

# Assessment of emergency physicians' awareness and knowledge of hereditary angioedema

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## ABSTRACT

**Aims:** Hereditary angioedema can occur with life-threatening attacks of severe laryngeal edema, and epinephrine is insufficient in the treatment of attacks. We sought an answer to the question, 'Do emergency physicians, who frequently encounter angioedema cases that are so important for the emergency department, have sufficient awareness about this issue?'

**Methods:** In this study, the online questionnaire was conducted among physicians working in adult emergency departments between April and August 2022. The questionnaire form consisted of two parts. The first part contained three questions about medical experience, academic degree, and encounter with hereditary angioedema patients. The second part of the questionnaire contained seven questions about the diagnosis and treatment of hereditary angioedema.

**Results:** A total of 103 physicians working in emergency departments participated in the survey. The proportion of physicians is as follows: The percentage of physicians with less than 15 years of experience was 92.2%. Research assistants represented the largest group of participants at 51.5%. When asked "What is not a symptom of hereditary angioedema?" Only 40.6% of physicians could answer the question correctly. While 39.8% of physicians thought that epinephrine and antihistamines were useful in treating these attacks, 53.4% felt that epinephrine and antihistamines were not. While there was a difference in hereditary angioedema awareness between the group with more than 15 years of professional experience and the group with less experience, there was no meaningful difference between research assistants, specialists, and academicians. According to this survey, professional experience was important, but academic title did not make a difference in terms of disease awareness.

**Conclusion:** It is necessary to increase the awareness of emergency physicians about hereditary angioedema, which can cause fatal attacks and whose diagnosis and treatment are different from other angioedemas.

**Keywords:** Hereditary angioedema, HAE, survey, emergency

## INTRODUCTION

Hereditary angioedema (HAE), which usually results from C1 esterase inhibitor (C1-INH) deficiency, affects the skin, gastrointestinal tract, and upper respiratory tract.<sup>1</sup> Symptoms of angioedema may also affect the face and tongue. The most important clue to HAE is the presence of angioedema that is not accompanied by urticaria and pruritus.<sup>2</sup> It is an autosomal dominant inherited disease.<sup>1</sup> HAE is more severe than allergic angioedema and takes longer to heal.<sup>3,4</sup> HAE symptoms usually do not respond to antihistamines, corticosteroids, or epinephrine.<sup>3</sup> Edema in the gastrointestinal mucosa (GI) is the cause of abdominal symptoms. HAE attacks of abdominal pain, nausea, vomiting, and diarrhea may be confused with acute abdomen and acute gastroenteritis.<sup>5,6</sup> Laboratory tests (C1-INH and C4 levels) are indicated in patients with symptoms. HAE attacks should be treated immediately. Plasma-derived C1-inh concentrates and recombinant C1 inhibitors are administered intravenously

or bradykinin B2 receptor antagonist and plasma kallikrein inhibitor are administered subcutaneously.<sup>7</sup>

Early diagnosis and treatment are critical to minimize mortality and morbidity. These patients can not be diagnosed for 1 to 6 years.<sup>8</sup> Sometimes these patients are misdiagnosed or treated incorrectly. Although not very common, emergency physicians are the physician group that encounters these patients most seriously. A significant number of patients experience a laryngeal edema attack at some point in their lives. These attacks can be fatal because they do not benefit from antihistamines and epinephrine. There may be delays and difficulties in managing these attacks in the emergency department. Therefore, it is very important to diagnose this condition in the emergency department, manage such attacks and provide post-treatment care. With this study, we aimed to determine if emergency physicians have sufficient knowledge, experience, and equipment to manage and treat HAE attacks in the emergency department.



## METHODS

The study was approved by the Ankara City Hospital Clinical Researches Ethics Committee No. 1 (Date: 29.12.2021, Decision No: E1-21-2282). The study was conducted in accordance with the Principles of the Declaration of Helsinki by informing the participants and obtaining their consent. An online questionnaire was sent to physicians working in emergency departments of all types of hospitals in different cities in Turkey in 2022. ‘Google Forms’ was used in this study, which indicates that it is confidential and secure, that it does not transfer information to third parties, and that it does not leak information to different channels. Online survey form was sent to 210 physicians. 103 physicians wanted to participate in the survey. The questionnaire form consisted of two parts. It included a total of ten questions. The first part included 3 questions about medical experience and academic degree. The second part included 7 questions related to the diagnosis and treatment of HAE in the emergency department.

### Statistical Analysis

First, the descriptive characteristics of the variables (number and percentage) were found. The total scores of the respondents were calculated according to the number of correct answers, assuming that those who answered all seven questions correctly would receive 100 points. The Chi-square test was used to compare categorical variables. When comparing continuous variables, the Mann-Whiney U was used to compare two groups, and the Kruskal-Wallis test was used to compare more than two groups. Risk factors for giving less than 4 correct answers were investigated with logistic regression analysis. First, single logistic regression was performed and those with  $p < 0.25$  were included in multiple regression analysis. The “Statistical Package for Social Sciences” SPSS 25 (IBM Corp., Armonk, NY, USA) program was used to evaluate the results.  $p < 0.05$  was accepted as significant.

## RESULTS

The percentage of physicians with 15 or more years of professional experience was 7.8%, while the percentage of physicians with less than 15 years of professional experience was 92.2% (Table 1). The highest participation rate was 52% in the group of assistants, followed by emergency medicine specialists with 41.2% (Table 1). The percentage of physicians who reported having already examined a patient with HAE was 58.3% (Table 1). You can also see all the questions and answers in Table 1.

40.6% correctly answered the question “Which finding does not belong to HAE?” with “itchy red lesions (Table 2).” Which is not a factor that triggers HAE?” the answer to the question was 32% correct and 68% incorrect (Table 2). “C1-esterase deficiency is the key factor involved in the etiopathogenesis of HAE” While 83.5% of the respondents answered the question correctly saying they agree, 7.8% gave the wrong answer and 8.7% said they had no idea (Table 1). While 39.8% of the population thought that epinephrine and antihistamines were useful in treating attacks, 53.4% disagreed (Table 1). When asked “Which agent should not be used in the treatment of HAE attacks?”, 51.5% of those who mentioned epinephrine gave the correct answer, while 48.5% gave the incorrect

Professional experience	n	%
<15 years	94	92.2
>=15 years	8	7.8
Profession group		
Assistant	53	52
Specialist	42	41.2
Academician	7	6.9
Have patients with HAE*		
Yes	60	58.3
No	43	41.7
Finding does not belong to HAE*		
Cutaneous swelling in different parts of the body	8	7.9
Stomachache	6	5.9
Diarrhea	39	38.6
Itchy red lesions	41	40.6
Shortness of breath	7	6.9
Not one of the factors triggering HAE*		
Oral contraceptive	5	5
Menstruation	21	21
Trauma	41	41
Danazol	32	32
Infection	1	1
C1-esterase deficiency is involved in the etiopathogenesis of HAE*		
Agree	86	83.5
No opinion	9	8.7
Not agree	8	7.8
Epinephrine and antihistamines are useful in treating attacks		
Agree	41	39.8
No opinion	7	6.8
Not agree	55	53.4
Should not be used in the treatment of HAE* attacks		
C1 esterase inhibitor	5	5
Fresh frozen plasma	21	20.8
Bradykinin	6	5.9
Epinephrine	52	51.5
Kallikrein	17	16.8
Non HAE* features		
Associated with stress	9	8,9
Takes longer to heal from allergic angioedema	9	8,9
Begins at an early age	10	9,9
Associated with food, pollen, and odors and odors	59	58.4
More severe than allergic angioedema	14	13.9
Not in the differential diagnosis of HAE*		
Acute abdomen	17	16.7
FMF**	6	5.9
Allergic angioedema	3	2.9
AGE***	40	39.2
Urticaria	36	35.3

\*HAE: Herediter angioedema, \*\* FMF: Familial Mediterranean Fever, \*\*\*AGE:Acute gastroenteritis n: Number of patients

answer (Table 2). When asked about non-HAE features, we got 41.6% wrong and 58.4% correct answers (Table 2). When asked about the differential diagnosis of HAE, we received 64.7% incorrect answers and 35.3% correct answers (Table 2). The average of correct answers to a total of 7 knowledge questions 3.54±0.7 and the median score was 4.

It was found that there was a significant difference in the mean of correct answers between those with less than 15 years of experience and those with more than 15 years of experience (Table 3).

There was no significant difference in the mean of correct responses between residents, specialist and academicians (Table 4).

Table 5 evaluated the relationship between the rate of correct answers to information-based questions and demographic data and previous encounters with a HEA patient. While previous encounter with a HAE patient and professional experience were significant, there was no difference between professional groups (Table 5).

**Table 2. Accuracy rates of answers to questions about the diagnosis and treatment of the disease**

Finding does not belong to HAE*	n	%
Incorrect	60	59.4
Correct	41	40.6
Not one of the factors triggering HAE*		
Incorrect	68	68
Correct	32	32
C1-esterase deficiency is involved in the etiopathogenesis of HAE*		
Incorrect	17	16.5
Correct	86	83.5
Epinephrine and antihistamines are useful in treating attacks		
Incorrect	48	46.6
Correct	55	53.4
Should not be used in the treatment of HAE* attacks		
Incorrect	49	48.5
Correct	52	51.5
Non HAE* features		
Incorrect	42	41.6
Correct	59	58.4
Not in the differential diagnosis of HAE*		
Incorrect	66	64.7
Correct	36	35.3
Number of correct answers	n	P
0	3	2.9
1	22	21.4
2	14	13.6
3	12	11.7
4	16	15.5
5	14	13.6
6	13	12.6
7	9	8.7
Correct answer group		
3 or less correct	50	49.0
4 or more correct	52	51.0
Point **	57.1 (28.6-71.4)	

\*HAE: Herediter angioedema, n: Number of patients \*\*Median value (25-75%)

**Table 3. Relationship between professional experience and correct answers**

	Professional experience				p value**
	<15 years		≥15 years		
	n	%	n	%	
Number of correct answers					0.001
0	3	3.2	0	0	
1	21	22.3	0	0	
2	14	14.9	0	0	
3	12	12.8	0	0	
4	15	16	1	12,5	
5	12	12.8	2	25	
6	11	11.7	2	25	
7	6	6.4	3	37,5	
Number of correct answers					0.006
<=3 Correct	50	53.2	0	0	
>=4 Correct	44	46.8	8	100	
Point*	42.9(14.3-71.4)		85.7(71.4-100.0)		0.001

\*Median Value (%25-75) \*\* p< 0.05 significant, n: Number of patients

**Table 4. The relationship of profession groups and correct answers**

	Assistant		Specialist		p**	
	n	%	n	%		
Number of correct answers					0.168	
<=3 Correct	29	54.7	17	40,5		
>=4 Correct	24	45.3	25	59,5		
	Assistant		Academician		p**	
	n	%	n	%		
Number of correct answers					1.000	
<=3 Correct	29	54.7	4	57.1		
>=4 Correct	24	45,3	3	42.9		
	Specialist		Academician		p**	
	n	%	n	%		
Number of correct answers					0.443	
<=3 Correct	17	40.5	4	57.1		
>=4 Correct	25	59.5	3	42.9		
Point*	42,9 (28,6-71,4)		57,1 (14,3-85,7)		42,9 (42,9-100,0)	0.223

\*Median value (%25-75), \*\* p< 0.05 significant, n: Number of patients

When logistic regression analyses were performed in Table 4, it was observed that having a previous HAE patient was effective in giving the correct answer, while it became clear that professional experience and professional group were insignificant.

## DISCUSSION

The survey was sent to 210 physicians online and 103 people responded with a rate of 49%. In Baran's thesis study,<sup>5</sup> 42% of the physicians responded to the survey, while in the study conducted by Riedl et al.<sup>9</sup> 3% of the physicians responded to the survey sent to 6750 physicians via e-mail. Although Baran attributed this difference to the fact that they conducted the survey face-to-face, our survey achieved higher participation

**Table 5. The relationship between professional years, groups, having any HAE and number of correct answers**

	Number of correct answers				p*
	<=3 Correct		>=4 Correct		
	n	%	n	%	
Professional years					0.006
<15 years		50	100,0	44	84.6
>=15 years		0	0.0	8	15.4
Profession groups					0.436
Asistant		29	58.0	24	46.2
Specialist		17	34.0	25	48.1
Academician		4	8,0	3	5.8
Have you ever had HAE?					0.037
Yes		24	47.1	36	69.2
No		27	52.9	16	30.8

\* p&lt; 0.05 significant

**Table 6. Logistic regression analyses for risk factors of giving fewer than 4 correct answers**

Risk factors for giving fewer than 4 correct answers	Single logistic regression analysis			Multiple logistic regression analysis				
	B	CI (%95)	p*	B	CI (%95)	p*		
Professional years (being more than 15 than being less than 15)	0.555		0.999					
Professional group (Being a specialist or a academician compared to being an assistant)	0.620	0.284	1.358	0.232				
HAE patient (have you ever had patient or not)	2.531	1.130	5.666	0.024	2.439	1.086	5.464	0.031

\* p&lt; 0.05 significant

despite being online. We can attribute this situation to sending it to all of the addressees one by one via WhatsApp instead of e-mail. Nevertheless, when we look at these rates, survey participation was evaluated as low, and considering that the experiences and opinions of physicians are very valuable, it was concluded that survey participation should be increased.

As a result of this study that awareness and knowledge of HAE, especially attack management in emergency department should be improved. We also concluded that having previously encountered a HAE patient was effective in giving a correct answer, but academic title or length of professional experience did not make a significant difference in terms of disease awareness. Not having a patient with hereditary angioedema increases the risk of less than 4 correct answers by 2.439 times (1.086-5.464)  $p=0.031$ .

Although there was a difference in HAE knowledge when physicians with more professional experience were compared to physicians with less professional experience, no significant difference was found when we looked at the logistic regression analysis. Unlike our study, young physicians heard about HAE more frequently than older physicians in Mete Gökmen et al.'s<sup>10</sup> study. We think that this difference may be due to the low rate of physicians with more than 15 years of experience in our study (7.8%) or the comparison of young physicians by age in the other study (35.9±8.2 years vs. 45.7±13.2 years,  $p=0.04$ ). No significant difference was found between academicians, experts, and residents in terms of the average of correct answers. This shows that there is no difference in the practice of HAE after medical school, specialization training

and afterwards. Recently, some faculties have been trying to increase HAE awareness. We would like to emphasize that this disease, which is of particular interest to emergency physicians, should be given more attention during emergency medicine specialization training, as it poses a life-threatening risk to patients due to laryngospasm that may occur during an attack and is treated differently than other angioedemas.

One of the aims of medical education is to provide continuous learning behavior. Continuous professional development, which includes self-learning activities as well as courses, conferences, lectures, is necessary for people to develop their knowledge and skills and their professional lives.<sup>11</sup>

In this study, the rate of physicians who reported that they examined a patient with HAE was 58.3%. In the 2016 dissertation study by M. Baran, the proportion of physicians who had a patient with HAE was 26%. The low rate in this study may be due to the fact that the physicians participating in the study were not only emergency physicians, but also physicians working in other units.<sup>5</sup> Similarly, in another study conducted by Mete et al.<sup>10</sup> with the participation of 155 internal medicine physicians, a significant portion of the physicians (93.5%) reported that they had heard of HAE and 41.9% reported that they followed at least one HAE patient.

The prevalence of the disease is reported to be 1:50,000 to 1:400,000.<sup>1,12</sup> According to the study conducted by Ozdemir et al.<sup>8</sup> the total number of patients diagnosed with HAE in Turkey is believed to be between 500 and 7500. This autosomal-dominant inherited disease is thought to be more common in society than is known, but it is difficult to diagnose. In the study conducted by Ozdemir and his friend

and published in 2017, 60 relatives of 4 diagnosed HAE patients were examined, and 38.2% of them were diagnosed HAE.<sup>8</sup> As awareness of the disease increases among physicians, the number of patients diagnosed with HAE will also increase, and thus awareness of treatment will become more important.

In our study, the rate of physicians who answered all questions requiring information was determined to be 8.7%. In the study conducted by Lisa Fu et al.<sup>13</sup> in Canada and including 34 physicians, it was determined that all physicians were aware of the HAE guidelines, however, it was stated that members of groups such as the Canadian Hereditary Angioedema Network, the Canadian Society of Clinical Immunology and Allergy, and the Canadian Hematology Association were included in this study. And this result showed that being in contact with various organizations and associations related to HAE increases awareness of the disease.

The awareness of the deficiency of the most important factor, C1-INH, in the etiopathogenesis of HAE was found to be very high 83.5%. In the study conducted by Mete Gökmen et al.<sup>10</sup> in 2014, only 22% of physicians knew the role of C1 inhibitor in HAE, while 38.7% had no idea about the pathogenesis of HAE. We think that the reason why awareness of this issue is so high is because it is a question that has recently been included in the medical specialty exam.

In our study, 39.8% thought that epinephrine and antihistamines could be used during an attack and were beneficial, while 6.8% had no idea and 53.4% gave the correct answer. In the other study 34.8% had no idea what drugs are used to treat HAE attacks, while 54.8% reported that they would treat the patients with drugs that have no effect in HAE, such as adrenaline or antihistamines. More than 80% of the doctors did not know which drugs are used in the prophylactic therapy of HAE.<sup>10</sup> One of the most important mistakes in treating HAE attacks is wasting time by giving antihistamines, steroids, and epinephrine to the patient. HAE is a disease related to the complement system, and replacing the missing C1-INH is the most important treatment regimen. 2 (0.8%) of the physicians who participated in the study by Terzioğlu et al.<sup>14</sup> chose the exact correct answers regarding emergency management. In a 2012 study of emergency departments by Jaiganesh et al.<sup>15</sup> it was found that although therapeutic C1-INHs were available in the emergency departments studied in England, there was a significant shortage regarding their use. In recognition of this shortage, a guideline for treatment was developed in the same study.

Another survey conducted in the U.S. published in 2021 shows that diagnostic and treatment patterns of physicians in the U.S. have improved significantly between 2010 and 2019 HAE.<sup>9</sup> Time is very important in this disease because many patients die before they are diagnosed. For this reason it is very important to keep an eye on this disease. It is necessary to increase the awareness of doctors about treatment. We can improve knowledge and awareness through a variety of training interventions like in a survey of pharmacists, e-learning programs were shown to increase knowledge about anaphylaxis, even in the long term.<sup>16</sup>

Another study conducted in Brazil among pediatricians, whether board certified in allergy and immunology or not, found insufficient knowledge about HAE, and attributed the large degree of unawareness among physicians to the fact

that HAE is a rare disease. This and many similar studies, in line with our study, argue that physicians' awareness of HAE should be increased.<sup>17</sup>

**The strength** of the survey is that it is the first survey we know of that measures emergency physicians' awareness of HAE. The survey is reliable. With this survey and its continuation, we can increase awareness, curiosity, and thus knowledge about the disease.

### Limitation

This study is limited by the nature of the survey instrument and the fact that the study was conducted via an Internet survey, by the lack of a standard questionnaire, by the high proportion of physicians with less than 15 years of experience, by the unequal number of groups, and by the small number of total academicians participating in the survey. We did not use a standardized and validated questionnaire. In addition, our study is a national study, which affects the generalizability of the results.

## CONCLUSION

As a result, HAE should definitely come to mind in patients presenting to the emergency department with angioedema without urticaria; in cases of angioedema that does not respond to treatments such as antihistamines, cortisol, adrenaline; in patients with widespread edema in the intestines; family history should be questioned and the patient should be referred to relevant departments such as internal medicine or allergy immunology for a definitive diagnosis. In this way, we can ensure that patients receive a more rapid diagnosis at a lower cost. Most importantly, In order to avoid catastrophic consequences such as mortality and morbidity due to laryngeal spasm, it is imperative that we increase awareness of this disease, especially its attack treatment, in emergency services.

Training about HAE should be increased. Programs need to be developed for diagnosis and treatment of the disease and for raising awareness. It is possible to increase the level of knowledge of physicians about HAE through regular training. Training can take the form of theoretical and practical courses, e-learning, or a combination of these and support from associations can be made available. These factors may be more meaningful to patients and may better reflect the benefits of treatment.

Although further study is needed, the results of the survey will shed light on the subject in planning what needs to be done to develop sufficient and necessary awareness.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was initiated with the approval of the Ankara City Hospital Clinical Research Ethics Committee No. 1 (Date: 29.12.2021, Decision No: E1-21-2282).

### Informed Consent

Written consent was obtained from the patient participating in this study.

## Referee Evaluation Process

Externally peer-reviewed.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

## Financial Disclosure

The authors declared that this study has received no financial support.

## Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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