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Review Article

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COVID-19 PANDEMIC: NEUROLOGICAL MANIFESTATIONS, COMPLICATIONS AND FUTURE PERSPECTIVE

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ABSTRACT

The Severe Acute Respiratory Syndrome Coronavirus Disease-2 (SARS-CoV-2) is the causative agent of coronavirus disease-19 (COVID-19). The World Health Organization has declared this outbreak a pandemic condition, and it has become a public health emergency of international concern. Most of the population is experiencing signs and symptoms similar to the flu and common cold. Despite that, alveolar destruction resulting in progressive lung failure has also been underlined. Although SARS-CoV-2 has been underlined principally to affect the lungs, other system involvement has been described too. Neurological involvement has also been emphasized in the literature. Neurological involvement (central nervous system and peripheral nervous system) in SARS-COV-2 usually corresponds to the following situations: (a) Neurological manifestation of the acute viral infection, (b) neurological manifestations of the post-COVID-19 infection, (c) neurological image of COVID-19 in patients with comorbidities. The actual disease pathogenesis is unknown; however, direct viral invasion of neuronal cells, followed by significant inflammation due to cytokine and inflammatory markers, activation of the complement system, and hypoxia resulting from viral-mediated lung injury leading to oxidative stress, and neuronal cell injury are the proposed mechanisms. Patients with neurological involvement usually experience a wide range of signs and symptoms such as headache, nausea, drowsiness, seizures, altered sensorium, vomiting, and hyposmia. The pandemic of SARS-CoV-2 has become an unprecedented challenge for the physicians and neurologists. Various neurological manifestations have been observed and reported in many cases, and neurological symptoms may precede classical respiratory signs and symptoms. This review summarized the data from published literature, including case reports and open-source data sets to describe the spectrum of neurological manifestations and complications observed in COVID-19 cases.

KEYWORDS: Most of the population is experiencing signs and symptoms similar to the flu and common cold.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2), the causative agent of COVID-19 (coronavirus disease-2019), first originated from Wuhan during late December 2019. It started as an outbreak which led to an epidemic with 44,672 confirmed cases in China by February 14, 2020, with a 2.3% reported mortality rate, which was comparatively lower than the previously known epidemics caused by human coronaviruses (Severe Acute Respiratory Syndrome Coronavirus [SARS-CoV] and the Middle East Respiratory Syndrome Coronavirus [MERS-CoV]) in 2003 and 2012 respectively.[1,2] It rapidly spread outside of China to the whole world, mainly through human-to-human transmission by airborne droplets or possibly through the fecal-oral route. Consequently, the World Health Organization (WHO) declared COVID-19 as a global pandemic on December 02, 2020.[3] With the disease spread to 216 countries, over 63,965,092 reported confirmed cases worldwide, including over 14,88,120 deaths as of September 09, 2020.[4] The infection presents most commonly as dry cough, fever, shortness of breath, and sore throat, with severe respiratory involvement in patients with advanced age (over age 80). The overall case fatality rate in this age group is about 14.3%.[5] The severity of this disease is

characterized by severe pneumonia, respiratory failure requiring mechanical support, sepsis, myocardial injury, multi-organ failure, and mortality increases in patients having underlying comorbidities such as cardiovascular disease, diabetes, chronic kidney disease, and chronic respiratory disease.[6,7] However, some patients may have very mild symptoms or act as asymptomatic carriers suggesting that the actual number of cases may be much higher than reported.[2] Given the rapid spread of the virus, researchers across multiple nations have dedicated themselves to understanding the virus, disease pathophysiology, and developing effective drugs and preventive vaccines.

Although COVID-19 has been reported principally to affect the respiratory system, neurological involvement has also been underlined in the published literature. The amount of literature on neurovascular involvement by COVID-19 is small. However, we believe that a structured summary of existing data would be requisite for the neurologist. Being well informed about the neurological presentations would provide support to them with a high index of clinical doubts and take obligatory precautions. This paper has summarized the information from published literature, including case reports and open-source data sets, to describe the spectrum of neurological manifestations and complications observed in COVID-19 cases.

MATERIAL AND METHODS

We reviewed the literature on COVID-19 and its relevance to our neurology practice. A comprehensive literature search was performed using a combination of keywords (MeSH terms and free text words), including 'COVID-19'/' SARS-CoV-2' and "neurology/ neurovascular." PubMed, EMBASE, and Cochrane Library were searched up to August 30, 2020. A limit of after December 2019 was imposed since COVID-19 was first reported in late 2019. Additional articles were sought from the reference lists of the included articles. All articles identified from the literature search were identified and screened by two independent reviewers. We included studies on SARS-CoV-2 in adult patients. Case series, observational studies, non-randomized studies, and randomized trials published in English were included in this review. Conferences abstracts, letters to editors, commentaries, and editorials were excluded. Studies related to obstetrics and gynecology were also excluded.

For eligible studies, study information including first authors, site of study, inclusion and exclusion criteria, sample size, age, and sex were recorded. A standardized form for data entry has been devised to focus on the following areas: (1) neurological manifestations of COVID-19; (2) special considerations in neurological conditions. Relevant data were analyzed and summarized.

REVIEW

Mechanism of COVID-19 neurovascular invasion and injury:

The genome of the SARS-CoV-2 comprises single-stranded positive-sense RNA encapsulated within a membrane envelope, which contains glycoprotein spikes giving SARS-CoV-2 crown-like appearance.[7] Of the four classes of coronaviruses (alpha, beta, gamma, and delta), SARS-CoV, MERS-CoV, and SARS-CoV-2, are included in the class beta. While SARS-CoV, MERS-CoV, and SARS-CoV-2, all attack the lung, especially the lower respiratory tract, SARS-CoV-2 also affects the heart, gastrointestinal system, and liver, kidney, and the central nervous system, eventually leading to multi-organ failure.[8,9] Glycosylated spike (S) protein, one of the structural proteins programmed by the coronavirus genome, is a chief inducer of host immune response. This protein binds to angiotensin-converting enzyme 2 (ACE2) receptor protein located on the host cell surface membrane and mediates the host cell invasion.[9,10] ACE2 (entry receptor for SARS-CoV) was particularly confirmed in COVID-19 infection regardless of mutations at key receptor-binding domains. Inhuman transmission and pathogenesis of COVID-19 are based on the interactions involving virus binding, receptor recognition, cleavage of protease, and membrane fusion.

Lung involvement is the primary target for SARS-CoV-2. However, neuro involvement may get involved in several ways. The invasion of SARS-CoV-2 is due to ACE2 receptors expressed in blood vessels and neuronal cells. These receptors are not expressed in neuron and microglial cells. Therefore, the only way for SARS-CoV-2 to enter the human brain cell is via the blood vasculature. The virus first enters blood vessels by disrupting the nasal epithelium. By recognizing these ACE2 receptors here, SARS-CoV-2 makes its route to the brain and reaches the central nervous system.[11] It was also proposed that leukocyte and inflammatory cytokines, especially interleukin-6, helps in the neural invasion of SARS-CoV-2, leading to inflammation of neural tissue and myelin sheath.[12] SARS-CoV-2 can also invade the neural tissue through the dissemination of the first cranial nerve. SARS-CoV-2 invades the olfactory nerve followed by peripheral neurons and then advance towards the central nervous system by the retrograde axonal transport mechanism. This mechanism involves synaptic spaces. Dissemination into the central nervous system through the olfactory nerve via the cribriform plate has been documented by the presence of SARS-CoV-2 in the nasal epithelium, olfactory bulb, and by the development of a new symptom: hyposmia.[13] Hence, the symptoms like anosmia, ageusia, and hyposmia could be the presenting symptoms of SARS-CoV-2.[14] However, this idea is not fully supported because the olfactory nerve does not express ACE2 receptors, and data also does not support the association between SARS-CoV-2 AND hyposmia.

In COVID-19, a hypoxic state coupled with hypercapnia, anaerobic metabolism, peripheral vasodilation, and collection of toxic metabolites leads to hypoxia, which gradually induces cerebral injury due to cerebral edema and neural swelling. Cytokine storm, disseminated intravascular coagulation, and immune-mediated damage by the virus further worsen neurovascular injury.[15,16] A rise in luminal pressure by the blood vasculature may also lead to intracerebral hemorrhage.

1: Neurological manifestation in acute viral infection

1.1 central nervous system symptomology

The neurological image in acute COVID-19 is further subdivided into the central nervous system (CNS) and peripheral nervous system (PNS). CNS clinical features involve headaches, ataxia, altered sensorium, dizziness, stroke, and PNS involvement, including weakness and hyposmia. Headache can be a symptom of COVI-19 infection, and its incidence has been reported in many cases, and the only headache as a single symptom is not concerned so far. However, if this particular symptom is the clinical presentation of viral meningitis along with drowsiness and seizure, it raises the concern. Meningitis has been reported in the literature in patients with COVID-19. Acute hemorrhagic necrotizing encephalopathy has also been underlined due to COVID.[17] Another important finding is the occurrence of cerebrovascular events (CVE) associated with this illness. The initial retrospective case series from Wuhan underlined that 5.7% of the cases with neurological involvement could be attributed to acute CVE.[18] Notably, four patients had an ischemic stroke, while one patient had cerebral hemorrhage who died later on. Another study analyzed 221 participants and reported that 5.88% of the cases had new-onset CVE.[18] Most of them presented acute ischemic stroke, while hemorrhagic stroke and cerebral venous sinus thrombosis were also found in one patient. Therefore, thrombotic clinical manifestations were way more common than hemorrhagic. These findings may be linked to the observation that patients with CVE were more prone to have enhanced inflammatory response as depicted in their C-reactive protein (CRP) and D-dimer levels. It might be possible that viral infection may have triggered the inflammatory storm that ultimately ended in accelerated thrombosis. The term "accelerated thrombosis" seems more eloquent if seen in the context of another finding in this specific retrospective study.

It was noted that patients with CVE were significantly older than those without CVE. The pre-existent vascular risk factors were also predominant in CVE patients. Moreover, any COVID-19 infection in a stroke patient prolongs the recovery and may deteriorate the condition and worsen the neurological deficit, the latter being sometimes attributed to hemorrhagic stroke. The mortality rate was notably found to be higher in COVID-19 stroke patients. It was reported that 38% of patients indicated a worse prognosis in this group of patients. The above paragraph brings out the two-way relationship between stroke and COVID-19. The subject becomes more complicated when treating a patient with ischemic stroke with a history of coronavirus infection. The application of antiplatelet therapy and anticoagulants is multifaceted because the SARS-CoV-2 is known to cause prominent lung involvement. The involvement of the nervous system may be responsible for respiratory impairment.

Impaired consciousness has been underlined in 7.5% of hospitalized COVID-19 patients.[19] Impaired consciousness usually results from severe infection. There can be multiple underlying etiologies in COVID-19 to present with impaired consciousness, including viral encephalitis, infectious, toxic encephalopathy, seizures with post-ictal confusion, metabolic derangements, and stroke. In a recent document, it was reported that altered sensorium certainly had strained the neurologists' attention, mostly due to delayed diagnostic procedures because COVID-19 is widely known to be a lung pathogen. In a case series of COVID-19 related ARDS patients (n=58), altered consciousness, including agitation and confusion, has been underlined in more than two-thirds of the cases.

Furthermore, 67% of the recruited patients had evident corticospinal signs.[20] Association of COVID-19 with seizure has also been reported in the literature. The seizure may be a clinical manifestation of SARS-CoV-2 entry into the CNS.

Secondly, COVID-19 causes fatal pneumonia leading to severe hypoxemia, resulting in brain injury and seizures. Thirdly, the patients with epilepsy and COVID-19 may exhibit increased frequency and severity of seizures, mainly because of threshold lowering associated with fever. The fact that neurological complications are more common in severely ill patients and also cardiovascular risk factors are predictors of severity, the drug interaction potential of many antiepileptic medicines would warrant attention in such clinical conditions. Therefore from a neurologist's perspective, a seizure in a COVID-19 patient will have some important clinical implications both from diagnostic and therapeutic perspectives.

1.2 Peripheral Nervous System Symptomology

PNS signs and symptoms of COVID-19 have also been reported in the literature. Mao et al. underlined the PNS effects of COVID-19 in the form of dysgeusia 5.6%, dysosmia 5.1%, visual disturbances 1.4%, and neuralgia 2.3%. Other studies identified anosmia and ageusia as the predominantly clinical presenting symptoms of PNS. Bagheri et al. found a significant association between anosmia and COVID-19 positivity in different provinces of Iran (Spearman correlation coefficient: 0.87, p-value <0.001. Furthermore, it was also reported that those with anosmia were more prone to have dysgeusia without typical signs and symptoms of COVID-19.[21] Giacomelli et al. studied 59 hospitalized patients to investigate the olfactory and taste disturbances. They reported that only

10.2% have taste symptoms, 5.1% have only olfactory disturbance, while 18.6% had both. They also underlined that patients with these symptoms tended to be younger and female.[22] In a study by Lechein et al., out of 417 patients, 85.6% reported olfactory dysfunction, of those 20.4% had anosmia, 12.6% with phantosmia, and 32.4% with parosmia, with the remaining having hyposmia. A total of 88.8% of cases had gustatory disorders. Of those, 78.9% had ageusia, and the rest of them had dysgeusia. These symptoms had a high degree of correlation with each other and have an association with the female gender. Recovery was generally deferred over weeks, with early recovery reported only in 44% of cases.[14]

Guillian-Barre syndrome (GBS) has also been reported in the literature. Gutiérrez-Ortiz et al. reported two cases of GBS in COVID-19 patients. MRI and CSF laboratory studies, as well as CSF culture, did not show any abnormality. Both patients were managed with immunoglobulins (IgG) and had a resolution of all of the signs and symptoms except for anosmia and ageusia at the time of discharge.[23]

Zhao et al. reported the case of a 61-year-old female with acute lower extremity weakness and severe fatigue. Physical examination exhibited areflexia and symmetric ascending lower motor neuron paralysis consistent with GBS. Initial laboratory studies revealed thrombocytopenia, lymphopenia. Nerve conduction studies were performed, which showed findings consistent with demyelinating neuropathy. Subsequent nasopharyngeal PCR was positive for COVID-19. She was admitted and managed with IV immunoglobulins (IV IgG) and had complete symptom resolution at thirty days.[24] Zhao et al. also underlined a case of acute myelitis in a COVID-19 positive. The patient presented on the sixth day with acute flaccid myelitis of the lower limbs with urinary and bowel incontinence and sensory level abnormality at the T10 level. CT scan of the brain showed bilateral basal ganglia and paraventricular lacunar infarcts along with brain atrophy. The patient was managed with a multitude of intravenous antibiotics, IV IgG, steroids, and Vitamin B12 and had significant improvement in his signs and symptoms.[25]

2: Post ineffective neurological complication

With more number of patients recovering from COVID-19, post-infective complications would pull attention with time. CNS demyelination has been documented previously following COVID-19.[26] An early GBS report is available from China, although there is a concern regarding the causality in this particular case.[24] The patient experienced typical symptoms of COVID-19 after seven days of hospitalization for GBS. A very recent correspondence reported five GBS cases collected from three hospitals in northern Italy among 100 to 1200 cases of SARS-CoV-2 infection over three weeks. Three of these cases correspond to criteria for the axonal variant of GBS, while the remaining two had prolonged distal latencies suggesting demyelinating neuropathy.

Another report from China underlined a case of acute myelitis, possibly affecting the cervical spinal cord, as evidenced by the clinical features, in a known patient of COVID-19.[25] In this particular case, the neurological signs and symptoms were co-incident with the disease's febrile period, pointing towards para-infectious demyelination rather than a post-infective impediment in real sense. The treating physicians documented lymphopenia accompanied by raised markers of inflammation. The patient established anti-viral therapy along with immune-suppressive and improved from his limb weakness. Although the literature is occasional at this point, the idea that COVD-19 can cause para-/post-infective complications affecting the neuro-axis at different levels appears truthful. Patients with an inflammatory storm will be more likely to mark this.

3: Neurological manifestation in patients with comorbidities

During this pandemic, another group of patients will warrant the attention of neurologists. This group encompasses of neurologically ill patients who have already been in follow-up for some time. The need for different groups will differ according to the nature of their disease. Data is unsatisfactory at this point to accomplish if chronic neurology patients are more inclined to obtain an infection. However, the subjects with reduced mobility and those on immune-suppression treatment may be foreseen to be more susceptible to infection.

Recent correspondence has already debated the challenges faced by dementia patients during this period of social distancing and home isolation.[27] The crisis will be more for those patients who depend on others for daily life activities. The condition will be similar for patients with significant motor problems. Due to their restricted mobility, social distancing is supposed to affect them for worse. Reduced mobility and dementia may also incline a patient to have a viral infection. So once again, the association becomes two-way. The patients who are on immunosuppressants are also of particular concern.

The data so far on COVID-19 shows that old age, as well as immune-dysregulated patients, are more likely not only to get the infection but also to show increased severity. Appropriate attention has to be practiced while dealing with such cases both from the neurologist and the patient's relatives. A recent study on this topic commends that the benefits of ongoing immunotherapy in patients with multiple sclerosis (MS) and related disorders may balance the risks of medication withdrawal in the apprehension of COVID-19. This is mainly because most infections are anticipated to be mild and self-limiting, as in the general population. However, the authors emphasize the need for individualized decision-making in such circumstances because one size" may not fit all, and some of the patients may land up in severe infection leading to discontinuation of therapy.[28]

CONCLUSION

The pandemic of COVID-19 presents for a neurologist some unprecedented challenges. We perceive that SARS-CoV-2 may have various neurological manifestations, and in many cases, the neurological signs and symptoms may precede typical respiratory symptoms. Holistic knowledge of the spectrum of the neurological consequences of COVID-19 is crucial to get a hold on the spread of the virus. The most vital clinical information which we meet is that diarrhea and abdominal pain may be a presenting feature of COVID-19. Therefore, a high catalog of suspicion for such patients will be essential to prevent or, at least, minimum exposure to health care providers and other patients. With the gradual settling of the outbreak, it can be predicted that several post-infectious neurological complications, including GBS, will surface up. The proper caution must be practiced while treating and managing patients with neurological comorbidities, particularly those on immunosuppressants. The above review of the neurological manifestations of COVID-19 will help the neurologist have a necessary preparation, which is of extreme importance to prevent infections.

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