CHAPTER-5

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Open Access Full Text Article
https://doi.org/10.26524/royal.37.5

CHAPTER-5

NEUROLOGICAL IMPACT OF COVID-19 PANDEMIC: LESSONS & CAUTIONS

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ABSTRACT

Coronavirus disease COVID-19 caused by SARS-CoV-2 infection leading the current precarious pandemic which is affecting most of the countries in the world. Clinical portrait of COVID-19 might vary from trivial to debilitating febrile illness. Recent hospital-based studies have recorded the possible neurological symptomatology of SARS-CoV-2 infection. Neurological complications might be of Central Nervous System (CNS) such as dizziness, headache, consciousness impairment, cerebrovascular illness, epilepsy, ataxia and encephalopathy. Peripheral Nervous System (PNS) illnesses include Guillain-Barré syndrome, hyposmia, hypogeusia, neuralgia. Positive results of Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and serological assays in patients before and during neurological symptoms infer the possibility of both para and post-infectious association

Keywords

COVID-19 ASSOCIATED NEUROLOGICAL DISORDERS

TRANSNEURONAL

HAEMATOGENOUS

NEUROPATHOGENESIS OF SARS-COV-2

NEUROVIRULENCE

of neurological disorders with SARS-CoV-2. Elements of SARS-CoV-2 have been spotted in cerebrospinal fluid (CSF) too. Neuropathogenesis by SARS-CoV-2 may result from some independent or interdependent cascades. Direct neuro invasion can lead to metabolic disruption in the nerves. Nerves might be affected indirectly through systemic complications. Cytokine storms which elicit aberrant immune response can damage the nervous system. Molecular mimicry mediated pathway in which antibodies erroneously encroach on central and peripheral nerve fibres may be operational. Intrusion into endothelial cells might permit the SARS-CoV-2 to slip away through the blood-brain and blood-nerve barrier and invade into the nervous system. It is imperative to be cautioned about the potential neurological complications of SARS-CoV-2 infection during the acute course of COVID-19 symptoms as well as post-COVID-19 neurological sequelae. Introduction of SARS-CoV-2 vaccines is anticipated to cut down the neurological disease burden added up by SARS-CoV-2.

1. A prologue to COVID-19 and SARS-CoV-2

SARS-CoV2 is a single strand RNA-genomic virus which belongs to the genus Beta-coronavirus under the family Coronaviridae, order Nidovirales and realm Riboviria [1].The SARS-CoV-2 infection causes the corona viral disease i.e. COVID-19. To date, 213 countries and geographical territories reported the outbreak as per the statistics of the UN Geoscheme dashboard.

The cough droplets are the major reason of contamination of this ribovirus between people. COVID-19 has become such a global scale pandemicin 2019-2020 mainly because international travellers played as carriers of this ribovirus and initiated community transmission chain in destination countries. The SARS-CoV-2 also represents the leading cause of death of travellers in the pandemic period. The clinical spectrum of the COVID-19 ranges from severe febrile and respiratory illness to oligosymptomatic or even complete absence of symptoms. As the SARS-CoV-2 infection can be asymptomatic, the definite number of infected cases in a geographic territory very likely to be under represented. Recently, as evidence amassed gradually, neurological disorders found to be associated with SARS-CoV-2 infected patients. Sometimes it becomes a challenge to reveal the association between a neurological complication to the SARS-CoV-2 infection due to lack of clinical co-presentation of COVID-19 and neuropathologies, and paucity of serological evidence. The incidence and increment of SARS-CoV-2-associated neurological complications differ country-wise because of differences in national preventive policies. A new consensus for the diagnosis and prophylactics of neurological COVID-19 cases seems imperative. This is particularly important for healthcare professionals who are unaccustomed with its wide range of clinical manifestations including atypical presentations. In this synthesis, we will delve into the nervous system complexities associated with SARS-CoV-2 infection with a deep look at the emerging theories postulated about its profound impact on the central and peripheral nervous system.

2. Does SARS-CoV-2 damage nervous system?

Penetration to the nervous system by respiratory viruses is not uncommon [2]. Viruses can pierce the nervous system in a process called neuroinvasion. After invasion, viruses distress neurons as well as glia, a phenomenon popularly termed neurotropism. The trigger of different neurological disorders by infectious agents termed as neurovirulence. The theory of neuroinvasive potential of SARS-CoV-2 is grounded on five lemmas:

i. Patients infected with SARS-CoV-2 presented neurological symptoms within the clinically significant time frame.
ii. Discoveries of neurological complications associated with coronaviruses in non-human species.
iii. Neurological impairment by SARS-CoV-1, MERS and other taxa of coronaviruses in human and other species
iv. Nervous system connection by respiratory viruses of families phylogenetically close to Coronaviridae.
v. Experimental evidence of neural infection potential from animal and cell models of coronaviruses.

3. Neurological complications of SARS-CoV-2

The manifestations of neurological symptoms following SARS-CoV-2 infection reported are related to diverse type of neurological disorders. Physiological events caused or abetted SARS-CoV-2 and predisposed host factors conjunctively partake in neuropathogenesis. Based on different lenses, COVID-19 associated neurological diseases are classified as discussed below.

A. Classification based on pathologic puncta

Depending on the site of pathology, neurological manifestations can be broadly subdivided into four categories as summarized in **Table1**.

Table1: Classification of neurological disorders based on site of damage

Site of pathologies	*Candidate Diseases*
CNS disorders associated with COVID-19	Encephalopathy, Headache
PNS complications of COVID-19	Guillain barre Syndrome, Hypogeusia
Cerebrovascular diseases of COVID-19	Seizure, Ataxia
Skeletal muscle damage of COVID-19	Musculoskeletal pain

i. CNS disorders associated with COVID-19:

A sheer number of clinical studies indicate the SARS-CoV-2 involved in a number of neuropathologies of the Central Nervous System (CNS). Future investigations are required to differentiate whether diseases are caused by the virus or it is a mere concurrent manifestation. Major CNS pathologies include headache, encephalopathy, meningitis delirium and impaired consciousness [3].

ii. PNS complications of COVID-19:

Contrasted with the articles published on CNS engrossment of SARS-CoV-2 the literature refers to Peripheral Nervous System (PNS) pathologies are inadequate. Guillain-Barré syndrome is the most reported PNS disorder found to be associated with SARS-CoV-2. Other pathologies include Miller Fisher Syndrome, hypogeusia, hyposomia, polyneuritis and neuralgia.

iii. Cerebrovascular complications:

Cases with vascular risks are more likely to have cerebrovascular abnormalities linked with COVID-19. SARS-CoV-2 associated cerebrovascular manifestations are haemorrhagic stroke, seizure, ataxia, ischemic stroke and cerebral sinus thrombosis. The virus SARS-CoV-2 binds ACE2 receptors on the plasma membrane of endothelial cells which can heighten blood pressure. Rise in blood pressure, thrombocytopenia and bleeding-related complications may add up susceptibility of ischemic as well as haemorrhagic strokes in patients with COVID-19. Cytokine storm could further add up to the existing risk of stroke.

iv. Skeletal muscle damages:

COVID-19 associated skeletal muscle dysfunctions are myopathy, rhabdomyolysis and myalgia. Patients of musculoskeletal complications associated with SARS-CoV-2 infection tested with elevated creatine kinase (an enzyme that maintains ATP homeostasis in muscle).

B. Classification based on temporal onset

There might be a time interval between the commencement of neurological signs and infectious illness. According to the temporal profile of development of neuropathologies in connection with COVID-19 can be categorized into two subtypes:

i. Parainfectious neuropathies:

Diseases which are reported to commence at the time acute SARS-CoV-2 infection described as parainfectious neuropathies. Anosmia (loss of smell), headache and skin rash are examples of parainfectious complications associated with SARS-CoV-2.

ii. Postinfectious neuropathies:

Diseases that onset after an interval period constitute parainfectious neuropathies of SARS-CoV-2. Guillain-Barré syndrome is a typical example of post infectious pathology of SARS-CoV-2. Postinfectious encephalopathy and neuromyelitis optica are also reported in patients with COVID-19.

C. Classification based on pathophysiology

SARS-CoV-2 can impact the human body by means of multiple pathophysiological gateways. Based on molecular pathophysiologies that underlie SARS-CoV-2-associated neurological disorders, four core categories can be formed as tabulated in **Table2**.

4. Possible Routes of neuroinvasion

The precise route of viral transfer of SARS-CoV-2 to the nervous system remained undiscovered [4]. Two salient biologically plausible routes for access to the nervous system by SARS-CoV-2 are described herein:

i. Transneuronal route:

Nerve fibres innervate the human organs including lungs which can be exploited by SARS-CoV-2 as an entrance to the nervous system. Polarized nature of neurons let them receive the signal first followed by processing and conveyance to more neurons and other cell types. Certain viruses are able to infect and traverse along the sensory or motor nerve fibres. Viruses utilize two motor proteins viz. dynein and kinesins to execute their migration inside the nerve cell. These motor protein duosfacilitate anterograde and

retrograde neuronal transportation. Olfactory neurons characteristically connect with the nasal epithelium as well as the olfactory bulb, the gate to the CNS. This passage is usually exploited by respiratory viruses which are known to infect the nervous system [5]. SARS-CoV-2 intranasally penetrate the body and hence possibly invade via olfactory neurons to reach the nervous system.

Table2: Diseases of COVID-19 association as per pathophysiology

Pathophysiology	*Candidate Diseases*
Viral neuroinvasion	Meningitis, Encephalitis
Autoimmune reactivity	Guillain Barré syndrome, Neuromyelitis optica
Dysfunction of metabolism	Metabolic encephalopathy
Neurovascular impediment	Ischemic stroke, haemorrhagic stroke

ii. Haematogenous route:

Most neurotropic viruses move into the blood stream during the viremic period when they try to gain access to the nervous system. After entry to the bloodstream, viruses might cross the blood-nerve or blood-brain barrier through paracellular migration (destabilizing tight junctions) or transcellular migration (infecting the endothelial cells) pathway. SARS-CoV-2 might also enter via Trojan Horse transit in which viruses infect blood leukocytes such as monocytes or macrophages. Viruses use those blood cells as a vehicle to travel through the paracellular pathway to navigate through permeable points of the nervous system's barricade. Transneuronal and haematogenous passages of SARS-CoV-2 migration are depicted in Figure1.

5. Mechanism of Neuropathogenesis

SARS-CoV-2 can manifest neurological symptoms through multiple mechanistic pathways. Here we will discuss about the four key mechanisms that SARS-CoV-2 exploit for neuropathogenesis:

i. Direct neurovirulence:

Direct neurovirulence can potentially happen by SARS-CoV-2 after viruses gain access to the nervous system through the transneuronal or haematogenous pathway. However direct virulence in the brain and nervous system is not reported in SARS-CoV-2 infected patients. The cases shown brain damage are mostly through other means or pre-existing comorbidities worsened by COVID-19 exposure

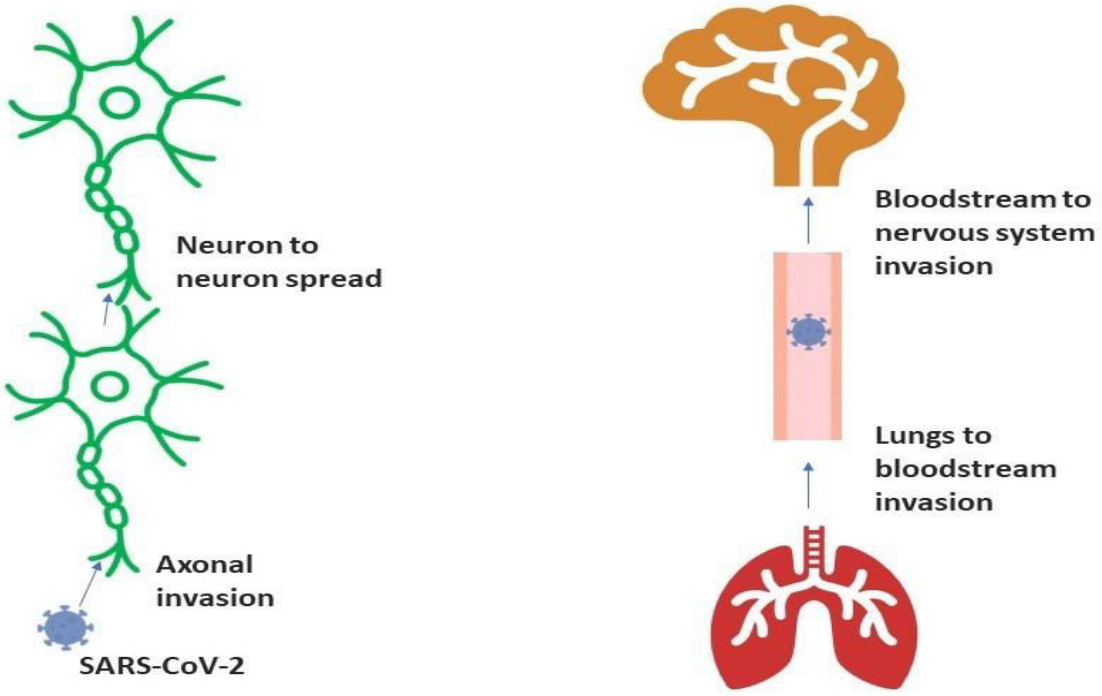

Figure1. Transneuronal (left panel) and haematogenous (right panel) passage of SARS-CoV-2 for entry into the nervous system. The blue arrow indicates the direction of migration of the virus.

ii. Indirect systemic neurodamage:

So far reported cases are predominantly affected by systemic means. During the proliferation of the SARS-CoV-2 in pulmonary cells, oedema and exudation happen. This impedes gas exchange inside lungs resulting hypoxia in the nerve cells which get mitigated by anaerobic metabolism in neuronal mitochondria. An acid build-up also might prompt vasodilation, neuron swelling, cerebral blood flow obstruction and ischemia-induced

headache. The hypoxia can deteriorate the nervous system function, develop cerebrovascular complications, drowsiness, and even loss of consciousness [6].

iii. Molecular mimicry-mediated pathogenesis:

Molecular mimicry is highly likely to happen for SARS-CoV-2 [7]. Guillain-Barré syndrome which is characterized as a template scenario of molecular mimicry, found to occur typically two weeks after COVID-19 onset in a large number of cases. More research is required to find out which human epitopes turning into autoantigens in the COVID-19 associated Guillain-Barré syndrome patients.

iv. Cytokine surge:

Nervous system impairment instigated by SARS-CoV-2 infection might be facilitated by the immunological malfunctions. The capacity of SARS-CoV-2 to invade inside macrophages and glial cells of the nervous system is especially critical. As a neurotropic virus, SARS-CoV-2 can potentially stimulate glial cells to evoke a pro-inflammatory event called a cytokine storm. Cytokine storm phenotype arises in patients with COVID-19 because of their immune system hyper activation which may turn out to be pathological [8]. Enhanced circulating levels of pro inflammatory cytokines and chemokines, which plays a crucial role in a cytokine storm, reportedly upregulate in COVID-19 [9]. Experimental studies suggest in vitro primary culture of glial cells exude inflammatory modulators like Interleukin (IL)-6, IL-12 and Tumour Necrosis Factor (TNF)-α after coronavirus infection [5]. Immune activation which remains unabated with time likely to consequence chronic inflammation and damage of the nervous system.

Conclusion

SARS-CoV-2 becomes the predominant source of pneumonia worldwide affecting all ages, particularly becoming serious in senior-aged and immunocompromised persons. The exact cascade of viral dissemination and neurotropic capabilities in nervous system not meticulously characterized hitherto. Diagnostic toolbox of COVID-19 neurological complications requires to be reevaluated especially for healthcare professionals who are unaccustomed with its diverse neurological manifestations. Current diagnostics of SARS-CoV-2 are based on real-time PCR assay to detect the viral RNA and/or serological

screening of immunoglobulins against the ribovirus. Additionally, the analysis of cerebrospinal fluid (CSF) for viral RNA and antibodies has proven potential as a diagnostic tool for COVID-19 associated neurological conditions which also provides important insight about the neuro pathogenesis of SARS-CoV-2. In pandemic hotspots or regions of tourists' interest, risks of SARS-CoV-2 infection which policymakers may need to think with high concentration. The association with SARS-CoV-2 with neurological difficulties likely to be neglected in patients who manifested mild or no respiratory difficulties. Refining diagnostic measures are instrumental for the superior prophylaxis of the COVID-19-associated neurological disorders and to circumvent long-duration hospitalization of patients. More research efforts need to be invested in the development of an effective vaccine to control the virus and eradicate of the COVID-19 altogether in the long run. At present, we are unaware of how SARS-CoV-2 triggers certain neurological sequelae and requires an urgent focus. Further investigations can bring up innovative provisions to deal with neuro-complications of COVID-19.

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