

## **Psychiatric and Clinical Characteristics of Hereditary Angioedema Patients Who Experienced Attacks during COVID-19**

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Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) enters the human body through the angiotensin converting enzyme 2 (ACE2) receptor found on type 2 pneumocytes. The cell membrane expression and function of ACE2 decrease after the receptor binding and the subsequent endocytosis of ACE2. ACE2 also plays a role in bradykinin (BK) metabolism. Enzymatic cleavage of Lys-BK derived from low molecular weight kininogen, results in the formation of Lys-des-Arg9-BK which is further inactivated by ACE2. Lys-des-Arg9-BK is a vasodilator agent that binds to the bradykinin B1 receptor [1].

Hereditary angioedema (HAE) is a rare disease characterized by recurrent non-pitting cutaneous and mucosal angioedema attacks. Increased bradykinin is known to be responsible for attacks in HAE patients with C1 inhibitor (C1INH) deficiency (C1INH-HAE) and in HAE patients with factor XII mutation (FXII-HAE).

Dysfunctional C1INH synthesis in HAE-C1INH or activated factor XII in FXII-HAE results in activation of the plasma kallikrein-kinin system, which generates bradykinin from high molecular-weight kininogen [2,3].

It is unclear whether increased bradykinin levels in HAE patients can cause more severe coronavirus disease 2019 (COVID-19) or whether SARS-CoV-2 infection can increase the frequency and severity of HAE attacks. Until now, COVID-19 has been reported in one HAE case series in which all the patients were receiving long-term

prophylaxis. The authors reported mild COVID-19 and no increase in HAE attacks during COVID-19 [4].

The HAE patients with COVID-19 were identified by searching all the member patients of the Turkish Hereditary Angioedema Patients Association and/or patients applied to the clinicians who were members of the Turkish Hereditary Angioedema Working Group. For this study, approval from Ege University Ethics Committee and Turkey Ministry of Health were obtained and written informed consent was obtained from each patient. Demographic (age, sex, HAE type), clinical (long-term prophylactic treatment, on-demand treatment, attack localization and treatment during infection) and laboratory (CRP, D-dimer, fibrin levels, absolute lymphocyte count, computed tomography [CT] and X-ray) characteristics of patients were obtained from medical records and telephone interviews during and after COVID-19 disease. Besides, the participants completed the Turkish version of Coronavirus Anxiety Scale (CAS) which has been developed to measure the anxiety level related to COVID-19, in which higher scores define higher anxiety level [5,6]. Furthermore, a psychiatrist (2<sup>nd</sup> author) contacted all the patients by a phone call and applied a semi-structured interview assessing the patients' mental status.

Between July 2020-November 2020, COVID-19 symptoms and positive RT-PCR nasopharyngeal swap results were detected in 11 patients (72.7% female) with HAE (Table 1). The mean age was  $37 \pm 11.41$  years. Despite having frequent attacks, 6 out of 11 patients were not using danazol or tranexamic acid for long term prophylaxis due to fear of side effects and inadequate effect in C1INH-HAE, respectively. While 2 out of 5 (40%) HAE patients who received prophylaxis had only one abdominal attack per patient during their COVID-19; 5 out of 6 (83.3%) C1INH-HAE patients who did not receive prophylaxis reported an increase in HAE attacks and had 2 to 10 attacks in

different localizations; eyelid, lips, chin, neck, shoulder, extremities, heels, soles of the feet, and abdomen within 1 week after the onset of COVID-19 symptoms. All HAE attacks were treated with bradykinin B2 receptor antagonist icatibant subcutaneously.

Comorbidities of the patients seemed to be uninfluential in the occurrence of HAE attacks during COVID-19. The patient with diabetes and hypertension was receiving prophylaxis and was attack-free. All the patients had received favipiravir which is recommended in all the steps of adult COVID-19 treatment guideline of Turkish Ministry of Health (Table 1).

During COVID-19, the initial coagulopathy as assessed by increased D-dimer and fibrin/fibrinogen levels may progress to disseminated intravascular coagulopathy. Also, it has been determined that D-dimer > 1000  $\mu\text{g}/\text{ml}$  at admission can predict the mortality risk [7]. D-dimer levels of all our patients whose analysis were performed (7 out of 11) were found to be above the normal limits whereas simultaneous fibrin levels were in normal range. Three patients received heparin therapy due to D-dimer levels > 1500  $\mu\text{g}/\text{ml}$ . All three patients were not receiving prophylaxis, had very frequent attacks, but none of them had severe COVID-19. A patient had D-dimer level > 9000  $\mu\text{g}/\text{ml}$  but no lung involvement on chest CT. It has been previously suggested that, in HAE patients D-dimer increase can be associated with acute HAE attacks, and should not be considered as a sign of thrombosis, necessarily [8].

Lung imaging was only performed on six out of 11 patients, since cough was not a prominent symptom in the remaining five. Imaging was normal in three; two patients showed multifocal patchy ground-glass opacities; another one displayed non-homogeneous infiltration in the left lower zone.

The psychiatrist assessed all the patients within 19-125 days after getting the COVID-19 diagnosis. There was no correlation between the time-period since the COVID-19 diagnosis and fear, personal protection, or CAS levels of the patients. Most of the patients said that they felt a great deal of emotional distress when they knew their diagnosis of COVID-19. Their anxiety diminished slowly as their COVID-19 symptoms did not get worse. Six patients stated that they had a fear of having an HAE attack and failing to reach urgent support from their caregivers when they were isolated. All but one HAE patients were psychologically affected by COVID-19 at the beginning; but at the time of psychiatric evaluation, only two patients were still having psychological problems interfering daily life (Table 2).

Unlike the recent publication of C1INH-HAE patients with COVID-19 [4] in our series, most of our HAE patients were not receiving prophylaxis (54.5%) and had frequent attacks with different localizations whereas HAE patients who were receiving prophylaxis reported no increase in their number of attacks.

Uncontrolled bradykinin production in HAE patients not receiving prophylaxis together with inadequate degradation of bradykinin due to SARS-COV-2 may lead to increased attack frequency in our case series. Unsurprisingly, patients who had an HAE attack during COVID-19 are more anxious, frightened about COVID-19 and psychologically more affected [9, 10]. Considering all our results and assumptions related to bradykinin overproduction, we recommend maintaining long-term prophylaxis for HAE patients during the pandemics to prevent attacks and protect their mental health.

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### **Conflicts of Interest**

All authors declare that there is no conflict of interest.

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