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DR AUDE BELBEZIER (Orcid ID : 0000-0002-6505-6596)

DR LAURENCE BOUILLET (Orcid ID : 0000-0001-8245-4767)

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Corresponding author mail id: abelbezier1@chu-grenoble.fr

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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], David Launay[2,6], Julien Lupo[7], 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]Université Lille Nord de France, Department of Internal Medicine, National Reference Centre for Autoimmune and Systemic Rare Diseases, Hospital

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Claude-Huriez, CHRU Lille, France; [7]Univ. Grenoble Alpes, CEA, CNRS, Virology Laboratory CHU Grenoble Alpes, IBS, 38000 Grenoble, France

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Key message: 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.

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

Blockage of angiotensin converting enzyme (ACE), an important enzyme degradating 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-

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2 and ACE2 binding supposedly downregulates ACE, thus interfering with bradykinin degradation and bradykinin concentration in extracellular space[3,4]. Therefore, we have concerns about showing the possibility of downregulated 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 C1inhibitor (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-COVID19 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 enroll 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 SARS-CoV-2 tests) associated with compatible COVID-19 symptoms (cough, dyspnea, fever, myalgia or arthralgia, anosmia, ageusia, fatigue, abdominal pain and headache) [9].

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

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(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), dyspnea (5), ageusia (9), anosmia (9), headache (5), abdominal symptoms (3). 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. 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 = 0.02). All developed iterative moderate attacks based on visual analog 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.

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Table 1 Characteristics of HAE patients in the AE-COVID19 (n = 13).

Patient	Sex	Age (y)	HAE type	COVID test results	Long-term pophylactic 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	Diabetis
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, C1Inhibitor 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

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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

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 (4)**	**Patients without (9)**	**p value ***
Sex, n (%)				0.5
Female (%)		2 (50)	6 (67)	
Male (%)		2 (50)	3 (33)	
Median Age (year)		33.5	42	0.26
Range (year)		29-44	26-85	
HAE subtype, n (%)				0.67
HAE I (%)		3 (75)	7 (78)	
HAE II (%)		0 (0)	1 (11)	
HAE III (%)		1 (25)	1 (11)	
Prophylactic treatment, n (%)		1 (25)	5 (55)	0.56
Danazol (%)		1 (25)	3 (33)	

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Lanadelumab (%)	0 (0)	2 (22)	
Number of attacks per month [range]	14 [4-36]	2 [0.2-12]	**0.02**
COVID 19			
	cough, dyspnea agueusia, anosmia abdominal symptoms	cough, dyspnea agueusia, anosmia respiratory distress	
Median time between last attack and COVID infection (day) [range]	70 [8-87]	133 [15-1753]	0.33
Location of care			1
Hospital (%)	0 (0)	2 (22)	
Home (%)	4 (100)	7 (78)	
Oxygen therapy (%)	0 (0)	2 (22)	
Max(L/min) (range)	0	12 (12)	
Deteted SARS-CoV2			1
Positive PCR (%)	3 (75)	7 (78)	
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)		

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

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