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ORIGINAL ARTICLE

Clinical factors associated with prehospital exacerbation of anaphylaxis in children

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ABSTRACT

BACKGROUND: The severity of anaphylaxis often varies with time. Because prehospital intervention and initial treatment at hospital are affected by changing symptoms, the aim of this study was to determine the clinical factors associated with prehospital remission and exacerbation in the course of anaphylaxis in children.

METHODS: Data from medical records on anaphylactic children who were treated for 3 years at Kobe Children's Primary Emergency Medical Center were retrospectively analyzed. Severity of symptoms was evaluated using Sampson's grade (S-G). Patients with increased S-G at the hospital visit from disease onset (worsened group) were compared with those with decreased S-G at the visit (improved group). Uni- and multivariate analyses were performed to identify clinical differences between the groups, with $P < 0.05$ considered statistically significant.

RESULTS: Among 115 anaphylactic children who showed S-G changes from onset to hospital visit, 43 were assigned to the worsened group and 72 to the improved group. Univariate analysis showed no significant differences in age, sex, history of asthma, prehospital treatment, type of antigen, or period from symptom onset to hospital visit between the groups. However, the time from antigen exposure to symptom onset was significantly longer, and S-G at onset was significantly lower in the worsened group than in the improved group. Multivariate analysis identified time from antigen exposure to symptom onset (odds ratio: 3.89, $P < 0.01$) and S-G at onset (odds ratio: 0.06, $P < 0.001$) as independent predictors of exacerbation.

CONCLUSIONS: Anaphylactic children with slower and milder symptoms at onset are more likely to show deterioration.

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Key words: Anaphylaxis - Child - Disease progression - Remission induction.

Anaphylaxis is the most serious type of systemic allergic reaction. Symptoms are highly variable and include skin, gastrointestinal, respiratory, and cardiovascular symptoms. Most cases of anaphylaxis involve type I allergic reactions that rapidly progress and require prompt treatment.¹ Anaphylaxis usually occurs outside of medical institutions. When providing initial treatment at hospital, the time

course, prehospital treatments, and the time from antigen exposure to hospital visit, in addition to the severity at the time of visit need to be considered. Some studies have suggested that providing the same treatment to patients with the same severity can easily lead to over- or under-treatment.²

Many studies have researched risk and promoting factors that aggravate anaphylaxis.²⁻⁹

The time of onset of anaphylaxis according to exposure to the allergen has also been clarified from previous studies.^{10, 11} Because patients with anaphylaxis by unknown antigens often visit pediatric emergency medical centers, studies focusing on the course after any antigen exposure and prehospital changes in symptoms are required to provide accurate treatments. Thus, the aim of this study was to investigate factors for predicting aggravation of anaphylaxis by analyzing anaphylactic children with exacerbation of symptoms or remission from onset of symptoms to the time of visiting a children's primary emergency medical center.

Materials and methods

Kobe Children's Primary Emergency Medical Center (KCPEMC), Kobe, Japan, provides medical services for pediatric patients during holidays and outside of working hours, most of whom come directly (walk-in). We retrospectively analyzed the medical records of children who were treated for anaphylaxis in KCPEMC from April 1st, 2011 to March 31st, 2014. Written informed consent for their chart review was obtained from patients and their parents. The study protocols were approved by the ethics committee at KCPEMC (approval no. 57-6).

Study methods

A chart review was conducted of 92,020 patients who presented to KCPEMC during the study period. Two hundred nine anaphylactic

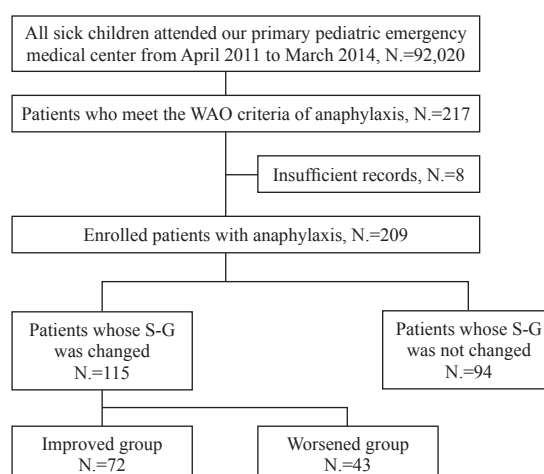


Figure 1.—Flow chart of enrolled patients. S-G: Sampson's grade; WAO: World Allergy Organization.

patients were enrolled with exclusion of an incomplete record of exposure to antigens, onset of symptoms, and the time course (N=8, Figure 1). Accordingly, patients with increased Sampson's grade (S-G) at the visit to KCPEMC from disease onset were assigned to the "worsened group," and those with decreased S-G at the visit were assigned to the "improved group." Clinical factors between the groups were compared by univariate analyses. Predictive contributors for exacerbation of anaphylaxis were determined by multivariate analyses.

Diagnostic criteria

The diagnostic criteria for anaphylaxis in the World Allergy Organization guidelines were

TABLE I.—Comparison of clinical factors between the worsened and improved groups.

Clinical factors	Worsened group (N.=43)	Improved group (N.=72)	P value
Age, years	3.7 (0.6-13.6)	4.1 (0.5-14.8)	0.80
Sex, M/F	26/19	40/32	0.61
History of asthma	7 (16%)	13 (18%)	0.81
Food antigen	38 (88%)	68 (94%)	0.24
Accordance of previous allergen	15 (35%)	29 (40%)	0.39
Time from antigen exposure to onset, h	0.25 (0-4.5)	0 (0-2)	0.015
S-G at onset	2 (1-3)	4 (2-4)	<0.001
Time from onset to visit, h	2 (0.5-7)	1.5 (0.1-6.5)	0.54
Prehospital treatment	10 (23%)	19 (26%)	0.71
S-G at visit	4 (2-5)	1 (0-3)	<0.001
Sign of infection	2 (5%)	4 (6%)	0.83

Data are expressed as median (range) or as number (percentage). S-G: Sampson's grade.

taken, which was produced by National Institute of Allergy and Infectious Diseases,^{2, 12} as indicated in Supplementary Table I (online content only).

Evaluation of symptom severity

Severity of symptoms was evaluated using S-G (Supplementary Table II, online content only).¹³

Statistical analysis

Data are expressed as the median and range, or as number and percentage. Statistical analysis was performed using JMP v. 10.0 software (SAS Institute, Cary, NC, USA). In univariate analyses, Fisher's exact test was used for categorical variables and the Mann-Whitney U-test was used for non-parametric continuous variables. Nine clinical candidates for exacerbation were then included in further analyses using a multivariate logistic regression model. In all analyses, $P < 0.05$ was regarded as significant.

Results

Of 209 anaphylactic patients with a complete medical record, changes in S-G were observed in 115 children. Of these patients, 43 (21%) were assigned to the worsened group and 72 (35%) to the improved group (Figure 1). The exacerbation of anaphylaxis was seen in 37 patients with respiratory symptoms (86%) and 6 patients with gastrointestinal symptoms (14%).

TABLE II.—*Predictive factors for exacerbation.*

Predictive factors	Odd ratio	95% CI	P value
Age	0.997	0.778-1.27	0.98
Sex	1.36	0.334-5.63	0.66
History of asthma	0.337	0.043-2.25	0.27
Food antigen	0.239	0.024-2.16	0.20
Time from antigen exposure to onset	3.89	1.38-17.1	<0.01
S-G at onset	0.064	0.019-0.16	<0.001
Time from onset to visit	0.849	0.463-1.52	0.58
Prehospital treatment	0.311	0.065-1.32	0.11
Sign of infection	0.231	0.016-3.69	0.28
S-G: Sampson's grade.			

Patients' characteristics

The median age of the 115 patients was 3.8 years (0.5-14.8 years). Male children accounted for 57% of the total. Twenty (17%) patients had a history of asthma and the antigen was food in 106 (92%) patients. Twenty-nine (25%) patients had received treatment before their visit. These treatments comprised antihistamines in nine patients, steroids in eight patients, a mix of antihistamines and steroids in nine patients, beta-agonists in two patients, inhaled beta-agonists in four patients, chromoglicic acid in one patient, and other over-the-counter drugs in one patient (with multiple agents in some patients). No patients were administered epinephrine.

The median time from antigen exposure to symptom onset was 0 hours (0-4.5 hours) and the median time from symptom onset to hospital visit was 1.75 hours (0.1-7 hours). The median S-G was 3 (1-4) at onset and 2 (0-5) at the time of hospital visit. Symptoms of infection were observed in six (5%) patients.

Comparison of clinical factors between the worsened and improved groups

Table I shows the results of univariate analysis. No significant differences in age, sex, history of asthma, antigen type, or consistency with allergen history were observed between the two groups. Similarly, no differences were evident in prehospital treatment, time from symptom onset to hospital visit, and symptoms of infection between the two groups. However, the time from antigen ingestion to symptom onset was significantly longer ($P = 0.015$), S-G at onset was significantly lower ($P < 0.001$), and S-G at the visit to KCP EMC was significantly higher ($P < 0.001$) in the worsened group compared with the improved group.

Predictive factors for exacerbation

Multivariate analysis showed that the time from antigen ingestion to symptom onset (odds ratio: 3.89, $P < 0.01$) and S-G at onset (odds ratio: 0.06, $P < 0.001$) were independent predictive factors for exacerbation (Table II).

Discussion

We retrospectively determined clinical factors associated with prehospital exacerbation patients by comparison with those with remission patients of anaphylaxis over a 3-year period. A longer time from antigen exposure to symptom onset and lower S-G at symptom onset were associated with aggravated subsequent symptoms, especially respiratory symptoms. The time from antigen exposure to symptom onset and S-G at onset were independent predictors of exacerbation of anaphylaxis.

The time from symptom onset to visiting the hospital has been previously reported as approximately 2 hours,¹⁴ with similar results obtained in this cohort (1.75 hours). S-G was found to change in more than half of the patients during the study period. While remission was common, occurring in approximately 35% of cases, exacerbation of anaphylaxis occurred in approximately 20%.

Cases without changes of S-G were excluded from the present study in favor of cases of anaphylaxis in which symptoms changed between symptom onset and the time of visiting hospital. The comparison of clinical factors between the patients with exacerbation and remission of anaphylaxis might produce clearer results in our study. Age,^{3, 4} sex,⁵ history of asthma and allergies,⁶⁻⁸ and stress from infection⁹ have previously been reported as risk factors for the aggravation of anaphylaxis. However, these factors were not exacerbating factors in our study. Other known exacerbating factors include drugs (beta-blockers, angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs, antidepressants, and sedatives), alcohol intake, exercise, and menstruation, all of which are described in the World Allergy Organization guidelines.² However, these factors are mainly associated with adults with anaphylaxis.

The present study showed that a longer time from antigen exposure to symptom onset and lower S-G at symptom onset were more likely to be associated with subsequent exacerbation of symptoms. In terms of pathophysiology of anaphylaxis, mechanisms that support these

clinical findings may be as follows. The antigenic foods often result in immunoglobulin (Ig)E-dependent anaphylaxis,¹ and the present findings strongly suggest that symptom onset was IgE-dependent. When antigenic stimulation is once again applied, mast cell and basophilic signal transduction occurs via IgE, which triggers degranulation and release of chemical mediators, including histamine. The larger the amount of chemical mediators released by this mechanism, the more serious the reaction. Large amounts of chemical mediators that are released within a short time are gradually consumed and depleted, and symptoms recede by the time of visiting the hospital. Conversely, when a slow, progressive reaction occurs, the continued release of chemical mediators or some type of vicious cycle enhances and aggravates symptoms. Primary physicians should keep in mind that such cases mainly with respiratory symptoms may later become aggravated.

Conclusions

This retrospective study is the first to show that subsequent symptoms of anaphylaxis are prone to exacerbation with a longer time from antigen exposure to symptom onset and milder symptoms at onset.

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For supplementary materials, please see the online version of this article at www.minervamedica.it.

SUPPLEMENTARY MATERIALS

SUPPLEMENTARY TABLE I.—Criteria for diagnosis of anaphylaxis (World Allergy Organization).²

Anaphylaxis is highly likely when any one of the following criteria is fulfilled:					
1) Acute onset of illness (minutes to several hours) with involvement of skin, mucosal tissue, or both (e.g., generalized urticaria, itching or flushing, swollen lips-tongue-uvula), and at least one of the following:					
a) respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia;					
b) reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonic collapse, syncope, incontinence);					
2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):					
a) involvement of the skin-mucosal tissue (e.g., generalized urticaria, itch-flush, swollen lips-tongue-uvula);					
b) respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia);					
c) reduced blood pressure or associated symptoms (e.g., hypotonic collapse, syncope, incontinence);					
d) persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting);					
3) reduced blood pressure after exposure to known allergen for that patient (minutes to several hours): infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure					
PEF: peak expiratory flow.					

SUPPLEMENTARY TABLE II.—Sampson's grading according to severity of clinical symptoms.¹³

Grade	Skin	Gastrointestinal tract	Respiratory tract	Cardiovascular system	Neurological system
1	Localized pruritus, flushing, urticaria, angioedema	Oral pruritus, oral "tingling," mild lip swelling			
2	Generalized pruritus, flushing, urticaria, angioedema	Any of the above, nausea and/or emesis x's 1	Nasal congestion and/or sneezing		Change in activity level
3	Any of the above	Any of the above, plus repetitive vomiting	Rhinorrhea, marked congestion, sensation of throat pruritus or tightness	Tachycardia (increase >15 bpm)	Change in activity level plus anxiety
4	Any of the above	Any of the above, plus repetitive diarrhea	Any of above, hoarseness, "barky" cough, difficulty swallowing, dyspnea, wheezing, cyanosis	Any of above, dysrhythmia and/or mild hypotension	"Light-headedness," feeling of "pending doom"
5	Any of the above	Any of the above, loss of bowel control	Any of above, respiratory arrest	Severe bradycardia and/or hypotension or cardiac arrest	Loss of consciousness