



Consequences of Corona Virus on the Central Nervous System.

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ABSTRACT

COVID 19, declared as a pandemic, has affected and currently is affecting millions of populations. It is considered as a severe health crisis which affects multiple organs. In this review article there is focus on how novel corona virus has shown an association with CNS involvement. Invasion of virus into the CNS has led to a myriad of neurological symptoms like headache, nausea. Damage to respiratory center and cerebral infarction also occurs. There is a vivid description of various portals of virus entry into CNS such as via olfactory route, hematogenous, neuronal and via ACE II receptors leading to neurological complications like stroke and encephalitis. In multiple cases, increased inflammatory markers are seen like IL6, CRP and leukocytes which classically points towards a cytokine storm occurring in the body contracted with COVID 19 infection. Deranged blood parameters like D-dimer, fibrinogen etc has also been reported in COVID19 patients. In a nutshell, COVID 19 infection has proven to be highly fatal in patients untreated with a delayed treatment access and could lead to severe complications. Hence, utmost level of care and treatment is required to be given which is precisely highlighted in this article.

Keywords- Covid 19, CNS, ACE II receptors, CRP, leukocytes, D-dimer, fibrinogen.

I. INTRODUCTION -

Coronavirus is a positive stranded RNA virus, with genome encased in a nucleocapsid, and surrounded by a host-derived membrane studded with glycoprotein spikes. They are titled for their appearance under the microscope, which resembles a corona, or a crown, with pointed structures surrounding them. In December 2019, a novel strain of coronavirus emerged from the Wuhan province of China which rapidly spread worldwide. This resulting disease was termed COVID-19 by the

World Health Organization (WHO). The virus that causes COVID-19 is designated as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). According to WHO, some initial cases were linked to a wholesale food market in Wuhan. Coronavirus transmission occurs from respiratory droplets and fomites. This outbreak of respiratory illness was first reported to WHO on December 31st 2019 and on January 30th 2020, where WHO declared COVID19 to be a global health emergency and global pandemic on March 11, 2020 [1]. Besides China in southeast Asia, a case was reported in Thailand on 13th January 2020 where a 61 years old woman from Wuhan was tested positive making Thailand the first country except China to report a case. On 2nd February, the first death was reported of a 44 year old Chinese man in Philippines.

A large proportion of community suffers from acquired upper respiratory tract infections post contracting the virus. People usually tend to experience symptoms within 14 days of being exposed to the infection however in some cases patients can be asymptomatic yet positive for the virus that often causes runny nose, common cold, fever and extreme weakness. Patients may complain of neurological symptoms including headache, weakness, anosmia, myalgia and disturbed consciousness. Avila, Long, Holladay, & Gottlieb in October 2020 selected 95 resources which included case reports and series, retrospective and prospective studies and others which stated that Corona virus is highly lethal and affects patients with co-morbidities. Complications of coronavirus infection include septic shock, disseminated intravascular coagulation and many more. Remotely in recent studies it is also found that Corona virus is associated with the risk of stroke since an association of hypercoagulable state causing cardiovascular and neurovascular complications is seen [2].



RISK FACTORS -

In a study from China, it stated that 36.4% of patients hospitalized with COVID-19 infection had neurological manifestations[3] such as dizziness, impaired consciousness, seizures or acute cerebrovascular disease. Hyposmia, dyssomnia and dysgeusia's were the initial indications of nervous System involvement in Covid 19 patients[4]. A study states that SARS CoV-2 infection is associated with cytokine storm syndromes, which happens to be a risk factor for Acute Cerebrovascular disease. Prior cerebrovascular disease is also a risk factor. Recent infections both viral and bacterial serve as independent risk factors for acute cerebrovascular ischemia[5]. COVID-19 infection is also an independent risk factor in developing imaging Confirmed Acute Ischemic Stroke. In the study it's seen that, the neuronal cells can be affected by postinfectious autoimmune reactions, structural resemblance is seen between SARS- CoV-2 epitopes and several human proteins, autoimmune post infectious demyelinating syndrome can occur due to molecular mimicry between the virus epitope and myelin basic protein. In patients with severe covid 19 patients the lab value of D- Dimer formed at the end of Coagulation Pathway is higher, resulting in altered Coagulation Cascade which contributes to the risk of developing a thrombus, hence may lead to stroke. There is deranged Hemostasis leading to consumption of coagulation factors which could lead to Disseminated Intravascular Coagulation (DIC). It is also observed that alterations in blood pressure control, serve as a risk factor for cerebral vascular complications.

VIRUS ENTRY –

The squamous, respiratory and the sensory olfactory mucosae are the three regions of our nasal cavity which mediates the virus to enter our Central Nervous System. Squamous region is lined with stratified keratinized squamous epithelium and in normal conditions is unlikely to be a site of infection. Respiratory region lined by non-keratinized pseudostratified epithelium and is innervated by trigeminal nerve, which stems from the pons in the brainstem and has a potential pathway for the route of the virus. The olfactory region located cephalically to the respiratory region is lined with pseudostratified monolayer of epithelial cells and has olfactory sensory neurons, sustentacular cells and basal cells. There are two routes- Hematogenous transmission route and olfactory neuronal transport route. Respiratory viruses may infect the lower respiratory tract and

lung epithelia, which are in close contact with fine blood capillaries for oxygen transport. Viruses travel towards the basolateral side of lung epithelia, enter the bloodstream, and eventually infect monocytes/macrophages in blood capillaries. As a "Trojan Horse" route, these infected monocytes can travel to the CNS. Virus migrates from one neuron to another via synaptic terminal, employing cell motor proteins to eventually reach the CNS, in the olfactory neuronal transmission pathway.

PATHOPHYSIOLOGY-

Coronavirus not only affects the respiratory system but also the Central Nervous System. It causes nerve damage by various ways as stated in the recent studies[6]. First step of viral infection in the pathogenesis of COVID 19 infection is binding to a target host cell surface molecule which mimics a ligand-receptor interaction. The activation of a viral protein use metalloprotease as recognition molecule and other membrane bound enzymes such as transmembrane serine protease 2 (TMPRSS2) which plays a key role in facilitating SARS-CoV2 spike fusogenic activity on host cell plasma membrane and hence entry of virus into cell. Corona virus has the capability of infecting nerve cells and this has been proven by the presence of SARS CoV-2 in the cerebrospinal fluid of the infected patients having the viral encephalitis. According to a study, the Angiotensin II receptors have been found in the neuron, located inside the blood brain barrier, hence according to this it shows that there is brain Angiotensin II system. There are 2 Angiotensin II systems in brain. Angiotensin receptors respond to Angiotensin present in the Brain or which is transported to Brain. Angiotensin II of peripheral origin is responded by the Angiotensin II receptors in cerebrovascular endothelial cells and circumventricular Organs[7]. Studies show that the "cytokine storm" may contribute to the mortality in COVID-19[8]. Increased levels of IL-6 is observed in both COVID-19 and stroke cases. It is possible that IL-6 may play a key role in COVID-19 patients and concomitant stroke[9].

POST COVID COMPLICATIONS –

Neurological manifestations most likely were seen in patients with severe Covid 19 infection and some of the nonspecific manifestations include fatigue, loss of smell (anosmia), loss of taste (ageusia), headache, dizziness, ataxia and seizures. Specific neurological symptoms are seizures – associated with COVID-19 and can occur after the encephalopathy or because of severe illness, others being Meningitis,



acute myelitis, encephalitis, encephalopathy, hemorrhage, subarachnoid Hemorrhage, Central Nervous System Demyelination

TREATMENT OPTIONS FOR POST COVID COMPLICATIONS –

In the current scenario apart from COVID-19 vaccine, symptomatic treatment has also been implied. According to a report [10], intravenous thrombolysis (IV rTPA) was given to patients from the Southeast Asian Population (Philippines) after a stenosis has been seen on CT Angiography in the left MI section of the Middle Cerebral Artery, and the patient's right leg weakness strengthened instantly after the infusion. Prophylactic dose Low Molecular Weight Heparin (LMWH) should be considered in all COVID 19 patients even non critical ones who are Hospitalized in absence of any Contraindication like active bleeding [11], Tang et al showed, the mortality in these patients with coagulopathy is reduced with anticoagulation. In COVID 19 patients some exhibiting features of coagulopathy suggest Disseminated Intravascular Coagulation, a combination of Heparin + Nafamostat mesylate is recommended for its treatment. According to studies mechanical thrombectomy in patients ≥ 18 years having acute ischemic stroke, occlusion of the internal carotid artery or proximal middle cerebral artery can be used to treat the patients within 6 hours. In this procedure the interventional radiologist removes the clot from patient's artery using a specialized equipment [12]. Other study shows, Tocilizumab as Interleukin 6 inhibitor.

Interleukins are cytokines secreted by macrophage and Interleukin 6 stimulates production of Acute phase reactants used to control Cytokine storm and is relatively safe. Other therapies to control cytokine storm are Programmed cell death protein (PD-1, PD-L1 Checkpoint inhibition), Intravenous immunoglobulins [8]. Corticosteroids are used in patients having severe complications like renal and cardiac involvement and acute respiratory distress syndrome.

PSYCHOLOGICAL IMPACT -

As said by Jim E Wallis 'sometimes it takes a natural disaster to reveal a social disaster'. The present pandemic is wreaking havoc on people's mental health and wellbeing COVID 19 affects people of all ages producing anxiety, sadness, obsessive disorders, sorrow, sleep and stress disorders, uncertainty, dread and post-traumatic stress disorder in the long run. Taking it back to 2020 when the government announced the

national lockdown for the containment of the COVID 19 and their policy of distancing and it has been associated with a feeling of mass hysteria, loneliness, vulnerability and dependence as the announcement served as an abrupt change in the society.

There are studies to have shown effects of loneliness in a long run being stroke, hypertension, cardiovascular disease and also decrease in cognition. Loneliness seemed to occur more in the ones already with an underlying psychiatric disorder, women managing household elderly age group, single's, children, and the ones in quarantine, it also led to suicidal thoughts. Whereas on the contrary protective factors to experiencing loneliness were recruited (work from home) staying with family or having a partner. Various stressors have played a role in hampering mental stability, the fear to contract the deadly virus, distancing from peers, loss of employment and eventually financial crisis and death of near ones.

According to reports in India post lockdown there was an increment by 20% in mental issues, especially the media in the current scenario seems to trigger the anxiety 100 folds causing rush of stigmatization. Tapering down the stigma to the health line workers who play a pivotal role in this pandemic, their struggle with this situation is surfacing, with the constant burn out working for consecutive hours in personal protection kits, uncertain prognosis of the patients, major workload, resource shortages, pressure from the workplace making them highly susceptible to experience psychological disbalance.

There are reports stating that children and adolescents have as well been targeted to the inevitable to stress which the pandemic gets along, especially children being exposed to the fear of rapid spread of virus and constant talks of the virus in house leading them to be more susceptible to fear of it, also their outdoor activities put entirely on halt and schools being completely shut has affected them in a huge way mentally leading to irritability, nervousness and lack of interest in concentrating on studies and adjustment issues. In studies its reported that the mental impact on child losing their parents runs long ahead leading to psychosis, mood disorder and increased suicidal ratio in adulthood.

Every age group has its own juggle, the elderly staying away from their children have been prone to develop severe loneliness and happen to suffer from comorbidities, requiring off n on health checkups but the lockdown has led to its halt and access to telemedicine has not been an easy to go option for them. Seized outdoor entertainment has



led to a greater population resorting to binge watching television and using gadgets causing behavioral disorder in the long run.

In studies its specified that the ones who developed neurological problems like strokes and encephalopathies often have acute and subacute neuropsychiatric sequence. Delirium is also noted in patients discharged post covid19 recovery. Pregnant women contracting the disease, the fetus in utero is at an increased risk of developing schizophrenia later in life, also the children and adults are at risk too. Overlooking the ray of light in this deadly pandemic, there are platforms to seek professional help in the form of psychological support and online psychotherapy, also telemedicine is a scope for better future via online consultation with the psychiatrist and it takes place in the comfort zone & can be easy expression of feelings. Limiting access to nonessential news is a better way to stay off the negativity taking rounds.

FUTURE DIRECTION -

In order to provide treatment, the patients should be monitored early for the neurological manifestation and prevent it by timely getting the CSF analysis, monitoring the blood parameters like the eosinophil, neutrophil counts, D-Dimer levels, C - reactive protein and troponin level's which happen to be increased and managing the complications might improve the mortality. Treatment can be stepped down sequentially as the parameters achieve a normal range. Further collaborative studies and exhaustive research will enhance our knowledge on neurological involvement and its therapeutic management[13].

II. CONCLUSION-

Information regarding COVID-19 is available in the form of a few large studies and case series, but bulk information is available only in the form of case reports. In this review article we have focused on how also the Central Nervous System has been affected in Covid-19 patients and has emerged to be a significant cause of morbidity and mortality. The underlying mechanism for CNS involvement includes binding of the virus to the target host cell surface molecule and the entry of the virus via hematogenous / olfactory route and via endothelial (ACE 2 receptor) pathway and causing a myriad of neurological manifestations.

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