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Hereditary Angioedema: Impact of COVID-19 pandemic stress upon disease related morbidity and well-being

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ABSTRACT

Background: Individuals with hereditary angioedema (HAE) experience stress-related sequelae, including enhanced disease morbidity and reduced quality of life. The pervasive societal strain that surround the coronavirus disease 2019 (COVID-19) pandemic may theoretically pose a disproportionate risk for patients with HAE.

Objective: To dissect the interrelationship(s) among the COVID-19 pandemic, stress, and HAE disease-related morbidity and overall well-being.

Methods: Subjects with HAE (either due to C1-inhibitor deficiency or with normal C1 inhibitor) as well as non-HAE household members (normal controls) completed online questionnaires that covered the impact of the COVID-19 pandemic on attack frequency, observed effectiveness of HAE medications, stress, and perceived quality of life and/or well-being. The subjects scored each of the questions to reflect their current status as well as their status before being aware of the pandemic.

Results: Disease morbidity and psychologic stress outcomes were significantly worse in patients with HAE during the pandemic compared with before they were aware of the pandemic. A COVID-19 infection further increased attack frequency. Control subjects also experienced deterioration of well-being and optimism. A comorbid diagnosis of anxiety, depression, or posttraumatic stress disorder (PTSD) was generally associated with worse outcomes. Women consistently showed greater decrements in wellness during the pandemic compared with men. Women also reported higher levels of comorbid anxiety, depression, or PTSD than men and experienced a higher rate of job loss during the pandemic.

Conclusion: The results implicated a deleterious impact of stress in the aftermath of COVID-19 awareness on HAE morbidity. The female subjects were universally more severely affected than were the male subjects. Overall well-being and/or quality of life, and optimism for the future deteriorated after awareness of the COVID-19 pandemic for the subjects with HAE and non-HAE household controls.

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Individuals with hereditary angioedema (HAE) have been speculated to comprise a vulnerable population for coronavirus disease 2019 (COVID-19) infection

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Supplemental data available at www.IngentaConnect.com

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and morbidity.^{1–3} We previously showed that individuals with HAE C1 inhibitor (C1-INH) who were not taking HAE medications demonstrate significantly higher reported infection rates.⁴ In the current investigation, we interrogated the impact of societal stress associated with the COVID-19 pandemic on parameters of HAE morbidity and well-being.

In parallel with the risk of infection, public health mandates imposed in an effort to limit the spread of COVID-19 by encompassing quarantines, travel bans, and restrictions on public gatherings created significant social and economic sequelae.⁵ The disruption of virtually every aspect of normal life amplified by the fear and uncertainty that surrounds the COVID-19 pandemic shaped a pervasive climate of societal stress.^{6,7} Isolation measures were broadly implemented that affected nearly one third of the world population by the spring of 2020.⁸ In the United States, online surveys collectively identified that nearly half of Americans (48%) were anxious about the possibility of acquiring the virus and an estimated 40% were anxious about becoming seriously ill or dying of complications at the outset of the pandemic.⁹

Table 1 Questions and possible Likert scale responses to questions

Question	Possible Response					
	1	2	3	4	5	6
Attack frequency	≥4/month	3/month	2/month	1/month	<1/month	None
Prophylactic medicine efficacy	Unsure	None	Slightly	Moderately	Very	Extremely
On-demand medicine efficacy	N/A, no attacks	None	Slightly	Moderately	Very	Extremely
Impact of emotional stress on the subject	Severe	Moderate	Mild	Minimal	None	
Likelihood of stress-induced HAE attack	Severe	Moderate	Mild	Minimal	None	
Impact of HAE on stress level	Severe	Moderate	Mild	Minimal	None	
Overall quality of life	Terrible	Poor	Fair	Good	Excellent	
Impact of HAE on quality of life	Severe	Moderate	Mild	Minimal	None	
Feelings about future	Very pessimistic	Somewhat pessimistic	Uncertain	Somewhat optimistic	Very optimistic	

N/A = not applicable; HAE = hereditary angioedema.

Systemic reviews from multiple countries identified increased anxiety and depression levels related to the COVID-19 pandemic in women,^{10–15} despite the evident increased death rate for men.¹⁶ Stress has a complex relationship with HAE. Although episodes of swelling are often unpredictable,¹⁷ stress is the most frequently cited known trigger of angioedema attacks and is widely appreciated to enhance disease morbidity.^{18,19} In addition, HAE, and especially HAE attacks, has been shown to cause significant stress in patients who are affected.²⁰

Our investigation of HAE and COVID-19 was conducted in the summer and fall of 2020, at which time there was an absence of clarity about risk factors for transmission, disease morbidity, and mortality. No controlled data were available with regard to effective treatments nor had any vaccine been deployed. In this study, we evaluated the role of societal stress about the pandemic on HAE morbidity and burden of disease. We structured our 2020 survey to determine whether individuals with HAE had a disproportionate impact amid the generalized societal trauma of the COVID-19 pandemic. We examined indices of disease morbidity, perceived treatment effectiveness, stress levels, an overall sense of well-being and/or quality of life, and feelings about the future. Analysis of HAE and of unaffected control subject data targeted to dissect the influence of pandemic stress formed the basis of this report.

METHODS

Subjects

Subjects were recruited from the US Hereditary Angioedema Association membership, with survey

invitations restricted to members with a physician-confirmed HAE diagnosis as previously described.⁴ The subjects with HAE comprised two self-reported cohorts: HAE-C1-INH and HAE with normal (nl) C1-INH. A third control cohort consisted of unaffected household members of the subjects with HAE (household controls). The occurrence of a COVID-19 illness and premorbid diagnoses were self-reported as previously described.⁴

Data Collection and Analysis

Each subject was given a link to record his or her responses in an online questionnaire created by using a University of California San Diego Altman Clinical and Translational Research Institute REDCap data base (UL1TR001442). Data were entered from August 4 to November 10, 2020. The study was anonymous and was approved by the University of California San Diego’s institutional review board with exemption status so that signed consent was not required. The information for the current report was collected simultaneously with our investigation by examining the vulnerability of the subjects with HAE to COVID infection, morbidity, and mortality.⁴ The questions and possible responses are shown in Table 1. The subjects were asked to answer each question with concern to the 4 months before becoming aware of the COVID pandemic and during the period since they became aware of the pandemic. In addition, the subjects were asked to rate the efficacy of prophylactic and on-demand medications during the time that they were ill with self-reported COVID-19. The full

Table 2 Demographics of subjects

Demographic	HAE-C1-INH Group (n = 695)	HAE-nl-C1-INH Group (n = 175)	Household Controls (n = 292)
Women, n (%)	515 (74.1)	155 (88.6)	126 (51.4)
Men, n (%)	180 (25.9)	20 (11.4)	119 (48.6)
Mean age ± SD	49.8 ± 16.0	47.9 ± 14.9	43.9 ± 21.5
Using on-demand, n (%)	538 (77.4)	123 (70.3)	N/A
Using LTP, n (%)	453 (65.2)	87 (49.7)	N/A
Comorbid anxiety, n (%)	95 (13.7)	76 (43.4)	35 (12.0)
Comorbid depression, n (%)	45 (6.5)	41 (23.4)	25 (8.6)
Comorbid PTSD, n (%)	20 (2.9)	17 (9.7)	8 (2.7)

HAE = Hereditary angioedema; C1-INH = C1 inhibitor; nl = normal; SD = standard deviation; LTP = long-term prophylaxis; N/A = not applicable; PTSD = posttraumatic stress disorder.

questionnaire has been included in the online Supplemental Repository.

Statistics

To improve data comprehension, raw Likert scores for each question were re-coded so that worsening was reflected by a decreased score, whereas improvement was reflected by an increased score. All analyses were performed by using nonparametric techniques. Raw scores were analyzed with contingency tables by using χ^2 tests. Differences in scores between prepandemic awareness and during the pandemic were analyzed by matched pair testing by using the Wilcoxon signed rank test. Differences between groups in the matched pair scores were analyzed by using the Wilcoxon rank sum test. *P* values < 0.05 were considered significant. Statistical analyses were performed by using JMP 16 (SAS Institute, Cary, NC).

RESULTS

Subjects

A total of 1162 subjects were studied, including 695 subjects with HAE-C1-INH, 175 subjects with HAE-nl-C1-INH, and 292 household controls. Demographic data on the subjects are shown in Table 2. Comorbid diagnoses were self-reported. The subjects with HAE-nl-C1-INH reported a significantly greater percentage of anxiety, depression, and posttraumatic stress disorder (PTSD) compared with either HAE-C1-INH or household controls (*p* < 0.0001, Fisher exact test).

Pre-COVID-19 Status

The subjects were asked to rate their responses to the nine items before knowing about COVID-19. The surveys were filled out between August 2020 and November 2020, and the subjects were asked when

they became aware of the pandemic. The mean ± standard deviation time between becoming aware of COVID-19 and filling out the survey was 4 ± 2 months. The median (interquartile range) and mode prepandemic responses in the three subject groups (HAE-C1-INH, HAE-nl-C1-INH, and household controls) are shown in Table 3. Compared with the HAE-nl-C1-INH group, the HAE-C1-INH group reported significantly worse scores in all the parameters except for the likelihood of stress to induce HAE attacks before the pandemic. Compared with the control group, the subjects with HAE-C1-INH reported significantly worse scores for the impact of their emotion stress and feelings about the future before the pandemic. The HAE-nl-C1-INH group reported worse scores in all parameters before the pandemic compared with the controls.

Change in Scores during the COVID-19 Pandemic Compared with Pre-Awareness Scores

We were interested in ascertaining how the awareness of the pandemic impacted the parameters being assessed. We compared the scores for each subject at the time he or she filled out the survey during the pandemic compared with his or her retrospective pre-COVID-19 awareness scores (Table 3). As noted above, all the surveys were performed during the early phase of the pandemic (August to early November 2020) before the availability of vaccines. All three groups reported significantly worsening in all the domains since the pandemic compared with the prepandemic scores.

Compared with the HAE-nl-C1-INH group, the HAE-C1-INH group reported significantly worse scores in all domains since the pandemic. Compared with the control group, the subjects with HAE-C1-INH reported significantly worse scores for the impact of emotion stress since the pandemic, whereas the HAE-

Table 3 Responses by subject group: before and after awareness of the COVID-19 pandemic

	HAE-C1-INH Group				HAE-nl-C1-INH Group				Controls			
	Before the Pandemic		Since the Pandemic		Before the Pandemic		Since the Pandemic		Before the Pandemic		Since the Pandemic	
	Median (IQR)	Mode	Median (IQR)	Mode	Median (IQR)	Mode	Median (IQR)	Mode	Median (IQR)	Mode	Median (IQR)	Mode
Attack frequency	5 (4-6)#	6	5 (4-6)##**	6	4 (2-5)	5	3 (1-5)**	1				
Prophylactic medicine efficacy	6 (5-6)#	6	6 (5-6)##**	6	5 (4-6)	6	5 (4-6)	6				
On-demand medicine efficacy	5 (4-6)#	6	5 (1-6)##**	6	5 (5-6)	6	5 (4-6)	5.5				
Impact of emotional stress on subject	3 (2-4)*¶	2	2 (2-3)*§**	2	2 (1-2)¶	2	2 (1-2)¶**	2	3 (2-4)	4	2 (2-3)**	2
Likelihood of stress-induced HAE attack	2 (2-3)	2	2 (1-3)**	2	2 (1-3)	2	2 (1-3)**	1				
Impact of HAE on stress level	3 (2-4)#	4	3 (2-4)##**	2	3 (2-3)	2	2 (1-3)**	2				
Overall quality of life	4 (4-5)#	4	4 (3-4)##**	4	4 (3-4)¶	4	3 (3-4)¶**	3	4 (4-5)	4	4 (3-4)**	4
Impact of HAE on quality of life	3 (2-4)#	3	3 (2-4)##**	3	2 (2-3)	2	2 (2-3)	2				
Feelings about future	4 (4-5)*§	5	4 (3-4)**	3	4 (3-5)¶	4	3 (2-4)¶**	3	5 (4-5)	5	4 (3-4.25)**	4

COVID-19 = Coronavirus disease 2019; HAE = hereditary angioedema; C1-INH = C1 inhibitor; nl = normal; IQR = interquartile range.

Compared with HAE-nl-C1-INH: * $p < 0.05$; # $p < 0.001$ by using the χ^2 test.

Compared with the controls: § $p < 0.05$; ¶ $p < 0.001$ by using χ^2 test.

Compared with the prepandemic response: || = $p < 0.05$; ** = $p < 0.001$.

nl-C1-INH group reported worse scores in all domains since the pandemic. We noted significant differences between the female and male subjects (Table 4 and Supplemental Fig. S1). The male subjects, particularly those with HAE-C1-INH, demonstrated less worsening and, in some cases, improvement in scores during the pandemic.

Impact of the COVID-19 Pandemic on Subject Responses

Next, we looked at whether the outcomes were affected by whether or not the subjects reported being ill with COVID-19. The change in the outcomes, comparing the subjects who reported COVID-19 illness to those who did not in each group is shown in Table 5 and Supplemental Fig. S2. The subjects with HAE-C1-INH and with COVID-19 illness reported significantly greater worsening in attack frequency but significant improvement in prophylactic efficacy and optimism about the future. The subjects with HAE-nl-C1-INH and with COVID-19 reported significantly greater worsening in quality of life and/or well-being. Again, marked differences were noted between the female and male subjects (Supplemental Fig. S2).

Impact of Preexisting Anxiety, Depression, or PTSD on Subject Responses

HAE-C1-INH has been reported to be associated with a significantly increased prevalence of depression compared

with controls.²¹ As shown in Table 1, we did not find this to be the case in the subjects with HAE-C1-INH in our study, although this was true in the subjects with HAE-nl-C1-INH. We compared changes in the studied parameters between the subjects with a prepandemic diagnosis of anxiety, depression, or PTSD with those without such a diagnosis in the three groups (Table 5 and Supplemental Fig. S3). A previous diagnosis of anxiety, depression, or PTSD was associated with a significantly greater worsening in attack frequency, prophylactic efficacy, and stress-induced HAE attacks in the subjects with HAE-C1-INH. These effects were almost entirely attributable to the female subjects with HAE-C1-INH (Supplemental Fig. S3). The subjects with HAE-nl-C1-INH who were positive for at least one of these diagnoses reported a significantly greater worsening of emotional stress.

Relationship between Job Loss and Outcomes

Because of the rapid job losses that occurred during the early phases of the pandemic, we analyzed the effect of this on our data. The women were significantly more likely to lose their jobs than the men ($p = 0.0012$). In addition, the subjects with HAE-nl-C1-INH were significantly more likely ($p = 0.04$) to lose their jobs than were the subjects with HAE-C1-INH. Losing a job was significantly associated with greater loss of on-demand medication efficacy ($p = 0.02$), quality of life ($p = 0.006$), and future optimism ($p = 0.0006$).

Table 4 Gender differences in impact of COVID-19 pandemic

Question	Group	Women vs Men, Change in Score (<i>p</i> value*)				
		All	COVID-19 Negative	COVID-19 Positive	ADP Negative	ADP Positive
Attack frequency	HAE-C1-INH	n.s.	n.s.	n.s.	n.s.	n.s.
	HAE-nl-C1-INH	n.s.	n.s.	n.s.	n.s.	<0.05
Prophylaxis efficacy	HAE-C1-INH	<0.01	<0.01	n.s.	n.s.	<0.05
	HAE-nl-C1-INH	n.s.	n.s.	n.s.	n.s.	n.s.
On-demand efficacy	HAE-C1-INH	n.s.	n.s.	n.s.	n.s.	n.s.
	HAE-nl-C1-INH	n.s.	n.s.	n.s.	n.s.	n.s.
Emotional stress	HAE-C1-INH	n.s.	n.s.	n.s.	n.s.	n.s.
	HAE-nl-C1-INH	n.s.	n.s.	n.s.	n.s.	n.s.
	Controls	<0.05	<0.05	n.s.	n.s.	n.s.
Stress-induced HAE attacks	HAE-C1-INH	<0.05	n.s.	<0.05	n.s.	n.s.
	HAE-nl-C1-INH	n.s.	n.s.	n.s.	n.s.	n.s.
HAE impact on stress	HAE-C1-INH	<0.05	n.s.	n.s.	n.s.	n.s.
	HAE-nl-C1-INH	n.s.	n.s.	n.s.	n.s.	n.s.
Quality of life and/or well-being	HAE-C1-INH	<0.01	<0.05	<0.05	<0.01	<0.05
	HAE-nl-C1-INH	n.s.	n.s.	n.s.	n.s.	n.s.
	Controls	n.s.	n.s.	n.s.	n.s.	n.s.
HAE impact on quality of life	HAE-C1-INH	n.s.	n.s.	n.s.	n.s.	n.s.
	HAE-nl-C1-INH	n.s.	n.s.	n.s.	n.s.	n.s.
Optimism for future	HAE-C1-INH	<0.001	<0.001	n.s.	<0.01	<0.05
	HAE-nl-C1-INH	n.s.	n.s.	n.s.	n.s.	n.s.
	Controls	n.s.	n.s.	n.s.	n.s.	n.s.

COVID-19 = Coronavirus disease 2019; ADP = anxiety, depression, or posttraumatic stress disorder; HAE = hereditary angioedema; C1-INH = C1 inhibitor; n.s. = not significant; nl = normal. Bold represents statistical significant results.

*Wilcoxon test, χ^2 test.

DISCUSSION

HAE is a rare autosomal dominant disease clinically characterized by recurrent episodes of swelling that affect cutaneous and submucosal tissues. Untreated attacks are associated with significant morbidity and, in the case of laryngeal angioedema, the risk of mortality. Despite advances in unraveling the pathophysiology of HAE, the mechanism(s) that initiates an episode of swelling remains enigmatic. Although individuals with HAE commonly describe the majority of their attacks as unpredictable,¹⁷ stress is the most frequently identified triggering event.¹⁹

We hypothesized that the societal stress associated with the COVID-19 pandemic would have a disproportionate impact on the subjects with HAE based on the demonstrated ability of stress to trigger attacks and the potential for attack escalation to intensify overall HAE morbidity. Our results confirmed that the COVID-19 pandemic had deleterious effects in the subjects with HAE. The scores across all nine questions that cover disease morbidity and psychologic stress were significantly worse in the subjects with HAE during the pandemic compared with before they became aware of the pandemic.

The subjects with HAE reported greater emotional stress and less optimism about the future than the controls before the pandemic. The controls reported improved quality of life compared with the subjects with HAE-nl-C1-INH before the pandemic, but there was no difference between the controls and the subjects with HAE-C1-INH in quality of life. It is worth noting that, before the pandemic, the overall quality of life and/or well-being for the subjects with HAE-C1-INH was close to that of their non-HAE household controls. This may reflect the broad use of long-term prophylactic medications in our subject cohort (65.2%). The figures from the current survey are in stark contrast to previous reports that reflected the burden of illness for individuals within this cohort.²¹ Surprisingly, the controls experienced a significantly greater increase in emotional stress during the pandemic than did the subjects with HAE.

The subjects with HAE-C1-INH who experienced a COVID-19 illness reported significantly increased attack frequency. These subjects showed little to no impact on worsening the other outcomes and actually experienced some improvement in a number of the

Table 5 Impact of reported COVID-19 infection or preexisting ADP on responses

	Impact of COVID-19 or preexisting ADP on the Change of Score (<i>p</i> value*)					
	HAE-C1-INH Group		HAE-nl-C1-INH Group		Control Group	
	COVID-19	ADP	COVID-19	ADP	COVID-19	ADP
Attack frequency	0.013	0.003	0.289	0.372		
Prophylactic medicine efficacy	0.044	0.003	0.0333	0.680		
On-demand medicine efficacy	0.539	0.700	0.113	0.800		
Impact of emotional stress on subject	0.562	0.297	0.151	0.022	0.803	0.515
Likelihood of stress-induced HAE attack	0.552	0.033	0.858	0.296		
Impact of HAE on stress level	0.258	0.501	0.885	0.539		
Overall quality of life	0.428	0.660	0.046	0.420	0.963	0.517
Impact of HAE on quality of life	0.821	0.076	0.236	0.138		
Feelings about future	0.023	0.402	0.699	0.477	0.367	0.722

COVID-19 = Coronavirus disease 2019; ADP = anxiety, depression, or posttraumatic stress disorder; HAE = hereditary angioedema; C1-INH = C1 inhibitor; nl = normal. Bold represents statistical significant results.

*Wilcoxon test, χ^2 test.

parameters, including emotional stress and quality of life, with a significant improvement in optimism about the future. We suspect that the fear of COVID-19 as reflected by comparisons in before and after awareness of the pandemic was a greater driver of negative outcomes than undergoing an actual illness. Morbidity was further augmented for the subjects with HAE-C1-INH with a comorbid diagnosis of anxiety, depression, or PTSD. Significant worsening was observed for attack frequency, prophylactic efficacy, and stress-induced HAE attacks. One of the striking results of our study was a disproportionate negative effect of the pandemic on the female subjects who reported greater worsening of outcomes compared with men as well as a greater job loss.

In our study, the female subjects reported significantly higher rates of comorbid anxiety, depression, and PTSD than did the male subjects (25% versus 15%; $p=0.0002$). These comorbid conditions were highest among the subjects with HAE-nl-C1-INH (39% in female and 20% in male subjects), who also showed greater worsening during the pandemic than did the subjects with HAE-C1-INH. Depression has been widely shown to be more prevalent in women than in men.²²⁻²⁴ Moreover, the COVID-19 pandemic has had a greater impact on stress and depression in women compared with men.^{10,13-15}

The fundamental explanation for this disparity has yet to be clarified with both genetic, societal, and

personality influences at play. Women have also consistently been reported to be more severely affected by HAE than their male counterparts. Although this may be, in part, related to hormonal factors, the basis for the gender morbidity disparity remains unclear.¹⁸ Strengths of our investigation included the large number of the subjects with HAE and the ability to compare results with nonaffected household controls. Acknowledged weaknesses include the absence of laboratory biomarkers either for HAE or COVID-19 infection, which were not feasible to gather during the time frame of our survey in 2020.

The limitations with respect to self identifying HAE, COVID-19 illness, and the retrospective design have been previously discussed.⁴ The diagnosis of HAE-nl-C1-INH remains difficult and uncertain, which calls for some caution in interpreting the results for this group. Usage of long-term prophylaxis and on-demand medicines in the HAE-nl-C1-INH group (60% and 76.9%, respectively) was similar to that in the HAE-C1-INH group (73.6% and 83.6%, respectively). Although our study design, which compared the subjects with HAE with others in their household, is considered a strong point of the investigation, the possibility of emotional contagion that affected the control subject's well-being if he or she was either a caretaker, relative, or partner of the subject with HAE also could not be excluded.

CONCLUSION

Our study supports the hypothesis that awareness of the COVID-19 pandemic has amplified HAE morbidity and stress-related attacks. Results do not seem to be driven by experiencing COVID-19 illness but rather the societal strain of the pandemic. The female subjects were universally more severely affected than were the male subjects. Overall stress, well-being and/or quality of life, and optimism for the future substantially deteriorated after awareness of COVID-19 for subjects with HAE and for non-HAE household controls.

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