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A REVIEW ON EFFECT OF COVID 19 ON NERVOUS SYSTEM

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Abstract

.COVID-19, in most patients, presents with mild flu-like illness. Elderly patients with comorbidities, like hypertension, diabetes, or lung and cardiac disease, are more likely to have severe disease and deaths. Neurological complications have emerged as a significant cause of morbidity and mortality in the ongoing COVID-19 pandemic. Beside respiratory insufficiency, many hospitalized patients exhibit neurological manifestations ranging from headache and loss of smell, to confusion and disabling strokes. COVID-19 is also anticipated to take a toll on the nervous system in the long term. Neurological complications are frequently reported in critically ill patients with comorbidities. In COVID-19, both central and peripheral nervous systems can be affected. The SARS-CoV-2 virus causes the disease COVID-19 and has the potential to invade the brain. The SARS-CoV-2 virus enters the brain either via a haematogenous route or olfactory system. The most severe neurological manifestations, altered sensorium (agitation, delirium, and coma), are because of hypoxic and metabolic abnormalities. Characteristic cytokine storm incites severe metabolic changes and multiple organ failure. Profound coagulopathies may manifest with ischemic or haemorrhagic stroke. Rarely, SARS-CoV-2 virus encephalitis like acute disseminated encephalomyelitis or acute necrotizing encephalopathy have been reported. Complete or partial anosmia and ageusia are common peripheral nervous system manifestations. Recently, many cases of Guillain-Barré syndrome in COVID-19 patients have been observed, and a postinfectious immune-mediated inflammatory process was held responsible for this. Myalgia/fatigue is also common, and elevated creatine kinase levels indicate muscle injury. Here, we will provide a critical appraisal of the potential for neurotropism and mechanisms of neuropathogenesis of SARS-CoV-2 as they relate to the acute and chronic neurological consequences of the infection. Finally, we will examine potential avenues for future research and therapeutic development. Due to its worldwide distribution and multifactorial pathogenic mechanisms, COVID-19 poses a global threat to the entire nervous system. Although our understanding of SARS-CoV-2 neuropathogenesis is still incomplete and our knowledge is evolving rapidly, we hope that this review will provide a useful framework and help neurologists in understanding the many neurologic facets of COVID-19.

Keywords: *Coronavirus; Guillain-Barre syndrome; encephalitis; encephalopathy; myalgia*

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INTRODUCTION:

The novel coronavirus, now called severe acute respiratory syndrome-coronavirus type 2 (SARS-CoV-2), is the agent of coronavirus disease 2019 (COVID-19),that was first diagnosed on December 8, 2019, in a patient in the city of Wuhan in central China. Common symptoms of COVID-19 include fever, cough, fatigue, and breath. Whereas most affected individuals have no or minor symptoms, some go on to develop pneumonia, acute respiratory distress syndrome (ARDS) and multiple organ failure. On January 30, 2020, the World Health Organization (WHO) declared it a Public Health Emergency of International concern. It has been estimated that the number of infected individuals during the early epidemic doubled every 2 days or number of people that can be infected by a single individual, may be as high as 4.7 to 6.6[1].

CORONA VIRUS:

What are coronaviruses and what makes SARS-CoV-2 so contagious?

A coronavirus is a type of virus that causes infections in the nose, sinuses, and upper throat. The majority of coronaviruses aren't harmful [2]. Coronaviruses, which have a diameter of approximately 100 nm, are named after their crown-like appearance on electron microscopy. They infect many animal species and are part of the family of Coronaviridae that contain four distinct Genera[1].

SARS-CoV-2 was discovered as a new kind of coronavirus by the World Health Organization in early 2020, following a December 2019 epidemic in China. The disease soon spread around the globe [3]. The full sequence of SARS-CoV-2 is like a β-coronavirus, similar to other human coronaviruses that are responsible for acute viral nasopharyngitis, also known as “common cold.” However, SARS-CoV-2 contains unique sequences, including a polybasic cleavage site in the spike protein, which is a potential determinant of increased transmissibility [2].COVID-19 is a sickness produced by the SARS-CoV-2 virus that can cause a respiratory tract infection. It can affect either the upper or lower respiratory system (sinuses, nose, and throat) (windpipe and lungs). It spreads in the same way that other coronaviruses do, primarily through direct contact between people. Infections can be minor or fatal[3]. The male sex is more susceptible to the infection, and disease severity and mortality are higher in older individuals [1]. Several varieties are currently circulating, some of which are proving to be more contagious and deadly than the original virus. Throughout the epidemic, scientists have been monitoring variations like as Alpha, Beta, Gamma, Delta, and Omicron [3].

There is increasing evidence that the nervous system is frequently involved in patients hospitalized with coronavirus disease. This is not surprising, because neurological manifestations have also long been described in infections from other respiratory viruses, including coronaviruses. However, the neurological manifestations of COVID-19 are common and disabling enough to have attracted widespread attention in the scientific and lay press for their short- and long-term impact on population health [4]. Here, we provide a summary of the nervous system involvement in COVID-19. In particular, we will focus on the mechanisms of pathogenicity, on the acute and delayed neurological manifestations reported to date, and on how the nervous system involvement compares to that of other respiratory viruses. Finally, we will attempt to flesh out unanswered questions that may help gain a better appreciation of this critical aspect of COVID-19 and chart a path forward to minimize its harmful nervous system involvement [5].

PATHOPHYSIOLOGY- CORONA VIRUS INVASION:

Coronaviruses have caused deadly outbreaks in the past. SARS-CoV-2 is one of seven coronaviruses that can cause serious illnesses such as Middle East respiratory syndrome (MERS) and sudden acute respiratory syndrome (SARS).

Several theories have been put forward for the pathogenesis of neurological manifestations [6]. Entering through angiotensin-converting enzyme 2 receptors, SARS-CoV-2 can damage endothelial cells leading to inflammation, thrombi, and brain damage. Moreover, systemic inflammation leads to decreased monoamines and trophic factors and activation of microglia, resulting in increased glutamate and *N*-methyl-D-aspartate (NMDA) and excitotoxicity. These insults induce new-onset or re-exacerbation of pre-existing neuropsychiatric symptoms (NPs).

Steps involved in corona virus invasion into brain

A) SARS-CoV-2 invades endothelial cells via transmembrane angiotensin-converting enzyme 2 (ACE2) receptor, enabled by transmembrane protease, serine 2 (TMPRSS2).
B) Cytokine elevation and microglia activation result in increased kynurenine, quinolinic acid, and glutamate, and depletion of neurotransmitter like serotonin, dopamine, norepinephrine.

C) Coagulation cascade and elevation of von Willebrand factor (vWF), fibrin deposition, and platelet activation leading to microthrombus formation.

D) Altered neurotransmission, excitotoxicity by increased glutamate, and hypoxic injury contribute to neuronal dysfunction and loss.

E) Neuropsychiatric symptoms such as attention deficits, cognitive defictics, depression, psychosis, seziures, anxiety, suicidal behavior [7].

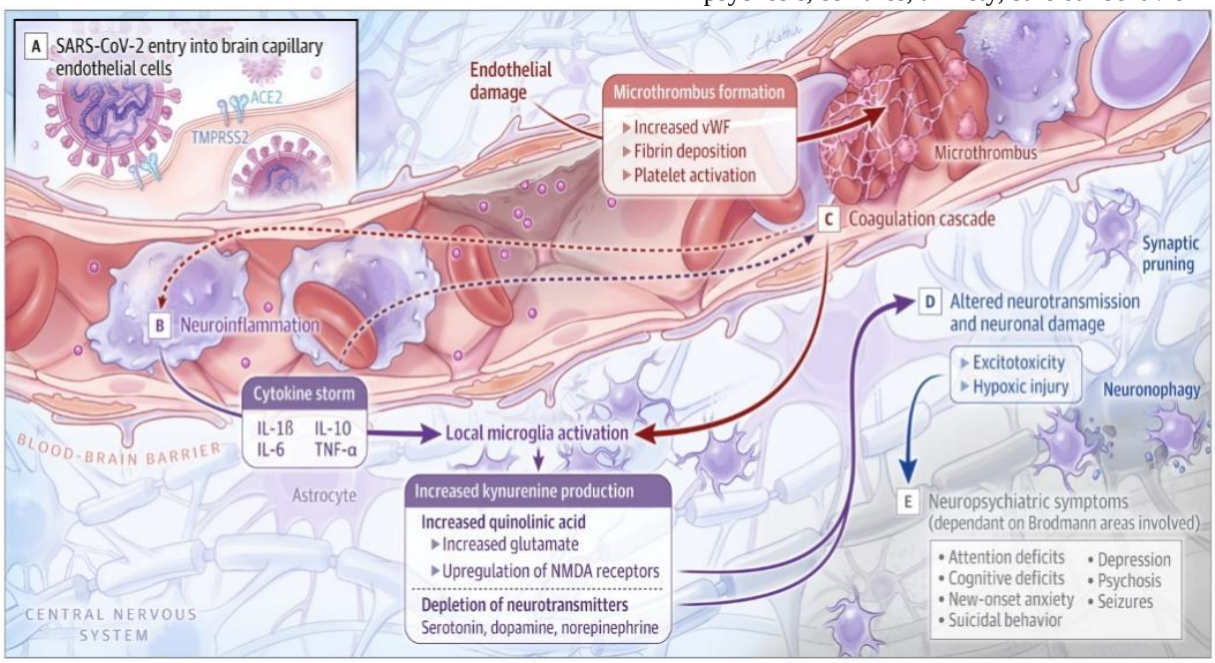

Fig.1: Brain Vascular Injury, Neurotransmitter System Dysfunction, Thrombotic Events, Neuronal Damage, and Neuropsychiatric Symptoms[7].

Potential Routes of Brain Entry:

Examination of how the virus could enter the nervous system may help assess the likelihood for direct invasion and pathogenicity. Based on other coronaviruses, several potential routes of entry for SARS-CoV-2 have been proposed [8].

Olfactory Route:

SARS-CoV-2 is known to penetrate the olfactory mucosa, causing loss of smell which is a frequent neurological manifestation in COVID-19 and with evidence of increased MRI signal in the olfactory cortex suggestive of infection. SARS-CoV-2 may enter the brain, migrating from the cribriform plate along the olfactory tract or through vagal or trigeminal pathways. The virus could be internalized in nerve terminals by endocytosis, transported retrogradely, and spread *trans*-synoptically to other brain regions, as described for other coronaviruses SARS-CoV-2 could pass the blood-brain barrier (BBB) because inflammatory cytokines induce BBB instability or via monocytes. It could reach brain tissue via circumventricular organs (CVOs), midline structures around the third and fourth ventricles that monitor blood and cerebral spinal fluid content via capillaries expressed in the BBB. Viral RNA was detected by reverse transcription–polymerase chain reaction in medulla and cerebellum. SARS-CoV-2 protein has been found in brain vascular endothelium but not in neurons or glia. Thus, detected viral RNA may represent contamination by vasculature in leptomeninges and Virchow-Robin spaces. Histopathologic analysis of whole human brain showed microglial nodules and phagocytosis of neurons (neuronophagia) in brain stem and less frequently in cortex and limbic structures, associated with sparse lymphocytic infiltration, and no correlations between histopathologic findings and levels of viral messenger RNA in the same brain. While ageusia, nausea, and vomiting may be related to CVO and brain stem viral invasion, other short-term and long-lasting NPs are more likely due to neuroinflammation and hypoxic injury. Brain stem involvement may explain persistent autonomic abnormalities and anxiety [8].

Blood-Brain Barrier

The blood-brain barrier (BBB) is a common route of entry of blood-borne viruses into the brain. In COVID-19, dissemination of the virus into the blood has been described and the virus could access the brain by crossing the BBB. Crossing the intact BBB would require internalization and transport of the virus across the cerebral endothelium, in which the expression of SARS-CoV-2 docking proteins remains unclear. SARS-CoV-2-associated cytokines, including interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF), and IL-17 disrupt the BBB and could facilitate the entry of the virus. SARS-CoV-2 has been postulated to induce endothelial infection and inflammation in peripheral vessels, but direct evidence in cerebral endothelial cells has not been thus far provided. Comorbidities often seen in COVID-19, including cardiovascular risk factor or pre-existing neurological diseases, could, alone or in combination with cytokines, increase BBB permeability. SARS-CoV-2 could also enter the brain through the median eminence of the hypothalamus and other circumventricular organs, brain regions with a leaky BBB due to openings (fenestrae) in the capillary wall. Although the size of the viral particle (80–120 nm) is larger than endothelial fenestrae, preliminary data suggest that median eminence capillaries and tanycytes express ACE2 and TMPRSS, which could allow virus entry into the hypothalamus. Owing to its widespread connection, the hypothalamus could serve as a gateway to the entire brain [8].

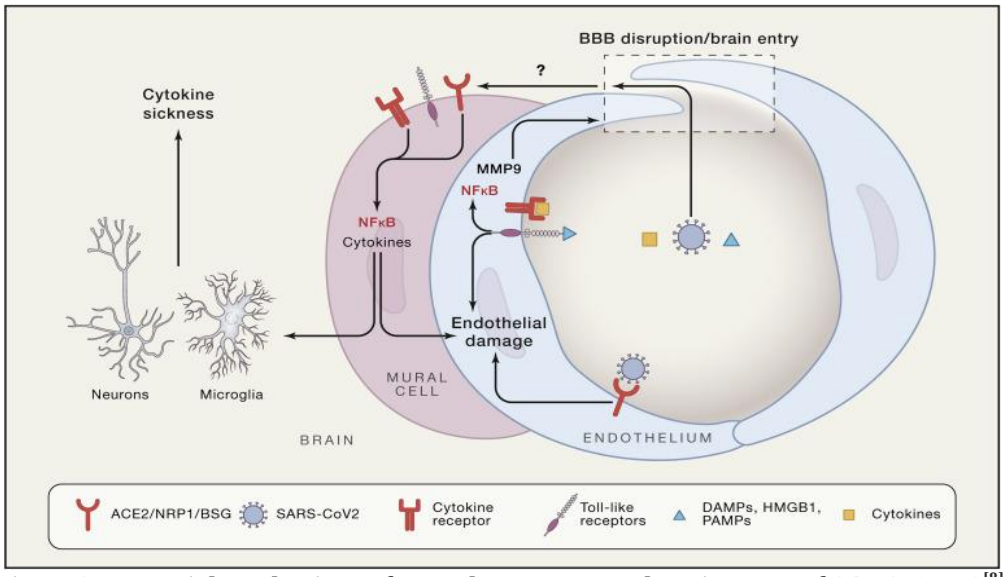

Figure 2: Potential Mechanisms of Vascular Damage and Brain Entry of SARS-CoV-2[8].

Cytokines and Microglia Activation Lead to Neurotoxicity:

Circulating virus, cytokines, DAMPs, and PAMPs could act on endothelial cells, leading to inflammation and opening of the BBB. Once in the perivascular space and these factors could induce inflammation in vascular mural cells and brain resident myeloid cells (microglia and macrophages). The resulting cytokine production could affect neuron neuronal function leading to the cytokine sickness, a potential cause of encephalopathy in COVID-19.Patients with severe COVID-19 infection have been reported to experience a severe cytokine storm, with increased serum levels of proinflammatory cytokines including interleukin (IL) 1, IL-6, IL-10, and tumor necrosis factor (TNF)-α. TNF-α can directly cross the BBB by transport (increased BBB permeability due to cytokine-induced damage) or CVOs. Once across the BBB, cytokines activate microglia and astrocytes.In addition to phagocytising damaged cells, activated microglia secrete inflammatory mediators, including glutamate, quinolinic acid, ILs, complement proteins, and TNF-α.Increased quinolinic acid results in higher glutamate and upregulation of NMDA receptors, possibly inducing altered learning, memory, neuroplasticity, hallucinations, and nightmares. Excitotoxicity and neuronal loss result in region- and neurotransmitter-specific NPs [9].

Inflammation:

Increased inflammation activates the enzyme indoleamine dioxygenase, which metabolizes tryptophan to kynurenine rather than serotonin. Reduced neurotransmitter release was

demonstrated in patients treated with interferon alfa who exhibited increased positron emission tomography fluorodopa F uptake and decreased turnover in caudate and putamen, which correlated with depression and fatigue severity. Similarly, interferon- or IL-based immunotherapy can induce depression. Inflammation leads to blunted monoamine neurotransmission, anhedonia, negative cognitive, psychomotor and neurovegetative symptoms, depression, and suicidal behaviour, which poorly respond to conventional antidepressants [10].

Infiltration of Infected Immune Cells:
Viruses can enter the brain carried by infected immune cells, which can also serve as reservoir. Monocytes, neutrophils, and T cells traffic into the brain through the vasculature, the meninges, and the choroid plexus, and these sites could be entry points for infected immune cells. SARS-CoV-2 nucleocapsid protein (NP) immunoreactivity was observed in $CD68^+$ cells in lymphoid organs, while single-cell RNA sequence data showed viral RNA in macrophages in bronchoalveolar lavage of COVID-19 patients. However, it remains unclear if this is due to actual virus propagation in macrophages or to phagocytic uptake of virus infected cells or extracellular virions. Furthermore, several autopsy series have revealed a notable lack of immune cell infiltration [8].

Indirect Brain Effects of Systemic Factors:
Several major organs are targeted by COVID-19 resulting in life threatening systemic complications.

Lung Damage and Respiratory Failure:
The lung is the organ most affected in COVID-19, with massive alveolar damage, edema, inflammatory cell infiltration, microvascular thrombosis, microvascular damage, and hemorrhage. SARS-CoV-2 has been detected mainly in pneumocytes and epithelial progenitors. The respiratory failure resulting from lung damage leads to severe hypoxia (acute respiratory distress syndrome [ARDS]) requiring assisted ventilation [11].

Systemic Inflammation and Immune Dysregulation:
A key feature of COVID-19 is a maladaptive immune response characterized by hyperactivity of innate immunity followed by immunosuppression. Improvement of T cell function coincides with remission of symptoms and declining viral loads, attesting to the link between immuno-suppression and disease severity. In patients with severe disease, the cytokine release syndrome can develop. Most COVID-19 patient's exhibit increased circulating levels of IL-6, IL-1β, and TNF, as well as IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP1, and MIP1α2, and serum levels of IL-6 and TNF reflect disease severity. Even in the absence of SARS-CoV-2 brain invasion, viral proteins shed in the circulation and molecular complexes from damaged cells, such as the nuclear protein high mobility group box 1 (HMGB1), could enter the brain through a compromised BBB. After brain entry, these molecules could act as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patters (DAMPs), and induce an innate immune response in pericytes, brain-resident macrophages, and microglia, which express toll-like receptors (TLR). TLR2 mediates the pro-inflammatory effects of SARS-CoV spike protein on human macrophages through nuclear factor κB (NF-κB). Such innate immune response increases cytokine production and impair brain function [12].

Hypercoagulable State:
Another key feature of COVID-19 is a profound coagulopathy responsible for some of the most frequent and harmful complications of the disease. COVID-19 coagulopathy is characterized by a distinctive pro-coagulant state with increased cloth strength, increased D-dimers (fibrin breakdown products indicative of intravascular thrombosis), and increased fibrinogen, without significant changes in the number of platelets or prolongation of clotting time parameters.Virus entrance into endothelial cells of brain vasculature activates neutrophils, macrophages, thrombin production, and complement pathways, promoting microthrombi deposition. Moreover, the complement cascade mediates synaptic pruning by microglia following viral infections.Coagulopathy and thrombosis may start in the lungs and other infected organs with endothelial damage, complement activation, the procoagulant action of IL-6, and neutrophilrecruitment. In turn, neutrophils release extracellular traps (NETs) in COVID-19, a lattice of chromatin and histones that activatesclotting, which contributes to intravascular thrombosis by trapping cells and platelets in many organs including the brain [13].

Systemic Organ Failure:COVID-19 also damages other organs. Metabolic and pathological evidence of damage to the kidney, heart, liver, gastrointestinal tract, and endocrine organs has been provided. The resulting systemic metabolic changes, including water and electrolyte imbalance, hormonal dysfunction, and accumulation of toxic metabolites, could also contribute to some of the more non-specific nervous

system manifestations of the disease, like confusion, agitation, headache, etc. Cardiac involvement could impact the brain by reducing cerebral perfusion and could be an embolic source leading to ischemic strokes [14].

Neurological Manifestations of COVID 19:

Covid infection can induce multi-system failure, resulting in systemic edema, electrolyte imbalance, hormonal dysfunction, and toxic metabolite accumulation, all of which are thought to cause neurological symptoms like headaches, confusion, agitation, muscle and joint pain, weariness, and "brain fog," as well as a loss of taste and smell, which can linger for weeks or months following infection. COVID-19 can also cause encephalitis or stroke in severe situations[14].

SARS-CoV-2 can invade and damage susceptible organs expressing ACE2 receptors either by direct infection or immune-mediated mechanism via cytokine storm, leading to manifestations resulting from central, peripheral, and autonomic nervous system involvement, either early or later in the course of COVID-19 illness[15].

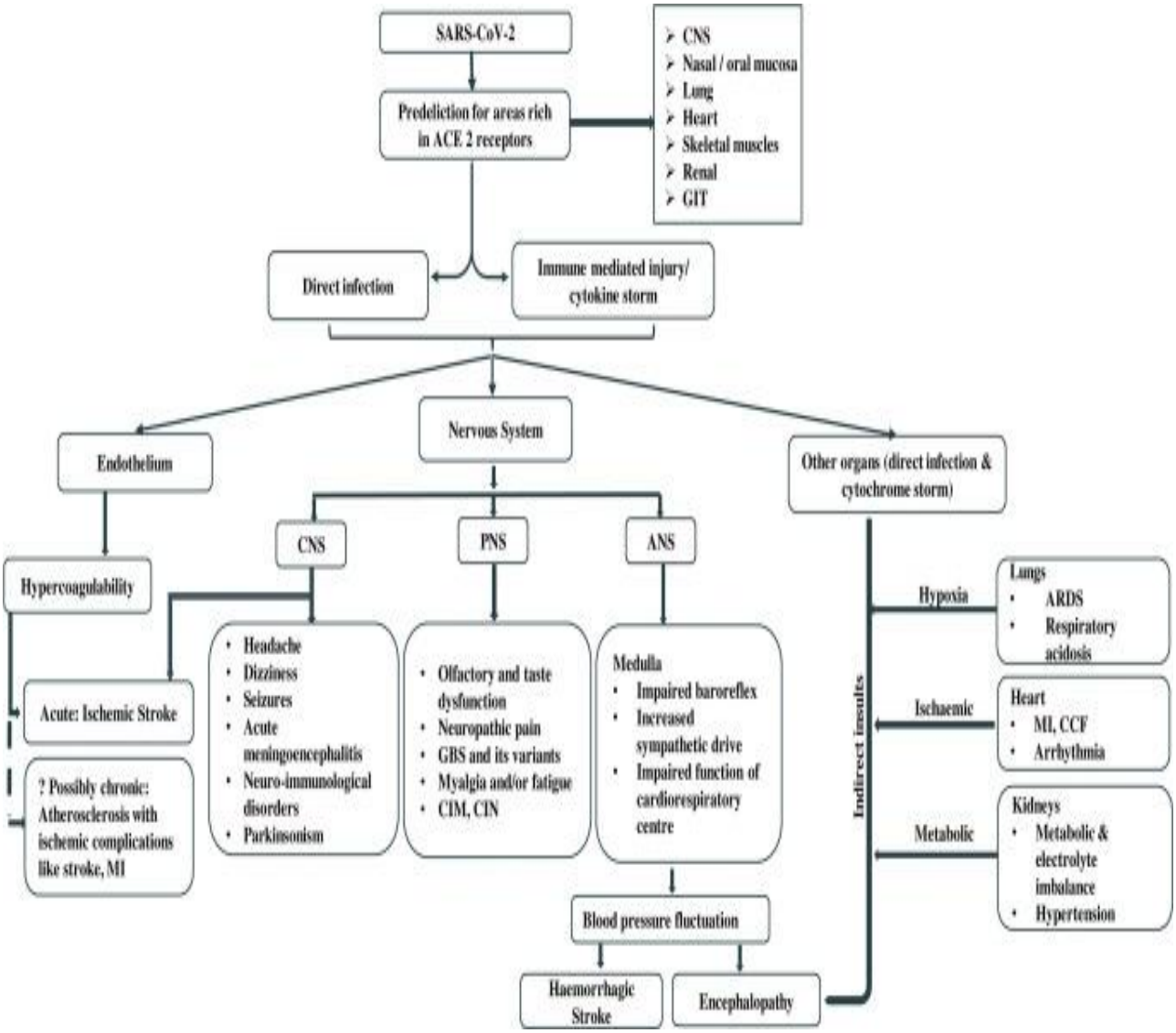

Figure 3: Possible pathophysiological effects and resulting neurological manifestations of SARS-CoV-2[15] .

Central Nervous System Involvement:
Central nervous system (CNS) manifestations involve common non-specific symptoms include headache, and altered mentation, several CNS syndromes including meningoencephalitis, cerebrovascular events, seizures, and CNS neuro-immunological disorders[16].

Headache:
Most cases describe headache due to COVID-19. Its pathophysiology and character may differ according to phase of COVID-19 illness. While acute headache related to flu-like illness, migraine, and tension-type headache predominate in initial days of illness, headache resulting from hypoxia and systemic inflammation due to cytokine storm may occur later in the course. Headache may also be a sentinel sign in COVID-19-related meningitis and venous sinus thrombosis. Interestingly, presence of headache in patients with COVID-19 pneumonia has been associated with a shorter course of non-neurological systemic illness, but disabling headache often persisted [17].

Altered mentation:
Impairment in the level or content of consciousness may involve up to 9% of hospitalized COVID-19 patients, especially severe cases. Various factors contributing to altered mentation in COVID-19 include toxic-metabolic encephalopathy resulting from cytokine storm with systemic hyperinflammation, cerebrovascular events, seizures, para- or postinfectious immune-mediated CNS syndromes and a possible CNS infection by SARS-CoV-2. In addition, new-onset immune-mediated psychotic symptoms have also been described in COVID-19 cases [18].

Neuroinflammatory disorders:
CNS neuroinflammatory lesions, include encephalitis, meningoencephalitis, and encephalomyelitis, with variable prevalence [19].

Infectious toxic encephalopathy:
Acute toxic encephalitis, also known as infectious toxic encephalopathy, is a type of reversible brain dysfunction syndrome induced by factors such as systemic toxaemia, metabolic abnormalities, and hypoxia during the acute infection process. Cerebral edoema is one of the most common clinical alterations in this condition, with no evidence of inflammation found in the CSF fluid. It has a wide range of clinical signs. Headache, dysphoria, mental instability, and delirium may occur in patients with a mild course of the disease Acute viral infection, such as a respiratory infection caused by CoV, is another key cause of this condition. COVID-19 patients frequently experience acute hypoxia and viremia, which can lead to toxic encephalopathy. Furthermore, nearly 40% of COVID-19 patients have headache, altered awareness, and other signs of brain dysfunction, and an autopsy investigation revealed that oedema was found in COVID-19 patients' brain tissue. Overall, these findings support the hypothesis that COVID-19 can induce infectious toxic encephalopathy, albeit more research is needed [20].

ACUTE DISSEMINATED ENCEPHALOMYELITIS:
Acute disseminated encephalomyelitis (ADEM) is a CNS inflammatory demyelinating disorder with fulminant multifocal neurologic damage and unique neuropathology features. ADEM is traditionally assumed to be preceded by vaccination or a systemic infection, the most prevalent of which are upper respiratory tract infections. ADEM typically results in a monophasic demyelinating episode with an immediate start of neurological symptoms based on which part of the SNC is affected, as well as encephalopathy, which can quickly deteriorate. The radiological features of ADEM can range from punctate to large lesions, affecting the periventricular and subcortical white matter, as well as the grey matter, including the cortex, basal ganglia, and thalamus. According to the leading idea, myelin antigens and the virus that causes ADEM have antigenic similarities [21].

It is diagnosed by performing Complete blood count, blood and cerebrospinal fluid cultures, serological (antibody) studies on blood and CSF to detect bacterial and viral organisms. A lumbar puncture is also performed to evaluate for evidence of inflammation in the cerebrospinal fluid (CSF). MRI of the brain and spine.

Early treatment of ADEM with large doses of steroids (methylprednisolone 500 mg IV daily for 5–7 days in adults) [22].

Coagulopathies:
Severe COVID-19 is associated with a severe coagulopathy. Coagulopathies are significant negative variables in patients with severe COVID-19, and they are invariably linked to poor outcomes. Elevated prothrombin time, elevated D-dimer level, and mild thrombocytopenia are the hallmark coagulopathy anomalies in COVID-19, however there is no hypofibrinogenemia. In COVID-19, DIC is the most

severe form of coagulopathy. Thrombocytopenia, a prolonged prothrombin time, and increased D-dimer and substantially raised D-dimer are all symptoms of DIC. COVID 19 coagulopathies increase the risk of stroke and other thrombotic events [23].

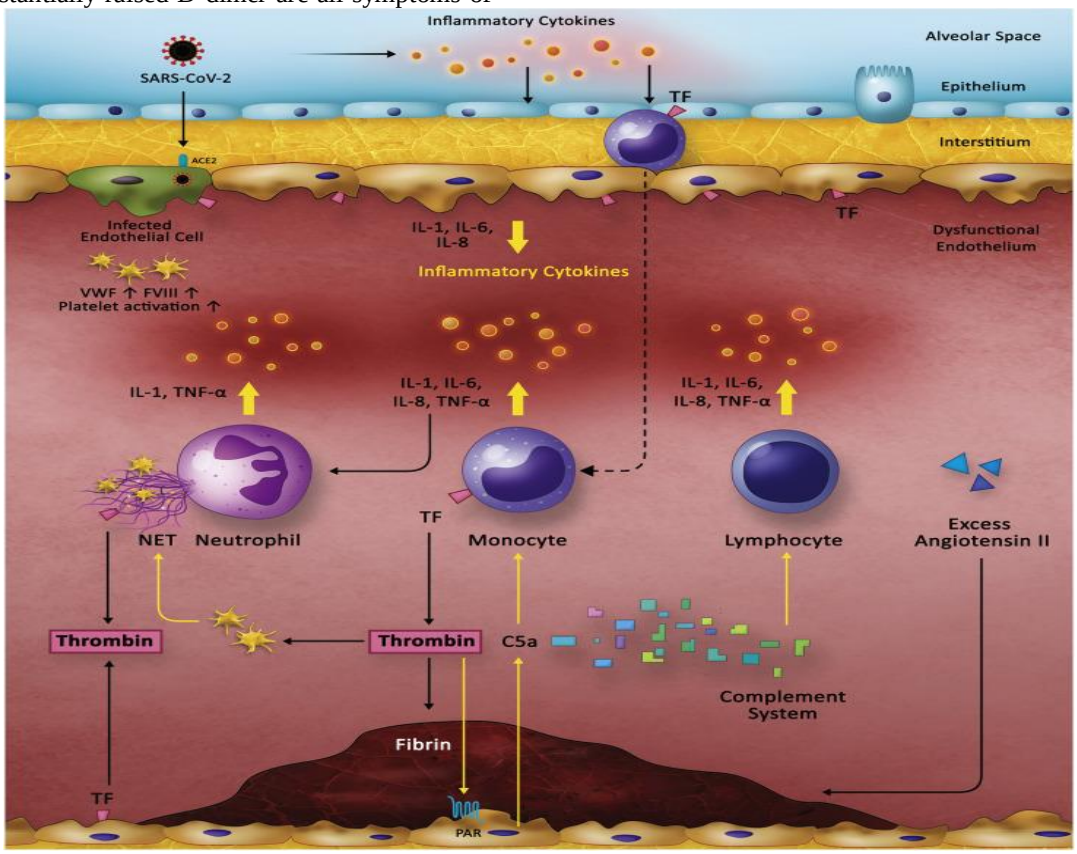

FIGURE: Pathophysiology of the Hypercoagulable State in COVID-19[23].

It is diagnosed by performing patients tests for haemostasis function and platelet count, evaluation of coagulation markers, elevated D-dimer level (for example, 3-4 fold increase in D-dimer levels over normal range), Prolonged prothrombin time (PT) , platelet count < 100 × 10^9/L, fibrinogen < 2 g/L, consider evaluating for DIC using ISTH DIC score, if score of< 5, DIC is unlikely[24].

The **treatment for** patients with COVID-19 who develop coagulopathy

- Consider prophylactic dose LMWH, abnormal coagulation results (prolonged PT or activated partial thromboplastin time) do not require correction in patients who are not bleeding.
- If coagulopathy worsens, blood products should be administered.
- in patients who are not bleeding, goal is to maintain platelet count > 25 × 10^9/L
- In patients who are bleeding, goal is to maintain platelet count > 50 × 10^9/L, fibrinogen > 1.5 g/L, PT ratio < 1.5 (not same as INR).

Management of bleeding:

- if platelet count is < 50 × 10^9/L, consider platelet transfusion (1 adult dose)
- if INR is > 1.8, consider fresh frozen plasma (4 units)
- if bleeding continues and fibrinogen level is < 1.5 g/L, consider cryoprecipitate (10 units) or fibrinogen concentrate (if approved for use) usually given at dose of 4 g
- in patients with severe bleeding, consider 4-factor prothrombin complex concentrate (for example, 25 units/kg) instead of plasma to reduce increase in volume status, which may be associated with respiratory compromise.

Cerebrovascular events -STROKE:

In multiple studies, stroke has been linked to infection with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[25].COVID-19 can induce strokes by causing blood clots and vascular damage to the body's veins, capillaries, and arteries,

even in young healthy persons who do not have the typical risk factors for stroke[26].

Ischemic and haemorrhagic arterial stroke, cortical venous sinus thrombosis (CVST), as well as intracranial vasculitis-induced microvascular occlusive disorder have been reported in COVID-19 cases, with ischemic stroke being most common. Stroke commonlyaffects elderly patients with severe COVID-19 illness along with vascular risk factors including hypertension, diabetes, and prior stroke. Although ischemic strokeusually appears later in the course of COVID-19 illness with a mean duration being 12 days, early occurrence has also been reported. COVID-19-related ischemic stroke often result from large vessel occlusion and may be multii-territorial. They likely present in the second week of infection with no sex predilection, with headache being the most common symptom followed by focal neurological deficit. Neuroimaging shows non-arterial infarct or haemorrhage.

Increased risk of arterial ischemic stroke in SARS-CoV-2 infection suggests a pro-coagulant state, which may result from either blood flow stasis, especially in critically ill and immobilized patients or due to hypercoagulability and direct endothelial damage via ACE-2 receptors.

A highly elevated C-reactive protein (CRP) and D-dimer in COVID-19 patients suggest hyperinflammation and hypercoagulable state, respectively. This in turn stimulates endothelial and mononuclear cells and facilitates tissue factor expression leading to excess free thrombin generation, which results in platelet activation and thrombosis. Thrombocytopenia along with raised CRP and D-dimer in COVID-19-associated stroke cases suggest possibility of underlying virus-associated microangiopathy. Significantly, elevated D-dimer and fibrin degradation product (FDP) along with prolonged PT and APTT on admission suggest poor survival in COVID-19 pneumonia.

ACE2 receptors in circumventricular organ and endothelial cells are essential in modulating cerebral autoregulation, cerebral blood flow, and central autonomic activity. Neuroinvasion of SARS-CoV-2 at these locations may disrupt cerebral autoregulation leading to blood pressure fluctuations resulting in intracerebral and/or subarachnoid hemorrhage reported in COVID-19 cases. Additionally, hyperinflammatory state resulting from cytokine storm along with sympathetic over activity may lead to aneurysm formation and/or trigger its rupture.

Brain MRI showed multiple areas of restricted diffusion along with scattered hypointensities in sequence. CSF was positive for SARS-CoV-2 RNA. This might have resulted from a systemic pro-coagulant state along with local and systemic inflammation–related endothelium damage and eventual immune-mediated vascular injury[27].

Diagnostic imaging of some COVID-19 patients reveals alterations in the white matter of the brain, which contains the long nerve fibres, or "wires," that carry information from one brain region to another. These alterations could be caused by a lack of oxygen in the brain, the immune system's inflammatory reaction to the virus, blood vessel injury, or leaky blood vessels. People with COVID-19 may experience cognitive impairments as a result of this "diffuse white matter illness." Diffuse white matter disease is common in people who need intense medical treatment, but it's unclear if it also happens in people who have a mild to moderate COVID-19 infection[28]. Strokes are diagnosed by performing physical tests and studying images of the brain produced during a scan. Brain scans which includes CT scan and MRI scan, Swallow tests, heart and blood vessels tests, carotid ultrasound scan, and echocardiography.

Strokes are usually treated with medication. This includes medicines to prevent and dissolve blood clots, reduce blood pressure and reduce cholesterol levels. In some cases, procedures may be required to remove blood clots. Surgery may also be required to treat brain swelling and reduce the risk of further bleeding if this was the cause of stroke. The following are the drugs to treat Stroke.

Thrombolytics: Alteplase (within 4-5 hrs), Aspirin and other **Antiplatelets:** clopidogrel, dipyridamole, **Anticoagulants:** warfarin, apixaban, edoxaban, rivaroxaban, **Thiazide diuretics, ACE inhibitors, Beta blockers, Calcium channel blockers,**
Statins (Rhabdomyolysis is observed in this categorical action of drugs given in the treatment) [29].

SEIZURES:
Seizures and/or status epilepticus (convulsive or non-convulsive) appears likely as SARS-CoV-2 may involve CNS either directly or indirectly related to hypoxia, metabolic and electrolyte imbalances. Few reports describe clinical or electrophysiological

evidence of new onset seizures or new-onset refractory status epileptics (NORSE) in COVID-19 patients, but larger studies failed to detect additional risk of acute symptomatic seizures. Breakthrough seizures are commonly reported in epileptic patients developing COVID-19. Reduced seizure threshold in COVID-19 patients may appear even in absence of overt inflammatory features, resulting in new-onset seizure or status epilepticus or reappearance of well-controlled seizures.

Seizures and epilepsy are among the complications that the virus can produce in the nervous system. The cytokine storm triggered by either the influx of pro-inflammatory cytokines from the periphery into the CNS or the synthesis of these cytokines by activated microglia is the principal cause of Covid-19's devastating effects in the central nervous system. In Covid-19 patients, secondary seizures can occur as a result of strokes, electrolyte imbalances, increased oxidative stress, and mitochondrial dysfunction. To prove the specific mechanism of seizures in Covid-19 patients, more research is needed.

A test to check brain activity called an electroencephalogram (EEG), or a brain scan to look for any problem in the brain. Brain scan mainly MRI scan and electroencephalogram (EEG)[30].
Seizures are treated with medicines called anti-epileptic drugs (AEDs) they are Sodium Valproate, Carbamazepine, Topiramate, Levetiracetam, Lamotrigine, surgery to remove a small part of the brain that's causing the seizures, a procedure to put a small electrical device inside the body that can help control seizures, special diet (ketogenic diet) that can help control seizure[31].

PERIPHERAL NERVOUS SYSTEM:
COVID-19 can impact the PNS even before the pneumonia clears up, making it a candidate for acute polyradiculoneuropathy.
The involvement of the PNS could be due to SARS-dysregulation CoV-2's of the systemic immune response. In COVID-19 patients, a systemic hyper-inflammation with macrophage activation syndrome has been hypothesised, also termed as secondary hemophagocytic lymphohistiocytosis. These immune-mediated signs usually appear after the infection's acute phase has passed [32].

Loss of smell/taste sensation:
Studies shown the prevalence of smell disorder. Additionally, assessed the prevalence of taste disorder. The olfactory dysfunction appeared before, in unison, and after the appearance of general symptoms respectively. In a study majority of patients with olfactory dysfunction reported that the onset of the olfactory dysfunction occurred at the same time or immediately after the onset of their other COVID-19 symptoms [33].

Guillain-Barré syndrome and its variants:
Indirect immune-mediated processes, such as molecular mimicry and neuroinflammation, may play a larger role in the development of COVID-19-related GBS than direct viral invasion. In addition, more molecular research is needed to determine the exact mechanism that causes GBS after SARS-CoV-2 infection [34].
To summarise, whereas multiple studies have found a correlation between SARS-CoV-2 infection and GBS, further data is needed to confirm the link and describe the exact mechanism. To approve the relationship between COVID-19 and GBS, epidemiological evidence related with the suspected infectious agent and GBS should be evaluated. However, based on recent reports, we recommend that in the present pandemic, all newly diagnosed Guillain-Barré cases be tested for SARS-CoV-2 infection, even if they have no respiratory symptoms [35].

Most variations of GBS are treated likewise with IVIG (intravenous immune globulin) or PE (plasma exchange). The related condition, is likewise treated with Plasma exchange and intravenous immune globulin be that as it may, in contrast to GBS, it additionally reacts to CORTICOSTEROIDS: like methyl prednisone 8 mg, Flagyl 500mg, Moxifloxacin 400mg, Solumedrol 1g [35].

Skeletal muscle manifestations-
Myalgia and Myositis:
Myalgia is a symptom of muscle pain and discomfort caused by a systemic or local infection. It's more prone to create referred pain because it's diffuse rather than localised. Patients with COVID-19 experience muscle complaints exhibited greater CK and LDH levels than those who did not. A skeletal muscle damage could induce myalgia. SARS-CoV-2 may bond with ACE2 to infect skeletal muscle, as ACE2 is found in skeletal muscle. The autopsy results of SARS-CoV-infected patients, on the other hand, revealed no evidence of SARS-CoV infection in skeletal muscle. As a result, more research into the mechanism is required. Second, cytokines can cause myalgia by stimulating the production of prostaglandin E2, which mediates pain via peripheral pain receptors. Furthermore, skeletal muscle injury is a symptom of nervoussystem

impairment. SARS-CoV-2 can enter the central nervous system through peripheral nerves or target the nervous system directly by binding to ACE2 and causing skeletal muscle damage [36].

The condition is treated by the following ways:

- Morphine and fentanyl have been observed to be the most immunosuppressive among others.
- Buprenorphine appears to be the safest for elderly patients who are prone to infection.
- Anti-inflammatory drugs:Ibuprofen is used.
- Corticosteroid:Methyl prednisone 8mg[36].

CRANIAL NERVES IMPAIRMENT:[37]

The involvement of cranial nerves in the context of COVID-19 infection is not uncommon, and it could be linked to GBS. The cranial nerves VII, VI, and III are the most commonly affected, resulting in hypogeusia/ageusia, facial palsy, or ophthalmoparesis. COVID-19 is usually modest in individuals with accompanying cranial nerve involvement, however involvement of cranial nerves, particularly GBS, may be ignored in patients with severe COVID-19 who require mechanical breathing. In COVID-19 individuals with isolated cranial nerve involvement, CSF studies are normally normal, but in patients with GBS and simultaneous cranial nerve involvement, CSF investigations indicate dissociation cyto-albuminique (DCA) or positive oligoclonal bands (OCB).

The pathogenesis of cranial nerve involvement is unknown, although it is possible that cranial nerve involvement is caused by virus absorption into the intracellular space of neurons at a distal region, followed by retrograde virus particle transit to the brain. Experimental findings show that SARS-CoV-2 migrates backwards into the CNS through cranial nerve axons.

Steroids are beneficial in the majority of cases with isolated cranial nerve involvement, whereas IVIG is beneficial in GBS cases with cranial nerve involvement. In isolated cases, the outcome is usually favourable, with more patients achieving total recovery than partial recovery. Patients with GBS who have cranial nerve involvement, on the other hand, are more likely to have a partial recovery rather than a complete recovery.

Recently, it was hypothesised that cranial nerve stimulation could be used to treat COVID-19. Transcutaneous, non-invasive vagal nerve stimulation has been demonstrated to enhance lung function in patients with severe COVID-19 who are on mechanical ventilation [37].

AUTONOMIC NERVOUS SYSTEM INVOLVEMENT

IMMUNE DYSREGULATION:

The HPA Axis' Potential Role in COVID-19 Immune Dysregulation:

The entry of cytokines and SARS-CoV-2 into the hypothalamus' median eminence could activate the autonomic nervous system, causing the release of adrenal catecholamines and hormones. As with stroke, brain trauma, and myocardial infarction, these neurohumoral effectors may operate on the bone marrow, causing immunosuppression and lymphopenia by releasing immunosuppressor neutrophils and myeloid cells (emergency myelopoiesis), as described in COVID-19. Furthermore, the release of calprotectin and cytokines from damaged lungs may aid in emergency myelopoiesis.

TREATMENT:

The addition of Tocilizumab 8mg/kg, a selective IL-6 pathway blocker, partially restored HLA-DR expression on monocytes in all individuals with immunological dysregulation [38].

CYTOKINE STORM:

Another mechanism implicated in the neurological signs of covid infection is cytokine storm. The term "cytokine storm" refers to inflammation that is dysfunctional, uncontrolled, and ongoing. Acute respiratory distress syndrome, renal failure, cardiac injury, the severity of the illness, the need for intensive care unit admission, the need for mechanical ventilation, and mortality are all consequences of this. Inflammatory markers like C-reactive protein and leukocytes confirm that a cytokine storm is present. There has been a report of widespread CNS disease, but a temporal link between inflammatory indicators and CNS impairment has yet to be established. It is known, however, that the production of interleukin-6 induces vascular leakage and activation of complement and coagulation cascades; also, patients with severe covid infection have increased levels of D-dimer, which is a hallmark of a hypercoagulable condition and endogenous fibrinolysis. These could be the causes of acute cerebrovascular illness. Arthralgia can also be caused by a cytokine strom.

The condition is treated by several ways , they are as follows:

IL-6 Inhibition- Tocilizumab (TCZ) -8 mg/kg is a recombinant humanized anti-human IL-6 receptor

monoclonal antibody, preventing IL-6 binding to its receptor to exert the immunosuppression promoted by IL- 6.
Glucocorticoid therapy is used. - PD-1 Checkpoint-Inhibitor: Nivolumab 240 mg/14 days
Intravenous Immunoglobulin (IVIG)
Antimalarial: Hydroxychloroquine (HCQ)6.5mg/ kg (maximum dose -400 mg), Artesunate 2.4mg/kg reduces the expression of TLR2 mRNA and Nod2 mRNA that upregulated by S. aureus/MRSA and also inhibits the activation of NF-κB, artesunate attenuated the release of TNF-α and IL-6 from macrophages by inhibiting TLR4-mediated autophagic activation [39]

CONCLUSION:

In conclusion, the neurological manifestations of COVID-19 constitute a major public health challenge not only for the acute effects on the brain, but also for the long-term harm to brain health that may ensue. These delayed manifestations are anticipated to be significant, because they are likely to also affect patients who did not show neurological symptoms in the acute phase. Therefore, clinical and laboratory efforts aiming to elucidate the mechanisms of the acute effects on the brain of SARS-CoV-2 need to be coupled with investigations on the deleterious delayed neuropsychiatric sequelae of the infection. These efforts should be driven by a close cooperation between clinical and basic scientists and take advantage of the wealth of clinical-epidemiological data and biological specimens that are accumulating worldwide. Considering that COVID-19 is still raging in many countries, including the United States, and there might be a seasonal resurgence of infection, it is imperative that a concerted effort is implemented swiftly and on a large scale [40]

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