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Neuropathophysiology of COVID-19

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Abstract

The COVID-19 pandemic has strained health systems all over the world. The SARS-CoV-2 which causes the disease is a corona virus that predominantly affects the respiratory systems. Since the outbreak of the novel disease in December, 2019 the scientific world has intensified efforts to elucidate its pathophysiology, mode of transmission, clinical manifestations, best mode of prevention and treatment options. Very little is known about its neuropathophysiology even though a significant number of patients come down with obvious neurological signs and symptoms. The virus has been reported to affect the nerves, muscles, the special senses and the central nervous system with a wide range of clinical manifestations. The mechanisms by which the virus causes all these are still not clear. This article attempts to review and articulate all possible existing theories surrounding the neurological effects of COVID-19

Keywords

COVID-19, SARS-CoV-2, Charnoly Body, Cytokine Storm, Agnosia, Ageusia

1. Introduction

Corona viruses are a large family of viruses which could cause illness in humans and animals. In humans they are known to cause a spectrum of respiratory diseases ranging from common cold to Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) [1] [2]. Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is a novel betacoronavirus that causes a variety of symptoms in patients known as corona virus disease (COVID)-19 [3]. It was first reported amongst a cluster of patients who came down with pneumonia of unknown cause which was linked to a seafood market in Wuhan, Hubei Province, China in December, 2019 [4].

The COVID-19 pandemic poses a significant threat to humanity as it is dangerously straining our healthcare and economic systems in ways that are significant and obvious [5]. The steady rise in the number of new cases in several countries has been attributed to paucity of knowledge with respect to the pathogen's biology, host response and treatment modalities [6].

The main manifestations of COVID-19 are fever, cough, respiratory distress with lymphocytopenia and ground-glass opacity changes on chest computed tomography. It is also becoming evident that severe infections result in neurological manifestations like headache, acute cerebrovascular disease (stroke), seizures, skeletal muscle injury and altered consciousness. Olfactory dysfunctions like anosmia or hyposmia are also prevalent and may be the initial symptoms [7] [8].

A recent observational study revealed that many patients (58 out of 64) who presented with acute respiratory distress syndrome (ARDS) due to COVID-19, manifested unusual neurological symptoms which included transient ischemic attack, partial epilepsy and mild cognitive impairment [9]. Another study also showed that COVID-19 could result in neurological diseases like acute demyelinating encephalomyelitis (ADEM), encephalitis and Guillain-Barre syndrome [10]. It is anticipated that long-term neurological sequalae in COVID-19 may include depression, cognitive impairment and unmasking of Alzheimer's disease [11].

The SARS-CoV-2 is constantly evolving; its mechanistic details are still rudimentary [12]. This article seeks to make a review on the neuropathophysiologic mechanisms of COVID-19 in a bid to proffer some scientific explanations.

2. Theories of Nervous System Injury by COVID-19

2.1. Charnoly Body Theory

Charnoly body (CB) is a pleomorphic, electron-dense, multilamellar, preapoptotic, mitochondrial biomarker of cell injury. Nutritional stress and environmental toxins can induce CB formation in highly vulnerable neurons because of compromised mitochondrial bioenergetics. Inhibition of charnolophagy (i.e autophagy of charnoly body) may lead to progressive neurodegenerative diseases accompanied by neuronal inclusions [13].

In general, viral infections can impair charnolophagy, a basic molecular mechanism of intra-cellular detoxification (ICD). Viruses can alter the pluripotency of neural progenitor cells in the brain and induce charnolosome (CS) destabilization which can cause inflammasome (particularly NRLP-3) activation. This whole process induces hypercytokinemia and charnoptosis (CB apoptosis) implicated in pyroptosis, apoptosis, and necrosis of sensitive hippocampal and other CNS neurons by releasing Panx-1, Viroporine, and gasdermins to cause Charnoly Body Molecular Pathogenesis (CBMP) implicated in the overall viral lytic cycle. It has been hypothesized that SARS-CoV-2 acts by same mechanism, causing compromise in neural immunity, mitochondrial bio-energetics and

charnolophagy (a process of intracellular detoxification in the CNS) as a result, causing neural injury and death via charnolosome destabilization [14].

2.2. Theory of Angiotensin Converting Enzyme 2 and Cytokine Storm

The binding of SARS-CoV-2 to angiotensin converting enzyme 2 (ACE2) is said to be a critical step in the pathophysiology of neurological manifestations in patients with COVID-19 [15]. ACE2 has a wide distribution in the chemical sense organs, the lungs, kidneys, liver, blood vessels, immune system, and the brain. When SARS-Cov2 binds ACE2 in respiratory and vascular epithelial cells it triggers the formation of a cytokine storm, with marked elevation in levels of interleukin-1, interleukin-6, and tumor necrosis factor. High levels of these cytokines increase vascular permeability, edema, hypercoagulation and widespread inflammation with resultant multiple organ damage. Combined hyperactivation of inflammatory markers, vascular injury, and coagulation factors contributes to acute respiratory distress syndrome (ARDS); multiple organ failure as well as multiple neurological disorders [11].

A recent report revealed that ACE2 binds to the SARS-CoV-2 ectodomain with an affinity of about 15 nM which translates to 10 to 20 fold higher affinity compared to SARS-CoV-1. This higher affinity of SARS-CoV-2 to human ACE2 may contribute to the rapid human to human spread [16]. To potentiate this, ACE2 can undergo an ADAM17 (*a disintegrin and metalloproteinase* 17)-mediated "shedding" from endothelial cells, resulting in the release of the ectodomain with a catalytic and bioactive power into the circulation [17].

A genetic study using infected *ACE*2 knockout mice verse wild-type mice revealed that there were significantly lower quantity of the virus in the lungs of the knockout mice when compared to control wild-type mice with SARS-CoV-1. Similarly, pathologic alterations in lungs were reduced in *ACE*2 mutant mice compared to wild-type mice, thus proving the genetic plausibility of ACE2 as indeed a crucial *in vivo* SARS receptor required for effective replication of the virus [18].

Accumulating evidences now reveal that a sub-group of COVID-19 patients have what is now described as a cytokine storm syndrome, resulting in blood brain barrier breakdown and features of acute necrotizing haemorrhagic encephalopathy. Imaging studies reveal multifocal infarcts and micro-hemorrhages in the brainstem, cerebrum, cerebellum and thalamus as well as nerve root enhancement [19] [10]. Magnetic resonance imaging (MRI) revealed varying levels of leptomeningeal space enhancement, bilateral fronto-temporal hypoperfusion, focal hyperintensity plus overlapping decreased apparent diffusion co-efficient. Electroencephalogram (EEG) findings also showed slowing of cortical activity which is consistent with encephalopathy [9].

There has been heightened speculation that angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may also increase the risk of SARS-CoV-2 infection similar to SARS-CoV-1 outbreak in 2003. Also

evidence exists to show that SARS-CoV-2 binds to ACE2 to gain entry to host cells on the respiratory tract epithelium. This explanation can be predicated on the fact that some animal studies have demonstrated increased ACE2 expression with ACE inhibitor or ARB administration, advancing a potential mechanistic link between SARS-CoV-2 infection, and these medications [20].

However, this has not been consistently demonstrated in human and animal studies. Paradoxically, mechanisms proposing that ACEIs and ARBs may be protective in SARS-CoV-2 infection are rapidly evolving. Animal studies have found that ACEIs and ARBs may promote and stabilize cell membrane complexes. In theory, these complexes may reduce the ability of the virus to enter host cells. Suppression of angiotensin II may also prevent virus-mediated acute lung injury and other organ dysfunction, which is another proposed mechanism by which use of ACEIs and ARBs may be beneficial in COVID-19 [21].

A study involving 2263 COVID-19 positive hypertensive patients showed a nearly 40% lower risk of hospitalization with the use of ACE inhibitors and ARBs. This finding gives some empirical evidence as to the potential benefits of ACE inhibitors in reducing the risk of severe illness especially among older individuals [22].

2.3. Theory of Direct CNS Viral Invasion

It is a known fact that a number of viruses (especially the zoonotic ones) are highly virulent and neurotropic. Viruses like the Japanese encephalitis virus, West Nile virus, Zika virus, Nipah virus, Rabies virus, Herpes simplex virus and Human immunodeficiency virus are able to penetrate the highly selective blood brain barrier of humans [23]. There is a possibility that the SARS-CoV-2 could penetrate the CNS from the periphery through neural pathways to cause neurological disease like encephalitis [24] [25]. The furin-like cleavage site on the spike protein of SARS-CoV-2 could be the facilitator of its neural invasion potential as seen in similar viruses like the MERS virus and SARS-CoV-1 [26]. The primary pulmonary explanation given for the respiratory failure in COVID-19 sufferers is recently being challenged as SARS-CoV-2 has been found to infiltrate the brainstem (the cardiopulmonary centres) of some patients [27].

2.4. Theory of Secondary Systemic CNS Effect

Binding of SARS-CoV-2 to the pulmonary epithelium is known to generate a global systemic inflammatory response (SIRS) with production of IL-6, IL-12, IL-15, TNF-α and activated glial cells. This results in a massive pro-inflammatory state, severe hypoxia and resultant cerebral vasodilatation, decompensation, oedema and ischaemia within the CNS [24]. COVID-19 encephalopathy has been linked to patients with severe disease who have comorbidities and eventually develop multi-organ system damage, hypoxaemia and elevated markers of systemic inflammation [12].

3. COVID-19 on Nerve and Muscle

COVID-19 patient have been noticed to come down with Guillian Barre syndrome. Symptoms of lower limb weakness, paraesthesia, and facial diplegia were noticed. Other symptoms were bulbar palsy, flaccid tetraparesis or tetraplegia. However, analysis of cerebrospinal fluids and electromyography were generally inconsistent as the typical albumin-cytologic dissociation and conduction slowing or blocks were not well documented [28]. In some sufferers COVID-associated Miller Fisher Syndrome and polyneuritis cranialis were recorded. They had albumin-cytologic dissociation and positive testing for GD1b-IgG antibodies [29]. It has been established that SARS-CoV-2 can cause serious injury to the cranial nerves, peripheral nerves and muscles. One of the diagnostic criteria for Guillain-Barré syndrome (GBS) or Miller Fisher syndrome is identification of a microbial ganglioside mimic [30]. This molecular mimicry has sometimes been implicated for SARS-CoV-2 vasculitis in and around nerves and muscles [11].

4. COVID-19 on the Special Senses

Anosmia and Aguesia

Viral upper respiratory tract infection is a common cause of olfactory dysfunction. The rhinoviruses, coronaviruses, influenza viruses, parainfluenza viruses, respiratory syncythial viruses, adenoviruses and the enteroviruses account for at least 70% of all common colds [31]. The pathogenesis for anosmia in COVID-19 may not be different from what has been known with other coronaviruses [32] [33]. Movement of the virus through the cribriform plate near the olfactory bulb helps the virus gain access to the brain and could be related to the altered or total loss of smell sense [34]. The slight variation lies in the fact that anosmia in COVID-19 unlike other viral-induced anosmia is not preceded by rhinorrhea and nasal congestion [35].

Direct damage of the gustatory receptor cells have been attributed to the aguesia in COVID-19 patients. Though it is also widely believed that ageusia may be secondary to olfactory dysfunction [36]. Another strong theory of ageusia, is the damage of the neurons of the tractus solitarius of the medulla via retrograde transport of the virus from the gustatory receptor cells in the tongue [11].

5. Conclusion

It is obvious that full understanding of the pathophysiology of COVID-19 is still not imminent. Theories are still evolving and the available information is still rudimentary. Since the outbreak, morbidity and mortality from the disease have mostly been attributed to the respiratory complications. It is however clear now, that serious neurological manifestations like muscle weakness, stroke (haemorrhagic and ischaemic), seizures and encephalopathy (altered consciousness) can worsen the outcome of the disease. Also, symptoms like hyposmia, anosmia and ageusia could precede the illness in some previously asymptomatic individuals. Most importantly the understanding of the neuropathophysiology of COVID-19

is quite necessary for preventing and treating some of the neurologic consequences of the disease. There is need for more intense research in this direction.

Authors' Contributions

All authors have taken equal part in the review

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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