylactic shock group in this study. This might be a limitation of a retrospective study; there might actually be less gastrointestinal symptoms, or it could be that gastrointestinal symptoms were omitted in the medical records. This study had another limitation, in that it was performed in a single institute, so the proportion of the shock in anaphylaxis might be different with previous studies. In addition, because all the study subjects were limited to the patients presented to the ED, most of the study subjects did not have further confirmative allergic testing.

5. Conclusion

The factors associated with shock development in anaphylaxis were old age and EMS use. In addition, in patients with radiocontrast media use and symptoms of cyanosis, syncope, and dizziness were at high risk for shock. Clinicians should be aware of the risk factors for shock in anaphylaxis and treat patients promptly.

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