IJMCM 13(1) (2023) 1779-1787 Doi: 10.22034/IJMCM.2023.699915

International Journal of
Molecular and Clinical Microbiology

Review Article

A comprehensive review of CNS and PNS manifestations of SARS-CoV-2 infection

Zahra Jalili[1], Mehrnoosh Nikpour[2], Bahareh Hajikhani[3], Sina Ghasemi[4], Saba Sayyari[5,6], Nooshin Nazarinejad[7], Fatemeh Sameni[8*]

1. Department of Medical Laser, Medical Laser Research Center, Yara Institute, ACECR, Tehran, Iran
2. Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran
3. Department of Microbiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
4. Lifestyle & Health Management Research Department, Academic Center for Education, Culture and Research, ACECR, Tehran, Iran
5. Neonatal Health Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran
6. Shahid Beheshti University of Medical Sciences, Imam Hussein Hospital, Tehran, Iran
7. Department of Microbiology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran
8. Department of Microbiology, Faculty of Medicine, Shahed University, Tehran, Iran

ARTICLE INFO

Article history:
Received 20 November 2022
Accepted 31 Junary 2023
Available online 1 March 2023

Keywords:
COVID-19,
Neurological manifestations,
CNS,
PNS,
SARS-CoV-2

ABSTRACT

The novel coronavirus (2019-nCoV, or COVID-19) was, for the first time, detected in Wuhan city (China) in 2019. It was subsequently spread worldwide which resulted in a viral pandemic associated with high rate of mortality. Although this virus mainly affects the pulmonary system, it has already been reported that COVID-19 could also affect the nervous system, either at the first stages of disease or during the *illness progress*. During COVID-19 pandemic, numerous neurological complications corresponding to Central Nervous System (CNS) disorders such as giddiness, headache, unconsciousness, encephalitis and ataxia, as well as Peripheral Nervous System (PNS) disturbances including Guillain-Barre syndrome (GBS), skeletal muscle malfunction, hyposmia, hypogeusia and muscle pain, were reported. In this regard, further *researches* about *neurological* manifestations of COVID-19 is suggested. Current review attempts to discuss various CNS and PNS manifestations of SARS-CoV-2 virosis.

1. Introduction

In December 2019, the first case of a viral pneumonia was reported in Wuhan, Hubei province, China which was caused by a *novel* coronavirus (Sameni et al., 2020; Sameni et al., 2021a). The diagnostic methods of COVID-19 rely on clinical symptoms, Computed tomography (CT) scan findings, and molecular and serological tests. Severe acute respiratory coronavirus 2 known as *SARS-CoV-2* infection, primarily entangles human pulmonary system accompanied by common symptoms including fever, cough, fatigue, dyspnea, headache and gastrointestinal manifestations (Sameni et al., 2021c; Dadashi et al., 2022; Fard et al., 2021). The neuroinvasive capabilities of coronavirus 2 (*SARS-CoV-2*) probably correspond to its potential to attack to CNS through respiratory

*Corresponding author: Fatemeh Sameni
E-mail: Sameni.f@yahoo.com

tract. Some infected people may even experience neurologic *disorders* as primary symptoms of the infection (Niazkar et al., 2020). As previous researches have claimed, a wide spectrum of CNS complications have been reported in severe acute lung infection status caused by two types of coronavirus named as coronavirus 1 / SARS-CoV-1 and Middle East respiratory syndrome coronavirus / MERS-CoV (Li et al., 2020).

The prevalence rate of neurological defects brought about by COVID-19 infection, is higher in severe infections which may be the consequence of cerebral hypoxia that is occurred due to the respiratory failure. These neurological defects may include a combination of nonspecific syndromes of systemic disease, nonspecific CNS disorders and also vascular inflammation of the CNS which is considered as the direct effect of SARS-CoV-2 virosis (Ellul et al., 2020).

Since different kinds of neurological disoerders including headache, confusion, generalized muscle weakness and unconsciousness are defined as nonspecific symptoms of SARS-CoV-2 virosis, it is a challenging mission for healthcare professionals to distinguish between direct implications of SARS-CoV-2 virus on CNS and nonspecific neural symptoms related to the systematic disorders such as metabolic derangement and hypoxia.

This review aimes to highlight the neurological complications of COVID-19 including CNS dysfunctions, PNS dysfunctions and musculoskeletal injuries.

2. Neurological manifestations

Numerous reports have claimed that besides acute respiratory syndromes, coronavirus infection can be associated with a range of neurologic dysfunctions from moderate to intense stages and it may influence skeletal muscles further (Table 1) (Josephson and Kamel, 2020). More than 35% of patients reveal neurologic disorders some of which are considered as initial symptoms of disease (Whittaker et al., 2020). However, various studies have shown that the virus induces neurological deficits on the 28th day of the virosis due to its isolation from the patient's brain (Baig, 2020; Pryce-Roberts et al., 2020). To assess whether viral neurological involvement has occurred in a patient or not, taking appropriate treatment strategies is crucial (Baig, 2020). although COVID-19 mainly affects pulmonary and cardiovascular organs, some neurological symptoms like hypogeusia, dizziness, headache, neuralgia, encephalopathy, acute cerebrovascular diseases, skeletal muscle injury and disrupted consciousness have been reported (Mao et al., 2020; Helms et al., 2020). It is supposed that anosmia is also a symptom of SARS-CoV-2 due to the neurological involvement of infection. The degree of neurological sequelae may be influenced by various reasons such as admission to hospital, the neuroinvasive feature of the virus and indirect consequences of diverse organs dysfunctionalities which needs to be fully investigated (Whittaker et al., 2020). Furthermore, some studies claim that not all COVID-19 patients show CNS direct infectious symptoms which should be investigated in different aspects (Helms et al., 2020).

There are two proposed ways via which the virus can enter CNS. These routes may or may not have implications for the enhanced rate of anosmia reports diagnosed in COVID-19 patients. The initial spread is caused by the systemic vascular dissemination of the virus (Baig, 2020). The second one is developed by crossing of virus through the cribriform plate of the ethmoid bone. The latter was detected in early-stage cases of COVID-19-affected patients and leads to the deficiency of smell sense and taste accompanied (Baig, 2020).

3. General Neurological Symptoms

Innumerable case reports from China reveal the existence of neuropsychiatric disorders dur to COVID-19 infection such as Impaired Consciousness (Yin et al., 2020) and encephalopathy (Filatov et al., 2020). A study on 214 Wuhan hospitalized patients reported 36.4% neurological symptoms probably while overlooking the stages of the disease. It showed that two most prevalent CNS manifestations were headache (17%) and dizziness (13%).

These symptoms are nonspecific and are considered as minor disturbances. The research claimed that persons who were severely infected by SARS-CoV-2 showed more neurological complications than patients in the early stages of the disease (the Author did not specify the methodology of making difference between an

intense and non-intense infectious status) (Mao et al., 2020). The major neurological disorders of COVID-19 which have been reported so far, are categorized in a review article by Imran Ahmad et al. as central and peripheral types as mentioned below (Ahmad and Rathore, 2020).

It illustrates that some COVD-19 patients at the first step of illness show just fever and headache. However, after a few days these symptoms may develop to sore throat, lymphopenia, cough and ground–glass appearance on their chest CT image (Mao et al., 2020).

Table 1. Nervous implications of COVID-19 infection according to studies

Central Nervous System (Mao et al., 2020)	Dizziness
	Headache
	Acute cerebrovascular disease
	Impaired consciousness
	Transverse myelitis
	Acute hemorrhagic necrotizing encephalopathy
	Encephalopathy & Encephalitis
	Epilepsy
	Ataxi
Peripheral Nervous System (Helms et al., 2020)	Hypogeusia
	Hyposmia
	Neuralgia
	GBS
	Skeletal muscle injury
	Hypogeusia

4. CNS manifestation

In some literatures related to COVID-19, some CNS operation disturbances were reported such as headache, dizziness, acute cerebrovascular infection, epilepsy, ataxia, acute disseminated encephalomyelitis, impaired consciousness (Wu et al., 2020; Wu et al., 2020; Wu et al., 2020; Wu et al., 2020; Xu et al., 2020), and viral encephalitis (Lahiri and Ardila, 2020; Achar and Ghosh, 2020). According to a study, both spinal cords and brains of patients were infected by virus. In Mao et al. conducted a retrospective case series form study in which 214 SARS-CoV-2 patients suffering from neurological complication, CNS and PNS disturbances and skeletal muscle injuries were studied. CNS disturbances were the most prevalent neurological symptoms. Furthermore, it was found that the more the severity of the infection is, the higher the level of the CNS disorders gets which is accompanied by high amounts of D-dimer formation (Mao et al., 2020). Table 2 summarizes the most important biomarkers in COVID-19 patients. In addition, acute cerebrovascular disease was detected in older COVID-19 patients who had numerous risk factors including diabetes, high levels of C-reactive protein and hypertension. Furthermore, MRI investigation revealed meningitis/ encephalitis, pan-paranasal and paranasal sinusitis in COVID-19 patients (Li et al., 2020).

4.1. Encephalopathy

The main manifestation of encephalopathy is diffuse brain dysfunction that transforms consciousness ranging from confusion, delirium or some time leads to come. Clinical symptoms of encephalopathy include headache, seizures or extrapyramidal signs. In fact, multiple dysfunctionalities of some organs such as cardiac, renal and hepatic failure and also acute respiratory insufficiency in COVID-19 patients lead to encephalopathy (Slooter et al., 2020). Although encephalopathy occurrence is negligible in recovered patients, Mao et al. recorded some manifestations in 40% of infected individuals (Mao et al., 2020). However, a retrospective study in China, done on 274 patients, illustrated 24 (8.8 %) patients with progressed hypoxic encephalopathy among which 23 (95.8%) cases developed to death and just 1 case (4.2%) was recovered (Chen et al., 2020). The first case of acute hemorrhagic necrotizing encephalitis (ANE) of COVID-19

patients was found in USA in 2020. ANE is a viral infectious complication such as influenza in which the cytokine storm is the main mechanism of incidence that occurs due to the blood-brain barrier damage (Filatov et al. 2020).

Table 2. Biochemical and immunological biomarkers in COVID-19 patients.

	Biomarkers	Diagnostic value	References
Biochemical biomarkers	Lymphopenia	Valuable diagnostic and prognostic marker of COVID-19 disease	(Baïsse et al., 2022)
	Increased neutrophil/lymphocyte ratio (NLR)	NLR greater than 6.5 may reflect the progression of the disease towards an unfavorable clinical outcome, the ratios higher than 9 may strongly result in death	(Pirsalehi et al., 2020)
	Increased platelet-to-lymphocyte ratio (PLR)	A marker of severity and mortality in COVID-19 infection	(Simadibrata et al., 2022)
	Increase in liver function markers (Aspartate transaminase [AST], Alanine transaminase [ALT], Bilirubin	- More common in patients with severe pneumonia - The mortality rate significantly increased with increased AST levels	(Omrani-Nava et al., 2020; Fan et al., 2020)
	Elevated C-reactive protein (CRP)	Indicates aggressive immune response towards viral infection	(Fazal, 2021; Sameni et al., 2021b)
	Lactate Dehydrogenase (LDH)	- Higher in patients with abnormal liver function -Associated with 6-fold increased odds of severe COVID-19 disease	(Szarpak et al., 2021)
Immunological biomarkers	IL-1b	Significantly elevated in patients with severe COVID-19	(Potere et al., 2022)
	IL-8	Increased of IL-8 in the CSF of COVID-19 associated with neurological symptoms	(Dadkhah et al., 2022)
	IL-10	Putative immune biomarker in surveying COVID-19 disease severity	(Lu et al., 2021)
	Tumor necrosis factor (TNF)-alpha	Reported in patients with severe COVID-19	(Hadjadj et al., 2020)
	IL-6	Positively correlated with disease stages and radiologic changes	(Santa Cruz et al., 2021)
	Increased blood neurofilament light chain (NFL)	Serve as an estimate of disease severity in hospitalized patients	(Erben et al., 2022)

4.2. Stroke

Numerous cases of stroke have been observed in COVID-19 patients that especially occurs in cases under 50 years of age. However, in noninfected people stroke normally happens in ages over 74 years old. An observational study on different regions of Wuhan, China, identified acute ischemic stroke in 5 % of patients. This article suggested that ischemic stroke was more prevalent in severe SARS-COV-2 cases. Furthermore, it demonstrated that older patients (71.6 ± 15.7 years versus 52.1 ± 15.3 years) who had health risks such as hypertension, previous cerebrovascular disease and diabetes had encountered this complication more than others (Diao et al., 2020). Some cases of large vessel stroke (Oxley et al., 2020) (1.6%) (Klok et al., 2020) and ischemic stroke (2.5 %) (Lodigiani et al., 2020) were also found in 3 separate studies which were done on infected people. It seems that thrombotic complications were quite high in these studies. In a research conducted by Connor and his colleagues, it was revealed that in infected patients, fibrinogen, platelet and D-dimer levels were elevated by 94%, 62%, and 100% respectively in camparison to healthy people. Moreover, it showed that compared to normal situation, the quantity of IL-6 which causes the pathophysiology of pro-thrombotic status in SARS-CoV-2 infection, may rise up to 100% (Connors and Levy, 2020).

5. PNS manifestations

5.1. Guillain-Barre syndrome (GBS)

One of the serious neurological disorder consequences of COVID-19 is GBS which was previously reported in China, Iran and Italy (Ebrahimzadeh et al., 2020; Filosto et al., 2021; Mao et al., 2020). A systematic review study on neurological implications in infected patients, showed numerable variations in the onset of GBS and COVID-19 respiratory symptoms. In some cases, GBS may be diagnosed just by mild fever at the onset of the disease while in some others it might be detected five to eleven days after the diagnosis of coronavirus (Whittaker et al., 2020). Some patients experience acute weakness in their legs along with severe fatigue that fully recovers after the administration of anti-viral drugs. This clinical heterogeneity of disease is associated with the inoculation of a wide variety of pathogens leading to GBS (Jacobs et al., 1998).

Two theories are proposed as the most probable mechanisms to provoke viruses to initiate an areflexic state in GBS. The first one is the production of antibodies against surface glycoproteins of virus that are similar to that exposed on neurons (Virani et al., 2020). The second one is the cytokine storm of macrophage activation (McGonagle et al., 2020).

5.2. Olfactory and Gustatory Dysfunctions

Olfactory and gustatory disorders are potential neurological outcomes of COVID-19 infection. Angiotensin-converting enzyme 2 (ACE2) is the major host cell place for SARS-CoV2 that is expressed in nasal epithelium and olfactory epithelial cells (Sameni et al., 2022). ACE2 also exisis in patient's tongue and mucosa so taste sense can be affected the same way as olfaction. Sino-nasal passage edema or inflammation could be another mechanism that can cause olfactory dysfunction. Edema may hinder odor molecules to reach the olfactory cleft (Soh et al., 2021). Anosmia (the partial or complete loss of smell) and ageusia (deficiency of taste functions of the tongue) was observed in adults after viral infection. Mucosal congestion is primarily the main cause of anosmia, which leads to the loss of smell sense. However, the observed coronavirus can lead to olfactory and taste disorders without causing a runny nose or nasal obstruction. In one study done in Europe, it was demonstrated that 85.6% and 88.8% of infected persons had olfactory and taste disorders, respectively. In terms of olfactory disorder, 79.6 % of patients had anosmia (full loss of smell) and 20.4% had hyposmia (decreased sense of smell). It is notable that among patients who had no runny nose or nasal obstruction (18.2 %), most cases (79.7%) had hyposmia or anosmia. In addition, ageusia and hypogeusia were observed in 78.9% and 21.1% of patients respectively. In a meta-analysis study, the outbreak of olfactory and taste deficiency in patients with confirmation of COVID-19 disease, were 61% and 49%, respectively. Furthermore, it was observed that hyposmia and hypogeusia were more prevalent among patients than anosmia and ageusia (Hajikhani et al., 2020). In a recent meta-

analysis, it was shown that women are more susceptible to olfactory dysfunction than men. This gender difference may be due to different inflammatory processes depending on sexual status. Also, olfactory deficiency is mostly observed in younger COVID-19 patients however, more studies are needed to discuss it decisively (Jain et al., 2020; von Bartheld et al., 2020).

A comparative study of COVID-19 patients admitted to ICU showed that the incidence of olfactory dysfunction was less among people with mild clinical symptoms. It also showed that infected people with anosmia or hyposmia might have mild clinical symptoms compared to COVID-19 patients with normosmia. However, in another study there was no correlation between olfactory dysfunction and intense SARS-CoV2 disease (Mendonça et al., 2021; Yan et al., 2020; Moein et al., 2020).

Conclusion

During the recent pandemic caused by COVID-19, healthcare professionals should be aware of a wide variety *of neurological* complications of SARS-CoV-2 infection in addition to respiratory *failure* since early detection, management, prevention and treatment have vital role in people survival. This novel coronavirus is associated with different neurological signs and symptoms including CNS and PNS involvement. Different data have approved the possible roles of CNS in pathophysiology of COVID-19. In this case, more specific epidemiological and diagnostic investigations are suggested for better identification of the probable neurological entanglement. This is to determine whether the observed manifestations are coincidental or causal.

Conflict of interest, the authors declare no competing interests.

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