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COVID-19 and Neurological Manifestations

COVID-19 ve Nörolojik Bulgular

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ABSTRACT Coronavirus disease 2019 (COVID-19) is a highly contagious infectious disease due to novel coronaviruses and substantially fatal in some high-risk groups. Human-to- human transmission is via droplets. Virus enters through mouth, nose and eyes to respiratory tract. The most common clinical signs are fever, fatigue, dry coughs and respiratory distress. Severely affected patients may develop multisystem failure and death. Neurological involvement is seen in 1/3 of the patients. The most common manifestations are dizziness, headache, impaired consciousness and acute cerebrovascular disease. SARS-CoV-2 enters nervous system via angiotensin converting enzyme 2 (ACE2) receptors on neurons and glial cells. In the future, patient data will elucidate the pathogenesis and help minimize the neurological damage.

Keywords: Coronavirus; COVID-19; nervous system

ÖZET Koronavirüs hastalığı 2019 (COVID-19) yeni koronavirusların oluşturduğu oldukça bulaşıcı ve riskli gruplarda ölüm oranı yüksek bir enfeksiyon hastalığıdır. İnsandan insana damlacık yoluyla bulaşır. Virüs ağız, burun ve gözden girip solunum sistemine yerleşir. En sık klinik bulgular ateş, halsizlik, kuru öksürük ve nefes darlığıdır. Ağır olgularda multi sistem yetmezliği ve ölüm gelişebilir. Nörolojik tutulum hastaların 1/3'ünde görülür. En sık baş dönmesi, sersemlik, baş ağrısı, bilinç bozukluğu ve akut serebrovasküler bozukluk görülmektedir. SARS-CoV-2 nöron ve glial hücrelerde bulunan anjiotensin dönüştürücü enzim 2 (ACE2) reseptörlerine bağlanarak sinir sistemine girmektedir. Gelecekte hasta verilerinin ışığında patogenez daha iyi anlaşılıp; nörolojik hasarlar azaltılabilir.

Anahtar Kelimeler: Koronavirüs; COVID-19; sinir sistemi

Coronavirus disease 2019 (COVID-19) is a highly contagious and sometimes fatal infectious disease caused by a novel coronavirus, Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2). It was first identified in a man working in the Huanan Seafood Wholesale Market in Wuhan, China. It, then spread quickly worldwide.[1] World Health Organization (WHO) named the disease as COVID-19 and declared the outbreak in January and a pandemic in March, 2020. The first case in Turkey was confirmed on 11 March and COVID-19 has since spread extensively. According to WHO, more than 3 million cases of COVID-19 have been reported resulting in more than 240,000 deaths worldwide and 124,000 cases resulting in 3,300 deaths in Turkey as of the end of April, 2020.[2]

Physicians are familiar with coronaviruses. The most well-known coronavirus outbreaks were SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome) causing a high amount of deaths. Coronaviruses are transmitted via droplets through mouth, nose and eyes and affect especially the upper respiratory tract. Incubation period is 14 days. Most people do not show symptoms, but transmit the virus. Some people have few mild symptoms that resolve without hospital treatment. The risk

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of serious disease increases in the elderly and in people with chronic conditions and may be fatal. First symptom is high fever and, in a few days, dry coughs, fatigue, taste and smell impairment, muscle and joint pains accompany. Towards the end of the first week, shortness of breath is seen. When treatment fails, following pulmonary injury, multiorgan failure especially renal failure and death may occur.[3] Recently, very serious dermatological signs, COVID-19 associated Kawasaki-like syndrome or hyper inflammatory response syndrome, especially in children have been reported.[4]

COVID-19 rarely presents with neurological symptoms. Therefore, attention should be paid to neurological signs during evaluation.[5] Immunological microglial activation, adaptation problems in cytokine profile and furthermore, hypotension, hypoxia, micro/macro-thrombosis lead to septic encephalopathy and delirium.[6,7] In a study of 214 COVID-19 patients from China, 78 (36.4%) had neurological signs; including 53 (24.8%) central nervous system (CNS), 19 (8.9%) peripheral nervous system and 23 (10.7%) skeletal muscle injuries. The most common CNS manifestations were dizziness in 36 (16.8%), headache in 28 (13.1%), impaired consciousness in 16 (17.2%) and acute cerebrovascular disease in 6 (6.5%) patients (five ischemic stroke, one cerebral hemorrhage). These neurological features were attributed to increased inflammatory response and blood coagulation.[8] Poyiadji et al. reported a patient in coma diagnosed with acute necrotizing encephalopathy. This patient had a history of fever and coughing for 3 days and developed altered mental status and was diagnosed with COVID-19 via real-time reverse transcriptase-polymerase chain reaction assay from a nasopharyngeal swab specimen. Her cranial magnetic resonance imaging (MRI) revealed features of acute necrotizing encephalopathy (hemorrhagic rim enhancing lesions within bilateral thalami, medial temporal lobes, and subinsular regions).[9] A 61-year-old woman in China presented with Guillain-Barré syndrome (GBS) signs (acute flask paralysis and areflexia) and developed classical COVID-19 symptoms on 8th day of admission. She recovered in a month with antiviral and intravenous immunoglobulin treatment.[10] The most common manifestations of peripheral nervous system involvement were smell and taste impairments.[11] There are reports of COVID-19-associated Miller Fisher syndrome and cranial neuropathies.[12] A patient with seizures due to meningitis was also reported as COVID-19.[13] The spinal cord and brainstem signs were attributed to involvement of synapses between lung and medullary cardio-respiratory center; stroke was attributed to virus-induced inflammatory effects in vascular bed and thrombotic and microangiopathic effects.

There are 4 hypotheses of SARS-CoV-2 effects on nervous system:[14] 1- SARS-CoV-2 may directly invade nervous system like Herpes Simplex virus. 2- Increased immune response (cytokine storm) to virus may result in passing of cytokines via blood-brain barrier and acute necrotizing encephalopathy. 3- Increased immune response to virus may lead to autoimmunity and harm in an indirect way as in GBS. 4- Due to systemic effects and secondary involvement of nervous system, critical disease myopathy and neuropathy may occur.

Theoretically coronaviruses directly go to brain, but this is unclear. Isolation of SARS-CoV-2 in cerebrospinal fluid (CSF) as well as in nasopharyngeal swab specimens, and presence of brain lesions on MRI point to its neurotropism.[15,16]

SARS-CoV-2 may enter CNS via hematogenous spread or retrograde neuronal transmission through olfactory neurons. Virus uses angiotensin converting enzyme 2 (ACE2) receptors for host nervous system entry and targets glial cells, neurons, skeletal muscle cells and other organ cells. ACE2 receptors are shown in neurons and glial cells.[17,18] Possibly, neuronal injury results in respiratory failure and need for ventilator support.[15,19,20]

In the future, autopsy and pathology reports will elucidate COVID-19 pathogenesis and appropriate treatment will minimize neurological damage.

Informing

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ayşe Serdaroğlu;* ***Literature Review:*** *Esra Serdaroğlu, Ayşe Serdaroğlu;* ***Writing the Article:*** *Esra Serdaroğlu, Ayşe Serdaroğlu;* ***Critical Review:*** *Ayşe Serdaroğlu.*

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