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COVID-19 affecting hereditary angioedema patients with and without C1 inhibitor deficiency

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Clinical Implications

- Patients with hereditary angioedema with deficiency or normal C1 inhibitor who presented severe acute respiratory syndrome coronavirus 2 infection were clinically characterized and the impact of coronavirus disease 2019 on hereditary angioedema symptoms was evaluated. Despite C1 inhibitor involvement in controlling several systems, the patients did not present severe coronavirus disease 2019.

At the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, age more than 60 years, hypertension, and diabetes mellitus have been identified as the major risk factors for severe cases of coronavirus disease 2019 (COVID-19). The knowledge about COVID-19's immunopathogenesis has been increasing rapidly. The pathogenicity of COVID-19 is not restricted to the respiratory system, and a relevant inflammatory response producing systemic involvement was associated with the severity of the disease. Also, thromboembolic phenomena were evidenced clinically and through laboratory tests.[1]

Hereditary angioedema (HAE) is a rare, potentially life-threatening disorder characterized by cutaneous and submucosal swelling attacks. It is caused by a deficiency of C1 inhibitor (C1INH); however, an additional type of HAE with normal C1INH (nC1INH) levels has been described. The contact system's primary role was recognized in the pathophysiology of HAE as well as the influence of the complement, coagulation, and fibrinolysis in the pathogeny of COVID-19.[2] To date, COVID-19 has been reported in only 1 patient with HAE, and manifested a mild disease without triggering an angioedema attack.[3] In addition, 1 patient with acquired nonhistaminergic angioedema was reported with mild COVID-19 and no angioedema.[4]

We characterized COVID-19 infection among patients with HAE with C1INH deficiency or with nC1INH (with or without FXII mutation). Patients with unknown mutations were included if they fulfilled the following criteria: clinical symptoms similar to HAE-C1-INH, hormonal trigger, nC1INH and C4 levels, family history of recurrent angioedema, and absence of mutation for FXII, plasminogen, angiopoietin 1, and serping 1. The patients were reported after an active search among reference centers belonging to the Brazilian Group of Study on HAE (Grupo de Estudos Brasileiro em Angioedema Hereditario [GEBRAEH]) and data from the Brazilian Association of HAE patients (Associação Brasileira de pacientes com Angioedema Hereditário [ABRANGHE]). The southeast region was more represented; this region is the most populous and primary focus of COVID-19 in our country. Patients presenting confirmed or highly suspected COVID-19 infection (symptomatic) were included. The diagnosis was based on epidemiological history and/or confirmatory tests (SARS-CoV-2 RT-PCR, rapid SARS-CoV-2 immunodiagnostic test, IgM and/or IgG SARS-CoV-2 serology). Patient confidentiality was respected and maintained. For each patient, the following data were collected from medical records: sex, age, HAE type, long-term prophylactic treatment, location of angioedema attacks during the infection, on-demand therapy, comorbidities, and COVID-19 symptoms. Results were reported for each parameter and summarized with descriptive statistics. Patients' consent was asked before inclusion.

From March 2020 until July 2020, 13 patients with HAE (85% females) were diagnosed with COVID-19 (Table I). The median (interquartile range) age was 36 years (23-48 years). The study population consisted of 8 patients with HAE type I and 5 patients with HAE-nC1-INH, 1 of them with FXII mutation, 2 with unknown mutation, and 2 untested. Most patients with HAE with C1INH deficiency (87.5%) were on long-term prophylactic care with attenuated androgens, and 1 was on tranexamic acid. Patients with HAE-nC1-INH were on tranexamic acid with progestins (40%) and on-demand therapy (60%). New therapies were not used because of restricted access related to the high cost and no governmental reimbursement. Seven (53%) patients had confirmed COVID-19 by RT-PCR, 3 (23%) confirmed by IgM and/or IgG SARS-CoV-2 serology, and 1 (8%) confirmed by rapid SARS-CoV-2 immunodiagnostic test. One patient was highly suspected of COVID-19 because of suggestive symptoms and contact with confirmed cases at home. Four of 8 patients with HAE-nC1-INH experienced angioedema attacks and 1 of 5 patient with HAE-nC1-INH developed the feeling of upper airway edema not requiring hospitalization. The latter had not suffered angioedema attacks in the previous 14 years. Among patients who experienced attacks, face and extremities were the most common locations of angioedema (reported by 2 patients for each 1) and 1 patient with HAE-C1-INH had abdominal pain. Fresh frozen plasma (FFP) was administered for attacks in 2 patients; 1 patient received icatibant; 1 patient increased attenuated androgen dose; and 1 did not receive any treatment. Most responses to on-demand treatment were the same as in former attacks, requiring only 1 therapy dose. The exception was a patient who needed an extra plasma concentrate in addition to her usual dose, totalizing 3 FFP concentrates. The option for on-demand therapy was based on the restricted availability of drugs in our country. Only 2 patients had comorbidities: hypertension (1) and obesity (1). The obese patient had an angioedema attack and FFP was administered for symptoms control.

The most frequent COVID-19 symptoms were anosmia (10 of 13 [77%]), dysgeusia (10 of 13 [77%]), fever, cough and

TABLE I. Clinical characteristics and laboratory diagnosis of patients with HAE with or without C1INH deficiency

Patient	Sex	Age (y)	HAE type	COVID test results	Long-term prophylactic care	HAE attack during COVID-19 (local)	HAE attack therapy	Comorbidities
1	F	45	C1INH-HAE	Rapid SARS-CoV-2 immunodiagnostic test	Oxandrolone	No	FFP	Hypertension
2	F	36	C1INH-HAE	RT-PCR	Oxandrolone	Face	Oxandrolone	Obesity
3	F	36	FXII-HAE	IgM and/or IgG SARS CoV-2 serology	On-demand therapy	No	None	No
4	M	24	C1INH-HAE	RT-PCR	Oxandrolone	No	None	No
5	F	40	C1INH-HAE	Rapid SARS-CoV-2 immunodiagnostic test	Oxandrolone	No	None	No
6	F	37	Unk-HAE	RT-PCR	Tranexamic acid plus progestogens	No	None	No
7	F	23	Unk-HAE	RT-PCR	Tranexamic acid plus progestogens	No	None	No
8	F	30	HAE-nC1-INH	RT-PCR	On-demand therapy	No	None	No
9	F	40	HAE-nC1-INH	RT-PCR	On-demand therapy	Feeling of upper airway obstruction	None	No
10	F	34	C1INH-HAE	IgM and/or IgG SARS CoV-2 serology	Tranexamic acid	Face and extremities	FFP	No
11	F	38	C1INH-HAE	High clinical suspicion	Oxandrolone	Extremities	None	No
12	M	48	C1INH-HAE	IgM and/or IgG SARS CoV-2 serology	Oxandrolone	No	None	No
13	F	37	C1INH-HAE	RT-PCR	Oxandrolone	Abdomen and extremities	Icatibant	No
Total = 13	11 F (84%); 2 M (16%)	36 (range, 26-48)	8 C1INH-HAE/5 nC1-INH-HAE	RT-PCR: 7; rapid immunodiagnostic test: 3; SARS-CoV-2 serology: 2	Oxandrolone: 7; tranexamic acid: 1; tranexamic acid + progestagens: 2	Face: 2; extremities: 3; abdomen: 1; upper airway 1	FFP: 2; oxandrolone: 1; icatibant: 1	Hypertension (1); obesity (1)

C1INH-HAE, Hereditary angioedema with C1INH deficiency; *F*, female; *FFP*, fresh frozen plasma; *FXII-HAE*, hereditary angioedema with FXII mutation; *M*, male; *HAE-nC1-INH*, hereditary angioedema with normal C1-INH not tested for known mutations; *Unk-HAE*, hereditary angioedema with normal C1INH and unknown mutation.

malaise (6 of 13 [46% each]), headache and dyspnea (4 of 13 [31%]), and pharyngitis (2 of 13 [15%]). One of the patients with HAE-nC1INH was hospitalized for 10 days, with the involvement of 25% of the lungs shown in tomography and mild respiratory symptoms. She received anticoagulant therapy due to high D dimer levels. No attacks occurred during the hospitalization or afterwards.

The complement system promotes inflammation, and its role in the acute respiratory distress syndrome triggered by influenza and the respiratory syncytial virus is well known.[5] Few studies demonstrating the involvement of the complement system in COVID-19 pathogenesis have been published, suggesting its participation in the pathogenesis of pulmonary symptoms and endothelial permeability, which is known to be crucial in the pathogenesis of angioedema.[6,7]

Concerning the contact system, gene expression of bronchoalveolar lavage cells harvested for SARS-CoV-2 research demonstrated an imbalance in the renin-angiotensin system, with reduced expression of angiotensin-converting enzyme as well as increased expression of angiotensin-converting enzyme 2, renin, renin-angiotensin system receptors, kininogen, and kallikrein. This pattern suggests the presence of an increase in bradykinin levels, responsible for vasodilation and increased vascular permeability and, admittedly, an essential molecule in the pathogenesis of nonhistaminergic angioedema.[2,6]

Considering that patients with HAE present high bradykinin levels during the attacks and complement system activation, we could support the hypothesis that SARS-CoV-2 infection could lead to severe disease. All patients with HAE reported here had mild symptoms of COVID-19, nor did they present thromboembolic complications due to infection, despite having a complement system disorder. Only 1 of the patients had severe laryngeal edema, and this patient was not under prophylactic therapy and did not use on-demand therapy. Another patient used icatibant for an abdominal attack and, recently, this kinin B2 receptor antagonist was tested for patients with COVID-19.[8]

All patients with HAE, except for 2, were on prophylactic treatment, which may have prevented angioedema attacks related to the infectious condition. We had several patients treated with plasmin inhibitors. Plasmin, a component of the fibrinolysis system, is related to increased virulence and pathogenicity of viruses that contain furin sequence in their envelope, which is the case of SARS-CoV-2. Diverse pathologies established as being at higher risk for severe COVID-19 show an increase in plasminogen,[9] a molecule also involved in HAE's pathogenesis. In addition, most of the patients (7 of 13) were under androgen prophylaxis and no specific correlation could be seen.

To our knowledge, this is the first study to report a series of cases of patients with HAE with SARS-CoV-2 infection. In our data, unlike we expected, patients with HAE and COVID-19 did not present severe acute angioedema attacks or severe COVID-19, despite complement system disorder. However, our population was predominantly female and with a median age below 50 years, usually reported as less susceptible to severe COVID-19. Also, recognizing the role of the complement and contact systems in SARS-CoV-2 infection could be useful for the therapeutic approach in severe cases of COVID-19.[5] Further real-life registry-based studies are needed to confirm our findings and extend the evidence that patients with HAE on prophylaxis are at low risk of developing angioedema attacks and severe COVID-19.

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