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Perspective

COVID-19 Pandemic: A Neurological Perspective

Suresh Bishokarma [a]

INTRODUCTION:

Even though severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) primarily affects the respiratory system, the nervous system is not spared either. SARS-CoV-2 has been isolated from the brain, olfactory bulb and cerebrospinal fluid. During the SARS (SARS-CoV-1) outbreak in 2002 to 2003, neurons had been found to be highly susceptible for infection and the virus could cause extensive neuronal damage. Similar to SARS-CoV-1, SARS-CoV-2 exploits the angiotensin-converting enzyme 2 (ACE-2) receptor to gain entry and infect both glial and neuronal cells which express ACE-2 receptors.[1] SARS-CoV-2 affects the central as well as peripheral nervous system presenting with diverse manifestations like myelitis, cerebrovascular events (CVE) and encephalitis to mention a few.[2,3] In-depth understanding of neurotropic potential of this virus will be helpful to individualize the treatment protocol from a neurological perspective.

REVIEW:

The first report of the viral infection attracted attention in late December 2019 in Wuhan, the capital of Hubei, which quickly surged to potential of global threat and rapidly succeeded from China to Europe and then to the United States of America in a matter of weeks was taxonomically designated as SARS-CoV-2 and diseases named as corona virus disease (COVID-19). COVID-19 was declared a pandemic on the March 11, 2020 by WHO.[4] Currently, SARS-CoV-2 has affected almost every country of the world with confirmed cases of 38,22,382 tolling 2,63,658 death. In Nepal, as of May 10, 2020 there were 109 confirmed cases with zero mortality.[5]

VIRUS:

SARS-CoV-2 is a single-strand RNA (ss-RNA) corona virus similar to SARS like coronavirus that had previously been reported in bats in China. The RNA genome of SARS-CoV-2 is enclosed by spike (S), envelop (E) and membrane (M) protein. Spike protein projecting from the virus membrane is the key structure for the infectivity and pathogenicity of this virus into host. The spike protein enables the attachment of the virion to the cell membrane by interacting with the host ACE-2 receptor.[6] It has been found that the spike protein of SARS-CoV-2 has 10-20 folds increased affinity to the ACE-2 receptor than SARS-CoV-1, making it highly contagious and infectious.[7,8]

MECHANISM OF NEURO INVASION:

The mechanism of action for SARS-CoV-2 neurological invasion is not yet specified. Capillary endothelium expresses ACE-2 receptors which is the vulnerable site for the access of the virus into the cerebral microcirculation. The lesion in the endothelial lining as a result of subsequent budding of the viral particle favors viral access to the brain. Once access into the cerebral environment, it interacts with the neuronal ACE-2 receptors and could initiate viral multiplication and neuronal damage has been seen in SARS-CoV in past and proposed for SARS-CoV-2 which need approval.[9] Although, low expression of ACE-2 in glia and cerebral neurons is well documented, the specific site of entry of SARS-CoV-2 is not clearly identified.[10] One of the proposed routes of access of virus to the brain is via the cribriform plate close to the olfactory bulb. Other postulations are trans-

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a - MCh Neurosurgeon, Department of Neurosurgery, Upendra Devkota Memorial National Institute of Neurological and Allied Sciences, Bansbari, Kathmandu, Nepal.

Corresponding Author:
Suresh Bishokarma
e-mail: drsureshbk@gmail.com
ORCID: https://orcid.org/0000-0001-9448-842X

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synaptic viral transfer after initial peripheral nerve invasion. Direct invasion, blood circulation pathway, neuronal pathway, hypoxia injury, immune injury/ cytokine storm syndromes have also been proposed. [11,12,13,14]

MANIFESTATION OF NEUROLOGICAL INVOLVEMENT:

Covid-19 is a highly contagious disease transmitted from droplets, aerosols and contact to nasal or ocular surfaces. The incubation period is generally 3-14 days but an extended period up to 24 days has been reported. Neurological symptoms vary with the level of nervous system involved. Involvement of central nervous system (CNS) manifests as dizziness, headache, impaired consciousness, acute cerebrovascular diseases, ataxia or seizure while peripheral nervous system (PNS) involvement manifests as taste impairment, anosmia, visual impairment or neuralgia.

Increased severity of COVID-19 increases the risk of neural involvement and complications.[15] Spectrum of complication of COVID-19 includes viral meningitis, encephalitis, post infectious acute disseminated encephalitis, post infectious brainstem encephalitis, Guillain Barre syndrome (GBS), acute necrotizing hemorrhagic encephalopathy.[2] ACE-2 at the level of blood brain barrier may jeopardize the protective barrier giving way to viral encephalitis while spinal cord membrane expressing ACE-2 receptor in a spinal vein may predispose to myelitis like feature. Systemic homeostasis dysregulation caused by pulmonary, renal, cardiac and circulatory damage in COVID-19 can result in secondary cerebral damage. However, a dominant cerebral involvement alone with the potential of causing cerebral edema in COVID-19 can take heavy toll before systemic dysregulation ensues.[8]

Cerebrovascular events (CVE) including hemorrhagic or ischemic stroke or cerebral venous sinus thrombosis could be a presenting feature of COVID-19. In a study done by Filatov A et al., among 221 patients, 5.88% (13 patients) had CVE of which majority (11 patients) of them presented with acute ischemic stroke (4.9%) while 0.45% patients presented with hemorrhagic stroke.[3]

In a retrospective study done by Mao L et al., in Wuhan, China among 214 patients hospitalized with laboratory confirmed diagnosis of SARS-CoV-2 infection. Seventy-eight (36.4%) patients had neurologic manifestations. More severe patients were likely to have neurologic symptoms (40 [45.5%] vs 38 [30.2%]), such as acute cerebrovascular diseases (5 [5.7%] vs 1 [0.8%]), impaired consciousness (13 [14.8%] vs 3 [2.4%]. [10] There can be multiple reasons for a patient with COVID-19 to present with impaired consciousness which includes viral encephalitis, metabolic perturbation, infectious toxic encephalopathy, seizure with post ictal confusion and stroke.[15]

Seizure in COVID-19 patients has minimal incidences as observed by Mao et al.[15] Association of seizure in COVID-19 can be multifaceted. Proposed mechanism could be due to direct viral invasion of CNS, severe hypoxia induced, metabolic, septic encephalopathy, gliosis due to encephalopathy or due to fever.[16]

GBS was recorded infrequently in different studies worldwide. In a very recent study done by Zhao et al., five cases of GBS diagnosed among COVID-19 patients, three presented as axonal variant while two cases presented as demyelinating variants.[17] Rapid deteriorating respiratory function of COVID-19 patients could be due to bulbar involvement by GBS and need to be accurately sought. On the basis of this observational series involving five patients, it is not possible to determine whether severe deficits and axonal involvement are typical features of COVID-19 associated GBS.

CONCLUSION:

SARS-CoV-2 can take a severe toll on the respiratory system. However, virus bears potential to infect the nervous system as well. Neural access via hematogenous route or cribriform plate ensues damage of either the central or the peripheral nervous system. Subtle neurological manifestation must be considered as a presenting feature of COVID-19 to early detect and treat this evil.

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