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Brain Fog and Neurological Aspects of COVID-19: A Review

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Abstract

Currently ongoing outbreak of COVID-19 disease is a defining and unrivalled worldwide crisis of this time in both magnitude and scale level. Though the respiratory tract is the primary target of this disease evidences revealed that the virus could also enter in central and peripheral nervous system leading to numerous neurological issues inclusion of little severe complication like seizures, improper consciousness and encephalitis. The virus could gain entry through CNS either from trans-synaptic way or from olfactory sensory neurons and also through epithelium in brain microvasculature which is damaged by usage of receptor ACE2 effective for neuropilin-1 cell surface receptor responsible for several aspects of infectivity in COVID-19 infection. The crucial symptoms among all of these are breathing problem seen in few of the patients. It could be indicative of irregular function within cardiopulmonary regulating center in brain. Thus these findings indicate the strong foundation for intense research is necessary for confirming the neurodegeneration of brain regulatory centers association with COVID-19 infection also if shares similarity with other strain of coronavirus which also have nervous system association. COVID-19 and its others strain of coronavirus infection associated neurological feature includes transmission pathways, invasion to the nervous system and other neurological disease. The receptor for this virus is found to be expressed in nervous system commonly known feature of this disease includes headaches, weakness, altered consciousness, hyposmia. Few mechanism are proposed for this diseases which are infection through cribriform plate, olfactory bulb they are involve in transmitting the olfactory nerves which carries the sense of smell and distribution through trans-synaptic transfer. The invasiveness of this disease to medullary cardiorespiratory center leads to refractory respiratory dysfunction in severe patients of COVID-19. An elevated number of COVID-19 cases with neurological complication are being supplemented to the experimental models with invasion to nervous system as a rational concern that this virus is a new neuropathogen. It leads to both chronic and acute neurological disorder needed to be elucidated in detail for future research.

Key words: COVID-19, Brain Fog, Encephalitis, Nervous system, Complication.

INTRODUCTION

As we all are aware from the disease COVID-19 and its associated symptoms like fever, coughing, breathing though few of the patients recover from this disease have been reported with lingering side effects in inclusion with brain fog. This had been perplexed by the medical investigating community through the study of long-term COVID-19 impact. Currently researchers of New-York described the potent symptoms of COVID-19 associated with neurological aspects which includes headache, dizziness, and drowsiness. The clinicians from entire country reported that patients had complained about these symptoms along with other like memory loss, confusion, problem in focusing something. A study conducted in COVID-19 patients for few months after hospitalization revealed approximately 30% patients were containing persistent memory loss problem but this was not seems to be noticed among patients were hospitalized even patients with mild symptoms found to be associated with neurological problems. Brain fog is basically describe as person containing disability in memorizing, finding words with attention and being swamp by simple task. The reason of brain fog occurrence could be release of molecules providing immune response against infection but effects of these molecule impacts nervous systems which causes brain fog.

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COVID-19 disease caused due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) works mainly through targeting angiotensin converting enzyme-2 (ACE2) receptor found on respiratory system and stimulates an immunological cascades instantly of cytokine response which affects vascular system and individual cells. Pathological mechanism involved with COVID-19 shows similarity with pathophysiological underpinning of acute Ischemia stroke caused due to the blockage in an artery which supplies blood to the brain. Nervous system association is common form early contagious stage (headache, contagious, anosmia and dizziness) to post infection brain fog and drowsiness with exploring assortment of cases and sequence of cases describing a broad array of neurological exemplification forming various research over it.[1] The association of COVID-19 with neurological disorders are divided into 5 main categories encephalopathies (disease affecting the brain), inflammatory central nervous system syndrome, ischemic strokes, peripheral neurological disorders and other central nervous system (CNS) disorders.[2] The investigations revealed longer extent post COVID-19 neurological consequences and symptoms provides an undebatable case for recognizing this effects also there is need of ongoing observation for all the cases of COVID-19 for post neuropsychiatric symptoms irrespective to clinical complexity of acute infection. The post syndrome effects extent has not been researched yet but various studies are reported in Belgium, Netherlands about this context in patient with mild to asymptomatic infection.[3] In United Kingdom many investigators has revealed the interminable symptoms frequently with COVID-19 infections from repeated observation with mention of brain fog and numerous other symptom among several of them.[4] As Post COVID-19 Neurological Symptoms (PCNS) is an evolving story which is being currently studied in a various sequence of patients. The first case of acute COVID-19 with severe neurological association had revealed the involvement of instant increment in immunological markers neutrophils/lymphocyte ratio (NLR) and increased inflammatory biomarker like C-reactive protein (CRP) D-dimer and its co-relation with complexity of disease.[5-8]

Likewise pro-inflammatory response of immune system for COVID-19 infection in few cases had resulted in extreme immune response by activation of neutrophils in larger scale, cytokine release and abnormalities in clotting, subsequently resulting in blockage of blood vessels neurovascular (thrombosis) and it leads to decreased blood supply to tissues and supply of oxygen and nutrients in affected area (ischemia) have been seen in various cases.[9,10] Infection induced activation of exterior coagulation system and reduced nitrous oxide level had been known for supporting the participation of vascular endothelium in COVID-19 pathobiology. Therefore, the ACE2 deficiency and hormonal system rennin-angiotensin both are found to be involved in worsening the COVID-19 prognosis and associated neurovascular involvement in patient consisting hypertension and diabetes

Post-infection of the disease

Pro-inflammatory component formation like interleukin-7, interferon gamma and various other cytokine are known for promoting and propagating post-stroke depression it had remarkable similarity with pathobiology of this disease.[11] As suggested earlier various potent patients of Post COVID-19 Neurological Symptoms (PCNS) are known, as described in many published articles.[12,13] There are 6 post-acute COVID-19 symptoms known that are dyspnea, pain in joints, chest, cough loss of smell or taste least common symptoms known are insomnia, fever, headache, reduced mental functioning (neurocognitive), myalgia, weakness, skin rash, depression, digestion related problems.

The rapid spread of this disease had resulted most of the respiratory illness seems to be involved in stimulation of neurological symptoms. Investigators of throat specialist had revealed that influenza found to be involved in up and down movement of nervous keyboard exciting disorder and pain in distinct parts of body. As few patient in 1889-92 influenza pandemic had reported to become troubled with paranoia, stabbing pains and nerve damage. Likely few of the investigators had linked the flu of 1981 pandemic to Parkinsonism, neuropsychiatric disorders and widely coinciding outbreak of sleeping sickness which could result in coma like state in patients. Still it had been debatable these two are causally connected.

The virus severe acute respiratory syndrome coronavirus (SARS-CoV-2) culprit of COVID-19 pandemic is found to be associated with neurological symptoms which is not really surprising, also other two strains of coronavirus Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV-1), had been involved with neurological symptoms. In a report it was published that 36% of COVID-19 patients developed neurological symptoms and various other like sensory impairments, impaired consciousness. Neurological symptoms are grouped into two distinct groups- first described can be manifested as confusion, delirious state encephalopathy or as strokes, nerve damage or any inflammation of brain. Second one represents long term symptoms following milder infection like sensations of numbness, headache and cognitive difficulties for occasionally seizures and inflammation of heart.

Effects of COVID-19 in human brain

The electron microscopic picture representing a proportion of ciliated cell in a COVID-19 patient's olfactory mucosa reveling the intact SARS-CoV-2 particles inside cells. Early in pandemic few researchers bothered about SARS-CoV-2 gaining access for brain and representing a neurotrophic virus. This offers an obvious hypothesis for few neurological symptoms observed also posing complex queries about how to therapeutically targeting pathological mechanism in brain. The genetic material of COVID-19 and MERS-CoV had been spotted in brains and even in common cold containing coronavirus protein are curiously known and this rarely leads to neurological symptoms.

This disease had led to greater than 120 million cases and 2.6 million mortality rate. Patients suffering from this disease contain both respiratory, gastrointestinal symptoms along with neuropsychiatric problems long and short term. The study revealed that some patients contain anosmia, cognitive, brain fog, depression, anxiety and even suicidal behavior. All these symptoms are found pre and post respiratory symptoms and are not relevant to respiratory insufficiency revealing individualistic behavior of brain damage.[14]

The study conducted in United States recognizes post COVID-19 neuropsychiatric symptoms in 20% to 70% of cases even in adolescent and in later months after symptoms associated with respiration is resolved this shows neurological association persistence. COVID-19 invasion from angiotensin-converting enzyme 2 (ACE-2) receptor could damage endothelial cells causing inflammation, blood clot and damage of brain. Beside results of pro-inflammatory actions which is release of cytokines from immune cells and activation of innate immune system leads to reduced production of monoamines (serotonin, dopamine, and norepinephrine), trophic factors and stimulation of microglia cells which enhances the production of glutamate, N-methyl-D-aspartate (NMDA) receptors there over activation leads to damage of neurons and many of the brain associated functioning.

This disease virus is also found to be known for penetrating olfactory mucosa which is the part of nasal mucosa and works as sensory organ for smell so the invasion of this virus to olfactory mucosa leads in loss of smell and taste which is one of the recovery or initial symptoms of COVID-19 and it could also enter to brain through cribriform plate with olfactory tract or from vagal pathways which provide neural connection between gastrointestinal tract and brain.

Therefore, evidences for it are not there till now. COVID-19 has the ability of crossing blood brain barrier due to inflammatory cytokines induced blood brain barrier instability or through monocytes.[15] This could arrive at brain tissue through circumventricular organ midline structures beside the ventricle monitors blood and cerebral spinal fluid content through capillaries lacking junction protein expressed in blood brain barrier. The proteins of COVID-19 virus were found in vascular endothelium cells of brain not in neuroglia cells.[16] Analysis done histopathologically of entire brain reveled microglial nodules phagocytosis of neurons in brain stem and least often in cortex and limbic structures associated in lymphocytic infiltration not any correlation was found between histopathological findings and amount of viral mRNA.[17] While other symptoms like ageusia, vomiting and dizziness could be associated with viral invasion of brain stem other long and short term neuropsychiatric symptoms are prone due to neuroinflammation and hypoxic injury. Brain stem involvement could be explained through persistent autonomic abnormalities and anxiety.

This disease could evident at acute phase or afterwards post-infections phenomena. Inconsistently involved neuropathological consequences of COVID-19 includes direct injury through virus, neural pathology emerging to hyper inflammatory state and further bleeding disorders which could be autoimmune neurological consequences of severe illness. The analysis of neurological problems in COVID-19 includes fatigue, dyspnea, muscles pain, nausea and headache. A sporadically reported symptom includes anorexia, malaise, dizziness, confusion.[18] The dyspnea problem in breathing is a neurological symptom perhaps is only presumptive attribution for investigators. Therefore, neurological divergence of dyspnea need to be examined in patients with its persistence and its neurophysiological correlation could be advantageous for understanding this disease in depth.

Central Nervous System (CNS) manifestations of COVID-19

The potential of COVID-19 in association of neuroinvasive is as of same class as MERS-CoV and SARS-CoV-1 strain of coronavirus which are involved in neurological injury. As ACE-2 had been considered as functional receptor for COVID-19 also it is found in many parts of human organs in inclusion of nervous system, respiratory system, vascular endothelium, making it potent target for COVID-19. Biologically, various assumptions had been made on its mechanism by which COVID-19 infection could directly influence the CNS. Directly its invasiveness had been suggested through olfactory sensory nerve, vascular endothelium at blood brain barrier greater amount of receptor Angiotensin-converting enzyme 2 (ACE-2) present in vascular endothelium and through migration of leucocyte across blood-brain barrier these all are the mechanism known for Central nervous system (CNS) associated direct invasion. Higher prevalence of both loss in smell and taste associated reports shows frontal lobe, restriction diffusion on MRI and swelling at upper part of nasal cavity named olfactory cleft.[19-22]

There could be involvement of olfactory nerve in forming hyposmia which a common finding in respiratory disease. Among the various cases in entire world some of the cases revealed neuro-invasiveness for this disease. Very low number cases of cerebrospinal fluid for this virus sequence positive demyelinating disease had been known.[23] The evidence reveled that neurological problems involvement with COVID-19 is not found to act directly.[24]

Peripheral Nervous System (PNS) manifestations of COVID-19

The commonly known disease for PNS which have been found to be related with COVID-19 is Guillain-Barre syndrome (GBS), neuropathies, brachial plexopathy and myopathies they shares symptoms with COVID-19 disease.[25,26] Infection of both para and post process are known to be the reason for various CNS and PNS associated neurological problems of COVID-19. It includes cytokine storm caused due to amplification and stimulation of immune system against this disease. Particularly innate immune system associated cells like neutrophil, natural killer cells, which secretes cytokine including IL-1,6,17, TNF alpha which could lead inflammatory cytokine cascades with collateral damage.[27] Other process of GBS is molecular mimicry of COVID-19 associated surface antigen leading to formation antibodies against ganglioside element of peripheral nerves. Also molecular mimicry is found to be postulated in post infections inflammation of brain and spinal cord with cross reactions against autoantigens of myelin.[28]

Various studies had revealed that COVID-19 virus could lead both hypogeusia and hyposmia disorders. The hyposmia could emerged from multiple causes like head trauma, exposure of toxic substances disease like Alzheimer's, Parkinson's and acute upper respiratory infection which damages the olfactory neuroepithelium named post-viral olfactory disorder. Various viruses have capability of invading the brain olfactory fila.[29] Viral infections may cause temporary olfactory dysfunction from inflammatory reaction of nasal mucosa and formation of rhinorrhea this is also found in few of the coronavirus infections.[30]

Mostly this disease patient complains PNS associated symptoms which are hypogeusia and hyposmia. The study conducted among COVID-19 patients revealed the prevalence of sense of smell and taste dysfunction which found in greater quantity in European population. This had been shown that COVID-19 cases olfactory symptoms could be seen earlier than any other symptoms suggesting that olfactory symptoms are important for detecting this disease at very initial stage.[31]

Partial or complete loss of both hypogeusia and hyposmia suddenly had been seen in initial stage of the disease.[32] Earlier studies had revealed few of the particular viruses in inclusion of COVID-19 could cause post-viral olfactory dysfunction from process beside nasal interference showing that this virus could directly influence the olfactory sensory epithelium. Similarly other study for this disease patient revealed chemosenstive irregularity in most cases and few reported with olfactory and gustatory disorders.[33] All of these reveled that COVID-19 infection could lead to both anosmia and hyposmia.

COVID-19 Infection and its associated morbidities

This disease had been known for causing moderate destruction of nervous system at both structural and functional level which results in inflammation of brain, neurological disorder due to neurotoxic and demyelinating

lesions.[34] Encephalitis is the condition occurs due to inflammation of brain which results from pathogen leading to neuronal destruction and lesions of neurological tissues. It is featured by sudden and unexpected incidence associated pre-exciting conditions and commonly seen symptoms like vomiting, fever, consciousness issues, convulsions and confusion.[35] This disease is also known for causing viral encephalitis and it was confirmed by the existence of viral genome in cerebrospinal fluid.[36] Beside this autopsy reports showed swelling in brain tissue and restricted neurodegeneration in dead patients.[37]

Acute toxic encephalitis is a kind of inconsistent brain disorder occurs due to various factors like dysfunction in metabolic pathways, toxemia and hypoxia resulting from this infection. Low level of oxygen (hypoxia) could leads to destruction of nervous system and their symptoms are found to be diverse and complicated. The patients with mild severity could result in symptoms like dysphoria (anxiety), headache, mental disorder and delirium while a severe infections this could result in development of coma, paralysis, loss in consciousness and disorientation.[38]

COVID-19 infected person also go through severe hypoxia and viremia condition and this could lead to toxic encephalopathy. Among all 40% of cases were found to report with the symptoms like headache, loss of consciousness and other brain associated difficulties also edema associated with brain tissue were revealed in autopsy report.[39] This all findings shown that COVID-19 could also lead to toxic encephalopathy in patients but in many of them moderate infectious cases neurological disorder is seen which could be ignored because they are under sedation. Various studies revealed that other strains of coronavirus could enter peripheral nerve terminals and further access to CNS from trans-synaptic pathway. Certainly such trans-synaptic conveyance occurs through COVID-19 virus is yet too understood.[40]

However, scanning of COVID-19 patients through computed tomography (CT), magnetic resonance imaging (MRI) showed acute necrotizing encephalopathy rarely found involved in viral infection of brain tissue reveling direct CNS infection by COVID-19.This encephalopathy is involved in cytokine release with intense quantity inside the skull this could lead to disintegration of blood brain barrier and elevation in shedding of viruses. Other ways known for viral infection of CNS either can be originated or carried from blood and lymphoid system. The route across a nerve synapse had been often suspicious for manifestation of PNS in COVID-19 infection in inclusion of hypogeusia and hyposmia

There are evidences of neurodegeneration found from MRI studies reveled that COVID-19 could be diagnosed in early stage. A report showed that unexpected neurological defacement with sudden temporary change in electrical impulse of brain in infected person owing to destruction in myelin sheath present as protective layer surrounding to the nerve fiber of brain. The investigation based on MRI report had shown newly detected demyelinating defects from COVID-19 infected patients hospitalized for complain of interstitial pneumonia which is a disorder associated in affecting tissue surrounded and separates the tiny air sacs of lungs and alteration associated with electrical impulse of brain.[41]

Hypoxia and Brain damage induced by COVID-19 infection

As coronavirus primary site of infection is respiratory tract and leads to respiratory depression. This could result to brain hypoxia which is more severe health problem. Brain is one of the important organs which consumes greater amount of energy and oxygen then other organ reduction in supply of oxygen to the brain is called hypoxia. Reduction in oxygen level decreases the energy production through cell and result to cell death. The hypoxia condition of brain leads to its injury hypertension, respiratory arrest stokes hypoxia brain could result in mild symptoms memory loss and coordination problem in body. Acute hypoxia condition of brain could lead to brain death and coma. The analysis done histologic reveals eosinophilic neuron are dead neuronal cells representation due to decreased level of oxygen.[42] Hypoxia inducible factor HIF-1 main transcriptional regulator of cellular and developmental response to hypoxia.[43] Multiple viral infection are been reported for influencing the HIF-1 alpha pathway stimulates distinct downstream effects like host cell associated alteration of cell metabolism, vesicle associated inflammation and expediting viral replication. The mechanism of viral stimulation of Hypoxia inducible factor (HIF-1α) by hepatitis B, Epstein-Barr viruses is by stabilizing it and through obstruction the posttranslational, prolyl hydroxylation or ubiquitination mechanism of HIF-1α.This disease infected person go through intense hypoxia and viremia condition containing capability of generating toxic encephalopathy. Few studies reveled that among all 40% of patients suffer from headaches, disconnected consciousness and other symptoms.[44]

Although, swelling in brain mostly forms hypoxia condition seen in brain tissues of infected patients by authors.[45] Frequently developing deterioration of lung functioning which results to hypoxemia condition is improved by oxygenation which is provided through prone position. The prone position elevates the oxygenation capability due to increased expression of nitric oxide in dorsal area of lungs in comparison to ventral vessels.[46] All facts provided through this revealed that decreased oxygen level in COVID-19 infected persons could be due to hypoxia condition associated lesions in brain.

Progression of the virus in the nervous system

COVID-19 disease associated virus invades the PNS and transport through ATP dependent transportation which is active transport through synaptic terminals and to cell body of neurons from retrograde transport in different location of brain this entire process is named neuronal dissemination model.[47] This process have been subsidize by studies associated with hemagglutinating encephalomyelitis virus strain 67N first strain found in invasion of procrine brain of coronavirus. The data of COVID-19 patients reveled neurological symptoms which includes headache, acute cerebrovascular disease, hyposmia and ataxia. This reveled that more critical patient's systemic presentation were more susceptible to neurological symptoms like inability of consciousness, cerebrovascular disease, and skeletal muscle injury in mild infection. Neurological symptoms which are least specific are also commonly observed with other viral infection in COVID-19 infection. Though its existence suggests slight degree of nervous system association but its advantages are still not clear in few of the patients.

Many of the patients of this disease had neurological destruction which may not denote the exact number of patients because many of the patients are sedated or are on ventilator. Neurological manifestation includes loss of consciousness which was seen in 88% of COVID-19 patients in few studies.[48]

Initial symptoms of COVID-19 includes loss of smell and taste in various cases a vulnerable way of initial entrance of virus from nose then migrating

upside from olfactory bulb and ultimately to upper area of brain including distal part of brain through trans-synaptic transport mechanism through which blood brain barrier diverged. This transportation of COVID-19 from outer periphery region to inner cortex and brainstem is a vulnerable process due to distinct reasons.

Various distinct viruses inclusion of avian bronchitis, alpha herpes, west nile, coronaviruses are found to associated in utilizing this process[49] The viral particles like herpes simplex virus (HSV1), rabies virus, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) are found in higher amount in distal part of brain constituting midbrain, pons, and medulla oblongata.[50] Neuroanatomy is basically the study associated with structure and organization of nervous system it had relatedness between nuclei of brainstem like solitary tract and the mechanical response associated receptor and chemoreceptor in lungs and respiratory tract as well as between nucleus uncertain of brainstem and airways cells. Few abnormalities may persuade to brainstem at risk of viral progression as seen for herpes virus.[60] Though, frequently breathing problem in COVID-19 cases could be due to cardiorespiratory center associated irregular function located in brainstem.[51] The patients cured from pneumonia which occurs due to COVID-19 infection are seen to collapse to disaffect from invasive mechanical ventilation the reason again is same due to irregular function of brain and central respiratory associated depression.[52]

Findings revealing that COVID-19 associated virus is neurotoxic specific to brainstem neurons and are constant with idea that it mediates respiratory damage from deterioration of neurons of brainstem occur because of budding of virus. Also frequent Computed tomography (CT)-scan reveals damage which occurs primarily in brainstem afterwards spread to other regions of brain.[53] As we all known breathing is an autonomous process regulated through pacemaker cells in brainstem in response of change in CO_2 or hydrogen ion concentration of arterial blood. Inspiration and expiration both process are regulated through voluntary action from direct input of motor neurons through cortex to respiratory muscle bypassing the brainstem. Though, from this it has been clearly known that frequent breathing problem had been seen in COVID-19 patients due to destruction of central respiratory neurons in brain it helps in elucidating the main molecular process of this disease. This indicates neuronal dysfunction leading to disability in respiration which had been important for instant undertaking prevention measures and also initiating treatments. There is requirement of knowing mechanism insights at larger scale of COVID-19 pathophysiology and virus effects on sensory organ, olfactory and gustatory function for initiating proper treatment. This virus could invade into the cells by proper spike protein subunit S1 binding to ACE2 promoted through Transmembrane protease serine (TMPSS2) by endocytosis clathrin coated complex.[54]

Main function of ACE2 is to convert angiotensinogen II to I reducing the harmful effect of angiotensin II like nitric oxide genesis, vasoconstriction, oxidation, inflammation and thrombosis by associating with angiotensin II type 1 receptor (AT1 receptor).[55]

ACE2 is also been associated in conversion of angiotensin II to Angiotensin (1-7) this provides benefits and opposite impact of angiotensin II inclusion of vasodilation and decreased inflammation from Mas-receptor (Mas-R) which performs homeostasis, proliferation of cells, fibrosis and mainly function oppose of ACE2 receptor.[56] There are currently evidences for spike protein of virus interaction with ACE2 expression and downregulation.[57] It invariably enhances ACE 1 signaling along with elevated level of transformation of angiotensin I to II as reimbursing process which decreases nitric oxide secretion and enhances oxidative stress, inflammation and loss of structure and function of neuron in CNS. Cytokine activation reveling the elevated proinflammtory interleukins in COVID-19 patients is well known.[58] Various reports suggested that COVID-19 patient's shows moderate endothelial destruction which shows it is a disease of endothelial abnormal functioning.[59] This kind of endothelial damage could also occur in capillary endothelium of brain. Virions of this disease are found in cerebrospinal fluid of infected patients which supported this assumption.

This endothelial destruction of cerebral capillaries could lead to blood loss with harmful repercussions in disease patients. The infected neurons displays disarranged, hyperphosphorylation of protein tau which are involved in stabilization of neuronal microtubules various etiological factors leads to hyperphosphorylation of this protein and which ultimately leads to neuronal death.[60] This dysfunctioning probably associated with wider scale of neurological problems reported in the patients. The manifestation of this disease is frequent, diverse and come up with significant morbidity of disease. While problems like encephalopathy predictable affects old age population, inflammation and problems associated with thromboembolism influence young population and do not entirely correlate with severity of disease.[61] Additionally for instant neurological explanation of this disease elevated facts of post COVID-19 infections like drowsiness and brain fog are seen. These facts had provided knowledge and guidance of neurological problems management at this time of pandemic.

The infected patients with persistent neurological problems have to be provided with sufficient and regular medication should be maintained and proper health resource services consultation consideration will be appropriate for preventing the brain fog and neurological degeneration.

CONCLUSION

This disease had become a challenging issue in all over world after its emergence in December 2019 as its symptoms are associated with respiratory distress. They are also known to be involved in neurological manifestation. The elevated counts of COVID-19 patients with neurological problems additionally from investigations shows neuroinvasive evidences provides a rational concern for this infectious. This disease causing virus had emerged as a new neuropathogen which remain under diagnosed. As other strains of coronavirus COVID-19 had also been found in cerebrospinal fluid of brain in infected patients. The neurotrophic feature of this virus and its capability of causing neurological disorders had been implied in patients. The Angiotensin-converting enzyme 2 (ACE-2) receptor distribution in Peripheral Nervous System (PNS), Central nervous system (CNS) and other cells had been found consistently at low level with other neurological manifestation of COVID-19. In fact similar to intracranial I infections through other viruses this also shows vast scale of CNS associated problems in inclusion of vertigo, seizures, headache, intracranial bleeding and sudden loss of sensory organ responsible for smell and taste. In above mentioned symptoms hypogeusia and hyposmia had been identified as early and important symptoms dysfunction of nervous system for this disease. Also inability in breathing is one of the crucial symptoms seen in patients. This make interesting investigation to see whether cardiopulmonary regulatory centers in thalamus and brain stem is associated with loss in spontaneous breathing activity. The virus of disease had been not known that much

so more basic and clinical facts are necessary for it by which appropriate therapy could be manifested timely initiated at identified mechanism basis. The exploration of neurological manifestation of this disease is an initiative for elucidating this virus and preventing its contingences rate and protecting the mortality rate of patients and also proper treatment of infected patients in this pandemic.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

SARS-CoV-2: Severe acute respiratory syndrome coronavirus; **ACE2:** Angiotensin-converting enzyme 2; **CNS:** Central nervous system; **PCNS:** Post COVID-19 Neurological Symptoms; **CRP:** C-reactive protein (CRP); **MERS-CoV:** Middle East respiratory syndrome; **CT:** Computed tomography (CT); **MRI:** Magnetic resonance imaging; **HIF-1:** Hypoxia inducible factor HIF-1; **PNS:** Peripheral Nervous System; **HSV:** Herpes Simplex Virus; **TMPSS2:** Transmembrane protease serine.

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