

# Investigation of the Patients with Angioedema who Applied to the Emergency Department

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## Abstract

**Aim:** This study aimed to describe the demographic and clinical characteristics of patients with angioedema admitted to the emergency department.

**Materials and Methods:** This prospective study was conducted in the Emergency Medicine Department of Erciyes University Medical School between April 15 and November 30, 2016. Patients older than 18 years presenting with angioedema were included in the study. The demographic and clinical data of the patients were then analyzed.

**Results:** This study included 100 patients with angioedema and the mean age of 41.48±14.10 years. Forty-five percent of the patients were experiencing their first attack. The most frequent complaints were swelling (93%) and itching and redness (54%). Edema was typically observed in the periorbital region and on the lips. Drug use (52%) was the most frequent cause of angioedema, with the use of nonsteroidal anti-inflammatory drugs being the most common drug-related cause (23%). All the patients received antihistamine and steroid therapy. Although most patients were administered adrenaline (67%), some were administered fresh frozen plasma and complement 1 inhibitor concentrate (3%). Furthermore, the dermatology department was consulted for most of the patients (89%).

**Conclusion:** Angioedema is a medical condition that requires hospitalization in most cases and has the potential to rapidly progress into a life-threatening stage. Therefore, the timely recognition and appropriate management of this clinical condition in the emergency department is of great importance.

**Keywords:** Angioedema, emergency department, urticaria, complement 1 inhibitor

## Introduction

Angioedema (AE) is a clinical presentation that usually manifests itself as a transient, localised, subcutaneous or submucosal non-pitting edema in the tongue, mouth, lips, larynx, and face (1,2). Tissue swelling is caused by a sudden increase in wall permeability of the vessels in the skin and submucosa (3). AE is a non-pitting type of edema, is not affected by gravity and is often asymmetrical. This type of edema is not itchy, usually no pain, but a feeling of burning or tingling might be observed (4). It may progress very quickly and may lead to swelling of the mouth, tongue, and larynx, leading to a respiratory-tract obstruction, thus might evolve into a life-threatening condition (5). If the gastrointestinal tract is affected, severe nausea, vomiting, and abdominal pain

may be seen (1,6). Imaging methods can be used in patients with acute symptoms affecting the neck and abdominopelvic region (7). It is categorised as allergic (mast cell or immunoglobulin E (IgE) mediated) or non-allergic (mediated by bradykinin) (8). Allergic AE is usually accompanied by urticaria. Different types of food, insecticides and drugs are the allergens that cause this type of IgE-mediated reactions (9). Non-allergic AE can be classified as; hereditary AE (HAE), acquired AE, angiotensin-converting enzyme inhibitor (ACEI)-related AE, pseudoallergic AE, and idiopathic AE (8).

AE is an urgent clinical condition which requires visiting emergency departments (ED). Emergency physicians may encounter various presentations of this clinical entity which



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may have life-threatening potential. The aim of this study is to investigate clinical and demographic properties of the patients presenting to the ED due to AE in particular and to detect the outcomes.

### Materials and Methods

This prospective study was carried out in the Emergency Medicine Department of Erciyes University Medical School between April 15, 2016 and November 30, 2016. The study was approved by the Ethics Committee of Erciyes University (protocol no: 2016/212). Those patients older than 18 years and presenting with AE were included in the study. The patients that were involved in the study, were informed about the scope of this study, and their informed consents were obtained. A total of 100 patients was included in the study. The following data were recorded in prepared forms: age, sex, occupation, time of the first episode, the number of attacks, medical history, history, medications used regularly by the patient, chief complaint, vital signs, and other conditions that might have an association with AE (eg pregnancy, menstruation, hormone replacement, drug use, smoking, alcohol use, trauma, infection, anxiety, physical stress, food intake, operation, tooth extraction, insect bite, contrast agent exposure), physical examination findings, consultations, treatment in the ED, response to the treatment, and outcome (admission or discharge).

### Statistical Analysis

Descriptive statistics (mean, median, percent, standard deviation) was used in the analysis of the data. Normal distribution of the continuous data was assessed by the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Mann-Whitney U test was used to compare the median values of the two independent groups, and the Kruskal-Wallis test was used to compare the median values of the multiple independent groups. The chi-square test was used to compare the per cent distributions of the categorical data. The evaluations were performed in the SPSS V20 program and  $p < 0.05$  value was considered significant.

### Results

Between 15.04.2016 and 30.11.2016, patients older than 18 years of age who were admitted to the ED with AE among all adult admissions were investigated. The mean age of the patients was  $41.48 \pm 14.097$  years (19-86), 46 of the 100 patients were female. The most frequent of the ED visits were in April (28%) and May (23%), especially during the seasonal transition periods (April-May and September) (Table 1).

Forty-nine percent of the patients were employed, and 51% of them were not working in a job. The most frequent occupational

group in the working group was civil servant (23%), and among the non-working group was housewife (35%). Urticaria was not present in the 78% of the patients with AE who were referred to the ED. When the effect of the gender on this parameter was investigated, urticaria was detected in 45.5% of male patients and 54.5% of female patients. There was no statistically significant difference between genders with respect to the presence or absence of urticaria in the patients with AE in the study ( $p=0.363$ ), (Table 2).

When the effects of the seasonal differences are assessed on the occurrence of urticaria in patients with AE, no statistically significant difference was found between the seasons ( $p=0.40$ ). Admission time of the patients in the study group to the ED is

**Table 1. The frequency of angioedema by months**

Months	Percentage value of the number of patients (%)
April	28
May	23
June	18
July	7
August	2
September	12
October	5
November	5
<b>Total</b>	<b>100</b>

**Table 2. Demographic data in angioedema groups with or without urticaria**

Demography	AE Total (n=100)	AE without urticaria (n=78)	AE with urticaria (n=22)	p
<b>Gender (number, %)</b>				
Female	46 (46)	34 (43.6)	12 (54.5)	0.363
Male	54 (54)	44 (56.4)	10 (45.5)	
<b>Month of admission</b>				
Spring	51 (51)	40 (51.3)	11 (50.0)	0.403
Summer	27 (27)	19 (24.4)	8 (36.4)	
Autumn	22 (22)	19 (24.4)	3 (13.6)	
<b>Admission time</b>				
24-12	51 (51)	38 (48.7)	13 (59.1)	0.390
12-24	49 (49)	40 (51.3)	9 (40.9)	
Age (mean ± SD)	41.48±14.09	42.59±14.54	37.55±11.85	0.134
Number of attacks ± SD	4.06±7.53	3.39±6.72	6.40 ±9.70	0.005
AE: Angioedema, SD: Standard deviation, n: Number				

classified into two groups; between 12:00 p.m. - 12:00 a.m. and 12:00 a.m. - 24:00 p.m. There was no statistically significant effect of the admission time on the presence or absence of urticaria complaints in the patients with AE ( $p=0.39$ ), (Table 2).

It was found that 45% of the patients were experiencing their first attack on the initial admission. The mean number of attacks in all AE patients was calculated as  $4.06 \pm 7.53$ . When the number of attacks was evaluated according to the presence of urticaria, the average number of attacks was  $6.40 \pm 9.70$  for patients with urticaria and  $3.39 \pm 6.72$  for patients without urticaria. A statistically significant difference was noted between the two groups ( $p=0.005$ ) (Table 2). The mean number of AE episodes in patients with anxiety-related AE was found to be higher than that of the ones without it ( $p=0.002$ ).

The most frequent chronic diseases in the patients' medical history were atopy (31%), urticaria (22%) and hypertension (12%). There were 4 cases with the history of HAE. The most frequent complaints in our study were swellings in the body. Edema was most frequently detected in the periorbital region and lips (48%), (Table 3). We identified the most frequent cause among the factors leading to the development of the onset as medications by 52%. No triggering factor was identified in 34% of

the cases. The most common type of drug (23%) in drug-induced AE were non steroidal anti inflammatory drugs (NSAID)s (Table 4). Dexketoprofen (7%) was the most common cause of the AE among the NSAID's (Table 5). Ten percent of the patients in the study were experiencing tachypnea, 2% was hypotensive, and in 12 of the patients, eosinophilia was detected in the laboratory findings.

All patients received antihistamine and steroid therapy. Adrenalin was administered in 67% of patients whereas fresh frozen plasma and complement 1 inhibitor (C1 INH) were given in 3% of patients. 89% of the patients were consulted the dermatology department. Seventy-three of the patients who were consulted were hospitalised. None of the patients' clinical prognosis was critical or mortal.

## Discussion

Rapid admission and evaluation of the AE patients by an Emergency Medicine Physician along with identification of the coincidental findings and initiation of the treatment as soon as possible are of utmost importance. The most appropriate treatment should be determined by the clinical presentation and underlying pathophysiological mechanism (4). Zingale et al.

**Table 3. Symptoms and findings of physical examination associated with angioedema**

Symptoms	AE Total (n=100)	AE without urticaria (n=78)	AE with urticaria (n=22)	p
Itching	54 (54)	40 (51.3)	14 (63.6)	0.304
Erythema	53 (53)	37 (47.4)	16 (72.7)	0.036
Swelling	93 (93)	72 (92.3)	21 (95.5)	0.609
Shortness of breath	28 (28)	22 (28.2)	6 (27.3)	0.931
Abdominal pain	4 (4)	1 (1.3)	3 (13.6)	0.009
Nausea	4 (4)	4 (5.1)	0 (0)	0.278
Vomiting	1 (1)	1 (1.3)	0 (0)	-
Diarrhea	0 (0)	0 (0)	0 (0)	-
Anaphylaxis	2 (2)	2 (2.6)	0 (0)	0.128
Changes in consciousness	0 (0)	0 (0)	0 (0)	-
Physical examination				
Periorbital edema	48 (48)	39 (50.0)	9 (40.9)	0.451
Edema in the lips	48 (48)	38 (48.7)	10 (45.5)	0.787
Macroglossia	4 (4)	3 (3.8)	1 (4.5)	0.882
Edema of the uvula	43 (43)	37 (47.4)	6 (27.3)	0.092
Extremity findings	37 (37)	25 (32.1)	12 (54.5)	0.050
Abdominal findings	1 (1)	1 (1.3)	0 (0)	0.594
Genital findings	0 (0)	0 (0)	0 (0)	-
Respiratory system findings	2 (2)	2 (2.6)	0 (0)	0.448

AE: Angioedema, n: Number

Situation	%
<b>Drug use (n=52)</b>	
NSAIDs	23
Antibiotic	11
Analgesic (paracetamol)	6
Angiotensin II receptor antagonist	2
Antivirals	2
Antidepressant	2
Contrast medium	2
ACEI	1
Cold medications	1
Hormone replacement	1
Iron preparation	1
<b>Cigarettes</b>	10
<b>Anxiety</b>	8
<b>Food intake</b>	6
<b>Infection</b>	4
<b>Tooth extraction</b>	4
<b>Insect bite</b>	4
<b>Physical stress</b>	2
<b>Menstruation</b>	1
<b>Hair dye</b>	1
<b>Epilation</b>	1
<b>Alcohol</b>	1
<b>Surgery</b>	0
<b>Trauma</b>	0
<b>Unknown</b>	34
NSAID: Nonsteroidal anti-inflammatory drugs, ACEI: Angiotensin-converting enzyme, n: Number	

(10) conducted a study between 1993 and 2003, classifying 776 patients with AE who were admitted to the hospital, according to the different causes of their AE. They reported triggering causes of the AE as following: due to external causes (medications, insect bite or food intake) was seen in 124 patients (16%), due to ACEI usage was observed in 85 patients (11%), AE due to autoimmunity or infections in 55 patients (7%), due to C1 INH deficiency in 197 patients (25%), and in 315 patients (41%) there was not any identified cause (10). According to our study, patients with AE due to allergies, were found to have the following triggering factors, insect stings (bee) 4%, food intake (fish and spice consumption) 6%, drug use 24% (antibiotics 11%, analgesics 6%, antivirals and antidepressants 2%, cold medications 1%, hormone replacement and iron preparation 1%), and in 1% of the patients there was the history of application of hair dye and epilation. In patients

Drug-active substance	%
<b>Analgesics</b>	
Etodolac	1
Metamizole sodium	1
Naproxen sodium	1
Parasetamolklorfeniraminmaleat	1
Acetamidine	1
Acetylsalicylic acid	2
Feniramidol HCL	2
Diclofenac sodium	2
Flurbiprofen	3
Ibuprofen	3
Paracetamol	6
Dexketoprofen	7
<b>Antibiotics</b>	
Doxycycline	1
Sefuroximeacetyl	1
Amoxicillin	1
Gemifloxacin	1
Moxifloxacin	1
Trimethoprim sulfamethoxazole	2
Penicillin	2
Ciprofloxacin	2
<b>Antihypertensives</b>	
Fosinopril	1
Olmesartanmedoxomil	1
Olmesartanmedoximilhydrochlorothiazide	1
<b>Iron preparation</b>	1
<b>Progesterone</b>	1
<b>Bupropion HCL</b>	1
<b>Escitalopram</b>	1
<b>Acyclovir</b>	1
HCL: Hydrochloride	

without allergies the causative agents were classified as, ACEI usage in 1%, ARB2 antagonists in 2%, NSAIDs in 23%, contrast dye in 2%. In 34% of the patients, there was no identified agent and they were classified as idiopathic. Four patients had a history of HAE. 4% of the patients who admitted concurrently had a history of infection and/or tooth extraction. We think that the differences between our study and the causes of the AE in other studies are due to the differences in the cultural structure

(nutrition habits, education levels), the time and duration of the study, the geographical conditions in which the studies have been made, and the way of life of the societies (village and city type life).

Bork et al. (11) reported that 221 patients with C1 INH deficiency were presented with edema in the extremities, face, genitalia or trunk in 97.4% of the time. Edema in the periorbital area (48%) and the lip (48%) was the most common locations in our study, whereas uvula edema was seen in 43%, edema in the extremities was observed in 37%, macroglossia was found in 4%, respiratory system findings in 2%, and findings in the abdomen in 1%. Genital involvement was not detected in any patient. We think that the differences between the studies are due to individual reasons.

In a study conducted by Champion et al. (12), it was found that 49% of 554 urticaria patients were accompanied by AE, and 11% of patients had AE alone. In our study, 22% of the patients were accompanied by urticaria. There are differences in the presence or absence of urticaria in patients with AE in these studies. We think that this difference is due to the fact that the causes of AE (allergic or non-allergic) are different. It has been reported in the literature that the co-occurrence rate of urticaria and AE caused by allergies, is higher (8).

The most common medications in the drug-related AE are; NSAIDs, ACEI, angiotensin II receptor antagonists, antibiotics, radiocontrast agents, proton pump inhibitors, statins, fibrinolytic agents, estrogens, diuretics, calcium channel blockers and psychotropic drugs. Acetylsalicylic acid and ibuprofen are appeared to be at the forefront of the NSAIDs. NSAID and acetylsalicylic acid intolerance are seen in 0.3-0.9 % of the population. However, there are no exact figures for the incidence of AE due to NSAIDs and acetylsalicylic acid (13). In our study, it was determined that the most common cause of AE was drug use, with 52%. The use of dexketoprofen (7%) was the most common cause of the AE among the NSAID's. Among other NSAID drugs as AE triggers, the following percentages were recorded: flurbiprofen and ibuprofen 3%, diclofenac sodium, acetylsalicylic acid and feranimadol HCl 2%, etodolac, metamizole sodium, naproxen sodium and acetaminin 1%.

ACEI-related AE is independent of the dose, can be seen with the initial administration of ACEI's, as well as months or years later. They are the most frequent cause of the recurrent drug-related AE (13,14). Banerji et al. (15) found that 30% of the 220 AE patients who applied for emergency services was due to ACEI usage. The most common findings in these patients were reported as: shortness of breath, lip and tongue swelling and laryngeal edema. In our study; the ACEI Fosinopril (1%) and the angiotensin II receptor antagonist Olmesartanmedoxomil (2%)

were found to cause AE clinical signs and symptoms after many years of usage. Patients were admitted to our ED between 6.00 p.m. and 9.00 p.m. with complaints of lipedema, macroglossia, uvula edema. One of the patient's AE was accompanied by urticarial lesions. Two of our patients were admitted to the dermatology department. Our other patient, whose clinical signs and symptoms were regressed, and was discharged after observation (<24 hours).

Iwamoto et al. (16) studied the patients with HAE in Japan in 2009; 54% of patients with HAE type I and II had swelling, 42% had a feeling of discomfort in the throat, and 37% had abdominal complaints. In the European Hereditary Angioedema Burden Research's survey conducted with HAE patients, it was determined that 73 of the patients were working full-time, 21 of the patients were working part-time, seven of the patients were studying, and 19 of the patients were both studying and working (17). Huang (18) reported in a study that was conducted with 63 patients with HAE in 2004 that, the patients were admitted to the ED with an average of 4.7 times per year, and in one-quarter of the patients, anaphylaxis was seen in the ED. Iwamoto et al. (16) conducted a study in HAE patients in Japan and reported that: 54% of patients with HAI type I and II had swelling, 42% had a feeling of discomfort in the throat, and 37% had abdominal complaints. In another study, C1 INH concentrate therapy was administered to 29% of patients who applied with an acute exacerbation of HAE (13,16). There were only four male patients with a history of HAE with the mean age of 36.75 in the 100 AE patients included in our study. All of our patients with HAE also had an HAE history in their family. Two patients were admitted to the hospital ED with twenty-fifth acute exacerbation of AE, the other two patients were admitted with their third attack. It was learned that C1 INH concentrate was available in the patients' home. Two patients with lip edema, one patient with uvula edema and one patient with periorbital edema were admitted to our ED. A patient with edema on the lips also had urticarial lesions. The clinical presentation of two HAE patients was triggered by anxiety, and the triggering causes of the other two were unknown. Only one patient was treated with C1 INH concentrate. Three patients were admitted to the dermatology department, and one patient was discharged after 24 hours of observation in the ED. When we looked at the occupational status of these four patients, we learned that two of them are civil servants and the others were tradesmen with their own business. At least 24 hours of daily activity and workforce productivity were lost after the ED admissions of these patients. When our patients with HAE were evaluated; were consistent with the literature concerning the loss of workforce, symptom similarity at the time of application, methods applied during treatment, follow-up time in the hospital, and results (13,16,17).

In the AHRQ-HCUP 2007 National Emergency Service Example, the number of patients referred to the Emergency Service with AE was 112,105 per year. It has been reported that 45% of HAE patients and 18.3 % of AE patients are admitted to the inpatient clinic (19). During our 7-month study in 2016 in the Emergency Medicine Department of Erciyes University Medical School only 4% of AE patients had an HAE history during this time period. Seventy-three per cent of the 100 AE patients that are included in the study group were hospitalized, and 27% were treated and discharged within the emergency care.

## Conclusion

In the light of all these findings, even though AE patients are not frequently encountered in emergency services, patients' clinical signs and symptoms may worsen rapidly, and AE can be mortal. Simultaneous evaluation and treatment of the patients would be life-saving. The deepening of information about the anamnesis, personal and family medical history of AE patients by emergency medicine physicians can help to classify the disease, thus allowing to determine the most appropriate treatment approach. In addition to this, the factors such as medication use, anxiety, and taking preventive measures during the transition seasons can cause great benefit in protecting patients from attacks.

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## Ethics

**Ethics Committee Approval:** The study was approved by Ethics Committee of Erciyes University and was conducted in accordance with the principles of the Declaration of Helsinki (protocol no: 2016/212).

**Informed Consent:** An informed consent form was obtained from each patient.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practices: A.E., Concept: A.E., Ö.L.A., Design: Ö.L.A., Data Collection or Processing: A.E., Ö.L.A., Ş.Ö., Analysis or Interpretation: A.E., Ş.Ö., Literature Search: A.E., Writing: A.E., Ş.Ö.

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