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Neurological Manifestations in COVID-19

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ABSTRACT

Background: Novel coronavirus infection results in Coronavirus infection (COVID-19) and is termed as "Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)". Mild to moderate symptoms are being reported in a major proportion of patients suffering from COVID-19 infection, which are mainly respiratory. A large percentage of COVID-19 infected cases are asymptomatic, while few had minor symptoms like rise in temperature, cough, difficulty in breathing, body aches, throat pains etc.

Main text: Although the COVID-19 disease is mainly associated with respiratory symptoms, there can be neurological symptoms in some patients with severe disease. Anosmia has emerged as a predominant feature of SARS-CoV-2. This also arises the probability of some degree of involvement of the CNS with the infection. The mechanisms suggested are that SARS-CoV-2 can enter the CNS via two routes, namely via blood stream or direct spread. Neurological manifestations are seen in patients having prolonged stay in ICU intensive care units. COVID- 19 involves both central nervous system and peripheral nerves. Neurological manifestations of the disease can be due to the neuro-invasiveness of the virus. It can also be an indirect manifestation of multi-organ system failure. The most common neurological manifestation was acute encephalopathy with an incidence of 50%. Manifestations like stroke and coma and also meningitis, encephalitis and myelopathy can occur.

Conclusion: Early diagnosis and management is needed for CNS manifestations as they pose a risk for serious complications. Considering the adverse effects of COVID-19 disease on the central nervous system, more research is needed. This will help evaluate the short and long term effects of SARS-CoV-2 on the functioning of the central nervous system.

Key words: COVID-19, Nervous system, SARS-CoV-2, Neurological complications, Acute encephalopathy Ischaemic stroke, Guillain-Barre syndrome

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INTRODUCTION

The initial patient of the COVID-19 infection was detected in the city of Wuhan in People's Republic of china during the year of 2019 in the month of December. The initial presentation was that of pneumonia of unknown aetiology, which was seen in major proportion of patients contracting the disease. Since then the COVID-19 disease has disseminated worldwide with rapid pace. The WHO officially announced COVID-19 infection as a pandemic in the month of March of 2020. Coronavirus belongs to coronaviridae family of viruses which are ss-RNA viruses. Few of these viruses are pathogenic to humans. The virus commonly infects the respiratory system and gastrointestinal tract.

Over the last few decades the world has seen several viral pandemics like the (sarscov), which occurred in 2020. Also there was the pandemic of Middle East Respiratory Syndrome coronavirus (MERS) [2].

Coronavirus infection is due to a new coronavirus and is termed SARS-CoV-2 [3,4]. COVID-19 is a potentially serious condition which mainly involves the respiratory system.

A large proportion of infections with COVID-19 disease have shown mild or moderate symptoms. A large number of COVID-19 infected cases were asymptomatic, while few had minor symptoms like rise of temperature, cough, shortness of breath, body ache, sore throat etc. In advanced infections of SARS-CoV-2 infection, systemic problems like dropping oxygen saturation, respiratory and metabolic acidosis, sepsis and hypercoagulable states and disseminated intravascular coagulation are predominantly seen. Reports have emerged, of the virus affecting various systems including the nervous system. The predominant symptoms that were described are headache and olfactory and gustatory sensation distortion. Anosmia which implies invasion of peripheral nervous system by the virus

presented early in 36% patients with COVID-19 infection in a Spanish case control study. This gustatory and olfactory disorder present more often in SARS-CoV-2 patients than on other infections by other viruses.

SARS-CoV-2 can enter the CNS *via* two routes. Firstly by systemic dissemination *via* the blood stream. After entering the systemic circulation, the virus enters the nervous tissue by property of neurotropism. Thereafter it binds to ACE2 receptors in the endothelial cells that line the capillaries. The second theory is that of local spread across the ethmoid bone *via* the cribriform plate. This may have some connection with the symptom of loss of smell, a symptom which patients with SARS-CoV-2 have shown [5].

Neurological signs and symptoms of the disease can be a consequence of the neuro-invasiveness of the virus. It can also be an indirect manifestation of multi-organ failure and altered biochemical parameters; however it is most likely a combination of both [6].

LITERATURE REVIEW

Rationale for review

CNS manifestations are seen in severe stage of the disease and therefore are seen in ICU settings treating critical patients. Hence we wish to disseminate information regarding neurological complications so that there can be awareness amongst health care providers and seekers, to help in detection at an early stage and prevention of complications and death.

Objective: To discuss and evaluate the neurological complications caused by SARS-CoV-2 corona virus.

Main text: COVID-19 is an infectious disease that affects individuals of all age groups in multiple ways. The most notable being viral pneumonia and ARDS, which may lead to multiple organ dysfunction and can be fatal. Most of the research has focussed on treatment of acute infection so as to prevent complications and death. Another area of research has been the development of vaccine. Many patients of COVID-19 exhibit an array of neurological signs and symptoms. More than 80% of hospitalised patients have had some form of neurological dysfunction during the course of the disease. Neuropsychiatric complications have been reported in many individual case reports. Another manifestation is immune dysfunction, a systemic immune response that leads to a pro-inflammatory state of severe systemic inflammation due to cytokine release.

Many COVID-19 patients have neurological manifestations. It is known that the human coronavirus can invade the CNS and cause neurological manifestations. Neurological manifestations can range from anosmia to cerebral haemorrhage. Neurological manifestations are seen in advanced stage of the disease. Nervous system problems are seen in patients having prolonged stays in the ICU intensive care units of the hospitals. Both the central nervous system and peripheral nervous system can be affected in COVID-19 [7].

Neurologic manifestations fall mainly in three categories [8].

- Central nervous system CNS involvement leading to headache, dizziness, acute cerebrovascular accidents, altered sensorium, seizures, and loss of balance.
- Peripheral nervous system involvement resulting in deterioration of olfactory and gustatory senses and visual distortions and nerve pains.
- Skeletal muscle affection is also likely

Spread to the CNS can be *via* various routes. Exact mechanism of its invasion into CNS is not clear.

- Detected in CSF
- Haematogenous
- Lymphatic system is another possible route for the virus to enter CNS.
- May penetrate cribriform plate

ACE2 or TMPRSS2 receptors are responsible for neural invasion by SARS-CoV-2. These receptors are seen in many areas of the body. Glial cells of brain and spinal neurons have also been shown to have ACE2 receptors [9,10]. ACE2 receptor provides a point of entry for the virus to enter the cell. The invading virus binds to ace2 receptors *via* spike protein which is present on the virus [11].

Endothelial cells lining the capillaries in the blood brain barrier and the epithelial cells of the blood CSF barrier act as another route for CNS invasion *via* SARS-CoV-2. After invasion of peripheral nerves of lungs by SARS-CoV-2 retrograde nerve transport can act as path to CNS [12]. Blood circulation and sympathetic neurons of the enteric nervous system can lead to CNS invasion [13,14].

Some of the neurological symptoms are immediate while others are long term complications. Severely ill patients have higher incidence of neurological complications as compared to those with mild disease. Some of the common manifestations are acute encephalopathy, stroke and seizure, Guillain-Barre syndrome, and the less common neurological manifestations are meningitis, encephalitis and myelopathy.

Acute encephalopathy

The most common neurological manifestation was acute encephalopathy having an incidence of 50%. There is a fivefold increase in hospital death in patients presenting with acute encephalopathy. This was in line with other multicentre studies [15,16].

The prevalence of acute encephalopathy in elderly patients with associated comorbidities was more and had more requirements of ICU support and a poor mortality rate. The increasing occurrence of stroke in SARS-CoV-2 infection was due to increasing thromboembolic complications. Manifestations like stroke and coma varied in incidence amongst studies [17,18].

Ischaemic stroke

In spite of the global pandemic, there is lack of studies on a larger scale regarding the CNS involvement of the coronavirus. The most commonly reported CNS manifestations were headache and dizziness at 17% and 13% respectively. Major neurological features such as cerebrovascular accidents and seizure had a low incidence. Confusion and headache were reported with an incidence of 9% and 8% respectively [19]. A study, detected severe neurological featuresin 6% patients. Major causes for mortality were ischemic stroke and cerebral vein thrombosis [20]. The rate of complications due to embolization of thrombus in patients with SARSCoV-2 and the prevalence of stroke due to thrombi blocking arteries was found to be 1.6% to 2.5% [21,22]. Connor, et al. found that formation of microvascular thrombi are due to elevated levels of fibrinogen, platelet and D-DIMER (100%) and IL-6 (100%) which have a potential to cause systemic thromboembolism.

Guillain-Barre Syndrome (GBS)

Guillain-Barre Syndrome (GBS) was found to be significant neurological sequelae. GBS has significant para infection and post-infectious situation. There have been studies and reports of GBS being a major neurological manifestation in SARS-CoV-2. Symptoms of GBS were reported by many patients five to eleven days post sarscov-2 infection [23,24]. Zhao et al. in their report suggest GBS was found as a symptom in patients who are suffering from SARS-CoV-2 infection but the nature of the association was unclear whether it was coincidental or a true association [25]. Between the initial infection by SARS-CoV-2 and the appearance of features of GBS there is a time lag which has reported classically and described as "post infectious" presentation.

Critical illness polyneuropathy

Critical illness polyneuropathy poses a problem with patients who have long inpatient stay. Post Intensive Care Syndrome (PICS) [26,27]. Upon clinical examination 80% patients were found to have at least one neurological symptom and 55% had a neurological sign or syndrome.

Least common neurological manifestations were meningitis, encephalitis and myelopathy with incidence of 0.1% and 0.2% respectively. Numerous case reports have suggested that few of the patients exhibited neuropsychiatric complications such as altered consciousness and encephalopathy [28]. Post Intensive Care Syndrome (PICS) posed a problem in patients with long hospital stays [27,26].

In some patients the deterioration of respiratory system and the need for ventilation can be explained by CNS infection by SARS-CoV-2. Hence, monitoring of the CNS signs and symptoms can give a clue or act as a warning of impending deterioration in patients with SARS-CoV-2 disease.

Neuropathology

Although the knowledge of neuropathology of clinical neurological manifestations is incomplete, it is gradually being discovered. In post mortem of an elderly patient suffering from SARS-CoV-2 disease, many neuropathological lesions were seen including those resembling demyelinating and vascular pathology. The lesions found were haemorrhagic white matter lesions which are pathognomic of haemorrhagic necrotising encephalitis with additional surrounding axonal injury and macrophages. Acute Disseminated Encephalomyelitis (ADEM) like findings, myelin loss and clusters of macrophages was seen in subcortical white matter were also seen. The typical findings of viral and post viral encephalitis were not found and hence direct injurious effects of the virus on the CNS seems unlikely, and that the virus may initiate a secondary phenomenon which is what causes the neurological features [29].

Psychological aspect of COVID-19

Due to the ongoing pandemic and the lockdown, there has been a rise in the psychological issues being faced by the population. There is a rising incidence of anxiety, depression, stress and sleep disorders in the general population as well as health care personnel. The healthcare workers are facing increased workload, the lack of resources for adequate testing and treatment of patients, scarcity of personal protective equipment and uncertainty about their health and safety of their family.

At risk groups having comorbidities and their relatives have fear about contracting the disease and the resulting prolonged confinement in quarantine. Lockdowns, fear of contracting diseases and the loss of near and dear ones, loss of personal freedom pose risk to mental health of people. Within a few weeks of lockdown India witnessed a significant increase in mental health issues. There has been a rise in mental afflictions and suicides in India during COVID-19 crisis. Many adolescents and children are succumbing to anxiety to disorders due to widespread lockdown and closing of schools & colleges and the widespread fear of spreading of the virus.

Symptoms associated with the skeletal system

In patients who are infected with SARS-CoV-2 there are accounts of skeletal muscle injury and myopathy. Critical illness muscle injury is seen in people suffering with serious form of COVID-19 disease. Severe respiratory disease, systemic inflammation and sepsis have been found to main causative agents for myopathy. Direct involvement of the muscle by the virus could be another causative factor in development of myopathy. The ability of SARS-CoV-2 to bind to ace2 receptors and invade a cell is another possible mechanism as muscles cells also express the ACE2 receptor. Immunological damage to muscles in advanced stages of COVID-19 infection is due to hyper inflammation and cytokine storm. Myopathy could be a cause for long term physical disability [30].

Multiple Sclerosis exacerbation

Early studies show that the possibility of infection and the morbidity in cases of multiple sclerosis are similar to the general population. Disease modifying agent therapies leading to worst outcomes have not been reported [31,32].

Movement disorders

There have been symptoms of movement disorders in sufferers of COVID-19. There have been accounts of involvement of muscles of the face, muscles of neck (sternocleidomastoid, trapezius) and upper limb muscles with generalised myoclonus and a positive or negative jerk. Myoclonus was spontaneous in these patients and they were extremely sensitive to stimuli. Immunotherapy proved to be beneficial in these patients. Another study reported an elderly patient with COVID-19 who presented with fluctuating levels of consciousness, generalised myoclonus, hypokinetic rigid syndrome and hypomania. DaT-SPECT showed asymmetric involvement of bilateral putamen with decreased presynaptic dopamine uptake. These symptoms subsided without any specific treatment. This association between viral disease and Parkinsonism was suggested way back during the Spanish flu times. However no definite association can be drawn due to lack of studies [33].

DISCUSSION

The SARS-COVID has spread over the globe, causing COVID, as dangerous respiratory condition. COVID can cause fever, hack, rhinorrhea, chest pain, free inner parts, vomiting, nausea, mix, and other symptoms and consequences. Some patients may be asymptomatic, while others may be experiencing symptoms. COVID-19 is detected through imaging and possibly serious clinical signs [7]. As a result, several COVID-19 clinical and examination office symptoms may be less common or overlooked, resulting in misdiagnosis of illnesses and further debasement of individuals. According to research, approximately 33% of COVID-19 patients will develop brain related symptoms at some point during their illness. Even in unambiguous cases, neurologic signs may be the primary or only manifestation of the COVID. Furthermore, cases with severe COVID tainting are likely to experience neurological signs and symptoms [6,8].

The severe neuro related symptoms of COVID-19 positive patients encompass headache, dazedness, skepticism, phenomenal cerebrovascular disease, seizures, disarray, anosmia, ageusia, and muscle agony demyelinating encephalomyelitis [9]. As a result, cardiovascular disease is not only a prevalent comorbidity among COVID-19 patients, but they can also develop CVDs as a result of COVID-19 pathophysiology in those with danger sections. Hyper excitability of provocative clotting factors alters the coagulation system, leading to aberrant D-dimer and platelet levels increasing the risk of CVDs. Anticoagulant medication has been shown to reduce the rate of obliteration in hospitalised patients [19].

As a standard PNS manifestation, COVID-19 is known to elicit anosmia and ageusia, especially in asymptomatic patients [35,36]. Some persons with Decreased sense of smell developed pulmonary symptoms later in life, while others go undiagnosed. As a result, even if there are no other common occurrences in the stream epidemic, these unintended implications should highlight the COVID-19 affirmation's weakness [40].

Inability to smell and inability to eat may be linked to the ubiquitous Angiotensin converting enzyme-2 receptors found in the nasal mucosa and tongue [41]. It's still unclear if nerve injury or olfactory nerve aggravation causes anosmia and ageusia. Some experts assume that the trigeminal or olfactory nerves are entrance routes for COVID because frontal cortex stem collusion has been addressed early in individuals and animal models of the wild outstanding respiratory issue COVID-19 (SARS-CoV) pollution. More research is needed in any situation [5]. Patients with irrational CNS thinking have lower lymphocyte and platelet counts, as well as greater blood urea nitrogen levels, whereas lab exposures in cases with PNS obligation or non-irrational CNS cooperation may be insignificant [9].

Direct infections by BBB obstruction *via* inflammatory markers and retrograde or progressive neural transport *via* dynein and kinesin protein have been proposed to explain the possible CNS idea regarding SARS-COV-2 [5]. The set plan, hypoxia produced by pneumonia, and, in addition, interacting with ACE2 receptors may all play a role in potential nerve damage. These receptors are known to exist in a variety of organs, including the CNS, lungs, sections, heart, kidney, and assimilation bundles. According to research [42], the SARS-CoV-2 spike protein may interact with ACE2 receptors, generating increased circulatory strain and raising the probability of cerebral transmission.

SARS-COVID may break the Blood brain barrier and centre the CNS by binding to hair like endothelium's Angiotensin converting enzyme-2 receptors. COVID damage brain stem neurons, which are sensitive to the cardio-respiratory rule, leading to respiratory confusion and hypoxia, according to Steardo, et al. in a review [42]. It possesses all of the characteristics of being SARS-COVID, which causes pneumonia as well as inadequacy of the frontal cortex stem cardio-respiratory rule, both of which result in hypoxia. Hypoxia, on the other hand, may be able to reverse the neuronal damage that has resulted in a dangerous constant circle. This leads to the higher likelihood of neurodegenerative consequences in severely injured patients. Because of the lack of declarations and the meaning of possible CNS professionals in COVID pathophysiology, more research is urged.

CONCLUSION

Although the predominant manifestation of SARS-CoV-2 infection occurs in the lungs, it is postulated that viral invasion of the brain stem may be the reason for the neurological signs and symptoms. COVID-19 patients can

show several neurological symptoms like headache, loss of consciousness, loss of olfaction and confusion disorders etc. Early diagnosis and management of these neurological manifestations is necessary to prevent serious complications. Neurological symptoms in COVID-19 usually are seen in patients having severe disease. Increasing number of patients with neurological features are being reported in a number of research papers but the assessment of the clinical impact requires more data. Further research is required to evaluate the neurological features which can result in serious complications.

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