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COVID-19 triggers attacks in HAE patients without worsening disease outcome

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Clinical Implications

We observed that acute respiratory syndrome coronavirus 2 infection can trigger attacks in hereditary angioedema with or without C1 inhibitor deficiency; however, COVID-19 is not more severe than in non–hereditary angioedema patients. Previous use of androgens did not influence any of these aspects.

Hereditary angioedema (HAE) is a rare genetic disease in which episodes of angioedema have a high impact on quality of life. Death due to airway obstruction can occur.[1] Two types of HAE are described: with C1 inhibitor deficiency (HAE-C1-INH) associated with *SERPING1* variants, and with normal C1-INH (HAE-nC1-INH) associated with several variants or unknown causes.[2]

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. C1 inhibitor deficiency inhibits other systems such as fibrinolytic, complement, and coagulation pathways; its deficiency leads to increased BK release. The mechanisms for HAE-nC1-INH are largely unknown and possibly variable, although they are presumed ultimately to be mediated by BK in most cases.[1] It was previously hypothesized that dysregulated BK signaling could be involved in COVID-19 respiratory complications owing to depletion of the angiotensin-converting enzyme 2 receptor by acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, resulting in increased levels of des-Arg(9)-bradykinin, a bioactive metabolite of BK associated with lung injury and inflammation.[3,4]

The clinical spectrum of COVID-19, the disease caused by SARS-CoV-2 infection, varies widely. Recognized risk groups for more severe infection are age over 60 years, hypertension, diabetes, and obesity.[5] Considering that HAE patients have an uncontrolled kallikrein-kinin system, we evaluated clinical characteristics of COVID-19 in these patients in a wider population than in our previous publication,[6] focusing on severity and evolution.

Hereditary angioedema reference centers in Latin American countries were consulted during December 2020 for patients who reported COVID-19 during that year. Patients' associations helped to pass on the information. There were no age or risk factor restrictions. Diagnosis of HAE was confirmed by clinical symptoms, biochemical tests, and family history; for patients with HAE-nC1-INH, whenever available, the *F12* variant was additionally evaluated. We registered the tests performed for SARS-CoV-2 infection confirmation: reverse transcription polymerase chain reaction, serology, and/or rapid test. A questionnaire was sent to the centers targeting age, sex, type of HAE, risk factors, variants for HAE-nC1-INH when available, prophylaxis for HAE, COVID-19 symptoms, occurrence of angioedema attacks and therapy used for treating each attack, hospitalization, period of symptomatology, evolution, and complications. Data were analyzed using the IBM SPSS Statistics for Windows, version 25 (IBM Corp, Armonk, NY). The type of statistics used in this study was descriptive and inferential, but without control for confounding variables or hypothesis analysis owing to its descriptive nature. Tests of normality were applied to quantitative variables using Shapiro-Wilk test ($n < 60$) to determine the measures of adequate central tendency and establish parametric or nonparametric methods adjusted to the variables. In the case of qualitative variables, we used association methods, in this case χ^2 test to establish measures of statistical significance. The project was approved by the ethics committee (CAAE: 40745220.0.1001.0082).

Of 20 HAE reference centers in Latin America, six countries (Chile, El Salvador, Guatemala, Honduras, Uruguay, and Venezuela) had no HAE patients with SARS-CoV-2 infection; two countries (Cuba and Dominican Republic) did not respond, and Bolivia identified no HAE patients. Ten countries contributed to this survey: Brazil ($n = 22$); Argentina ($n = 7$); Colombia ($n = 11$); Mexico ($n = 6$); Peru ($n = 3$); Paraguay ($n = 2$); Puerto Rico ($n = 2$), and Panama, Ecuador, and Costa Rica with one patient each. A total of 56 patients (mean age, 41.25 ± 14.3 years; 78.6% female) had a confirmed diagnosis of HAE-C1-INH and HAE-nC1-INH, corresponding to 44 of 56 [78.6%] and 12 of 56 [21.4%], respectively. *F12* mutation was identified in five of 12; there was unknown mutation in four of 12 and no sequencing was done in three of 12. Diagnosis of

TABLE I. General characterization of HAE patients with COVID-19 (n = 56)

Clinical characteristics	HAE C1-INH (n = 44)	HAE nC1-INH (n = 12)	Total (n = 56)	*P*
Mean age, y (SD)	42.07 ± 14.6	38.2 ± 13.3	41.25 ± 14.3	
Age, y (n [%])*				
10-19	1 (2.7%)	1 (8.3%)	2 (3.6%)	
20-29	8 (18.1%)	1 (8.3%)	9 (16.1%)	
30-39	11 (25%)	5 (41.6%)	16 (28.6%)	
40-49	14 (31.8 %)	2 (16.6%)	16 (28.6%)	
50-59	4 (9%)	2 (16.6 %)	6 (10.7%)	
60-69	3 (6.8 %)	1 (8.3%)	4 (7.1%)	
>70	3 (6.8%)	0	3 (5.3%)	
Sex, n (%)				
Male	12 (27.3)	0	12 (21.4)	.051†
Female	32 (72.7)	12 (100)	44 (78.6)	
Prophylaxis, n (%)				
No	29 (51.8%)	9 (16%)	38 (67.8)	.674†
Androgens	6 (10.7 %)	2 (3.5%)	8 (14.2)	
Tranexamic acid	2 (3.6 %)	1 (1.8%)	3 (5.4)	
pdC1-INH	3 (5.4%)	0	3 (5.4)	
Progestins with or without tranexamic acid	4 (7.1%)	0	4 (7.1)	
Attacks during COVID-19, n (%)				.529‡
Yes	20 (35.7)	4 (7.1)	24 (42.9)	
No	24 (42.9)	8 (14.3)	32 (57.1)	
Attack treatment				
Icatibant	6	2	8	
pdC1-INH	3	0	3	
Icatibant + pdC1-INH	0	1	1	
Icatibant + FFP	1	0	1	
Icatibant + rhC1-INH	1	0	1	
FFP	2	0	2	
LMWH	1	0	1	
None	6 (30%)	1 (25%)	7(29.2%)	
Comorbidities, n (%)				
None	29 (51.8)	9 (16.1)	38 (67.8)	
Obesity	6 (10.7)	2 (3.6)	8 (14.3)	
Diabetes mellitus	2 (3.6)	1 (1.8)	3 (5.4)	
Arterial hypertension	3 (5.4)	0	3 (5.4)	
Others (neoplasia, autoimmunity)	4 (7.1)	0	4 (7.1)	
Period with symptomatology (median d [interquartile range])	10 (7-14)	8.5 (3-15)	—	
Evolution, n (%)				
Recovered	41 (73.2)	12 (21.4)	52 (92.8)	
Sequelae§	2 (3.6)	0	2 (3.6)	
Deceased	1 (1.8)	0	1 (1.8)	

HAE C1-INH, hereditary angioedema with C1 inhibitor deficiency; *HAE nC1-INH*, hereditary angioedema with normal C1 inhibitor; *pdC1-INH*, plasma derived C1 inhibitor. *P* = HAE-C1-INH vs HAE-nC1-INH.

*Percentage of patients in relation to whole population (HAE-C1-INH = 44; HAE-nC1-INH = 12).

†χ^2 test.

‡Fisher test.

§Sequelae was considered for patients maintaining respiratory symptoms for longer than 60 d after the onset of COVID-19 symptoms.

SARS-CoV-2 infection was by reverse transcription polymerase chain reaction in 41 (73.2%), serology in 14 (25%), and rapid test in one (1.8%). Comorbidities were not identified in 67.8% of patients. Of 86 patients, obesity was present in eight (14.3%), diabetes in three (5.4%), arterial hypertension three (5.4%), and neoplasia and other conditions in four (7.1%). Median duration of disease was 10 days (interquartile range, 7-14 days) and 8.5 days (interquartile range, 3-15 days) in patients with HAE-C1-INH and HAE-nC1-INH, respectively. Eight patients were hospitalized, one of them owing to an HAE attack.

Angioedema attacks occurred in 24 of 56 patients (42.9%) during SARS-CoV-2 infection, predominantly in HAE-C1-INH (20 of 44; 45.5%) compared with HAE-nC1-INH (4 of 12; 33.3%); however, there was no significant difference ($P > .05$). Nineteen of 24 patients who developed attacks were free of attacks in the previous 6 months before SARS-CoV2 infection. In

66 patients, attacks affected the face and tongue in seven (10.6%), extremities in 12 (18.2%), abdomen in seven (10.6%), and larynx in four (6.1%). Discriminating by sex, no association was confirmed between groups ($P = .525$); however, attacks occurred predominantly in women with HAE-C1-INH (32 of 44; 72.7%) during COVID-19. Fifty percent of patients who experienced attacks during COVID-19 (12 of 24) were not receiving prophylaxis; however, no statistical significance was observed in relation to long-term prophylaxis. Complete recovery was observed in 53 patients (92.8%), severe respiratory insufficiency in two, and death in one HAE-C1-INH. The cause of death was septic shock resulting from bacterial pulmonary co-infection. Disease progression was not different based on sex, therapy, or type of HAE ($P = .803$) (Table I).

This was a collaborative study evaluating 56 patients with HAE-C1-INH and HAE-nC1-INH. We found no differences in COVID-19 outcomes compared with the general population. Hereditary angioedema has been hypothesized to be a potential risk factor for severe COVID owing to baseline contact system dysregulation and the theorized role of the contact system in COVID-associated lung disease.[3,4,7]

Our findings confirmed the possibility of SARS-CoV-2 infection triggering HAE attacks; however, the course of COVID-19 was not influenced by the previous diagnosis of HAE. Besides considering the viral infection that was responsible per se for angioedema symptoms, it is important to consider the psychological stress of the COVID-19 pandemic as a potential confounding factor for the development of HAE attacks, as reported by Eyice Karabacak et al.[8] On the other hand, some circumstances were favorable for a better prognosis in the current population. A higher severity of COVID-19 was reported in men,[9] and females were predominant in this group. In addition, only seven HAE patients were greater than age 60 years, and approximately 68% had no comorbid risk factors for severe COVID-19. A 71-year-old patient died of pulmonary complications and multiorgan disfunction related to COVID-19, with no previously reported comorbidity.

Of 24 patients who experienced attacks, 19 were clinically asymptomatic in the 6 months preceding the SARS-CoV-2 infection. Four reported feeling an upper airway obstruction and laryngeal edema, not well-characterized; facial edema was present in two of them. Eight patients were treated with tranexamic acid, and no thromboembolic event occurred. One patient with HAE-nC1-INH and no variant identified was hospitalized owing to high D-dimer and recovered with no complications. Treatment of acute episodes of HAE included icatibant, a BK receptor 2 antagonist, in almost half of the attacks, and the clinical response was successful.

We evaluated a representative number of patients with HAE C1-INH and HAE-nC1-INH. Our results suggest that SARS-CoV-2 infection could trigger angioedema attacks without influencing the prognosis of the disease in HAE patients, as we previously observed in a much smaller cohort.[6]

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