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Research Article

Depression and anxiety may be cause or effect of attacks in hereditary angioedema

Herediter anjioödemde anksiyete ve depresyon, atakların nedeni veya sonucu olabilir

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Abstract

Introduction: The study aims to determine the depression and anxiety levels of patients with hereditary angioedema using the Beck depression inventory(BDI), Beck anxiety inventory (BAI) and to compare the results with the patients' demographic characteristics, the number of attacks, attack types, and healthy controls.

Methods: 60 hereditary angioedema patients and 60 healthy controls were included in the study. The demographic characteristics of the patients, the total number of attacks/months before treatment, the number of attacks according to the localization of the attacks, and the number of attacks/month after treatment were filled in retrospectively from their hospital records. BDI and BAI were used for anxiety and depression levels.

Results: Median BAI (11 vs 5; p=0.001) and BDI (11 vs 7; p=0.024) in HAE patients, the ratio of patients with moderate anxiety (21.7% vs 1.7%; p=0.001) and the ratio of patients with severe anxiety (8.3% vs. 0%; p=0.001) were compared to the control group, was high. There was no statistically significant difference between the number of attacks under treatment and the BAI and BDI scores. A positive correlation was found between the number of untreated attacks and the number of attacks under treatment and the BAI score (r=0.759; p=0.001) and BDI score (r=0.599; p=0.001).

Conclusions: Due to the high prevalence of depression and anxiety in HAE patients, health care providers should be attentive of this comorbidity and refer patients to mental health specialists, when needed.

Keywords: Hereditary Angioedema, Beck Depression Inventory, Beck Anxiety Inventory

Öz

Giriş: Çalışmanın amacı Herediter Anjioödem hastalarında depresyon ve anksiyete düzeylerini Beck depresyon ve anksiyete ölçeği ile belirlemek ve sonuçlarını hastaların demografik özellikleri, atak sayıları, atak yerleri ve sağlıklı kontroller ile karşılaştırmaktır.

Yöntem: Çalışmaya 60 Herediter Anjioödem ve 60 sağlıklı kontrol çalışmaya dahil edildi. Hastaların demografik özellikleri, toplam atak sayıları/ay, atakların yerine göre atak sayısı, tedavi sonrası atak sayısı/ay dosyalarından retrospektif olarak kaydedildi. Anksiyete ve depresyon düzeyi için Beck depresyon ölçeği (BAÖ, BDÖ) kullanıldı.

Bulgular: Herediter Anjioödem hastalarında medyan BAÖ(11'e 5; p=0,001) ve BDÖ (11'e 7; p=0,024) orta düzeyde anksiyetesi olan hastaların oranı (%21,7'ye karşı %1,7; p=0,001) ve şiddetli anksiyetesi olan hastaların oranı (% 8,3 vs. %0; p=0,001) kontrol grubuna göre anlamlı oranda yüksek olarak saptandı. Tedavi altındaki atak sayısı ile BAÖ ve BDÖ skorları arasında istatistiksel olarak anlamlı bir fark yoktu. Tedavi edilmeyen atak sayısı ile tedavi altındaki atak sayısı ile BAÖ skoru (r=0,759; p=0,001) ve BDÖ skoru (r=0,599; p=0,001) arasında pozitif korrelasyon bulundu.

Sonuç: Herediter Anjioödem hastalarında depresyon ve anksiyete prevalansının yüksek olması nedeniyle, sağlık hizmeti sunucuları bu komorbidite konusunda dikkatli olmalı ve gerektiğinde hastaları ruh sağlığı uzmanlarına yönlendirmelidir.

Anahtar Kelimeler: Herediter Anjioödem, Beck Depresyon Ölçeği, Beck Anksiyete Ölçeği

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Introduction

Hereditary angioedema (HAE) is an autosomal-dominant disease that affects an estimated 1 in 50,000 people worldwide [1]. C1 inhibitor dysfunction due to quantitative or qualitative deficiency results in uncontrolled activation of complement and contact pathways that leads to the release of vasoactive substances such as bradykinin, which is the main mediator for increased vascular permeability and edema formation [2, 3]. HAE is characterized by recurrent, unpredictable episodes of swelling of subcutaneous tissues and mucous membranes in many parts of the body, especially the face, larynx, extremities, gastrointestinal tract, and genital organs. Some episodes, such as larynx swelling, may be fatal due to the risk of asphyxiation. Intestinal mucosal edema may lead to transient intestinal obstruction and severe abdominal pain that might be confused with the acute abdomen [3].

Although the triggers of some of the attacks are unknown, trauma, surgical operations, dental procedures, hormonal changes caused by some drugs, infections and stress can cause attacks [4]. It has been reported that the most common triggers of HAE attacks are anxiety, stress, and low mood [5]. In their study, Zotter et al. showed that the patients detected mental stress is a common trigger factor (59%), which accounts one-third of the edematous episodes they had experienced [6]. Simultaneously, HAE itself causes anxiety and depression, which leads to a vicious circle of increased emotional stress and higher attack frequency [5, 7]. Several previous studies suggested that interaction between the immune system and the central nervous system could explain the effects of mood and anxiety. Increased activation of inflammatory mechanisms, especially IL-1β, may be associated with exacerbating symptoms associated with HAE, swelling attacks and mood changes in adults [7, 8].

Angioedema attacks last for 3–5 days, affecting the daily activities of the patients and leading to the need for medical treatment or hospital admission. A study conducted by Lumry et al. found that this has an impact on the health-related quality of life of patients with HAE [9]. The study also found that mean Hamilton Depression Inventory-Short Form (HDI-SF) scores were higher in patients with HAE than in the general population. In another study, 39% of participants were found to be experiencing depressive symptoms by using the HDI rating scale, and 15% of participants showed prominent anxiety by using the Hamilton Anxiety Rating scale [7]. However, the role of trigger factors in the pathophysiology of edema has not yet been clarified.

The aim of this study is to determine the depression and anxiety levels of patients with HAE using the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) and to compare the results with the patients' demographic characteristics, number of attacks, attack types, and healthy controls.

Methods

Hereditary angioedema patients followed in the adult Allergy/Immunology outpatient clinic of Adana City Training and Research hospital between January 2017 and January 2021 were included in the study. Inclusion criteria for patients were: 1) aged 18 years and older, 2) diagnosis of HAE type I or II, 3) not being pregnant or breastfeeding, 4) having given consent, and 5) not diagnosed with cancer and chronic inflammatory disease. Inclusion criteria for age- and sex-matched control groups were: 1) not being pregnant or breastfeeding, 2) having given consent, and 3) not diagnosed with cancer and chronic inflammatory disease.

Among the patients with HAE followed up in the outpatient clinic, those who have frequent attacks take oral danazol treatment or tranexamic acid regularly if there is no contraindication, and all the patients are given the treatment with subcutaneous icatibant to utilize at home in case of attacks. Despite all these treatments, if there is a severe attack or a laryngeal attack, C1 inhibitor replacement is performed in the hospital. C1 esterase inhibitor therapy is also used in an acute attack and prophylaxis (invasive procedures, tooth extraction). Only one of our patients received 1000 mg c1 esterase inhibitor replacement for 6 months, 2 days a week, regularly due to frequent laryngeal attacks. None of the patients use birth control pills and angioconverting enzyme inhibitors, which are known to cause attacks. The monthly average of the attacks of the patients with follow-up in the last 6 months was taken as the "total number of attacks under treatment." The monthly average of the attacks of the patients without treatment, follow up or non-diagnostic period in six months was taken as the "total number of attacks without treatment".

The demographic characteristics of the patients, total number of attacks/month before treatment, number of attacks according to the localization of the attacks, and number of attacks/month after treatment were noted retrospectively from their hospital records. Anxiety and stress levels were measured using the BDI and BAI. This was performed in the outpatient clinic after obtaining consent from randomly selected controls. Patients with HAE also completed the BDI and BAI in the outpatient clinic.

Beck depression Inventory (BDI): This consists of 21 items investigating how the patients have been feeling in the last week. It was developed to determine the risk of depression, the level of depressive symptoms, and the change in severity of depression.
The total score obtained from the scale varies between 0 and 63 [10]. A Turkish validity and reliability study was conducted, and the limit value of the scale was determined as 17 [11]. The scores are as follows:

0–13 – no or minimal depression
14–19 – mild depression
20–28 – moderate depression
29–63 – severe depression.

Beck Anxiety Inventory (BAI**)**: This is a self-assessment scale that is answered according to the severity and how much the symptom in each item has affected the patient for the last week, including the same day [12]. Some of the symptoms experienced by the patients when they are anxious or worried are listed in 21 items. Ulusoy et al. conducted a study to assess the validity and reliability of the BAI [13]. The scores are as follows:

1–9 – normal
10–18 – minimum anxiety
19–29 – medium anxiety
30–63 – severe anxiety.

Ethical Approval, informed consent, and permissions

Following approval of our study by the Local Ethics Committee of Cukurova University (No: 10/1/2020: 95), the charts of 60 (41 females, 19 males) patients with HAE and the charts of 60 (36 females, 24 males) individuals who had presented for routine health control examination were retrospectively investigated.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences program for Windows (IBM SPSS Inc., Chicago, IL, USA version:20.0). The normal distribution of the data was evaluated with the Kolmogorov-Smirnov test. Numerical variables showing normal distribution were expressed as mean±standard deviation, and numerical variables not showing normal distribution were expressed as median (minimum, maximum). Categorical variables were expressed as numbers and percentages. Chi-Square and Fisher's Exact Chi-Square test were used to compare categorical data. Student T test or Mann-Whitney U test was used to compare numerical variables between two groups according to normality of distribution. ANOVA test (post hoc: Bonferroni test) or Kruskal-Wallis H test (post hoc: Dun's correction) was used in the distribution of numerical variables between groups according to attack frequency. The relationship between numerical variables was evaluated with Spearman correlation analysis. The predictive value of the Beck anxiety score was analyzed using the ROC Curve analysis and Youden index method. P< 0.05 (*) value was accepted as significant in statistical analysis.

Results

The study population consisted of 60 controls (median age: 36 years, 60% female) and 60 patients with HAE (median age: 34 years, 68.3% female). There was no statistically significant difference in age, gender, Body Mass Index (BMI), marital status, income level, and smoking and alcohol habits rates between the HAE and control groups. The ratio of university graduates was lower in the HAE group than in the control group, and the ratio of primary school-high school graduates was higher in the HAE group (Table 1).

Table 1. Demographic characteristics of HAE and controls

Variables	Control n=60	HAE n=60	p
Age, year	36(18-54)	34(18-73)	0.923**
Gender, n(%)			
Female	36(60.0)	41(68.3)	0.447*
Male	24(40.0)	19(31.7)	
Height, cm	167.8±9.4	164±22.7	0.232**
Weight, kg	76.2±11.6	73.1±14.9	0.199**
BMI, kg/cm^2	27.2±4.7	26.6±5.9	0.544**
Marital status, n(%)			
Married	37(61.7)	40(66.7)	0.705*
Single	23(38.3)	20(33.3)	
Education, n(%)			
İlliterate	1(1.7)	1(1.7)	0.001*
Literate	9(15.0)	1(1.7)	
Primary school graduate	-	15(25.0)	
Secondary school graduate	1(1.7)	4(6.7)	
High school graduate	17(28.3)	19(31.7)	
College graduate	32(53.3)	20(33.3)	
Level of income, n(%)			
<2200	12(20.0)	14(23.3)	0.940*
2200-3500	13(21.7)	13(21.7)	
3500-5000	12(20.0)	13(21.7)	
>5000	23(38.3)	20(33.3)	
Smoking, n(%)	7(11.7)	9(15.0)	0.789*
Alcohol, n(%)	3(5.0)	4(6.7)	0.999*

*Chi-Square and Fisher's Exact Chi-Square test. **Student T test or Mann-Whitney U test. Categorical variables were expressed as numbers (%). Numerical variables showing normal distribution were shown as mean±standard deviation, and numerical variables not showing normal distribution were shown as median (minimum, maximum).

The median BAI score (11 vs 5; p=0.001), ratio of patients with moderate anxiety (21.7% vs 1.7%; p =0.001) and ratio of patients with severe anxiety (8.3% vs. 0%; p=0.001) were higher in patients with HAE compared with the control group. The median BDI score (11 vs 7; p=0.024) was found to be high in patients with HAE. There was no statistically significant difference in BDI severity between the HAE and control groups

(Table 2). A positive correlation was found between BAI and BDI scores in both the control group and the HAE group (r = 0.656; p=0.001; r = 0.673; p=0.001, respectively). Median age (39 vs 29; p = 0.004), mean weight (77.2 ± 15.9 vs 67.7 ± 11.7; p = 0.010), and mean BMI (28.4 ± 6.5 vs 24.2 ± 3.9; p = 0.003) were higher in patients with HAE compared with those who did not develop laryngeal edema. Other demographic characteristics and BAI and BDI scores were not correlated with the presence of laryngeal edema (Table 3).

Table 2. BAI and BDI of HAE and control group

Variables	Control n=60	HAE n=60	p
BAI (Beck Anxiety Inventory)	5(0-29)	11(0-38)	0.001**
Anxiety n(%)			
Normal-Mild	59(98.3)	42(70.0)	
Moderate	1(1.7)	13(21.7)	0.001*
Severe	-	5(8.3)	
BDI(Beck Depression Inventory)	7(0-35)	11(0-40)	0.024*
<17, n(%)	52(86.7)	43(71.7)	0.071*
≥17, n(%)	8(13.3)	17(28.3)	
BDI n(%)			
Normal	42(70.0)	31(51.7)	
Mild	10(16.7)	12(20.0)	0.120*
Moderate	7(11.7)	12(20.0)	
Severe	1(1.7)	5(8.3)	

*Chi-Square and Fisher's Exact Chi-Square test. **Student T test or Mann-Whitney U test

Table 3. Demographic characteristics associated with attack frequency in HAE

Variables	Larynx edema		p	Abdominal attack/pain		p
	No n=26	Yes n=34		No n=18	Yes n=42	
Age, year	29(19-59)	39(18-73)	0.004*	43(21-67)	33(18-73)	0.061**
Gender, n(%)						
Female	16(61.5)	25(73.5)	0.405	11(61.1)	30(71.4)	0.547*
Male	10(38.5)	9(26.5)		7(38.9)	12(28.6)	
Height, cm	167.7±8.6	161.2±29.1	0.272	167.4±8.6	162,6±26.5	0.450**
Weight, kg	67.7±11.7	77.2±15.9	0.010*	77.6±15.3	71.2±14.5	0.128**
BMI, kg/cm^2	24.2±3.9	28.4±6.5	0.003*	28.0±6.5	26.0±5.5	0.221**
Marital status, n(%)						
Married	15(57.7)	25(73.5)	0.271	15(83.3)	25(59.5)	0.084*
Single	11(42.3)	9(26.5)		3(16.7)	17(40.5)	
Education, n(%)						
İlliterate	-	1(2.9)		-	1(2.4)	
Literate	-	1(2.9)		-	1(2.4)	
Primary school graduate	7(26.9)	8(23.5)	0.214	6(33.3)	9(21.4)	0.814*
Secondary school graduate	3(11.5)	1(2.9)		1(5.6)	3(7.1)	
High school graduate	5(19.2)	14(41.2)		5(27.8)	14(33.3)	
College graduate	11(42.3)	9(26.5)		5(27.8)	15(35.7)	
Level of income, n(%)						
<2200	9(34.6)	5(14.7)		5(27.8)	9(21.4)	
2200-3500	4(15.4)	9(26.5)	0.261	6(33.3)	7(16.7)	0.404*
3500-5000	4(15.4)	9(26.5)		3(16.7)	10(23.8)	
>5000	9(34.6)	11(32.4)		4(22.2)	16(38.1)	
Smoking, n(%)	3(11.5)	6(17.6)	0.770	1(5.6)	8(19.0)	0.344*
Alcohol, n(%)	2(7.7)	2(5.9)	0.999	1(5.6)	3(7.1)	0.999*
BAI (Beck Anxiety Inventory)	8(0-35)	12,5(0-38)	0.586	10(0-33)	11(2-38)	0.290**
Anxiety, n(%)						
Normal-Minimal	12(46.2)	10(29.4)		7(38.9)	15(35.7)	
Mild	4(15.4)	13(38.2)	0.220	5(27.8)	12(28.6)	0.999*
Moderate	4(15.4)	6(17.6)		3(16.7)	7(16.7)	
Severe	6(23.1)	5(14.7)		3(16.7)	8(19.0)	
BDI(Beck Depression Inventory)	13(0-36)	9(0-40)	0.506	14(0-36)	10(0-40)	0.639*
<17, n(%)	17(65.4)	26(76.5)	0.396	12(66.7)	31(73.8)	0.755*
≥17, n(%)	9(34.6)	8(23.5)		6(33.3)	11(26.2)	
BDI, n(%)						
Normal-Minimal	11(42.3)	19(55.9)		9(50.0)	21(50.0)	
Mild	6(23.1)	7(20.6)	0.718	3(16.7)	10(23.8)	0.883*
Moderate	6(23.1)	6(17.6)		4(22.2)	8(19.0)	
Severe	3(11.5)	2(5.9)		2(11.1)	3(7.1)	

*Chi-Square and Fisher's Exact Chi-Square test. **Student T test or Mann-Whitney U test. BDI≥17=Depression

Demographic characteristics and BAI and BDI scores were not associated with abdominal attacks in patients with HAE compared with those without abdominal attacks (Table 3). In patients with HAE, the mean age at diagnosis was 25 (3–72) years, the mean age of onset of symptoms was 11 (1–65) years, and the mean delay in diagnosis was 12.65 years (standard deviation [SD] 12.20).

The facial swelling rate (85.3% vs 57.7%; p = 0.021) and median total number of attacks without treatment (5 vs 3; p = 0.018) were found to be higher in patients with laryngeal edema compared to those without. There was no statistically significant difference in other clinical features with the presence of laryngeal edema (Table 4).

Table 4. Clinical features associated with the development of attacks in patients with HAE

Variables	HAE total	Larynx edema		p	Abdominal attack/pain		p
		No	Yes		No	Yes	
	n=60	n=26	n=34		n=18	n=42	
Age of diagnosis, year	25(3-72)	22.5(3-59)	26,5(3-72)	0.282**	36(3-65)	21(3-72)	0.024**
Diagnostic delay, n(%)							
No	15(25.0)	10(38.5)	5(14.7)		5(27.8)	10(23.8)	
1-10 year	12(20.0)	6(23.1)	6(17.6)	0.056*	2(11.1)	10(23.8)	0.473*
>10 year	33(55.0)	10(38.5)	23(67.6)		11(61.1)	22(52.4)	
Onset of symptoms, year	11(1-65)	14(1-44)	10(1-65)	0.289**	13(3-65)	10,5(1-53)	0.528**
Angioedema location, n(%)							
Hand	55(91.7)	24(92.3)	31(91.2)	0.999*	17(94.4)	38(90.5)	0.999*
Face	44(73.3)	15(57.7)	29(85.3)	0.021*	12(66.7)	32(762)	0.656*
Genital region	32(53.3)	12(46.2)	20(58.8)	0.435*	8(44.4)	24(57.1)	0.534*
Lower extremity	14(23.3)	7(26.9)	7(20.6)	0.759*	5(27.8)	9(21.4)	0.842*
Other				0.320*			0.700*
Cutaneous swelling episode	2(1-9)	2(1-9)	2(1-9)	0.999**	2(1-8)	2(1-9)	0.741**
Larynx edema, n(%)							
No	26(43.3)	26(100)	-	-	9(50.0)	17(40.5)	0.575*
Yes	34(56.7)	-	34(100)		9(50.0)	25(59.5)	
Larynx edema frequency n(%)							
No	26(43.3)	26(100)	-		9(50.0)	17(40.5)	
Monthly 1	8(13.3)	-	8(23.5)	-	3(16.7)	5(11.9)	0.780*
Yearly 1	7(11.7)	-	7(11.7)		1(5.6)	6(14.3)	
Lifetime 1-2	19(31.7)	-	19(55.9)		5(27.8)	14(33.3)	
Abdominal attacks, n(%)							
No	18(30.0)	9(34.6)	9(26.5)	0.575*	18(100)	-	-
Yes	42(70.0)	17(65.4)	25(73.5)		-	42(100)	
Frequency of abdominal attacks, n(%)							
No	18(30.0)	9(34.6)	9(26.5)		18(100)	-	
1 attack/month	12(20.0)	6(23.1)	6(17.6)	0.547*	-	12(28.6)	-
2-3 attack/month	15(25.0)	7(26.9)	8(23.5)		-	15(35.7)	
4-6 attack/month	15(25.0)	4(15.4)	11(32.4)		-	15(35.7)	
Attacks number with no treatment	7(1-17)	3(0-8)	5(1-10)	0.018**	5(1-11)	8(0-17)	0.002**
Attacks number under treatment	1(0-4)	1(0-4)	1(0-4)	0.161**	0(0-3)	1(0-4)	0.003**

*Chi-Square and Fisher's Exact Chi-Square test. **Student T test or Mann-Whitney U test

Median age at diagnosis was lower in patients with abdominal attacks (21 vs 36; p = 0.024); however, median total number of attacks without treatment (8 vs 5; p = 0.002) and the median total number of attacks under treatment (1 vs 0; p = 0.003) were high. There was no statistically significant difference between other clinical features and the frequency of abdominal attacks (Table 4).

A positive correlation was found between the number of untreated total attacks and BAI score (r = 0.691; p=0.001) and BDI score (r = 0.584; p= 0.001) in patients with HAE. There was no statistically significant difference between the number of attacks under treatment and the BAI and BDI scores. A positive correlation was found between the number of untreated attacks and the number of attacks under treatment and the BAI score (r = 0.759; p=0.001) and BDI score (r = 0.599; p=0.001) (Table 5).

Table 5. Correlations of clinical features associated with the frequency of attacks in patients with HAE

	Number of attacks with no treatment		Number of attacks under treatment		difference	
	r	p	r	p	r	p
Age	0.073	0.582	-0.096	0.463	0.165	0.208
Height	-0.038	0.773	0.244	0.060	-0.134	0.308
Weight	0.031	0.813	0.050	0.703	0.043	0.747
BMI	0.054	0.683	-0.018	0.889	0.092	0.483
BAI	0.691	0.001	0.027	0.837	0.759	0.001
BDI	0.584	0.001	0.099	0.453	0.599	0.001
Diagnostic age	0.076	0.562	-0.113	0.390	0.148	0.258
Diagnostic delay	0.096	0.468	0.001	0.992	0.131	0.319
Onset of symptoms	0.142	0.278	-0.127	0.333	0.198	0.130

*Student T test or Mann-Whitney U test

The median number of attacks with no treatment was found to be higher in HAE patients with abdominal attacks compared to those without abdominal attacks (8 vs 5; p=0.002). İt was determined that the number of attacks without treatment increased as the frequency of abdominal attacks increased. The median number of attacks under treatment was found to be higher in patients with high school or higher education compared

to those with less than high school education (1 vs 0; p=0.028), in smokers (2 vs 1; p=0.036) and those with abdominal attacks (1 vs 0; p=0.003). As the frequency of abdominal attacks increased, the median total number of attacks under treatment increased. The difference between the frequency of attacks without treatment and the frequency of attacks while receiving treatment was found to be high in those with abdominal attacks (6 vs 4; p=0.017). The median number of attacks under treatment increased as the frequency of abdominal pain attacks increased (Table 6).

Table 6. Demographic, clinical findings and frequency of attacks in HAE

	Number of attacks with no treatment	p	Number of attacks under treatment	p	Difference	p
Gender						
Female	6(3-16)	0.581	1(0-4)	0.123	6(2-16)	0.968
male	8(1-17)		1(0-4)		6(1-17)	
Marial status						
Married	7(1-17)	0.705	1(0-4)	0.804	6(1-17)	0.800
Single	7(3-16)		1(0-3)		6(2-16)	
Education						
Under high school	6(3-17)	0.858	0(0-2)	0.028	6(3-17)	0.463
High school and college	7(1-16)		1(0-4)		6(1-16)	
Level of income						
<2200	6(3-12)	0.727	0(0-3)	0.094	6(2-11)	0.983
2200-3500	6(4-15)		1(0-3)		5(3-14)	
3500-5000	7(3-14)		1(0-4)		6(3-11)	
>5000	8(1-17)		1(0-4)		6(1-17)	
Smoking						
No	6(1-17)	0.092	1(0-4)	0.036	6(1-17)	0.218
Yes	10(3-13)		2(0-4)		7(3-12)	
Alcohol						
No	7(1-17)	0.447	1(0-4)	0.228	6(1-17)	0.678
Yes	9(4-13)		2(1-2)		7(3-12)	
Diagnostic delay						
No	4(1-12)	0.458	1(0-3)	0.446	4(1-11)	0.218
1-10 years	10(3-16)		1(0-4)		8(2-16)	
>10 years	7(3-17)		1(0-4)		6(3-17)	
Larynx edema						
No	6(1-16)	0.165	1(0-4)	0.161	5(1-16)	0.229
Yes	7(3-17)		1(0-4)		6(3-17)	
Frequency of larynx edema						
No	6(1-16)	0.324	1(0-4)	0.446	5(1-16)	0.354
1attack/month	11(3-17)		1(0-3)		8(3-17)	
1attack/year	6(4-15)		1(1-2)		5(3-14)	
1-2/ lifetime	7(3-14)		1(0-4)		6(3-12)	
Abdominal attacks						
No	5(1-11)	0.002	0(0-3)	0.003	4(1-11)	0.017
Yes	8(3-17)		1(0-4)		6(2-17)	
Frequency of abdominal attacks						
No	5(1-11)	0.001	0(0-3)	0.007	4(1-11)	0.004
≤1/month	6(3-10)		1(0-3)		5(2-10)	
2-3/month	8(3-13)		1(0-4)		7(3-12)	
4-6/month	10(6-17)		1(0-4)		8(4-17)	

*Chi-Square and Fisher's Exact Chi-Square test

The cut-off value for the BAI scores in patients with HAE compared with the control group was found to be > 9, with 55% sensitivity and 86.7% specificity (AUC ± SE = 0.745 ± 0.05; p=0.001). The cut-off value for the BDI scores was found to be > 7, with sensitivity of 63.3% and specificity of 56.7% (AUC ± SE = 0.619 ± 0.05; p = 0.020) (Figure 1).

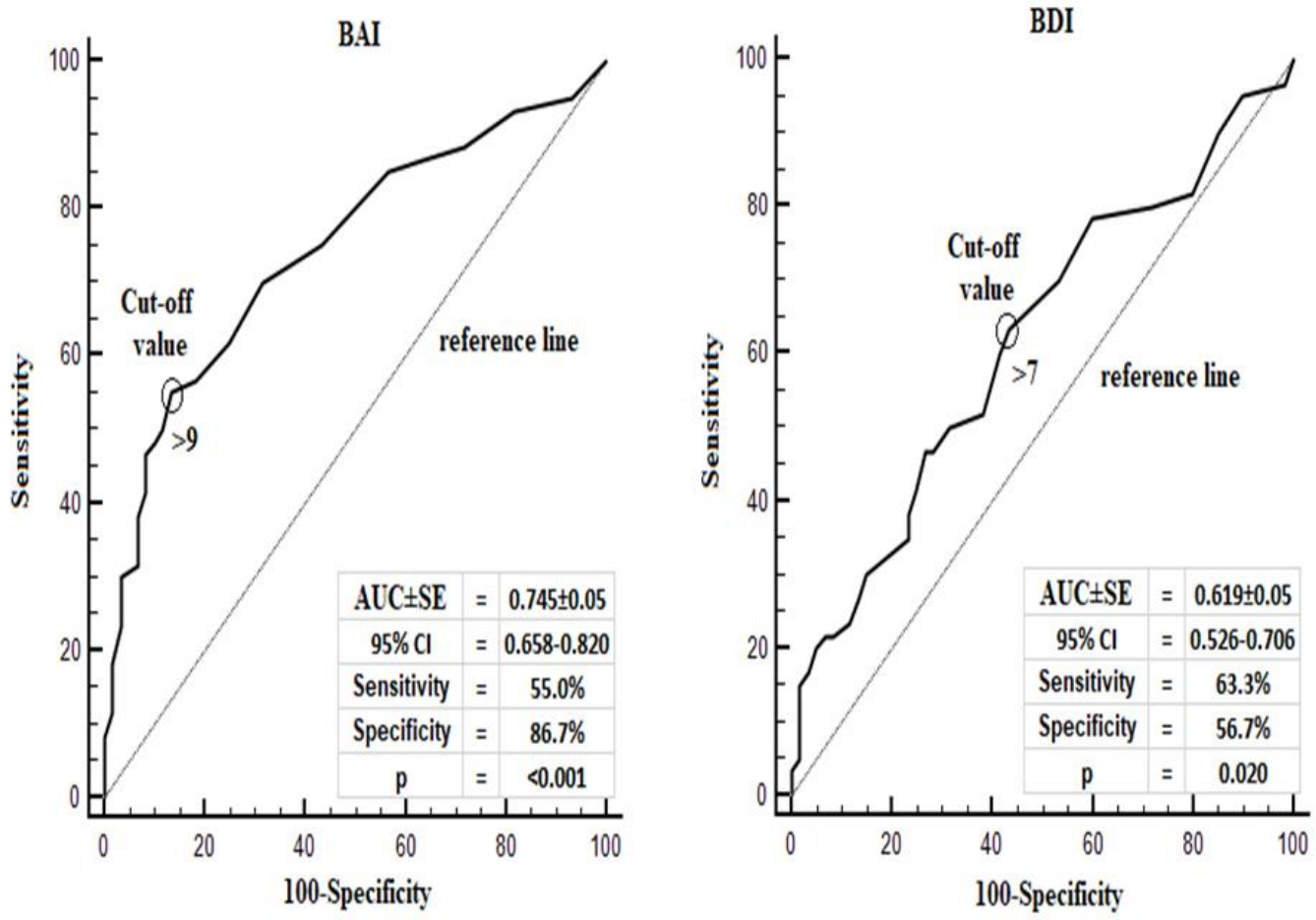

Figure 1. Cut off values of BAI and BDI in HAE

*ROC Curve analysis and Youden index method

Discussion

Since HAE is a disease that progresses with attacks, it is important to determine the situations that trigger the attacks. However, it has been shown that symptoms of anxiety and depression are common in patients with HAE, and these may trigger HAE attacks. Due to unpredictable and spontaneous attacks, anxiety sensitivity may be high in patients with HAE. An increase in HAE attacks may lead to anxiety. Furthermore, the authors reported severe levels of depression among 26 patients[7]. Another feature of HAE is the variability of attack frequency and severity observed among the patients during their lifetime. As a result, some patients with HAE may have severe and frequent attacks and receive long-term treatment, whereas others may receive on-demand treatment for mild disease. HAE not only cause of short-term disability associated with attacks, but also may lead to the development of persistent anxiety between attacks. Savarese et al. examined 21 articles on HAE by using the keywords psychology, anxiety, stress, and depression[14]. Although the articles confirm that stress can induce a variety of physical diseases, the authors concluded that multiple factors contribute to HAE expression. In our study, we found a statistically significant difference in median BDI and BAI scores between the HAE group and the control group. In addition, there was a positive correlation between the total number of attacks before treatment and BAI and BDI scores; however, no significant correlation was found with the total number of attacks after treatment that reduced the number of attacks with treatment.

Anxiety and depression disorders were detected in patients with HAE, family caregivers' narratives, and ad hoc questionnaires administered to adult patients[15, 16, 17, 18]. Reported anxiety and depression levels of these patients were found to be higher than in the controls[7, 17, 19, 20]. Bygum et al. found symptoms of depression in 42% of patients[21]. Anxiety and depression were common comorbidities, affecting 35.3% and 20.9% of patients, respectively [22]. Consistent with the literature, we found a significant difference in median BDI and BAI scores between the HAE group and control group. We detected symptoms of depression (mild, moderate, severe) in 48.5% of patients with HAE by using the BDI. İn our study, 68.3% of the patients were female, the mean age at onset of symptoms was 11 years, the mean age at diagnosis was 25 years, and the delay in diagnosis was approximately 12 years. A recent study reported that in females (78.2%), mean (SD) age at onset of symptoms and age at diagnosis were 12.5 (9.1) and 20.1 (13.7) years, respectively, with a mean delay in diagnosis of 8.4 (10.6) years. Delay in diagnosis was found to be 13 years in a study conducted in Spain in 2005 [23], 10 years in a study conducted in 2009 [24], and 13 years in a study conducted in 2018 in Brazil [25], and the results are similar to those of our study. Similarly, Jolles et al. found that the delay in diagnosis was 10 years in their study[26].

However, in the same study, no delay in diagnosis was found in 3% of the patients because of disease in their family members. The reason why this rate is high in our country (25%, 15 patients) may be due to the earlier marriage age.

In a recent study with 445 patients with HAE, abdomen (58.0%) and extremities (46.1%) were commonly affected sites. According to the Hospital Anxiety and Depression Scale, 49.9% and 24.0% of respondents had anxiety and depression, respectively. Anxiety and depression were common comorbidities, affecting 35.3% and 20.9% of patients, respectively. Although two-thirds of patients in this survey used prophylactic medications (primarily C1-INH products or androgens) on an ongoing basis over the past year, they experienced high frequency of attacks and a high rate of anxiety and depression [22]. It was found that 28.3% had a BDI score ≥ 17 and 30% had a BDI score representing a moderate or severe level. Although the difference between the studies was due to the small number of patients and their evaluation with different scales, the rates of depression and anxiety were found to be high in patients with HAE.

In a study of 249 patients, the annual frequency of swellings per patient affecting the subcutaneous tissue was 8, abdomen 5, and airway 0.5 [26]. In our study, the total number of attacks of the patients under treatment was 1 (0–4) per month. When the number of attacks is taken annually instead of monthly, it can be seen that the total number of attacks is similar. Pre-treatment abdominal attacks were present in 70% of the patients. Facial subcutaneous swelling (73.3%) was detected as the most common attack in our study. Swelling attacks of extremities (hand, lower extremity) were common (91.7%, 23.3%). In a study of 51 patients with HAE, subcutaneous edema was found most frequently at a rate of 93.5% (43/46) [25]. Perricone et al. [27] detected 96.6% abdominal attack, 100% subcutaneous tissue edema mostly in the face (83.3%) in HAE patients. In the same study, no statistically significant difference was found between the patient and control groups in the mean BDI score. Similar to this study, we detected subcutaneous swelling in 59 of 60 patients; however, in our study, there was no statistically significant difference between the HAE and control groups in the BDI score. These differences may be due to the fact that the number of patients in our study was double the number of patients in this study.

In a long-term follow-up study examining the factors triggering attacks according to the attack sites, it was shown that emotional stress triggered abdominal pain attacks and it was found to be statistically significant. Furthermore, the authors reported that the most common trigger factor of attacks was emotional stress [6]. Although BDI and BAI scores were found to be higher in those without abdominal pain attacks, no statistically significant difference was found.

The BMI of patients with HAE was 26.6 ± 5.9 and they were overweight. There was no statistically significant difference between BMI and the total number of attacks before and after the treatment. No significant correlation was found between abdominal pain attacks of abdomen and laryngeal attacks and mean BMI. Similarly, in the study conducted by grouping 342 patients according to their BMI, there was no significant difference in frequency and severity of attacks across BMI groups. BMI did not have an effect on the frequency of laryngeal attacks, but abdominal pain attacks were less frequent in those with a normal BMI [28]. In our study, BMI was used as the median value, and grouping was not used.

We found depression (mild, moderate, severe) in 48.3% of 60 patients who completed the BDI and BAI (moderate and severe) in 30% of patients. A larger study of almost 500 participants found that 42.5% [9] of participants were experiencing depression according to the 9-item HDI-SF. In a recent study including 26 patients with HAE, 39% of participants were identified as experiencing depression of mild (50%), moderate (40%) or severe (10%) levels. Moreover, 15% of participants displayed prominent anxiety, 50% of whom had mild anxiety, 25% moderate anxiety, and 25% severe anxiety [7].

In our study, the median BAI and BDI scores and the rate of moderate and severe anxiety were found to be statistically significantly higher in the HAE group than in the control group. Although the number of patients and the scales used varied between studies, the rate of depression and anxiety was found to be high in the HAE group, similar to the studies in the literature. The cut-off value for the BAI score in patients with HAE compared with the control group was found to be > 9, with 55% sensitivity and 86.7% specificity. The cut-off value for the BDI score was found to be > 7, with sensitivity of 63.3% and specificity of 56.7%.

Furthermore, as shown in previous studies [29], higher frequency of attacks was generally associated with a greater burden of illness, including worsening anxiety and depression, and increased work and activity impairment. As a result of the high prevalence of depression reported in this patient population, health care providers caring for patients with HAE should be conscient of this comorbidity and refer patients to mental health specialists when needed.

Limitations

The limitation of our study was its retrospective design and the data being obtained from files. Another limitation was a cross-sectional study and could not identify a clear cause–effect relationship.

Conclusions

Our data demonstrated that depression and anxiety symptoms are more common in patients with HAE than in the control group. Anxiety and depression can be seen as cause or effect in patients with HAE. Therefore, mental health support or treatment should be provided when these are considered as factors triggering attacks or as a result of angioedema.

Conflict of interest: There is no conflict of interest in our study.

Author Contributions		Author Initials
SCD	Study Conception and Design	GO, MB
AD	Acquisition of Data	GO
AID	Analysis and Interpretation of Data	GO, MB
DM	Drafting of Manuscript	GO, MB
CR	Critical Revision	GO

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