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Earthquake as a Trigger of Acute Attacks in People with Hereditary Angioedema

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Abstract

Objectives: Two major earthquakes with 7.7 and 7.6 magnitudes struck the southeastern region of Turkey on February 6th, 2023. Hereditary angioedema (HAE) is an inherited disease that can be worsened by psychological factors and physical trauma.Our study aimed to evaluate the effect of earthquake and earthquake-related anxiety, depression and stress factors in HAE patients.

Methods: The study was conducted on patients with HAE who are located in the southeastern region of Turkey.The mental-health-status was evaluated with Depression-Anxiety-Stress-Scale(DASS-21).

Results: Sixty-three HAE patients were includedin the study. More than half(n:33, 52.4%) were female andthe median age was 31(26-42) years. DASS-Stress, DASS-Anxiety,and DASS-Depression scores revealed that 25(39.7%), 37(58.7%) and 32(50.8%) patients had abnormal stress, anxiety and depression status, respectively. The numbers of post-earthquake attacks and icatibant injections were significantly higher than the ones in the pre-earthquake period(p<0.001). The attacks in the post-earthquake period were more severe than those in the pre-earthquake period(p<0.001). In the correlation analysis, the damage level in the buildings significantly correlated with the number of attacks and attack severities in the post-earthquake period(p:0.025, r:0.281 and p:0.042, r:0.257; respectively).

Conclusions: The study revealed an increase in both the number and severity of attacks among HAE patients following the earthquake. Positive correlations between the number, and severity of HAE attacks and DASS-21 anxiety, stress and depression were observed.Hence, it is crucial to offer psychological support to HAE patients in the event of an earthquake.

Keywords: Earthquake, Hereditary angioedema, Depression-Anxiety-Stress, Fear of Earthquake

Deprem Herediter Anjiyoödemde Akut Atakların Tetikleyicisidir

Öz

Amaç: 6 Şubat 2023'te Türkiye'nin Güneydoğu bölgesinde 7.7 ve 7.6 büyüklüğünde iki büyük deprem gerçekleşti. Herediter anjiyoödem (HAÖ), psikolojik faktörler ve fiziksel travmalarla daha da kötüleşebilen kalıtsal bir hastalıktır. Çalışmamızın amacı HAE hastalarında deprem ve depreme bağlı anksiyete, depresyon ve stres faktörlerinin etkisini değerlendirmektir.

Yöntemler: Türkiye'nin Güneydoğu bölgesindeki üç şehirde üçüncü basamak immünoloji merkezinde psikiyatrik tanısı olmayan ve/veya psikiyatrik ilaç kullanmayan HAÖ hastaları dahil edildi. Depresyon-Kaygı-Stres Ölçeği (DASS-21) kullanıldı.

Bulgular: Çalışmaya 63 HAÖ hastası dahil edildi. Yarısından fazlası (n:33, %52.4) kadındı ve ortanca yaş 31 (26-42) yıldı. DASS-Stres, DASS-Anksiyete, DASS-Depresyon skorları sırasıyla 25 (%39,7), 37 (%58,7) ve 32 (%50,8) hastaların anormal stres, anksiyete ve depresyon durumuna sahip olduğunu gösterdi. Deprem sonrası atak ve ikatibant enjeksiyon sayıları deprem öncesine göre anlamlı derecede yüksekti (p<0.001). Deprem sonrası ataklar, deprem öncesine göre daha şiddetliydi (p<0.001). Korelasyon analizinde binalardaki hasar düzeyinin deprem sonrası atak sayısı ve şiddeti ile anlamlı düzeyde ilişkili olduğu görüldü (sırasıyla p:0.025, r:0.281 ve p:0.042, r:0.257).

Sonuç: Herediter anjiyoödem hastalarında deprem sonrasında atakların hem sayısında hem de şiddetinde artış olduğunu saptadık. HAÖ ataklarının sayısı ve şiddeti ile DASS-21 anksiyete, stres ve depresyon arasında pozitif korelasyon gözlendi. Bu nedenle HAÖ hastalarına deprem anında psikolojik destek sağlanması büyük önem taşımaktadır.

Anahtar kelimeler: Deprem, Herediter anjiyoödem, Depresyon-Anksiyete-Stres, Deprem korkusu.

INTRODUCTION

Hereditary angioedema (HAE) is a rare genetic disease. HAE causes recurrent, unpredictable and, nonpruritic episodes of edema in various mucosal or submucosal areas of the body, such as the face, larynx, extremities, and gastrointestinal or genitourinary systems. Sometimes attacks can be fatal. Although most attacks occur spontaneously, mechanical trauma, infection, hormonal changes, emotional stress, anxiety, and depression are possible triggers[1].

KahramanmaraşPazarcık earthquake (7.7-magnitude) and Elbistan earthquake (7.6-magnitude) that took place consecutively on February 6, 2023, caused devastating damage to 10 cities, especially in the Southeastern Anatolia region. There were over fifty thousand deaths. After the earthquake, emotional changes were expected to occur in HAE patients considering their unawareness about the course of their disease and the effects of disease-related medications. Hereditary angioedema control is also important because diseases that progress with attacks such as hereditary angioedema in disasters will create a patient burden in health institutions. The mechanism involved in HAE-C1-INH is a lack of control of the contact and kallikrein-kinin systems, resulting in bradykinin (BK) release, after high-molecular-weight kininogen cleavage by kallikrein. Accordingly, long-term prophylaxis drugs (danazol and tranexamic acid), c1 esterase inhibitors (pC1-INH, intravenous) and bradykinin receptor antagonists (icatibant, subcutaneous) used in acute attacks are included in its treatment. In natural disasters, it may be a problem for them to reach their treatment. There may be patients who need a dose increase or additional treatment.

Previous studies indicated that HAE attack numbers, DASS-21 stress, anxiety, depression and total DASS-21 scores,were higher in COVID-19 quarantine period[2].

There are no studies in the literature that examined the exacerbation frequency of patients with HAE during an earthquake. We aimed to contribute valuable data to increase the clinical knowledge about attacks on HAE patients with this study. Our study aimed to evaluate the effect of earthquake and earthquake-related anxiety, depression and stress factors in HAE patients.

METHOD

Study design

In our multicenter study, in the Immunology and Allergy outpatient clinics of tertiary care centers in Şanlıurfa, Gaziantep, and Batman, between April 2023 and May 2023, a questionnaire was applied to hereditary angioedema patients without psychiatric diagnosis and/or receiving psychiatric medications.Patients older than 18 years of age,who have been diagnosed with hereditary angioedema (HAE) in accordance with the latest guidelines from WAO/EAACI[3]. In adherence to the Declaration of Helsinki, the study received approval from the ethics committee at University of Health Sciences, Mehmet AkifInan Training and Research Hospital(Approval No:HRÜ/23.05.12, Date:27.03.2023). Informed consent forms were obtained from the patients.

Populations and scales

Demographic information (age, gender, marriage status, educational status, occupation), comorbid conditions, duration of HAE, HAE medications used, emergency admission due to an attack before and after the earthquake, and hospitalizations were recorded. Injuries in the earthquake, the level of damage to their houses, and whether there were deceased relatives were questioned. The status of obtaining and using medicines after the earthquake was questioned.

The severity of HAE attacks was assessed with a 10-point visual analogue scale (VAS10)[4].The mental health status was evaluated with Depression-Anxiety-Stress-Scale (DASS-21) and Fear-of-Earthquake-Scale (FES). Psychological factors were appraised by the Turkish version of Depression, Anxiety and Stress Scales-21 (DASS-21) which is a 4-point Likert scale, consisting of 21 items with three dimensions of 7 items for each scale with a rating system ('0' = Never; '1' = Sometimes; '2' = Frequently; and '3' = Always) to measure depression, anxiety and stress, separately[5-7].Earthquake fear test; It consists of seven items rated by participants on a 5-point Likert scale (1 "strongly disagree" and 5 "strongly agree"). By calculating the average score, higher scores indicate a greater fear of earthquakes[8].

Statistical Analysis

The statistical analysis was conducted using version 24 of the SPSS software.Frequency and percentage summaries were utilized for categorical variables.Continuous variables were given as mean values and standard deviations or median (IQR or minimum-maximum) values according to the distribution of the data. The Wilcoxon test was employed to compare non-normally distributed data.To assess distinct groups, both the Mann-Whitney U test and the Kruskal-Wallis test were performed.The distribution of numerical data was determined using the Kolmogorov-Smirnov test, while the comparison of categorical variables was performed using the Chi-square test (or Fisher's exact test for frequencies <5). The relationship between the number of HAE attacks per one-month period in post-earthquake, severity and DASS-21, and FES were analysed by Spearman's correlation test. The two-sided $p < 0.05$ determined the statistical significance.

RESULTS

Demographic characteristics of the study population

The demographic and clinical characteristics of 63 patients are listed in Table 1. Of these, 62 (98.4%) had type I, and one (1.6%) had type II HAE. The

median age was 31 years (26-42 years) and 33 were women (52.4%).The median symptom duration of HAE was 14 years (6-23 years). The median onset age of HAE was 17 years (12–21 years). A total of 10 patients were being followed up under long-term prophylaxis, seven patients were on danazol, and three patients were on tranexamic acid.

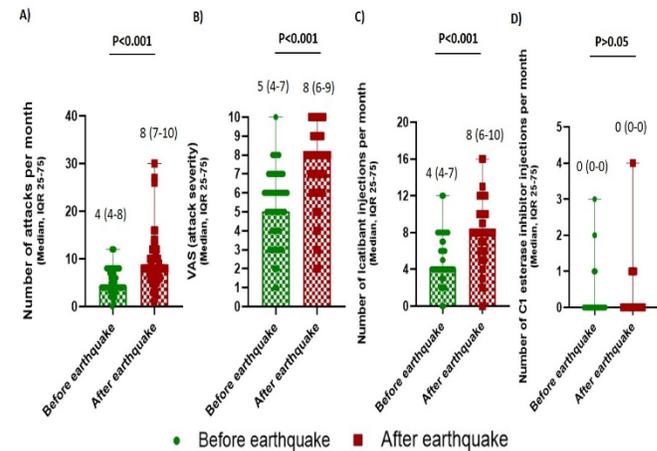**Table I:** Demographic characteristics of HAE patients.

Clinical Characteristics	Total (N = 63)
Female ,n (%)	33 (52.4)
Age (years) (median, IQR)	31 (26-42)
Body Mass Index (mean±SD)	26.38±4.08
Smoker,n (%)	13 (20.6)
Alcohol consumption,n (%)	7 (11.1)
Marriage status,n (%)	
Single	15 (23.8)
Married	45 (71.4)
Widow	1 (1.6)
Divorced	2 (3.2)
Education status,n (%)	
Illiterate	3 (4.8)
Literate	8 (12.7)
Primary	27 (42.9)
High school	17 (27)
University	8 (12.7)
Employment status,n (%)	
Employed	29 (46)
Unemployed	31 (49.2)
Retired	1 (1.6)
Student	2 (3.2)
HAE symptoms, n (%)	
Pre-earthquake	
Abdominal	51 (81)
Larenx	21 (33.3)
Face	26 (41.3)
Extremity	52 (82.5)
Genital	14 (22.2)
Post-earthquake	
Abdominal	40 (63.5)
Larenx	20 (31.7)
Face	19 (30.2)
Extremity	41 (65.1)
Genital	12 (19)
HAE attack number (mean±SD)	
Pre-earthquake	5.2 ± 2.6
Post-earthquake	9.2 ± 5.2
Long term prophylaxis,n (%)	
Danazol	7 (11.1)
Tranexamic acid	3 (4.8)
C1 esterase inhibitor	0 (0)
None	53 (84.1)
HAE type,n (%)	
Type 1	62 (98.4)
Type 2	1 (1.6)
C4 level (median, IQR) (mg/dl) (n:62)	4 (2-7)
C1 esterase inhibitor level (median, IQR) (mg/dl) (n:62)	5.77 (4-8.82)
C1 esterase inhibitory function (%) (n:1)	<10

HAE, hereditary angioedema; IQR, interquartile range; SD, standard deviations

Physical condition after the earthquake

The effect of an earthquake on the course of hereditary angioedema according to individual answers was worsened in 45 (71.4%) patients, and not affected in 18 (28.6%) patients. The median (IQR) attacks of HAE were 8 (7-10) after the earthquake. The most common symptoms after the earthquakeincluded extremity edema (65.1%), abdominal pain (63.5%), larynx edema (31.7%), face edema (30.2.5), and genital edema (19%).

The use of icatibant after the earthquake was 61 (96.8%). The numbers of post-earthquake attacks and icatibant injections were significantly higher than the ones in the pre-earthquake period (p<0.001) (Figure 1). The use of C1 esterase inhibitors after the earthquake was 12 (19%). C1 esterase inhibitor use did not significantly change (p>0.05). The median (IQR) VAS10 for attack severity was 8 (6-9). The attacks in the post-earthquake period were more severe than those in the pre-earthquake period (p<0.001) (Figure 1).

Figure 1. (A) Median number of HAE attacks in pre- and post-earthquake, **(B)** The median VAS severity scores of HAE attacks in pre- and post-earthquake, **(C)** Median number of icatibant injections in pre- and post-earthquake, **(D)** Median number of c1 esteraseinhibitor injections in pre- and post-earthquake. Abbreviations: IQR, interquartile range; VAS, visual analogue scale; HAE, hereditary angioedema

Psychological condition after the earthquake

As shown in Table 2, DASS-Stress, DASS-Anxiety, DASS-Depression subscale analysis revealed that 25(39.7%), 37(58.7%) and 32(50.8%) patients

had abnormal stress, anxiety and depression status, respectively. DASS-Stress, DASS-Depression, DASS-21 total scores and FES scores were significantly higher in women than men. Although the rate of patients with worsened HAE during the earthquake was higher in women (60%) than men (40%), it was not statistically significant (p=0.06). DASS-Stress, DASS-Anxiety, DASS-Depression and FES scores were significantly higher in patients with worsened HAE during earthquake than others (Table 3). Positive correlations between the number, and the severity of HAE attacks and DASS-21 anxiety, stress and depression were observed in Table 4.

Table II: The frequencies of DASS-21 and FES scale analysis in HAE patients after earthquake

	N =63	Female (n=33)	Male (n=30)	P value
DASS-Stress analysis, n (%) **Normal** **Mild** **Moderate** **Severe** **Very severe**	38 (60.3) 6 (9.5) 6 (9.5) 10 (15.9) 3 (4.8)	16 (48.5) 5 (15.2) 2 (6.1) 9 (27.3) 1 (3)	22 (73.3) 1 (3.3) 4 (13.3) 1 (3.3) 2 (6.7)	0.06
DASS-Anxiety analysis, n (%) **Normal** **Mild** **Moderate** **Severe** **Very severe**	26 (41.3) 8 (12.7) 2 (3.2) 5 (7.9) 22 (34.9)	11 (33.3) 5 (15.2) 1 (3) 1 (3) 15 (45.5)	15 (50) 3 (10) 1 (3.3) 4 (13.3) 7 (23.3)	0.12
DASS-Depression analysis, n (%) **Normal** **Mild** **Moderate** **Severe** **Very severe**	31 (49.2) 6 (9.5) 10 (15.9) 6 (9.5) 10 (15.9)	13 (39.4) 3 (9.1) 4 (12.1) 6 (18.2) 7 (21.2)	18 (60) 3 (10) 6 (20) 0 3 (10)	**0.04**
Scores of DASS-Stress, median (min-max)	6(0-18)	8 (0-18)	5(0-18)	**0.01**
Scores of DASS-Anxiety, median (min-max)	5(0-20)	7(0-20)	4(0-18)	0.07
Scores of DASS-Depression, median (min-max)	5(0-19)	7(0-18)	2(0-19)	**0.01**
Total scores of DASS-21, median (min-max)	18(0-54)	23(0-53)	10.5(0-54)	**0.02**
Fear of earthquake Scale, median (min-max)	25 (7-35)	27(7-35)	20.5(7-35)	**0.04**

DASS, Depression-Anxiety-Stress-Scale;IQR, interquartile range

Table III: Clinical characteristics of patients according to AE attacks status after earthquake

	Patients with worsened HAE during earthquake (n = 45)	Patients without (n = 18)	P value
Gender, n (%) Female Male	27 (60) 18 (40)	6 (33.3) 12 (66.7)	0.06
Age (years), median(min-max)	29 (18-77)	35 (21-63)	0.17
Body Mass Index, mean ± SD	26.6 ± 4.1	25.9 ± 4.04	0.53
HAE attack number, mean ± SD Pre-earthquake Post-earthquake	4.7 ± 2.3 10.2 ± 5.4	6.3 ± 3 6.6 ± 3.6	**0.02** **0.01**
HAE attack severity, median (min-max) Pre-earthquake Post-earthquake	5 (1-10) 8 (5-10)	6.5 (2-8) 6 (2-8)	0.14 **<0.001**
Long term prophylaxis, n (%) Danazol Tranexamic acid C1 esterase inhibitor	3 (6.7) 1 (2.2) 0	4 (22.2) 2 (11.1) 0	0.95* 0.19* 0
Damage level in buildings, n (%) Intact Slightly damage Moderately damaged Severely damaged Collapsed	14 (32.6) 21 (48.8) 5 (11.6) 3 (7) 0 (0)	8 (44.4) 10 (55.6) 0 (0) 0 (0) 0 (0)	0.38 0.63 0.31* 0.55* 0
Death in the first degree relatives,n (%)	3 (6.7)	0 (0)	0.55*
Death in their acquaintances, n (%)	16 (35.6)	1 (5.6)	**0.03***
Scores of DASS-Stress, median (min-max)	8 (0-18)	1.5 (0-9)	**<0.001**
Scores of DASS-Anxiety, median (min-max)	9 (0-20)	2 (0-12)	**<0.001**
Scores of DASS-Depression, median (min-max)	8 (0-19)	1 (0-10)	**<0.001**
Total scores of DASS-21, median (min-max)	23 (0-54)	6 (0-25)	**<0.001**
Fear of earthquake Scale, median (min-max)	28 (8-35)	12 (7-30)	**<0.001**

HAE, hereditary angioedema; IQR, interquartile range; SD, standard deviations;DASS, Depression-Anxiety-Stress-Scale

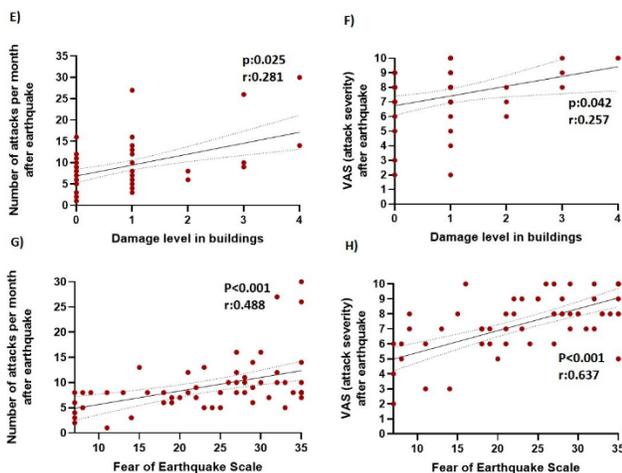**Table IV:** The correlation analyses between psychological features and frequency and severity of HAE attacks

	Number of attacks		Severity of attacks	
	r	p	r	p
DASS-21 stress	0.517	<0.001	0.646	<0.001
DASS-21 anxiety	0.409	0.001	0.529	<0.001
DASS-21 depression	0.518	<0.001	0.624	<0.001
DASS-21 total	0.497	<0.001	0.628	<0.001
FES	0.488	<0.001	0.637	<0.001

DASS-21, Depression, Anxiety and Stress Scales-21; FES, Fear-of-Earthquake-Scale

Health conditions and medications after the earthquake

Three (4.8%) patients lost their first-degree relatives and 17 (27%) patients lost acquaintances in the earthquake.

The damage to the houses of the patients due to earthquakes was intact in 22 (34.9%), slightly damaged in 31 (49.2%), moderately damaged in 5 (7.9%), severely damaged in 3 (4.8%), and collapsed in 2 (3.2%). In the correlation analysis, the damage level in the buildings significantly correlated with the number of attacks and attack severity in the post-earthquake period (p:0.025, r:0.281 and p:0.042, r:0.257; respectively) (Figure 2).

Figure 2. The number and severity of HAE attacks after the earthquake according to the damage level in the buildings and FES score. Abbreviations: VAS, visual analogue scale; HAE, hereditary angioedema; FES, Fear-of-Earthquake-Scale

After the earthquake, 7 (11.1%) patients had problems in accessing icatibant. While 8 (12.7%) patients applied to the emergency department (ED), 14 (22.2%) patients did not go to the ED due to fear of earthquakes even though they needed it.

DISCUSSION

Until now, there have been no published studies assessing the impact of earthquake-induced mental health issues on the progression of HAE, making our findings significant in this regard. First, for about 70% and 50% of patients with HAE, the experience of the earthquakes exacerbated their physical and psychological symptoms, respectively. Second, about 10% of the patients with HAE experienced an interruption in medical welfare services following the earthquakes.

In the present study, patients with HAE experienced a significant increase in the number and severity of attacks after the earthquakes. While individuals with HAE often characterize most of their attacks as occurring without warning, stress emerges as the most commonly recognized triggering factor[1]. In other research, stress emerged as the most commonly cited trigger, with trauma and infection following closely behind[9,10].

In our post-earthquake study, we observed a significant correlation between the number and severity of HAE attacks and psychological factors, including depression, anxiety, stress, and earthquake-related fear. These psychological parameters were assessed using two validated tools, namely DASS-21 and FES. In a study conducted by Karabacak et al., similar to our research, they reported positive correlations between the frequency and severity of HAE attacks and DASS-21 anxiety, stress, and depression scores, as well as the DASS-21 total scores, during the COVID-19 pandemic[2].

In our study, anxiety was observed in 58.7% of hereditary angioedema patients following the earthquake, while depression was detected in 50.8%. In patients with HAE, clinically significant anxiety symptoms have been reported by up to 15–46%, and relevant depressive symptoms have been observed in 18–42%[11,12].In the general population, the prevalence of depression after the Kumamoto earthquakes has been reported as 20.2%[13]. After conducting a systematic review and meta-analysis of studies pertaining on the 2010 Haiti earthquake, it was determined thatthe median prevalence of anxiety and depression in participants was 20.5% and 32.2%, respectively[14]. In our study, we were unable to examine the impact of pre-earthquake anxiety and depression statuses on the course of attacks as these were unknown for the patients. However, in our study, when compared with the literature, we observed elevated rates of anxiety and depression in measurements taken after the earthquake, both in comparison to typical HAE patients and to the post-earthquake population. In our study, the high prevalence of anxiety and depression among hereditary angioedema patients may be attributed to the fact that they already suffer from a life-threatening condition, which is further compounded by the occurrence of a natural disaster.

In our study, female patients exhibited significantly higher rates of anxiety, depression, and fear compared to their male counterparts following the earthquake. In the study by Christiansen et al., significantly higher rates of anxiety and depression were reported in women with HAE compared to men during the COVID-19 pandemic[15].It is well-established that the prevalence of depression is higher in women than in men, even in non-disaster or non-pandemic contexts[16].Furthermore, in the case of HAE, women have consistently exhibited a higher propensity for experiencing more severe manifestations compared to their male counterparts, as reported in various studies[17].However, in our study, while women exhibited a more pronounced deterioration in their HAE compared to men, this discrepancy did not achieve statistical significance.

In the research about the Great East Japan Earthquake, severe damage to the home and disruption of psychiatric care were reported as predictors of depressive symptoms after a big earthquake[18].In our study, we observed a significant correlation between the level of damage in buildings and the number of attacks as well as their severity during the post-earthquake period. In addition to other earthquake victims, psychological and healthcare support should be provided particularly to HAE patients with severely damaged buildings.

The number of patients who lost access to their medications was lower than our initial expectations. It would serve patients with HAE well to always have at least a month of medicine available. The prompt regulatory measures implemented by the Ministry of Health to facilitate access to registered medications without requiring a prescription may have played an effective role. It is essential to keep in mind the importance of establishing consistent protocols for all earthquakes.

There are several limitations to this study. Firstly, the inability to assess the mental health status of our patients using identical scales during the pre-earthquake period limited our ability to draw more precise conclusions. Nevertheless, we believe that by excluding individuals who were on psychiatric medications or had psychiatric diagnoses, we have bolstered the robustness of our findings. Second, we could not compare our findings with a healthy control group exposed to the earthquake.

CONCLUSION

We identified the impacts of significant earthquakes on patients with HAE. The mental well-being of the patients was more susceptible to deterioration than their physical health.

In our study, we discovered that psychological factors, including anxiety, depression, stress, and fear, have the potential to exert a detrimental impact on the disease progression in individuals with HAE. This could potentially account for the heightened frequency of HAE attacks. As a result, it is recommended that individuals with HAE should be provided with early psychological support to address anxiety, stress, depression, and fear in the event of an earthquake.

Ethics Committee Approval: In adherence to the Declaration of Helsinki, the study received approval from the ethics committee at University of Health Sciences, Mehmet AkifInan Training and Research Hospital(Approval No:HRÜ/23.05.12, Date:27.03.2023). Informed consent forms were obtained from the patients.

Conflict of Interest: The authors declared noconflicts of interest.

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