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Review Article

Neurological Complications in COVID Patients

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ABSTRACT

COVID-19 has a very cataclysmic impact on the world's panoramic view of human well being in terms of healthcare and management. The COVID-19 Infection with an increasing number of patients has not only affected the physical but also the mental state of society. The symptoms manifested by COVID-19 range from fever, malaise, myalgia, headache, to respiratory system symptoms of cough, stuffy/runny nose, and difficulty breathing. The novel coronavirus is known to affect the central nervous system, producing critical and some long-lasting neurological concerns. It has an impact on the pre-existing mental and affective ill patients as well as healthy individuals with anxiety, worrying, and panic symptoms, and fear conditioning, which has become a big concern. Although COVID-19 is a respiratory infection and the cardiovascular event is the main cause of fatality, medical professionals must understand its neurological complications to reduce the mortality rate in infected patients. Further research on specific risk factors or determinant protective factors from the neurological symptoms is needed to reduce the risk of complication in COVID-19 infection cases. This review highlights the possible pathogenesis and mechanisms of invasions with the associated Neurological impacts like GBS, encephalitis and meningitis based on various case reports and research articles to date.

INTRODUCTION

Since the end of 2019, we have been struggling with the severe pandemic of SARS-CoV-2 (severe acute respiratory syndrome by Coronavirus-2). Consequently, the World Health Organization (WHO) confirmed the infections caused by SARS-CoV2 as Coronavirus disease 2019 (COVID-19).^[1]

The first case of Covid-19 infection emerged in December 2019 in Wuhan, China and was found to be rapidly spreading over a large amount of worldwide population leading to more than millions of cases of Covid infection. The Coronavirus strain causing COVID-19 is a positive-sensed, single-stranded RNA belonging to the genus *Betacoronavirus* of family Coronaviridae thus making it contagious.^[2]

Initially, it was found that coronavirus was primarily associated with the upper respiratory tract. However, gradually visible Neurological presentations were ranging

from nonspecific and moderate to severe symptoms associated with CNS and PNS discovered among patients. Thus various researches were carried out on the Neurological impact of the COVID-19 virus and concluded various outcomes regarding its neurological impact which are further discussed in the review article. This review is based on the date, recent review and research articles regarding Neurological Manifestations due to the COVID-19 virus.

NEUROLOGICAL MANIFESTATIONS OF COVID-19: CAUSALITY OR COINCIDENCE?

The coronavirus strain causing COVID-19 belongs to the genus *Betacoronavirus* that can be contagious. There are in all seven viruses of genus *Betacoronavirus* that are known to cause human respiratory tract infection and transmission. They are responsible for causing diseases

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such as the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome coronavirus (SARS-CoV).

The most common manifestations with their reasons are mentioned in Table 1.^{[3][9][11][7]}

Pathophysiology and Mechanism of SARS-COV 2 Invasion^[4,5,7,8,10,12,17,26-31]

Structure: Coronaviruses are members of the Coronaviridae family. There are four subtypes of coronaviruses, are:

1) Alpha coronavirus,

Table 1: Common manifestations and occurrence of COVID-19

Sr No.	Common manifestations	Occurrence
1	Cerebrovascular	- Approximately 1.5% of emergency or hospitalized COVID-19 patients underwent ischemic stroke, about 7.5 times higher than those in influenza patients - According to the study by Mao et al. (2020), stroke occurred in 5.7% of patients with severe disease, and 0.8% of patients with mild disease - According to the available reports, most patients with COVID-19 combined with cerebrovascular disease have risk factors for cerebrovascular diseases, such as hypertension, diabetes, coronary artery disease, hyperlipidemia, atrial fibrillation, and smoking. This has an impact on the proportions of the population with risk of ischemic and hemorrhagic stroke, which were $\geq 50\%$ and $\geq 75\%$, respectively. - The uncertainty of stroke may therefore be increased in a case of infection and systemic inflammation. However, direct damage to the cerebrovascular system caused by SARS-CoV-2 infection must be considered based on the current literature.
2	Demyelinating lesions of the central nervous system	- The development of demyelinating lesions by SARS-CoV-2 infection can be correlated to the immune response to the viral infection. - Viral infection is associated with multiple sclerosis, and human CoVs were present in autopsies of multiple sclerosis patients. - Human CoVs are also detected in the cerebrospinal fluid (CSF) of some children with acute disseminated encephalomyelitis. - Thus SARS-CoV-2 can be a direct cause of demyelinating lesions in the CNS.
3	Encephalopathy and encephalitis	- Encephalopathy and encephalitis are serious CNS manifestations of SARS-CoV-2 infection. COVID-19 patients with encephalopathy/encephalitis frequently have a poorer diagnosis. - They are mostly elderly patients who may have a high number of associated comorbid chronic diseases or immune deficiency. - Many COVID-19-related encephalopathy or encephalitis have normal cerebrospinal fluid reports. While the presence of SARS-CoV-2 in cerebrospinal fluid could be due to the virus breaking the blood-brain barrier and entering the CNS, it could also be due to contamination of the cerebrospinal fluid. - It can also be due to contamination of the cerebrospinal fluid. However, there is still a lack of adequate evidence to prove SARS-CoV-2 virus infection directly invades the CNS and then causes encephalopathy or encephalitis.
4	Guillain-Barre syndrome (GBS)	- There is no evidence that SARS-CoV-2 infection can be caused or is subordinately associated with GBS. But the possible involvement of COVID-19 in the peripheral nervous system cannot be denied. - It is unclear if the respiratory failure observed is associated with neuromuscular dysfunction due to GBS or is by previous severe respiratory infection. - The post-infection molecular simulation plays an important role in the development of GBS, this role has only been confirmed in animal models of <i>Campylobacter jejuni</i> infection and not in animal models of other viral infections. It therefore may not be considered as a mechanism for SARS-CoV-2 correlated to GBS.
5	Dysosmia and dysgeusia	- Impairments of the smell and taste senses are two of the most prevalent symptoms of SARS-CoV-2 infection during epidemics of novel coronavirus pneumonia. - Approximately 70% of patients appear to have a reduced sense of smell and taste during the disease. - If the impact of SARS-CoV-2 infection on neurological functions is deemed to be causal, then impairments of the senses of smell and taste are the most reliable evidence. As primarily in the study of olfactory dysfunction in patients with a viral infection, some patients had normal nasal acoustic reflex measurements but still had olfactory deficits. - This suggests that nasal inflammation and nasal obstruction are not the only causes of olfactory deficits following viral infection, but may be related to deficits in the olfactory nerve or olfactory center. - The viruses can migrate retrogradely along the cranial nerves into the brain and damage the nuclei of cranial nerves. It is thus prudent to speculate that olfactory impairment may be a sign of CNS damage following SARS-CoV-2 infection.



Sr No.	Common manifestations	Occurrence
6	Others:	
	a) Respiratory failure:	- The SARS-CoV-2 not only infects the lungs, but also has severe effects on neurons, majorly of the medulla oblongata that regulates respiratory, pulmonary, and cardiac functions, leading to respiratory failure. - Therefore some patients with SARS-CoV-2 may develop respiratory failure despite no significant deterioration being visible in imaging examinations, and we should consider the possibility that SARS-CoV-2 may have directly invaded the respiratory center of the nervous system.
	b) Headaches, dizziness, and muscle aches:	Headaches, dizziness, and muscle aches can be manifestations of neurological injury as well as also by nonspecific injury due to respiratory and pulmonary infections. These symptoms often occur as nonspecific symptoms after SARS-CoV-2 infection, which may act as a warning against possible neurological damage during the COVID-19 epidemic.
	c) Skeletal muscle damage:	- It is a nonspecific symptom of SARS-CoV-2 infection. - This can be a direct viral attack causing skeletal muscle lysis, and the immune response to viral infection

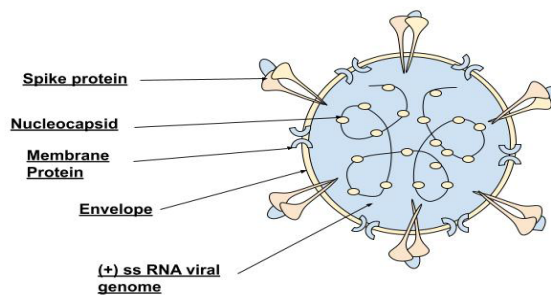


Fig. 1: Structure of SARS-CoV

- 2) Beta coronavirus,
- 3) Gamma coronavirus
- 4) Delta coronavirus.

Both Alphacoronavirus and Betacoronavirus usually infect mammals, while Gamma Coronavirus and Deltacoronavirus mostly infect birds.

COVID-19 is a Betacoronavirus, enveloped, pleomorphic or spherical particles, 60 to 140 nm in diameter, single-stranded ribonucleic acid (RNA), unsegmented, nucleoprotein capsid, matrix and S protein, which can infect both humans and animals (Fig. 1). The genome of the SARS-CoV-2 contains single-stranded positive-sense RNA encapsulated within a membrane envelope, which contains glycoprotein spikes conferring SARS-CoV-2 crown-like appearance.^[4] Genetically SARS-CoV-2 is 79% identical to SARS-CoV and 50% to MERS-CoV.^[5] The ultimate viral proteins are nucleocapsid protein, membrane glycoprotein and spike glycoprotein. The differentiating factor of COVID-19 from other coronaviruses is the presence of an additional glycoprotein that has acetyl esterase and hemagglutination properties.^[6]

The envelope spike protein of the COVID-19 recognizes human angiotensin-converting enzyme II (ACE2) as an entry receptor and mostly infects lung epithelial cells. The receptor-binding area of the spike protein attaches onto the ACE2 receptor and then, the host serine transmembrane proteases 2 (TMPRSS2) splits the spike

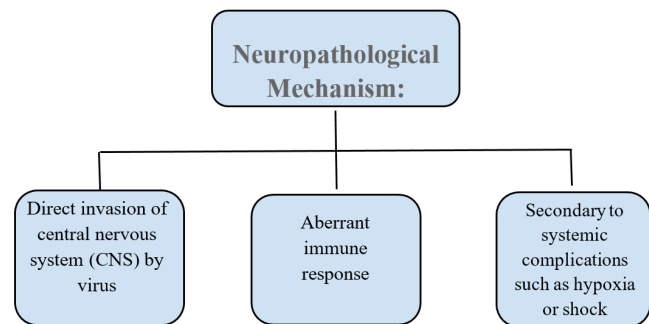


Fig. 2: Different mechanisms of SARS-CoV Invasion

protein to manifest fusion peptides capable of fusing the viral and cell membranes. ACE2 is found in many human tissues. Therefore, infection in COVID-19 can show various symptoms depending on which tissues are infected. The most typical COVID-19 symptoms are fever, cough, and lethargy. However, other symptoms of autoimmune mediation, the inner immune to immune-mediation, have been observed, such as headache and anosmia. These demonstrate that COVID-19 can involve other human organs, such as neurology.

SARS-CoV, MERS-CoV, and SARS-CoV-2, all these viruses infect the lung, especially the lower respiratory tract, whereas SARS-CoV-2 also affects the heart, gastrointestinal system, and liver, kidney, and the central nervous system, eventually leading to multi-organ failure.^[4]

SARS COV has shown to have a zoonotic origin with bats adapted by humans as the primary reservoir. It has been shown to spread via respiratory droplets, fomites, and person-to-person contact. Transmission via stool shedding has also been established but has limited evidence.^[5]

Neuropathological Mechanism

The overall mechanism of SARS COV invasion can be summarized under:

In direct invasion of the Central Nervous System (CNS), SARS-CoV-2 will enter the CNS by 2 routes—following a

neural pathway or through body fluids (lymph, blood). The virus might enter into a nerve terminal, multiply, and be retrogradely transported to a cell body of neurons, for instance, dysomia in SARS-CoV-2. In Aberrant response, SARS CoV - a pair of infections triggers an aberrant response which might result in CNS manifestations thanks to immune mechanisms targeting CNS or Peripheral Nervous System as in GBS and renal neuropathies (Fig. 2).

In secondary to general complications like drive or shock, SARS-CoV-2 will cause multiple organ failure and CNS involvement may be secondary to general involvement, for instance, hypoxic brain disease, pathology brain disease, intracranial bleed or occlusion by disseminated intravascular coagulopathy (DIC).^[7]

In order to know every mechanism intimately, they're simplified as:^[5,8]

1. Direct infection injury
2. Blood circulation pathway
3. vegetative cell pathway
4. Immune-mediated
5. Hypoxic injury

Direct Infection of SARS-CoV-2 from Cribriform Plate to Brain

In this SARS-CoV-2 enter into brain tissues via dissemination and unfold from the cribriform the plate that is in proximity to the olfactory bulb. This idea of direct unfolding is backed by the manifestation of dysnomia and dysnomia in COVID-19 patients as represented by Mao *et al.*

The routes by that it enters the CNS area unit are as follows:^[9]

- *Olfactory epithelium:* Retrograde entry to CNS might occur through the cribriform plate
- *Cellular infection and invasions:* The infected macrophages act as a microorganism reservoir and unfold to the brain. Each hematogenous in addition to humor routes are represented epithelial tissue cells of the blood-brain barrier area unit known to specific SARS-CoV receptors—the angiotensin-converting enzyme-2(ACE-2) and CD209L. ACE-2 is additionally determined in interstitial tissue cells, cerebral blood vessels, funiculus, and skeletal muscles.
- *Transsynaptic route:* Transmission may additionally occur via the peripheral nerves

Haematogenous Spread of SARS-CoV-2 to Target CNS

The SARS COV identifies ACE as a pair of operative receptors with varied expression and distribution of ACE2 receptors in several organs deciding the severity of clinical manifestation of SARS-CoV-2. ACE2 receptors are a unit expressed on interstitial tissue tissues, neurons, and brain vasculature that build them a target for the attack by SARS CoV-2. The role of the blood-brain barrier in preventing the virus entry continues to be established, however, clinical manifestations of medicine symptoms

in patients of SARS-CoV-2 in an exceedingly recent study was established.

S spike supermolecule (encoded by mRNA) allows the binding of SARS-CoV-2 with ACE2 receptors within the same method because it will for SARS-CoV, and in an exceedingly study it had been seen that the binding affinity of SARS-CoV-2 supermolecule S was 10 to 20-folds more than SARS-CoV supermolecule S. The presence of the virus generally allows virus entry into cerebral circulation, wherever sluggish blood movement in small vessels allows interaction of the infectious agent spike supermolecule with ACE2 receptors of capillaries epithelium. This after ends up in infectious agent budding from capillary endothelium; resultant injury to the epithelial tissue lining favors infectious agent entry into the surroundings of the brain, wherever infectious agent interaction with ACE2 receptors expressed over neurons may end up in injury to the neurons while not a considerable inflammation—seen antecedently with SARS-CoV infection. The avid binding of the virus to the ACE2 receptors also can end in their destruction via unknown mechanisms, resulting in hemorrhage within the brain. Since ACE2 may be a cardio-cerebral tube protective issue, its injury causes a leak of the virus within the central nervous system. It's necessary to say that before the prevalence of anticipated vegetative cell injury with the virus, the epithelial tissue injury in cerebral capillaries with ensuing injury will have fatal consequences in COVID-19 patients.

Neuronal Pathway

The neurotropic viruses just like the coronaviruses will reach the central nervous system by anterograde and retrograde transport with the assistance of motor proteins Kinesins and dynein via sensory and nerve endings particularly via corticopetal nerve endings of the cranial nerve from the lungs.

In addition to the current, SARS-CoV-2 also can cause chanel infection and may unfold to the central nervous system via enteric nerve and sympathetic corticopetal. Moreover, Exosomal cellular transport is additionally a plausible pathway of SARS-CoV-2 general dissemination and resultant central nervous system entry.

Immune-Mediated Injury to CNS

SARS-CoV-2 is projected to cause injury to the CNS by a surge of inflammatory cytokines (mainly Interleukin-6), known as protein storm syndrome (CSS), within the same method as several neurotropic viruses area units assumed to induce the synthesis of IL-6 from interstitial tissue cells, leading to protein storm syndrome.

In the associate degree in vitro study, activated interstitial tissue cells were seen to cause chronic inflammation and brain damage by manufacturing pro-inflammatory cytokines like IL-6, IL-2, IL-5, and TNFa.

SARS-CoV-2 infection of the central nervous system activates CD4+ cells of the system and CD4+ cells in turn



induce the scavenger cell to secrete interleukin-6 (IL-6) by manufacturing granulocyte-macrophage colony-stimulating issue. IL-6 may be a predominant element of CSS and ends up in multiple organ failure—a major explanation for fatality in COVID-19.

Hypoxic Brain Associated Damage

Uncompromising respiratory illness will cause systemic hypoxia that damages the central nervous system. The chance factors comprise physiological condition, peripheral vasodilatation, anaerobic metabolism with cyanogenic compound accumulation, hypoxia. This can cause neuronal swelling and brain oedema that eventually leads to neurological injury

Thus, summarizing all we can conclude the mechanism as:^[10]

- Peripheral nerve infection (e.g., direct intranasal immunization, mechanoreceptors and chemoreceptors within the respiratory organs and lower metastasis airways, the inner perhaps oropharyngeal)
- Olfactory receptor nerve cell infection through direct inoculation
- Retrograde trans-synaptic transmission once infection of the peripheral nerve
- Direct central nervous system neural entry
- BBB disruption and infection of microvascular epithelial tissue cells following viraemia
- Infection of current leukocytes³⁸ that traffic the virus across the BBB (Trojan horse entry)
- Indirect mechanisms for neural cell injury
- Systemic inflammation (includes hypercoagulable state and protein storm)
- Endothelial invasion, injury, and occlusion
- Hypoxic-anoxic brain injury once internal organ failure
- CNS demyelination

PSYCHOLOGICAL IMPACTS OF COVID-19

In the Fig. 3, the inner circle represents the reasons for psychological problems and the outer circle represents its psychological effects.

In today's conditions, the COVID-19 pandemic has vastly led to the epidemiological and psychological crisis. With the rise in the days of lockdown worldwide, living in isolation, changes in our daily lives, job loss, money hardship, and death of treasured ones have staggeringly wedged on the potential to affect mental health-related problems.

During the time of social distancing, psychological symptoms and mental state problems have been raised around the world.^[11]

Although isolation and quarantine have distinct meanings in the application, they each involve the separation of a private from their treasured ones, traditional activities, and routines for the aim of infection

hindrance. The psychological impact of quarantine and isolation was added on with the harmful impact of limited physical activity and variations in dietary practices. Such changes might lead to dramatic and long-lived psychological impacts. A study was conducted on segregated and isolated people with severe acute metabolism syndrome (SARS) and H1N1 rumored posttraumatic stress symptoms, confusion, and anger. Stressors involve longer quarantine, infection fears, frustration, boredom, inadequate supplies, inadequate information, financial loss, and stigma.

A study conducted by Pappa et al. (2020) supported the protocols registered on PROSPERO that relies on the information pooled mistreatment random-effects meta-analyses to review the prevalence of specific mood-related problems. The PROSPERO study was conducted on health care professionals where a complete variety of 33,062 participants with thirteen studies were enclosed for the meta-analyses. In twelve studies, anxiety was assessed with a prevalence rate of 32%, and major depression in ten studies with an incidence rate of 22.8%.^[12-14] Further, female health care professionals discovered higher rates of mental health-related symptoms compared to male health care staff. Moreover, sleep disorder prevalence was calculable at 38.9%, suggesting that sleep disturbances were discovered to be a big issue. Thus considering these issues as proof, health care professionals et al. area units experiencing mental state problems, together with sleep disturbances, throughout this natural event. Hence, it's extremely essential to launch new ways in which of interventions through counseling, social interactions, and psychotherapy through “telemedicine” underneath these unsure pandemic conditions.^[11]

NEUROLOGICAL MANIFESTATION OF COVID-19

Though the implications of COVID-19 have fewer psychological state problems, the brain biotypes and

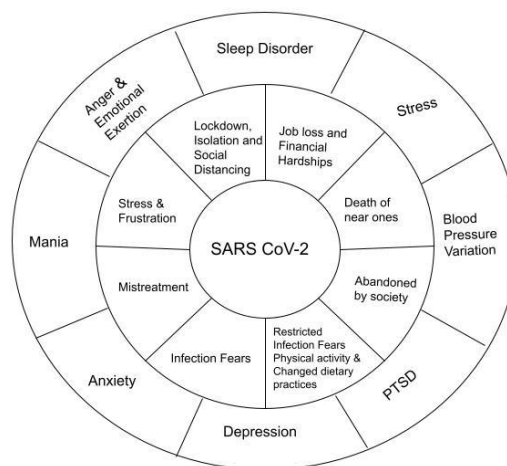


Fig. 3: Psychological impact of SARS CoV-2;

brain or the neural taxonomy are likewise affected even if COVID-19 primarily affects the respiratory system, recent studies have shown its direct involvement within the CNS (central nervous system). The major psychological symptoms among individuals embrace signs of hysteria, panic attacks, depression, and suicide. To elaborate, the symptoms embrace persistent worrying or feeling overcome by emotions; restlessness and irritability; sleep issues like sleep disorder or excessive sleeping; sweating, trembling, shortness of breath, or a way of choking; and lack of interest, important weight loss/gain, feelings of worthlessness or excessive guilt, and perennial thoughts of death or suicide.^[9]

A cohort-based mostly study on medical specialty manifestations of COVID-19 has been reported during this retrospective study of 214 Covid-19 patients in the metropolis, China, 36.4% suffered from medical specialty neurological symptoms. The researchers and neurologists analyze the information and categorize the symptoms into 3 classes. If the CNS are affected, the patients develop symptoms like dizziness/vertigo, headache, impaired consciousness, acute neural structure sickness, ataxia, and seizure. Patients with affected peripheral system (PNS) have clinical manifestations together with vision, smell, and taste impairment likewise as nerve pain. The final class is for patients who have suffered a sustained injury to their skeletal-muscular system.^[15]

Patients who have additional severe infections, likewise as those that are older and produce other underlying disorders like cardiovascular disorder like hypertension, are additional seemingly to own these neurological

symptoms. Patients with additional severe infections were 5.1% additional seemingly to own acute cerebrospinal diseases, 12.4% additional seemingly to own impaired consciousness, and 14.5% additional seemingly to own a skeletal muscle injury. Recent literature has reported cases of multiple neuritides (GBS) as a complication of the novel coronavirus. 26-27 GBS may be a polyneuropathy that unremarkably develops post-infection. Immune attack of nerve cells causes the everyday tingling within the extremities that's unremarkably reportable as being the primary symptom of GBS. very little is understood about the interaction between SARS-CoV-2 infection and GBS. However, clinicians ought to remember the chance of GBS complication once treating patients WHO have tested positive for SARS-CoV-2.^[15]

Additionally, a clinical image that cherishes a central hypoventilation syndrome ("Ondine's curse") was reportable from a COVID-19 survivor in Wuhan.^[13]

Notably, patients had ischemic strokes, cerebrovascular events, CNS vasculitis, intracerebral hemorrhage and other cerebrospinal events. Hence, it's extremely essential to know the underlying biological mechanism of how these psychoneurological events are suffering from COVID-19.

Some of the key medical specialty symptoms are given in Table 2 with a few mentioned further:

Neurological Manifestation in CNS

Headache and Dizziness

Headache and vertigo/dizziness square measure the foremost ordinarily delineated symptoms of medicine involvement. Mao *et al.* rumored that several COVID-19 patients with neurological manifestation ab initio given with fever and headache. However, many days later, they developed a cough, throat pain, lymphocytopenia, and a ground-glass look on their chest computerized tomography (CT) pictures. Real-time reverse-transcription PCR (RT-PCR) analysis of nasopharyngeal swabs confirmed COVID-19 infection in these patients.^[16] The incidence ranges from three to 12.1%.^[8,17] Meningeal inflammation and meningeal irritation, and increased intracranial pressure are postulated as attainable mechanisms inflicting headache. Worsening of associate underlying primary headache syndrome, new-onset PPE (personal protective Equipment)-related headache, stress, and tension sort headaches will be alternative causes of headache.

Meningeal Involvement

Their square measure restricted studies concerning infectious disease or phrenitis related to COVID-19 in bodily fluid (CSF) or brain. Meningitis is the inflammation of the coverings of the brain and medulla spinalis. Seizure and altered sensorium squares measure common displays. SARS-CoV-2 polymer was detected in bodily fluid (CSF) of many patients of COVID-19 mediate cerebral meningitis. Microorganism clearance in CSF might precede the

Table 2: Neurological disorders associated with COVID-19

Neurological disorders of COVID-19:²⁰

Central Nervous System Diseases

- Encephalitis, meningitis, myelitis, meningoencephalitis
- CNS demyelinating disease
- Post-infectious acute disseminated encephalomyelitis
- Post-infectious brainstem encephalitis
- Encephalopathy
- Movement disorders
- Acute hemorrhagic necrotizing encephalopathy
- Cerebrovascular disease: ischemic and hemorrhagic stroke, cerebral venous sinus thrombosis, venous and arterial thrombosis, subarachnoid hemorrhage
- Associated with immune thrombocytopenic purpura

Peripheral Nervous System

- Guillain-Barré syndrome
- Miller Fisher syndrome
- Mononeuropathy
- Polyneuritis cranialis
- Optic neuritis
- Dysautonomia

Muscle Involvement

- Myalgia
- Myopathies
- Rhabdomyolysis



medicine involvement and thus the detection is also delayed. many cases were discovered giving the following predictions:

- (1) SARS-CoV-2 is neuroinvasive.
- (2) We cannot exclude SARS-CoV-2 infection through associate RT-PCR for SARS-CoV-2 as it negatively affects a patient's nasopharyngeal specimen.
- (3) SARS-CoV has been detected within the brain on autopsy by real-time RT-PCR with a powerful signal within the Hippocampus and during this patient inflammation was additionally found within the hippocampus; this reinforces the very fact that SARS-CoV and SARS-CoV-2 share the ACE2 as a practical receptor.

Encephalitis

The most common underlying etiology of phrenitis or acute inflammation of the brain is infectious agent infections like herpes simplex virus (HSV), chickenpox herpes virus (VZV), herpes virus (CMV), respiratory disorder virus,^[15] and lots of alternative metabolism viruses like severe acute metabolism virus coronavirus (SARS-CoV) and geographic region metabolism virus (MERS-CoV). Encephalitis is the inflammation of the brain parenchyma, sometimes caused by associate degree infection or the body's immune defences. Though it's to be precise a pathological designation, for sensible functions, clinical proof of brain inflammation is accepted, like a CSF pleocytosis, imaging changes, or focal abnormalities on encephalogram. Detection of the virus within the CSF doesn't offer a designation of phrenitis if there's no proof of brain inflammation SARS-CoV-2 may also have neurotrophic effects as a result of several COVID nineteen patients given with medicine symptoms additionally to common metabolism symptoms. Moreover, recently the presence of SARS-CoV-2 ribonucleic acid within the spinal fluid has been detected by ordering sequencing in a patient with clinically tested meningoencephalitis.^[5] Acute necrotizing hemorrhagic encephalitis associated with intracranial protein storm might occur and has been associated with a worse prognosis.^[18] Dogan *et al.* additionally thought of response phrenitis in their six patients, based mostly upon their clinical symptomatology and response to pheresis. fifteen Another case of anti-NMDA-R protein positivism was rumoured by Panareillo *et al.* These findings highlight the importance of activation of associate degree indirect pathway involving the system in SARS-CoV-2 infection.^[19] Rhombencephalitis inflicting motor ataxia, leukoencephalopathy with diffuse corticospinal involvement, delirium, govt disturbances, activity disturbances, sleep disorders, dementia, and movement disorders are alternative syndromes related to COVID-19. No specific treatment exists for SARS-CoV-2 phrenitis. As for alternative kinds of phrenitis, queries can emerge regarding the relative contributions of infectious agent injury and host inflammatory response, and whether

or not corticosteroids could be helpful. Clinical trials appear unlikely, given the present low variety of cases.^[20]

Encephalopathy

Encephalopathy could be a pathobiological method within the brain that sometimes develops over hours to days and may manifest as modified temperament, behaviour, cognition, or consciousness (including clinical shows of delirium or coma). In patients with nervous disorder and COVID-19, in whom brain inflammation has not been tested, the big selection of alternative causes to contemplate includes drive, drug toxins, and metabolic derangements. The largest study thus far, from Wuhan, China, retrospectively delineate 214 patients with COVID-19, of whom 25% had system symptoms, as well as lightheadedness ([17%] patients), headache ([13%]), and impaired consciousness [7%]. A total of 51% of the patients with system symptoms had severe respiratory disorder, however, there was very little additional detail. in a very French series of fifty-eight medical care patients with COVID-19, 84% had medical complications, as well as forty (69%) with a nervous disorder and 67% with pyramidal tract signs.^[20]

Vascular Involvement

Amongst all the neurological manifestations associated with COVID-19, especially in those who suffer from a severe form of illness, the acute cerebrovascular disease is also observed. Mao *et al.* concluded that 5.7% of patients with severe COVID-19 developed acute cerebrovascular disease^[21] and it usually presents as a stroke, with ischemic strokes being more common than hemorrhagic strokes. SARS-CoV-2 infection associated with hypercoagulability is called "sepsis-induced coagulopathy (SIC)" and the depletion of angiotensin-converting enzyme 2 (ACE2) results in tissue damage, including stroke. This was underscored by the fact that thrombolytic prophylaxis amongst critically ill ICU patients reduces the thrombotic complications with a better outcome. avid binding to SARS-CoV-2 with ACE2 (a cardio-cerebrovascular factor) damages ACE2 and can lead to strokes.^[22] Moreover, cytokine storm syndrome associated with SARS-CoV-2 infection is also a potential cause of neuronal damage and stroke.^[5]

Patients who developed CVD were more likely to present with severe COVID-19, and to have cardiovascular risk factors such as hypertension, diabetes, and previous medical history of CVD^[23] of particular interest is the cerebrovascular involvement with COVID-19. The incidence of strokes observed in hospital COVID-19 registries of the European and Chinese is up to 2.5 to 6%. Mao *et al.* in his cohort noted strokes in 6 (2.8%) out of 214 COVID-19 patients (5 ischemic, 1 hemorrhagic stroke). In these cases there were large vessel strokes and also were in association with severe COVID-19 illness. Cortical Venous thrombosis was also observed in some

cases. Similarly in the series by Oxley *et al.*, large vessel strokes were noted in four men and one woman which were in the middle cerebral artery territory. They had no typical symptoms of COVID-19 infection at the outset in three of the five patients. The proinflammatory and prothrombotic mechanisms causing stroke in COVID-19 have further increased the curiosity. Endothelial dysfunction, DIC and thrombotic microangiopathy associated with thrombocytopenia the elevated D-dimer and prolonged prothrombin time have been hypothesized as precursors. With profoundly elevated D-dimer levels, COVID-19 has been considered a highly prothrombotic state. Along with factors like immobilization, hypoxia, inflammation and stress, accelerated thrombosis is also observed in severely ill/ICU-bound patients. Wherein the role of antiphospholipid antibodies causing multifocal infarction has also been suggested by a few. Prevalence of lupus anticoagulants in as high as 91% of patients has been reported. Autopsy studies denoting venous thrombosis in lower limbs, lungs and pulmonary circulation along with Endotheliitis in kidney and small intestine vessels. Extrapolating these findings to cerebral vasculature explains the etiopathogenesis of ischemic and hemorrhagic arterial and venous strokes.^[9]

Brainstem and Spinal CORD Involvement

Human coronaviruses (HCoV-OC43) cause mild respiratory infections but sometimes many, like MERS-CoV, can cause severe neurological manifestations like an acute disseminated postinfectious disease. Encephalomyelitis and post-infectious brainstem encephalitis^[4] because of their potential neurotropic traits. SARS-CoV-2, as of its type, can also result in these manifestations, especially in patients with autoimmune diseases like multiple sclerosis, myasthenia gravis, and sarcoidosis. But this is too early a stage for such manifestations of SARS-Cov-2 to be present and we need more research and investigation on it. Immunosuppressive therapies cause systemic immune suppression and could be of great concern.^[5] A handful of case reports of patients with necrotizing myelitis are available. It is observed that the severe and refractory gastrointestinal or respiratory involvement could be contributed by affected central pathways involving area postrema or chemoreceptor trigger zone. Mortality due to respiratory failure is postulated to be neurogenic, resulting from the involvement of respiratory centres of the brain.

Epilepsy

Epileptic seizures throughout COVID-19 unwellness occur as acutely symptomatic seizures within the context of primary central nervous system involvement because of SARS-CoV-2 (meningoencephalitis, secondary central nervous system injury, e.g. COVID-19-associated stroke or ICH, and through ECMO medical aid. There are many problems between seizure and COVID-19. Firstly, a seizure

is also a signal of infectious agent invasion to the brain. Secondly, COVID-19 leads to fatal respiratory illness and causes severe hypoxemia, which can result in brain injury. Thirdly, COVID-19 patients with a history of brain disorder might have a higher frequency and severity of the seizure.^[6]

Thus there are 2 major clinical things to be distinguished:

1. The primary prevalence of seizures in COVID-19 patients
2. With notable epilepsy brain disorder encephalopathy brain unwellness COVID-19 disease is prevalent in an exceedingly patient observed in 0.6 to 0.7 of the population.

Acute symptomatic seizures are outlined as epileptic seizures occurring within seven days of acute brain injury. The amount of this era is also longer because the unwellness will stay active for an extended period within the case of meningitis. They conjointly occur often with pre-existing Epilepsy of a unique etiology within the context of COVID-19 unwellness, seizure recurrences or accumulations occur but seizure occurrences are comparatively rare. Lu *et al.* failed to report acute symptomatic seizures in an exceedingly cohort of three hundred severely sick COVID-19 patients in an exceedingly any study of 214 COVID-19 patients (41% of whom were severely sick in step with metabolism criteria), only in one patient (0.5%) asymptomatic seizure was ascertained. Seizures can also occur as Status Epilepticus. It is conjointly notable from the last severe acute respiratory syndrome epidemic that patients with chronic brain disorder have reduced access to doctors and medicines and may suffer withdrawal attacks. For this reason, it's necessary to confirm that patients having pre-existing brain disorders continuously have access to patient neurologic care which stop providing shortages timely and enough medication is prescribed.^[24]

Neurological Manifestation in PNS

Guillain Barré Syndrome

GBS is AN acute polyradiculoneuropathy that usually presents with progressive monophasic generalized and symmetrical weakness involving each higher and lower extremities and related to hyporeflexia or symptom. Since the COVID-19 pandemic, there have been some studies of the potential relationship between COVID-19 and GBS. COVID-19 square measure is thought to be the etiology of GBS through neuron capacities and inflammatory mechanisms. Guillain-Barré syndrome causes immune-mediated injury to the peripheral nerves that typically occur after respiratory and gastrointestinal illnesses. commonest antecedent infections square measure Zika virus, Campylobacter jejuni and contagious disease virus (influenza). Neuromuscular disorder (contractile organ disorder) has been observed according to SARS-CoV by Tsai *et al.* and similar neurological manifestations like



Bickerstaff's encephalitis overlapping with Guillain-Barré syndrome were additionally seen with MERS-CoV.^[5] As SARS-CoV-2 is extremely just like SARS-Cov and MERS-Cov, it may be an antecedent to Guillain-Barré syndrome. As with different infective agent diseases, postinfectious genesis will be assumed, though the latency between the initial manifestation of COVID-19 and also the incidence of GBS seems to be short.^[24]

As cytokine storm increases the level of IL-6 followed by that stimulates Inflammatory cascade and harm the tissues. There square measure many studies regarding developing GBS in COVID-19 infection. Caress et al incontestable that the mean solar time of the onset of systema nervosum manifestations, together with paraesthesia, limb weakness and nerve symptoms, from the onset of COVID-19 was 11 ± 6.5 days (range, 3–28 days). Limb paraesthesia and weakness were the foremost often symptoms of the presentation. Acute inflammatory demyelinating polyneuropathy (AIDP, 64.8%) was the foremost common variety of GBS, whereas acute motor nerve fibre pathology (AMAN, 2.7%) was the smallest common variety of GBS seen during this study.

Sanctis et al presented that the time between the onset between COVID-19 infection to the symptoms of GBS was 9 days (range 8–24 days). In line with Caress et al, this study also found AIDP (55.56%) as the most prevalent type of GBS, while AMAN (5.56%) was the least prevalent type of GBS.^[6]

Chemosensory Dysfunction and Anosmia

Goblet cells and ciliated cells are suggested to play an important role in anosmia due to COVID-19 infection.^[31] These two cell types contain a high concentration of ACE2, which is the COVID-19 receptor, and TMPRSS2, which promotes COVID-19 infection. The sense of smell depends on the sensory cell. COVID-19 can damage sensory cells on the olfactory mucosa, which consists of epithelium cells, blood vessels, and axons from olfactory neurons, and initiate an inflammatory response. The sensory cell is joined with the olfactory bulb by the cribriform plate, which allows for the transmission of sense of smell at the base of the frontal lobe as well as transmission of the virus to the brain. This pathway shows the possible linkage between CNS and PNS.^[6]

For the first time, Mao *et al.* described neurological symptoms in COVID-19 patients, including olfactory disorders in 11/214 patients (5%).^[24] This was followed by a large number of reports on olfactory and taste disorders in COVID-19. As during the pandemic period, contradictory and preliminary results were published very rapidly, the extremely heterogeneous data we get. Even if we didn't get finally clarified details, some essential points are currently emerging:

In COVID-19, taste and smell disorders are common. They appear especially in mild progressive disease, in

young people, more often in previously healthy individuals and in women more frequently than among men. Taste and smell disorders can be rarely the only and first symptom of a COVID-19 disease. In COVID-19 odor disorders are generally not related to symptoms of rhinitis (rhinorrhoea, obstruction, sneezing, congestion,) and are different in the respect to pathophysiologically from other post-viral olfactory disorders and also phenomenologically. During the regeneration phase and the course of the disease parasomnias may occur. A new olfactory disorder/anosmia (with or without the subjective impression of an additional gustatory disorder) occurring during the pandemic should be an immediate cause for:

- quarantine/Self-isolation– SARS-CoV-2 testing (via telephone contact to health office or family doctor)

- Use of personal protective equipment in professional contact with affected persons.^[24]

It is well-known that viral infections including coronaviruses can lead to smell dysfunction. In adults, the leading cause is post-viral anosmia for loss of sense of smell, it was observed in up to 40% of cases of anosmia.^[19] Primarily mucosal congestion is the underlying cause that leads to conductive olfactory loss and nasal obstruction.

However, the novel coronavirus is thought to cause olfactory and gustatory disorders without causing rhinorrhea or nasal obstruction. A multi-centre european study showed that 85.6% and 88.8% of COVID-19 patients developed olfactory and gustatory disorders respectively.^[25] Regarding the olfactory disorders, 79.6% of the patients were anosmic and 20.4% were hyposmic. Interestingly, among the 18.2% of patients without nasal obstruction or rhinorrhea, 79.7% were hyposmia or anosmia, suggesting that the inflammatory reaction of the nasal mucosa is not the cause of smell dysfunction in this case. The gustatory dysfunction consisted of discontinued, reduced, or distorted ability to taste flavours (salty, sour, bitter, and sweet) in 78.9% and 21.1% of patients, respectively.^[23]

Oculomotor Nerve Palsy

The oculomotor nerve palsy associated with COVID-19 was reported firstly in Wuhan, China. A 62-year-old man was admitted to the hospital with a history of diplopia and complete ptosis on the left eyelid. No history of common manifestations associated with COVID-19, such as cough, shortness of breath, fever, headache and chest pain were found. Inflammation markers were significantly elevated in this patient. Head imaging ruled out new infarction, bleeding of brainstem or pituitary apoplexy, tumor, multiple sclerosis, and aneurysm. Unenhanced CT scan showed wide, multiple, diffuse ground-glass opacities in both lungs. Nasopharyngeal throat swab was positive for COVID-19. Therefore, the patient was diagnosed with oculomotor nerve palsy associated with COVID-19 infection as there was not found no underlying

causes of oculomotor nerve palsy. The mechanism of how COVID-19 infected the oculomotor nerve needs further understanding. The hypothesis suggests that oculomotor nerve palsy could be triggered by myelin and axon damage due to virus infection.^[6]

SKELETAL MUSCLE DAMAGE

In COVID-19 cohorts the combination of myalgia, fatigue and elevation of blood-creatinine kinase levels is the most common form 40–70% of skeletal muscle affection.^[24]

In 17 (19.3%) cases in the seriously ill and 6 (4.8%) cases in the non-severe category, Mao *et al.* reported skeletal muscle lesions. Skeletal muscle damage was identified as a subject with raised serum creatine kinase level beyond 200 U/L and myalgia. Researchers settled that it was not obvious whether this was due to the direct muscle tissue effect of the virus or other subsequent reasons. Another potential mechanism suggested was the infection mediated immune response that induced raised serum pro-inflammatory cytokines resulting in damage to the skeletal muscles. It should be remembered, however, that in addition to increased muscle enzymes, patients in the seriously ill community also had raised liver enzymes and disordered renal functions that may have driven to this clinical feature. Besides, no clear confirmatory diagnostic study such as NCS/EMG or muscle cell histopathology has been done. Therefore it is difficult to exclude that in addition to skeletal muscle injury, these patients may have essential disease myopathy and neuropathy.^[30] Rhabdomyolysis was detected in 0.2% and elevated CK levels in 13.7% in a series of 1099 COVID-19 patients.^[24]

However, it is important to note that groups of patients that are severely ill in addition to raised muscle enzymes, also had elevated liver enzymes and deranged renal functions which could have contributed to this clinical picture. Moreover, there is no specific diagnostic workup for confirmation like muscle histopathology or NCS/EMG was performed. Therefore, it is difficult to exclude that these patients might be having critical illness myopathy and neuropathy in addition to skeletal muscle damage.^[17]

CONCLUSION

The scenario of the world has changed because of this covid-19 pandemic. Coronavirus is contagious by nose and mouth via droplets and affects the upper respiratory tract majorly. However, some people are asymptomatic but can transmit the disease while some show very mild symptoms and can be cured without much hospital treatment. COVID 19 has an incubation period of 14 days. The risk is high in elderly patients and people who are already suffering from some other fatal disease.

Firstly, symptoms are high fever, dry coughs, difficulty in breathing, fatigue, ageusia (loss of taste), anosmia (loss of smell), etc. When treatment fails, pulmonary injury,

multiorgan failure especially renal failure and death may occur.

We have been facing this pandemic situation for a long time so not only the physical but mental health of the general public is in danger due to the increase in stress, depression, worries about normalizing future and financial problems etc. after that many neurological events such as headache, dizziness, or cerebrovascular symptoms, anosmia and ageusia is also observed in covid patients which we saw briefly in this review. With these psychological impacts and neurological manifestations, we also discussed the pathophysiology and mechanism of COVID-19. After discussing these points we can conclude that there are many effects on the mental health of patients due to either treatment of COVID-19 (with some still unknown) or due to the stress on a social or personal level due to the pandemic.

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REFERENCES

1. Luis Enrique Fernández-Garza, Alejandro Marfil. "Neurological aspects that should not be forgotten during the COVID-19 pandemic." *InterAmerican Journal of Medicine and Health* (2020) [CrossRef]
2. Verstrepen Kato, Baisier Laure, De Cauwer Harald. "Neurological manifestations of COVID-19, SARS and MERS." *Acta Neurologica Belgica* (2020) [CrossRef]
3. Fangfang Zhao, Ziping Han, Rongliang Wang, Yumin Luo. "Neurological Manifestations of COVID-19: Causality or Coincidence?" *Aging and Disease* 12.1 (2021) 27 [CrossRef]
4. Sidra Kalsoom Fazal Rahim Wazeen. "COVID-19 Pandemic: A Comprehensive Review of Neurological Manifestation, Complications And Future Prognosis." *Zenodo* (2020) [CrossRef]
5. Muhammad Umer Ahmed, Muhammad Hanif, Mukarram Jamat Ali, Muhammad Adnan Haider, Danish Kherani, Gul Muhammad Memon, Amin H. Karim, Abdul Sattar. "Neurological Manifestations of COVID-19 (SARS-CoV-2): A Review." *Frontiers in Neurology* (2020) 518 [CrossRef]
6. Chandra Wirawan, Shierly.. "Neurological manifestations in COVID-19 infection." *International Journal of Research in Medical Sciences* (2020) 4168 [CrossRef]
7. Neeraj Balaini, Manish Modi. "COVID-19 and Neurological Manifestations." *Annals of the National Academy of Medical Sciences (India)* (2020) [CrossRef]
8. Arash Azhideh, Iman Menbari-Oskouie, Maryam Yousefi-Asl. "Neurological Manifestation of COVID-19: A Literature Review." *International Clinical Neuroscience Journal* (2020) 164-170 [CrossRef]
9. Aastha Takkar, Monika Singla. "The Neurological Aspects of COVID-19: Do Women Respond Differently?" *Indian Journal of Cardiovascular Disease in Women WINCARS* (2020) [CrossRef]
10. Anna S. Nordvig, Kathryn T. Rimmer, Joshua Z. Willey, Kiran T. Thakur, Amelia K. Boehme, Wendy S. Vargas, Craig J. Smith, Mitchell S.V. Elkind. "Potential neurological manifestations of COVID-19." *Neurology Clinical Practice* 11.2 (2020) 10.1212/CPJ.0000000000000897 [CrossRef]
11. Eric Hartono Tedyanto, Febe Alodia Widjaja, Ni Komang Sri Dewi Untari. "Neurological manifestations of coronavirus disease: a

