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NEUROLOGICAL MANIFESTATION OF COVID-19: A SHORT REVIEW

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ABSTRACT

During the ongoing COVID-19 infection, one must understand all the aspects of this deadly disease caused by SARS-CoV-2 virus, to make the world disease-free. This review which attempts at understanding the causes, mechanisms and symptoms of various neurological diseases manifested post-COVID infection is one such aspect. SARS-CoV-2 virus invades the human systems through receptors namely ACE-2 and TMPSS2, through haematological, neurological or the inflammatory route. The epithelial cells for olfaction and sensory ciliated neurons are affected, impairing smell perception. The viral replication within the taste buds and peripheral chemoreceptors damages the cranial nerves responsible for gustation. Encephalopathy occurs in various forms including lesion of the right temporal lobe, delirium, corpus callosum injury, oedema, nystagmus and cerebritis. The clumping of blood within the vessels is common. Since endothelium is spread all over the body, no organs, except a few, are spared from viral infection. GBS characterized by weakness of lower limbs, paralysis, myelitis and Miller-Fisher syndrome are prominent. Blurred vision, pupillary defects, retinal vasculitis occur during optic neuritis damaging optic nerves of the orbital cortex. Hearing loss, clot-formation in cochlea and auditory pathway occur during sensorineural impairment. Nociceptors get hyper-stimulated causing pain. The cytokine storm releasing inflammatory mediators is another manifestation.

KEYWORDS: COVID-19, neurological, coagulopathy, encephalopathy, inflammation.

INTRODUCTION

Coronaviruses belong to the Coronaviridae family in the Nidovirales order. Corona represents crown-like spikes on the outer surface of the virus; thus, it was named Coronavirus. The

SARS-CoV-2 was found to be a positive- stranded RNA virus belonging to the genus beta coronavirus with a crown due to the presence of spike glycoproteins on the envelope. The most common clinical symptoms of COVID-19 are fever and cough, shortness of breath, other breathing difficulties, non-specific symptoms like headache, dyspnoea, fatigue and muscle pain. Patients also complain of digestive symptoms such as diarrhoea and vomiting. Absence of fever cannot rule out the possibility of COVID-19 as patients initially have fever with or without respiratory symptoms, various degrees of lung abnormalities develop later.[1] Although the above stated symptoms are considered as the most common clinical symptoms of COVID-19, manifestations of neurological disorders are not uncommon. Although neurological and neuropsychiatric manifestations of COVID-19 are abundant; these are only beginning to unravel.

General Mechanisms By Which Sars-Cov-2 Invade Nervous System

Direct viral invasion

It can be stated that the specific intrathecal antibody production can be caused by SARS-CoV-2 as is evident by the presence of SARS-CoV-2 in the CSF.[2]

Immunological Invasion

The probability of human cells to get affected by SARS-CoV-2 and severity of the infection depends on the ability of the virus to evade the immune defence system; and during the process the immune response is heavily affected due to modifications in interaction and activation of WBCs and depletion of natural killer cells (NK) which results in prominent reduction of such defence responses thereby impairing the immune system. More complex B and T cell mechanisms are required in order to effectively prevent the host's body from viral attack.[3]

Immunological invasion in respiratory system

Cytokine storm, characterized by elevated serum levels of proinflammatory mediators (of which monocytes and macrophages are the main uncontrolled sources of mediators like TNF-α and IL-6 in respiratory tract as well as peripheral blood, in case of COVID -19 patients) is also found during acute respiratory distress syndrome (ARDS).[4]

Haematological & Neurological invasion

SARS-CoV-2 can be thought to have a high neuroinvasive potential due to the high expression level of ACE-2 receptors in the neurons, endothelial cells and astrocytes. The

virus disrupts the blood-brain barrier and/or finds its way through the passage between meninges and ventricular wall, in brain, thus invading the nervous system. Other invasive routes include viral transfer by retrograde machinery transport, trans-synaptic spread of virus through membrane-coated exocytosis followed by endocytosis, in post-synaptic neurons; though many other routes are possible[5] due to which the infected endothelial cells of BBB and the leucocytes may spread the virus to other tissues, hence increasing the severity of the infection.

Haematological & Neurological Invasion in the respiratory system

SARS-CoV-2 enters lung cells via the ACE2 receptor. The virus is engulfed by the macrophages before causing any cellular attack which can then spread to other organs and infect ACE2-expressing cells at local sites, causing other organs to be injured as well.[6]

Neurological Manifestations During Covid-19

1. Anosmia

SARS-CoV-2 enters into human cells through two major targets: i) ACE-2 which encodes the main receptor protein and ii) TMPRSS2 (which encodes an enzyme thought to be important for SARS-CoV-2 entry into the cell). The cells in the olfactory epithelium (specialized tissue in the roof of the nasal cavity responsible for odour detection that contains olfactory sensory neurons and a variety of supporting cells) exhibits high level of expression of these two receptors. ACE2 is expressed in epithelial cells of the tongue; but probably not in taste buds but ACE2 inhibitor drugs are known to induce taste (and smell) disorders.[7] Increased ACE-2 expression in the ciliated cells, in particular; and nasal respiratory epithelium, in general; causes intranasal viral entry into the human host.[8] The virus is sheltered in the sensory ciliated neurons which performs the function of perceiving smell from odorous molecules which first disrupts lamellar olfactory epithelium and then causes its apoptosis. So, coronavirus infection eventually spreads to the olfactory bulb (first cerebral relay station), where viral RNA and consequently inflammation might be present.[9] The virus enters into the host cell by cell protease-mediated activity which causes priming of the S protein (spike protein), which break the S protein at the S1/S2 domain boundary and at the S2' site, so that S1 dissociates and S2 undergoes a structural change. This causes the virus to fuse with the host cell membranes. Other alternative mechanisms for S protein activation after binding with ACE-2 includes endocytosis and cleavage by pH dependent cysteine protease.[10]

2. Ageusia

A partial or complete loss of taste sensation or dysgeusia is often one of the most frequently manifested neurological symptoms during COVID-19. However, taste sensation is less severely affected than smell sensation.[11] SARS- CoV-2 invades epithelial cells of taste buds and salivary glands as these have sufficient ACE-2 receptors; expression of which suffices the novelty of infection. This permits viral replication and accumulation destroys ACE-2 expressing cells of taste buds and peripheral taste neurosensory chemoreceptors or direct damage to cranial nerves (VII, IX or X) responsible for gustation; by the viral lytic pathway.[12] Recovery from gustatory dysfunction is more rapid as compared to olfactory sensation compromise, which is a continued improvement of chemosensory function indicating that the viral pathogenetic mechanism has more diminishing effects on taste receptors or local inflammation rather than central nervous system invasion causing permanent damage.[13] Although mechanisms are different; among the three taste disorders, dysgeusia has a higher prevalence (41.3%) than ageusia (28%) and hypogeusia (33.5%).[14] Presence of taste alterations may not be present during other severe symptoms like dyspnoea, fever and cough. In most of the patients, one or more specific taste modalities are selectively decreased (most often the salty taste), instead of affecting the only the general taste sensation, hence assuring this as a more confirmatory symptom of the disease.[15]

3. Encephalopathy

The SARS-CoV-2 virus enters the brain from the lungs and gut through the olfactory system by using the retrograde axonal transport system. This invasion is mediated through a wide variety of mechanisms which include entry through ACE-2 receptors of neurons and endothelial cells, transport of WBCs to the required site in order to encourage the immune system to fight the viral infection (the Trojan Horse Mechanism). Although a group of these patients may not show any neuroimaging abnormalities, these properties of virus-induced encephalopathy may be identified by high intensity T2-FLAIR signals in two or more patches in white matter of cerebral cortex, subcortex, brainstem, optic nerves and spinal cord.[16] Pre-existing neurological disorder, chronic kidney disease, sepsis-induced encephalopathy, delirium are conditions that make SARS-CoV-2 patients extra-prone to COVID-induced encephalopathy.[17] Toxic metabolic encephalopathy occurs in 12% of the COVID-19 patients and accounts for an increased risk of in-hospital mortality.[18] Encephalopathy gives rise to other symptoms like lack of cognition, delirium, coma and other behavioural changes,

however detection of virus in CSF alone cannot confirm encephalitis if there is no brain inflammation.

The occurrence of epilepsy in right temporal region during the very initial stages of the viral infection and cerebral dysfunction, toxic metabolic encephalopathy in late stages of the infection can be detected through EEG. Contrast-free MRI proves the prevalence of cerebritis due to the presence of necrotized tissue patches called lacunar infarcts in cortical (parieto-occipital lobe) and para-ventricular regions.[19] These conditions come along with brainstem impairment, lesions in white matter, delirium and corpus-callosum injury.[20] Additionally, the content of right temporal lobe may become sparsely dense if embolic stroke pre-exists and waves of left temporal lobe may show sharply discrete waves due to left temporal dysfunction which can be confirmed with the help of CT Scan and EEG respectively.[21] The varieties of encephalopathy may range from acute necrotizing encephalopathy with extended symptoms like systemic inflammatory response syndrome (SIRS), cytokine storm or myocarditis to encephalitis accompanied by increased levels of interleukins and ACE in the CSF, which is symbolic of inflammation.[22]

Encephalopathy may be one of the many symptoms that are likely to be manifested. If encephalopathy is prevalent with symptoms like decreased level of alertness, hypoxia-induced leukoencephalopathy, cytokine cascade causing cerebral microbleeds from small vessels of brain tissue, oedema in pons and basal ganglia, demyelination; then COVID 19 viral infection may be more precisely confirmed.[23]

The general causes of encephalopathy are numerous and varied; they include infections, anoxia, metabolic problems, toxins, drugs, physiologic changes, trauma, and other causes. Encephalopathy is a general term that means brain disease, damage, or malfunction. The major symptom of encephalopathy is an altered mental state but when encephalopathy persists along with other symptoms of COVID -19, the case might be fatal.

Wernicke's encephalopathy is another variety that might occur in COVID -19 patients in which nystagmus, ataxia and confusion are the primary expressions indicating impairment in ophthalmology[24] but it is often lately detected as diagnostic procedures includes thiamine depletion.[25]

4. Coagulopathy

A COVID-19 infection of more serious concern or high severity level makes the patients more prone to occurrence of coagulopathy characterized by prolonged prothrombin time, increased levels of fibrinogen, D-dimer and critically reactive protein (CRP) in blood.[26] Blood vessels of the brain get affected during COVID-19 due to the presence of ACE-2 receptors in the pericytes, smooth muscles of blood vessels of choroid plexus and the neurons of the neocortex. Here basigin and neurophilin 1 are used by the virus as alternative receptors to dock on the membrane of neural cells.[27] The viral attack of SARS-CoV-2 causes infiltration of cells in most of the organs including the brain causing lack of fibrin-splitting enzyme and imbalance of enzymes like serine protease leading to disturbed fibrinolytic regulation, consequently producing antibodies against phospholipids, an essential component of cells. Clogging of arteries within the heart leads to clotting of blood within the brain (thrombosis) which blocks the blood vessels of the brain parenchyma which evokes a situation known as a stroke.[27] The set of reactions of coagulation pathway and formation of blood clots are stimulated by increasing TF expression by endothelial cells and elevating VEGF levels caused by cytokine production which alters production of platelets.[28] Patients of COVID-19 may be affected by infarction of cerebral tissue on both the sides of the mid-axis. Haemorrhage in the intraventricular tissue and sub-arachnoid space may also be developed though evidences till date are rare. Binding to ACE 2 receptors of the CNS, increases the blood pressure and causes rupture of vascular walls due to deviations of autoregulation from normal and in the process endothelial cells of blood-brain barrier and epithelium of blood-CSF barrier get affected by SARS-CoV-2 after utilizing the haematological invasive pathway.[29] If brainstem is inflamed, failure to cause stimulation of phrenic muscles and elicitation of respiratory centres and interneurons located in the brainstem occurs, which lead to failure of coordination of responses triggered by mechanical, chemical, irritant stimuli. Muscular weakness and reduced power of contraction arise due to inadequate blood supply which results in oxidative stress.[30]

5. Guillain-Barre syndrome (GBS)

As triggered by other viral infections, SARS-CoV-2 can also cause GBS within about one week from the day of commencement of the viral infection – a phase when symptoms of the infection and those due to GBS cannot be separately recognised, probably due to novel autoantibody formation and activation of T-cells.[31] If Guillain-Barre syndrome is expressed as a manifestation of COVID-19 symptom, it exists from the very initial days unlike

neuropathy or myopathy where GBS occurs at a much later stage during advanced stage of the disease; for instance, polyradiculopathy.[32] The most common form of GBS occurring during COVID-19 is acute inflammatory demyelinating polyradiculoneuropathy (AIPD) and the inflammatory response mimics that of the gangliosides in the peripheral nerves. The other properties are weakness in the lower limbs, paralysis and flaccidity of limbs on both sides of the body, paraesthesia (tingling sensation due to pressure on nerves), loss of deep tendon reflexes (areflexia), diffusion of compound muscle action potential within the temporal lobe recorded from peroneal nerve, dispersion of sensory potentials, increased duration of latent period, decrease in velocity of conduction due to loss of myelin[33], cranial nerve impairment, radicular pain, acute motor axonal neuropathy, myositis and loss of plantar responses (flexion of the great toe performed by corticospinal tract.[34] Patients who had suffered from ill-effects of Epstein-Barr virus, Zika virus, Mycoplasma pneumonoae and Campylobacter jejuni[35] or have history of GBS and/or other neurological disorders, are more pre-disposed to the risk of developing COVID-19 infection. The extended symptoms after occurrence of GBS during COVID-19 infection are Miller Fisher syndrome, difficulty in sensory-motor transmission, myelitis, alteration in the pharyngeal and cervical region, ataxia, asymmetrical pain, fever, cough, headache, diarrhoea and dysphagia.[36]

6. Optic Neuritis

Specially in the old-aged, optic nerves may get inflamed as a result of SARS-CoV-2 infection along with inflammation of the optic papilla on only one side of the body. Optic neuropathy can be a more common case rather than optic neuritis in the age group of sixties, with high myelin oligodendrocyte glycoprotein (MOG) antibody levels in blood, a molecule required for maintaining oligodendrocyte function.[37] Blurring of vision, redness of eyes, pupillary defects, central scotoma, defective contrast-cum-colour vision, inflammation of vitreous and retinal vessels, papillary oedema, conjunctivitis, uveitis are other ailments associated with this condition.[38] In due course of the infection, hampered eye movements including diplopia, ptosis, nystagmus, fast downward and slow upward ocular movements called ocular bobbing, opsoclonus-myoclonus ataxia syndrome and other defects with visual fields are not uncommon.[39] Hypertrophy of various segments within the canalicular and orbital segments of either of the optic nerves confirm the presence of optic neuritis.[40] Optical neuritis due to COVID-19 infection is often inflammatory and usually unilateral.[41] Severely affected patients may report of soreness of eyes, mucoid discharge, swelling of eyelids, chemosis, episcleritis, sinusitis, dacryoadenitis and epiphora.[42]

7. Sensorineural Hearing Loss

Most of the cases of sensorineural losses during SARS-CoV-2 infection are sudden with properties like loss of hair cells and decrease in number of supporting cells of Organ of Corti, but ear canals and tympanic membranes may remain unaffected initially.[43] The nominal level at which hearing loss is observed is at 30 decibels which can affect any age group which has no inherent cause other than the viral attack caused by affected endothelium and clot formation within the cochlea or damaged central auditory neural pathways.[44] Ringing in the ears and tinnitus might be the related symptoms, though exact cause of tinnitus is unknown. The complains of sensory neural hearing loss show a recent gastric increase which is in sync with the increased number of COVID-19 infected cases.[45] This condition is more common among the females than the males and may lead to fullness in ears and dizziness**.** Sensorineural hearing loss demands timely treatment.[46]

8. Nerve Pain

The SARS-CoV-2 virus is likely to affect the brain and nerves not only in patients who are currently suffering from the infection but also those who have undergone recovery. The most assumed cause of nerve pain is the immune response due to arousal of cytokines which causes blood and lymph to leak from their respective vessels, characterized by numbness, tingling, muscle weakness and fatigue, though long term confinement to bed and being static at the time of COVID-19 attack might be another probable cause.[47] Patients who already had neurological pain had got their pain worsened after being affected by COVID-19 infection indicating a great neurotoxic potential of the SARS-CoV-2 virus.[48] The virus can affect both the central and peripheral nervous system. The motor nerves responsible for walking and other activities may get impaired producing cramps and weakness sensory nerves responsible for perceiving and relaying specific sensations may get damaged producing loss of sense of touch, smell, temperature or pain and lastly the autonomic nerves which are associated with physiological processes of digestion, breathing, cardiac cycle might become malfunctioning to initiate disorders like excess or absence of sweating, fall in blood pressure, heat intolerance and postural orthostatic tachycardia syndrome.[49] The neuropathic pain in corona-affected patients may be secondary to diabetes, spinal cord injury or prodromal pain but the main types include post stroke pain which is due to failure of inhibition in the process of central sensitization, ischaemic stroke and changes in the thalamus; acute transverse myelitis with burning sensations in areas innervated by spinal peripheral nerves and GBS-induced neuropathic pain.[50] The effects of neural damage are always more pronounced on muscles,

so myalgia and arthralgia are manifested due to increase in concentration of Prostaglandin E2 and cytokines in the blood accompanied by allodynia and hyperalgesia.[51] Nociceptors, which are the pain mediating receptors of peripheral nervous system, get excessively stimulation resulting in pain sensation.[52]

9. Acute Flaccid Paralysis and Acute Flaccid Myelitis (AFM)

Acute flaccid paralysis occurs due to atrophy of motor neurons in anterior horn of spinal cord or damage to the peripheral nervous system with associated symptoms like areflexia, hyporeflexia, sometimes even infecting neuromuscular junctions as well.[53] In addition to this there might be paralysis of lower limbs, retention of urine and loss of sphincter control.[54] Myelitis is due to COVID-19 infection is possible as ventral horns get affected, a Condition which can be featured by abdominal pain and inability to urinate.[55] The diagnosis of AFM being difficult, is often very misleading and may coexist with diffused oedema and cord signal changes. So, one must be careful to consider AFM as one of the rare manifestations of COVID -19.[56] This condition may also result if the patient has a history of low potassium levels or being paralysed at regular intervals; however, in such cases the condition may be restored to normal after adequate potassium supplementation.[57] The role of microorganisms like Mycoplasma pneumoniae, EBV, CMV, rhinovirus and measles in pathogenesis of acute myelitis is also widespread.[58]

10. Myositis

SARS-CoV-2 virus has the potential to cause myositis along with interstitial pneumonitis indicating autoimmune nature of the disease making it comparable with bilateral myositis, dermatomyositis, necrotizing myositis and specific overlap myositis.[59] Patients may also suffer from dyspnoea, myalgia, oedema of gastrocnemius muscle on both sides along with myositis manifested during COVID-19.[60] Of the various types, dermatomyositis is the most common one, and the condition exaggerate those patients who previously had suffered from myositis. The idiopathic inflammatory myositis and other autoimmune rheumatic diseases are prevalent.[61] Depending on the degree of seriousness of the COVID-19 infection, rhabdomyolysis, proximal weakness and muscular oedema may.[62] The decreased movement of shoulder and arms, tenderness of deltoid muscle, increase in myoglobin content, toxic myopathy come hand-in-hand.[63] More damage may be caused by type 1 interferon, necrosis of muscle, parvovirus, enterovirus, T cell lymphotropic virus accompanied by difficulties in performing daily activities.[64]

11. Impact of cytokine storm

Cytokine storm manifested during COVID-19 triggers many neurotoxic processes brought into effect by cell-mediated immune response, which is a result of chimeric antigen receptor T-cell (CAR-T) administration which is a fundamental treatment in patients with malignant haematological diseases. The other features of cytokine storm during COVID-19 can be explained through dysexecutive syndrome, failure in articulation of language, akinetic mutism and delirium – all due to neuroinflammatory processes elicited by cytokine storm predominantly by the NF-k(beta) signalling pathway caused by diffusion of astrocyte, microglial activation and immune cell trafficking.[65] The wrongful elevation in levels of pro-inflammatory cytokines during SARS-CoV-2 infection is persistent with impaired interleukin and interferon associated functions. Type 1 interferons (alpha, beta and capital omega forms) are expressed in the endothelium of organs including those of the CNS, which upregulate interferon-stimulated gene to produce antiviral response after being passed through different signalling cascades suggesting a protective role.[66] Cytokine storm, which elevates certain inflammatory and pro-inflammatory mediators, cause immense damage to the skeletal muscles- thus cytokine storm can account for subsequent neurological symptoms like ataxia, seizures, and headache, apart from the sole reason of ACE-2 receptors being present in those organs.[67] The various inflammatory routes adopted by the host body as a defending mechanism against the virus have deleterious effects which range from cognitive and motor dysfunction to other serious aberrations like anxiety and audio-visual disabilities. These sequential neurological damages may be manifested even after good ten years from the onset of primary infection, when all genomes, proteins, toxins of the virus have long been lost from the body of the host.[68] The limitless inflammation caused by cytokine storm, most of the times, lead to respiratory distress, injury to myocardium, kidney failure and adds to the severity of the disease. Cytokines released increases secretion of glucocorticoids and norepinephrine which together diminish spleen functioning due to immunosuppression via activation of the hypothalamo-pituitary-adrenocortical (HPA) axis. The cytokine storm is well-known for its role in demyelination; the cytokine storm within the cranium disrupts the blood-brain barrier, and it also affects the peripheral nervous system with acute dysimmune neuropathology just before the onset of pneumonia in a pre-infected COVID-19 infection.[69] The prevalence of cytokine storm may now be confirmed by performing medical tests like non-contrast CT scan of head which reveals decreased wave activity of bilateral medial thalami and MRI indicating haemorrhage in medial temporal lobes and sub insular regions.[70]

CONCLUSION

Neurological attack in COVID-19 patients is quite common, early recognition and treatment of which may produce positive outcomes, both in case of new-onset and pre-existing neurological diseases. A variety of neurological complications have been reported in COVID-19 through various studies. Headache, myalgia and malaise are common initial neurological symptoms. Severe neurological complications are either because of direct neural invasion, immunological reaction or hypoxic metabolic changes. The more light thrown on the diverse neurological aspects of COVID-19, more will the medical professionals be acquainted with the extent of these disorders during the infection, better will be the improvement and faster will be the recovery of the patient's health through various combinations of more stringent confirmatory diagnostic tests. All these new insights will indicate both the indirect and neurotropic roles of the SARS-CoV-2 virus and categorize them into graded groups according to the severity of the infection to provide better treatment and huge relief to those patients who have suffered the ill-effects of this deadly viral infection.

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