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Impact of SARS-CoV-2 (COVID-19) on the Nervous System: A Critical Review

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ABSTRACT:

The present study is based on the thorough and critical review of more than 30 research and review articles published in highly reputed scientific journals during past two years and available on prestigious scientific search engines like PubMed, MEDLINE, EMBASE, and Google Scholar, after the emergence and worldwide occurrence of Corona virus disease (COVID-19). Most of the studies indicate that other body systems like the cardiovascular system, hepatic system, renal system and nervous system are also affected by the corona virus along with the respiratory tract leading to multiple organ failure and other co-morbidities. Adequate preliminary reports suggest that the corona virus severely devastates the peripheral and central nervous system after invading through many direct or indirect neural pathways. Earlier studies indicate that the virus exhibits a wide range of neurological manifestations including Cerebro-vascular implications, acute polyneuropathy, headache, encephalopathy, encephalitis, seizures, hypogeusia as well as some non specific symptoms. However more studies are needed to authenticate the impact of the virus on the different components of the brain and Neuro- endocrine system. In the present study the impact of impact of corona virus on the different segments of the nervous system and their postulated molecular mechanism as well as manifestations have been reviewed. In addition, the possible neural pathways that lead to the entry of the virus within the nervous system have also been thoroughly discussed.

Keywords: Neuroinvasion, Neurotropism, COVID-19, cytokine storm, immune response, cerebro spinal fluid.

INTRODUCTION

A highly pathogenic virus named Severe Acute Respiratory Syndrome (SARS)-CoV-2 emerged in December 2019 in the city of Wuhan situated in Hubei region of China. Owing to its high transmission rate, it gradually apocalypse more than 200 nations leading to a mammoth death toll. This virus belongs to the Coronaviridae family that encompasses alpha, beta, gamma and delta strains. SARS-CoV-2 is a beta corona virus that belongs to the Ortho-coronavirinae subfamily and comprises a 29903 base single-stranded RNA genome which is surrounded by spike-shaped membrane glycoproteins (Pennisi, M. et.al. 2020). The glycoprotein located on the outer surface forms a three-dimensional structure in the receptor-binding domain of the host cell that facilitates the viral anchorage (Zou,X. et.al.2020) The corona viruses are pleomorphic with a diameter ranging 80 to 120 nm. The genome of the virus is single-stranded RNA, the largest known genome, with a length of 30kb. The genome of corona virus codes for four proteins ; spike (S) protein that gives it crown shape; and binds to host cell; a small and hydrophobic envelope protein(E); membrane protein(M); **(Fig.1)** which plays a crucial role in the assembly of virus and nucleo-capsid which is strongly associated with RNA (Vargas, et.al. 2020). Structurally, SARS-CoV-2 has a defined structure comprising of 14 binding sites that interact with the human Angiotensin-Converting Enzyme-2 (ACE-2) receptor (Fehr, A.R. et.al.2015; Yuan,Y. et.al. 2017).

Earlier experiments indicated about the neurotropism of the CoVs into the central nervous system causing neurological damage (Carod-Artal,F.J. et.al.2020)). The penetration of several respiratory viruses has been shown

through a mechanism called 'neuroinvasion' affecting both neurons and glial cells (Khan, S. et.al.2020). The neurological manifestation of SARS-CoV-2 has been supported based on previous reports on neurovirulence cased by neuro-invasion of other CoVs of the same virus subfamily (Desforges, M. et.al.2019). The neurological implications of SARS-CoV-2 are manifested in form of symptoms like acute polyneuropathy, headache, encephalopathy, encephalitis, seizures, hypogeusia, dizziness, taste and smell disorders (Orsini, et.al; 2020). Thus in the present study a thorough review has been done for the plausible invasive pathways of the virus within the nervous system, its neuro-pathogenicity and predicted molecular mechanisms based on the available scientific research literature.

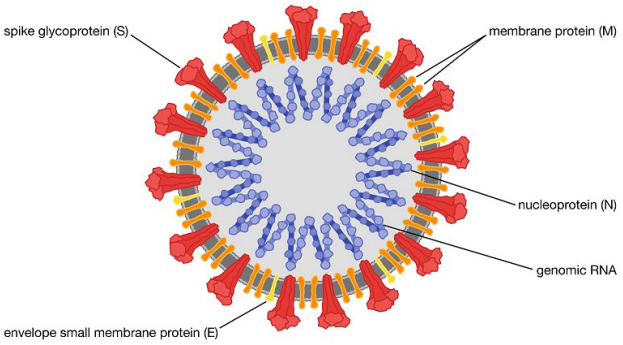

Fig.1- Molecular structure of COVID-19

Neuro-invasive pathways of SARS-CoV-2:

The reports on the neurological manifestations and their complications are increasing exponentially. SARS-CoV-2 mainly attacks respiratory, urinary, hepatic, gastrointestinal and endovascular systems and could reach the central nervous system (CNS) and peripheral nervous system (PNS) as well. However the presence and entrance of the whole virus within the nervous system of the infected patients is least evident but the components of viral particles within the different parts of the brain and peripheral nervous system are well reported (Orsini,et. al.;2020). Thus the pathogenecity of the virus could be due to fragments of the virus and its immune mediated responses. Based on the available recent reports seven possible routes have been enumerated and out of these routes, the blood –endothelial barrier is considered to be the most prominent route of neuro-invasion (Uversky,et. al.;2020). Data obtained from the experiments on human cell lines obtained from SARS-CoV-2 infected patients indicated its modest replication in the neuronal (U251) cells which highlighted the potential of this virus to cause neurological manifestations (Chu,et.al.2020). The viral particles were found in the neuronal cell body extending in to neurite structures. The neuronal cell model expressed ACE-2 receptor on the surface of host cells, however, the transmembrane protein serine protease -2 (TMPRSS2) required for the docking and priming of the surface protein(S) of the virus was absent. This suggests the presence of an alternate proteolytic tool within the neural cells (Bullen, et.al. 2020).

Recent literature postulated that at least three mechanisms are possible for the formation of immune-mediated lesions in the CNS. They include,1)- a systemic inflammatory response syndrome which occurs as a result of the excessive host response to the infection leading to CNS damage;2)- a direct infection in CNS immune cells such as astrocytes, microglia and macrophages leading to cytokine storm with the release of IL-6, IL-12,IL-1beta, TNF-alfa which subsequently damage the nerve cells; 3)- An autoimmune response against the host epitopes (Natoli,et.al.2020). Moreover, immune-mediated events may cause demyelination either through T-cells or by other cytokines and chemokines (Wu, et.al.2000).

The viral kinetics of the SARS-CoV in transgenic mice revealed that the infection began in the respiratory epithelium and the virus entered the brain through the olfactory nerve and invaded cortical and subcortical regions (Netland et.al.; 2008). Further,the infection extended to many brain stem nuclei such as the nucleus tractus solitarii, the dorsal motor nucleus of the vagus and area postrema. Injuries to this region of the brain stem could be detrimental to the maintenance of homeostasis leading to cardio-respiratory disorders (Uversky, et.al. 2020; Li Bai et.al.2020). ACE-2 which acts as a cellular entry receptor with its affinity to a surface protein of the virus is adequately expressed in the neuroendothelial cells and brain suggesting the neuro-invasive potential of the virus. ACE-2 is expressed in neurons and neuroglia (Yamagata, et.al. 2020). Thus the hematogenous route can be the most likely pathway to the brain (Paniz-Mondolfi et.al.2020).

However possible methods of entry of the virus within the nervous system are as follows:

1. **Olfactory route**- This route is the most proximal axonal area of the brain that is endowed with regenerative neurons. The ACE-2 receptor is expressed 200 to 700 fold in the neuro-epithelial cells relative to nasal epithelial cells. The main neurological manifestation of the olfactory route is the loss of smell and taste. (Chen,Shen et.al;2020). Thus it becomes favorable for the release and recruitment of leukocytes and cytokines resulting in impairment of chemosensory functions (Cooper, et.al. 2020).

2. **Blood – nervous system barriers:** This is the main route SARS-CoVs use to hijack the nervous system. The CNS contains four such type of barriers which are blood-brain barriers (BBB); the choroid plexus found in cerebral ventricles; the blood cerebrospinal fluid barrier and the lymphatic vessel brain barrier. In addition an additional barrier in called the blood nerve barrier (BNB) is present in PNS. Some viruses may directly invade these barriers through interacting with neuro-epitheial cells (ECs) while others use host immune cells to travel within peripheral nerves by inducing the expression of cytokines, chemokines and cell adhesion molecules.

   It is postulated that SARS-CoV-2 directly invade the BBB through neuro-invasion and the direct interaction of neuronal components with the virus spike proteins leads to neuropathogenesis which is manifested in form of multiple COVID symptoms. The comorbidity of hypertension in COVID-19 corroborates this finding (Espinosa, et.al; 2020; Gold et.al.2020).

3. Moreover the disrupted and deregulated immune system is another way to favour the entrance of SARS-CoV-2 by creating a 'Cytokine storm' which leads to breach in BBB and enhanced vascular activity within the brain. The interactions of virus spike proteins and ACE-2 have been noticed to enhance the level of cell adhesion molecules (CAMs) like MMP3,CCLS,CXCL-10,ICAM-1,VCAM-1 and interleukins IL-1beta and IL-6 and their proinflammatory responses on brain ECs (Buzhdygan et.al 2020).

4. Another significant route of neuro-invasion is BNB in which the virus gains entry through interaction between spike protein and ACE-2 receptors of ECs accessing the CNS through axonal transport machinery and regulated vascular endothelial growth factor VEGF (Yin, et.al.2020).

5. Blood cerebrospinal fluid barrier (BCSFB) cells are highly vascular and sometimes leaky thus these are more susceptible to the viral entry. Though the direct presence of the virus is not reported, the presence of few fragments of the virus has been confirmed through the RT-PCR test in infected patients.

6. The lymphatic brain drainage system route which is a recently discovered glial cell-based waste clearing sytem and is highly vascular structure has been reported to be a route of virus entry (Bostancikliogl et.al. 2020). Though many reports contradict it, the expression of ACE-2 and TPMRSS2 genes suggests that the virus can easily access. Peripheral nerve route entry of the virus is also reported.

7. It is postulated that the brain stem invasion may occur via the vagal afferents of the lung and gastrointestinal (GI) tract (Esposito et.al.2020). GI epithelium has high relative expression of ACE-2 receptor than lung thus the probable entry of the virus in to the nervous system through the GI tract is presumed to be high which may act as entry door.

In addition to above mentioned direct routes, many cargo routes are reported to assist the virus in neuro-invasion. The alveolar and interstitial macrophages in the lung express ACE-2receptor and TMPRSS2/Furin protease which act as sheddase (enzymes acting as a protease for the extracellular domain of transmembrane proteins) of ACE-2. The virus can also replicate in macrophages (Abassi et.al.2020) and dendritic cells (Yang, et.al.2020).

Furthermore, many postmortem electron microscopic studies on dead covid-19 patients have shown the presence of SARS-CoV-2 particles in multiple immune cells that may directly or indirectly enter the brain carrying the viral particles. Many viruses including SARS-CoV are reported to replicate and be transported through extracellular double membrane vesicle (EDMV) (Elrashdy et.al.2020). Postmortem histopathological studies support a similar avenue about the replication and release of SARS-CoV-2 (Ogando et.al.2020). In cultured glial cells, EDMVs are reported to be released and transported in nerve cells and these vesicles can pass the BBB thereby gaining entry into the brain. Thus SARS-CoV-2 employs multiple direct and indirect routes for its replication, and transmission within human body organs including PNS and CNS **(Fig.-2).**

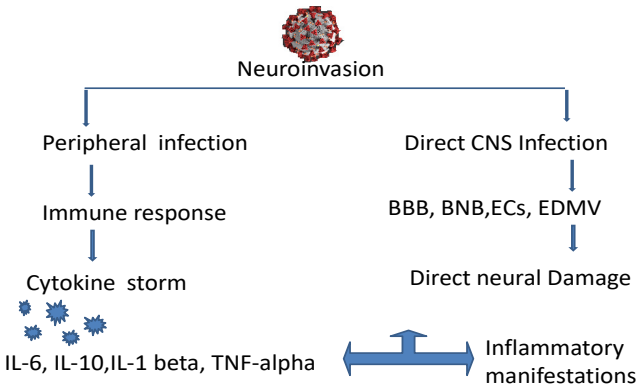

Fig.2:Neuroinvasive effects of SARS-CoV-2 and its Neurological manifestations

Neurological manifestations of SARS-CoV-2:

Individuals infected by SARS-CoV-2 exhibit many short terms and prolonged neurological impairments depending upon the severity of infection which may be in the form of neuropsychiatric, neuroanatomical, neurophysiological, neurobehavioural or neurochemical changes with early or late symptoms. Alterations in mental status characterized by confusion, agitation, disorientation and somnolence which are collectively defined as encephalopathy have been reported in COVID-19 infections (Ladecola,C. et.al.2020). Delirium is considered to be the most common psychiatric symptom in the acute phase of the infection which may be due to inflammatory response or due to direct interaction of the virus with brain cells. Inflammatory responses produce IL-6,IL-10,TNFs,IL-1beta that may breach the BBB, activate microglia and astroglia leading to an imbalance in neurotransmitter and delirium (Vargas et.al.2020). Glial cells in aged infected brains are reported to be more prone to the neurotoxic response. Neuroinvasion of microglia or astrocytes produces high levels of inflammatory mediators resulting in release of the interferons, TNF-alpha, interlukins (IL-6.IL-10,IL-1beta), Chemokines and colony-stimulating factors which is leads to cytokine storm (Vargas et.al.2020). This inflammatory response may result in stoke, neurodegenerative disorders, ischemia, and aging. Recent transcriptiomic studies have confirmed the overexpression of ACE-2 in the middle temporal gyrus and posterior singulate gyrus of the brain (Vargas et.al.2020). Hence it is postulated that proinflammatory responses of cytokine storm and other mediators of glial cells and immune cells may be the leading cause of neurodegenerative disorders which are primarily manifested in form of symptoms like headache, encephalopathy, encephalitis, seizures **(Fig.3).**

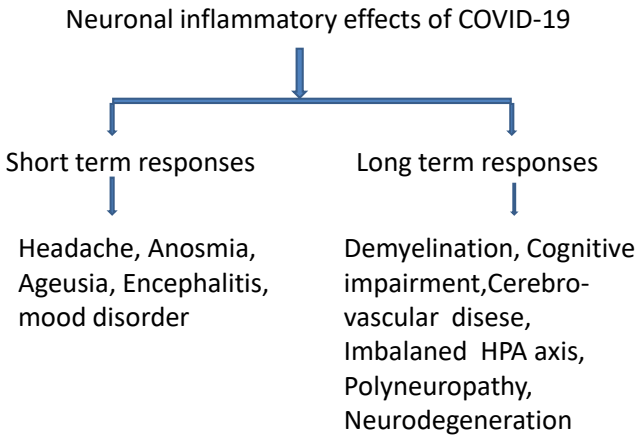

Fig.3: Short term and long term neuronal manifestations of COVID-19

Anosmia and taste disorders are more prevalent in corona infection resulting in gustatory dysfunction. Cytokine directly damages the olfactory receptor nerve but the direct neuro-invasion of the virus through olfactory nerve is not reported. Guillain-Barre syndrome (GBS) *i.e.* acute inflammatory demyelinating polyneuropathy has been reported in SARS-CoV infections in which viruses share epitopes similar to peripheral nerve components which activate the T-cells and B-cells to raise antibodies that invade the peripheral nerves and cause neuronal dysfunction (Pennisi et.al.2020).

Even in absence of direct neuro-invasion of the virus, viral proteins present in circulation could enter the brain and can act as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) and could trigger the immune response in pericytes, macrophages present in brain and microglia. These immune responses increase cytokine production and impaired brain function and cytokine-mediated sickness. Many cytokines activated during SARS-CoV-2 infection like IL-6,IL-1 beta and TNF trigger the hypothalamic-pituitary-adrenocortical (HPA) axis (Ladecola, et.al. 2020). HPA axis is activated by BBB dysfunction and neurovascular inflammation leading to the release of norepinephrine and glucocorticoids. Importantly, during SARS-CoV-2 infection, HPA activation and glucocorticoid levels are correlated with neutrophilia and lymphopenia (Chen,et.al.2020).

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Abbreviations: ACE-2: Angiotensin –converting enzyme-2; **BBB**; Blood-brain barrier; **CNS**: Central nervous system; **PNS**: Peripheral nervous system; **CoV**: Corona virus; **CoVs**: Corona viruses; **CSF**: Cerebro-spinal fluid; **GBS**: Guillain-Barre syndrome; **IL**: Interleukin; **RT-PCR**: Real-time reverse polymerase transcriptase chain reaction; **TMPRSS2**: Trans-membrane protease serine 2; **TNF**: Tumor necrosis factor; **PAMPs**: Pathogen-associated molecular patterns; **DAMPs**: Damage-associated molecular patterns; **HPA** axis: Hypothalamic-pituitary-adrenocortical axis; **EDMV**:Extracellular double membrane vesicle; **GI**: gastro-intestinal; **ECs**: Neuro-epitheial cells; **BCSFB**: Blood Cerebrospinal fluid barrier; **CAMs**: Cell adhesion molecules

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