Research Square

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Patients With Hereditary Angioedema Do Not Develop More Severe COVID-19 but SARS-CoV-2 Infection May Trigger Attacks: 66 Cases

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Research Article

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Abstract

Purpose

Hereditary angioedema (HAE) is a rare genetic disease with hyperactivated contact and kallikrein-kinin systems leading to bradykinin (BK) release and edema. SARS-CoV-2 infection results in inflammatory exacerbation. C1 inhibitor (C1-INH) deficiency could aggravate clinical outcomes, with HAE patients at a greater risk of adverse outcomes of COVID-19, however, data are still limited. Our aim was to characterize the course and severity of COVID-19 in patients with HAE.

Methods

Latin American HAE reference centers evaluated SARS-CoV-2 infection in this population. Patients with confirmed diagnosis of HAE with (HAE-C1-INH) or without C1-INH deficiency (HAE-nC1-INH) were included. HAE symptomatology and the course of COVID-19 were characterized with the application of a questionnaire.

Results

66 patients from 10 countries (HAE-C1-INH 80,3%; HAE-nC1-INH 19.6%) were reported with SARS-CoV-2 infection. Comorbidities were absent in 69.7% of the patients and obesity present in 12.1%. Attacks occurred in 45.5% of patients with HAE during SARS-CoV-2 infection. Long term prophylaxis was reported in 52% (34/66) of HAE patients. Complete cure was observed in 61 patients (92.4%), pulmonary sequelae in 4 and death in one HAE-C1-INH patient. The cause of death was septic shock secondary to bacterial pulmonary coinfection. Disease progression was not impacted by sex, therapy or type of HAE (p = 0.803).

Conclusion

Attacks occurred in almost half of HAE patients suggesting that SARS-CoV-2 infection is a trigger. HAE did not represent a risk factor for a worse outcome of COVID-19, even in use of androgens.

Highlights

Data regarding the course of COVID-19 in HAE patients are still limited. We observed that SARS-CoV-2 infection can trigger attacks in HAE with or without C1-INH deficiency, however, severe disease had a similar incidence in HAE patients.

Introduction

Hereditary angioedema (HAE) is a rare genetic disease with autosomal dominant inheritance characterized by localized and asymmetric episodes of subcutaneous and submucosal edema with a high impact on quality of life [1,2,3]. Unnecessary surgeries and death due to airway obstruction can occur [2,4]. Two types of HAE are recognized: HAE with deficiency and/or dysfunctional C1 inhibitor (HAE-C1-INH)

and HAE with normal C1-INH (HAE-nC1-INH); and the estimated prevalence is 1:50,000 and 1:400.000, respectively [4,5]. Gene variants involved with HAE-C1-INH are identified in *SERPING1* gene and variants in genes encoding for coagulation factor XII (*F12*), Plasminogen, Kininogen 1, Angiopoetin1, Myoferlin and, more recently, heparan sulfate (HS)-glucosamine 3-O-sulfotransferase 6[6] were associated with HAE-nC1-INH. There is a cluster of patients with unknown variants within the HAE-nC1-INH group[2].

The mechanism involved in HAE is the activation of the contact and kallikrein-kinin systems, resulting in the release of bradykinin (BK), after the cleavage of high molecular weight kininogen (HK) by kallikrein. Kallikrein is the active cleaved form of pre-kallikrein formed after cleavage by activated FXII. After release, BK or its derivative des-Arg9-bradykinin (DABK), binds to B2R or B1R, respectively, generating increased vascular permeability, which causes angioedema. C1-INH inhibits not only contact and kallikrein-kinin systems but also fibrinolytic, complement and coagulation pathways and its deficiency or dysfunction leads to increased BK release. In most HAE-nC1-INH, the same mechanism is observed[7,8].

The clinical spectrum of COVID-19, the disease caused by SARS-CoV-2, varies widely, from asymptomatic or mild symptoms similar to common colds to severe respiratory failure with risk of death. Recognized risk groups for the severity of the infection are age over 60, hypertension, diabetes and obesity[9]. Several fatal complications have been observed in the course of the disease: heart, liver or kidney failure, among others[9,10].

SARS-CoV-2 uses surface proteins to invade host cells. The virus' spike glycoprotein binds to the angiotensin-converting enzyme 2 (ACE2), which is highly expressed on the surface of respiratory cells, and this interaction is considered essential for SARS-CoV-2 to enter target cells. In some cells, the "spike" glycoprotein can bind to other surface proteins, such as TCD4 + cells[10,11]. The binding of SARS-CoV-2 causes negative regulation of ACE2, influencing the regulation of the renin-angiotensin system, possibly related to changes in blood pressure and inflammation[10].

Considering the action of ACE2 inhibitors in the kallikrein-kinin system and the observation that anti-inflammatory treatments have limited efficacy in respiratory distress, the relationship between the activated contact and kallikrein-kinin systems and the pulmonary manifestations of COVID-19 is a strong possibility[12-15]. Clinical studies with small number of patients and severe COVID-19 treated with recombinant or plasma-derived C1 inhibitor, or even icatibant, showed improved clinical, laboratory and radiological parameters[12-14], reinforcing the role of these systems[15].

A patient with HAE and COVID-19 has been reported, which manifested a mild illness without triggering an attack of angioedema[16]. In addition, a patient with acquired non-histaminergic angioedema was reported with mild COVID-19 and without angioedema attack[17]. A recent casuistry showed mild disease in HAE patients[18].

Considering the scarcity of data about hereditary angioedema with or without C1 inhibitor deficiency and COVID-19, we collected clinical characteristics of these patients in a wider population focusing the

severity and evolution of the infection.

Methods

HAE Referral Centers in Latin American countries were consulted about patients with SARS-CoV-2 infection. For inclusion in the study, there was no age limit or restriction to risk factors for COVID-19. The diagnosis of HAE was confirmed by typical clinical symptoms, biochemical tests evaluating the dosage and / or function of C1 inhibitor, family history and for patients with HAE-nC1-INH, whenever possible, *F12* variants were evaluated. We registered the tests performed for the confirmation of SARS-CoV-2 infection: PCR, serology and / or rapid test. A questionnaire was distributed to the centers including 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, need for hospitalization, period of symptomatology, evolution and complications. The project was submitted and approved by the Ethics Committee (CAAE: 40745220.0.1001.0082).

Results

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 to the inquiry and Bolivia has no HAE patients identified. Ten countries contributed to the casuistry: Brazil (n=25); Argentina (n=11); Colombia (n=11); Mexico (n=9); Peru (n=3); Paraguay (n=2); Puerto Rico (n=2) and Panama, Ecuador and Costa Rica with one patient each. We report 66 patients (mean age = 39.5 ± 15.1 years old; 77.3% females) with confirmed diagnosis of HAE-C1-INH and HAE-nC1-INH, corresponding to 80.3% and 19.6%, respectively. Diagnosis of SARS-CoV-2 infection was performed by RT-PCR in 41 (62.1%); serology in 7 (10.5%); rapid test in 3 (4.5%); clinical symptomatology in 12 (18.2%) and close contact and symptoms in 3 (4.5%).

Comorbidities were not identified in 69.7% of the patients, obesity was present in 12.1%, diabetes in 6.0%, arterial hypertension 4.5%, neoplasms and other conditions in 7.7%. Median time of disease was 11 (IQR: 7-15) and 10 (IQR 3-15) days in patients with HAE-C1-INH and HAE-nC1-INH, respectively. Complete cure was observed in 61 patients (92.4%), pulmonary sequelae in 4 and death in one patient (Table 1). The disease progression had no difference in relation to the sex or type of HAE (p = 0.803).

Angioedema attacks occurred in 45.5% of patients with HAE during SARS-CoV-2 infection, predominantly in HAE-C1-INH (26/53) comparing with HAE-nC1-INH (4/13), however, there was no significant difference (p>0.05). 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, a significant association was evidenced between the groups (p = 0.030), with the attacks occurring mainly in women with HAE-C1-INH during COVID-19. Most of the patients who suffered attacks were not receiving prophylaxis and no association between the occurrence of attacks and the use of prophylaxis was observed (p = 0.648). Androgens was used for long term prophylaxis in 48.4% of the patients (32/66),

among which 93.3% progressed to cure after suffering SARS-CoV2 infection with no sequelae. Only a 71-year-old woman was reported as deceased within this group due to septic shock.

Treatment of the SARS-CoV-2 infection in these patients was based on analgesics and antipyretics in 53%, mainly paracetamol (acetaminophen) (42.4%), antibiotics in 22.7%, azithromycin being the most used (18.1%), followed by anti-inflammatories in 11%. Combined therapies, based on the aforementioned drugs, were utilized by 22.1% of the cases; and other therapies such as vitamins and ivermectin were prescribed in 7.6%.

Discussion

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first emerged in Wuhan (Hubei Province, China), in December 2019, and COVID-19 pandemic has spread rapidly worldwide. Only a small percentage of patients develop the potentially lethal complications of acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), and multiorgan failure (MOF)[19,20]. After entering the host, SARS-CoV-2 elicits a series of innate and adaptive immune responses, which are responsible for viral clearance as well as inflammation. Emerging evidences suggest that complement is chronically activated in severe COVID-19 and plays a key role in critically ill patients, due to a dysregulated inflammation characteristic of severe COVID-19[21]. Therefore, we decided to evaluate HAE patients infected with SARS-CoV-2 in order to describe its influence on their prognosis. Of interest, we compared with patients diagnosed with HAE-nC1-INH, considering that C1-INH is normal in this HAE type.

As a collaborative study, we were able to collect data from 66 patients and no differences were evidenced comparing patients with or without C1 inhibitor deficiency. This result was not expected since C1-INH is a major regulator of all three pathways of complement activation[22]. Through covalent bond formation with the complement components C1s, C1r, MASP1 and MASP2 and reversible binding to C3a, C1-INH attenuates the consequences of complement activation, including the generation of proinflammatory anaphylatoxins, especially C5a, and the formation of the membrane attack complex (MAC) that leads to cell lysis[22,23]. Coagulation and fibrinolytic pathways are also regulated by C1-INH and it is presumed that the lower C1-INH activity could predispose to more severe SARS-CoV-2 infection[24]. Moreover, C1-INH has been demonstrated to interact with components of the extracellular matrix, leading to the hypothesis that these components concentrate C1-INH at the local site of inflammation in order to regulate complement and contact systems[25].

The similar course of disease in our patients compared to the general population, can be explained by some findings. Females were the predominant sex in our group as it is described in most HAE casuistries[26-30]. Men have been described with higher severity of COVID-19 in comparison with women[31,32]. The median age observed by us was in the 30s and it may have influenced the prognosis. Seven HAE patients were older than 60 years of age and this is a risk factor for severe COVID-19. Unfortunately, one 71-year-old patient died from pulmonary complications and multiorgan disfunction related to COVID-19, 28 days after the beginning of symptoms. No additional comorbidity was reported in

this patient and she was under HAE prophylaxis with danazol. This death accounted for 1.5% of total cases, less than the mortality reported for general population in Latin American countries[33]. Furthermore, approximately 70% of our HAE patients had no comorbidities; however, 12% of them were obese. Additionally, low C4 serum levels found in HAE patients might prevent further complement activation and deleterious clinical effects derived from increased complement activity. All these factors could contribute to the better prognosis observed in our population. Different trials inhibiting complement activation, targeting either C3 or C5, have been proposed for critically ill patients[34].

Long term prophylaxis was reported in 52% (34/66) of HAE patients, and attacks occurred in 45.5% of patients with HAE during SARS-CoV-2 infection. Four patients reported feeling an upper airway obstruction and laryngeal edema, not well characterized; facial edema was associated in two of them. The continued depletion of ACE2 by SARS-CoV-2 infection increases the extracellular levels of des-Arg9-Bradykinin and bradykinin[23]. This effect could contribute to attacks in patients with both HAE-C1-INH and HAE-nC1-INH. In addition, the loss of inhibitory activities of C1-INH would be expected to enhance complement activation together with microvascular injury, leading to worse evolution of SARS-CoV-2 infection[25].

Androgens, which are able to induce C1-INH liver production, have been the most accessible therapy in Latin American countries; therefore, it is possible that prophylaxis improved the evolution or severity of COVID-19 in HAE patients. On the other hand, a role of a co-receptor for SARS-CoV-2 infection, transmembrane protease serine 2 (TMPRSS2), was described to be upregulated by androgens in a lung-derived cell line model, but not confirmed in physiologic settings[35]. Although this might be a concern in male patients treated with androgens because of the possibility to influence the outcome of COVID-19, none of our 13 male patients had severe clinical manifestations of SARS-CoV-2 infection.

Eight patients were treated with tranexamic acid and no thromboembolism was reported. One patient with HAE-nC1-INH and no variant identified was hospitalized due to high D-dimer values; however, this finding is described in HAE patients during attacks[36] and in COVID-19. This patient was not experimenting angioedema symptoms and evolved with no complications except for involvement of 25% of the lungs during the symptomatic phase.

Long term prophylaxis treatment, to reduce the severity and frequency of HAE episodes, includes infusion of C1-INH, which not only reduces kinin-kallikrein activation and BK production, but also might protect against lung injury by inhibiting the cytotoxic activity of extracellular histones[37]. This treatment may improve the outcome of HAE patients with SARS- Cov-2 infection, however, access in Latin America is still limited.

Treatment of acute episodes of HAE includes icatibant, a bradykinin receptor 2 antagonist, or ecallantide, a kallikrein antagonist both of which reduce BK production having a modulatory effect on the “bradykinin storm” described in the pathophysiology of COVID-19[38]. Some of our patients were treated with icatibant for acute episodes and the clinical response was adequate.

We evaluated a more representative number of patients with HAE C1-INH and HAE-nC1-INH infected with SARS-CoV-2. The expression of the COVID-19 was not different from the population without HAE, possibly due to the predominance of female and young patients as well as HAE therapy. Our findings suggest that SARS-CoV-2 infection is a trigger for angioedema attacks, however, the prognosis was not influenced, as previously observed by us and others in a much smaller casuistry[18,39]. Fortunately, none of our children had MIS-C; and it is believed that pediatric COVID-19 has a more favorable prognosis[40]. This study exposes the paradox of COVID-19 in HAE patients in real life.

Abbreviations

ACE2, Angiotensin converting enzyme 2; ARDS, acute respiratory distress syndrome; BK, bradykinin; B1, bradykinin receptor 1; B2, bradykinin receptor 2; C1-INH, C1 inhibitor; COVID-19, coronavirus disease 2019; DABK, des-Arg9-bradykinin; FXII, factor XII; HAE, hereditary angioedema; HAE C1-INH, hereditary angioedema with deficiency of C1 inhibitor; HAE nC1-INH, hereditary angioedema with normal C1 inhibitor; HK, high molecular weight kininogen; IQR, interquartile range; MIS-C, multisystem inflammatory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Declarations

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Conflict of Interest

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

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Tables

Table 1. General characterization of HAE patients with COVID-19 (n=66)

	HAE C1-INH (n=53)	HAE nC1-INH (n=13)	Total
Mean age (SD)	39.6 ± 15.7	38.9 ± 13.0	39.5 ± 15.1
Age (years)	N (%)	N (%)	
0 - 9	1 (1.5%)	0	1 (1.5%)
10 - 19	4 (6.1%)	1 (1.5%)	5 (7.6%)
20 - 29	9 (13.6%)	1 (1.5%)	10 (15.1%)
30 - 39	13 (19.6%)	5 (7.6%)	18 (27.3%)
40 - 49	15 (22.7%)	3 (4.5%)	18 (27.3%)
50 - 59	5 (7.6%)	2 (3.0%)	7 (10.6%)
60 - 69	3 (4.5%)	1 (1.5%)	4 (6.1%)
> 70	3 (4.5%)	0	3 (4.5%)
Sex	N (%)	N (%)	
Male	15 (22.7)	0	15 (22.7%)
Female	38 (57.6)	13 (19.7)	51 (77.3%)
Prophylaxis	N	N	N
No	25 (37.9)	7 (10.6)	32 (48.5)
Androgens	13 (19.7)	2 (3)	15 (22.7)
Tranexamic acid	7 (10.6)	1 (1.5)	8 (12.1)
pdC1-INH	3 (4.5)	0	3 (4.5)
Others	5 (7.6)	3 (4.5)	8 (12.1)
Prophylaxis maintained during COVID-19	24	6 (9.1)	30
Attacks during COVID-19	N (%)	N (%)	N (%)
Yes	26 (39.4)	4 (6.1)	30 (45.5)
No	27 (41)	9 (13.6)	36 (54.5)
Comorbidities	N (%)	N (%)	
None	37 (56.1)	9 (13.6)	46 (69.7)
Obesity	6 (9.1)	2 (3.0)	8 (12.1)
Diabetes mellitus	3 (4.5)	1 (1.5)	4 (6)

Arterial hypertension	3 (4.5)	0	3 (4.5)
Others (Neoplasia, Autoimmunity)	4 (6,1)	1 (1,5)	5 (7.6)
Period with symptomatology			
Median days (IQR)	11 (7-15)	10 (3-15)	-
Hospitalization N(%)	6 (9.1)	2 (3.0)	8 (12.1)
Evolution	N (%)	N (%)	
Cure	49 (74,2)	12 (18,2)	61 (92.4)
Sequelae	3 (4,5)	1 (1,5)	4 (6)
Deceased	1 (1,5)	0	1 (1.5)

SD, Standard deviation; pdC1-INH, plasma derived C1 inhibitor; IQR Interquantile range

Table 2. Therapy instituted in HAE patients infected with SARS-CoV-2

Treatment	Yes		No	
	N	%	N	%
Analgesics	35	57.6	31	42.4
Non steroidal Anti-inflammatories	7	10.6	59	89.4
Anticoagulant	8	12.1	58	87.9
Steroids	13	19.7	53	80.3
Antibiotics	15	22.7	51	77.3
C1 inhibitor	2	3	64	97
Convalescent plasma	1	1.5	65	98.5
Others	17	25.8	49	74.2

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