

Missed Diagnosis of Anaphylaxis in Patients With Pediatric Urticaria in Emergency Department

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Objectives: This study was to determine the characteristics of missed diagnosis of pediatric anaphylaxis that were registered as urticaria only at the emergency department (ED) by comparing those who had only urticaria symptoms with those who had both anaphylaxis and urticaria symptoms.

Methods: Subjects were classified into missed anaphylaxis and urticaria group according to whether satisfied anaphylaxis diagnostic criteria or not. Anaphylaxis group, those who were initially registered as anaphylaxis with urticaria and anaphylaxis symptoms simultaneously, were further investigated.

Results: The missed anaphylaxis group included 37 patients of 1051 pediatric urticaria patients. The anaphylaxis group included 11 patients. The time from symptom onset to ED arrival in the missed anaphylaxis group was shorter than the urticaria group. More patients in the missed anaphylaxis group had a history of past food allergy. Seafood, egg, and milk were more common causes of allergy in the missed anaphylaxis group; however, idiopathic causes were more common in the urticaria group. Symptom was more severe in the missed anaphylaxis group than the urticaria group. More treatments except antihistamine were performed at ED in the missed anaphylaxis group. Cardiovascular symptoms were more common in the anaphylaxis group than the missed anaphylaxis group.

Conclusions: Of all pediatric urticaria patients, 3.5% of patients were not registered as anaphylaxis although they had anaphylaxis symptoms. Missed diagnosis of anaphylaxis in pediatric urticaria patients at ED was associated with a history of past food allergy, milk, egg, and seafood as causes of allergy, treated with fluid administration, steroid, and epinephrine.

Key Words: anaphylaxis, urticaria, diagnosis

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Urticaria is one of the most frequent symptoms in the pediatric emergency department (ED). It is also a common allergic symptom along with rhinorrhea and asthma. The number of patients who visit ED for symptoms of acute allergic reaction is gradually increasing every year.¹ The prevalence of anaphylaxis, the most severe form of acute allergic reaction, is also increasing. Anaphylaxis also has various forms of symptoms, with a cutaneous symptom being the most frequent one.² Many studies have been performed on the increasing prevalence of anaphylaxis. However, precise diagnosis of anaphylaxis is essential to obtain an accurate result of its prevalence.³

Clarifying the cause of anaphylaxis since the first attack is very important because of its high prevalence in young children.⁴ In addition, most patients have a history of anaphylaxis.⁵ Because the frequency of ED visit due to pediatric anaphylaxis is increasing,⁶ prompt and precise diagnosis and treatment in ED are crucial. Although definite diagnostic criteria of anaphylaxis are

disseminated,⁷ they are subjective and symptom dependent. A single-objective diagnostic modality for anaphylaxis is still lacking.⁸ Even if symptoms meet the diagnostic criteria, there is a possibility that a patient is registered simply according to their symptoms, not as anaphylaxis, especially when there is cutaneous symptom. This can eventually lead to diagnosis of simple urticaria or angiodema.⁹ Because patients involved in previous studies concerning prevalence of anaphylaxis are those who are only registered as anaphylaxis, accurate diagnosis and registration are essential to obtain accurate prevalence data.

Although most patients who come to ED with symptoms of urticarial have simple urticaria, some urticaria patients with partial symptoms of anaphylaxis should have been diagnosed as anaphylaxis. However, studies on characteristics of those falsely diagnosed and registered patients are limited. Therefore, the objective of this study is to determine the characteristics of missed diagnosis of anaphylaxis in pediatric patients who were registered as urticaria only at ED by comparing those who had only urticaria symptoms with those who had both anaphylaxis and urticarial symptoms. Furthermore, missed diagnosis and correct diagnosis of anaphylaxis in pediatric urticaria patients were compared.

METHODS

This retrospective study enrolled urticaria patients among a total of 28,792 pediatric patients who visited ED of a single university hospital located in the southeast coast of South Korea from January 2014 to December 2015. This study was reviewed by our institutional review board.

According to *International Statistical Classification of Disease and Related Health Problems-10*, the following disease classification codes were used to search urticaria patients: L28.2 (other prurigo, urticarial papulosa), L50.0 (allergic urticaria), L50.1 (idiopathic urticaria), L50.2 (urticaria due to cold and heat), L50.3 (dermatographic urticaria), L50.4 (vibratory urticaria), L50.5 (cholinergic urticaria), L50.6 (contact urticaria), L50.8 (other urticaria), and L50.9 (urticaria, unspecified). Medical records review was conducted for those who were registered with these disease classification codes. Those who failed to satisfy the anaphylaxis diagnostic criteria were assigned to the urticaria group. Those who satisfied the anaphylaxis diagnostic criteria were assigned to the missed anaphylaxis group. We also reviewed patients registered as anaphylaxis. Those who had urticaria symptoms at the same time were classified into the anaphylaxis group. As a result, all patients who were initially registered as anaphylaxis with urticaria symptom were included in the anaphylaxis group (Fig. 1). Anaphylaxis diagnosis criteria written in world allergy organization guidelines for assessment and management of anaphylaxis published in 2011 were used in this study.¹⁰

General characteristics (age, sex, transport to ED, fever, recent infection, history of allergy, and comorbidity), cause of urticaria, clinical characteristic, and treatment were collected. Fever was defined as body temperature of 38°C or greater. Recent infection was defined as sustaining fever longer than 1 day in recent 10 days. If the cause of urticaria was drug, it was subdivided into

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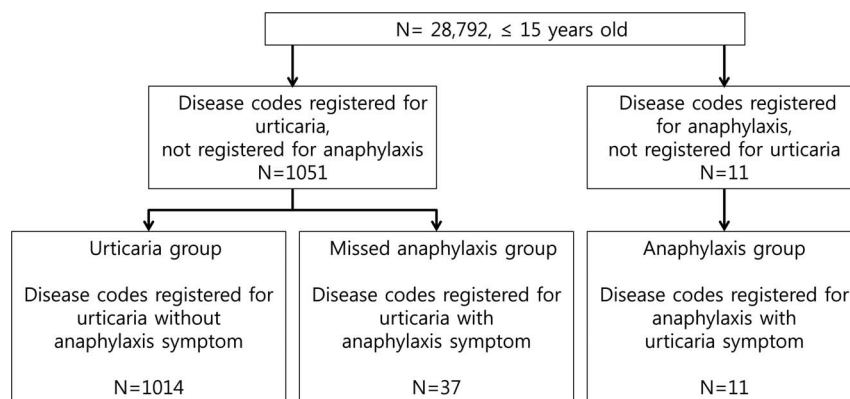


FIGURE 1. Study subjects belonging to different groups.

nonsteroidal anti-inflammatory drug, penicillin, cephalosporin, and vaccination. In case of insect, it was subdivided into bee, ant, etc. Food was subdivided into seafood, flour, buckwheat, pupa, nut, egg, beef, and milk/dairy product. For additional causes, exercise-induced, food-dependent exercise-induced, and idiopathic were considered. Clinical characteristics included symptom type, systemic symptom, symptom severity, blood pressure at the time of ED visit, shock, and mental status. Symptom type was defined as uniphasic (if the symptom happened briefly once), biphasic (if the symptom went away and came back shortly), and protracted (if the symptom persisted for more than 1 day). Systemic symptom was subdivided into cutaneous, respiratory, cardiovascular, gastrointestinal, and neurologic. Severity of allergic reaction was subdivided into the following 3 categories: mild (1 systemic symptom), moderate (2 or more systemic symptoms), and severe (shock, mental change, cardiac arrest, or apnea).¹¹

Shock was defined as systolic blood pressure (SBP) of less than 60 if the patient was between ages of 0 and 28 days, SBP of less than 70 if the patient was between the ages of 1 month and 12 months, SBP of less than 70+ (age × 2) if the patient was between the ages of 1 year and 10 years, and SBP of less than 90 if the patient was older than 10 years.⁷ Treatment in ED included oxygen (O₂) supply, fluid administration, antihistamine use, steroid use, epinephrine use, bronchodilator use, and diagnostic tests.

For comparison between the urticaria group and the missed anaphylaxis group, univariate analysis was conducted using χ^2 test, Fisher exact test, Mann Whitney *U* test, and Student *t* test. To identify factors affecting missed anaphylaxis, univariate logistic regression analysis was performed. Using factors with a *P* value of less than 0.05 from univariate analysis, multivariate logistic regression analysis was then performed using forward method. For characteristic comparison between the missed

TABLE 1. General Characteristics of Patients With Urticaria or Missed Anaphylaxis

	Urticaria (n = 1014)	Missed Anaphylaxis (n = 37)	<i>P</i>
Average age, y	3.9 ± 3.7*	4.1 ± 5.3*	0.772
Sex, male, %	562 (55.4)	18 (48.6)	0.501
Transportation to ED, %			0.000
Public ambulance	2 (0.2)	2 (5.4)	
Individual transportation	1009 (99.5)	33 (89.2)	
Other medical facility	3 (0.3)	2 (5.4)	
Elapsed time from, min			
Exposure to symptom onset	5 (0–90)†	10 (0–30)†	0.597
Symptom onset to ED arrival	240 (62.25–741)†	113 (38.5–360)†	0.014
History of allergy, %	205 (20.2)	16 (43.2)	0.001
Anaphylaxis	1 (0.1)	0 (0.0)	1.000
Asthma	12 (1.2)	1 (2.7)	0.374
Allergic rhinitis	32 (3.2)	1 (2.7)	1.000
Atopic dermatitis	71 (7.0)	2 (5.4)	1.000
Drug allergy	7 (0.7)	1 (2.7)	0.250
Food allergy	87 (8.6)	10 (27.0)	0.001
Comorbidity, %	25 (2.5)	2 (5.4)	0.245
Fever, %	78 (7.7)	5 (13.5)	0.206
Infection, %	159 (15.7)	6 (16.2)	0.930

*Mean ± standard deviation.

†Median (interquartile range).

anaphylaxis group and the anaphylaxis group, univariate analysis was performed using χ^2 test, Fisher exact test, and Mann Whitney *U* test with factors of general character, clinical character, and ED treatment. All data analyses were conducted using SPSS 21 (IBM Inc, Armonk, NY). Statistical significance was considered at a *P* value of less than 0.05.

RESULTS

Of 1051 pediatric urticaria patients, 1014 (96.5%) belonged to the urticaria group whereas 37 (3.5%) were assigned to the missed anaphylaxis group. However, only 11 patients were originally registered to have anaphylaxis (Fig. 1). There was no difference in age or sex between the urticaria group and the missed anaphylaxis group. Although most patients came to the ED using their own transportation, more patients in the missed anaphylaxis group used public ambulances or were transferred from other medical facilities. There was no significant difference in the time from exposure to allergen to symptom onset between the 2 groups. However, the time from symptom onset to ED arrival in the missed anaphylaxis group was shorter than that in the urticaria group. Regarding allergic history, more patients in the missed anaphylaxis group had a history of past food allergy (Table 1).

Seafood, egg, and milk were more common causes of allergy in the missed anaphylaxis group. However, idiopathic causes were more common in the urticaria group (48.2% vs 8.1%) (Table 2).

Respiratory and gastrointestinal symptoms were common in the missed anaphylaxis group. Dominant symptom pattern was uniphasic in both groups. There was no significant difference in blood pressures between the 2 groups. However, symptom severity in the missed anaphylaxis group was all moderate, whereas mild severity was dominant in the urticaria group. Oxygen, fluid, steroid, epinephrine, and bronchodilator were used more at ED in the missed anaphylaxis group. On the other hand, antihistamine was used more in the urticarial group. Diagnostic tests such as complete blood count, eosinophil count, and total IgE were performed more often in the missed anaphylaxis group (Table 3).

TABLE 2. Causes of Urticaria and Missed Anaphylaxis

	Urticaria (n = 1014)	Missed Anaphylaxis (n = 37)	<i>P</i>
Drug, %	46 (4.5)	3 (8.1)	0.246
NSAIDs	7 (0.7)	1 (2.7)	0.250
Penicillin	8 (0.8)	0 (0.0)	1.000
Cephalosporin	6 (0.6)	0 (0.0)	1.000
Vaccine	6 (0.6)	1 (2.7)	0.222
Insect sting, %	6 (0.6)	0 (0.0)	1.000
Food, %	237 (23.4)	31 (83.8)	0.000
Seafood	44 (4.3)	5 (13.5)	0.025
Wheat	24 (2.4)	1 (2.7)	0.596
Buckwheat	1 (0.1)	1 (2.7)	0.069
Pupa	1 (0.1)	0 (0.0)	1.000
Nut	11 (1.1)	1 (2.7)	0.351
Egg	36 (3.6)	4 (10.8)	0.048
Pork	21 (2.1)	0 (0.0)	1.000
Cow milk	58 (5.7)	14 (37.8)	0.000
Idiopathic, %	489 (48.2)	3 (8.1)	

NSAID indicates nonsteroidal anti-inflammatory drug.

TABLE 3. Clinical Characteristics of Patients With Urticaria or Missed Anaphylaxis

	Urticaria (n = 1014)	Missed Anaphylaxis (n = 37)	<i>P</i>
Symptoms, %			
Cutaneous	1014 (100)	37 (100)	NA
Respiratory	13 (1.3)	16 (43.2)	0.000
Cardiovascular	1 (0.1)	0 (0.0)	1.000
Gastrointestinal	24 (2.4)	24 (64.9)	0.000
Neurologic	0 (0.0)	0 (0.0)	NA
Symptoms pattern			0.176
Uniphasic	911 (89.8)	31 (83.8)	
Biphasic	72 (7.1)	3 (8.1)	
Prolonged	31 (3.1)	3 (8.1)	
Blood pressure, mm Hg			
SBP	101 ± 9*	98 ± 19*	0.342
Diastolic blood pressure	64 ± 9*	61 ± 14*	0.145
Heart rate, beat/min	121 ± 27*	131 ± 33*	0.028
Non-alert consciousness, %	1 (0.1)	0 (0.0)	1.000
Shock	0 (0.0)	0 (0.0)	NA
Severity grade			0.000
Mild	1001 (98.7)	0 (0.0)	
Moderate	13 (1.3)	37 (100)	
Severe	0 (0.0)	0 (0.0)	
ED treatment, %			
O ₂ supply	0 (0.0)	1 (2.7)	0.035
Fluid administration	37 (3.6)	6 (16.2)	0.003
Antihistamine use	997 (98.3)	34 (91.9)	0.030
Steroid use	140 (13.8)	13 (35.1)	0.000
Epinephrine use	12 (1.2)	4 (10.8)	0.002
Bronchodilator use	6 (0.6)	5 (13.5)	0.000
Diagnostic tests, %	54 (5.3)	7 (18.9)	0.004

*Mean ± standard deviation.

NA indicates not available.

Univariate logistic regression analysis was performed to identify factors affecting missed diagnosis of anaphylaxis in pediatric urticaria patients at ED. Significant factors included past food allergy history, seafood, egg and milk as cause of allergy, heart rate per minute, respiratory symptom, gastrointestinal symptom, O₂ supply, fluid administration, antihistamine use, steroid use, epinephrine use, bronchodilator use, and diagnostic tests. After excluding factors that might distort results because of too wide confidence interval such as respiratory symptom, gastrointestinal symptom, and bronchodilator use, multivariate logistic regression analysis was performed using the rest of significant factors from univariate logistic regression analysis. Factors associated with missed diagnosis of anaphylaxis in pediatric urticaria patients were the following: past allergy history, seafood, egg and milk as the cause of allergy, treatment with fluid administration, steroid, and epinephrine. The odds ratio in case of antihistamine use was 0.198 (Table 4).

There was no difference in age or sex between the anaphylaxis group and the missed anaphylaxis group. However, an atopic history was higher in the anaphylaxis group. Cardiovascular symptom was more common in the anaphylaxis group, whereas gastrointestinal symptom was more common in the missed

TABLE 4. Risk Factors Associated With Missed Anaphylaxis

	Odds Ratio	95% Confidence Interval	P
Univariate logistic regression			
History of food allergy	3.946	1.849–8.422	0.000
Seafood, as allergen	3.445	1.280–9.268	0.014
Egg, as allergen	3.293	1.107–9.791	0.032
Cow milk, as allergen	10.033	4.907–20.516	0.000
Heart rate, beat/min	1.013	1.001–1.025	0.029
Respiratory symptoms	58.667	25.077–137.247	0.000
Gastrointestinal symptoms	76.154	34.663–167.308	0.000
Fluid administration	5.111	2.009–13.002	0.001
Antihistamine use	0.193	0.054–0.691	0.011
Steroid use	3.382	1.682–6.797	0.001
Epinephrine use	10.121	3.099–33.054	0.000
Bronchodilator use	26.250	7.612–90.519	0.000
Diagnostic tests	4.148	1.743–9.873	0.001
Multivariate logistic regression			
History of food allergy	3.375	1.420–8.023	0.006
Seafood, as allergen	3.931	1.249–12.371	0.019
Egg, as allergen	4.387	1.305–14.746	0.017
Cow milk, as allergen	10.782	4.871–23.869	0.000
Fluid administration	3.354	1.102–10.206	0.033
Antihistamine use	0.198	0.047–0.824	0.026
Steroid use	2.672	1.224–5.832	0.014
Epinephrine use	4.089	1.004–16.657	0.049

anaphylaxis group. Regarding treatment at ED, fluid administration, epinephrine use, bronchodilator use, and diagnostic tests were used more often in the anaphylaxis group (Table 5).

DISCUSSION

Results of this study showed that 3.5% of pediatric urticaria patients at the ED met the anaphylaxis diagnostic criteria. According to a previous study, approximately 4% of all ED visiting patients are anaphylaxis patients.⁶ Another study on clinical characters of anaphylaxis patients has reported that there are a substantial number of anaphylaxis patients among those who are diagnosed as urticaria or angioedema.¹² If someone only analyzes patients who are registered as anaphylaxis, there must be unseen and missed anaphylaxis patients.¹³ Therefore, physicians at ED must clearly understand the diagnostic criteria and precisely register disease classification codes. In addition, proper physical examination is crucial along with careful history taking for patients with risk factors.

Food, hymenoptera stings (venom), and drugs are common causes of anaphylaxis in one study.⁹ Another study has shown that milk, egg, and nut are common causes of anaphylaxis.¹⁴ Despite some differences in details, food was also the most common cause of anaphylaxis in the present study. Cow milk (37.8%), seafood (13.5%), and egg (10.8%) were common causes of anaphylaxis in this study. This result was similar to that of a previous study showing that common causes of anaphylaxis are milk (28.4%), egg white (13.6%), nuts (13.2%), and seafood (7.2%).¹⁵ Milk, regardless of age, has been found to be the single most frequent cause of anaphylaxis, accounting for 28.4% among all food causes.¹⁵ The first anaphylactic attack due to milk mostly (95.5%) happens to patients who are 1 year or younger.^{16–18} This could be due to the immature immune system and gastrointestinal

organs of these patients. When they are exposed to milk, milk allergy or anaphylaxis might have been triggered.^{16,19} Cutaneous, respiratory, and gastrointestinal symptoms are frequently found to be associated with milk anaphylaxis.²⁰ The severity of anaphylaxis is more severe when it is accompanied by cardiovascular or neurologic symptoms.²¹ Because milk is easily and frequently exposed to children, clinicians need to pay more attention to patients with symptoms associated with milk.

World allergy organization guidelines for the assessment and management of anaphylaxis recommend that epinephrine should be injected intramuscularly immediately after anaphylaxis is diagnosed.^{2,10} Although epinephrine is paramount in the treatment of anaphylaxis, epinephrine is not always necessary for the treatment of anaphylaxis. A previous study has reported that although only 39% of adult patients have received epinephrine for anaphylaxis, 98% of ED treatment is appropriate for anaphylaxis.²² In our study, only 10.8% of missed anaphylaxis group received epinephrine. This might be due to lower severity in children compared with adults. There was no severe patient in the missed anaphylaxis group. However, patients treated with fluid, steroid, and epinephrine had higher possibility of having missed diagnosis of anaphylaxis compared with those who did not receive such treatment. Because epinephrine injection is the first-line treatment. It is also an important index of care quality,²³ and clinicians need to consider epinephrine injection when anaphylaxis is suspected.

More cardiovascular symptoms were found in the anaphylaxis group, whereas more gastrointestinal symptoms were present in the missed anaphylaxis group. This means that we might need to suspect anaphylaxis when patients have cardiovascular symptoms. We also need to suspect anaphylaxis when patients present with gastrointestinal symptoms. Many pediatric patients often have complaints of gastrointestinal symptoms such as abdominal pain, nausea, vomit, and diarrhea. Furthermore, many of those complaints are idiopathic. Therefore, physicians in ED should carefully interpret these symptoms and consider that these symptoms could be associated with anaphylaxis.

TABLE 5. Characteristics of Patients With Anaphylaxis or Missed Anaphylaxis

	Anaphylaxis (n = 11)	Missed anaphylaxis (n = 37)	P
Average age, y	6.6 ± 5.4*	4.1 ± 5.3*	0.104
Sex, male, %	5 (45.5)	18 (48.6)	0.852
History of atopic dermatitis, %	4 (36.4)	2 (5.4)	0.019
Symptoms, %			0.000
Cutaneous	11 (100)	37 (100)	NA
Respiratory	7 (63.6)	16 (43.2)	0.235
Cardiovascular	5 (45.5)	0 (0.0)	0.000
Gastrointestinal	2 (18.2)	24 (64.9)	0.006
Neurologic	1 (9.1)	0 (0.0)	0.229
ED treatment, %			
Fluid administration	10 (90.9)	6 (16.2)	0.000
Antihistamine use	10 (90.9)	34 (91.9)	1.000
Steroid use	7 (63.6)	13 (35.1)	0.162
Epinephrine use	7 (63.6)	4 (10.8)	0.001
Bronchodilator use	6 (54.5)	5 (13.5)	0.010
Diagnostic tests, %	10 (90.9)	7 (18.9)	0.000

*Mean ± standard deviation.

NA indicates not available.

This study only included patients who visited ED. Patients who visited outpatient department and those who had self-limiting symptoms were not included in this study. Moreover, this study was conducted in only 1 training hospital. The quality for registration of disease classification codes was not validated before. Therefore, results of this study could not be generalized. Another limitation was that a high ratio of idiopathic cause of both urticaria and missed anaphylaxis group due to retrospective chart review.

CONCLUSIONS

Of all pediatric urticaria patients, 3.5% of patients were not registered as anaphylaxis although they had anaphylaxis symptoms. Missed diagnosis of anaphylaxis in pediatric urticaria patients at ED were associated with a history of food allergy with milk, egg, and seafood as causes of allergy, treated with fluid administration, steroid use, and epinephrine use. Consideration for whether the diagnosis of anaphylaxis is missed in pediatric urticaria patients is necessary to obtain accurate prevalence data of pediatric anaphylaxis.

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