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COVID-19 in the Central Nervous System- clinical manifestations and post-COVID syndrome - an update

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Abstract:

Introduction:

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), represents a significant global public health challenge. While respiratory symptoms dominate, the virus's impact on other systems, particularly the central nervous system (CNS), has gained increasing attention. SARS-CoV-2 demonstrates tropism for Angiotensin-Converting Enzyme 2 (ACE2) receptors, expressed in the olfactory epithelium, lungs, endothelium, kidneys, enterocytes, and neurons, contributing to neurological manifestations observed during the acute phase of the disease.

Materials and Methods:

A literature review was conducted using PubMed, Scopus, Web of Science, and ScienceDirect databases. Keywords included: *COVID-19*, *Post Acute COVID-19 Syndrome*, *SARS-CoV-2 Virus*, *Neurological Manifestations*, and *Central Nervous System Viral Diseases*. A total of 58 articles were selected for analysis based on relevance and quality of evidence regarding neurological symptoms and complications associated with COVID-19.

Basic Results:

The acute phase of COVID-19 frequently involves neurological symptoms such as frontal and holocranial headaches, dizziness, gustatory and olfactory dysfunctions, and alterations in consciousness. Severe complications, though less common, include encephalitis, ischemic and hemorrhagic stroke, cerebral venous thrombosis, and myelitis. These conditions often present as altered mental status, seizures, aphasia, headaches, or focal deficits, contributing substantially to patient morbidity and mortality.

Conclusions:

Neurological symptoms and complications constitute a significant aspect of COVID-19, highlighting the virus's potential to affect the CNS. While severe complications are rare, their profound impact on prognosis underscores the importance of early recognition and management. Further research is essential to understand the pathophysiology and optimise therapeutic approaches for affected patients.

Key words: COVID-19, Post Acute COVID 19 Syndrome, SARS-CoV-2 Virus, Neurological Manifestations, Central Nervous System Viral Diseases

Introduction

The pandemic of the acute infectious disease coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become the most severe global public health threat in many years. According to World Health Organization (WHO) data, globally, as of March 2024, there have been confirmed 774,834,251 infections with SARS-CoV-2 and 7,037,007 reported deaths. Acute respiratory failure is considered the main cause of mortality in COVID-19. According to the WHO, COVID-19 remains a persistent and ongoing health issue [1].

Although the primary target of the coronavirus infection is the respiratory tract and lungs, the widespread distribution of key Angiotensin-Converting Enzyme 2 (ACE2) receptor-bearing cells in various vital human organs allows for potential damage to the heart, gastrointestinal tract, kidneys, liver, eyes, central nervous system (CNS), and peripheral nervous system (PNS) [2]. The most commonly observed symptoms related to neurological damage in the course of COVID-19 include dizziness, headaches, alterations in consciousness, disturbances in taste and smell, visual impairments, nerve pain, and symptoms related to muscle damage [3]. Furthermore, in patients with a severe systemic COVID-19 infection, reports have indicated seizures, strokes, ataxia, and balance disorders.

COVID-19 and Central Nervous System Manifestations

Cephalalgia and dizziness

Cephalalgia, dizziness, and vertigo are among the most common neurological symptoms associated with the SARS-CoV-2 infection. The comparison of the incidence rate of COVID-19 clinical manifestations in the CNS is summarized in Table 1.

Clinical manifestation	Incidence and Notes	References
Cephalalgia	3.7- 43% 27.7% 23.7%	[4] [5] [6]
Dizziness	0.03- 20% 12.2%	[9] [10]
Vertigo	0,004- 12%	[9]
Anosmia	48%	[12]
Ageusia	43.93%	[15]
Encephalitis	0.215% 0.11- 0.12%	[20] [21]
Seizures	0.8% 4.3%	[25] [26]
COVID-19 associated myelitis	A series of case reports (2023; 33 cases)	[28]
Ischemic stroke	0.9- 2.7% 1.1%	[32] [34]
Haemorrhagic stroke (ICH and SAH)	ICH- 0.5% SAH- 0.07% ICH- 0.2%	[35] [35] [36]
Cerebral Venous Thrombosis (CVT)	0.08%	[41]
Post-COVID Cephalalgia	37.8% (six weeks after recovery from acute COVID-19) 12.9% (one month after recovery from acute COVID-19) 19% (three months after recovery from acute COVID-19) 16% (nine months after recovery from acute COVID-19)	[7] [46] [47] [47]
Post-COVID Chronic fatigue syndrome (CFS)	69% 45.2%	[52] [54]
Brain fog and cognitive impairment in post-COVID syndrome	81% (six weeks after recovery from acute COVID-19)	[57]

Table 1. COVID-19 associated clinical manifestations in the CNS and their incidence rate.

In patients with systemic COVID-19 disease, cephalalgia has been reported in varying proportions, ranging from 3.7% to 43% of cases [4]. In a retrospective study of a group of 108 COVID-19 patients, cephalalgia occurred in 28 (27.7%) individuals during the acute phase of COVID-19 [5]. This manifestation predominantly affected males (58.3%) with comorbidities (75%). Onset of headache occurred on the initial day of symptomatic COVID-19 disease in half of the cases. Notably, 75% of patients had no documented history of recurrent headaches preceding their SARS-CoV-2 infection. Headaches most frequently occurred in the morning, with a duration lasting between 1 to 24 hours in the majority of cases (62.5%), while headaches persisting beyond 24 hours were reported by 33.3% of patients. The frontal region was the most common site of pain (50%), followed by involvement of the entire skull-

holocranial (33.3%) [5]. In another retrospective cohort study of 576 hospitalised patients with COVID-19, cephalalgia was present in 137 cases (23.7%) [6]. In this group, 26% of patients experienced headache as their initial symptom of COVID-19, while in 74% of cases, headache manifested within 72 hours of the onset of other COVID-19 symptoms. The occurrence of headaches was also associated with lower mortality due to COVID-19 and a more favourable prognosis during hospital treatment [6]. In a prospective cohort study involving 130 hospitalised COVID-19 patients, the onset of early cephalalgia during hospitalisation was also linked to a better prognosis and a milder course of COVID-19 [7]. The study found that the early onset of headaches during hospitalisation was more frequent in middle-aged women, often with a pre-pandemic history of headaches. Its occurrence served as a robust predictor of a shorter and milder course of COVID-19 [7]. The aetiology of cephalalgia in patients in the acute phase of COVID-19 is linked to a cytokine storm and an uncontrolled inflammatory response of the organism. Various mechanisms have been proposed through which the heightened inflammatory state could provoke pain symptoms, including proinflammatory activation of trigeminal nerve endings, damage to the endothelial cells of brain vessels, or direct infection of nerve endings by SARS-CoV-2 [8]. Although several cytokines have been suggested to play a role in cephalalgia, no specific cytokine panel has been identified yet [8].

Dizziness and vertigo can be among the initial neurological symptoms of COVID-19. According to a comprehensive systematic review from 2022, the prevalence of dizziness ranged from 0.03% to 20% among all COVID-19 patients, while vertigo ranged from 0.004% to 12% of all cases [9]. A 2021 meta-analysis of nine studies estimated the prevalence of dizziness among COVID-19 patients at 12.2% [10]. A notable challenge in the current qualitative analysis of the prevalence of dizziness and vertigo in COVID-19 lies in their frequent omission in diagnostics, the low quality of evidence, and the lack of standardised tests [10]. These issues require attention in the near future. The pathomechanism underlying the development of balance disorders during the course of COVID-19 has not been comprehensively elucidated thus far. Potential pathomechanisms include damage to the vestibular nuclei in the brainstem resulting from direct neuroinvasion by SARS-CoV-2 or through vasculitis and vasculopathy in the course of COVID-19 [11]. Balance disturbances may also arise from the induction of neuroinflammation in the brainstem centres responsible for equilibrium [10]. Additionally, dizziness and vertigo could be a consequence of

endothelial damage in the vessels supplying the inner ear caused by SARS-CoV-2, resulting in ischemia and subsequent damage to the hair cells of the vestibular system [10].

Anosmia and ageusia

Loss of smell (anosmia) and loss of taste (ageusia) are among the most recognizable symptoms of SARS-CoV-2 infection. According to a systematic review of 83 studies, it was estimated that anosmia occurred in 48% of patients during the acute phase of SARS-CoV-2 infection [12]. Anosmia is reported more frequently by younger patients and affects women more often. For many patients, anosmia occurs as one of the first symptoms of COVID-19 infection. Within 2-3 weeks after infection, most patients experience a spontaneous regression of symptoms, and long-term deficits are uncommon. However, in 10-20% of cases, varying degrees of persistent olfactory deficits may remain [13]. It is pertinent to note that in numerous COVID-19 patients, olfactory disturbances manifest themselves even in the absence of nasal mucosa inflammation and catarrhal symptoms, suggesting a direct involvement of the nervous system. Several mechanisms leading to olfactory epithelium damage have been postulated, including direct invasion of the olfactory epithelium's supporting and basal cells by SARS-CoV-2, disruption of the water-ion balance in the vicinity of olfactory receptor neurons, stemming from damage to the supporting cells, and endothelial vessel damage leading to epithelial hypoperfusion [14]. Nevertheless, the precise mechanism underlying anosmia has not been elucidated.

Ageusia, alongside anosmia, is one of the initial symptoms of SARS-CoV-2 infection and may also be the sole manifestation in patients with only mild symptoms. A systematic review of nine observational and retrospective studies, encompassing 1390 patients in the acute phase of COVID-19, demonstrated a 43.93% prevalence of ageusia in mild and moderate stages of the disease [15]. In most patients, the restoration of taste sensation typically occurs within 2-3 weeks of the illness. However, a minority may experience enduring deficits in taste perception.

COVID-19 Encephalitis

Encephalitis and meningoencephalitis are severe neurological sequela in the course of SARS-CoV-2 viral infection. COVID-19-associated encephalitis most commonly affects patients burdened with comorbidities and experiencing a severe course of SARS-CoV-2 infection. The exact mechanism underlying the development of encephalitis in SARS-CoV-2 infection remains incompletely understood. Three proposed mechanisms include direct invasion of the

CNS by the virus through transsynaptic or hematogenous routes [16], hypercytokinemia (cytokine storm) leading to uncontrolled inflammation within the CNS [17], and SARS-CoV-2 molecular mimicry triggering the development of an autoimmune response [18]. Encephalitis associated with COVID-19 tends to manifest, on average, approximately 14.5 days following the onset of systemic symptoms. In rare instances, it may present as the sole manifestation of SARS-CoV-2 infection [19]. A comprehensive retrospective analysis conducted in 2021, comprising 610 studies from 17 countries and involving a total population of 129,008 patients, identified COVID-19-associated encephalitis in 138 cases, resulting in an estimated incidence rate of approximately 0.215% [20]. In a separate large-scale retrospective cohort study conducted in 2022 on a population of 1,284,437 patients from diverse countries, the prevalence of encephalitis in adults fell within the range of 0.11-0.12% [21]. While rare, COVID-19-associated encephalitis significantly compromises patient prognosis, with a notable mortality rate of approximately 13.4% within this cohort [22]. In a systematic review of 11 studies, predominant manifestations of encephalitis in the context of COVID-19 include disturbances in consciousness (77.1%), alterations in mental status (72.3%), seizures (38.2%), headaches (27.3%), and weakness (15.4%). Less frequently encountered symptoms encompass ataxia, myoclonus, and aphasia [20]. On head MRI (magnetic resonance imaging) using T2 and FLAIR sequences, prevalent findings encompass hyperintensity in the subcortical white matter, focal hemorrhages, brain edema, and infrequently, thrombosis of the venous sinuses of the dura mater. EEG (electroencephalography) examinations may indicate generalized slowing of the recording in select patients. Cerebrospinal fluid analysis (CSF) reveals elevated levels of glucose and total protein, along with heightened pleocytosis and increased IgG (immunoglobulin G) levels [20].

Seizures

Seizures constitute a rare yet potentially dangerous neurological manifestation in the patients with COVID-19. The aetiology of seizures in SARS-CoV-2 infection is intricate, multifactorial, and remains incompletely understood. It has been postulated that systemic factors such as hypoxemia, immune system dysfunction, uncontrolled inflammatory response along with hypercytokinemia, and multi-organ metabolic disturbances may lower the seizure threshold in patients with the severe COVID-19, leading to the development of new-onset seizures [23]. Direct CNS invasion by the SARS-CoV-2 is rare in most cases, and viral RNA is not typically isolated from CSF in the majority of patients [24]. Seizures may manifest in patients either as an isolated neurological symptom or accompany other neurological

complications of COVID-19, such as ischemic stroke, hemorrhagic stroke, encephalitis, or encephalopathy. In a large retrospective study of 509 COVID-19 patients, isolated seizures, without other neurological sequela, were observed in merely 4 individuals (0.8%) [25]. In another study involving a cohort of 439 hospitalized patients with COVID-19, seizures occurred in 19 individuals (4.3%), with 14 of them experiencing seizures as a secondary neurological complication of stroke or encephalitis. Prognosis is generally favourable, as demonstrated in a meta-analysis of 175 patients with seizures, where the majority (66.3%) exhibited no enduring neurological deficits following the course of treatment [26].

Spinal cord manifestations in COVID-19

The spinal cord in the course of COVID-19 is susceptible to varied and potentially fatal complications. The aetiology of spinal complications is intricate and may arise from direct invasion of the spinal cord by the SARS-CoV-2, hypercytokinemia, uncontrolled inflammatory states, or stimulation of the host organism's autoimmune response [27]. A systematic review of literature from 2023 identified 33 case reports of patients with COVID-19 neurological sequela involving the spinal cord [28]. These cases predominantly affected older patients over 60 years of age or those burdened with multiple comorbidities. Most patients (64%) did not exhibit respiratory symptoms at the onset of neurological manifestations. The predominant spinal manifestation identified was acute transverse myelitis (55%). Additionally, there were cases of acute disseminated encephalomyelitis (ADEM) (9%), acute necrotizing myelitis (9%), SARS-CoV-2-associated myelitis (6%), epidural abscess (6%), neuromyelitis optica associated myelitis (6%), myelitis associated with Anti-Myelin Oligodendrocyte Glycoprotein (anti-MOG) antibodies (3%), ischemic myelopathy (3%), acute flaccid myelitis (3%), and spinal cord infarction (3%) [28]. Following symptoms resolution, permanent neurological deficits were noted in 45.45% of the described cases [28]. The rich clinical spectrum highlights the complexity of mechanisms leading to spinal cord damage in the course of COVID-19. Furthermore, the presence of autoimmune-mediated spinal inflammation implies a substantial involvement of SARS-CoV-2 molecular mimicry and host’s autoimmune response in the pathogenesis of spinal manifestations [29].

Cerebrovascular diseases in COVID-19

In patients with the severe COVID-19, the risk of cerebrovascular diseases, such as stroke or cerebral venous thrombosis, is notably heightened within the first 6 months after infection. Risk factors contributing to an increased likelihood of developing cerebrovascular sequela include the presence of classical cardiovascular risk factors, arterial hypertension, ischemic

heart disease, atrial fibrillation, a history of cerebrovascular diseases, and advanced age [30]. The pathomechanism of cerebrovascular complications in COVID-19 is complex and multifactorial. The primary mechanism underlying pathological changes seems to entail damage and dysfunction of the cerebral vascular endothelium due to direct invasion by SARS-CoV-2 or through an excessive systemic inflammatory response of the host's organism. Furthermore, the dysregulation of the renin-angiotensin-aldosterone system (RAAS) is significant due to viral binding to the ACE2 receptor, leading to its inactivation. Other mechanisms involved in the pathogenesis may encompass coagulopathy, myocardial damage leading to arrhythmias and cardiac embolism, as well as systemic hypoxemia and hypoperfusion in severe COVID-19 [31].

Cerebral ischemic stroke (IS) occurs in 0.9 to 2.7% of COVID-19 patients with underlying risk factors [32]. In a 2020 study of 174 COVID-19 patients who experienced IS, the most common symptoms were motor deficits (67.8%), dysarthria (46%), and sensory deficits (42%) [33]. According to the National Institutes of Health Stroke Scale (NIHSS) assessment, IS patients with active COVID-19 often achieve higher scores compared to IS patients without an active COVID-19 infection [33]. In a comprehensive international cohort study conducted in 2021 involving 14,483 COVID-19 patients, 156 cases (1.1%) of ischemic stroke were identified [34]. In this study, among 129 patients, COVID-19 associated ischemic stroke was classified based on aetiology into the following categories: cryptogenic (42.6%), cardioembolic (27.1%), large vessel atherosclerosis (11.6%), small vessel occlusion (3.1%), with other aetiologies (8.5%) [34]. Mortality in COVID-19 patients with IS of cryptogenic aetiology exceeded that observed in groups with alternative stroke aetiologies. Moreover, individuals with cryptogenic and cardioembolic stroke demonstrated a significantly heightened risk of secondary haemorrhagic transformation of the stroke lesion [34].

Haemorrhagic stroke is divided into intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH). In a retrospective cohort study comprising 4,071 COVID-19 patients, intracerebral ICH occurred in 0.5% of cases, with the incidence of SAH being minimal (0.07%) [35]. In-hospital mortality in the group of patients with ICH/SAH was significantly higher than in the group without ICH (84.6% vs. 4.6%) [35]. In a retrospective analysis of a population of 21,483 COVID-19 patients, ICH was documented in 0.2% of cases [36]. Mortality in the group with ICH was significantly higher than in the group with COVID-19 alone (48% vs. 18%) [36]. In a retrospective cohort study of 33 COVID-19 patients with ICH, the mortality rate was 42.4%. The majority of ICH (92.9%) in these patients constituted

secondary haemorrhagic conversion of an ischemic locus [37]. During the neurological examination, 51.5% of the patients presented symptoms indicative of encephalopathy, 21.2% exhibited focal motor deficits, 12.1% had absent brainstem reflexes, 6.1% experienced seizures, and only 3% reported aphasia [37].

Cerebral Venous Thrombosis (CVT) occurs in COVID-19 patients at approximately three times higher rate than observed in the general population [38]. The precise underlying mechanism leading to CVT in COVID-19 has not been yet fully elucidated. However, it is likely that the interplay of various factors such as endothelial damage, a hypercoagulable state, disturbed blood flow in vessels, and an uncontrolled inflammatory response and hypercytokinemia contribute to its pathogenesis during SARS-CoV-2 infection [39,40]. Primary risk factors for CVT in COVID-19 have been identified in three retrospective studies as older age [39,40], male gender [40], and severe COVID-19 [40]. In a comprehensive systematic review conducted in 2021, it was estimated that CVT occurs in 0.08% of all COVID-19 cases. Among 90% of affected individuals, CVT symptoms typically develop around 13 days following the onset of respiratory symptoms, with an estimated mortality rate of 40% among all hospitalized patients with CVT [41]. In the same study the most frequently affected vessels encompassed the transverse sinus (47%), superior sagittal sinus (44%), and straight sinus (21%). In 37% of cases, the deep cerebral venous system was implicated, while cortical surface veins were least frequently affected (21%). CVT rather involved multiple vessels (67%), with secondary haemorrhagic foci noted in 42% of patients [41]. Predominant clinical manifestations observed in patients with COVID-19-associated CVT were focal motor deficits, seizures, and disturbances in consciousness [38,41]. Table 2. shows the summary of potential pathomechanisms involved in the clinical manifestations of COVID-19 in the CNS.

Clinical manifestation	Potential patomechanisms	References
Cephalalgia	Cytokine overproduction/storm; Proinflammatory activation of trigeminal nerve endings; Vascular endothelial damage; Direct invasion of nerve endings by SARS-CoV-2	[8]
Dizziness and vertigo	Damage to the vestibular nuclei in the brainstem resulting from direct neuroinvasion by SARS-CoV-2; Vasculitis and vasculopathy; Neuroinflammation in the brainstem equilibrium centers	[10]
	Vascular endothelial damage in the inner ear; Ischemic damage of the inner ear	[11]
Anosmia	Direct invasion of olfactory epithelium by SARS-CoV-2; Disruption of the water-ion balance in the vicinity; of olfactory receptor neurons; Vascular endothelial damage	[14]
Encephalitis	Direct invasion of the CNS by SARS-CoV-2	[16]
	Cytokine overproduction/storm	[17]
	SARS-CoV-2 molecular mimicry, autoimmune response to CNS antigens	[18]
Seizures	Lowered seizure threshold in severe COVID-19 due to systemic factors hypoxemia, immune system dysfunction, hypercytokinemia, multi-organ metabolic disturbances	[23]
COVID-19 associated myelitis	Cytokine overproduction/storm; Direct invasion of the spinal cord by SARS-CoV-2; SARS-CoV-2 molecular mimicry, autoimmune response to CNS antigens	[27]
	SARS-CoV-2 molecular mimicry, autoimmune response to CNS antigens	[29]
Ischemic and Haemorrhagic stroke	Vascular endothelial damage; Cytokine overproduction/storm; Dysregulation of RAAS system; Coagulopathy; Myocardial damage leading to arrhythmias and cardiac embolism; Systemic hypoxemia and hypoperfusion in severe COVID-19	[31]
Cerebral Venous Thrombosis	Vascular endothelial damage; Coagulopathy; Disturbances cerebral blood flow; Cytokine overproduction/storm	[39] [40]
Post-COVID Cephalalgia	Cytokine overproduction/storm; Intensified inflammatory state	[45]
Post-COVID Chronic fatigue syndrome (CFS)	Viral dose; Host-dependent factors; Autoimmune reactions; Muscle damage in the acute COVID-19; Intensified inflammatory state; Immobility due to severe COVID-19	[55]
Brain fog and cognitive impairment in post-COVID syndrome	Direct invasion of the CNS by SARS-CoV-2; Intensified inflammatory state; Vascular endothelial damage	[58]

Table 2. COVID-19 associated clinical manifestations in the CNS and their potential pathomechanisms.

Post-COVID syndrome and neurological symptoms

Post-COVID syndrome, also known as long-COVID or PASC (post-acute sequelae of SARS-CoV-2 infection), refers to chronic ailments and symptoms affecting various organs and systems. These develop in patients during the course of acute COVID-19 or during the recovery period, and persist for more than three months from the time of diagnosis. Numerous reports confirm the long-term effects of COVID-19, presenting with pulmonary, cardiovascular, neurological, nephrological, haematological, gastroenterological, endocrinological, and psychosocial symptoms.

Neurological symptoms are among the common clinical manifestations of post-COVID syndrome. Nearly one-third of patients receive a diagnosis of neurological or psychiatric disease within six months after the acute phase of COVID-19 [42]. Although several clinical manifestations of post-COVID syndrome related to the CNS and the PNS have been described, many of these manifestations are likely associated with dysfunction in other organs, systemic disturbances, and social and psychological factors [43].

Chronic sequelae of post-COVID syndrome may include chronic fatigue, insomnia, headache, "brain fog," decreased muscle strength, persistent anosmia or ageusia, anxiety disorders, mood disorders, and depressive states [44].

Cephalalgia

Cephalalgia is a prevalent neurological symptom during acute COVID-19, affecting between 3.7% to 43% of patients [4]. Most headaches in the acute phase of COVID-19 are considered to be headaches likely resulting from intensified, generalized inflammatory states and hypercytokinemia; many patients show improvement over time [45]. Chronic cephalalgia is a commonly reported condition in patients diagnosed with post-COVID syndrome.

Chronic cephalalgia in the course of post-COVID syndrome has been documented by Caronna et al. [7] In their prospective study involving 74 COVID-19 patients, 37.8% of them experienced chronic cephalalgia six weeks after recovery [7]. Among them (60.7%) reported experiencing daily headaches, and 50% of the surveyed patients had never suffered from recurrent headaches before contracting COVID-19 [7]. In a cross-sectional study of a population of 2194 COVID-19 patients, by Garcia-Azorin et al. demonstrated that headaches persisting for more than 1 month after recovery were present in 12.9% of patients [46]. In another prospective study involving a group of 905 COVID-19 patients, 19% of patients experienced chronic cephalalgia three months after recovery, and 16% of patients reported persistent headache nine months after SARS-CoV-2 infection [47]. Further research revealed that chronic headache associated with COVID-19 is bilateral, long-lasting, and resistant to analgesic medications [48]. Another study also indicated that 80% of COVID-19-related headaches were bilateral [46].

Chronic fatigue syndrome (CFS)

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), is a prolonged illness characterized by at least six months of fatigue and exhaustion [49].

The coronavirus causing severe acute respiratory syndrome (SARS) may lead to the development of CFS. After the SARS epidemic in 2003, 54% of coronavirus-infected patients reported general weakness, muscle weakness, and fatigue six months after the illness [50]. Interestingly, chronic fatigue symptoms persisted in 27.1–40.3% of individuals after four years [51].

CFS is characterized by a profound feeling of fatigue, regardless of rest. Symptoms of CFS may worsen with physical or mental activity. Symptoms of CFS include headache, painful lymph nodes, fatigue and weakness, myalgia, arthralgia, difficulty concentrating, insomnia, sensitivity to light, and depression [49].

Currently, it has been observed that approximately 69% of hospitalized COVID-19 patients complain of a constant feeling of fatigue [52]. Patients describe it as debilitating fatigue, neurocognitive impairment, and a worsening of overall well-being during daily psychophysical activities [53]. Many patients also experience symptoms of CFS after recovery. The global prevalence of chronic fatigue syndrome among patients with a prolonged course of COVID-19 was 45.2%, with a total of 127,117 participants in the study [54].

The exact cause of CFS is not fully understood at this time. However, there are studies suggesting that multiple factors such as the viral dose, host-dependent factors, for example, genetic susceptibility or induction of anti-inflammatory cells and proteins, along with autoimmune reactions and formation of autoantibodies may influence CFS [55]. Minor muscle damage and inflammation after recovering from COVID-19, as well as immobility associated with a severe course of the disease, may contribute to fatigue.

Brain fog and cognitive impairment in post-COVID syndrome

"Brain fog" is a subjective term coined to describe a condition in which a patient experiences a lack of mental clarity and encounters difficulties in concentration and focus, resulting in a decreased quality of life and hindering daily functioning [56].

According to a prospective study conducted on a group of 100 patients at the Neuro-COVID-19 Clinic at Northwestern University during the pandemic, "brain fog" was the most commonly reported (81%) neurological symptom persisting beyond 6 weeks in patients after the resolution of acute COVID-19 symptoms [57]. Difficulties in concentration and focus persisted for up to 5 months after the resolution of the acute phase of the disease [57].

Patients experiencing post-COVID syndrome have reported various cognitive deficits, including short-term memory loss, difficulty concentrating, attention deficits, excessive fatigue during mental tasks, difficulty selecting appropriate vocabulary, chronic fatigue and weakness, and drowsiness [44].

Currently, a specific cause explaining the cognitive dysfunction underlying the development of brain fog is not known. However, several factors contributing to the clinical symptoms of post-COVID syndrome, including brain fog, have been described. These include direct viral infiltration into the brain, an inflammatory state associated with microglial activation, or damage to small blood vessels in the brain [58].

Conclusions

The neurological manifestations of COVID-19 are diverse, ranging from mild symptoms like headaches and olfactory disturbances to severe complications such as cerebrovascular accidents or encephalitis, which are associated with significant disability and mortality rates. Older individuals and those burdened with multiple comorbidities appear to be particularly susceptible to these serious outcomes. The pathophysiological mechanisms underlying the development of central nervous system symptoms in COVID-19 are complex and remain incompletely understood. They are likely the result of various factors and mechanisms. For some patients, symptoms persist for more than three months after recovering from the acute phase of COVID-19. These symptoms can present challenges to daily functioning, including headaches and cognitive impairments that are characterized by 'brain fog.' The cause of these symptoms has not yet been fully understood.

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References:

1. World Health Organization. Statement on the Fifteenth Meeting of the IHR (2005) Emergency Committee on the COVID-19 Pandemic. World Heal Organ; 2023 [online] https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic [accessed on January 8, 2024].
2. Renu K., Prasanna PL., Valsala Gopalakrishnan A. Coronaviruses pathogenesis, comorbidities and multi-organ damage - A review. Life Sci. 2020; 255: 1-15, doi: 10.1016/j.lfs.2020.117839.
3. Mao L., Jin H., Wang M., Hu Y., Chen S., He Q. et al. Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020; 77(6): 683-690, doi: 10.1001/jamaneurol.2020.1127.
4. Ousseiran Z.H., Fares Y., Chamoun W.T. Neurological manifestations of COVID-19: a systematic review and detailed comprehension. Int J Neurosci. 2023; 133(7): 754-769, doi: 10.1080/00207454.2021.1973000.
5. Dos Anjos de Paula R. C., de Maria Frota Vasconcelos T., da Costa F. B. S., de Brito L. A., Torres D. M., Moura A. E. F. et al. Characterization of Headache in COVID-19: a Retrospective Multicenter Study. Mol Neurobiol. 2021; 58(9): 4487-4494, doi: 10.1007/s12035-021-02430-w.
6. Trigo J., García-Azorín D., Planchuelo-Gómez Á., Martínez-Pías E., Talavera B., Hernández-Pérez I. et al. Factors associated with the presence of headache in hospitalized COVID-19 patients and impact on prognosis: a retrospective cohort study. J Headache Pain. 2020; 21(1): 1-10, doi: 10.1186/s10194-020-01165-8.
7. Caronna E., Ballvé A., Llauradó A., Gallardo V. J., Ariton D. M., Lallana S. et al. Headache: A striking prodromal and persistent symptom, predictive of COVID-19 clinical evolution. Cephalalgia. 2020; 40(13): 1410-1421, doi: 10.1177/0333102420965157.
8. Thepmankorn P., Bach J., Lasfar A., Zhao X., Souayah S., Chong Z. Z. et al. Cytokine storm induced by SARS-CoV-2 infection: The spectrum of its neurological manifestations. Cytokine. 2021; 138: 2-10, doi: 10.1016/j.cyto.2020.155404.
9. Korres G., Kitsos D. K., Kaski D., Tsogka A., Giannopoulos S., Giannopapas V. et al. The Prevalence of Dizziness and Vertigo in COVID-19 Patients: A Systematic Review. Brain Sci. 2022; 12(7): 948, doi: 10.3390/brainsci12070948.

10. Jafari Z., Kolb B.E., Mohajerani M.H. Hearing Loss, Tinnitus, and Dizziness in COVID-19: A Systematic Review and Meta-Analysis. Can J Neurol Sci. 2022; 49(2): 184-195, doi: 10.1017/cjn.2021.63.

11. Viola P., Ralli M., Pisani D., Malanga D., Sculco D., Messina L. et al. Tinnitus and equilibrium disorders in COVID-19 patients: preliminary results. Eur Arch Otorhinolaryngol. 2021; 278(10): 3725-3730, doi: 10.1007/s00405-020-06440-7.

12. Saniasiaya J., Islam M.A., Abdullah B. Prevalence of Olfactory Dysfunction in Coronavirus Disease 2019 (COVID-19): A Meta-analysis of 27,492 Patients. Laryngoscope. 2021; 131(4): 865-878, doi: 10.1002/lary.29286.

13. Berlit P., Bösel J., Gahn G., Isenmann S., Meuth S. G., Nolte C. H. et al. "Neurological manifestations of COVID-19" - guideline of the German society of neurology. Neurol Res Pract. 2020; 2(1): 2-10, doi: 10.1186/s42466-020-00097-7.

14. Brann D.H., Tsukahara T., Weinreb C., Lipovsek M., Van den Berge K., Gong B. et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. Sci Adv. 2020; 6(31): 1-15, doi: 10.1126/sciadv.abc5801.

15. Tong J.Y., Wong A., Zhu D., Fastenberg J.H., Tham T. The Prevalence of Olfactory and Gustatory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis. Otolaryngol Head Neck Surg. 2020; 163(1): 3-11, doi: 10.1177/0194599820926473.

16. Pennisi M., Lanza G., Falzone L., Fisicaro F., Ferri R., Bella R. SARS-CoV-2 and the Nervous System: From Clinical Features to Molecular Mechanisms. Int J Mol Sci. 2020; 21(15): 5475, doi: 10.3390/ijms21155475.

17. Pezzini A., Padovani A. Lifting the mask on neurological manifestations of COVID-19. Nat Rev Neurol. 2020; 16(11): 636-644, doi: 10.1038/s41582-020-0398-3.

18. Scoppettuolo P., Borrelli S., Naeije G. Neurological involvement in SARS-CoV-2 infection: A clinical systematic review. Brain Behav Immun Health. 2020; 5: 1-8, doi: 10.1016/j.bbih.2020.100094.

19. Rifino N., Censori B., Agazzi E., Alimonti D., Bonito V., Camera G. et al. Neurologic manifestations in 1760 COVID-19 patients admitted to Papa Giovanni XXIII Hospital, Bergamo, Italy. J Neurol. 2021; 268(7): 2331-2338, doi: 10.1007/s00415-020-10251-5.

20. Siow I., Lee K.S., Zhang J.J.Y., Saffari S.E., Ng A. Encephalitis as a neurological complication of COVID-19: A systematic review and meta-analysis of incidence, outcomes, and predictors. Eur J Neurol. 2021; 28(10): 3491-3502, doi: 10.1111/ene.14913.

21. Taquet M., Sillett R., Zhu L., Mendel J., Camplisson I., Dercon Q. et al. Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients. Lancet Psychiatry. 2022; 9(10): 815-827, doi: 10.1016/S2215-0366(22)00260-7.
22. Baud D., Qi X., Nielsen-Saines K., Musso D., Pomar L., Favre G. Real estimates of mortality following COVID-19 infection. Lancet Infect Dis. 2020; 20(7): 773, doi: 10.1016/S1473-3099(20)30195-X.
23. Nikbakht F., Mohammadkhanizadeh A., Mohammadi E. How does the COVID-19 cause seizure and epilepsy in patients? The potential mechanisms. Mult Scler Relat Disord. 2020; 46:102535, doi: 10.1016/j.msard.2020.102535.
24. Carroll E., Melmed K. R., Frontera J., Placantonakis D. G., Galetta S., Balcer L. et al. Cerebrospinal fluid findings in patients with seizure in the setting of COVID-19: A review of the literature. Seizure. 2021; 89: 99-106, doi: 10.1016/j.seizure.2021.05.003.
25. Liotta E. M., Batra A., Clark J. R., Shlobin N. A., Hoffman S. C., Orban Z. S. et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann Clin Transl Neurol. 2020; 7(11): 2221-2230, doi: 10.1002/acn3.51210.
26. Shamim D., Ganatra F., Khan M., Gronseth G. New Onset Seizures in Hospitalized COVID-19 Patients; A Systematic Review and Meta-Analysis. Neurohospitalist. 2024; 14(1): 34-43, doi: 10.1177/19418744231202317.
27. Mondal R., Deb S., Shome G., Ganguly U., Lahiri D., Benito-León J. COVID-19 and emerging spinal cord complications: A systematic review. Mult Scler Relat Disord. 2021; 51: 1-9, doi: 10.1016/j.msard.2021.102917.
28. Garg R.K., Paliwal V.K., Gupta A. Spinal cord involvement in COVID-19: A review. J Spinal Cord Med. 2023; 46(3): 390-404, doi:10.1080/10790268.2021.1888022.
29. Ismail I.I., Salama S. Association of CNS demyelination and COVID-19 infection: an updated systematic review. J Neurol. 2022; 269(2): 541-576, doi: 10.1007/s00415-021-10752-x.
30. Kummer B.R., Klang E., Stein L.K., Dhamoon M.S., Jetté N. History of Stroke Is Independently Associated with In-Hospital Death in Patients With COVID-19. Stroke. 2020; 51(10): 3112-3114, doi: 10.1161/STROKEAHA.120.030685.
31. Tsivgoulis G., Palaiodimou L., Zand R., Lioutas V. A., Krogias C., Katsanos A. H. et al. COVID-19 and cerebrovascular diseases: a comprehensive overview. Ther Adv Neurol Disord. 2020; 13: 1-18, doi: 10.1177/1756286420978004.

32. Tan Y. K., Goh C., Leow A. S. T., Tambyah P. A., Ang A., Yap E. S. et al. COVID-19 and ischemic stroke: a systematic review and meta-summary of the literature. J Thromb Thrombolysis. 2020; 50(3): 587-595, doi: 10.1007/s11239-020-02228-y.
33. Ntaios G., Michel P., Georgiopoulos G., Guo Y., Li W., Xiong J. et al. Characteristics and Outcomes in Patients With COVID-19 and Acute Ischemic Stroke: The Global COVID-19 Stroke Registry. Stroke. 2020; 51(9): 254-258, doi: 10.1161/STROKEAHA.120.031208.
34. Ramos-Araque M. E., Siegler J. E., Ribo M., Requena M., López C., de Lera M. et al. Stroke etiologies in patients with COVID-19: the SVIN COVID-19 multinational registry. BMC Neurol. 2021; 21(1): 1-11, doi: 10.1186/s12883-021-02075-1.
35. Kvernland A., Kumar A., Yaghi S., Raz E., Frontera J., Lewis A. et al. Anticoagulation use and Hemorrhagic Stroke in SARS-CoV-2 Patients Treated at a New York Healthcare System. Neurocrit Care. 2021; 34(3): 748-759, doi: 10.1007/s12028-020-01077-0.
36. Leasure A. C., Khan Y. M., Iyer R., Elkind M. S. V., Sansing L. H., Falcone G. J. et al. Intracerebral Hemorrhage in Patients With COVID-19: An Analysis From the COVID-19 Cardiovascular Disease Registry. Stroke. 2021; 52(7): 321-323, doi: 10.1161/STROKEAHA.121.034215.
37. Dogra S., Jain R., Cao M., Bilaloglu S., Zagzag D., Hochman S. et al. Hemorrhagic stroke and anticoagulation in COVID-19. J Stroke Cerebrovasc Dis. 2020; 29(8): 1-6, doi: 10.1016/j.jstrokecerebrovasdis.2020.104984.
38. Tu T. M., Goh C., Tan Y. K., Leow A. S., Pang Y. Z., Chien J. et al. Cerebral Venous Thrombosis in Patients with COVID-19 Infection: a Case Series and Systematic Review. J Stroke Cerebrovasc Dis. 2020; 29(12): 1-9, doi: 10.1016/j.jstrokecerebrovasdis.2020.105379.
39. Li Y., Li M., Wang M., Zhou Y., Chang J., Xian Y. et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke Vasc Neurol. 2020; 5(3): 279-284, doi: 10.1136/svn-2020-000431.
40. Hameed S., Wasay M., Soomro B. A., Mansour O., Abd-Allah F., Tu T. et al. Cerebral Venous Thrombosis Associated with COVID-19 Infection: An Observational, Multicenter Study. Cerebrovasc Dis Extra. 2021; 11(2): 55-60, doi: 10.1159/000516641.
41. Baldini T., Asioli G. M., Romoli M., Carvalho Dias M., Schulte E. C., Hauer L. et al. Cerebral venous thrombosis and severe acute respiratory syndrome coronavirus-2 infection: A systematic review and meta-analysis. Eur J Neurol. 2021; 28(10): 3478-3490, doi: 10.1111/ene.14727.

42. Taquet M., Geddes J.R., Husain M., Luciano S., Harrison P.J. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry. 2021; 8(5): 416-427, doi: 10.1016/S2215-0366(21)00084-5.
43. Crook H., Raza S., Nowell J., Young M., Edison P. Long covid-mechanisms, risk factors, and management. BMJ. 2021; 374: 1-18, doi: 10.1136/bmj.n1648.
44. Nikitina A.Y., Chimagomedova A.S., Levin O.S. Neurological Complications of COVID-19 in the Elderly. Neurosci Behav Physiol. 2022; 52(5): 625-634, doi: 10.1007/s11055-022-01287-3.
45. Sampaio Rocha-Filho P.A. Headache associated with COVID-19: Epidemiology, characteristics, pathophysiology, and management. Headache. 2022; 62(6): 650-656, doi: 10.1111/head.14319.
46. García-Azorín D., Sierra Á., Trigo J., Alberdi A., Blanco M., Calcerrada I. et al. Frequency and phenotype of headache in covid-19: a study of 2194 patients. Sci Rep. 2021; 11(1): 1-10, doi: 10.1038/s41598-021-94220-6.
47. Garcia-Azorin D., Layos-Romero A., Porta-Etessam J., Membrilla J. A., Caronna E., Gonzalez-Martinez A. et al. Post-COVID-19 persistent headache: A multicentric 9-months follow-up study of 905 patients. Cephalalgia. 2022; 42(8): 804-809, doi: 10.1177/03331024211068074.
48. Uygun Ö., Ertaş M., Ekizoğlu E., Bolay H., Özge A., Kocasoy Orhan E. et al. Headache characteristics in COVID-19 pandemic-a survey study. J Headache Pain. 2020; 21(1): 1-10, doi: 10.1186/s10194-020-01188-1.
49. Pendergrast T., Brown A., Sunnquist M., Jantke R., Newton J. L., Strand E. B. et al. Housebound versus nonhousebound patients with myalgic encephalomyelitis and chronic fatigue syndrome. Chronic Illn. 2016; 12(4): 292-307, doi: 10.1177/1742395316644770.
50. Islam M.F., Cotler J., Jason L.A. Post-viral fatigue and COVID-19: lessons from past epidemics. Fatigue. 2020; 8(2): 1-9, doi: 10.1080/21641846.2020.1778227.
51. Moldofsky H., Patcai J. Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. BMC Neurol. 2011; 11: 1-7, doi: 10.1186/1471-2377-11-37.
52. Wostyn P. COVID-19 and chronic fatigue syndrome: Is the worst yet to come?. Med Hypotheses. 2021; 146: 1-5, doi: 10.1016/j.mehy.2020.110469.

53. Lopez-Leon S., Wegman-Ostrosky T., Perelman C., Sepulveda R., Rebolledo P. A., Cuapio A. et al. More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. Scientific Reports. 2021; 11(1): 1-22, doi: 10.1101/2021.01.27.21250617.
54. Salari N., Khodayari Y., Hosseinian-Far A., Zarei H., Rasoulpoor S., Akbari H. et al. Global prevalence of chronic fatigue syndrome among long COVID-19 patients: A systematic review and meta-analysis. Biopsychosoc Med. 2022; 16(1): 1-12, doi: 10.1186/s13030-022-00250-5.
55. Seeßle J., Waterboer T., Hippchen T., Simon J., Kirchner M., Lim A. et al. Persistent Symptoms in Adult Patients 1 Year After Coronavirus Disease 2019 (COVID-19): A Prospective Cohort Study. Clin Infect Dis. 2022; 74(7): 1191-1198, doi: 10.1093/cid/ciab611.
56. Hill E., Mehta H., Sharma S., Mane K., Xie C., Cathey E. et al. Risk Factors Associated with Post-Acute Sequelae of SARS-CoV-2 in an EHR Cohort: A National COVID Cohort Collaborative (N3C) Analysis as part of the NIH RECOVER program. medRxiv. 2022; 2022.08.15.22278603: 1-30, doi: 10.1101/2022.08.15.22278603.
57. Graham E. L., Clark J. R., Orban Z. S., Lim P. H., Szymanski A. L., Taylor C. et al. Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 "long haulers". Ann Clin Transl Neurol. 2021; 8(5): 1073-1085, doi: 10.1002/acn3.51350.
58. Takao M., Ohira M. Neurological post-acute sequelae of SARS-CoV-2 infection. Psychiatry Clin Neurosci. 2023; 77(2): 72-83, doi:10.1111/pcn.13481.