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 binding to the receptor and subsequent endocytosis of ACE2. ACE2 also plays a role in the metabolism of bradykinin. 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 nonpitting 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 (FXII) mutation (FXII-HAE). Dysfunctional C1INH synthesis in HAE-C1INH (C1INH-HAE) and in HAE patients with factor XII mutation (HAE-FXII-HAE) results in activation of the 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. To date, there has been only 1 HAE case series in which all the patients were receiving long-term prophylaxis and had COVID-19. The authors reported mild COVID-19 and no increase in HAE attacks during the infection [4].

HAE patients with COVID-19 were identified by searching all the members of the Turkish Hereditary Angioedema Patients Association and/or patients cared for by clinicians who were members of the Turkish Hereditary Angioedema Working Group. Ege University Ethics Committee and the Turkish Ministry of Health approved the study and patients gave their written informed consent. Data were obtained from medical records and telephone interviews during and after COVID-19 disease. These included demographic data (age, sex, HAE type), clinical data (long-term prophylactic treatment, on-demand treatment, site of attack, and treatment during infection), and laboratory data (C-reactive protein, D-dimer, fibrin levels, absolute lymphocyte count, computed tomography [CT] and x-ray). The participants also completed the Turkish version of Coronavirus Anxiety Scale (CAS), which was developed to measure the level of anxiety related to COVID-19 (higher scores define a higher level of anxiety) [5,6]. Furthermore, a psychiatrist (second author) telephoned all the patients and applied a semistructured interview to assess mental status.

Between July 2020 and November 2020, COVID-19 symptoms and positive RT-PCR nasopharyngeal swab results were detected in 11 patients (72.7% female) with HAE (Supplementary Table 1). The mean age was 37 (11.41) years. Despite having frequent attacks, 6 out of 11 patients were not taking danazol or tranexamic acid for long-term prophylaxis owing to the fear of adverse effects and inadequate effect on C1INH-HAE, respectively. While 2 out of 5 (40%) HAE patients who received prophylaxis had only 1 abdominal attack during their COVID-19 infection, 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 at different sites (eyelids, lips, chin, neck, shoulder, extremities, heels, soles, and abdomen) within 1 week after the onset of COVID-19 symptoms. All HAE attacks were treated with the bradykinin B2 receptor antagonist icatibant administered subcutaneously.

Comorbid conditions did not seem to affect the occurrence of HAE attacks during COVID-19. The patient with diabetes and hypertension was receiving prophylaxis and remained attack-free. All the patients had received favipiravir, which is recommended in all the steps of the adult COVID-19 treatment guideline of the Turkish Ministry of Health (Supplementary Table 1).

During COVID-19, the initial coagulation disorder—as assessed by increased D-dimer and fibrin/fibrinogen levels—may progress to disseminated intravascular coagulopathy. In addition, it has been determined that D-dimer >1000 µg/mL at admission can predict mortality [7]. The D-dimer levels of all the patients for whom an analysis was performed (7 out of 11) were found to be above the normal limits, whereas simultaneous fibrin levels were in the normal range. Three patients received heparin because of D-dimer levels >1500 µg/mL. None of the 3 patients were receiving prophylaxis, and all frequently experienced attacks, although none had severe COVID-19. One patient had a D-dimer level >9000 µg/mL but no lung involvement on the chest CT scan. It has been suggested that increased D-dimer in HAE patients may be associated with acute HAE attacks and should not necessarily be considered a sign of thrombosis [8].
Only 6 out of 11 patients underwent lung imaging, since cough was not a prominent symptom in the remaining 5. Findings were normal in 3 patients (2 with multifocal patchy ground-glass opacities and 1 with nonhomogeneous infiltration in the lower left lobe).

The psychiatrist assessed all the patients within 19-125 days after confirmation of the COVID-19 diagnosis. There was no correlation between the time since diagnosis and fear, personal protection, or CAS score. Most of the patients said that they felt considerable emotional distress when they knew that they had COVID-19. Their anxiety diminished slowly, as they realized that their COVID-19 symptoms were not worsening. Six patients stated that they feared experiencing an HAE attack and failing to receive urgent support from their caregivers when they were isolated. All HAE patients but 1 were psychologically affected by COVID-19 at the beginning, although, at the time of the psychiatric evaluation, only 2 patients reported psychological problems interfering with their daily life (Supplementary Table 2).

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

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

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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