

The Vitiated Highbrow- Brain in COVID-19

Anubha Bajaj*

Department of Histopathology, Panjab University/A.B. Diagnostics, India

***Corresponding Author:** Anubha Bajaj, Department of Histopathology, Panjab University/A.B. Diagnostics, India.

Received: May 21, 2021; **Published:** June 23, 2021

Preface

The global pandemic induced by novel coronavirus or SARS-CoV-2 is singularly infective and transmissible despite occurrence of an asymptomatic phase. COVID-2019 was initially discovered in Wuhan, China on December 8, 2019. Furthermore, pulmonary parenchyma is the principal target and the virus may disseminate to organs such as renal parenchyma, gastrointestinal tract, myocardium, vascular articulations and brain.

SARS-Cov-2 respiratory pathogens are innately neuro-invasive and may establish a persistent infection within the central nervous system. Although SARS-CoV-2 induced neurodegeneration is of obscure aetiology, it is surmised that the human respiratory pathogens may initiate or exacerbate neurological diseases.

Spike proteins (S) necessitated for viral entry into host cells engender the neuro-invasive potential of SARS-CoV-2. S protein of SARS-CoV-2 adhere to cell receptor angiotensin converting enzyme 2 (ACE2), usually manifest upon non-immune cells such as endothelial cells, renal tubular cells, cerebral neurons, respiratory or intestinal epithelial cells and immune cells as alveolar monocytes or macrophages.

Physiology and pathogenesis

SARS-CoV-2 is a single-stranded ribonucleic acid (RNA) virus constituted of spherical or elliptical genome of 26kb to 32 kb magnitude and an average diameter of 100 nm. Extraneous viral surface is superimposed by frequently mutating, crown-shaped spike (S) proteins wherein proportionate viral recombination is around ~ 25%. Aforesaid characteristics represent viral adaptability which modifies viral infectivity [1,2].

Although SARS-CoV-2 predominantly implicates respiratory system, the neuro-invasive virus may be accompanied by neurological complications. Angiotensin-converting enzyme 2 (ACE2) receptors are abundantly discerned in the pulmonary parenchyma. Spike proteins of SARS-CoV-2 adhere to ACE2 receptors with cellular ingress and potentiate viral infectivity with genesis of innumerable viral copies [1,2].

ACE2 receptors are optimal for invasion of host cell with SARS-CoV-2. The receptors contribute significantly in vasoconstriction, regulation of blood pressure and associated cardiovascular functions [1,2].

ACE2 receptors are discerned in several cellular subtypes such as pulmonary, renal, intestine and brain. ACE2 receptors discerned in brainstem nuclei are associated with regulation of cardio-respiratory function [1,2].

Thus, interaction of spike proteins with ACE2 receptors within the brainstem nuclei may engender respiratory symptoms in COVID-19. The virus may disseminate through the neurons to distant brain regions. The virus spreads from pulmonary parenchyma to neural synapses and cardiorespiratory neurons confined to the brain medulla with consequent dysfunction of infected cardiorespiratory neurons which may prohibit spontaneous breathing [1,2].

ACE2 receptors manifested within the capillary endothelium interact with SARS-CoV-2 virus which disrupts the blood brain barrier and infiltrates vascular articulations with consequent ingression of cerebral circulation and central nervous system. Stagnant microcirculation may facilitate adherence of spike proteins to ACE2 receptors situated upon the capillary endothelium [2,3].

Additionally, disrupted endothelial lining due to amplified, adherent viral particles can expedite viral ingress into the brain. Blood brain barrier (BBB) is a common mode of SARS-CoV-2 viral ingress into the brain. Intact blood brain barrier can be traversed by internalization and viral transport across the cerebral endothelium with ambiguous manifestation of SARS-CoV-2 docking proteins [2,3].

SARS-CoV-2 associated cytokines such as interleukin 6(IL-6), interleukin 1 β (IL-1 β), tumour necrosis factor (TNF) and interleukin 17(IL-17) disrupt the blood brain barrier and facilitate viral ingress [2,3].

SARS-CoV-2 is posited to induce endothelial infection and inflammation of peripheral vascular articulations [1,3].

Comorbidities associated with COVID-19 such as cardiovascular disease or pre-existing neurological diseases may enhance permeability of the blood brain barrier in concurrence with cytokine secretion.

SARS-CoV-2 may invade the brain through median eminence of hypothalamus, circumventricular organs and various brain regions along with a permeable blood brain barrier demonstrating fenestrae in the capillary walls. Manifested ACE2 and transmembrane protease serine 2 (TMPRSS2) receptors may permit viral invasion into the hypothalamus which provides a portal of entry into the entire brain [3,4].

Non-neuronal cells of the olfactory epithelium manifest ACE2 receptors which facilitates binding, replication and accumulation of SARS-CoV-2. ACE2 and TMPRSS2 receptors are discernible within the proteins and ribonucleic acid (RNA) of epithelial, sustentacular cells of nasal mucosa although olfactory neurons are devoid of receptors. Thus, it may be surmised that brain infection commences at the olfactory epithelium although viral incrimination of olfactory epithelium or olfactory neurons remains debatable [3,4].

With neuronal appearance of the virus, spike proteins interact with ACE2 receptors manifest upon cerebral neuronal cells and initiate viral replication along with neuronal destruction in the absence of significant inflammation [3,4].

SARS-CoV-2 may invade the brain through infected immune cells which function as a viral reservoir. Monocytes, neutrophils and T lymphocytes infiltrate the brain through vascular articulations, meninges and choroid plexus. However, mode of viral transmission within immune cells as posited with viral propagation within macrophages or phagocytic uptake of virus infected cells or extracellular viral particles remains debatable. SARS-CoV-2 is internalized within nerve terminals through the mechanism of endocytosis, retrograde transport and trans-synaptic dissemination in order to disperse to diverse brain regions [3,4].

Molecular insignnia

An estimated three hundred human genes interact with SARS-CoV-2 proteins wherein around seventy three genes are expressed with brain manifestations. Aforesaid genes are enriched in energy metabolism and implicate cellular functions such as oxidation-reduction, nucleotide binding, electron carrier activity, transport and regulation of neuronal apoptosis. Additionally, genetic influence is observed in aminoacyl-tRNA biosynthesis [4,5].

Genes are significantly associated with emergence of pertinent features such as intellectual disability, developmental and cognitive delay, mental and motor retardation, occurrence of generalized hypotonia, neurodegenerative disease and mitochondrial complex I deficiency. Thus, it may be surmised that genetic signatures are preponderantly implicated in neurological manifestations following SARS-CoV-2 infection [4,5].

Hub genes such as LOX, FBN1, PRKACA, RHOA, PCNT, AKAP9 and CEP135 appear to be influential in regulating molecular network. Several genes such as PRKACA, CEP135, PCNT and AKAP9 interact with NSP13 of SARS-CoV-2. Genes such as LOX interact with ORF8 of SARS-CoV-2, a protein which is fundamental in viral replication [4,5].

Elderly subjects depict moderately upregulated genes in the cerebellum, hypothalamus, substantia nigra, hippocampus and frontal cortex [4,5]. Downregulation of genes occur in the olfactory bulb, thalamus and cortical regions of the brain which appear associated with impairment of sensory system, memory and cognition. Aforesaid genes are predominantly enriched within neurons and astrocytes and manifested in multiple brain regions, especially in the elderly [4,5].

Significant expression of pathogenic genes such as CYB5R3, ITGB1, COL6A1, NPC2, RHOA and RAB7A is observed in adult brain. The genes are consistently expressed in diverse viscera and manifest multi-system involvement in COVID-19. Gene interaction network is predominantly enriched with guanosine triphosphate (GTPase) activity and extracellular organization [4,5].

Spike protein of SARS-Cov-2 demonstrates intense binding affinity for ACE2 and transmembrane protease serine 2 (TMPRSS2) receptors with consequent viral ingress into the host. Implicated gene such as integrin beta-1 (ITGB1) interacts with hub genes as FBN1, PRKACA and RHOA with possible emergence of multiple neurological disorders [4,5].

Alternatively, modified expression of genes directly interacting with SARS-CoV-2 may prohibit viral adherence to the receptors and provide a potential therapeutic strategy [4,5].

Infective itinerary

Neurotrophic, neuro-invasive SARS-CoV-2 infiltrates the brain via multiple direct and indirect pathways. Virus entry in central nervous system occurs by infecting endothelial cells of the blood-brain-barrier, epithelial cells of choroid plexus generating the blood-cerebrospinal fluid (CSF) barrier or through inflammatory cells, a feature denominated as myeloid cell trafficking. SARS-CoV-2 may ingress the central nervous system through vascular articulations, olfactory or trigeminal nerves, cerebrospinal fluid (CSF) and the lymphatic system. Nevertheless, precise route of viral ingress remains unidentified [5,6].

Haematogenous or lymphatic route of infectivity appears improbable, especially in instances of preliminary infection. Possibly, SARS-CoV-2 initially invades peripheral nerve terminal and accedes the central nervous system through synapse-connected route or as a trans-synaptic transfer. Viral circulation in the bloodstream, interaction and subsequent derangement of capillary endothelium and configuration of viral particles determines viral access to the brain. Destruction of brain capillary endothelium and haemorrhage within the brain tissue may be lethal.

Thus, viral ingress in the brain may occur on account of vascular endothelium dysfunction and neuro-inflammation of the brain, especially in the elderly [6,7].

Additionally, the virus can utilize retrograde axonal transport to access the nervous system. Retrograde axonal transport emerges through the olfactory, respiratory and enteric nervous system networks. Following infection of nasal cells the virus can directly invade the brain possibly through olfactory bulbs and briskly progress into specific areas such as the thalamus or brainstem, thereby engendering inflammation and neural demyelination [6,7].

SARS-Cov-2 may infect nasal passages and disrupt sense of smell and taste. The virus may accede central nervous system through a synapse-connected route following invasion of peripheral nerve terminals of the respiratory network [6,7].

SARS-CoV-2 can utilize sympathetic afferent neurons of the enteric nervous system (ENS) in order to ingress the central nervous system (CNS) during gastrointestinal tract infection [6,7].

An average time of eight days from appearance of preliminary symptoms to admission in intensive care is contemplated to be a sufficient window period for invading and destroying medullary neurons [6,7].

Provenance of central nervous system

Infection with SARS-CoV-2 triggers the “cytokine storm” which engenders nervous system damage. Cytokines are miniature, chemically induced signal molecules which create a healthy immune response. Cytokine storm demonstrates significantly enhanced levels of certain cytokines which initiates an autoimmune response with immune cells damaging healthy tissues.

Acute haemorrhagic necrotizing encephalopathy induces neuro-inflammation with brain dysfunction engendered from a cytokine storm which characteristically depicts elevated production of interleukin 6 (IL-6) [7,8].

Cytokine interleukin 6 (IL-6) appears due to activated T helper cells which configure granulocyte macrophage colony stimulating factor (GM-CSF). Also, cytokine storm may create a gush of interleukins, interferons, monocytes, macrophage inflammatory proteins and tumour necrosis factor with consequent emergence of hyper-inflammation. Induced systematic inflammation engenders severe encephalopathy which may cause stroke [7,8].

Immune-mediated events with cytokine or chemokine pathways or T cell interference may ultimately generate vascular leakage, demyelination, activation of complement and coagulation cascade followed by end-organ damage [7,8].

SARS-CoV-2 induced nervous system damage with accompanying activation of the immune system is concurrent to severity of COVID-19 symptoms [7,8].

SARS-Cov-2 infection is associated with cerebrovascular accidents. Massive haemorrhage within the brain hemispheres with intraventricular and subarachnoid extension may ensue. Cytokine storms and hyper-inflammatory reaction may engender acute myelitis. Acute flaccid paralysis of lower limbs and sensory symptoms at T-10 with uncontrollable leakage of urinary bladder and bowel is encountered [7,8].

Symptoms and significance

Disease onset is indicated by fever, cough and anorexia. Neurologic manifestations are categorized as central nervous system (CNS), peripheral nervous system (PNS) and skeletal muscle involvement [9,10].

Central nervous system (CNS) manifestations are demonstrated as dizziness and headache. Altered consciousness, agitation, hyperkinetic delirium, dysexecutive syndrome composed of inattention, disorientation and poorly organized movements on command may ensue. Infection of olfactory system is consistently associated with anosmia [9,10].

Associated comorbid conditions such as hypertension, diabetes, cerebrovascular disease, chronic renal disease and malignant neoplasms may enhance disease severity [9,10].

Cerebrovascular manifestations with ischemic stroke, intracerebral haemorrhage, central nervous system (CNS) vasculitis, altered mental status and encephalitis are observed. Additionally, psychiatric manifestation with psychosis, neurocognitive (dementia-like) syndrome and an affective disorder may ensue [9,10].

Central nervous system manifests SARS-CoV-2 infection by demonstrating epilepsy, ataxia, encephalitis, impaired consciousness, acute haemorrhagic necrotizing encephalopathy (ANE), headache, bilateral facial weakness, diplopia and oscillopsia. Headache and dizziness are contemplated to be non-specific minor symptoms of SARS-CoV-2 infection [9,10].

Subjects with COVID-19 may demonstrate neurological symptoms such as nausea, vomiting, encephalopathy, acute cerebrovascular diseases, meningitis, multi-territorial infarcts, large vessel occlusion and infrequently, ischaemic stroke. Anomalous clotting of blood may clog brain arteries and engender a stroke [9,10].

Impaired consciousness and delirium are associated with enhanced tendon reflexes, ankle clonus and bilateral extensor plantar reflexes. COVID-19-related impaired consciousness and delirium possibly arise due to infectious, toxic or septic encephalopathy engendered due to systemic inflammatory response syndrome-related toxemia and hypoxia [10,11].

Acute haemorrhagic necrotizing encephalopathy (ANE) occurs due to cytokine storm with disruption of the blood brain barrier along with neuro-inflammation with consequent brain dysfunction [10,11].

Neuropsychiatric manifestations of acute illness with SARS-CoV-2 appear as insomnia, anxiety, memory impairment, depression and confusion [10,11].

Post-illness stage represents sleep disorder with insomnia, fatigue, memory impairment with traumatic memories, irritability, anxiety and depression [10,11].

Subjects in intensive care exhibit delirium, altered consciousness, encephalopathy with agitation or confusion and corticospinal tract signs. Individuals with COVID-19 pneumonia in intensive care may demonstrate thrombotic complications such as pulmonary thromboembolism, venous thromboembolic events and ischemic stroke. Thromboembolic complications appear due to a pro-coagulant profile occurring in COVID-19 with elevated D-dimer, hyper-fibrinogenemia and platelet and fibrinogen induced tough clots with increased values of interleukin 6 (IL-6) [10,11].

Acute onset cerebellar ataxia followed by encephalopathy may appear following SARS-CoV-2-induced pneumonia. Severity of clinical symptoms is enhanced in COVID-19 subjects with pre-existing neurological disorders [10,11].

Severely hypoxic SARS-CoV-2 infected individuals demonstrate central nervous system injury with occurrence of cerebral vasodilation, swelling of brain cells, interstitial oedema, cerebral blood flow obstruction, ischemia, congestion and acute cerebrovascular disease [10,11].

Infrequently discerned clinical symptoms are intracerebral haemorrhage, cerebral venous thrombosis, mild neck stiffness, generalized myoclonus, seizures, status epilepticus, acute epileptic encephalopathy, haemorrhagic posterior reversible encephalopathy syndrome, acute necrotizing encephalopathy, meningo-encephalitis, inflammatory lesions of the white matter and globus pallidum, diffuse leuko-encephalopathy with micro-haemorrhages, steroid-responsive encephalitis, neuroleptic malignant syndrome and post-infectious acute transverse myelitis [10,11].

Haemorrhagic white matter lesions are disseminated within the cerebral hemispheres circumscribed by foci of axonal injury and macrophages. Subcortical white matter demonstrates clusters of macrophages, axonal injury and perivascular acute disseminated encephalomyelitis (ADEM)-like appearance [10,11].

Immune mediated neurological complications of SARS-CoV-2 infected central nervous system appear with decimation of acute phase and simulate classic post infectious inflammatory conditions such as acute disseminated encephalomyelitis and acute necrotizing haemorrhagic encephalopathy [10,11].

Neurological manifestations like Guillain-Barre syndrome (GBS) and olfactory dysfunction are delineated [11].

Oedema of brain tissue and partial neuronal degeneration can be discerned on autopsy [9,11].

Histological elucidation

Transmission electron microscopic examination depicts neuro-invasive nature of SARS-CoV-2 and possible routes of transmission to the central nervous system (CNS). Viral particles of 80 nanometres to 110 nanometres may appear within the frontal lobe and appear confined within miniature vesicles of endothelial cells. Ingress or egress of blebs of viral particles within the endothelial wall is indicative of viral movement across brain microvascular endothelial cells into the neural system [4,5].

Besides, neural cell bodies exhibit enlarged cytoplasmic vacuoles constituted of enveloped viral particles with distinctive, stalk-like projections [4,5].

Assay and analysis

Viral encephalitis in COVID-19 is associated with the presence of ribonucleic acid (RNA) of SARS-CoV-2 within the cerebrospinal fluid (CSF) which can be detected with genome sequencing [8,9].

Clinical symptoms of acute haemorrhagic necrotizing encephalopathy occurring in COVID-19 may be discerned with computerized tomography (CT) and magnetic resonance imaging (MRI) [8,9].

Magnetic resonance imaging (MRI) of the brain may demonstrate hyper-intense signals along lateral ventricular walls, mesial temporal lobe or hippocampus, possibly indicating meningitis due to SARS-CoV-2 [8,9].

MRI may depict an enhanced signal intensity within the olfactory cortex indicative of SARS-CoV-2 infection [8,9].

Polymerase chain reaction (PCR) may also be employed to confirm a SARS-CoV-2 infection [9,10].

Olfactory epithelium of the nasal cavity is contemplated to be an appropriate tissue for detecting SARS-CoV-2 in preliminary infection, in contrast to sputum or nasopharyngeal swabs [9,10].

Severe infection with SARS-CoV-2 is associated with significantly elevated levels of D-dimer, indicative of consumptive coagulopathy [9,10].

Coagulation dysfunction with elevated fibrinogen and D-dimer values commonly discerned in COVID-19 are concurrent to disease severity. Disease alleviation and recovery is indicated by normalization of fibrinogen levels and activated partial thromboplastin time [10,11].

Epilepsy appearing in concurrence with SARS-Cov-2 infection necessitates evaluation of pertinent pharmacological interactions. Non-convulsive status epilepticus appearing in COVID-19 may be investigated with continuous electroencephalographic (EEG) monitoring. Electroencephalography (EEG) may depict nonspecific features [10,11].

Currently, a specific treatment protocol for managing neurological repercussions of SARS-CoV-2 infection is absent and singular clinical manifestations mandate pertinent, individualistic therapy [10,11].

SARS-CoV-2 proteins	Genes
M protein	AASS, ACADM, ETFA, PMPCA, TARS2
N protein	RBM28, SNIP1
E protein	AP3B1
NSP1	PKP2, POLA1
NSP4	ALG11
NSP12	BCKDK, TCF12
NSP7	COMT, CYB5R3, DNAJC19, GNB1, MOGS, NDUFAF2, RAB18, RAB7A, RHOA, SCARB1
NSP8	EXOXC3, EXOSC8, LARP7, NARS2, SEPSECS
NSP9	FBLN5, FBN1, FN2, MIB1, NUP62, POR
NSP2	GIGYF2
NSP14	GLA
NSP6	SIGMAR1
NSP13	TBK1, PRKACA, RDX, NIN, PCNT, GCC1, CEP135, CENPF, CDK5RAP2, AKAP9
ORF9c	ACAD9, BCS1L, NDUFAF1, NDUFB9, PIGO, WFS1
ORF9b	SLC9A3R1
ORF8	ADAM9, COL6A1, DNMT1, FKBP10, GDF15, IL17RA, ITGB1, LOX, MFG8, NEU1, NGLY1, NPC2, PLAT, SIL1, SMOC1, TOR1A

Table: SARS-CoV-2 molecular targets in the brain [4].

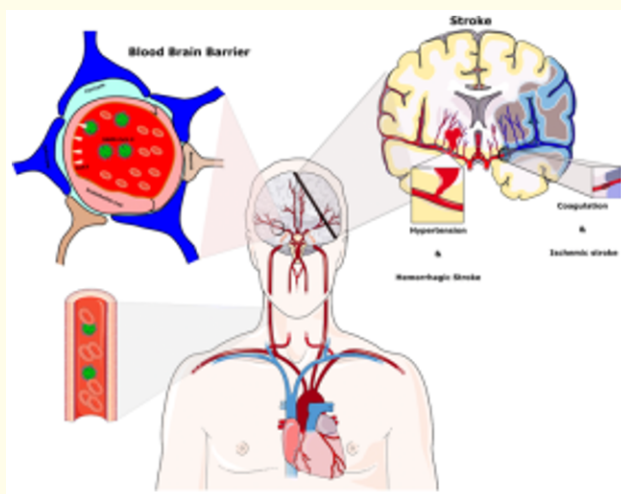


Figure 1: Brain infection with SARS-CoV-2 with viral ingress through the blood brain barrier and associated clinical symptoms [12].

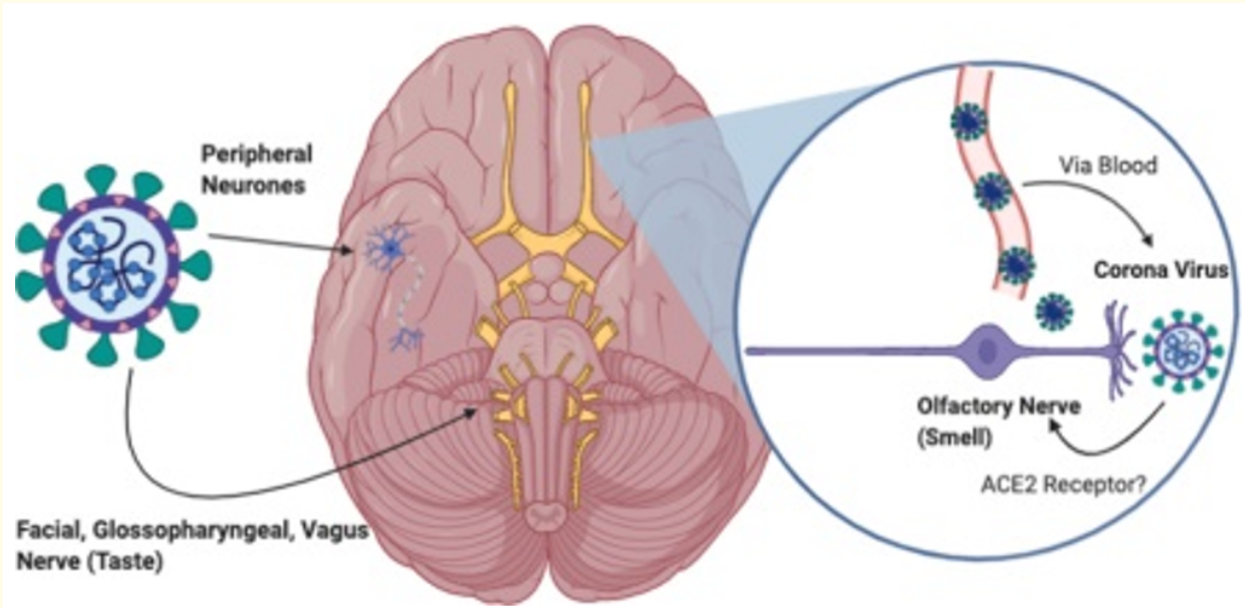


Figure 2: Brain infection in SARS-CoV-2 with viral invasion of neurons engendering clinical symptoms and implicated receptors [13].

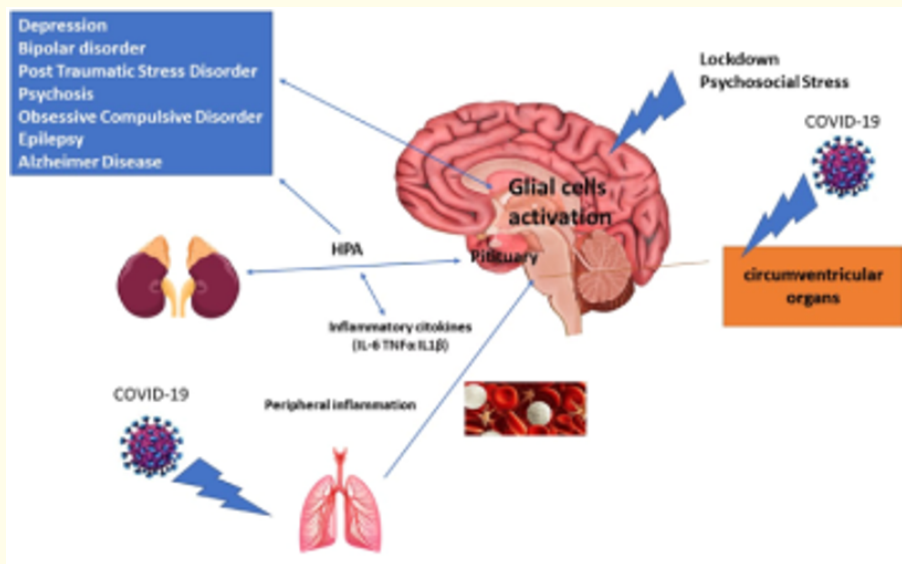


Figure 3: Brain infection in SARS-CoV-2 with incriminated cytokines and diverse clinical manifestations [14].

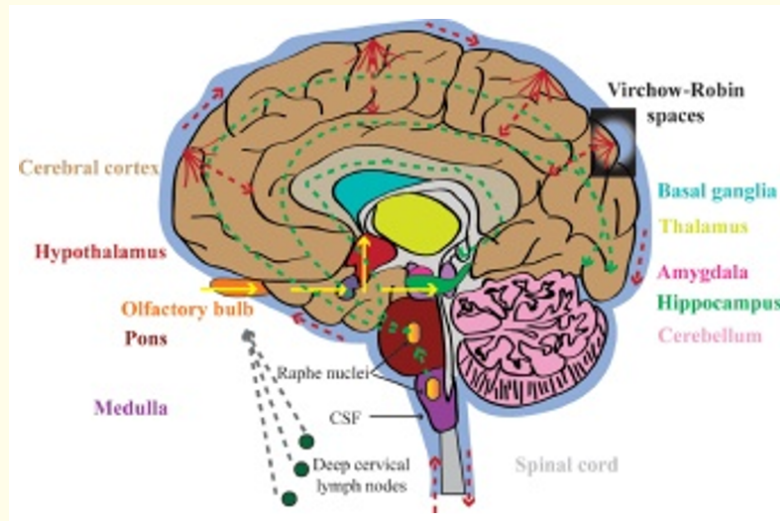


Figure 4: Brain infection ins SARS-CoV-2 demonstrating different regions of the brain with viral invasion [15].

Bibliography

1. Nuzzo D and Picone P. "Potential neurological effects of severe COVID-19 infection". *Journal of Neuroscience Research* 158 (2020): 1-5.
2. Iadecola C., et al. "Effects of COVID-19 on the Nervous System". *Cell* 183.1 (2020): 16-27.
3. Orsucci D., et al. "Neurological features of COVID-19 and their treatment: a review". *Drugs Context* (2020).
4. Khatoon F., et al. "Neurological manifestations of COVID-19: available evidences and a new paradigm". *Journal of Neurology* 26.5 (2020): 619-630.
5. Filatov A., et al. "Neurological complications of coronavirus disease (COVID-19): encephalopathy". *Cureus* 12.3 (2020).
6. Gklinos P. "Neurological manifestations of COVID-19: a review of what we know so far". *Journal of Neurology* 267 (2020): 2485-2489.
7. Gokhman D., et al. "Gene ORGANizer: linking genes to the organs they affect". *Nucleic Acids Research* 45.1 (2017): W138-W145.
8. Cervellati C., et al. "Inflammation in neurological disorders: the thin boundary between brain and periphery". *Antioxidants and Redox Signaling* (2020): 9.
9. Belvis R. "Headaches during COVID-19: my clinical case and review of the literature". *Headache* (2020).
10. Helms J., et al. "Neurologic features in severe sars-cov-2 infection". *The New England Journal of Medicine* (2020).
11. Sanders BJ., et al. "Hyperactive delirium requires more aggressive management in patients with COVID-19: temporarily rethinking "low and slow". *Journal of Pain and Symptom Management* 20 (2020): S0885-3924.

12. Image 1 Courtesy: Springer link.
13. Image 2 Courtesy: Wiley online library.
14. Image 3 Courtesy: Nature.com.
15. Image 4 Courtesy: Lancet.

Volume 13 Issue 7 July 2021

© All rights reserved by Anubha Bajaj.