

Title page

Impact of anxiety, stress and depression related to COVID-19 pandemic on the course of hereditary angioedema with C1 inhibitor deficiency

Running head: COVID-19 and hereditary angioedema

Deniz Eyice Karabacak¹, Semra Demir¹, Osman Ozan Yeğit¹, Ali Can¹, Kadriye Terzioğlu², Derya Erdoğan Ünal¹, Müge Olgaç³, Raif Coşkun⁴, Bahauddin Çolakoğlu¹, Suna Büyüköztürk¹, Aslı Gelincik¹

1. Department of Internal Medicine, Division of Immunology and Allergic Diseases, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

2 Kartal Lütü Kirdar Education and Research Hospital, Adult Immunology and Allergy Clinic Istanbul, Turkey

3 Şişli Hamidiye Etfal Education and Research Hospital, Adult Immunology and Allergy Clinic, Istanbul, Turkey

4 Prof Dr Cemil Taşçioğlu City Hospital, Adult Immunology and Allergy Clinic, Istanbul, Turkey

Corresponding author:

Aslı Gelincik MD, Prof Dr

Department of Internal Medicine, Division of Immunology and Allergic Diseases Istanbul University, Istanbul Faculty of Medicine, Turgut Özal Millet Cad, 34390, Fatih, Istanbul

gelincikasli@hotmail.com

Phone: +905422370665

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Author contributions:

Deniz Eyice Karabacak has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

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Osman Ozan Yeğit has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Ali Can has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Kadriye Terzioğlu has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Derya Erdoğan Ünal has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Müge Olgaç has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Raif Coşkun has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Bahauddin Çolakoğlu has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Suna Büyükoztürk has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Aslı Gelincik has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Abstract:

Background: Hereditary angioedema (HAE) attacks can be provoked with psychological factors. The aim of this study was to assess the effects of anxiety, depression and stress related to COVID-19 pandemic on disease activity of HAE patients during the quarantine period (QP) and the return to normal period (RTNP).

Methods: This prospective study was conducted between March 2020 and September 2020 in four allergy centres. Demographic, clinical features and mental health status were evaluated in QP (from March to the beginning of June) and RTNP (from June to the beginning of September) was applied by the government. The 10-point visual analogue scale (VAS10) was used to define the severity of HAE attacks. Depression-Anxiety- Stress Scale-21 (DASS-21) and Fear of Covid-19 (FC-19) scales were performed to assess mental health status.

Results: 139 HAE patients were included in the study. In QP, median attack numbers and median VAS10 scores were 5 (min-max: 0-45) and 6 (min-max: 0-10), respectively. HAE attack numbers, DASS-21 stress, anxiety, depression and total DASS-21 scores, as well as FC-19 scores were higher in QP than RTNP ($p=0.001$, $p<0.001$, $p=0.001$, $p<0.001$, $p<0.001$, $p<0.001$, respectively). However, there was no difference in attack severity scores between the two periods ($p>0.05$).

Conclusions: This study revealed that the restriction measures during Covid-19 outbreak causes an increase in the number of HAE attacks in relation to anxiety, depression, stress and fear of Covid-19 pandemic. Therefore, it is important to provide psychological support to HAE patients during the pandemic.

Keywords: coronavirus, COVID-19, hereditary angioedema, pandemic, psychological effects

Introduction

Health crises like a pandemic have deep psychological effects on human beings. Several studies have shown that increased stress during or after crises are potentially associated with long-term negative effects including physical and mental health consequences ^{1, 2}. After the outbreak of Coronavirus disease 2019 (Covid-19) was declared as an international public health crisis on January 30, 2020 and a pandemic on March 11, 2020 by the World Health Organization³, the first case in Turkey was reported on March 11, 2020 by the Turkish Ministry of Health (MoH). People throughout the world were restricted to their homes due to nation-wide lockdowns and limited quarantine applications which were implemented to set the transmission of the disease under control ⁴. Eventually, this unprecedented development has caused diverse clinical consequences including anxiety and stress in populations ⁵.

Several studies have been published to evaluate susceptible individuals with chronic diseases for more severe Covid-19 outcomes. Patients with cardiovascular diseases, diabetes, chronic respiratory syndrome, immunosuppression, cancer have been determined as high vulnerable groups for severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection and predisposition to Covid-19 in such conditions have been recently investigated ⁶. The clinical implications of Covid-19 on patients with chronic diseases have also been reported ^{7, 8} however its impact on orphan diseases like hereditary angioedema (HAE) have not been evaluated so far. Recently, a case series of SARS-Cov-2 infected HAE patients have been published but still the psychological effects of the pandemic and related restrictions on HAE patients are unknown ⁹.

HAE with C1-inhibitor deficiency (C1-INH HAE) as a rare autosomal dominant disorder is characterized by unpredictable potentially life-threatening recurrent attacks of swelling in larynx, abdomen, extremities, face and genitalia without pruritus^{10, 11}. Although most attacks occur spontaneously, mechanical trauma, infection, hormonal changes, emotional stress, anxiety and depression are possible triggers ¹²⁻¹⁴. Stress and anxiety are the most frequent emotional factors influencing patients' attacks ^{13, 15}.

Recent data have revealed possible relations between the elements of immune system related to HAE and the psychological signs and symptoms like changes in mood and anxiety. As an example, a proinflammatory cytokine IL-1 β which is known to enhance bradykinin-mediated vascular permeability ^{16, 17}, can induce behavioural changes in animal models ¹⁸. Moreover, TNF- α as a potent agonist for bradykinin B1 receptors has been reported to directly mediate depressive symptoms in animal models ¹⁹. These data put forward the possible immunological background of the emotional changes seen in animal models for HAE however we can assume that various environmental stimuli and unpredictable nature of the disease can also influence the development of emotional changes in HAE patients. HAE patients are susceptible to the development of anxiety and depression due to their illnesses ²⁰. Recently, published data have suggested that HAE impairs the quality of life and affects social activities even between episodes ^{20, 21}. Although recent data about the role of stress and psychological factors in HAE are limited, it is so interesting that HAE can lead to anxiety and depression which in turn increase the frequency of attacks as in a vicious circle ^{15, 22}.

With the onset of the Covid-19 pandemic in Turkey, 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 during the pandemic. Furthermore, some patients were possibly worried about having frequent attacks due to the presence of the infection and the possibility of experiencing difficulties in accessing to the hospital and drug supply. Therefore, we aimed to investigate the presence of psychological factors such as depression, stress, anxiety and fear related to the Covid-19 pandemic and related social restrictions, and their effects on disease activity in HAE patients by validated instruments.

Methods

Patients recruitment

This multicentre, prospective, exploratory study was conducted on adult patients with HAE Type I or Type II in the coordinating centre of the study, the adult immunology and allergy clinic at Istanbul Faculty of Medicine in Istanbul University and also in three other outpatient adult immunology and allergy clinics (Kartal Lutfi Kırdar Education and Research Hospital, Şişli Etfal Education and Research Hospital, Cemil Taşcıoğlu City Hospital) in Istanbul in two different time periods outlined according to the degree of restriction measures applied by the government. The first period included the pandemic quarantine period (QP), the time period with strict restrictions beginning from 10th of March 2020 to the end of May 2020 and the first study assessments were completed in the last two weeks of May. The second period was 'the return to normal period' (RTNP) defined as the time period between the 1st of June 2020 and the end of August 2020 during which controlled social life was permitted ²³. The second study assessments were completed at the beginning of September. Patients older than 18 years of age with a confirmed diagnosis of C1-INH HAE according to the recent WAO/EAACI guideline for at least 6 months were included ²⁴. The patients who were not eligible for the study communication routes, those who did not give informed consent, those having severe HAE defined with severity scores of more than 30 for the last year ²⁵, those having more than 3 attacks in the last three months before the pandemic (BP) and those having psychiatric diagnosis and/or receiving psychiatric medications were excluded from the study.

Evaluation of HAE severity and mental health status

Demographic and clinical data including frequency, localization and severity of HAE attacks and treatment options both for HAE attacks and long-term prophylaxis (LTP) were collected from the patient medical charts and from the daily diaries kept by the patients. Severity of HAE attacks were assessed with 10-point visual analogue scale (VAS10) ²⁶. During the first assessment in May, patients were evaluated with questionnaire forms questioning patients' experiences and opinions about Covid-19 during clinical visits and/or via online and/or phone call interviews (Table Suppl 1). Information about LTP and attack treatments in the RTNP was re-evaluated via the same communication methods.

Psychological factors were appraised by the Turkish version of Depression Anxiety and Stress Scale 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, "3"= Always) to measure depression, anxiety and stress, separately ²⁷ (Table Suppl-1). Additionally, we used the Turkish version of Fear of Covid-19 scale (FC-19), a unidimensional 7-item, 5-point Likert scale with a rating system of "strongly disagree," "disagree," "neither agree nor disagree," "agree," and "strongly agree" ²⁸. The total score ranged from 7 to 35, meaning the higher the score the greater the fear of Covid-19 ²⁸ (Table Suppl-1). Both DASS-21 and FC-19 scales were eligible for self-administration and did not require a psychiatrist for evaluation. Both scales were performed during the two assessment periods, comprising knowledge of previous three months.

This study was approved by the Turkish MoH (2020-06-03T14_19_36). The institutional review board and the Ethics Committee of the coordinating centre approved the study (113239, 2020/ 78363) and informed consent was obtained from all study participants.

Statistical analysis

Statistical analysis was performed by SPSS.21 version. GraphPad Prism software was used for graphical analysis. Categorical variables were summarized as frequencies and percentages. Continuous variables were given as mean values and standard deviations or median (min-max) values according to the distribution of the data. The Wilcoxon test was used for comparison of data that were not normally distributed. Mann-Whitney U test and Kruskal-Wallis test was conducted to evaluate the different groups. The relationship between HAE attack rates, severity and DASS-21, FC-19 scores were analysed by Spearman's correlation test and multiple regression analysis. The two-sided p value <0.05 determined the statistical significance.

Results

Demographic and clinical findings of the study participants

A total of 140 patients were enrolled in the first assessment. One patient experiencing anosmia, cough and fever at the beginning of the study was considered as being infected by SARS-Cov-2 and excluded from the study. The demographic and clinical characteristics of 139 patients are listed in Table 1. 86.3% of patients (n=120) and 13.6% (n=19) had Type 1 and Type 2 C1-INH HAE, respectively. The median symptom duration was 24 years (min-max :0-63). LTP and attack treatments in QP and RTNP are shown in Table 1.

Results of specific questions related to Covid-19

62.6% of patients (n=87) stated that they were afraid of having an attack during the pandemic and 31.6% (n=44) reported that they thought their disease was risky in terms of Covid-19. 77.7% (n=108) and 75.5% (n=105) were afraid of applying to the hospital and emergency units for attack treatment during the pandemic. 23% (n=32) did not apply to the emergency units despite the need of treatment.

49 patients were not working before the pandemic, 8 patients were retired and 17 were students. 58.4% (n=38) of the 65 employed patients were working from home or in workplaces with flexible working conditions while earning their normal salaries. 23% (n=15)

were on unpaid leave by the employer or had to terminate their own businesses while 3% (n=2) were fired (Table 1).

38.8% (n=54) and 7.9% (n=11) were on LTP with danazol and tranexamic acid, respectively. During the pandemic, 33.8% (n=22) increased the doses of their medication, 55.3% (n=36) did not change the doses or the dose intervals, 10.7% (n=7) decreased their LTP usage and only one patient discontinued LTP. 38.4% (n=25) did not use 2 or more consecutive doses. During the QP, only one patient reported that she had problems to obtain LTP and 6.4% (n=9) had difficulties in obtaining pdC1-INH concentrate.

Evaluation of HAE attacks in QP and RTNP

The median number of HAE attacks and VAS severity scores are shown in Figure 1. The number of HAE attacks were higher in QP than RTNP and BP ($p=0.001$, $p<0.001$) respectively) while severity of attacks was similar among QP and RTNP ($p>0.05$) (Figure 1 A.B).

The attack sites of the patients during both QP and RTNP are shown in Figure 2. The distribution and percentages of the attack sites remained the same in both periods.

Results of mental health status measures in QP and RTNP

In the QP, DASS-21 results for stress, anxiety, and depression of 139 patients showed that 13.7%, 22.3%, 8.6% and 1.4% of participants experienced mild, moderate, severe and very severe stress symptoms; 12.9%, 10.8%, 8.6% and 10.1% of participants experienced mild, moderate, severe and very severe anxiety symptoms; and 15.1%, 27.3%, 4.3% and 3.6% of participants experienced mild, moderate, severe and very severe depressive symptoms, respectively. The median scores of the subscales of stress, anxiety, depression and total DASS-21 items were 7 (min-max: 0-19), 3 (min-max: 0-18), 5 (min-max: 0-18), and 16 (min-max: 0-55), respectively. The mean of FC-19 scores in the QP was 23.5 ± 6.6 (Figure 3).

126 patients were re-evaluated in the RTNP with the same scales. DASS-21 assessment showed that 12.9%, 5.8%, 1.4%, 2.9% of participants experienced mild, moderate, severe and very severe stress symptoms; 12.2%, 7.9%, 5.8%, and 4.3% of the patients experienced mild, moderate, severe and very severe anxiety symptoms; and 10.1%, 15.1%, 2.2%, and 3.7% of participants experienced mild, moderate, severe and very severe depressive symptoms, respectively. The median scores of the subscales of stress, anxiety, depression and total DASS-21 items were 5 (min-max: 0-19), 2 (min-max: 0-18), 3 (min-max: 0-19), and 11 (min-max: 0-55), respectively and the mean of FC-19 scores in the RTNP was 18.3 ± 6.8 (Figure 3).

In comparison of the patients' psychological features in two periods, all three dimensions of DASS-21 scale (stress, anxiety, depression), DASS-21 total scores and FC-19 scores were higher in the QP than the RTNP ($p<0.001$, $p=0.001$, $p<0.001$, $p<0.001$, $p<0.001$, respectively) (Figure 3).

Correlation analysis between clinical features and mental health status in QP and RTNP

Positive correlations between the frequency, severity of HAE attacks and DASS-21 anxiety, stress, depression, DASS-21 total scores, and FC-19 scores were observed in QP and RTNP (refer to Table 2 for each r , p values) (Table 2).

In the QP, DASS-stress ($p<0.001$), DASS-anxiety ($p<0.001$), DASS-depression ($p<0.001$), DASS-total ($p<0.001$) and FC-19 [OR 3.00 (95% CI: 0.72- 5.28; $p=0.010$)] scores were higher in female patients. Although we did not observe significant correlations between education level, age, BMI, three dimensions of DASS-21 scale in the QP, older ages indicated higher FC-19 scores [OR 0.106 (95% CI 0.03- 0.18; $p=0.007$)].

Similarly, DASS-stress ($p<0.001$), DASS-anxiety ($p<0.001$), DASS-depression ($p<0.001$), DASS-total ($p<0.001$) and FC-19 scores [OR 4.04 (95% CI 1.56-6.52); $p=0.002$] were higher in female patients in the RTNP. We did not observe significant correlations between education level, age, BMI, three dimensions of DASS-21 scale in the RTNP however we observed higher FC-19 scores in older patients [OR .10 (95% CI 0.01-0.18; $p=0.019$)].

We did not observe significant differences in three dimensions of DASS-21, total DASS-21 scores, FC-19 scores, frequency and severity of HAE attacks among employed and unemployed patients and also among active/flexible working patients and on unpaid leave patients /fired ones in QP and RTNPs.

We observed higher number of attacks in those who were not receiving LTP ($n=74$ in QP, $n=69$ in RTNP) than those who were on LTP ($n=65$ in QP, $n=57$ in RTNP) in both periods ($p=0.05$ in QP, $p=0.015$ in RTNP). We did not observe significant differences between the groups receiving or not receiving LTP about attack severity, three dimensions of DASS-21, total DASS-21 and FC-19 scores.

Discussion

This novel study assesses for the first time the effects of psychological factors related to Covid-19 on HAE activity and severity. It indicates that psychological factors including anxiety, depression, stress and fear can negatively influence the activity of the disease in HAE patients and this effect can be higher during the application of strict social restrictions to reduce the transmission of the viral infection among populations.

In our study during the QP, the number and severity of HAE attacks increased in correlation with depression, anxiety, stress and fear related to Covid-19 which were determined with two validated tools, DASS-21 and FC- 19. Recent studies have reported that psychological stress is the most common trigger for HAE attacks and deterioration in depression and anxiety might influence the severity of HAE ^{12, 22}. Previous reports also showed that an attack cannot only cause depression and anxiety, but also depression and anxiety can lead to occurrence of an attack as in a vicious circle ^{15, 22}. Although there have been no reports regarding the influence of a pandemic on mental and physical health status of HAE patients so far, negative effects of Covid-19 on psychology and disease activity of other chronic diseases like systemic lupus erythematosus and multiple sclerosis have been reported (29,30).

During the Covid-19 pandemic, various personal measures such as social distancing, self-isolation, wearing masks, hand washing and measures affecting populations like lockdowns of countries have been used to reduce the spread of the virus. However, the number of reported cases and death rates are rapidly growing. All pandemic related factors have been shown to have negative effects on mental health even in healthy subjects in general population ²⁹. During the outbreak of the Covid-19 pandemic, widespread fear, anxiety, depression, adjustment disorders were seen not only in SARS-Cov2 infected patients but also in healthy individuals. In a Turkish study, during the pandemic, healthy participants reported high depression and anxiety frequencies of 23.6% and 45.1%, respectively ³⁰.

Although we have no data about the mental health status of our HAE patients before the pandemic, when we consider the effect of the pandemic about healthy subjects in general population, we can speculate that the pandemic has potentially increased anxiety, stress, depression and fear among our HAE patients. Besides, we did not include patients with known psychiatric disorders and/or those receiving such medications which may further strengthen our assumption.

Since the number of Covid-19 patients noticeably decreased in Turkey during the RTNP as a result of strict isolation measures in the QP, most social isolation rules were gradually loosened starting from the beginning of June as in most of the other countries. We observed a significant decrease in DASS-21 and FC-19 scores together with the decrease in the attack numbers in the RTNP. We can assume that this is a consequence of people getting used to living with the pandemic beside the loosened rules of quarantine in this period. All these factors might be important in decreasing the scores together with the number and severity of HAE attacks, however social restrictions must have played the major role on our results.

In the current study, another finding was that depression, anxiety, stress and fear related to Covid-19 were higher in female patients, showing the psychiatric impact during the pandemic and that related social restrictions may influence women more than men. Previous studies indicated that anxiety and depressive disorders are more frequent in women and being a female has a negative effect on post-traumatic stress disorder symptoms during the Covid-19 pandemic ³¹. Also it was shown that female HAE patients suffer more frequent and severe angioedema attacks than males, especially in reproductive ages due to hormonal alterations, during pregnancy and delivery periods ³². The fact that age can negatively affect anxiety, stress and depression is well observed in quality of life studies in chronic diseases ³³. However, we only observed higher FC-19 scores in older participants. Since it has been reported that patients older than 65 years of age are at risk for more severe Covid-19, it is acceptable to observe that older age has worse FC-19 scores. However, it might be speculative to make a conclusion in our study since only 5 patients were within this risky age group. Although BMI is another important issue that can be related to higher frequency of depression and anxiety in previous studies ^{34, 35} and patients with higher BMI are more vulnerable to Covid-19 ³⁶, we have not observed such a relation in our patients. Besides our study group consisted of a homogenous group of non-severe HAE patients according to their attacks in the last year. Moreover, both mental health status and HAE attack frequency changed during different restriction periods, despite the fact that same age, gender and BMI factors remained the same.

We did not observe significant differences in the frequency or severity of attacks, DASS-21 and FC-19 scores in the two periods among employed and unemployed patients, also among active/flexible working patients and unpaid leave patients /fired ones. The influence of changes in working conditions due to the pandemic on our results can be ignored since the majority of the working patients had more flexible or working from home opportunities and few were on unpaid leave or fired during the pandemic.

As expected, we observed higher number of attacks in patients without LTP compared to those receiving LTP. However, scales we used to determine mental health status revealed no difference among these groups (37,38). Since the majority of the patients were able to reach both attack medications and LTP during the pandemic, other factors seemed to be more important for disease severity in our patients.

In our study the majority of attack sites were the extremities, followed by the abdomen. In a previous study including pediatric population, mental stress-triggered attacks were mostly on abdomen ¹³. This difference might depend on the fact that we did not include pediatric patients in our study.

As a limitation of this study, we could not evaluate the mental health status of our patients with the same validated tools prior to the study which restricted us from determining the clear effects of the pandemic over our study group. However as discussed earlier, we have assumed that this pandemic might have influenced our patients as it did to the healthy individuals in studies on the general population. Hopefully, after this outbreak we plan to perform the same measures on our study group in order to see the accurate long-term effects of the pandemic. During the study, we could not perform the initial severity score assessment method used for the inclusion of the participants since it necessitates over a 6-month period of follow up. Also, we could not use a specific angioedema activity scale during the study such as the recently published AECT as it has not been linguistically validated yet ³⁷. Furthermore, we believe VAS10 is a quick, easy, self-administered method to assess severity of HAE that is suitable for application during the pandemic.

Interestingly, during the interviews in our study every patient was glad to be contacted and thanked us about not feeling alone. This important observation indicates the importance of psychological support during a pandemic and we believe that telemedicine applications may be beneficial in patients with chronic diseases during a pandemic when hospital admissions are reduced.

In conclusion, our results showed that HAE patients can be mentally deteriorated by a pandemic despite not being infected and eventually their disease controls may be disrupted. Management of HAE should include multidisciplinary integration including medical, social, psychological interventions during crisis like a pandemic and telemedicine should become widespread for such vulnerable patient groups.

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Conflicts of interest

Authors state that there is no conflict of interest about this study.

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Figure legends

Figure 1. (A). Median number of attacks in BP, QP and RTNPs. Higher attacks were observed in QP. **(B).** The median VAS severity scores of HAE attacks in QP and RTNPs. There was no difference regarding the severity of HAE attacks. Abbreviations: BP, before pandemic period; QP, quarantine period; RTNP, return to normal period; BT last three before pandemic IQR, interquartile range; min, minimum; max, maximum; VAS, visual analogue scale

Figure 2. Distribution of HAE attack localizations during QP and RTNPs. In both periods, the most common site of HAE attacks was extremities. Abbreviations: QP, quarantine period; RTNP, return to normal period

Figure 3. (A). Median scores of DASS-21 dimensions in QP and RTNPs. Three dimensions of DASS-21 and DASS-21 total scores were higher in QP than those in RTNP. **(B).** Mean scores of Fear of Covid-19 (FC-19) scale in QP and RTNPs. FC-19 scores were higher in QP than those in RTNP. Abbreviations: QP, quarantine period; RTNP, return to normal period; IQR, interquartile range; SD, standard deviation.

Table 1. Demographic and clinical features of the study group

	QP n=139	RTNP n=126
Female/Male (n)	95/44	87/39
Age, years (mean \pm SD)	38.3 (13.9)	38.1(13.8)
BMI		
<18.5	7	7
18.5-24.9	55	51
>25	77	68
Education (n)		
literate	3	3
Primary	48	44
High school	31	28
University	57	51
Employment status (n)		
Employed	65	60
Active work	10	9
Flexible work	28	26
Salary without work	10	9
Unpaid leave	15	14
Fired	2	2
Unemployed	49	43
Retired	8	7
Student	17	16
Type 1 / Type 2 C1-INH-HAE (n)	120/19	110/16
LTP (n)		
Danazol	54	47
Tranexamic acid	11	10
None	74	69
Treatment of attacks (n)		
Pd C1-INH	36	42
Icatibant	66	56

QP: quarantine period, RTNP: return to normal period, SD: standard deviation, BMI: body mass index, C1-INH-HAE: HAE with C1-inhibitor deficiency, LTP: long term prophylaxis, Pd C1-INH: Plasm derived C1 inhibitor concentrate

Table 2. The correlation analyses between psychological features and frequency and severity of HAE attacks

	Quarantine period				Normalization period			
	Number of attacks		Severity of attacks		Number of attacks		Severity of attacks	
	r	p	r	p	r	p	r	p
DASS-21 stress	.353	<0.001	.314	0.001	.422	<0.001	.455	<0.001
DASS- 21 anxiety	.286	0.001	.357	<0.001	.347	<0.001	.412	<0.001
DASS-21 depression	.279	0.001	.364	<0.001	.362	<0.001	.340	<0.001
DASS-21 total	.336	<0.001	.379	<0.001	.414	<0.001	.445	<0.001
Fear of Covid-19	.184	0.03	.230	0.013	.284	0.001	.395	<0.001

DASS: depression anxiety stress scale

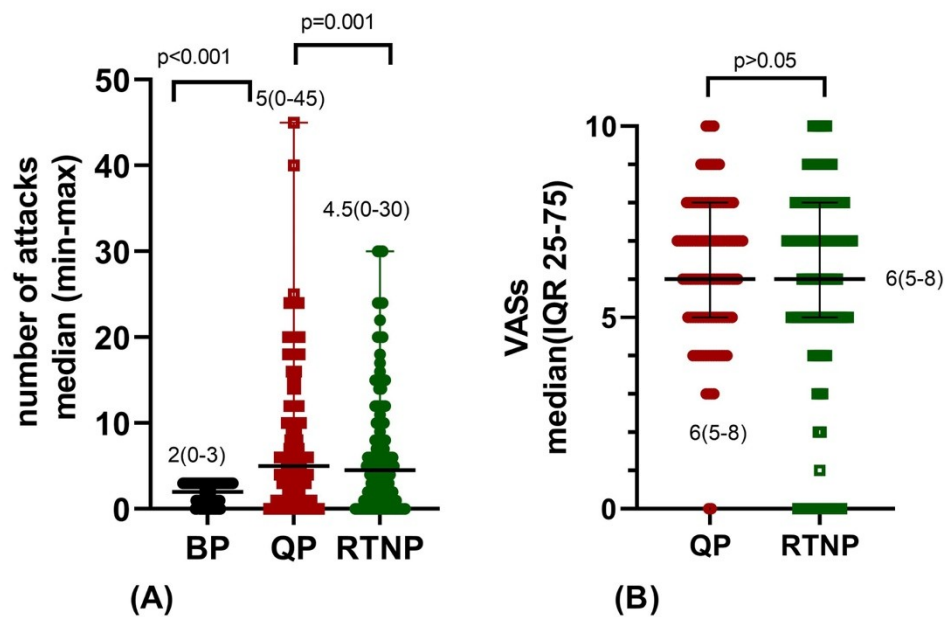


Figure 1. (A). Median number of attacks in BP, QP and RTNPs. Higher attacks were observed in QP. **(B).** The median VAS severity scores of HAE attacks in QP and RTNPs. There was no difference regarding the severity of HAE attacks.

Abbreviations: BP, before pandemic period; QP, quarantine period; RTNP, return to normal period; BP last three months before pandemic IQR, interquartile range; min, minimum; max, maximum; VAS, visual analogue scale

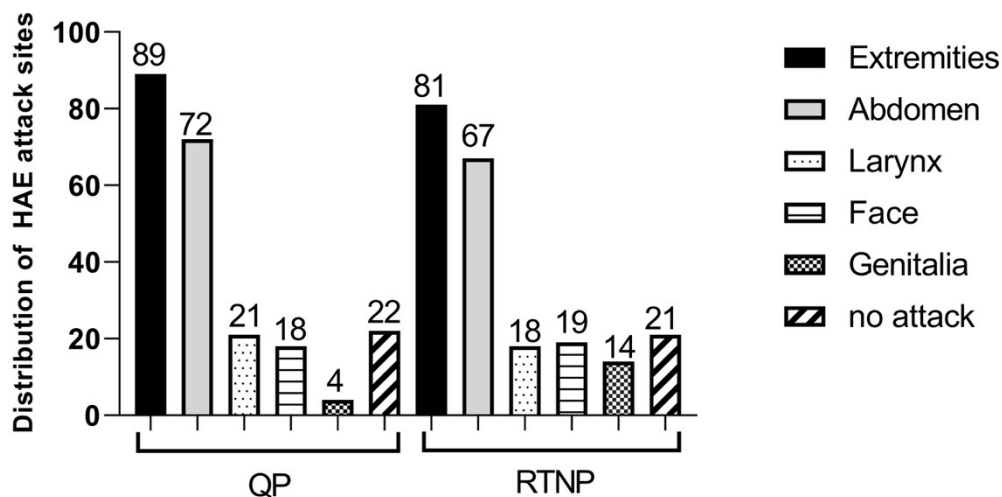


Figure 2. Distribution of HAE attack localizations during QP and RTNPs. In both periods, the most common site of HAE attacks was extremities. Abbreviations: QP, quarantine period; RTNP, return to normal period

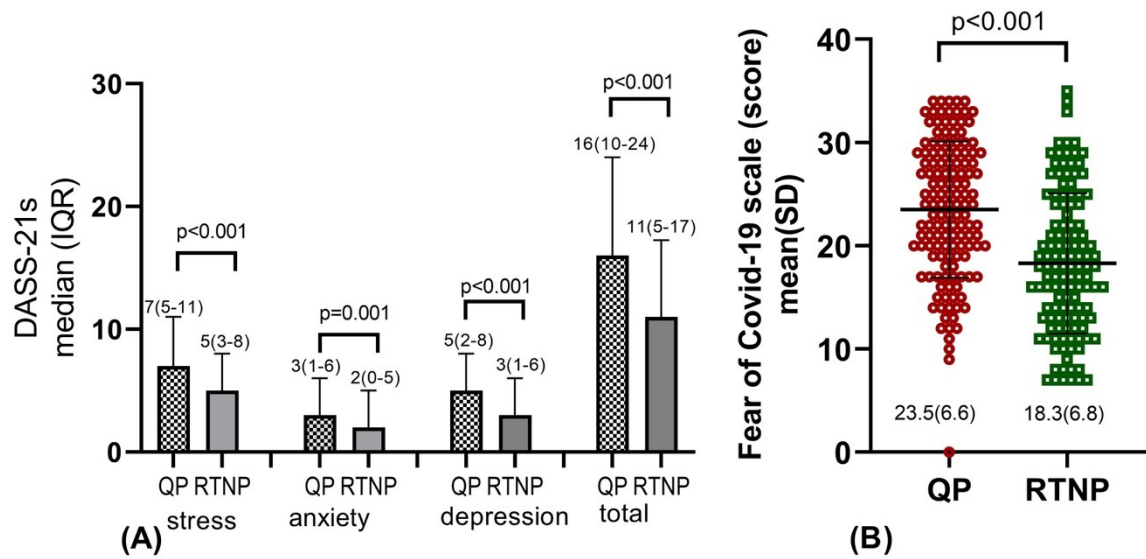


Figure 3. (A). Median scores of DASS-21 dimensions in QP and RTNPs. Three dimensions of DASS-21 and DASS-21 total scores were higher in QP than those in RTNP.

(B). Mean scores of Fear of Covid-19 (FC-19) scale in QP and RTNPs. FC-19 scores were higher in QP than those in RTNP. Abbreviations: QP, quarantine period; RTNP, return to normal period; IQR, interquartile range; SD, standard deviation.

Supplement

Table Supplement 1. Specific questions for Covid-19 in relation to HAE and the psychological scales used in the evaluation of study patients

Specific questions for Covid-19 in relation to HAE		DASS-21 scale ³⁸	0 Did not apply to me at all 1 Applied to me to some degree, or some of the time 2 Applied to me to a considerable degree, or a good part of time 3 Applied to me very much, or most of the time
Have you ever been diagnosed as Covid-19? How Is your business life affected because of the pandemic?	Yes/ No Active work Flexible work No work with salary Unpaid leave Fired Yes/ No	I found it hard to wind down I was aware of dryness of my mouth I couldn't seem to experience any positive feeling at all I experienced breathing difficulty (e.g., excessively rapid breathing, breathlessness in the absence of physical exertion)	0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3
Have you ever been afraid of that your disease will worsen during the pandemic? Have you ever been afraid of having a HAE attack during the pandemic? Have you ever thought that HAE is risky in terms of Covid-19? Have you ever been afraid of admitting to the hospital due to HAE during the pandemic? Have you ever been afraid of admitting to the emergency unit due to HAE during the pandemic? During the pandemic, have you ever been unable to go to the emergency room despite being necessary due to an HAE attack? Have you had any problems due to the pandemic when you try to obtain your disease related medication? How did you use your LTP medications during pandemic period?	Yes/ No Yes/ No Yes/ No Yes/ No Yes/ No Not changed Increased Decreased Discontinued Yes/ No	I found it difficult to work up the initiative to do things I tended to over-react to situations I experienced trembling (e.g., in the hands) I felt that I was using a lot of nervous energy I was worried about situations in which I might panic and make a fool of myself I felt that I had nothing to look forward to I found myself getting agitated I found it difficult to relax I felt downhearted and blue I was intolerant of anything that kept me from getting on with what I was doing I felt I was close to panic I was unable to become enthusiastic about anything	0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3
Fear of Covid-19 scale ²⁸	1 strongly disagree 2 disagree 3 neither agree nor disagree 4 agree 5 strongly agree	I felt I wasn't worth much as a person I felt that I was rather touchy I was aware of the action of my heart in the absence of physical exertion (e.g., sense of heart rate increase, heart missing a beat)	0 1 2 3 0 1 2 3 0 1 2 3
I am most afraid of coronavirus-19. It makes me uncomfortable to think about coronavirus-19. My hands become clammy when I think about coronavirus-19. I am afraid of losing my life because of coronavirus-19. When watching news and stories about coronavirus-19 on social media, I become nervous or anxious. I cannot sleep because I'm worrying about getting coronavirus-19. My heart races or palpitates when I think about getting coronavirus-19.	1 2 3 4 5 1 2 3 4 5 1 2 3 4 5 1 2 3 4 5 1 2 3 4 5 1 2 3 4 5	I felt scared without any good reason I felt that life was meaningless	0 1 2 3 0 1 2 3

Abbreviations: HAE: hereditary angioedema, LTP: long term prophylaxis, DASS-21: depression anxiety stress scale