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KEY WORDS: Human coronaviruses, SARS-CoV, Encephalopathy, Stroke, Altered Sensory status, Post-COVID complications.

DOABLE PATHOGENESIS FOR SARS-CoV RELATED NEUROLOGICAL COMPLICATIONS

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ABSTRACT

The numerous neurological manifestations have been described in SARS-CoV patients. But, the solid shreds of evidence to understand the pathogenic mechanism behind these disorders are poorly known. In COVID-19 patients, mostly observed acute encephalitis is the most common neurological complication. Also, patients may be affected with ischemic or hemorrhagic stroke and an altered sensory status, impaired consciousness, confusion, deliriousness, or agitation. The previous studies reported the presence of COVID-19 viruses in CSF and post-mortem brain tissue of patients with post-COVID encephalitis. On the other hand, there are contrary findings that may indicate that the post-COVID neurological complications are mainly due to austere systemic inflammation and not the direct invasion into the brain. The present study suggested that the SARS-CoV could invade the CNS via the same routes as the other Human coronaviruses (HCoVs) like the hematogenous route or by using retrograde or antegrade transference mechanisms from peripheral to the CNS.

INTRODUCTION

Severe acute respiratory syndrome-related Coronavirus - 1 (SARS - CoV-1), Severe acute respiratory syndrome-related Coronavirus - 2 (SARS-CoV-2), Omicron variant SARS-CoV-2 and Middle East Respiratory Syndrome related Corona (MERS-CoV) viruses are the member of the Coronaviridae, which is a large family of single-stranded RNA viruses (ssRNA) that can be found in a variety of animal species [1]. The viral respiratory infection pandemic is one of the most common medical outbreaks in our medical history. Respiratory infection eruptions are reported early in 1173 AD. The early confirmed pandemic respiratory infections were first observed in 1580. [2]. More recently, in the 20th and 21st centuries, there have been several reports of such pandemics and outbreaks, including the Spanish Flu pandemic of the early 20th century, the SARS-CoV-1 epidemic in 2003, and the MERS-CoV outbreak in 2012 [2,3].

SARS-CoV membrane is characterized by the presence of the spike (S) glycoprotein, which facilitates entry into cells. SARS-CoV is mainly transmitted by coughing and sneezing through respiratory droplets. It invades the respiratory system by attaching to the respiratory epithelium or vascular endothelium and it enters the cells through binding to the angiotensin-converting enzyme 2 (ACE2), Basigin (BSG) or Neuropilin-1(NRP-1) receptors. The viral incubation period varies among patients and ranges from three to seven days [1]. Based on the mode of viral transmission and entry, SARS-CoV mainly targets the respiratory system inducing pathological pulmonary changes, such as alveolar damage, hyaline membrane formation, interstitial fibrosis, and immune infiltration [4].

COMMON SARS-CoV NEUROLOGICAL COMPLICATIONS

Human coronaviruses (HCoV) which cause human infections were first discovered in 1965 [5]. Until now seven types of CoV have been discovered: SARS-CoV-1, SARS-CoV-2, and MERS-CoV which are associated with the three epidemics and caused severe disease in humans, HCoV-OC43, HCoV-229E, HCoV-NL63 and HCoV-HKU1 [6]. HCoV may invade the CNS, disseminate, and participate in the induction of neurological diseases. Before MERS-CoV and SARS-CoV- 2, three other types including SARS-CoV-1, HCoV-229E, and HCoV-OC43 had been shown to cause neurological complications [6].

The previous researchers studied the Neurological Dysfunction in COVID-19s, and they found that "eight out of ten hospitalized COVID-19 patients developed neurological complications. Many of these conditions were mild to moderate, but more than 50% of the patients had an altered brain function, and almost 20% of patients were in a coma [7]. Among the COVID-19 patients, acute encephalopathy is the most common neurological complication. In COVID-19 the patients may be affected with ischemic or hemorrhagic stroke and an altered sensory status, impaired consciousness, confusion, deliriousness, or agitation [8].

DOABLE PATHOGENESIS

The previous studies reported the presence of COVID-19 viruses in CSF and post-mortem brain tissue of patients with post-COVID encephalitis [9-17]. On the other hand, there are contrary findings that may indicate that the post-COVID neurological complications are mainly due to austere systemic inflammation and not the direct invasion into the brain [18-25]. The present study suggested that the SARS-CoV could invade the CNS via the same routes as the other Human coronaviruses (HCoVs) like the hematogenous route or by using retrograde or antegrade transference mechanisms from peripheral to the CNS (Figure 1-5) [26-31].

A. TRANSCELLULAR MIGRATION

The foremost possible mechanism of SARS-CoV-related neurological complication is the hematogenous route. SARS-

CoV will bind to the receptors on blood-brain-barrier (BBB) endothelial cells, then it passes through the endothelial cells by transcytosis, and finally reaches the brain tissue through circulation (Figure -1) [9, 32]. The infected endothelial cells do not involve in any viral replications [31]. Because in the brain microvasculature the BSG and NRP1 are more highly expressed than ACE2, it is more likely that the SARS-CoV would utilize these receptors to enter the brain tissue [33].

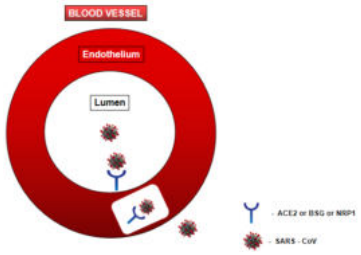

Figure – 1:Transcellular Migration

B.TROJAN-HORSE MECHANISM

The next projected mechanism for SARS-CoV-related neurological complication is the "Trojan horse" mechanism". In this, the SARS-CoV virus involves the immune cells that express ACE2, such as monocytes, granulocytes, and/or lymphocytes to reach the brain tissue (Figure-2) [34-38]. The infected immune cells may then carry SARS-CoV to the CNS circulation, where it can reach and infect the brain tissue [39]. SARS-CoV viral RNA was detected in the lung macrophages of SARS-CoV patients in post-mortem studies. However, SARS-CoV viral replications in immune cells and any immune infiltration into the brain tissue may need some extended studies [40].

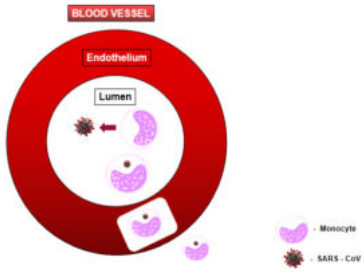

Figure – 2:Trojan-Horse Mechanism

C. PARACELLULAR ROUTE

The third possible mechanism is the paracellular route, the SARS-CoV viruses reach the brain tissue by inflammation caused by the viremia. SARS-CoV passes through the disrupted vascular endothelial cells' tight junctions at the CNS vascularization (Figure-3) [41 - 42].

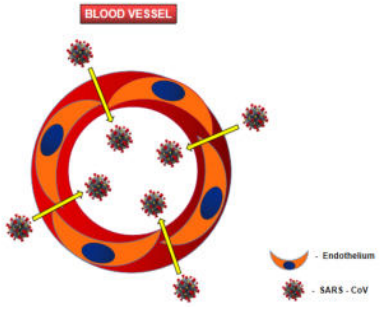

Figure – 3: Paracellular Route

D. OLFACTORY ROUTE TRANSMISSION

SARS-CoV may also reach the brain tissue by retrograde or antegrade transference mechanisms from the peripheral to the CNS [43, 44]. Especially, in the olfactory linings have some high expression of ACE-2 and the priming protease transmembrane serine protease-2 (TMPRSS2) in the sustentacular cells, stem cells of the olfactory epithelium, and olfactory bulb, these may allow an antegrade or retrograde transference of SARS-CoV into the brain tissue (Figure-4) [45-49].

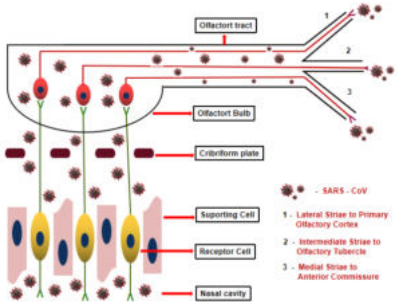

Figure – 4: Olfactory route transmission

E. VON-WILLEBRAND - PLATELETS AGGREGATION MECHANISM

The Von-Willebrand factor is an important prognostic indicator of endothelial dysfunction and its level varies depending on sex and age. Significantly, drugs used in the treatment of SARS-CoV treatment, can influence VWF secretion and consequently its level and activities. An increase in the VWF levels might reciprocal increase in the platelets aggregation over the injured endothelial area, this might be one of the pathological mechanisms for SARS-CoV-related neurological complications (Figure-5a - 5c) [50].

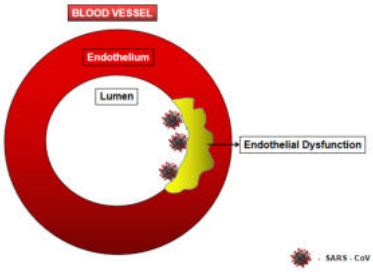

Figure – 5a: Von-Willebrand – Platelets aggregation mechanism - SARS-CoV cause endothelial dysfunction.

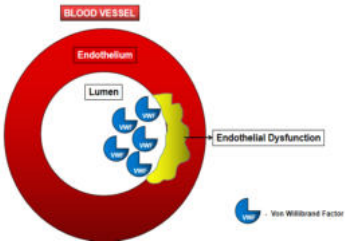

Figure – 5b: Damaged endothelial cells attracts Von-Willebrand factors

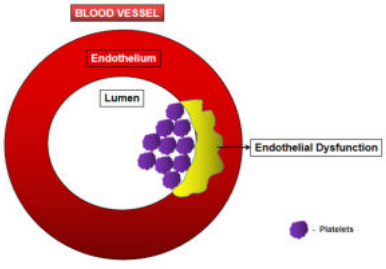

Figure – 5c: Damaged endothelial cells attracts Von-Willebrand factors cause excessive aggregation of platelets in vascular lumen

DISCUSSION

Angiotensin-converting-enzyme-2 (ACE2) has several physiological functions, including the regulation of blood pressure. SARS-CoV used this receptor as an entry route into the vascular lumen that's may lead to its depletion, and the accumulation of Angiotensin-II (Ang-II) [51-53]. Elevated Ang-II would result in increased blood pressure due to vasoconstriction and fluid retention [53]. Furthermore, the high levels of Ang-II would promote inflammation and blood coagulation. SARS-CoV-related neurological complications are mainly due to ACE2 depletion, which could be manifested as various cerebrovascular diseases in COVID-19 patients. Other-hand, the SARS-CoV may cause elevated levels of ACE2 in the brain tissue and peripheral nerves, which infects the nervous system and cause neurological damage, which is manifested as several neurological complications secondary to SARS-CoV infection [26].

Hypoxia in acute respiratory distress syndrome (ARDS) due to the consequence of severe SARS-CoV infection may lead to deleterious effects on the brain tissues which include brain tissue inflammatory changes like edema, congestion, and neuronal degeneration [35]. The hypoxia-induced brain damage is characteristically seen in hypoxic-encephalopathy and ischemic-stroke secondary to SARS-CoV infection [54-55]. Conversely, it is significant to note that any direct damage to the brain tissues caused by the SARS-CoV virus could also lead to the respiratory-failure and hypoxia [61].

Inflammation due to ARDS releases an excessive amount of proinflammatory cytokines that may responsible for tissue damage in the lungs and other organs including the brain [54, 56-57]. Severe inflammatory changes are observed in the brain tissue after SARS-CoV invasion, leading to the production of proinflammatory cytokines by astrocytes and microglia [58]. This also contributes to brain damage. Consequently, the treatment protocol for SARS-CoV such as IL-6 receptor monoclonal antibodies aims to reduce the inflammation-dependent complications in SARS-CoV patients [59].

In SARS-CoV, the infection of endothelial cells will activate the coagulation cascade by the Von-Willebrand factor, which leads to hypercoagulability and disseminated-intravascular-coagulation (DIC) will cause ischemic stroke [60, 60-67].

The serial-systemic-immune-inflammation-indices (SSIIi) are determined based on neutrophil, platelet, and lymphocyte counts, which are clinically correlated with peripheral and central nervous tissue damages [68]. Hence, SSIIi could be used as a biomarker for post-COVID neurological complications.

In SARS-CoV patients, there is severe immunosuppression like a significant reduction in the circulatory T-cell [69]. In some cases, there is an elevated IL-6 but without elevations in other pro-inflammatory cytokines due to the less activated blood mononuclear cells. In both cases, the immune responses may be impaired, which could lead to uncontrolled viral spread and tissue and organ damage including the central nervous system (CNS) [69].

In severe COVID-19 patients, there is an overproduction of proinflammatory cytokines [70], and high levels of anti-SARS-CoV spike protein IgG antibodies [71]. Antibodies against SARS-CoV-2 can also cross-react with antigens in the nervous system causing complications such as GBS [72]. It indicates that antibody-dependent-enhancement (ADE) of infection is mediated by the infection of immune cells that express the Fc receptor for IgG [73, 74].

Based on these observations, hyper-activation of the immune system leads to hyper-inflammation. However, immunosuppression may result in the dissemination of SARS-CoV to the various tissues. Both of these mechanisms would ultimately cause tissue damage [75].

CONCLUSION

All over the world, the healthcare systems featured a huge challenge to manage the COVID-19 pandemic outbreak. Numerous neurological complications have been manifested in post-COVID-19 patients. However, more research needs to be carried through to understand the possible pathogenic mechanisms of SARS-CoV-related neurological complications. Understanding the pathogenesis behind these post-COVID-19 neurological complications to better treat such patients with suitable drugs and in a timely manner. Summarizing these facts, we hypothesized some possible pathological mechanisms for SARS-CoV-related neurological complications. We also suggest that a detailed comprehensive studies on SARS-CoV-related neurological complications to unclear the complexity of the pathogenesis mechanisms must be performed.

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