COVID-19 and hereditary angioedema: Incidence, outcomes, and mechanistic implications

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ABSTRACT

Background: *Patients with hereditary angioedema (HAE) have been postulated to be at increased risk for coronavirus disease 2019 (COVID-19) infection due to inherent dysregulation of the plasma kallikrein-kinin system. Only limited data have been available to explore this hypothesis.*

Objective: *To assess the interrelationship(s) between COVID-19 and HAE.*

Methods: *Self-reported COVID-19 infection, complications, morbidity, and mortality were surveyed by using an online questionnaire. The participants included subjects with HAE with C1 inhibitor (C1INH) deficiency (HAE-C1INH) and subjects with HAE with normal C1-inhibitor (HAE-nl-C1INH), and household controls (normal controls). The impact of HAE medications was examined.*

Results: *A total of 1162 participants who completed the survey were analyzed, including: 695 subjects with HAE-C1INH, 175 subjects with HAE-nl-C1INH, and 292 normal controls. The incidence of reported COVID-19 was not significantly different between the normal controls (9%) and the subjects with HAE-C1INH (11%) but was greater in the subjects with HAE-nl-C1INH (19%; $p = 0.006$). Obesity was positively correlated with COVID-19 across the overall population ($p = 0.012$), with a similar but nonsignificant trend in the subjects with HAE-C1INH. Comorbid autoimmune disease was a risk factor for COVID-19 in the subjects with HAE-C1INH ($p = 0.047$). COVID-19 severity and complications were similar in all the groups. Reported COVID-19 was reduced in the subjects with HAE-C1INH who received prophylactic subcutaneous C1INH (5.6%; $p = 0.0371$) or on-demand icatibant (7.8%; $p = 0.0016$). The subjects with HAE-C1INH and not on any HAE medications had an increased risk of COVID-19 compared with the normal controls (24.5%; $p = 0.006$).*

Conclusion: *The subjects with HAE-C1INH who were not taking HAE medications had a significantly higher rate of reported COVID-19 infection. Subcutaneous C1INH and icatibant use were associated with a significantly reduced rate of reported COVID-19. The results implicated potential roles for the complement cascade and tissue kallikrein-kinin pathways in the pathogenesis of COVID-19 in patients with HAE-C1INH.*

(Allergy Asthma Proc 42:506–514, 2021; doi: 10.2500/aap.2021.42.210083)

The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 was declared a global pandemic on March 11, 2020. The clinical presentation of COVID-19 ranges from an asymptomatic infection to severe disease with high mortality. Although, characteristically, a respiratory tract illness, broader systemic consequences that involve cardiovascular, respiratory, gastrointestinal, neurologic, hematologic, and immune system compartments are evident.[1] While everyone is vulnerable, various individual characteristics and comorbid medical disorders have been correlated with COVID-19 morbidity and mortality.[2–6] Social determinants and genetic variations have also been linked to COVID-19 outcomes.[4, 7–11]

Despite the evolving recognition of the threat posed by COVID-19 for certain populations, the implications for individuals with orphan or rare diseases remains largely unexplored. Hereditary angioedema (HAE) due to C1 inhibitor (C1INH) deficiency (HAE-C1INH) is a rare autosomal dominant and potentially life-threatening disease clinically characterized by swelling attacks of the subcutaneous (SC) tissue and mucous membranes due to dysregulation of the plasma kallikrein-kinin system with enhanced generation of bradykinin.[12,13] The

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The project was partially supported by the National Institutes of Health (NIH) grant UL1TR001442. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH
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incidence and outcomes of COVID-19 in HAE-C1INH are unknown. Individuals with HAE-C1INH have been hypothesized to be at enhanced risk for COVID-19 infection and complications because angiotensin-converting enzyme 2, a key protein involved in severe acute respiratory syndrome coronavirus 2 infectivity, also degrades kinins, and bradykinin excess has been hypothesized to play a pathologic role in the severe respiratory complications of COVID-19.[14–16] The impact of on-demand and long-term prophylactic (LTP) HAE therapies have also been a topic of conjecture with regard to their ability to influence the course of COVID-19–related illness.[14, 17]

The current study was designed to assess whether there is a measurable difference in COVID-19 susceptibility, manifestations, and complications between subjects with HAE-C1INH and household non-HAE controls (normal controls). The subjects who self-identified as having HAE with normal C1INH (HAE-nl-C1INH) were included as a separate cohort for the analysis. We further investigated the relationship between the use of HAE treatments and the susceptibility and course of COVID-19 infection. The findings of our investigation form the basis for this report.

METHODS

Study Design and Patient Recruitment

We collected data by using an anonymous online survey (Online Supplemental Material) of households with at least one individual affected by HAE. The US Hereditary Angioedema Association (HAEA) recruited subjects from its members known to have HAE by sending a link to the online survey through e-mail, the US HAEA newsletter, and direct mail correspondence. Individuals requested to participate after learning about the study through the US HAEA website, or social media postings directed to the US HAEA, which checked that the potential subject had a physician-confirmed HAE diagnosis. Those who met the criteria were sent the URL link to the survey. The subjects with HAE were asked to share the link with other members of their household, irrespective of whether they had HAE. The self-completed anonymous survey was conducted through a URL link to a REDCap survey instrument maintained by the University of California San Diego Altman Clinical and Translational Research Institute (UL1TR001442), from August 4 to November 10, 2020. The study was approved by the University of California San Diego's institutional review board, exemption status (exempt category 2) was granted, and signed consent was not required. C.L. Veronez and S.C. Christiansen contributed equally.

Statistical Analysis

Results are based on the number of the participants who responded to the specific query rather than the entire group. Descriptive analyses were used to report frequencies and proportions of the characteristics of the study population. Analyses of discrete variables were performed by using the Fisher exact test, and the means of continuous variables were compared by using the Wilcoxon Kruskal-Wallis test. All statistical tests were performed by using JMP Pro (SAS Institute, Cary, NC).

RESULTS

Demographics

The survey was completed by 1445 participants, including 1153 subjects with angioedema (80%) and 292 household members (related or nonrelated) without angioedema (normal controls). The participants with angioedema and with diagnoses of acquired angioedema (17) or HAE of unknown type (266) were excluded, which left 1163 subjects: 870 subjects with angioedema (695 [80%]) reported a diagnosis of HAE-C1INH (type I or type II) and 175 (20%) reported a diagnosis of HAE-nl-C1INH (Table 1). Overall, 1136 participants who were analyzed reported an ethnicity. Of these, 951 self-identified as white (84%), 81 as Hispanic (7%), 60 as black (5%), 20 as Native American (2%), 22 as Asian (2%), and 2 as Pacific Islander (<1%). Females comprised 72% of the total participants; 74% of the subjects with HAE-C1INH, 89% of subjects with HAE-nl-C1INH, and 51% of the normal control. The geographic distributions and the ages of the participants are shown in Fig. 1

Influence of Demographic Characteristics and HAE on COVID-19 Risk

The participants were asked whether they developed symptoms of COVID-19 illness. The incidence of self-reported COVID-19 was 69 of 647 participants with HAE-C1INH (10.7%). This was not significantly different from the incidence in the normal controls (21/228 [9.2%]; $p = 0.613$). Thirty-one of 160 subjects with HAE-nl-C1INH (19.4%) reported that they had COVID-19, which was significantly different compared with the normal controls ($p = 0.006$) or the subjects with HAE-C1INH ($p = 0.005$). Of the 121 participants reporting COVID-19, including subjects with HAE-C1INH, normal controls, and subjects with HAE-nl-C1INH, 41 had polymerase chain reaction testing with 29 positive (71%), 10 negative (24%), and 2 indeterminate (5%).

The potential influence of demographic covariates (such as age, gender, ethnicity, and comorbidities) on the risk of reporting COVID-19 are shown in Table 1. There was a significant association between younger age and increased reported COVID-19 in the entire population ($p < 0.003$) and in the HAE-C1INH group ($p < 0.04$). The same trend was seen but did not reach significance between the HAE-nl-C1INH ($p < 0.055$)

Table 1 **Demographics and COVID-19 distribution#**

	Normal Controls		Subjects with HAE-C1INH		Subjects with HAE-nl–C1INH	
	Total	COVID-19	Total	COVID-19	Total	COVID-19
Participants, *n* (%)	228	21 (9.2)	647	69 (10.7)	160	31 (19.4)**
Age, mean ± standard error	44.8 ± 1.5	39.6 ± 4.6	49.8 ± 0.7	46.2 ± 1.9	48.4 ± 1.3	43.9 ± 2.6
Age range, *n* (%)						
<21 y	47	5 (10.6)	33	2 (6.1)	7	0 (0)
21–50 y	83	10 (12.0)	288	42 (14.6)	79	21 (26.6)
51–60 y	42	3 (7.1)	148	9 (6.1)	45	7 (15.6)
61–70 y	36	3 (8.3)	121	15 (12.4)	23	3 (13.0)
>70 y	20	0 (0)	57	1 (1.8)	6	0 (0)
Gender, *n* (%)						
Female	118	8 (6.8)	477	53 (11.1)	141	29 (20.6)
Male	110	13 (11.8)	170	16 (9.4)	19	2 (10.5)
Race or ethnicity, *n* (%)¶						
White	195	20 (10.3)	563	61 (10.8)	130	27 (20.8)
Hispanic	19	1 (5.3)	44	2 (4.6)	12	3 (25.0)
Black	15	0	22	2 (9.1)	16	3 (18.8)
Asian	3	0	13	1 (7.7)	6	1 (16.7)
Native	3	0	7	2 (28.6)	5	0
Pacific	1	0	1	0	0	0
Comorbidities, *n* (%)						
Diabetes	17	2 (11.8)	40	2 (5.0)	18	3 (16.7)
Hypertension	35	2 (5.7)	114	9 (7.9)	25	3 (12.0)
Heart diseases	15	0	29	4 (13.8)	6	0
Lung diseases	4	0	15	1 (6.7)	7	0
Obesity	55	5 (9.1)	202	28 (13.9)	57	13 (22.8)
Immune system deficiency	2	0	13	1 (7.7)	8	1 (12.5)
Immunosuppressed	5	1 (20.0)	16	2 (12.5)	7	0
Cancer	13	1 (7.7)	32	2 (6.3)	7	0
Liver diseases	1	1 (100)	6	2 (33.3)	3	0
Kidney diseases	1	0	12	0	3	0
Autoimmune diseases	13	2 (15.4)	37	8 (21.6)*	19	4 (21.1)

COVID-19 = Coronavirus disease 2019; HAE = hereditary angioedema; C1INH = C1 inhibitor; nl = normal.
#Percentages are based on the number of subjects who responded to that survey question.
*Statistically significant: *$p < 0.05$; **$p < 0.0005$.*
¶The numbers add to more than the number of subjects because the subjects could choose more than one ethnicity.

and the normal control ($p = 0.22$) groups. No significant differences were seen in the reported incidence of COVID-19 between the gender and the race or ethnic categories in any of the groups. The geographic impact on the reported incidence of COVID-19 is shown in Online Supplement Table S1.

We examined the impact of comorbidity on reported COVID-19 (Table 1). Obesity (body mass index ≥ 30 kg/m^2) was positively correlated with COVID-19 in the overall survey population (COVID-19 in 10.1% non-obese versus 15.5% obese; $p = 0.012$), with a similar but nonsignificant trend for the HAE-C1INH (COVID-19 in 9.2% non-obese vs 13.9% in obese) and the HAE-nl-C1INH (COVID-19 in 17.5% non-obese vs 22.8% in obese) groups but not in the normal control group (9.3% versus 9.2%). Autoimmune disease was associated with an increased risk of COVID-19 illness in the subjects with HAE-C1INH ($p = 0.047$) but not those with HAE-nl-C1INH. The relationship between HAE attack frequency and the incidence of reported COVID-19 was examined (Fig. 2). The subjects with HAE-C1INH who had two or more attacks per month had a significantly increased incidence of reported COVID-19 (20/138 [14.5%]) compared with those with fewer than two attacks per month (42/502 [8.4%]; $p = 0.0355$). Attack frequency did not impact the reported COVID-19 in the subjects with HAE-nl-C1INH.

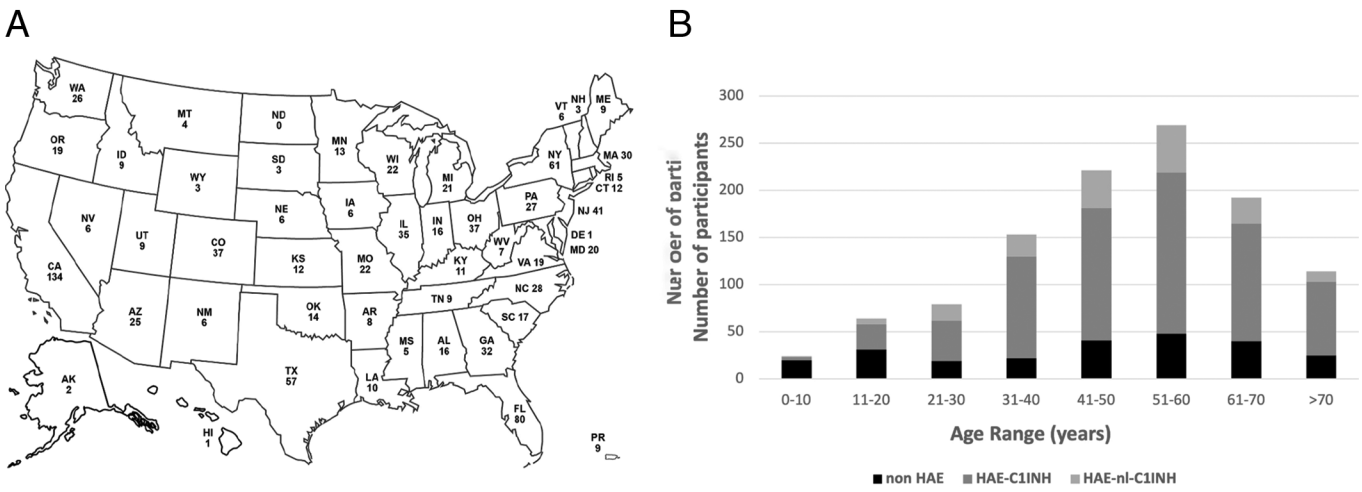

Figure 1. *Demographics of study population. (A) Geographic distribution of the subjects by state. (B) Age distribution of the subjects by group.*

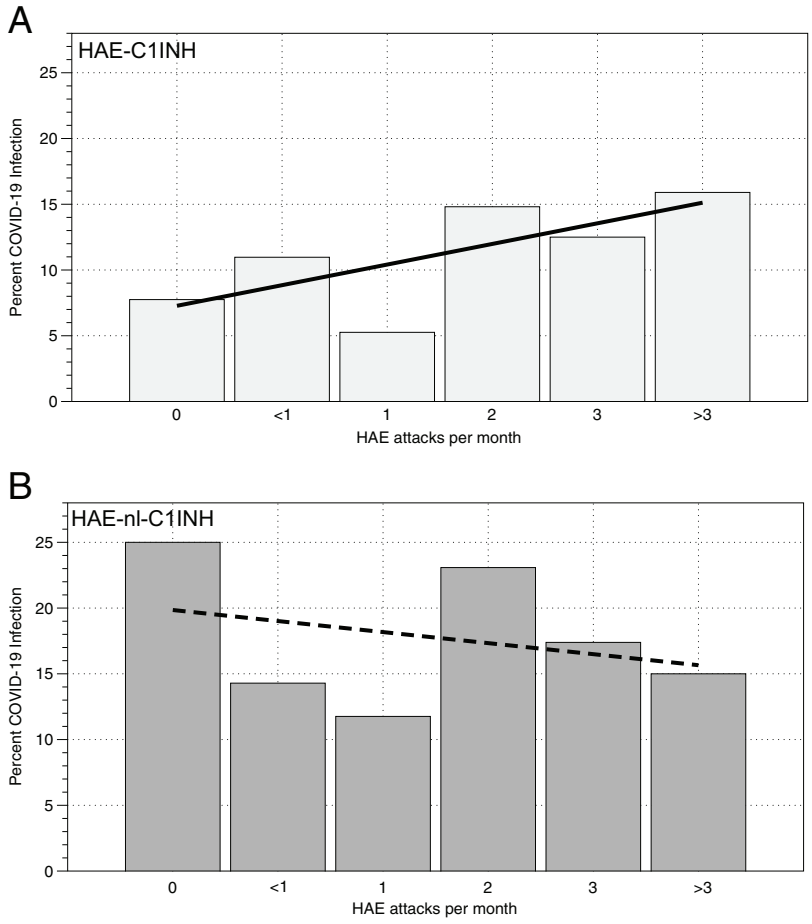

Figure 2. *Relationship between attack frequency and COVID-19 infection rates. (A) The subjects with HAE-C1INH; (B) The subjects with HAE-nl-C1INH. The percent who reported COVID-19 infection is shown with bars. Linear regression is shown with a superimposed line. COVID-19 = Coronavirus disease 2019; HAE = hereditary angioedema; C1INH = C1 inhibitor; nl-C1INH = normal C1-inhibitor.*

Relationships between HAE Medications and Reported COVID-19

We evaluated the impact of HAE prophylactic and on-demand medications on reported COVID-19 (Table 2). The subjects who used SC plasma-derived C1INH (pd–C1INH) had significantly less reported COVID-19 (7/126 [5.6%]) compared with 11.9% of the subjects with HAE-C1INH who did not receive SC pd–C1INH (62/521; $p = 0.0371$) and 14.6% in the subjects who did not receive any LTP treatment for HAE ($p = 0.0111$). SC pd–C1INH had no significant impact on the incidence of reported COVID-19 in the subjects with HAE nl–C1-INH (18.8% not on SC pd-C1INH versus 19.4% on SC pd-C1INH; not significant). Other HAE prophylactic medicines did not show a significant association with decreased reported COVID-19 illness rates.

Lanadelumab demonstrated a small but nonsignificant impact on COVID-19 illness in both the HAE-C1INH group (9.4% with COVID-19 taking lanadelumab versus 11.4% with COVID-19 not taking lanadelumab; $p = 0.511$) and the HAE-nl-C1INH group (16.3% with COVID-19 taking lanadelumab versus 20.7% with COVID-19 not taking lanadelumab; $p = 0.665$).

The incidence of COVID-19 was also significantly reduced in the subjects with HAE-C1INH who received on-demand icatibant (34/434 [7.8%]) compared with 35 of 213 subjects (16.4%) who did not use icatibant ($p = 0.0016$). No association of icatibant was seen among the subjects with HAE-nl-C1INH (21.0% with COVID-19 taking icatibant versus 16.4% with COVID-19 not taking icatibant; $p = 0.535$). The subjects with HAE-C1INH who did not use any HAE medications had a higher incidence of self-reported COVID-19 (24.5%) compared with the normal controls (9%; $p = 0.006$) (Table 2). Taking no HAE medications had no impact on reported COVID-19 in the subjects with HAE-nl-C1INH (19.2% with COVID-19 taking an HAE medication versus 19.4% with COVID-19 not taking an HAE medication).

Impact of HAE on COVID-19 Symptoms and Disease Severity

Fatigue was reported as a symptom of COVID-19 by significantly more normal controls (90%) than the subjects with HAE-C1INH (65%) ($p = 0.029$). The subjects with HAE-nl-C1INH reported chills more often than did the normal controls (65% versus 29%, respectively; $p = 0.023$). Otherwise, there were no significant differences in symptoms or reported complications between the subjects with HAE and the normal controls (Table 3). The rates of emergency department visits and hospitalizations among the subjects who reported COVID-19 are shown in Table 4. There were 18 COVID-19–related deaths reported in family members of subjects with HAE-C1INH (1 of these 18 also had HAE-C1INH), and 11 deaths reported in the family members of subjects with HAE-nl-C1INH (3 of these 11 also had HAE-nl-C1INH).

DISCUSSION

Our study comprised a large controlled effort to analyze the risk of COVID-19 for patients with HAE. Previous publications that examined COVID-19 infections in patients with HAE include a case report[18] and smaller series of patients.[19–21] In our dataset, the incidence of reported COVID-19 was 9% of 228 household normal controls, 10.7% of 647 subjects with HAE-C1INH, and 19.4% of 160 subjects with HAE-nl-C1INH, the latter being significantly higher compared with normal controls ($p = 0.0165$) and HAE-C1INH ($p = 0.0132$). Although the total HAE-C1INH group did not show an increased incidence of COVID-19, the subjects with untreated HAE-C1INH (who took neither LTP nor on-demand therapy) had a significantly increased risk of COVID-19 (24.5%; $p = 0.006$) compared with the normal controls or the subjects with HAE-C1INH who took any LTP or on-demand medication (9.5%; $p = 0.003$). The subjects with HAE-C1INH and with two or more attacks per month had a significantly increased incidence of reported COVID-19 (20/138 [14.5%]) compared with those with fewer than two attacks per month (42/502 [8.4%]; $p = 0.031$) (Fig. 2).

COVID-19 symptoms and complications in the subjects with HAE-C1INH were broadly similar to those reported in the normal controls, except for a significantly decreased report of fatigue in the subjects with HAE-C1INH and increased chills in the subjects with HAE-nl-C1INH (Table 4). Severity surrogates, including medical attention, emergency department visits, or hospitalizations, showed no significant difference between these groups. These results were largely consistent with a previous study of subjects with HAE-C1INH with laboratory-confirmed COVID-19.[19] The small number of the subjects with HAE-C1INH who reported COVID-19 symptoms who received neither on-demand nor LTP therapy showed a striking increase in the frequency of seeking medical care or emergency evaluation.

Given the rarity of HAE-C1INH (prevalence of ~1:50,000) and the suspected lower prevalence of HAE-nl-C1INH, the HAE group sizes were robust, with a wide geographic distribution (Fig. 1). The study design incorporated household members (relatives or non-relatives) without angioedema as controls, which allowed for analysis of a comparable epidemiologic COVID-19 risk. Factors anticipated to enhance the risk of infection (such as suspected contact with COVID-19 as well as employment or behaviors that involved close proximity and exposure to multiple individuals) were generally associated with a higher likelihood of COVID-19 for the subjects with and without HAE (Online Supplemental Table S2). Smoking, vaping, alcohol, cannabis, cocaine, opioids, methamphetamine, ecstasy, and use of other drugs did not have a significant influence on COVID-19 (Online Supplemental Table S3).

Consistent with previous reports that examined comorbidities, obesity (body mass index ≥ 30 kg/m^2) was a significant risk for COVID-19 ($p = 0.012$). In contrast, we did not find older age, ethnicity, or male gender as specific predictors of COVID-19 infection or enhanced morbidity. Autoimmunity was a significant risk factor for reported COVID-19 illness among the HAE-C1INH cohort (21.6% COVID-19 in subjects with autoimmunity versus 10.0% COVID-19 in subjects without autoimmunity; $p = 0.047$). The prevalence of autoimmunity has been reported to be increased in HAE-

Table 2 **HAE medications and incidences of COVID-19**

	HAE-C1INH (n = 647)				HAE-nl-C1INH (n = 160)			
	On Medication*		Off Medication#		On Medication*		Off Medication#	
	n	COVID-19, n (%)	n	COVID-19, n (%)	n	COVID-19, n (%)	n	COVID-19, n (%)
All subjects, with or without treatment	647	69 (10.7)	n/a	n/a	160	31 (19.4)	n/a	n/a
Prophylactic								
Any prophylaxis	476	44 (9.2)	171	25 (14.6)	96	19 (19.8)	64	12 (18.8)
Lanadelumab	244	23 (9.4)	403	46 (11.4)	49	8 (16.3)	111	23 (20.7)
SC pd–C1INH	126	7 (5.6)¶	521	62 (11.9)	16	3 (18.8)	144	28 (19.4)
IV pd–C1INH##	35	3 (8.6)	612	66 (10.8)	10	3 (33)	150	28 (18.7)
Androgens	18	3 (16.7)	629	66 (10.5)	2	0	158	31 (19.6)
Berotralstat	25	3 (12)	622	66 (10.6)	0	0	160	31 (19.4)
Recombinant C1INH	14	4 (28.6)	633	65 (10.3)	7	1 (14.3)	153	30 (19.6)
Tranexamic acid	1	0	646	69 (10.7)	4	0	156	31 (19.9)
Progestin	0	0	647	69 (10.7)	8	3 (37.5)	152	28 (18.4)
Other	30	5 (16.7)	617	64 (10.4)	11	2 (18.2)	149	29 (19.5)
On demand								
Any on demand	541	47 (8.7)¶	106	22 (20.8)	123	23 (18.7)	37	8 (21.6)
Icatibant	434	34 (7.8)‖	213	35 (16.4)	105	22 (19.4)	55	9 (16.4)
IV pd–C1INH##	76	9 (11.8)	571	60 (10.5)	5	2 (40)	155	29 (18.7)
Recombinant C1INH	46	4 (8.7)	601	65 (10.8)	20	5 (25)	140	26 (18.6)
Ecallantide	15	3 (20)	632	66 (10.4)	16	2 (12.5)	144	29 (20.1)
IV pd–C1INH	26	3 (11.5)	621	66 (10.6)	2	1 (50)	158	30 (19)
Other	6	1 (16.7)	641	68 (10.6)	2	0	158	31 (19.6)
Combined LTP and on demand								
Any LTP or on demand	598	57 (9.5)¶	49	12 (24.5)	134	26 (19.4)	26	5 (19.2)
Any pd–C1INH or icatibant	527	43 (8.2)¶	120	26 (21.7)	107	22 (20.6)	53	9 (17.0)

HAE = Hereditary angioedema; COVID-19 = coronavirus disease 2019; C1INH = C1 inhibitor; nl = normal; n/a = not applicable; SC = subcutaneous; pd = plasma-derived; IV = intravenous; LTP = long-term prophylactic.

**Corresponds to the number and percentage of the subjects who used the specified medication and who reported having COVID-19.*

#Corresponds to the number and percentage of the subjects who did not use the specified medication and who reported having COVID-19.

Statistically significant when comparing on-medication with off-medication:

¶$p < 0.05$.

‖$p < 0.0005$.

##IV pd-C1INH combines the data from the different IV pd-C1INH products used by the subjects.

C1INH;[20–22] possibly due to dysregulation of the classic complement pathway (Table 1).

Much of the data was gathered before the widespread availability of accurate testing in the United States. We analyzed the likelihood that the self-reported COVID-19 was accurate by using five selected symptoms previously shown in large datasets to correlate with a diagnosis of COVID-19 (loss of smell or taste, fever, cough, shortness of breath, and fatigue).[23,24] More than 90% of all participants who reported COVID-19 had at least one of these symptoms. Although the reliance on self-report versus confirmed testing was a limitation of our study, retrospective self-reported symptom reports have been shown to be accurate for the diagnosis of COVID-19.[23–25] However, the low number of the participants with self-declared infection in the normal control and HAE-nl-C1INH groups is considered a limitation of the study from the standpoint of the COVID-19 risk.

Table 3 **COVID-19 symptoms and complications**

	Normal Controls, *n* (%)	HAE-C1INH, *n* (%)	HAE-nl-C1INH, *n* (%)
Symptoms			
Fever	11 (52.4)	33 (47.8)	21 (67.7)
Cough	14 (66.7)	35 (50.7)	22 (71.0)
SOB	11 (52.4)	21 (30.4)	16 (51.6)
Fatigue	19 (90.5)	45 (65.2)*	28 (90.3)
Loss smell	7 (33.3)	22 (31.9)	14 (45.2)
Loss taste	7 (33.3)	20 (29.0)	13 (41.9)
Chills	6 (28.6)	33 (47.8)	20 (64.5)*
Aches	16 (76.2)	38 (55.1)	21 (67.7)
Sore throat	11 (52.4)	24 (34.8)	21 (67.7)
Chest pain	8 (38.1)	20 (29.0)	19 (61.3)
Complications			
Confusion	3 (14.3)	4 (5.8)	5 (16.3)
Memory	3 (14.3)	5 (7.3)	6 (19.4)
Rash	1 (4.8)	4 (5.8)	5 (16.1)
Wheeze	3 (14.3)	5 (7.3)	2 (6.5)
Generalized inflammation	1 (4.8)	4 (5.8)	6 (19.4)
Cytokine storm	1 (4.8)	0 (0)	3 (9.7)

COVID-19 = Coronavirus disease 2019; HAE = hereditary angioedema; C1INH = C1 inhibitor; nl = normal; SOB = shortness of breath.
**p < 0.05 compared with normal controls.*

Table 4 **COVID-19 outcomes**

	HAE-C1INH, *n*/total *n* (%)			HAE nl–CINH, *n*/total *n* (%)		
Selection	**Seek Prescription**	**ED**	**Hospital**	**Seek Prescription**	**ED**	**Hospital**
All subjects	28/62 (45.2)	10/69 (14.5)	2/69 (2.9)	14/29 (48.3)	6/31 (19.4)	3/31 (9.7)
On SC pd–C1INH	1/7 (14.3)	0/7 (0)	0/7 (0)	1/3 (33.3)	1/3 (33.3)	0/3 (0)
No SC pd–C1INH	27/55 (49.1)	10/62 (16.1)	2/62 (3.2)	13/26 (50)	5/28 (17.9)	3/28 (10.7)
On icatibant	17/34 (50)	5/34 (14.7)	0/34 (0)	10/22 (45.5)	6/22 (27.3)	2/22 (9.1)
No icatibant	11/28 (39.3)	5/35 (14.3)	2/35 (5.7)	4/7 (57.1)	0/9 (0)	1/9 (11.1)
No LTP or on demand	4/5 (80)	3/12 (25)	0/12 (0)	2/3 (66.7)	0/5 (0)	0/5 (0)
Comparison group: normal controls	6/20 (30)	2/21 (9.5)	2/21 (9.5)	6/20 (30)	2/21 (9.5)	2/21 (9.5)

COVID-19 = Coronavirus disease 2019; HAE = hereditary angioedema; C1INH = C1 inhibitor; nl = normal; ED = emergency department; SC = subcutaneous; pd = plasma-derived; LTP = long-term prophylactic.

Among the most interesting results of our survey was the apparent influence of medications used for the treatment of HAE. Within the HAE-C1INH population, LTP with SC pd–C1INH was associated with a significantly lower rate of reported COVID-19 ($p = 0.02$). The use of intravenous pd–C1INH or recombinant C1INH did not show a similar effect (Table 2), which raises the possibility that achieving a steady-state functional C1INH level of >40%[26] may be important for conferring any protective effect against developing COVID-19 illness within the HAE-C1INH cohort. No significant correlation between the severity of COVID-19 and the use of SC pd–C1INH was possibly due to the small number of subjects in this group.

C1INH regulates multiple proteolytic cascades, including the classic complement, plasma contact, and fibrinolytic and intrinsic coagulation systems. The lack of significant benefit observed from the plasma kallikrein inhibitor lanadelumab intimates that the observed

beneficial effect of C1INH replacement may involve other actions of this inhibitor, such as regulating classic complement system activation. There is compelling evidence in the literature for a role of complement activation and dysregulation in the course of COVID-19,[26,27] which may ultimately provide support for a protective effect of SC pd–C1INH replacement in patients with HAE-C1INH as it relates to the risk of COVID-19. The lack of a protective effect of SC pd–C1INH in the self-reported HAE-nl–C1INH group suggested that increasing C1INH above the normal levels may not be beneficial in reducing the COVID-19 risk. Furthermore, we caution that, among the self-reported subjects with HAE-nl-C1INH, diagnostic accuracy is limited by the absence of commercial biomarkers. Our data would support that, in general, individuals with normal levels of functional C1INH would be unlikely to benefit from pdC1INH therapy with respect to COVID-19 risk.

Use of icatibant also resulted in a highly significant decrease in reported COVID-19. Other on-demand therapies did not show a protective effect (Table 4). The reason for this effect was unclear, particularly in light of the relatively short half-life of icatibant. Another puzzling question is why icatibant, a bradykinin B2 receptor (BDKB2R) antagonist, significantly decreased reported COVID-19 within the HAE-C1INH group ($p = 0.0002$) (Table 4), whereas lanadelumab, a potent plasma kallikrein inhibitor that prevents the generation of bradykinin, failed to do so. These results may be reconciled by considering that kinins can be efficiently generated by another system, *viz.*, the tissue kallikrein system. Interplay among the tissue kallikrein system, contact, complement, and coagulation systems has been suggested to participate in COVID-19.[28–31]

A role for tissue kallikrein was previously demonstrated in connection with viral illness, including facilitating human papilloma virus cellular entry[32] and enhancing influenza A replication in the respiratory tract.[33] More directly, increased levels of active human tissue kallikrein have been identified in bronchoalveolar lavage fluid during experimental rhinovirus infections.[34] Activation of BDKB2R by bradykinin or lysl-bradykinin has also been shown to suppress type I interferon responses.[35] The bradykinin B1 receptor (BDKB1R), although not expressed in normal tissue, is inducible under pathologic conditions. Both activation of the BDKB2R and double-stranded RNA have been shown to increase both expression and function of the BDKB1R.[36] Tissue kallikrein has also been specifically linked to infection of human epithelium by human coronavirus HKU1.[37] The implications of these findings will require further elucidation to understand the role of the tissue kallikrein-kinin system in the pathogenesis of COVID-19.

CONCLUSION

We showed that the subjects with HAE-C1INH who were not taking HAE medications seemed to be at significantly increased risk of reported COVID-19 compared with the normal controls, although no significant increase in COVID-19–associated complication was observed. SC pd–C1INH and icatibant use was associated with a significant reduction in reported COVID-19 in the subjects with HAE-C1INH. The subjects with HAE-nl-C1INH identified more COVID-19 symptoms than did the normal controls, but HAE medications did not have a significant impact on the risk of infection. Our results may support the hypothesis that the classic complement and tissue kallikrein systems play important roles in COVID-19 illness.

Acknowledgments

We thank Anthony J. Castaldo for his invaluable help and the US HAEA in helping to recruit the subjects for the survey and review of the manuscript.

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