



NEUROLOGICAL MANIFESTATIONS OF COVID-19: A SYSTEMATIC REVIEW

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ABSTRACT

The commonest symptoms of infection with Covid-19 are related to the respiratory system. Yet, there have been reports that COVID-19 patients had neurological manifestations as well and the incidence of these manifestations is rising as the pandemic is on the rise. The neurological symptoms are thought to occur as a part of complications occurring secondary to a systemic disease, as a result of viral infection directly, or as a post-infectious inflammation of the nervous system and its related vasculature. The current review aims to highlight the common neurological presentations seen in Covid-19 patients. It revealed that the commonest manifestations related to the central nervous system include dizziness, headache, impaired conscious level, seizures, acute stroke, encephalitis, ataxia, and Guillain-Barre syndrome. Thus, guiding physicians in ruling out the suspicion of Covid-19 and detecting it earlier, aiding in preventing morbidity and mortality associated with it.

KEYWORDS: Covid-19, SARS-COV2, Neurological manifestations, CNS presentations, and Seizure.

INTRODUCTION

Globally, more than 4.9 million cases and a mortality rate of more than 300,000 deaths have been confirmed of Covid-19 since May, 2020^[1] {can we update it to recent stats}. Since influenza in 1918, the Covid-19 pandemic is considered the largest and the most severe one.^[2] Despite that the respiratory symptoms have been the commonest and the most important clinical presentation of this virus, reports have revealed that neurological manifestations of Covid-19 are increasing as well.^[3] The neurological symptoms are thought to occur as a part of complications occurring secondary to a systemic disease, as a result of viral infection directly, or as a post-infectious inflammation of the nervous systems and its related vasculature.^[4]

Although complications related to the central nervous system are rare in severe acute respiratory syndrome coronavirus (SARS-COV2) and Covid-19, yet the current magnitude of pandemic denotes that even a small percentage of such cases can give rise to a greater proportion.^[5] Literature has shown that in SARS, complications related to the central nervous system

(CNS) have a prevalence rate of 0.04% and for complications related to the peripheral nervous system (PNS), the rate of prevalence has been 0.05%.^[1] Niazzkar et al. (2020) revealed that around 35% of patients who suffer from Covid-19 have neurological issues and some individuals suffering from it may present initially with neurological features alone.^[6] In patients with a severe lung infection, there may be increased neurological problems as a result of hypoxic injury to the brain areas.^[7]

The majority of the literature that is available on the neurological manifestations of Covid-19 is based on case reports and a limited number of case series.^[8] Hence, it is difficult to have a correct estimate of the incidence and prevalence of these symptoms.^[9] Another unavoidable problem while interpreting the overall results of these studies is the differences in the methodology.^[10] Therefore, to overcome these issues, further studies are required. The current review aims to highlight the common neurological presentations seen in Covid-19 patients. It will help in guiding treating physicians in ruling out the suspicion of Covid-19 and detecting it

earlier and thus, will help in preventing morbidity and mortality associated with it.

METHODOLOGY

The databases that were reviewed in the literature search included the studies that were published before May, 2021 and included Google Scholar, PubMed, and China National Knowledge Infrastructure (CKNI). Search optimization was done by using keywords such as Covid-19, SARS-COV2, neurological manifestations, Covid pandemic, CNS presentations, and Seizure. For ensuring that the studies met the eligibility criteria, the titles of the studies, their abstracts, and full literature

were screened. Studies (case reports, observational studies, and pre-prints) that were published in the English language and reported the neurological presentations of SARS-COV2 were included in the review. Exclusion of all hypothesis papers, review articles, and those that reported neurological presentations of MERS-CoV and other similar viruses were excluded. The selection of studies for the review is represented in figure 1.

The results of the review were divided into two domains i.e. manifestations related to CNS and manifestations related to PNS.

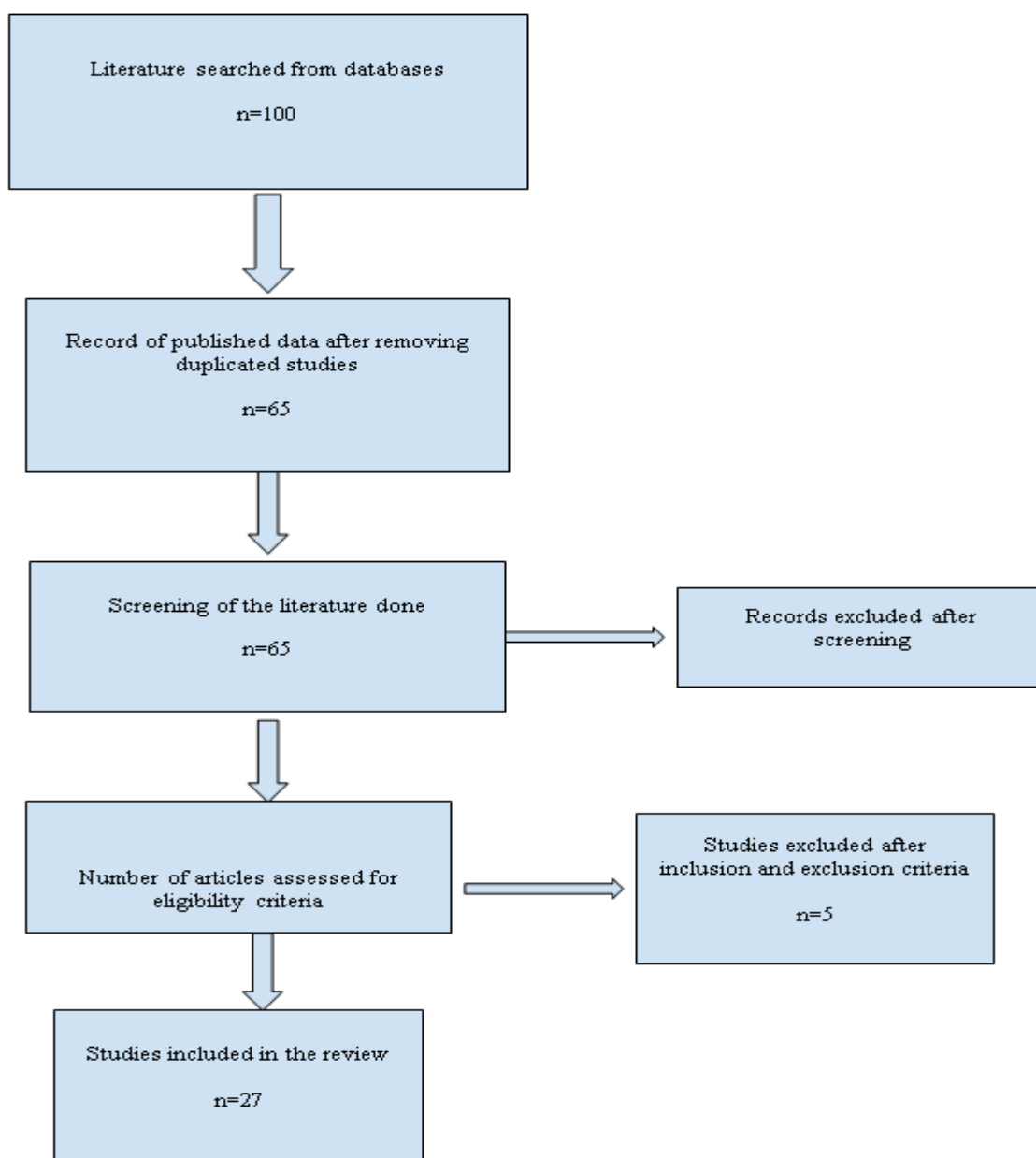


Figure 1: Flow chart showing the process of Screening and Selection of studies for review.

RESULTS

After a thorough screening of the published data, a total of 27 studies were included and reviewed. Table 1 summarizes the studies characteristics that were

involved, i.e. name of author, country, publication year, and neurological symptoms reported. The central nervous system symptoms were more commonly revealed and were reported in 25 out of 27 publications,

whereas symptoms related to the peripheral nervous system were only reported in 7 publications. The commonest manifestations related to the central nervous system were dizziness, headache, impaired conscious level, seizures, acute stroke, encephalitis, ataxia, and

Guillain-Barre syndrome (Figure 2), whereas common manifestations related to the peripheral nervous system in patients who had an infection of Covid-19 were anosmia, hyposmia, and hypogeusia (Figure 3).

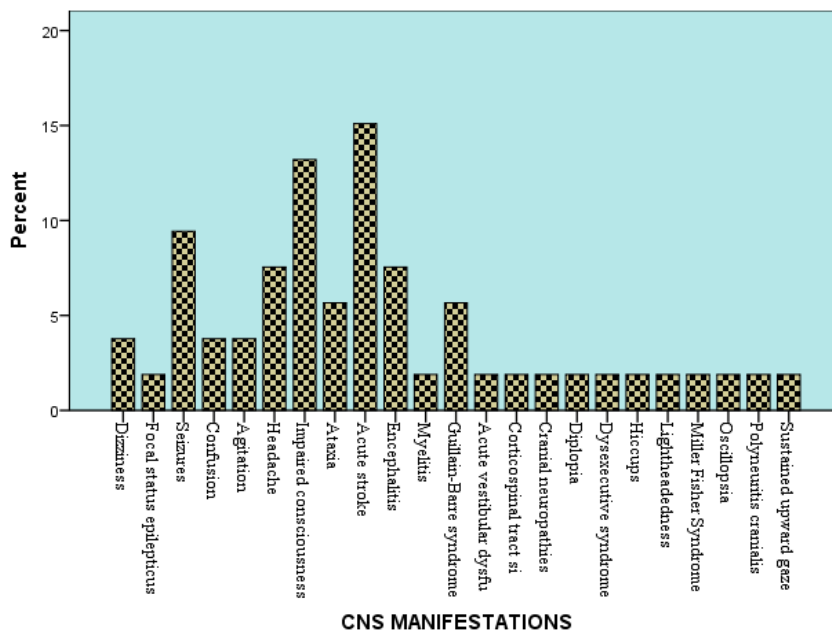


Figure 2: Central nervous system manifestations of Covid-19 Infection.

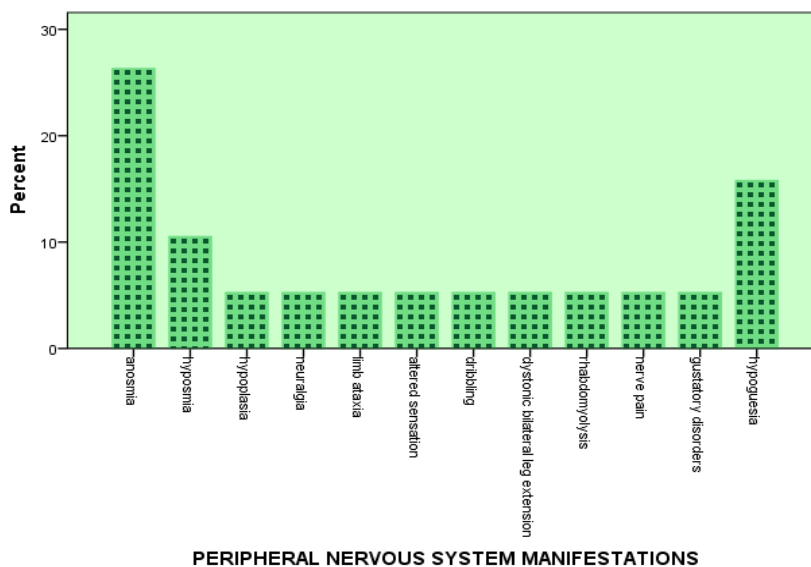


Figure 3: Peripheral nervous system manifestations of Covid-19 infection.

Table 1: Neurological manifestations of covid-19.

Sr. No.	Study author	Type of publication	Country	Neurological manifestations	
				Central nervous system	Peripheral nervous system
1	Azhideh a. (2020) ^[8]	Case report	Iran	<ul style="list-style-type: none"> • Dizziness • Headache • Impaired 	<ul style="list-style-type: none"> • Hyposmia • Hypoplestia • Neuralgia

				<ul style="list-style-type: none"> consciousness ● Acute cva ● Ataxia ● Seizures 	<ul style="list-style-type: none"> ● Hypogeusia
2	Moriguchi t. (2020) ^[10]	Case report	Japan	<ul style="list-style-type: none"> ● Seizures ● Impaired consciousness ● Meningitis/encephalitis 	Na
3	Sohal s. (2020) ^[11]	Case report	United states	<ul style="list-style-type: none"> ● Headache ● Lightheadedness ● Seizures ● Altered conscious level 	Na
4	Wong pf. (2020) ^[12]	Case report	United kingdom	<ul style="list-style-type: none"> ● Ataxia ● Diplopia ● Oscillopsia ● Hiccups ● Rhombencephalitis/myelitis 	<ul style="list-style-type: none"> ● Limb ataxia ● Altered sensation in unilateral arm ● Dribbling while feeding
5	Dugue r. (2020) ^[13]	Case report	New york	<ul style="list-style-type: none"> ● Sustained upward gaze ● Altered consciousness 	Dystonic bilateral leg extension
6	Helms j. (2020) ^[14]	Case series	France	<ul style="list-style-type: none"> ● Agitation ● Confusion ● Corticospinal tract signs (enhanced tendon reflexes, ankle clonus, and bilateral extensor plantar reflexes) ● Dysexecutive syndrome (inattention, disorientation, or poorly organized movements in response to command) 	Na
7	Mao l. (2020) ^[15]	Case series	China	<ul style="list-style-type: none"> ● Dizziness Headache ● Acute cerebrovascular disease Impaired consciousness Ataxia ● Seizures 	<ul style="list-style-type: none"> ● Impaired taste, vision or smell ● Nerve pain
8	Poyiadji n. (2020) ^[16]	Case report	Michigan	<ul style="list-style-type: none"> ● Acute necrotizing encephalitis (ane) 	Na
9	Paniz-mondolfi a. (2020) ^[17]	Case report	New york	<ul style="list-style-type: none"> ● Confusion ● Agitation 	Na
10	Zanin r. (2020) ^[18]	Case report	Italy	<ul style="list-style-type: none"> ● Impaired conscious level ● Seizures 	<ul style="list-style-type: none"> ● Anosmia ● Ageusia
11	Zhang t. (2020) ^[19]	Case report (preprint)		<ul style="list-style-type: none"> ● Acute disseminated encephalomyelitis 	Na
12	Zhao k. (2020) ^[20]	Case report (preprint)		<ul style="list-style-type: none"> ● Acute myelitis 	Na
13	Camdessanche jp.	Case report	France	<ul style="list-style-type: none"> ● Guillain-barré syndrome 	Na

	(2020) ^[21]				
14	Toscano g. (2020) ^[22]	Case series	Italy	<ul style="list-style-type: none"> Guillain-barre syndrome 	Na
15	Zhao h. (2020) ^[23]	Case report	China	<ul style="list-style-type: none"> Guillain-barre syndrome 	Na
16	Gutiérrez-ortiz c. (2020) ^[24]	Case reports	Spain	<ul style="list-style-type: none"> Miller fisher syndrome, Polyneuritis cranialis 	Na
17	Dinkin m. (2020) ^[25]	Case reports	New york	<ul style="list-style-type: none"> Cranial neuropathies 	Na
18	Pellitero se. (2020) ^[26]	Case report	Spain	<ul style="list-style-type: none"> Acute vestibular dysfunction 	
19	Jin qt. (2020) ^[27]	Case report	China	Na	<ul style="list-style-type: none"> Rhabdomyolysis
20	Lechein jr ^[28]	Case series	Belgium, france, italy, spain	Na	<ul style="list-style-type: none"> Anosmia Hyposmia Phantosmia Parosmia Gustatory disorders
21	Avula a. (2020) ^[29]	Case series	United states	<ul style="list-style-type: none"> Acute stroke 	Na
22	Beyrouti r. (2020) ^[30]	Case series	United kingdom	<ul style="list-style-type: none"> Acute stroke 	Na
23	Li y. (2020) ^[31]	Observationa l study	China	<ul style="list-style-type: none"> Acute stroke 	Na
24	Morassi m. (2020) ^[32]	Case series	Italy	<ul style="list-style-type: none"> Acute stroke 	Na
25	Oxley tj. (2020) ^[33]	Case reports	New york	<ul style="list-style-type: none"> Acute stroke 	Na
26	Al saiegh f. (2020) ^[34]	Case reports	United states	<ul style="list-style-type: none"> Acute headache Loss of consciousness Acute stroke 	Na
27	Vollono c. (2020) ^[35]	Case report	Italy	<ul style="list-style-type: none"> Focal status epilepticus 	Na

DISCUSSION

Globally, Covid-19 has become the biggest health concern.^[8] A variety of signs and symptoms may accompany Covid-19 such as fever, flu, cough, chest pain, diarrhea, nausea, vomiting, confusion etc, and few individuals may stay even asymptomatic.^[9] Covid-19 infection is diagnosed by the clinically suspicious symptoms and imaging modalities.^[10] Keeping this in view, a lot of time the clinical picture may yield uncommon findings that may get neglected and patients can be misdiagnosed, which may lead to further spread of the virus as proper containment of such patients is not done.^[11]

Based on the studies conducted, it has been revealed that among patients who have Covid-19 infection, more than one-third have a neurological presentation during the course of infection.^[32] Even few patients may present initially or solely with neurological complaints. Furthermore, patients who have a severe infection with Covid-19, have a higher incidence of neurological

complaints.^[33] The current review revealed that the commonest manifestations related to the central nervous system were dizziness, headache, impaired conscious level, seizures, acute stroke, encephalitis, ataxia, and Guillain-Barre syndrome. Keeping this in view, it is postulated that cerebrovascular diseases are not only the major comorbidities seen in patients with Covid-19, but may also occur as a result of the pathophysiology of Covid-19 in individuals who have associated risk factors.^[36] The risk of cerebrovascular accidents is increased in Covid-19 infection as a result of hyperactivation of inflammatory markers that lead to disruption of the coagulation system which in return causes abnormalities in D-dimers and platelets (figure 4).^[8] Furthermore, it has been shown that anticoagulants reduce the rates of mortality in patients with Covid-19 who were hospitalized.^[40] Thus denoting that coagulopathy plays part in precipitating a cerebrovascular event in patients suffering from this infection.^[37]

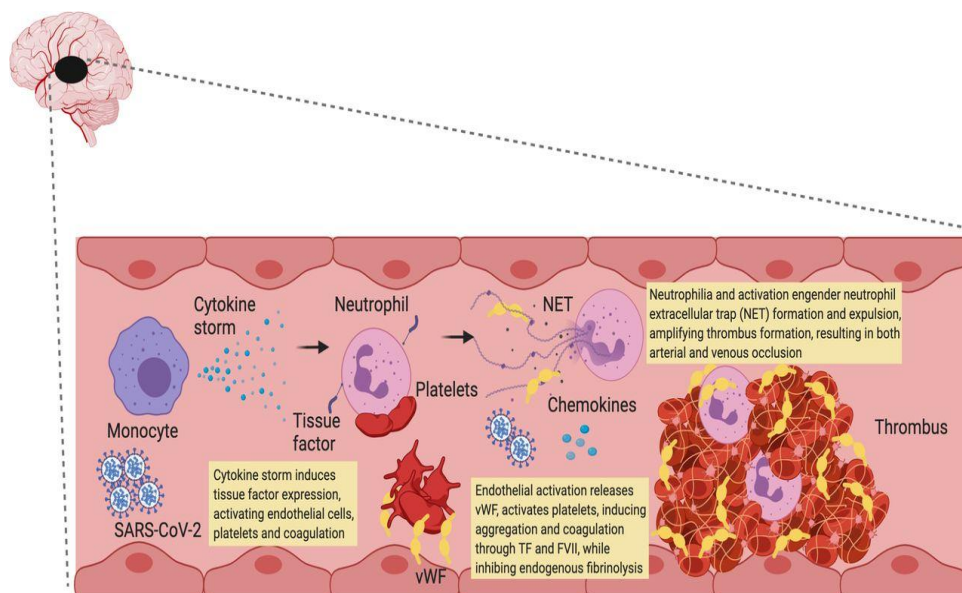


Figure 4: Covid-19 associated coagulopathy.

The current review revealed that the commonest peripheral nervous system manifestations in patients with Covid-19 are anosmia and hypogeusia. The majority of patients who have such symptoms are otherwise asymptomatic, however, some may have respiratory symptoms in later phases.^[38] These symptoms in individuals even without the presence of other symptoms typically seen in Covid-19 infection, should raise the suspicion of Covid-19.^[39] The presence of these symptoms has been shown to be associated with higher

expression of ACE-2 receptors in the nasal mucosa and tongue (figure 5).^[7] It is still under debate whether these symptoms occur as a result of injury to the nerve or olfactory nerves inflammation.^[41] Since previous reports postulated that involvement of brain stem occurs in Covid-19 patients, it is believed that the pathways for coronaviruses for entering into the central nervous system include peripheral trigeminal or olfactory nerves.^[42]

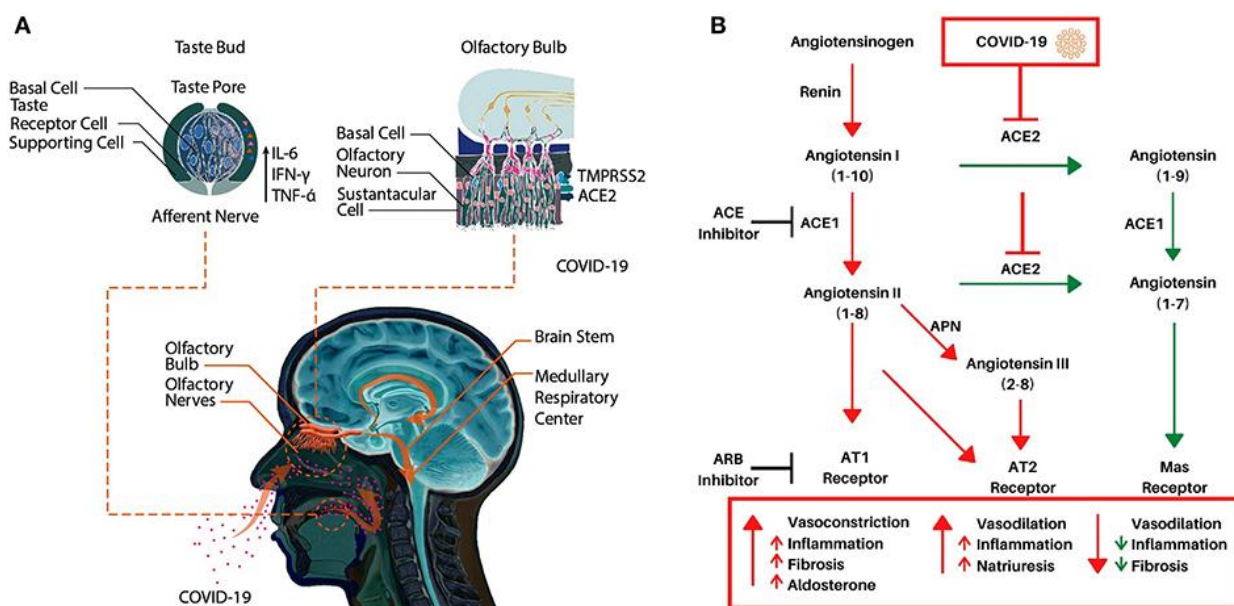


Figure 5: (A) A schematic representation of potential molecular mechanisms underlying COVID-19 induced anosmia and dysgeusia. (B) The Renin-Angiotensin System (RAS) and its interaction with COVID-19.

In individuals who have severe involvement of the central nervous system, it has been shown that there is a decrease in the counts of platelets and lymphocytes and an increase in the levels of blood urea nitrogen.^[40] In contrast, laboratory investigations are not helpful in

individuals who have involvement of the peripheral nervous system or who do not have severe involvement of the central nervous system.^[43] Numerous mechanisms have been thought to play a part in the involvement of central nervous system during infection with SARS-

COV-2 such as virus invasion directly into the CNS by disrupting the blood-brain barrier that occurs after cytokines are released and neuronal transport occurs either anterograde or retrograde, via dynein and protein kinases.^[43,44] Additionally, the immune system, hypoxia as a result of pneumonia and/or attachment to the ACE2 receptors, mediates damage to the nerves.^[44] ACE2 receptors are involved in blood pressure regulation and it has been revealed by different studies that SARS-COV-2 spike proteins may have an interaction with these

receptors and thus lead to hypertension and an increased risk of intracerebral hemorrhage.^[44] Similarly, the virus binds with the ACE2 receptors that are located in the endothelium of the capillaries and leads to disruption of the blood-brain barrier and enters the brain (Figure 5).^[44] Steardo et al. revealed that the neurons in the brainstem are infected by coronavirus, which is responsible for disturbed regulation of the cardio-respiratory system, hence resulting in hypoxia and respiratory failure.^[45]

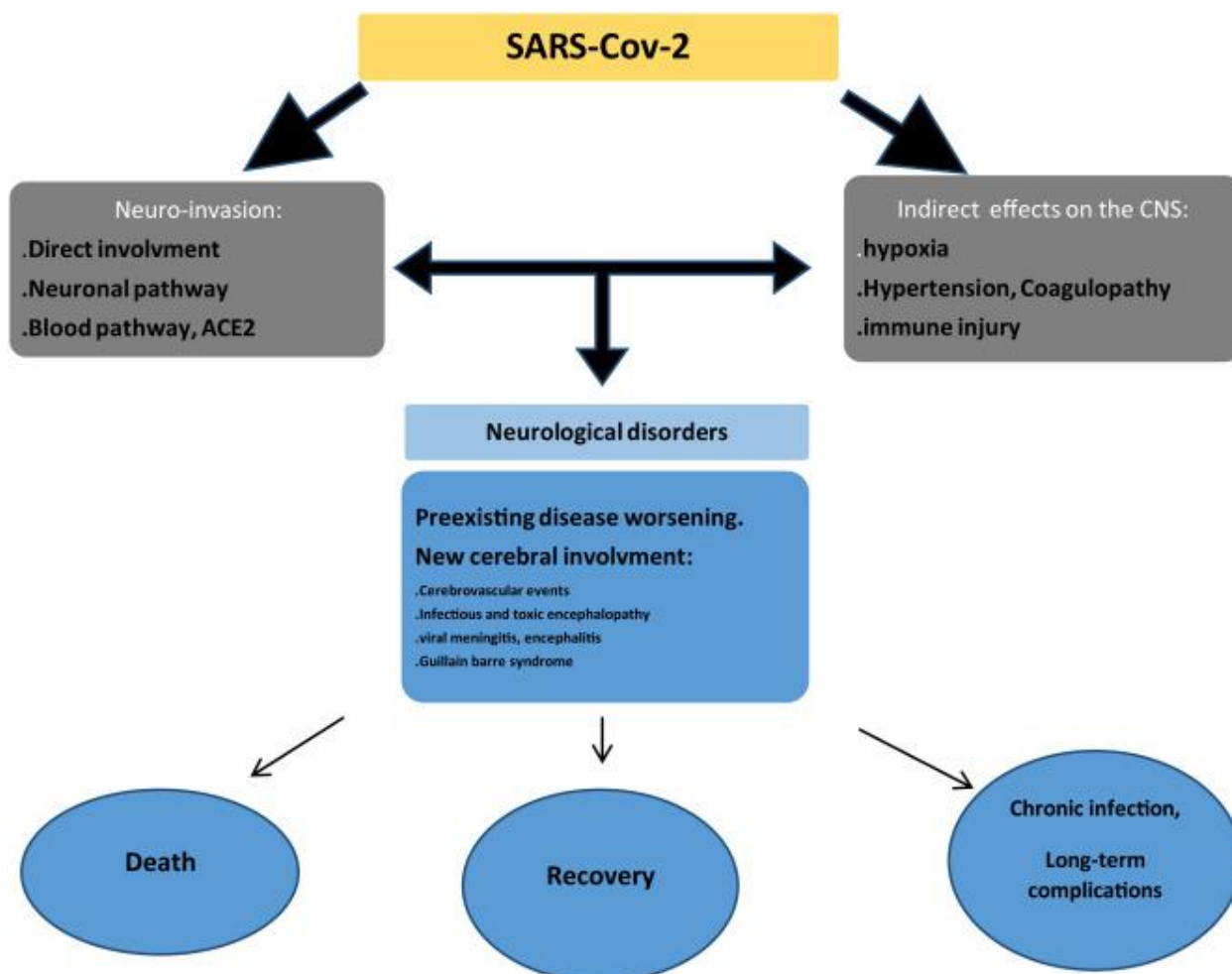


Figure 6: Direct and Indirect Involvement Of CNS in Covid-19 Infection.

A two-way hypothesis related to hypoxic damage has been postulated in Covid-19 infection affecting the brain.^[6] One is that SARS-COV-2 causes pneumonia as well as impairs the regulatory center in the brainstem that controls the circulation and breathing, thus resulting in hypoxia. On the other hand, hypoxic injury leads to increased neuronal injury resulting in a vicious cycle.^[6] This may support the higher incidence of neurological manifestations in patients who are severely affected by Covid-19 infection. Future studies must be carried out to confirm the evidence present.

CONCLUSION

The review revealed a variety of neurological manifestations of Covid-19 infection affecting the central

as well as the peripheral nervous system. It revealed that the commonest manifestations related to the central nervous system include dizziness, headache, impaired conscious level, seizures, acute stroke, encephalitis, ataxia, and Guillain-Barre syndrome. In the period of the current pandemic of Covid-19, the physicians must be aware of the variety of neurological manifestations of Covid-19 to establish diagnosis earlier and isolate the patients promptly to control the spread of this deadly virus. Different evidence supports that CNS plays a role in the pathophysiology of Covid-19. Keeping this in view, it is suggested that further studies must be carried out to validate the findings of involvement of the central nervous system in Covid-19 infection.

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