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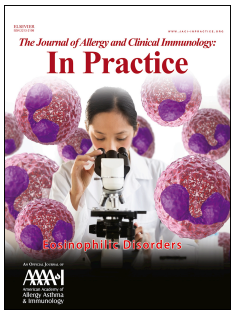

COVID-19 triggers attacks in HAE patients without worsening disease outcome

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

Running title: Hereditary Angioedema and COVID-19

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Conflict of Interest

All authors declare that they have no conflicts of interest for this publication.

General conflicts of interest of the authors:

María Margarita Olivares[1] Speaker and medical advisor for Takeda; speaker for CSL Behring, Pint Pharma, Novartis and Sanofi.
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CLINICAL IMPLICATIONS

We observed that SARS-CoV-2 infection can trigger attacks in HAE with or without C1-INH deficiency; however, COVID19 is not more severe than in non-HAE patients. Previous use of androgens did not influence any of these aspects.

KEYWORDS: Hereditary Angioedema; C1 inhibitor; COVID-19; SARS-CoV-2; Androgen; Risk factor; Hereditary Angioedema with normal C1-INH

Manuscript: 1170 words

One Table

CLINICAL COMMUNICATION

Hereditary angioedema (HAE) is a rare genetic disease with episodes of angioedema causing 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 the lack of control of the contact and kallikrein-kinin systems, resulting in bradykinin (BK) release, after high molecular weight kininogen (HK) cleavage by kallikrein. C1-INH inhibits other systems such as fibrinolytic, complement and coagulation pathways and, its deficiency leads to increased BK release. The mechanisms for HAE-nC1-INH are largely unknown and possibly variable, though presumed to ultimately be mediated by BK in most cases.[1] It was previously hypothesized that dysregulated BK signaling could be involved in coronavirus disease 2019 (COVID-19) respiratory complications due to depletion of angiotensin-converting enzyme 2 (ACE2) receptor by acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, resulting in increased levels of des-Arg(9)-bradykinin (DABK), 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, hypertension, diabetes and obesity. [5] Considering that HAE patients have an uncontrolled kallikrein-kinin system, we evaluated clinical characteristics of COVID19 in these patients in a wider population than our previous publication, [6] focusing on severity and evolution.

HAE reference centers in Latin American countries were consulted during the month of December 2020, for patients who reported COVID19 during this year. Patients' associations helped to pass on the information. There was no age or risk factor restrictions. Diagnosis of HAE was confirmed by clinical symptoms, biochemical tests, family history, and for patients with HAE-nC1-INH, whenever available, *F12* variant was additionally evaluated. We registered the tests performed for SARS-CoV-2 infection confirmation: RT-PCR, 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 if 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 SPSS V25 program. The type of statistics used in this study was descriptive and inferential, but without control for confounding variables or hypothesis analysis due to its descriptive nature. Tests of normality were applied to the quantitative variables using the Shapiro-Wilk test (n <60), to determine the measures of adequate central tendency and to establish parametric or non-parametric methods adjusted to the variables. In the case of qualitative variables, association methods were used, in this case using the chi-square test to establish the measures of statistical significance. The project was approved by the Ethics Committee (CAAE: 40745220.0.1001.0082).

Out of 20 HAE reference centers in Latin America, 6 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 has no HAE patients identified. 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. Fifty-six patients (mean= 41.25 ±

14.3 years old; 78.6% females) had a confirmed diagnosis of HAE-C1-INH and HAE-nC1-INH, corresponding to 44/56 [78.6%] and 12/56 [21.4%], respectively. *F12* mutation was identified in 5/12; unknown mutation in 4/12 and no sequencing was done in 3/12. Diagnosis of SARS-CoV-2 infection was by RT-PCR in 41 (73.2%); serology in 14 (25%); rapid test in one (1.8%). Comorbidities were not identified in 67.8% of patients; obesity was present in 8/56 (14.3%), diabetes in 3/56 (5.4%), arterial hypertension 3/56 (5.4%), neoplasia and other conditions in 4/56 (7.1%). Median duration of disease was 10 (IQR: 7-14) and 8.5 (IQR: 3-15) days in patients with HAE-C1-INH and HAE-nC1-INH, respectively. Eight patients were hospitalized; one of them due to an HAE attack.

Angioedema attacks occurred in 24/56 (42.9%) of patients during SARS-CoV-2 infection, predominantly in HAE-C1-INH (20/44; 45.5%) compared with HAE-nC1-INH (4/12; 33.3%); however, there was no significant difference ($p>0.05$). Nineteen out of 24 patients who developed attacks were attack free in the previous 6 months prior to SARS-CoV2 infection. Attacks affected the following sites: face and tongue in 7/66 (10.6%); extremities in 12/66 (18.2%); abdomen in 7/66 (10.6%) and larynx in 4/66 (6.1%). Discriminating by sex, no association was confirmed between the groups ($p = 0.525$), however, attacks occurred predominantly in HAE-C1-INH women (32/44; 72.7%) during COVID-19. Fifty percent (12/24) of patients who suffered attacks during COVID-19 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 2 and death in one HAE-C1-INH patient. The cause of death was septic shock secondary to bacterial pulmonary coinfection. Disease progression was not different based on sex, therapy or type of HAE ($p = 0.803$) (Table 1).

202 This is a collaborative study evaluating 56 patients with HAE-C1-INH and HAE-nC1-INH
203 and no differences in COVID-19 outcomes were found in comparison to the general
204 population. HAE has been hypothesized to be a potential risk factor for severe COVID due
205 to baseline contact system dysregulation and the theorized role of the contact system in
206 COVID-associated lung disease [3,4,7].

207 Our findings confirmed the possibility of SARS-CoV-2 infection triggering HAE attacks;
208 however, the course of COVID-19 was not influenced by the previous diagnosis of HAE.
209 Besides considering the viral infection *per se* responsible for angioedema symptoms, it is
210 important to consider the psychological stress of the COVID-19 pandemic as a potential
211 confounding factor for the development of HAE attacks, as reported by Karabacak, et al. [8]
212 On the other side, some circumstances were favorable to have better prognosis in our
213 population. Higher severity of COVID-19 was reported in men [9], and females were
214 predominant in our group. In addition, only 7 HAE patients were older than 60 years of age
215 and approximately 68% had no comorbid risk factors for severe COVID-19. A 71-year-old
216 patient died from pulmonary complications and multiorgan disfunction related to COVID-
217 19, with no previously reported comorbidity.

218 We have to emphasize that 19 out of 24 patients who suffered attacks were clinically
219 asymptomatic in the period of 6 months preceding the SARS-CoV-2 infection. Four reported
220 feeling an upper airway obstruction and laryngeal edema, not well characterized; facial
221 edema was present in two of them. Eight patients were treated with tranexamic acid and no
222 thromboembolic event occurred. One patient with HAE-nC1-INH and no variant identified
223 was hospitalized due 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 previously observed by us in a much smaller cohort. [6]

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264 Table 1. General characterization of HAE patients with COVID-19 (n=56)

265 **Table 1**

	HAE C1-INH (n=44)	HAE nC1-INH (n=12)	Total (n=56)	p value
Mean age (SD)	42.07 ± 14.6	38.2 ± 13.3	41.25 ± 14.3	
Age (years)	N (%)[1]	N (%)[1]	N (%)[1]	
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 (%)	N (%)		
Male	12 (27.3)	0	12 (21.4)	0.051[a]
Female	32 (72.7)	12 (100)	44 (78.6)	
Prophylaxis	N	N	N	
No	29 (51.8%)	9 (16%)	38 (67.8)	0.674[a]
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 (%)	N (%)	N (%)	0.529 [b]
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 (%)	N (%)	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 days (IQR)	10 (7-14)	8.5 (3-15)	-	
Evolution	N (%)	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)

Abbreviations: HAE C1-INH, hereditary angioedema with C1 inhibitor deficiency; HAE nC1-INH, hereditary angioedema with normal C1 inhibitor; SD, Standard deviation; pdC1-INH, plasma derived C1 inhibitor; IQR Interquartile range; [1] It refers to the percentage of patients in relation to the whole population (HAE-C1-INH=44; HAE-nC1-INH=12)
[a] chi square test; [b] Fischer test.
* p value = HAE-C1-INH vs HAE-nC1-INH **Sequelae was considered for patients maintaining respiratory symptoms for a period longer than 60 days of the onset of COVID-19 symptoms.