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COVID-19 AND THE NERVOUS SYSTEM

COVID-19 VE SİNİR SİSTEMİ

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Öz

Nörolojik komplikasyonlar, COVID-19 pandemisinde önemli bir morbidite ve mortalite nedenidir. Birçok hastada solunum yetmezliği dışında; baş ağrısı, baş dönmesi, koku-tat duyusunda azalma, akut serebrovasküler hastalık, ensefalopati, ensefalit tablosu gibi nörolojik bulgular görülmektedir. Bu komplikasyonlar, virüs kaynaklı hiperinflamasyon ve hiperkoagülasyon, merkezi sinir sisteminin doğrudan virüs ile enfeksiyonu ve postenfeksiyöz immün aracılı süreçler gibi çeşitli mekanizmalarla açıklanmaktadır. COVID-19 pandemisi sırasında, spesifik olan veya olmayan nörolojik bulgularla başvuran hastalarda SARS-CoV-2 enfeksiyonu mutlaka hatırlanmalıdır.

Anahtar Kelimeler: COVID-19, nörolojik bulgular, pandemi.

Abstract

Neurologic complications are a significant cause of morbidity and mortality during the COVID-19 pandemic. Besides respiratory diseases, neurological manifestations such as headache, dizziness, hyposmia, hypogeusia, acute cerebrovascular disease, encephalopathy, encephalitis are common. These complications may result from various mechanisms; virus-induced hyperinflammation and hypercoagulable states, a direct viral effect on the central nervous system, and post-infectious autoimmunity. We must keep in mind diagnosing SARS-CoV-2 infection when patients present with specific or non-specific neurological symptoms during the COVID-19 pandemic.

Keywords: COVID-19, neurologic manifestations, pandemic.

Introduction

Coronaviruses are RNA viruses. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a beta coronavirus that causes symptoms known as coronavirus disease (COVID-19) (1). These viruses primarily target the human respiratory system, but multiple systems can be affected (1,2). Neurologic manifestations are the combination of non-specific systemic disease complications, direct viral infection effects, and inflammation on the nervous system and vasculature (3-7).

Pathogenesis

The spike protein of the virus plays the most critical role in the COVID-19 pathogenesis. The binding of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE2) is crucial in pathophysiology. The immune response can be adaptive (attacking and inactivating the virus) or maladaptive (inducing a massive immune reaction). After binding ACE2, the virus triggers a cytokine storm, with the enormous release of pro-inflammatory agents that increase vascular permeability and edema. The cytokine storm also triggers hypercoagulation cascades that cause

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thromboembolism. Hyperactivation of inflammatory markers, vascular injury, and hypercoagulobility contribute to multiorgan failure and multiple neurological conditions (5,7). Glial cells and neurons have ACE2 receptors, making the brain a target of COVID-19 (8-10,14).

Mechanisms of Neuroinvasion

The central nervous system is a highly protected organ; however, viruses can still enter the central nervous system (CNS). The virus can infect the CNS either by transsynaptic transfer across infected neurons, entry via the olfactory nerve, infection of vascular endothelium, or leukocyte migration across the blood-brain barrier (BBB). Once the virus invades the CNS, the first line of defense is microglia activation that triggers the neuroinflammatory events. Neuroinflammation causes secondary damage by secretion of cytokines, neurotrophic factors, and proteases. Microglia may serve up neuroprotection or trigger neurodegeneration depending on the interplay between pro-inflammatory and anti-inflammatory cytokines released (5,7,9,10,13,14).

Neurologic Manifestations

Neurologic manifestations can result in a direct viral effect on the nervous system, secondary effect of systemic inflammatory responses triggered by infection, secondary effect associated with the vascular and prothrombotic impact of the virus on the vasculature, para-infectious or post-infectious autoimmune response, related therapies, and recovery.

The incidence of neurological complications is about 37%. The neurological manifestations could be central and peripheral. The most common central neurologic manifestations in COVID-19 are headaches, dizziness, anosmia, ageusia, cerebrovascular events, consciousness changes, seizure, gait difficulties, encephalitis, encephalopathy. Peripheral disorders include isolated cranial nerve dysfunction, neuropathies, and myositis-like muscle injury (3,4,6,7).

Central Nervous System Manifestations

Headache/dizziness

One of the most common manifestations in patients is headache. The release of cytokines that triggers nociceptive sensory neurons or secondary events such as encephalitis, vasculitis, intracranial hypertension may explain the pathophysiology (2,4).

Encephalopathy

Encephalopathy is frequently reported. The mechanisms are multifactorial and include hypoxic respiratory distress, severe systemic inflammation, cytokine storm, sepsis with multiorgan failure, toxic-metabolic disturbances, and side effects caused by medication. The virus causes an immune-mediated rather than a direct viral encephalopathy. The activation of cytokines causes injury to the BBB, resulting in the cytokine penetration into the brain parenchyma (9,10).

Menengitis/Encephalitis

The direct infection of the brain results in acute encephalitis/meningitis. The direct effect of the virus or the host's immune response can damage the brain (11,12).

Seizure

Epileptic seizures occur as acutely symptomatic seizures due to primary CNS involvement and secondary CNS damage. CNS inflammation and excessive cytokine release can lower the seizure threshold and support epileptogenesis (3,6,9,10).

Cerebrovascular Events

Ischemic stroke is another manifestation of COVID-19 infection. Hyper-inflammation-mediated endotheliopathy and consumption hypercoagulopathy are often implicated. Hypercoagulopathy is related to sepsis, cytokine release, or immune system dysregulation. The crosstalk between systemic inflammation, endothelial dysfunction, and coagulation cascades plays a vital role in the thromboembolic events' pathogenesis (15-17).

S protein can reduce the expression/function of ACE2 proteins, which leads to uncontrolled hypertension and cerebral hemorrhage. If SARS-CoV-2 spreads within the cerebral microvasculature, damage to the capillary endothelial cells may result in a tear of the vasculature, causing parenchymal bleeding. The patients may have both thrombocytopenia and coagulopathy, leading to secondary brain parenchymal hemorrhage (15-19).

Peripheric Nervous System Manifestations

Anosmia And Ageusia

Smell and taste disorders are common, mainly in mild cases, and can be the first symptoms of a COVID-19 disease. They occur due to the nasal and oral mucosa epithelial cells infection. Parosmias may also occur during the illness and the regeneration phase (6,20,21).

Bell's palsy

Facial nerve involvement is also known (22,23).

Skeletal Muscle Manifestations

Myalgia/myositis

Myalgia and fatigue are common skeletal muscle symptoms of the disease (22).

Post-infectious CNS autoimmunity

Guillain-Barre Syndrome

Some cases of Guillain-Barré Syndrome (GBS) are reported in COVID-19 disease. The postinfectious mechanisms can be accepted, although the latency between the initial symptoms of the disease and the GBS occurrence appears very short. The complaints range from mild sensitive deficits to severe tetraparesis. There was no association between the severity of the disease and the occurrence/course of GBS (24-25).

Acute Necrotizing Encephalomyelitis

It is a post-infectious CNS autoimmune disorder defined by acute reduced consciousness and neurological decline following viral infections causing severe neurological disability and mortality (20).

Acute Disseminated Encephalomyelitis

This is an immune-mediated demyelinating disorder that occurs as a rare complication following the infection (20).

Conclusion

COVID-19 is frequently associated with neurological complications. We must keep in mind diagnosing SARS-CoV-2 infection when patients present with specific or nonspecific neurological symptoms during the pandemic. Respiratory symptoms are the primary reported diagnostic criteria used in COVID-19 disease. Still, we should be aware of these neurological manifestations, representing themselves even in the absence of prominent respiratory symptoms.

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