Swedish Science Pioneers

Journal of Experimental & Clinical NeuroSciences

Journal homepage : www.JECNS.com

Review Article

Central Nervous System as a Target for SARS-CoV-2: A Review Article

Sama Rahnemayan [a], Sarvin Sanaie [b*]

[a]*Student Research Committee Tabriz University of Medical Sciences, Tabriz, Iran.*

[b]*Neurosciences Research Center, Aging Research institute, Tabriz University of Medical Sciences, Tabriz, Iran*

Abstract

Although neurological symptoms are not frequent in coronavirus infection, the high number of patients with SARS-CoV-2 infection may explain the presence of the virus in the central nervous system and increase the likelihood of early- or delayed-onset neurological symptoms. It is highly possible that some of these patients, particularly those who have a severe illness, have central nervous system involvement and neurological manifestations. The mechanism of injury is not fully understood but SARS-CoV-2 via direct infection, immune dysfunction, and hypoxemic injury as well as angiotensin-converting enzyme 2 receptors can result in infectious toxic encephalopathy, viral encephalitis and acute cerebrovascular accident. Personalized and targeted documentation of neurological symptoms, detailed clinical, neurological, and electrophysiological assessment of the patients, attempts to isolate SARS-CoV-2 from cerebrospinal fluid, and autopsies of the COVID-19 victims may clarify the role played by this virus in causing neurological manifestations. In order to ensure optimum neurological patient management, ongoing study of treatment algorithms will be essential for updating and adapting these approaches as the COVID-19 pandemic evolves. In this review we discussed about the different neurologic manifestations of COVID-19 patients.

Keywords: *COVID-19; Coronavirus, Central nervous system, Neurological manifestation*

Correspondence

Sarvin Sanaie
Neurosciences Research Center, Aging Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran
Tel: +98 9143116744
Fax: +98-41 33342178
Email: sarvin_so2000@yahoo.com

Received: 2020-04-29
Accepted: 2020-06-22

DOI: 10.13183/jecns.v7i2.110

Introduction

Since the beginning of Coronavirus Disease 2019 (COVID-19) in Wuhan, China, on December 2019, the patients affected by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) have shown multiple and sometimes strange and unexpected epidemiological and clinical outcomes. The clinical findings of the disease was reported to be fever, sore throat, cough, dyspnea, sputum production, diarrhea, myalgia and fatigue, and, less frequently, headache (8.0%) at the first 2 months of the COVID-19 pandemic [1-7]. However, an increasing number of neurological manifestations such as hyposmia, anosmia, hypogeusia, dysguesia, and ageusia have recently been reported in patients with COVID-19 [8]. Same as many viruses including herpesviruses, arboviruses, measles virus, influenza virus, and HIV which can reach the central nervous system (CNS) and brain [9–11]. Coronaviruses may also infect the CNS leading to a high incidence of neurological symptoms [12,13]. It was recently reported that 36.4% of patients with confirmed SARS-CoV-2 infection develop neurological symptoms in addition to systemic and respiratory symptoms; they include headache, paresthesia, and disturbed consciousness [14].

The presence of headache in these patients can be suggestive of the potential neurotropism and neurovirulence of the novel coronavirus like other naturally neurotropic coronaviruses [15–18].

This article reviews the recent and available evidence on the neurologic manifestations of SARS-CoV-2, and its possible mechanisms.

The Hypothesis of the Brain as a Reservoir for SARS-CoV-2

SARS-CoV and SARS-CoV-2 seems similar in many respects, but they are genetically and structurally different [19]. The novel coronavirus is more contagious than SARS-CoV.

It is characterized by its high ability to spread via respiratory droplets and contact with infected objects and individuals [4,20]. Moreover, it can also spread by asymptomatic infected individuals [21–23]. Similarly to SARS-CoV which was detected in the brains of some patients, the novel coronavirus has been suggested to affect the CNS [24]. Different clinical features including olfactory alterations, seizures, and hallucinations in patients infected with SARS-CoV-2 support the hypothesis of a specific affinity for the CNS. However, these symptoms had not been reported in patients with SARS-CoV or MERS-CoV infection [25–27]. Coronaviruses are spherical or oval in shape and have an average diameter of 100 nm. They are positive-sense single-stranded RNA viruses harboring the largest genome among the RNA viruses, with a genome length of about 26–32 kb. The coronavirus has large spikes of viral membrane glycoproteins on its surface, and looks like a typical crown under electron microscope [28]. Differences in fusion protein and accessory proteins, ORF3b and ORF8, are the main structural differences between SARS-CoV and SARS-CoV-2. The genome of coronaviruses encodes four main structural proteins; i.e. spike, envelope, membrane, and nucleocapsid proteins [29]. The viral surface glycoprotein S may induce neurodegeneration [30]. When the virus enters the host cells, its genome is translated into two large precursor polyproteins, which are processed by ORF1a-encoded viral proteinases into 16 mature nonstructural proteins (nsp1-nsp16). Nonstructural proteins are of an essential role in viral RNA replication and transcription, whilst ORF3b has been associated with the immune response [31,32]. SARS-CoV-2 spike glycoprotein S1 subunit receptor-binding domain binds to angiotensin-converting enzyme 2 (ACE2) receptors as seen in SARS-CoV. This is the site of viral entry into the host cell and leads to the possibility of creating an experimental model of SARS-CoV-2 infection [33]. Meanwhile, the ACE2 receptor is widely expressed in the brain; this can support the of CNS involvement in the SARS-CoV-2 infection [34,35]. Viruses can enter the CNS through the olfactory or trigeminal nerves via the haematogenous route. Therefore, the high incidence of olfactory changes seen in COVID-19 patients may indicate viral entry into the CNS. Findings from studies of the mouse hepatitis virus model and also the detection of coronovirus in patients' brains propose that the virus can remain in the host's CNS for a long time and in fact the brain can act as a viral reservoir [36].

Neurological Manifestations in Patients with COVID-19

Neurological symptoms have been seen in patients with COVID-19. These symptoms can be categorized as followings: intracranial infection related symptoms, acute cerebrovascular disease related symptoms, peripheral nervous system symptoms and neuromuscular symptoms. Sensory abnormalities, neuralgia, and sphincter disturbances are among other reported manifestations [37]. Several symptoms are indicative of CNS involvement and are reported in almost one-third of COVID-19 patients including headache, smell/taste disorders(STD), dizziness, ataxia, , impaired or loss of consciousness, seizures, and acute cerebrovascular disease [38]. Results of a study by Beltrán-Corbellini et al. revealed that new-onset STD is significantly more frequent among patients with COVID-19 compared to influenza. This symptom usually manifested as an initial symptom with acute onset, suggesting that STD assessment can be a helpful clinical assay in patients with COVID-19 [39]. A case of a young, middle aged, obese female with a history of diabetes was presented by Duong et al. She complained of fever, headache, and a new onset seizure. She was diagnosed as viral meningitis. Meanwhile, COVID-19 testing was ordered because of her febrile illness. After 72 hours, the results of COVID-19 testing were positive. She was started on hydroxyl-chloroquine and her mentation started to improve by the 5th day of admission [40]. Gutiérrez-Ortiz et al. reported two patients infected with SARS-CoV-2). The first patient acutely presented with Miller Fisher syndrome. He was a 50-year-old man presenting with ataxia, anosmia, ageusia, areflexia, right internuclear ophthalmoparesis, right fascicular oculomotor palsy, albuminocytologic dissociation and positive testing for GD1b-IgG antibodies. He reported of having fever, malaise, low back pain, cough, and headache, five days before the admission. The second patient was presented with polyneuritis cranialis. He was a 39-year-old man presenting with ageusia, areflexia, bilateral abducens palsy, and albuminocytologic dissociation. He had developed a low-grade fever, diarrhea and a poor general condition three days before the admission. The oropharyngeal swab test for COVID-19 by qualitative real-time reverse-transcriptase– polymerase-chain-reaction (rRT-PCR) assay was positive in both cases and negative in the cerebrospinal fluid. A complete neurological recovery was achieved in both subjects two weeks after treatment; however, anosmia and ageusia was remained in the first case [41]. In an observational series of 58 of 64 consecutive patients who were admitted to the hospital because of acute respiratory distress syndrome (ARDS) due to COVID-19, the neurologic features was reported. The neurologic findings were recorded in 14% of patients (8 of 58) on admission to the ICU and before treatment, and in 67% of patients (39 of 58) after withholding the sedation and neuromuscular blocker. Agitation was present in 69% of patients (40 of 58) when neuromuscular blockade was discontinued. A total of 26 of 40 patients had confusion. Diffuse corticospinal tract signs as ankle clonus, enhanced tendon reflexes, and bilateral extensor plantar reflexes were present in 67% (39 of 58). Of the discharged patients, 33% (15 of 45) had a dysexecutive syndrome consisting of disorientation, inattention, or poorly organized movements in response to command. In these series of patients, SARS-CoV-2 related ARDS was associated with confusion, prominent agitation, encephalopathy, andcorticospinal tract signs [42]. Lechien et al. assessed the occurrence of gustatory and olfactory dysfunctions in European patients with laboratory-confirmed COVID-19 infection. They concluded that gustatory and olfactory disorders are prevalent symptoms in these patients, even without nasal symptoms. Sudden onset of ageusia or anosmia should be recognized as important symptoms of the COVID-19 infection [43]. Lu et al. aimed to reveal the incidence and risk of acute symptomatic seizures (ASS) in patients with COVID-19 in a multicenter study. They reported no evidence suggesting an additional risk

of ASS in patients with COVID-19. Neither the virus nor the potential risk factors for seizures seem to be significant risks for the occurrence of ASS in COVID-19 patients [44]. Mao et al. evaluated 214 patients with COVID-19 and their neurologic features in an observational retrospective case series. Of all 214 patients, 78 patients (36.4%) had neurologic symptoms. The neurologic manifestations of patients with more severe infection were as %]), impaired consciousness (13 [14.8%] vs. 3 [2.4%]), acute cerebrovascular diseases (5 [5.7%] vs. 1 [0.8and skeletal muscle injury (17 [19.3%] vs. 6 [4.8%]) compared to those with mild or moderate infection [14]. Bonilla-Aldana et al. presented a case report in which a physician presented with headache, myalgias, abdominal pain, diarrhea, and chills, with no fever, persisting for five days. Her rRT-PCR test showed the viral RNA of SARS-CoV-2 [45]. Sedaghat et al. reported the symptoms of Guillain Barre syndrome (GBS) in a patient infected with COVID-19. The patient was a 65-years- old male complaining of acute progressive symmetric ascending quadriparesis. He had fever and cough two weeks before hospitalization. The rRT-PCR test was reported positive for COVID-19 infection [46]. Zhao et al. report a case of COVID-19 patient who initially presented with acute Guillain-Barré syndrome. She was 61 years old presenting with severe fatigue and acute weakness in both legs. The symptoms progressed within one day. On day eight, she developed a fever of 38.2°C and dry cough. Chest CT-scan showed ground-glass opacities in both lungs. Oropharyngeal swabs were positive for SARS-CoV-2 on RT-PCR assay [47]. Zhou et al. reported a case of 56-year-old patient in whom gene sequencing confirmed the presence of SARS-CoV2 in the cerebrospinal fluid. The patient's CNS was attacked by SARS-CoV-2 and was diagnosed with viral encephalitis. This reveals that SARS-CoV-2 can directly invade the nervous system, in addition to injuring it through the immune response [48]. Yin et al. reported a case of a patient who was tested positive SARS-CoV-2 nucleic acid in his throat swab. He manifested with concomitant neurological symptoms. The patient had fever and respiratory symptoms prior to muscle soreness, and then suffered from altered consciousness and psychiatric symptoms. On the neurological examination, positive signs were observed [49]. Sharifi Razavi et al. presented a case of 79-year-old man with a history of cough and fever for three days who was referred to emergency department with acute loss of consciousness. At the admission he had fever, tachycardia, tachypnenia with no history of hypertension and anticoagulation therapy. In the physical axamination he had a Glasgow Coma Scale of 7, bilateral extensor plantar reflexes, and coarse rales in the lower lobe of left lung. Lung CT-scan showed the ground glass opacity in left lower lobe and brain CT-scan revealed a massive intra-cerebral hemorrhage in right hemisphere accompanied by intra-ventricular and subarachnoid hemorrhage. COVID-19 infection was confirmed by RT-PCR of oropharyngeal swab [50].

The Therapeutic Candidates for COVID-19

From the evidence achieved from various studies and the known nature of coronaviruses which possess neuroinvasive properties, the neurological manifestations of COVID-19 are not unexpected. In those patients suffering from early-onset neurological symptoms, such as loss of smell or taste or even seizures, clinical suspicion must be directed to COVID19 and the patient should be kept under consistent observation of a neurologist. As the virus can completely destroy the medullary neurons and threaten the life of the patient, complete monitoring of the patient is necessary [24]. Since good progress in understanding the key interactions between the hACE2 and the receptor-binding domain of the spikeprotein in SARS-CoV-2 has been achieved, effective antiviral intervention strategies can be developed soon. Some antibody drugs can be designed following the epitopes on the SARS-CoV-2 receptor-binding domain (RBD). Moreover, RBD can be used as a subunit vaccine [51]. On the other hand, the nature of the interactions between hACE2 and RBD are protein−protein interactions; hence, designing of peptide-based therapeutics can be considered. Many structure-guided therapeutics like peptides or small molecules interfering with the receptor recognition of the virus may cease the progression of the disease [52]. Actually, transmembrane serine protease 2 (TMPRSS2) is the surface protease that cleaves and activates the spike protein of SARS-CoV to release its infective potential. Inhibition of TMPRSS2 was once considered as an effective therapeutic intervention to stop the viral spread, but later the idea was dropped because of the unknown physiological impact of TMPRSS2 blockade [35]. Additionally in patients with hyper-inflammation due to cytokine storm, selective cytokine blockers like tocilizumab, appropriate steroids, , antibody therapy, and inhibitors of the JAK pathway should be considered [53]. Moreover, in order to have deeper insights into the neurological pathway of COVID-19 infection, autopsies of not only the lungs but also the brains should be performed.

Conclusions

Alterations in purinergic signaling have been described in Neurological manifestations of COVID-19 have not thoroughly been studied yet; but, in patients with severe illness, neurological manifestations and CNS involvement are reported. To completely define and clarify the roles of novel coronavirus in causing neurological manifestations, precise and targeted documentation of the neurological symptoms and signs (like headache, dizziness, STD, change in mental status, meningeal signs, etc.), detailed clinical and neurological examination, electrophysiological investigations especially in those with a change in mental status, isolation of SARS-CoV-2 from CSF, and brain autopsies of the COVID-19 victims should be performed. Accordingly, based on the neurological consequences of COVID-19, patients suffering from an inability to taste or smell or altered mental health must be tested for COVID-19 and not be neglected. In addition, patients who already have neurological features should be closely monitored in order to symptoms not aggravate over the following days of the infection. This strategy should also be considered as a preliminary screening strategy in case of large scale community transmission of COVID-19. As this infection has a high tendency for turning out to be neurological, a neurologist should be included in the health care units taking care of infected patients. Moreover, autopsies on the brains of

COVID19 victims with neurological manifestations should be performed to establish the neuroinfection track of the disease.

Acknowledgment

Not applicable.

Conflict of Interest

The authors declare no conflict of interest

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