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RESEARCH LETTER

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# COVID-19 as a trigger of acute attacks in people with hereditary angioedema

To the Editor,

Blockage of angiotensin-converting enzyme (ACE), an important enzyme degrading bradykinin into its metabolites, is known to play a key role in bradykinin-mediated angioedema.[1] SARS-CoV-2 has been shown to enter human cell via ACE2 during COVID-19.[2] The SARS-CoV-2 and ACE2 binding supposedly down-regulates ACE, thus interfering with bradykinin degradation and bradykinin concentration in extracellular space.[3,4] Therefore, we have concerns about showing the possibility of down-regulated ACE2 activity during COVID-19 resulting in bradykinin-mediated angioedema attacks in patient with hereditary angioedema (HAE). HAE is a rare, life-threatening, genetic disease[5] characterized by transitory recurrent subcutaneous and/or submucosal swelling episodes which mainly affect skin, gastrointestinal tract, and upper airways.[6] It should be divided in three forms according to the level of C1 inhibitor: HAE type I (HAE I) or II (HAE II) with C1-inhibitor deficiency (HAE C1-INH),[6] and HAE with normal C1 inhibitor (HAE nC1-INH) level.[7] 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.[8] We proposed to study the impact of the COVID-19 disease on HAE attacks.

The National Angioedema Reference Centre (CREAK) created the AE-COVID-19 registry in order to collect data on the HAE COVID-19 impact in France (approved by the CNIL (the French commission for informatics and freedom) and the Ethics Committee (ref: MR1316170420). It aims to enrol all HAE patients who presented an acute COVID-19 infection. A case of COVID-19 was defined as positive serum anti-SARS-CoV-2 IgG antibodies (Wantai total antibody ELISA or Roche Elecsys total antibody assay) or as positive nasopharyngeal SARS-CoV-2 RNA (Abbott Alinity or Roche Cobas

**TABLE 1** Characteristics of HAE patients in the AE-COVID-19 ($n$ = 13)

| Patient | Sex | Age (y) | HAE type | COVID test results | Long-term prophylactic care | HAE attack during COVID-19 | HAE attack therapy | Comorbidity |
|---|---|---|---|---|---|---|---|---|
| 1 | M | 65 | HAE 2 | RT-PCR | Danazol | No | | Hypertension |
| 2 | M | 85 | HAE 1 | RT-PCR | Danazol | No | | Hypertension |
| 3 | M | 29 | HAE 1 | RT-PCR | No | Extremities | Icatibant | Diabetes |
| 4 | F | 37 | HAE 1 | IgM and/or IgG SARS-CoV-2 serology | No | No | | Obesity |
| 5 | F | 37 | HAE 1 | RT-PCR | No | No | | Obesity |
| 6 | M | 31 | HAE 1 | IgM and/or IgG SARS-CoV-2 serology | No | Extremities | Icatibant, C1 Inhibitor concentrate | No |
| 7 | M | 52 | HAE 1 | IgM and/or IgG SARS-CoV-2 serology | Danazol | No | | No |
| 8 | F | 44 | nC1-inh HAE | RT-PCR | 0 | Face | Exacyl | No |
| 9 | F | 59 | HAE 1 | RT-PCR | No | No | | No |
| 10 | F | 26 | HAE 1 | RT-PCR | Lanadelumab | No | | No |
| 11 | F | 42 | nC1-inh HAE | RT-PCR | No | No | | No |
| 12 | F | 30 | HAE 1 | RT-PCR | Lanadelumab | No | | No |
| 13 | F | 36 | HAE 1 | RT-PCR | Lanadelumab | Abdominal | Icatibant | No |

*Note:* All values are median, range.

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

  

SARS-CoV-2 tests) associated with compatible COVID-19 symptoms (cough, dyspnoea, fever, myalgia, or arthralgia, anosmia, ageusia, fatigue, abdominal pain, and headache).[9]

Thanks to this registry, we could analyse prospectively data from 13 HAE patients including in 4 different centres between April 2020 and January 2021. Oral consent from all patient was collected.

**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 (4) | Patients without (9) | *p* Value[a] |
|---|---|---|---|
| Sex, *n* (%) | | | |
| Female (%) | 2 (50) | 6 (67) | .5 |
| Male (%) | 2 (50) | 3 (33) | |
| Median Age (year) | 33.5 | 42 | .26 |
| Range (year) | 29–44 | 26–85 | |
| HAE subtype, *n* (%) | | | |
| HAE I (%) | 3 (75) | 7 (78) | .67 |
| HAE II (%) | 0 (0) | 1 (11) | |
| HAE III (%) | 1 (25) | 1 (11) | |
| Prophylactic treatment, *n* (%) | 1 (25) | 5 (55) | .56 |
| Danazol (%) | 1 (25) | 3 (33) | |
| Lanadelumab (%) | 0 (0) | 2 (22) | |
| Number of attacks per month [range] | 14 [4–36] | 2 [0.2–12] | **.02** |
| COVID-19 | Cough, dyspnoea ageusia, anosmia abdominal symptoms | Cough, dyspnoea ageusia, anosmia respiratory distress | |
| Median time between last attack and COVID infection (day) [range] | 70 [8–87] | 133 [15–1753] | .33 |
| Location of care | | | |
| Hospital (%) | 0 (0) | 2 (22) | 1 |
| Home (%) | 4 (100) | 7 (78) | |
| Oxygen therapy (%) | 0 (0) | 2 (22) | |
| Max (L/min) (range) | 0 | 12 (12) | |
| Detected SARS-CoV-2 | | | |
| Positive PCR (%) | 3 (75) | 7 (78) | 1 |
| Positive IgG serology (%) | 1 (25) | 2 (22) | |
| AE attack during COVID infection | | | |
| Number of attacks [range] | 2.5 [2–5] | | |
| Anatomical location | | | |
| Abdominal (%) | 1 (25) | | |
| Laryngeal/Facial (%) | 0 (0) | | |
| Peripheral (%) | 2 (50) | | |
| Multiple locations (%) | 2 (50) | | |
| Attack intensity (%) | Moderate | | |
| Attack treatment (%) | 4 (100) | | |
| Exacyl (%) | 1 (25) | | |
| Fyrazyr (%) | 2 (50) | | |
| Berinert (%) | 1 (25) | | |

*Note:* Categorical variables were compared using the Chi-square test (if number of patients was >5 patients) or using the McNemar test. All tests were two-sided.

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

[a]Continuous variables were compared using the non-parametric Mann-Whitney test.

Continuous variables were compared using the non-parametric Mann-Whitney test. Categorical variables were compared using the Chi-square test (if number of patients was >5 patients) or using the McNemar Test. All tests were two-sided.

The majority of patients were women (8/13) with a median age of 37 (range: 26–85). Two patients had a previous history of high blood pressure, one of diabetes and two of obesity. Clinical and biological characteristics of the patients are presented in Table 1. Ten were diagnosed with HAE I, 1 with type HAE II, and 2 with HAE nC1-INH (one with plasminogen mutation and one with factor XII deficiency). The last attack occurred with a median time of 80 days before COVID-19 (range interval: 8–1753). Six patients received prophylactic therapy (Danazol [3], Lanadelumab [3]).

SARS-CoV-2 infection was symptomatic for all patients: asthenia (6), cough (8), dyspnoea (5), ageusia (9), anosmia (9), headache (5), and abdominal symptoms (3). The two oldest patients (85 and 65 years 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. They did not receive systematic HAE on-demand therapy after SARS-CoV-2 infection diagnostic to prevent attack.

Four of thirteen patients developed HAE attacks during COVID-19 convalescence (median time between first symptoms and the end of follow-up: 90 days, range 8–193) (Table 2). These patients presented a lower HAE disease control than the other patients (median number of attacks per month 14 (range: 4–36) and 2 (range: 0.2–12) respectively, $p = .02$). All developed iterative moderate attacks based on visual analogue scale (VAS) (median attack number: 2.5, range: 2–5) during the convalescence. They described attacks affecting the face (1), abdominal area (3), and extremities (4). All patients were treated with on demand therapy: three of them received Icatibant, a B2 receptor antagonist which was recently tested for patient with COVID-19.[4] The median duration was 37.5 hours (with broad range: 3–96).

In summary, in our cohort, only 31% of HAE patients developed attacks during SARS-CoV-2 infection. These results are in line with those of Grumach et al.[10] Indeed, in their cohort of 13 patients, 5 (38%) experienced attacks days after SARS-CoV-2 infection, mostly affected extremities and face. Acute attacks could occur during the convalescent phase of COVID-19 illness, more commonly in patients with a history of frequent attacks. However, it is unclear whether the acute attacks during the convalescent phase are specifically triggered by COVID-19 or not. This current study has, however, several limitations among them, the small sample size. Nonetheless, it adds to the evidence that patients with a good HAE disease control are at low risk of developing angioedema attacks.

## KEYWORDS

angiotensin-converting enzyme inhibitor, COVID-19, HAE, hereditary angioedema

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## CONFLICT OF INTEREST

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.

## AUTHOR CONTRIBUTIONS

Aude Belbezier contributed to acquisition of data, analysis, interpretation of the data, drafting the manuscript for intellectual contents, and final approval of the version to be published. Mélanie Arnaud and Chloé McAvoy contributed to acquisition of data and final approval of the version to be published. Isabelle Boccon-Gibod, Fabien Pelletier, Delphine Gobert, Olivier Fain, Aurélie Du-Thanh, David Launay, and Julien Lupo contributed to acquisition of data, critical revision of manuscript for intellectual content, and final approval of the version to be published. Laurence Bouillet contributed to study concept and design of the study, critical revision of manuscript for intellectual content, study supervision, and final approval of the version to be published.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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