Epileptic Seizure in Patients with COVID-19: Two Cases

To the Editor,
Coronaviruses are community-acquired, zoonotic viruses that transmitted from animal to human. Pneumonia cases of unknown etiology were reported in the city of Wuhan, Hubei province of China, on December 31, 2019. Later, cause of these pneumonias was identified as a new type of coronavirus, COVID-19. Most common symptoms of COVID-19 infection are respiratory problems such as cough, dyspnea, and fever. Consolidated areas, nodular and ground glass opacities on CT scans support diagnosis of viral COVID-19 related pneumonia. However, recent studies suggest that coronavirus is not only limited to the respiratory pathways but also involved in pathologies of central nervous system because of its neuroinvasive properties.[1-3]

This article discusses epileptic seizures in two separate cases with COVID-19 associated pneumonia.

Case 1
A 37–year-old male patient presented to emergency service with seizure. He didn’t have previous medical history and drug use, had fever for 2 days, and had a seizure today. Vital findings of patient was as following: Blood pressure: 130/80 mmHg, heart rate: 80 beats/min, fever: 38°C, and oxygen saturation: 97%. His Glasgow Coma Scale score was 15. His physical examination was unremarkable with the exception bilateral rales on chest oscultation. Laboratory results of patient are shown in Table 1. Head and chest computed tomography imagings were performed. Head tomography results were evaluated as normal. Air cysts were seen in the upper lobes, evaluated as normal.

Table 1: Laboratory Values of the Patients on Admission

| Category                        | First case | Second case | Normal range   |
|---------------------------------|------------|-------------|----------------|
| White blood cells (μL)          | 13,900     | 18,000      | 3.600-10.200   |
| Hemoglobin (g/dL)               | 16.3       | 15.8        | 12.5-16.3      |
| Hematocrit (%)                  | 45.9       | 47.9        | 36.7-47.1      |
| Platelets (μL)                  | 224,000    | 325,000     | 152,000-348,000|
| Glucose (mg/dL)                 | 94         | 150         | 74-106         |
| Aspartate transaminase (U/L)    | 22         | 49          | 5-50           |
| Alanin transaminase (U/L)       | 24         | 19          | 5-50           |
| Lactate dehydrogenase (U/L)     | 256        | 240         | 5-248          |
| Blood urea nitrogen (mg/dL)     | 23         | 29          | 17-43          |
| Creatinine (mg/dL)              | 0.74       | 0.75        | 0.67-1.17      |
| Sodium (mmol)                   | 138        | 142         | 136-146        |
| Potassium (mmol/L)              | 4.51       | 4.9         | 3.5-5.5        |
| Calcium (mg/dL)                 | 9.3        | 10.0        | 8.8-10.6       |
| C-Reactive Protein (mg/L)       | 4.6        | 2.3         | 0-5            |
| High sensitivity Troponin I (ng/L) | 5         | 16          | 0-16           |
| Creatinine kinase-MB (μg/L)     | 4.7        | 9.9         | 0.6-6.3        |
| Prothrombin time (sec)          | 10.7       | 12.8        | 10.5-14.5      |
| APTT (sec)                      | 22.4       | 24.8        | 25-34          |
| INR                             | 0.87       | 1.05        | 0.8-1.2        |
| Arterial Blood Gases            |            |             |                |
| pH (mm-Hg)                      | 7.36       | 7.39        | 7.35-7.45      |
| pO 2 (mm-Hg)                    | 76.9       | 49.7        | 83-108         |
| pCO 2 (mm-Hg)                   | 43.2       | 39.5        | 35-45          |
| HCO 3 (mEq/L)                   | 23.4       | 23.3        | 22-28          |
pleural thickening and frosted glass areas in were detected in lower lobes [Figure 1]. Patient was hospitalized with diagnoses of COVID-19 related pneumonia and seizure.

**Case 2**

A 67-year-old male patient was presented to emergency service with ataxia and recent falling. Vital findings of patient were as following: Blood pressure: 150/90 mmHg, heart rate: 75 atm/dk, fever: 36°C, and oxygen saturation: 99%. His Glaskow Coma Scale score was 15. Patient had no previous medical history or drug use. His physical examination was unremarkable with the exception of bilaterally decreased lung sounds. Head and chest CT imagings and diffusion MRI were performed. Meanwhile, patient had an epileptic seizure in the emergency room. Head CT and diffusion magnetic resonance imagings were normal, bilateral widespread ground glass opacities and patchy areas were detected in lower lobes in chest CT [Figure 2]. Patient was hospitalized with diagnoses of COVID-19 related pneumonia and seizure.

COVID-19 is usually suspected and diagnosed by clinical findings, bilateral infiltrations seen in chest tomography, biochemical parameters such as leukopenia and lymphopenia, and polymerase chain reaction (PCR) tests. Fever, shortness of breath, and cough are primary symptoms of this disease. As a result of these symptoms being most common in COVID-19, diagnosis and treatment of the disease primarily focuses on the lower respiratory tract. However, new evidence increasingly draws attention to complications and findings of COVID-19 on other organs and systems, especially the central nervous system, due to its neuroinvasive potential. Although epilepsy is a common neurological disease, Yasri et al. emphasize that the association of COVID-19 and epilepsy has not been reported in a recent article.

SARS genome sequences were detected in brain samples of SARS autopsies, and most intense signals were found in neurons in the cortex and hypothalamus. Coronaviruses can reach central nervous system by following a retrograde spread through synapses of peripheral nerve endings. Although this transsinapti c transfer has been shown in SARS-CoV, it is possible that SARS-CoV-2 has similar potential due to its high structural similarity. A high percentage of COVID-19 positive patients with severe clinical condition have neurological symptoms and complications such as cerebrovascular disease and worsening of consciousness. These symptoms may be directly related to the virus or secondary to complications of the disease. Detection of COVID-19 genome in the cerebrospinal fluid of COVID-19 positive patients in Beijing Ditan Hospital shows this disease itself can lead to viral encephalitis. Metabolic disorders, toxic encephalopathy secondary to hypoxia and sepsis, acute cerebral events due to cytokine storm caused by COVID-19 are other potential neurological problems.

Although most of neurological complications are risk factors for epilepsy in itself, a directly related pathophysiological process between COVID-19 and the risk of convulsion has not been defined yet. Seizures occur when alterations in excitability of cortical neurons result in an abnormal, exaggerated, hypersynchronous discharge. Changes in voltage-gated ion channels, increase in expression of excitator neurotransmitters such as glutamate, and a decrease in activity of GABA, a major inhibitory neurotransmitter, lead to this hyperexcitable state, which is the main mechanism of seizure pathophysiology. The demonstration of authoreactive T cells capable of recognizing both myelin structures and virus antigens in neurological patients with CoV RNA suggests that exaggerated immune response caused by coronaviruses may also lead to an increase in neurological events in genetically susceptible individuals or patients with predisposing conditions. It has been shown in experimental studies that human coronavirus OC43 (HcoV-OC43) increases proinflammatory cytokines and neuronal degeneration through glutamate excitotoxicity. Cytokines synthesized reactively to virus by microglial cells have been observed to prevent glutamate reuptake by down-regulating Glutamate transporter 1 (GLT-1) receptor in HcoV-OC43 infection. Increased glutamate levels and activity are one of the primary mechanisms of

![Figure 1: Computed tomography of chest image of the first case](image1.png)

![Figure 2: Computed tomography of chest image of the second case](image2.png)
Seizures, therefore inhibition of glutamate reuptake may be an underlying mechanism of a COVID related seizure process. With that being said, hypoxia, metabolic disorders and multiple organ failure observed in COVID-19 patients may also reduce the seizure threshold regardless of the neuromodulatory effect of coronavirus. SARS-CoV, another betacoronavirus, has also been shown to cause neuronal ischemia and edema in the cortex and hypothalamus as a result of direct viral infiltration.[9] Neural cell death is usually a result of epilepsy, however it can also be a triggering factor for seizures. This is thought to be possible by two main mechanisms, replacing destroyed synapses during neuronal cell ischemia with new, maladaptive circuits created by axonal branching along the excitatory pathways, and damaged neurons activating molecular signals associated with inflammatory cascades.[10]

Betacoronaviruses are both directly and indirectly associated with the neurological system in several different ways. Some of these processes seem to be related to the pathophysiological processes of seizures. Today, more studies are needed to describe the relationship between seizures and COVID-19, but considering the COVID-19 infection within possibilities in patients with seizures could lead to an early diagnosis and treatment of this novel coronavirus infection.

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There are no conflicts of interest.

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