Title: COVID-19 in HAE patients: a prospective study

Running Title: COVID-19 in HAE

Authors:

Aude Belbézier[1], Mélanie Arnaud[1], Isabelle Boccon-Gibod[1,2], Fabien Pelletier[2,3], Chloé McAvoy[4], Delphine Gobert[2,4], Olivier Fain[2,4], Aurélie Du-Thanh [2,5], Julien Lupo[6], Laurence Bouillet[1,2]

Affiliations: [1]Department of Internal Medicine, Grenoble University Hospital, Grenoble, France; [2]National Reference Centre for Angioedema, CREAK, France; [3]Department of Internal Medicine, Besancon University Hospital, Besancon, France; [4] Sorbonne Université, service de médecine interne, AP-HP, Hôpital Saint Antoine, F-75012 Paris , France; [5]Department of Dermatology, CHU Montpellier, Montpellier, France.; [6] Univ. Grenoble Alpes, CEA, CNRS, Virology Laboratory CHU Grenoble Alpes, IBS, 38000 Grenoble, France

Acknowledgements:
This study is supported by French Reference Center for Angioedema, CREAK, and by research grants CNRS (GREPI/AGIM CNRS FRE 3405)
The authors thank Kenz Le Gouge.

Author Disclosures:
All authors report no disclosures

We certify that the submission is not under review at any other publication.
The principal author, Laurence Bouillet takes full responsibility for the data, the analyses and interpretation, and conduct of the research. Bouillet has full access to all data and has the right to publish any and/or all data, separately from or with any sponsor. No financial or other relationships exist that might lead to a perceived conflict of interest.

Conclusion paragraph: COVID-19 could induce attacks in HAE patients but only in those who do not have prophylactic treatment. HAE Patients with prophylactic treatment may be at low risk of developing attack in case of COVID-19.

Key words:
HAE, COVID-19, hereditary angioedema, angiotensin-converting-enzyme inhibitor

Letter to the editor

Hereditary angioedema (HAE) is a rare genetic disease characterized by transitory recurrent subcutaneous and/or submucosal swelling episodes (1). It should be divided in three forms according to the level of C1 inhibitor: HAE type I or II with C1-inhibitor deficiency, and HAE with normal C1inhibitor (nC1Inh HAE) level (1). In all forms, the swelling episodes are explained by a sudden, localized and bradykinin-mediated increase of vascular permeability. Some triggers have been identified such as infection (2). Coronavirus disease 19 (COVID-19) is a spreading pandemic disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To infect cells SARS-CoV-2 virus has to enter via the transmembrane protein, angiotensin converting enzyme 2 (ACE2) (3). This binding supposedly downregulates ACE, thus enhancing bradykinin expression (4,5). This suggest that SARS-CoV-2 could be an angioedema attack trigger, especially in patients with predisposing AE attacks condition such as HAE (6).

The AE-COVID19 registry was created in France in 2019 to collect data on the HAE patients who developed COVID-19 infection. It aims to enroll all HAE patients who presented an acute COVID-19 infection. The primary objective was to describe the severity and frequency of HAE attacks after SARS-CoV-2 infection. SARS-CoV-2 infection was defined by detection of SARS-CoV-2 RNA from a nasopharyngeal specimen (Abbott Alinity or Roche Cobas SARS-CoV-2 tests) or presence of anti-SARS-CoV-2 antibodies in serum (Wantai total antibody ELISA or Roche Elecsys total antibody assay). Thanks to this registry we could analyze prospectively data from 11 HAE patients between April and November 2019. Oral consent from all patient was collected.

The majority of patients were women (6/11) with a mean age of 42 (range: 26-85). Clinical and biological characteristics of the patients are presented in Table 1. Eight were diagnosed with type I HAE, 1 with type II HAE and 2 with nC1Inh HAE (one with plasminogen mutation and one with factor XII deficiency). The last attack dated back a median of 80 days before COVID-19 (range interval: 15-1753). Four patients received prophylactic therapy (Danazol (3), Lanadelumab (1)).

SARS-CoV-2 infection was symptomatic for all patients: asthenia (6), cough (7), dyspnea (5), agueusia (8), anosmia (9), headache (4), abdominal symptoms (2). The two oldest patients (85 and 65 year-old) presented severe hypoxemic respiratory failure secondary to SARS-CoV-2 requiring oxygen therapy. The younger one was treated with mechanical ventilation after

orotracheal intubation. They both recovered after 60 and 18 days of hospitalization respectively.

Three of our 11 patients developed HAE attacks after COVID-19 diagnosis (Table 2). Two of them had a type 1 HAE, the third a HAE associated with plasminogen mutation. The last attack dates back 80 days before COVID-19 (range 58-87). None of them had prophylactic therapy. The median delay between the COVID-19 first symptoms and HAE acute attacks was 2 days (range 1.10). All developed iterative moderate attacks (median attack number: 3, range: 2-5). They described attacks affecting the face (1) and extremities (3). The median delay before attacks resolution was 48 hours (with broad range: 3-72).

In summary, in our cohort, 27% of HAE patients developed attacks during SARS-CoV-2 infection. When we exclude patients under prophylactic therapy, 42% of patients experienced attacks during COVID-19. Patients who developed attacks during infection, presented iterative moderate attacks, especially on extremities. It suggests a possible link between AE development and SARS-CoV-2 infection in HAE patients, especially in those who do not beneficiate from a prophylactic HAE treatment. Patients with prophylactic treatment may be at low risk of developing attack in case of COVID-19. We cannot recommend systematic prophylaxis treatment in case of COVID-19. HAE prophylaxis during COVID-19 should be discussed on a case-by-case basis.

References

1. Agostoni A, Aygorenpursun E, Binkley K, Blanch A, Bork K, Bouillet L et al. Hereditary and acquired angioedema: Problems and progress: Proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. Journal of Allergy and Clinical Immunology 2004;114:S51–S131.

2. for the IOS Study Group, Caballero T, Maurer M, Longhurst H, Aberer W, Bouillet L et al. Triggers and Prodromal Symptoms of Angioedema Attacks in Patients With Hereditary Angioedema. Journal of Investigational Allergology and Clinical Immunology 2016;26:383–386.

3. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020;181:271-280.

4. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Medicine 2020;46:586–590.

5. van de Veerdonk FL, Netea MG, van Deuren M, van der Meer JW, de Mast Q, Brüggemann RJ et al. Kallikrein-kinin blockade in patients with COVID-19 to prevent acute respiratory distress syndrome. eLife 2020;9:e57555.

6. Xu Y, Liu S, Zhang Y, Zhi Y. Does hereditary angioedema make COVID-19 worse? World Allergy Organization Journal 2020;13:100454.

Table 1 Characteristics of HAE patients in the AE-COVID19 (n = 11).

Characteristic	Population (T= 11)
Sex, n (%)	
Male	5 (55)
Female	6 (45)
Median age [range]	42 [26-85]
HAE subtype	
HAE I	8 (73)
HAE II	1 (9)
nC1Inh HAE	2 (18)
Symptoms	
Abdominal	9 (82)
Laryngeal/facial	9 (82)
Median time between attacks (month)	6 [0.75-60]
Median time between last attack and COVID infection (day)	80 |15-1753]
Age at first attack (years)	14 [2-50]
Age at diagnosis (years)	26.5 [10-55]
Prophylactic treatment (%)	4 (36)
Danazol	3 (27)
Lanadelumab	1 (9)

All values are median, range. HAE: hereditary angioedema; nC1Inh HAE: hereditary angioedema with normal C1 Inhibitor; SARS-CoV-2: severe acute respiratory syndrome coronavirus.

Table 2: Clinical and biological characteristics of patients according to AE attacks status after COVID-19 disease

Population (No)	Patients with AE attacks during COVID (3)	Patients without (8)
Sexe		
Female (%)	1 (33)	5 (62)
Male (%)	2 (67)	3 (38)
Median Age (year)	31	47
Range (year)	29-44	26-85
HAE subtype		
HAE I	2 (67)	6 (75)
HAE II	0 (0)	1 (12.5)
nC1Inh HAE	1 (33)	1 (12.5)
COVID 19		
	cough, dyspnea agueusia, anosmia abdominal symptoms	cough, dyspnea agueusia, anosmia respiratory distress
Median time between last attack and COVID infection (day)	80 [58-87]	74 [15-1753]
Location of care		
Hospital	0 (0)	2 (25)
Home	3 (100)	6 (75)
Oxygen therapy	0 (0)	2 (25)
Max(L/min) (range)	0	12 (12)
Deteted SARS-CoV2		
Positive PCR	2 (67)	6 (750)
Positive serology	1 (33)	2 (25)
AE attack during COVID infection		
Number of attacks (range)	3[2-5]	
Anatomical location		
Abdominal	1 (50)	
Laryngeal/Facial	0 (0)	
Peripheral	3 (100)	
Multiple locations	1 (33)	
Attack intensity (%)	moderate	
Attack treatment (%)	3 (100)	
Exacyl	1 (33)	
Fyrazyr	1 (33)	
Berinert	1 (33)	

HAE: hereditary angioedema; nC1Inh HAE: hereditary angioedema with normal C1 Inhibitor; SARS-CoV-2: severe acute respiratory syndrome coronavirus.