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REVIEW ARTICLE

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Brain and Peripheral Neuronal Injury in Covid-19: The Panorama and Dispute

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ABSTRACT

Infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coronavirus results in significant mortality and long-term disability. Coronavirus infectious disease 2019 (Covid-19), is caused by SARS-CoV-2 binds by glycoproteins expressed on its surface to the receptor of the angiotensin-converting enzyme 2 (ACE2), which is highly distributed in the respiratory tract epithelium. ACE2 is highly expressed on nervous tissue cells like neurons and astrocytes. Once inside the nerve cell, SARS-CoV-2 can alter the cellular transport function to facilitate its transmission from one neuron to another. Upon infection and because of other forms of damage neuroglial cells become reactive, representing the most classic neuro-pathological situation of the ongoing neuro-inflammation. Consequently, it is likely that the SARS-CoV-2 infected brain regions triggers reactive astrogliosis and activation of microglia. The mechanism of involvement of peripheral nervous system is not fully understood. It is mostly thought to be immune-mediated. In patients with rapid evolution of Guillain-Barrè syndrome (GBS) after the onset of COVID-19 symptoms, direct cytotoxic effects of virus on peripheral nerves is a postulated mechanism.

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Background

Infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coronavirus results in significant mortality and long-term disability. Global costs of coronavirus disease 2019 (COVID-19) are predicted to reach as much $35.3 trillion through 2025. The full spectrum of disease associated with COVID-19 is not yet fully characterized, yet 35% of adult COVID-19 patients report they have not returned to their usual state of health 2–3 weeks after testing positive for the SARS-CoV-2 virus. Emerging data indicate the presence of brain injury in a subset of COVID-19 patients, consistent with the known ability of coronaviruses to infect the CNS. However, the clinical manifestations, frequency of CNS effects, and associated primary or secondary mechanisms underlying neurological injury produced by SARS-CoV-2 infection are not well understood [1].

Respiratory viruses are the leading cause of acute respiratory diseases. Coronaviruses (CoVs) commonly cause enteric and respiratory diseases in animals and humans. Human CoVs were responsible of two worldwide outbreaks: the severe acute respiratory syndrome CoV (SARS-CoV) and the Middle East respiratory syndrome CoV (MERS-CoV). SARS-Cov-2 is a beta-coronavirus [figure1] that shares similarities with SARS-CoV. So far, it is proposed that it binds by glycoproteins expressed on its surface to the receptor of the angiotensin-converting enzyme 2 (ACE2), which is distributed in the respiratory tract epithelium, the lung parenchyma and other areas such as the gastrointestinal tract, endothelial cells, among others [2, 3].

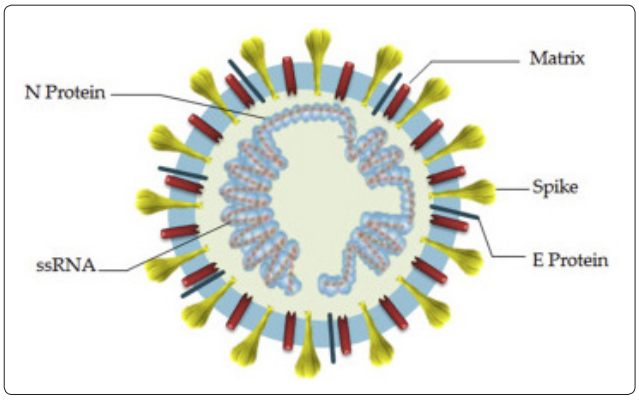

Figure 1: Structure of SARS-CoV-2

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The initial clinical sign of the SARS-CoV-2-related disease Covid-19 was pneumonia. Additional contemporary reports also designate gastrointestinal symptoms and asymptomatic infections, especially among young children. Explanations so far suggest a mean incubation period of five days and a median incubation period of 3 days. The percentage of individuals infected by SARS-CoV-2 who remain asymptomatic through the development of infection has not yet been definitely assessed. In symptomatic patients, the clinical manifestations of the disease typically start after less than a week, consisting of fever, cough, nasal congestion, fatigue and other signs of upper respiratory tract infections [4]. The infection cans advancement to severe disease with dyspnoea and severe chest symptoms consistent to pneumonia in approximately 75% of patients. Pneumonia commonly occurs in the second or third week of a symptomatic infection. Protuberant signs of viral pneumonia include decreased oxygen saturation, blood gas deviations, changes visible through chest X-rays and other imaging techniques, with ground glass abnormalities, patchy consolidation, alveolar exudates and interlobular involvement, eventually indicating deterioration. Lymphopenia appears to be common, and inflammatory markers and pro-inflammatory cytokines are elevated [5, 6].

Primary infection of SARS-CoV-2 targets specific cells, such as nasal and bronchial epithelial cells and pneumocytes, through the viral structural spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor. Besides, type 2 transmembrane serine protease (TMPRSS2), present in the host cell, promotes viral uptake by cleaving ACE2 and triggering the SARS-CoV-2 S protein, which facilitates SARS-CoV-2 entry into host cells (figure 2) [7].

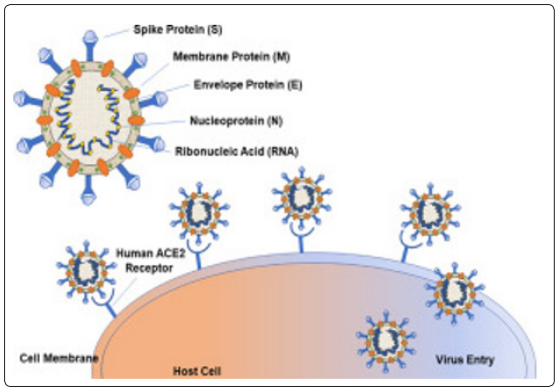

Figure 2: SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor

ACE2 and TMPRSS2 are expressed in host target cells, predominantly alveolar epithelial type II cells. In addition, the viral inflammatory response, consisting of both the innate and the adaptive immune response blights lymphopoiesis and increases lymphocyte apoptosis. Although up-regulation of ACE2 receptors from ACE inhibitor and angiotensin receptor blocker medications has been hypothesized to increase susceptibility to SARS-CoV-2 infection, large observational cohorts have not found an association between these medications and risk of infection or hospital mortality due to Covid-19 [8].

In advanced stages of infection, when viral replication quickens, epithelial-endothelial barrier integrity is compromised. Furthermore to epithelial cells, SARS-CoV-2 infects pulmonary capillary endothelial cells, accentuating the inflammatory reaction and activating an influx of monocytes and neutrophils. Pulmonary edema filling the alveolar spaces with hyaline membrane formation follows, compatible with early-phase acute respiratory distress syndrome (ARDS). Together, endothelial barrier disturbance, dysfunctional alveolar-capillary oxygen transmission, and compromised oxygen diffusion capability are characteristic features of Covid-19 [4].

Neuronal Transmission of SARS-CoV-2

ACE2 is broadly expressed on nervous tissue cells like neurons, astrocytes, and oligodendrocytes. Substantia nigra, ventricles, and olfactory bulb express ACE-2 receptor in high concentrations. Virus may gain entry to nervous tissue from vascular endothelial cells. Once inside the nerve cell, SARS-CoV-2 can alter the cellular transport function to facilitate its transmission from one neuron to another [9].

Since SARS-CoV-2 is a respiratory virus, the virus particles have been shown in the CD 68 macrophages in the biopsy of nasal tissues from patients presenting with Covid-19-related olfactory dysfunction. Patients with olfactory dysfunction may have inflammation and edema of olfactory bulb. In animal studies, it has been shown that coronavirus may utilize olfactory pathway to gain entry into central nervous system [10]. Neuronal changes have been detected in hypothalamus and cortex of SARS-CoV victims. Retrograde transmission of the virus from peripheral nerve terminals through nerve synapses with the help of neural proteins dynein and kinesin have also been postulated. SARS-CoV-2 RNA has also been demonstrated in the CSF [11].

This tendency has been persuasively recognized for the SARS-CoV, MERS-CoV and the coronavirus responsible for encephalomyelitis. Preceding verdicts validate that ACE2 represents the key, but not the high-class, site of entry of the virus into the cell. The ACE2 is expressed in the brain, being in chiefly existing in the brain stem and in the regions responsible for regulation of cardiovascular function including subfornical organ, paraventricular nucleus, nucleus of the tractus solitarius, and rostral ventrolateral medulla; expression of ACE2 was found in both neurones and glia [12].

Non-ACE2 paths for virus infection of neural cells also can be excepted; the noticeable penetration of coronavirus into the liver, an organ with lower levels of ACE 2 compared to the CNS, toughly supports the postulation that the cell entry routes can vary. Therefore, the CNS infection with both SARS-CoV-1, MERS-CoV has been reported and SARS-CoV-1 has been identified in neurones from tissues obtained from infected patients [13].

The intranasal administration of SARS-CoV-1 or MERS-COV resulted in the rapid invasion of viral particles into the brain, conceivably via the olfactory bulb via trans-synaptic route. This pathway when virus enters peripheral nerves and spreads to the CNS through synaptic contacts has been well-documented for several viruses

including CoVs [14]. The brainstem, which armies the respiratory neuronal circuit in the medulla, was strictly infected with both types of viruses, which may contribute to squalor and failure of respiratory centers. When the nasal infecting charges were delivered in extremely low doses, only the CNS was colonized, with virus being absent in other tissues including lungs, verifying the potent neurotropism of these coronarovirus strains [15]. Though direct evidence is presently lacking, the high identity between SARS-CoV-1 and SARS-CoV-2 suggests, that the latter viral strain could also infect the CNS, an ability clearly demonstrated by other members of the family to which they belong. The β-coronavirus NCoV-OC43, which causes upper respiratory tract disorder, has been found to infect neural cell lines as well as primary neurons in culture; it was also found to cause encephalitis associated with neuronal apoptosis and necrosis in mice [16].

It is of substantial attention that organ distribution studies have shown that the presence of SARS-CoV-1 in the cerebrum, but not in cerebellum. These two parts of the brain exhibit distinct ratios between neurons and neuroglia; in the neocortex the number of non-neuronal cells (most of which are represented by neuroglia) is almost four times larger than the number of neurons, while in the cerebellum neurons account for ~90% of all cells [17]. Upon infection and because of other forms of damage neuroglial cells become reactive, representing the most classic neuro-pathological situation of the ongoing neuro-inflammation. Consequently, it is likely that the SARS-CoV-2 infected brain regions triggers reactive astrogliosis and activation of microglia [figure 3] [18].

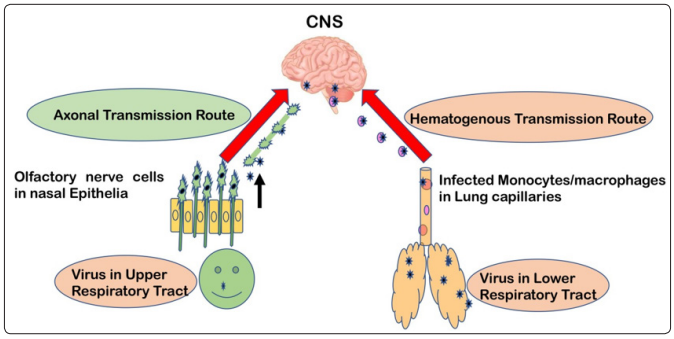

Figure 3: Brain involvement in Covid-19

The mechanism of involvement of peripheral nervous system is not fully understood. It is mostly thought to be immune-mediated. In patients with rapid evolution of Guillain-Barrè syndrome (GBS) after the onset of Covid-19 symptoms, direct cytotoxic effects of virus on peripheral nerves is a postulated mechanism. GBS is usually considered an immune-mediated disease of peripheral nerve myelin sheath or Schwann cells. The glycoproteins on the surface of the virus resemble with glycoconjugates in human nervous tissue. The antibodies formed against the viral surface glycoproteins acts against the glycoconjugates on the neural tissue [19]. This mechanism of nerve injury is famously known as “molecular mimicry”. SARS-CoV-2 shares two hexapeptides with human shock proteins 90 and 60. Both these proteins have immunogenic potentials, and they are among the 41 human proteins associated with GBS and chronic inflammatory demyelinating polyneuropathy. The other neuropathies reported in patients with Covid-19 may also be secondary to immune-mediated mechanisms [20].

Another fundamental aspect of the effect of SARS CoV2 infection and CNS is that this infection triggers a substantial systemic inflammatory storm with a massive release of cytokines, chemokine, and other inflammation signals with a following noteworthy breakdown of BBB, which prompts and intensifies the neuro-inflammatory process [21]. Numerous preclinical and clinical studies consistently demonstrate that systemic inflammation, regardless of its nature, be it bacterial, viral or toxic, compromises BBB, injures glia limiting, activates Toll-like receptors residing in microglia and astrocytes and is associated with the innate immunity, ultimately promoting neuro-inflammation that may severely disturb brain homeostasis and cause neuronal death [22]. Therefore, the neuro-inflammatory process associated with functional brain damage could explain the clinical knowledge rendering to which even in patients who overcome pneumonia, the start or the development of cognitive impairment associated with behavioral changes is observed. Delirium and cognitive deficits and behavioral abnormalities are clearly caused by a situation in which systemic inflammation associated with conditions of prolonged hypoxia induces a persistent and uncontrolled neuro-inflammation responsible, in turn, for damage to hippocampus and cortical areas associated with cognitive functions and behavioral alterations [23, 24].

Elderly patients recuperating from pneumonia often display delirium or shortages in attention and memory that continue over time and necessitate treatment, which is regularly strangely challenging. Delirium is usually triggered by peripheral infection associated with systemic inflammation. Elevated concentrations of serum pro-interleukins and S100B, (recognized as index of BBB disruption), have been pragmatic during delirium in elderly patients [25]. Neuro-inflammation appears as an almost obligatory component in neurodegenerative disorders and has been concerned in psychiatric pathologies from acute psychosis to schizophrenia, autism spectrum disorder, affective disorders to name but a few. There is a robust connotation between systemic inflammation and depressive syndromes with infections raising the risk of depressive episodes. In animal models, injections of cytokines instigates sickness behaviour ; which is very similar to a human “flu-like syndrome” manifested by anorexia, fever, fatigue, increased pain, sleep disturbances, and confusion. Likewise, severe respiratory failure accompanying Covid-19 triggers long-lasting hypoxia, which debatably affects the brain and causes neurocognitive alterations [26].

Post-Infective Neurological Complications

Through more number of patients improving from the SARS-CoV-2 infection, it is authoritative that post-infective complications would attraction consideration with time. CNS demyelinations have been recognized formerly subsequent coronavirus infection. An early report of Guillain-Barre syndrome (GBS) is obtainable from China, while there is an apprehension regarding the connectedness in this particular case. This observation is ominous because of, there is a chance of inadvertent exposure to the infectious virus in the neurology ward both for attending health care staffs and other patients; and GBS is a disorder known to rapidly affect respiratory muscles particularly if bulbar involvement sets in which can cause sudden poorly explained worsening of a patient's status if the

diagnosis of Covid-19 has not already been established [27, 28].

As well, acute myelitis, perhaps affecting the cervical spinal cord, as evidenced by the clinical features, in a known patient of SARS-CoV-2 infection. In this particular description also the neurological symptoms were co-incident with the febrile period of the illness pointing towards para-infectious demyelination rather than post-infective complication in true sense [29]. Additionally, since about 10% of hospitalized patients need assistance in intensive care wards, neurological monitoring must also be aimed at verifying the onset of the so-called "critical illness neuro-myopathy"[30].

Patients with neurological co-morbidity are more predisposed to acquire infection. However, patients with reduced mobility and those on immune-suppression therapy may be anticipated to be more susceptible to infection [31].

Contemporary neurology has seen wide use of immune-suppressive agents to combat several disorders of both CNS and PNS. The prototypical among these disorders is multiple sclerosis that calls for long term immunosuppression. The data so far on Covid-19 reveals that old age, as well as immune-dysregulated subjects, is more likely not only to acquire the infection but also to manifest increased severity [32]. Therefore, similar to the oncology ward, patients in the neurology ward admitted receiving cyclic immunosuppressive drugs need attention. Appropriate caution has to be practiced while dealing with such cases both from the part of the neurologist as well as the patient's relatives. A recent article on this topic recommends that the benefits of continuing immunotherapy in patients with multiple sclerosis (MS) and related disorders may outweigh the risks of medication withdrawal in the apprehension of Covid-19. This is particularly because most infections, as in the general population, are anticipated to be mild an2d self-limiting. However, the authors emphasize the need for individualized decision-making in such circumstances because one size" may not fit all, and some of the patients may land up in severe infection leading to discontinuation of therapy [33].

Therefore, this view point showed that Covid-19 is associated with central and peripheral neurological disorders due to direct SARS-CoV-2 invasion or induction of cytokine storm or autoimmunity [figure 4].

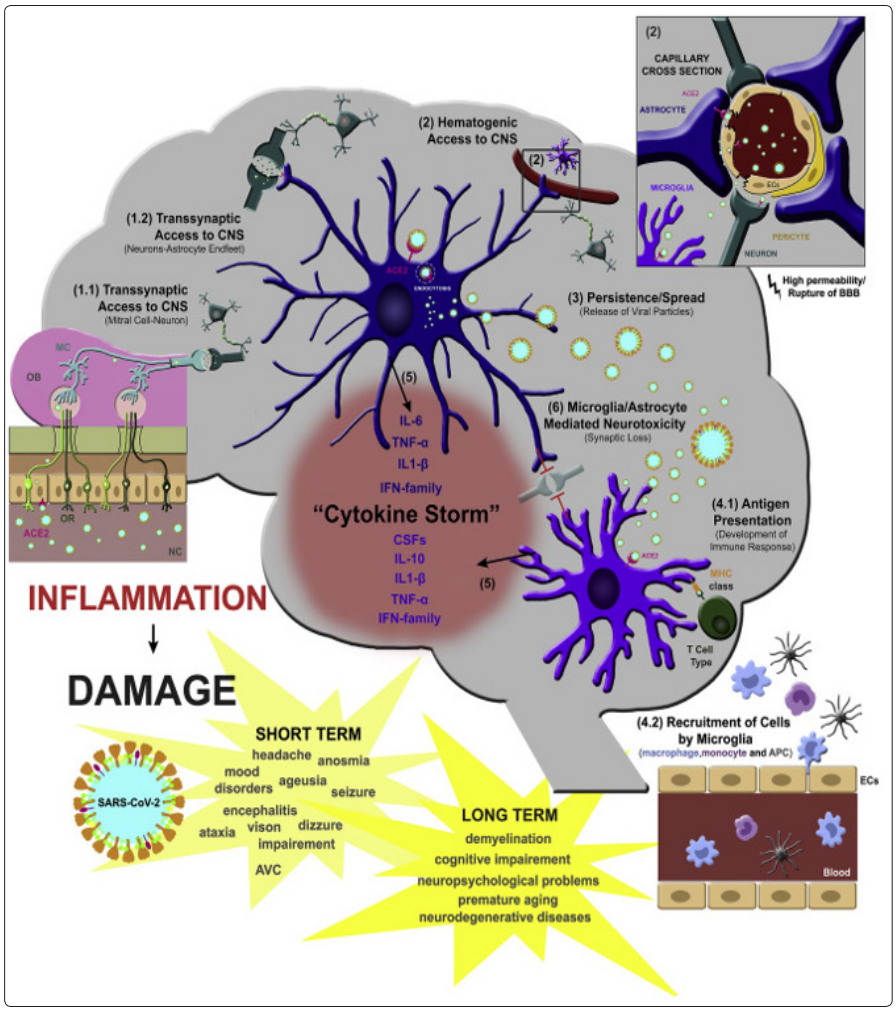

Figure 4: Neurological disorders in SARS-CoV-2 infection

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