REVIEW ARTICLE

Neurological and Neuropsychiatric Impacts of COVID-19 Pandemic

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Abstract: ***Background:*** Albeit primarily a disease of respiratory tract, the 2019 coronavirus infectious disease (COVID-19) has been found to have causal association with a plethora of neurological, neuropsychiatric and psychological effects. This review aims to analyze them with a discussion of evolving therapeutic recommendations. ***Methods:*** PubMed and Google Scholar were searched from 1 January 2020 to 30 May 2020 with the following key terms: "COVID-19", "SARS-CoV-2", "pandemic", "neuro-COVID", "stroke-COVID", "epilepsy-COVID", "COVID-encephalopathy", "SARS-CoV-2-encephalitis", "SARS-CoV-2-rhabdomyolysis", "COVID-demyelinating disease", "neurological manifestations", "psychosocial manifestations", "treatment recommendations", "COVID-19 and therapeutic changes", "psychiatry", "marginalised", "telemedicine", "mental health", "quarantine", "infodemic" and "social media". A few newspaper reports related to COVID-19 and psychosocial impacts have also been added as per context. ***Results:*** Neurological and neuropsychiatric manifestations of COVID-19 are abundant. Clinical features of both central and peripheral nervous system involvement are evident. These have been categorically analyzed briefly with literature support. Most of the psychological effects are secondary to pandemic-associated regulatory, socioeconomic and psychosocial changes. ***Conclusion:*** Neurological and neuropsychiatric manifestations of this disease are only beginning to unravel. This demands a wide index of suspicion for prompt diagnosis of SARS-CoV-2 to prevent further complications and mortality.

RÉSUMÉ : Les impacts neurologiques et neuropsychiatriques d'une infection à la COVID-19. ***Contexte*** **:** Bien qu'il s'agisse principalement d'une maladie des voies respiratoires, la maladie infectieuse à coronavirus apparue en 2019 (COVID-19) s'est avérée avoir un lien de causalité avec une pléthore d'impacts d'ordre neurologique, neuropsychiatrique et psychologique. Cette étude entend donc analyser ces impacts tout en discutant l'évolution des recommandations thérapeutiques se rapportant à cette maladie. ***Méthodes*** **:** Les bases de données PubMed et Google Scholar ont été interrogées entre les 1er janvier et 30 mai 2020. Les termes clés suivants ont été utilisés : « COVID-19 », « SRAS – CoV-2 », « Pandémie », « Neuro – COVID », « AVC – COVID », « Épilepsie – COVID », « COVID – encéphalopathie », « SRAS – CoV-2 – encéphalite », « SRAS – CoV-2 – rhabdomyolyse », « COVID – maladie démyélinisante », « Manifestations neurologiques », « Manifestations psychosociales », « Recommandations thérapeutiques », « COVID-19 et changement thérapeutiques », « Psychiatrie », « Marginalisés », « Télémédecine », « Santé mentale », « Quarantaine », « Infodémique » et « Médias sociaux ». De plus, quelques articles de journaux relatifs à la pandémie de COVID-19 et à ses impacts psychosociaux ont également été ajoutés en fonction du contexte. ***Résultats*** **:** Il appert que les manifestations neurologiques et neuropsychiatriques des infections à la COVID-19 sont nombreuses. Les caractéristiques cliniques d'une implication des systèmes nerveux central et périphérique sautent désormais aux yeux. Ces caractéristiques ont fait l'objet d'une brève analyse systématique à l'aide de publications scientifiques. En outre, la plupart des impacts d'ordre psychologique de cette pandémie se sont révélés moins apparents que les changements réglementaires, socioéconomiques et psychosociaux. ***Conclusion*** **:** Les manifestations neurologiques et neuropsychiatriques de cette maladie ne font que commencer à être élucidées. Cela exige donc une capacité accrue de vigilance en vue d'un diagnostic rapide, et ce, afin de prévenir des complications additionnelles et une mortalité accrue.

Keywords: SARS-CoV-2, COVID-19, Neuro-COVID, Axonal transport, Neurotropism, Neurovirulence, Neuroinvasion, Encephalopathy, Encephalitis, Stroke, Cerebrovascular events, Epilepsy, Seizures, Demyelination, Ataxia, Myelitis, Myoclonus, Polyradiculopathy, Therapeutic paradigm shift, Psychosocial, Psychiatric, Addiction COVID

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Background

The medical havoc wreaked by the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) has grown exponentially to pandemic proportions within a short span of time, starting in December 2019. As of WHO reports of 20 May 2020, more than 4.7 million people worldwide have been infected, and death tolls have crossed 0.3 million.[1] The most common symptoms of presentation are fever, non-productive cough, fatigue, anorexia, myalgia and diarrhoea. Pulmonary, renal, gastrointestinal and hematological complications have been reported in severe cases, and, not surprisingly, nervous

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system involvement has been reported too. Several studies have described varied neurological manifestations of the disease.[2–4] There are burgeoning concerns of people already suffering from chronic neurological ailments and of people receiving immunosuppressant therapies (IST) or immunomodulator therapies (IMT) for their underlying illnesses, making them more susceptible to 2019 coronavirus infectious disease (COVID-19). Essential steps also need to be taken to forestall a possible mental health crisis.

This review aims to analyze the neurological and neuropsychiatric manifestations as well as the psychological effects with a discussion of evolving therapeutic recommendations.

Methods

PubMed and Google Scholar were searched from 1 January 2020 to 30 May 2020 with the following key terms: "COVID-19", "SARS-CoV-2", "pandemic", "neuro-COVID", "stroke-COVID", "epilepsy-COVID", "COVID-encephalopathy", "SARS-CoV-2-encephalitis", "SARS-CoV-2-rhabdomyolysis", "COVID-demyelinating disease", "neurological manifestations", "psychosocial manifestations", "treatment recommendations", "COVID-19 and therapeutic changes", "psychiatry", "marginalised", "telemedicine", "mental health", "quarantine", "infodemic" and "social media". A few newspaper reports related to COVID-19 and psychosocial impacts were also added as per context.

Results/Discussion

Neurotropic Properties of SARS-CoV-2

Viral infections of the respiratory tract, identified as a major medical problem even as early as the 1930s, are a leading cause of morbidity and mortality worldwide, especially amidst children, elderly and immune-compromised individuals.[5–7] Children are more susceptible, often experiencing multiple infections every year till the age of 10.[8]

The respiratory epithelium, first line of defense against pathogens, often serves as a target for different respiratory viruses to percolate into human host. Infections can remain self-limited and localized or can progress to more severe respiratory diseases[9] or even spread to other tissues, including the central nervous system (CNS), where they could induce other types of pathologies,[10] depending upon the competency of the host immune response.

Over the years, several different respiratory viruses have been shown to be able to penetrate the CNS (neuroinvasion). Most of them can infect neurons and glial cells (neurotropism) and result in the induction of neurological diseases (neurovirulence).[11] Some common pathogens include the respiratory syncytial virus, measles virus, influenza virus, West Nile Virus, emerging pathogens such as the Hendra virus and the Nipah virus and, recently, the coronavirus.[12–16]

Coronavirus belong to a family of enveloped, positive-stranded RNA viruses. Taxonomically, grouped in the family Coronaviridae, order Nidovirales, they are further classified within four different genera, namely Alpha, Beta, Gamma and Delta coronaviruses.[17,18] However, it has now been proven indubitably that they do possess neurotropic and neuroinvasive properties in various hosts, including humans, rats, pigs, rodents and fowls.[19,20] Their non-segmented 30 kb positive, single-stranded polyadenylated RNA, the largest among RNA viruses, possesses four or five genes encoding structural proteins (S, E, M, N and hemagglutinin-esterase for the genus betacoronaviruses) and several genes encoding non-structural proteins, all of which play well-defined roles in determining the pathogenicity of the virus.[17,18] The spike protein (S) is a type-1 glycosylated transmembrane protein, which helps in recognising the host cell receptor, thus enabling the virus to infect a susceptible cell. The envelope (E) protein, the membrane (M) protein and the nucleocapsid (N) protein are responsible for maintaining the shape and structure of the virion.[17,18] Some species of the betacoronaviruses express a special protein-0, the hemagglutinin-esterase that interacts with different types of sialic acid, thus plausibly playing a role in hemagglutination.[17,18] It also possesses an acetyl-esterase function, which may be important during early infection or during the release of viral particles from the infected cells at the end of the replication cycle of betacoronaviruses.[21]

It is a well-established fact that coronaviruses are known to infect a wide variety of animal species, mostly exhibiting selective tropism towards the respiratory tract or the gut. Notably, some among these, the feline coronavirus and porcine hemagglutinating encephalitis virus variants, have also been implicated in neurological diseases, infecting the brain, meninges or even the spinal cord.[22–26] The close structural and biological similarities of the human coronavirus (HCoV) to the neurotropic animal coronaviruses have led to the speculation about possible involvement of HCoV in neurological diseases. Data confirming such association is still largely elusive. However, HCoV-22 E and HCoV-OC43,[27–30] as well as SARS-CoV[31,32] were shown to be neuroinvasive and neurotropic.

SARS-CoV-2 may gain entry to the nervous system predominantly by two routes: hematogenous or neuronal transmission.

Hematogenous Route

SARS-CoV-2 may infect the endothelial cells of the blood–brain barrier or the leucocytes to get disseminated to other tissues. HCoV-229 E and HCoV-OC43 have been shown to infect the human monocytes/macrophages.[33,34] Additionally, HCoV-229 E has also been reported to infect murine dendritic cells expressing human aminopeptidase-N.[35] Similar findings have also been demonstrated by SARS-CoV.[34,36,37] Following infection of these cell lines, monocytes get activated, differentiate into macrophages and serve as reservoirs for the virus, thus facilitating its passage to other tissues, including the nervous system.[27,32,33,36] On the other hand, infection of dendritic cells results in wavering of innate immunity, and further perpetuating spread.[37]

Neuronal Route

This occurs when the virus infects peripheral nerves and enters the CNS in a retrograde manner via active axonal transport.[38] Once in the brain, for example, HCoV-OC43 has been demonstrated to spread from the olfactory bulb to the cortex and further down to the medulla.[21] The cerebellum, however, remains unaffected. This strain has also been known to infect the hippocampus and from there the spinal cord.[21] Further neurodegeneration by the coronavirus can occur because of misdirected host immune responses and/or direct damage to neuronal cells by replicating viral particles as in acute encephalitis.[21]

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Possible Mechanisms of Neurovirulence of SARS-CoV-2

Hypoxia-Related Neurovirulence

Firstly, the respiratory tract, being the most commonly and severely affected system, often leads to hypoxia, which may subsequently result in hypoxic brain injuries.[39]

Inflammation-Related Neurovirulence

The viral infection is also known to propagate via a cytokine storm responsible for its clinical features.[40] Inflammatory injury to the nervous system thus does not seem far-fetched especially with a surge of interleukin-6, which has been shown in several studies to be causally related to the severity of infection.[40]

Angiotensin Converting Enzyme-2 (ACE-2) Binding-Related Neurovirulence

Binding of the virus to ACE-2 both in the blood–brain barrier and in the meninges covering the spinal cord attenuates the protective capacity of this enzyme towards neural tissue, thus making them more susceptible to injury leading to encephalitis or myelitis.[41] There have been reported cases of intracerebral hemorrhages occurring due to SARS-CoV-2, also attributable to the viral binding to ACE-2 present in the cerebral blood vessels, thus raising luminal pressure.[42] Similarly, binding to these receptors in the skeletal muscles has resulted in skeletal myopathies.[42] Reports demonstrate that binding of SARS-CoV-2 to ACE-2 receptors leads to a decrease in the levels of ACE-2 and a subsequent surge in ACE-1 within the nervous system.[43] ACE-1 is known to result in neuronal damage, inflammation, degeneration and death of neurons.[43] Notably, these receptors are highly concentrated in the sub-fornical regions, nucleus tractus solitarius, rostral ventro-lateral medulla and the paraventricular regions.[43] Additionally, ACE-2 receptors are also found to be present on the endothelial cells across multiple organs, including the nervous tissue, binding of SARS-CoV-2 to which would lead to widespread endothelial dysfunction, systemic endotheliitis associated with apoptosis, culminating in neuronal cell death. The presence of viral elements inside endothelial cells substantiates the hypothesis of a direct causative role of SARS-CoV-2 in pathogenesis.[44]

Knowledge from Previous Epidemics

Rare instances of neurological manifestations from patients in Taiwan were reported by Tsai et al.[45], which included five cases of large-vessel ischemic stroke, three cases of axonal polyneuropathy, two cases of myopathy and three cases of rhabdomyolysis, all of them occurring a few weeks after the onset of the 2003 SARS epidemic caused by SARS-CoV. There was evidence of muscle weakness and raised creatine kinase levels in patients who had previously suffered from SARS-CoV infection.[46,47] However, a direct attack on the nervous system by the virus could not be determined conclusively, and these cases were considered to belong to the spectrum of critical illness neuropathy and myopathy or developing as a result of steroid use or cachectic disuse atrophy and weakness following long-term bed rest.[46,47] Autopsy studies in patients showed cerebral edema, meningeal vasodilatation, lymphocytic infiltration and ischemic demyelination of neurons; in some instances, viral particles and genome sequences of SARS-CoV were detected.[48–51]

Middle East respiratory syndrome, caused by MERS-CoV (in 2012), is also known to be potentially neuroinvasive with features ranging from altered mentation, confusion, ataxia and ophthalmoplegia to focal neurological deficits and coma.[52] Radiological findings have been shown to range from intracerebral hemorrhages, ischemic strokes to encephalitic features.[52] Involvement of the peripheral nervous system in the form of Guillain–Barré syndrome (GBS) and critical illness polyneuropathy have also been reported.[52] In a retrospective study by Saad et al.[53] in 2014, CNS manifestations in the form of confusion, headache and seizures were noted in 25.7%, 12.9% and 8.6% of patients, respectively. Rhabdomyolysis was seen in 14.3% of MERS-CoV patients.[53]

Neurological Manifestations of SARS-CoV-2

As the number of COVID-19 cases are rising across the world, more and more neurological manifestations involving central and peripheral nervous systems as well as skeletal muscles are coming to the surface. In one seminal work by Mao et al.[4], 78 out of 214 patients studied – a whopping 36.4% – had neurological involvement. In another retrospective study from Wuhan, 6% of infected hospitalized patients developed acute cerebrovascular events following COVID-19 infection.[54] Outside China, a study from France by Helms et al.[55] found neurologic manifestations in 14% of their patients admitted to the intensive care unit (ICU), and notably in another 67% of patients once their sedation and neuromuscular blockade was withdrawn. Several other studies have shown neurologic involvement as the presenting feature of SARS-CoV-2 infection or have reported post-infectious neurologic complications.[3,42,56–58]

Broadly speaking, these para-infectious neurological features can be classified based on the part of the neuroaxis involved, namely CNS manifestations and peripheral nervous system involvement, including skeletal muscle injury.

CNS Manifestations

Headache and Dizziness

Several studies considered headache and dizziness as the most common neurologic symptom reported by patients affected by SARS-CoV-2.[3,4] Mao et al.[4] described a wide array of CNS manifestations, the most common being dizziness (16.8%) followed closely by headache (13.1%). In a large study conducted across China throughout January 2020, which included 1099 patients, headache was reported overall in 13.6% of patients.[3] A more noteworthy finding was that a greater percentage (15%) of those with more severe illness complained of headache.[3] Although mostly considered a rather non-specific symptom of any viral infection, headache has been largely present in most studies conducted across the world, ranging from 3% to as high as 13% in some studies.[3,4,59–61] Nevertheless, headache can often be a forerunner of viral meningitis or encephalitis and is often the premonitory symptom of a cerebrovascular event.[60]

Anosmia and Hypogeusia/Ageusia

Post-viral anosmia, one of the leading causes of olfactory dysfunction in adults, accounts for up to 40% of cases infected by SARS-CoV-2.[62] Previous coronavirus epidemics have reported

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10–15% of cases with similar symptomatology.[63] Reports of similar associations are seen in more than one study from China, South Korea, France, Italy, Iran, UK and USA, and it is frequently combined with hypogeusia/ageusia.[62,64–66] An Italian study published reports of 33.9% of SARS-CoV-2-infected patients having at least one symptom of olfactory or taste disturbances, and 18.3% had both.[62] In a study by Heidari et al.[67], 83% of SARS-CoV-2-infected patients had anosmia as their first symptom, and two-thirds of them were female. Noticeably, in some cases of COVID-19, olfactory disturbances occurred even without significant nasal inflammation and coryzal symptoms.[67] Hence, it might be concluded that the virus directly targets odour-processing mechanisms.[68] Keeping in view of this, it was seen that in human and mouse, the olfactory sensory neurons do not express the two key genes required for SARS-CoV-2 entry: ACE-2 and transmembrane protease serine-2.[69] In contrast, olfactory epithelial support cells and stem cells are found to express both, as do cells in the nasal respiratory epithelium.[69] Based on these findings, Brann et al.[69] have postulated several plausible mechanisms of viral entry into the olfactory epithelium. Firstly, local infection of the vascular and sustentacular cells in the nasal epithelium could result in significant inflammation that effectively blocks the conduction of smell and alters the functions of olfactory sensory neurons.[69] Secondly, damage to these cells also brings into being water and ionic imbalances in them, indirectly influencing signalling from olfactory sensory neurons to the brain.[69] Vascular damage causing hypoperfusion may also be responsible for olfactory bulb dysfunctions. Despite all these findings, the exact mechanism of involvement of the olfactory system remains obscure. Then again, the most implicated receptor, ACE-2, has been found to be present in abundance in the oral mucosal epithelium, thus proving an entry source to the virus.[70]

Cerebrovascular Events

A much more crucial area of thought, which deserves a greater attention of neurologists, is the appearance of cerebrovascular events in the setting of SARS-CoV-2 infection.[71] Evidences of cerebrovascular events attributable to previous coronavirus epidemics have already been documented.[45,72,73] Decidedly, it has also been established that a history of cerebrovascular events is associated with a longer duration of hospital stay, almost always associated with acute respiratory distress syndrome (ARDS) and associated with a poorer overall outcome.[74,75] Predictably enough, in the wake of this ongoing medical catastrophe, there have been several studies reporting cerebrovascular events in the setting of SARS-CoV-2 infection. Mao et al.[4] reported that six out of 214 patients suffered such neurologic compromise later in the course of their illness, five of whom reportedly had more severe disease. A larger proportion of this subset were shown to have acute ischemic stroke, with only one patient having an intracerebral hemorrhage (ICH), who succumbed subsequently to respiratory failure.[4] In divergent studies conducted across China during this pandemic, cerebrovascular events have been reported in a multitude of observations, ranging from as low as 2% to as much as 17%.[3,60,76–79] Predictably enough, the larger proportion of these were acute ischemic stroke.[54] In a single-centre observational study from China, apart from the 5% of COVID-19 patients who had acute ischemic stroke, cerebral venous sinus thrombosis and ICH were also documented in one patient each.[54] Thirty-eight per cent of total deaths in this study occurred due to cerebrovascular events. In a more recent British study reporting about neurological and neuropsychiatric complications of COVID-19, a mighty 62% of patients presented with cerebrovascular events, 74% with acute ischemic stroke and 12% with ICH, and one patient with CNS vasculitis.[80] In a majority of studies, strokes were noted in older patients, having multiple comorbidities, mainly hypertension, diabetes and prior stroke. They had a severe course of illness and later perished to an ominous outcome.[54,81,82] On the contrary, a few studies have documented cerebrovascular events in patients aged <50 years, sometimes occurring earlier in the course of viral infection as compared to an average duration of 10–12 d[61,84] as reported by Mao et al.[4] It has also been noted that stroke patients who were positive for COVID-19 had significantly higher in-hospital mortality, incidences of delirium and a greater morbidity compared to those without COVID-19.[85]

Research has proved, time and again, that recent viral or bacterial infection is quite a plausible cause of cerebrovascular ischemia,[84] and it is only pertinent under the given circumstances that we consider the linkage of COVID-19 infection with the occurrence of coagulopathy and increased risk of thrombotic events. Several cases of thromboembolism, both arterial and venous, have been reported in numerous studies.[86–89] But how SARS-CoV-2 incites this hypercoagulable response remains elusive. There are significant data suggesting the development of a systemic inflammatory response syndrome in these patients. There is substantial proof that increased severity of illness and risk of thrombosis is invariably associated with a higher level of C-reactive protein, fibrinogen and D-dimer. All of this is likely to be a result of endothelial inflammation resulting in upregulated levels of von-Willebrand factor and Factor VIII, and other markers of inflammation.[86–89] On the other hand, SARS-CoV-2, being primarily a respiratory pathogen, induces fatal hypoxemia in the most severe cases. This again may result in vasoconstriction, reduced blood flow, vascular stasis and vessel occlusion.[86–89] Another feasible theory lies in the fact that this hypoxemia prompts the activation of several hypoxemia-inducible factors, chiefly HIF-2α, which is known to induce or inhibit several important genes taking part in normal hemostatic mechanisms.[86–89] Tissue factor and plasminogen activator inhibitor-1 is expected to rise in such situations, which culminates in a reduced capacity to clear fibrinous and other proteinaceous exudates from the system, thus blunting the normally protective fibrinolytic process. This is of paramount importance given that the bulk of patients with cerebrovascular events are also the ones harbouring ARDS.[86] The study by Helms et al.[87] also had 87.7% of patients testing positive for lupus anticoagulant (LA), which is an anti-phospholipid antibody. It was concluded that these were no false-positive LA due to the presence of heparin, as most patients had very low plasma heparin levels, which were adequately neutralised by heparin-neutralising agents present in dilute Russell Viper venom reagents. Cellular damage due to infection possibly causes plasma membrane remodelling and exposure of otherwise masked phospholipids and microparticles to the immune system. This leads to the development of antibodies against them, identified as anti-phospholipid antibodies, whose presence is known to enhance both arterial and venous thromboses.[87]

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Meningoencephalitis and Encephalopathy

A potentially fatal presentation of SARS-CoV-2 is the development of encephalopathy. Symptoms may range from mere headache, fever and neck rigidity to more sinister signs of brain involvement like altered sensorium, agitation, seizures, coma or even focal neurological deficits. One of the first cases of viral encephalitis was reported from Japan,[90] where a 24-year-old man presented with unconsciousness and generalized convulsions 9 d after he first sought medical care for non-specific symptoms of fever and fatigue. Brain imaging showed signs of right lateral ventriculitis and encephalitis, primarily centered on the right mesial temporal lobe and hippocampal region.[90] Interestingly, SARS-CoV-2 RNA was detected in his CSF, but nasopharyngeal swabs remained negative.[90] Encephalitis as a clinical manifestation of COVID-19 has been reported by many since then.[91–96] Early in April 2020, a young female from Los Angeles was diagnosed with SARS-CoV-2 encephalitis.[96] It was only when she failed to show any response to the usually followed treatment protocols for viral meningoencephalitis that COVID-19 testing was ordered.[96] She was started on hydroxychloroquine, showing improvement in her clinical picture.[96] One putative mechanism of viral encephalitis could be a direct invasion of the CNS by the virus, where genomic sequencing has confirmed the presence of SARS-CoV-2.[97] However, a direct invasion might not always be the case, and speculations have led us to believe a possible hypothesis of immune-mediated inflammatory injury and cerebral oedema to be responsible for such encephalopathic changes.[91]

Encephalopathy in patients with COVID-19 does not involve a diagnosis of viral encephalitis. Other causes behind an encephalopathy-like clinical presentation – replete with mental confusion, delirious states and impaired levels of consciousness, agitation or signs of corticospinal tract involvement – are acute toxic encephalopathies, metabolic imbalances, hypoxic encephalopathies, strokes, as discussed above, or seizures with post-ictal confusion. Helms et al.[55] noted agitation in 40% of their patients of COVID-19, all of whom were admitted in the ICU due to ARDS. More than half of these patients showed confusion of varying degrees, and 67% of cases demonstrated diffuse corticospinal tract signs.[55] Subsequently, 13 of them were subjected to MRI of the brain, and 8 out of 13 showed evidences of leptomeningeal enhancement.[55] CSF samples of all these patients were negative for SARS-CoV-2.[55] However, data specifically designating a particular symptomatology to a specific etiology are still inconclusive. Elderly patients with chronic underlying conditions or prior neurological ailments have been seen to suffer from more severe infection and are at a greater risk of encephalopathy at initial presentation.[55] Reportedly, children are being considered to harbour a less severe form of SARS-CoV-2.[98] An index case of acute hemorrhagic necrotising encephalopathy, most likely due to cytokine storm in the setting of SARS-CoV-2, has been described.[93] Another case of acute necrotising encephalitis has been reported by Virhammer et al.[99] wherein SARS-CoV-2 RNA was isolated from the CSF of the patient. It is therefore imperative on the part of the neurologist to keep in mind SARS-CoV-2 infections while dealing with such cases as expeditious isolation of positive cases is deemed indispensable to stall further spread of the infection.

Seizures and SARS-CoV-2

A rather sinister complication of COVID-19 is the occurrence of seizures, which often heralds a grim outcome.[100] Seizures can occur because of encephalitis, electrolyte disturbances and metabolic/hypoxic/toxic encephalopathy. Effects of COVID-19 on patients with epilepsy and whether it increases the risk of contracting infection remain unclear as of now. No definite association between epilepsy and COVID-19 has been reported. However, fever itself is known to lower seizure thresholds and hence can precipitate convulsions in a known patient with epilepsy syndromes.[100] A study conducted by Lu et al.[100] in the Hubei province, China, the epicentre of the ongoing pandemic, validates this point. Out of the selected 304 patients of SARS-CoV-2 infection, 84 (27%) showed evidences of systemic or direct cerebral involvement that increased chances of developing a new-onset seizure or status epilepticus, the most common etiology being hypoxemia (77%).[100] However, clinical course of none of these patients was complicated by seizures.[100] Mao et al.[4] reported only a single case with seizures in their study. Only three other case reports of convulsions associated with COVID-19 have been reported thereof.[101,102] The first is the case of a neonate with positive nasopharyngeal and anal swab tests for both SARS-CoV-2 and rhinovirus.[101] Coronaviral RNA was however undetected in CSF, serum or plasma.[101] Possibly, seizures resulted as a cause of febrile illness, although rhinoviral-induced pathology could not be ruled out with certainty.[101] Vollono et al.[102] reported focal status epilepticus as the presenting feature of the second case, who incidentally was on antiepileptic drugs for a prior history of herpes encephalitis. Though she tested positive for SARS-CoV-2 on nasopharyngeal and oropharyngeal swabs, no direct proof of CNS invasion by the virus could be ascertained.[102] The most suitable rationale is that a mounting systemic response to the viral infection triggered this status.[102] Non-compliance to medication could be a second probability.[102] The third case was the previously mentioned case of encephalitis documented by Moriguchi et al.[90] who presented with new-onset seizures with a positive CSF sample for SARS-CoV-2 RNA. Albeit some studies have reported incidences of viral infections associated with sudden unexplained/unexpected deaths in epilepsy,[103,104] such associations with COVID-19 are yet to be demonstrated.

Cerebellar Ataxia in SARS-CoV-2

A rather uncommon manifestation of CNS involvement by SARS-CoV-2 is ataxia.[4] A study conducted from Wuhan in the early times of the pandemic reported ataxia in only one of their cases.[4] However, the apparent cause behind this compromise could not be validated. Lahiri et al.[105] reported a 72-year-old patient presenting with acute-onset cerebellar ataxia followed by encephalopathy. Neurological manifestation in this case was antecedent to a diagnosis of SARS-CoV-2 infection.[105] Post-viral acute cerebellar ataxia is quite familiar in history and is often seen to be associated with varicella, mumps, Epstein-Barr virus and parvovirus B19, to name a few. Pathological examination of extra-pulmonary organs in patients infected with severe SARS had shown changes in the cerebellum as well.[106,107] Consideration of similar findings in the SARS-CoV-2 pandemic is thus not far-fetched. It does need contemplation, given that

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patients developing ataxia will need caregiver support to maintain ambulatory autonomy, which can be a potential problem at present.

Myoclonus in SARS-CoV-2

In a recent study, Rábano-Suárez et al.[108] reported three cases of hypersomnia and generalized myoclonus in COVID-19, which responded to immunotherapy. Another patient suffered from bilateral myoclonus without impairment of consciousness instigated by underlying electrolyte disturbances.[100]

Spinal Cord Involvement in COVID-19

Data regarding spinal cord involvement are scarce. Post-infectious myelitis is not uncommon with several organisms ascribable to its cause, *Mycoplasma pneumoniae* being the most common.[109] Myelitis following an infection with Epstein-Barr virus, cytomegalovirus, measles virus or rhinovirus is common. CoV-OC43 has been associated with acute disseminated encephalomyelitis.[50] Since all coronaviruses share a structural homology to an extent, in all probability, SARS-CoV-2 can only be expected to cause similar spinal cord involvement. Only one case of acute myelitis following COVID-19 infection has been described from Wuhan hitherto.[110] It is only reasonable to assume that the virus gained entry to the spinal cord by attaching itself to ACE-2 receptors present on spinal cord neurons as well.[110]

Peripheral Nervous System Involvement

Myopathy and SARS-CoV-2

Skeletal muscle damage (myopathy) in association with SARS-CoV-2 infection has been observed to range from asymptomatic rises in creatine kinase and lactate dehydrogenase to rhabdomyolysis.[111,112] Myalgia, weakness and fatigue are common symptoms of SARS-CoV-2 as with any other viral illness, reported in 11–70% of patients with COVID-19.[2–4,59,60] Even though rare, instances of rhabdomyolysis have also been reported in this pandemic, one as a late complication of viral infection[111] and the other as a presenting feature.[111,112] Both patients had significantly raised levels of myoglobin, lactate dehydrogenase and creatine kinase.[111,112] Mechanisms of injury could be multifarious[111,112]: (1) direct viral invasion via ACE-2 receptors, (2) damage to muscle cell membranes by circulating viral toxins and (3) a strong cytokine-mediated immune response ("cytokine storm") causing muscle damage. Underlying hepatic and renal disease are a risk factor for skeletal muscle damage, and this damage further deters their functioning.[111,112] It is important to treat rhabdomyolysis with adequate fluid resuscitation to prevent acute renal shutdown, keeping in mind that excessive fluid can worsen hypoxemia and respiratory failure.[111,112]

SARS-CoV-2 Infection and Critical Illness Neuropathy/Critical Illness Myopathy

A growing concern regards the development of critical illness neuropathy and critical illness myopathy in patients with severe SARS-CoV-2 infection requiring mechanical ventilation. The use of non-depolarising neuromuscular blocking agents is associated with an increased risk of critical illness neuropathy/critical illness myopathy and should be administered with caution.[113] Disuse atrophy and resultant weakness due to damage to type 2 muscle fibres are common in patients bedridden for prolonged periods, and could be worrisome for neurologists in the coming days.[113]

COVID-19 and Polyradiculopathy

There is a known risk of GBS, often succeeding influenza virus, Zika virus, dengue virus, H1N1 and Epstein-Barr virus, among others.[114] Rare instances of GBS following coronaviral infections in previous epidemics are also apparent,[52] the principle behind this being an act of molecular mimicry between viral proteins and proteins on peripheral nerves (e.g. gangliosides). This subsequently leads to an immune dysregulation and a resultant autoantibody-mediated damage to myelin or axons of peripheral nerves. Since the reporting of the first case by Zhao et al.[58] from Wuhan, several cases of GBS related to SARS-CoV-2 infection have been reported so far.[57,58,115–120] Toscano et al.[115] described three cases of axonal and two of the demyelinating variants of GBS, respectively, from three hospitals in northern Italy. All of them had a preceding SARS-CoV-2 infection, the interim duration ranging from 5 to 10 d.[115] It is interesting to note that, in a handful of these cases, the supposedly autoimmune process overlapped with the viral infection, thus giving rise to ideas reckoning the para-infectious nature of the disease rather than it being post-infectious.[120]

Cases of COVID-19 presenting with ophthalmoparesis from multiple cranial nerve palsies and Miller-Fisher (MFS) variant of GBS have been reported.[121,122] Anti-Gd-1b antibodies were found to be positive in one of the cases reported by Gutiérrez-Ortiz et al.,[121] instead of the more common anti-Gq1b antibody. Anti-Gd1b antibody is associated with a better prognosis,[123] but it is too early to conclude any definite association between SARS-CoV-2 infection and this milder variety of MFS.[121] RT-PCR tests done on oropharyngeal swabs taken from both patients were positive for SARS-CoV-2, and CSF studies in both were negative, hence perpetuating our previous knowledge about MFS being an autoimmune process rather than resulting from a direct viral invasion.[121,122] Finsterer et al.[124] claimed that SARS-CoV-2 infection-induced GBS is not triggered by a direct attack of the virus on nerve; rather damage of myelin due to an immune-mediated mechanism is more likely.

Neurological Comorbidities and Living Through the Pandemic

A growing body of research has proven unequivocally that the presence of an underlying comorbidity is a risk factor for more severe SARS-CoV-2 infection.[4,77,125,126] Guan et al.[3] showed that 15% of their cohort had prior cerebrovascular accident, and 11% of them suffered a more severe illness compared to 4% in the non-severe group. Herman et al.[126] studied several reports and analysed that 8% of hospitalized patients diagnosed and treated for COVID-19 had an underlying neurological illness. Albeit the case fatality rates of COVID-19 are low, most of the patients succumbing are those with an underlying illness.[81] In view of this, the role of neurologists caring for patients living with an underlying disorder becomes multifaceted.

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Due consideration needs to be given to the risk of patients contracting SARS-CoV-2 infection. The risk is underscored by increasing age, presence of associated comorbidities and use of IST or IMT. A multi-data-based study conducted in the Unites States showed patients with multiple sclerosis (MS) had a higher incidence of contracting infections compared to non-MS people.[127] The crude rate of infections was higher in those taking interferon-beta and glatiramer acetate, and still higher in those taking fingolimod, natalizumab or rituximab.[127] Consequently, COVID-19 infection was diagnosed in an MS patient under treatment with fingolimod in May 2020 from Iran.[128] Severity of the underlying illness also contributes to this accentuated risk. Neuromuscular diseases not involving the respiratory muscles, for instance, seem to be at a lower risk. Patients with Alzheimer's disease and other types of dementia are at a greater threat, given their advanced age, coexistence of other comorbidities and poor cognition. They may fail to comply with the hygiene and sanitization standards set out by the guidelines; may not be able to acknowledge, appreciate or remember most of these recommendations; may be unable to self-monitor and report presence of symptoms; and may wander outside, compromising efforts to maintain isolation. Caregiver support is an important handicap to these patients under present circumstances.

A fundamental area of concern for neurologists is how COVID-19 affects patients with an underlying neurological illness. Infections are known to unmask or exacerbate several autoimmune neuromuscular diseases, viz. myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, multifocal acquired demyelinating sensory and motor neuropathy and some degenerative disorders like amyotrophic lateral sclerosis and spinal muscular atrophy. Patients with mitochondrial and metabolic myopathies are at an increased risk of rhabdomyolysis with fever and infection. The magnitude of these risks is yet to be studied on a large scale to outlay definite precautionary measures.

Other pressing issues could be the widespread use of IST/IMT among these patients, which may increase the chance of acquiring viral infection. IST/IMT may reduce the efficacy of vaccines, which should become available to us soon. Whether or not these medicines should be stopped at present requires precise guidelines. However, the aim is to allay conditions mandating an increase in the dose of IST/IMT or hospitalization. Therefore, one must weigh the risks and benefits of continuing/stopping such medications. As such, there is no immediate need to stop these drugs in the absence of infection. Recommendations regarding the timing of vaccination with the dosing of IST/IMT are required once vaccines against SARS-CoV-2 have been developed.

It is unavoidable that a diagnosis of new neurological disorders will be delayed due to the unavailability of sufficient manpower directed at this, healthcare being targeted largely at the prevention, diagnosis and management of COVID-19. There was a definite fall in the number of stroke patients undergoing imaging at a centre in the United States compared to the pre-pandemic times.[129] Patients will be unable to visit clinics due to transportation restrictions. There is an acute shortage of hospital beds, ventilators, and most elective workups for chronic diseases are being held up. This may adversely affect patients with pre-existing neurological disorders in ways more than one. Obtaining maintenance drugs, regular check-ups, monitoring for adverse effects of drugs may be troublesome.

Long-Term Implications

The impact of any disaster is always long-lasting. Complications of SARS-CoV-2 are unravelling gradually, the most common being ARDS. There is evidence that ARDS contributes to cognitive impairment in several ways – damage to the blood–brain barrier and use of mechanical ventilation being important ones.[130] As more and more patients come out of assisted ventilator support systems, long-term effects on their cognition remain under threat. There is an increased need of rehabilitative services at present. Once this pandemic is over, there will be an increasing demand and strain on the healthcare system regarding the diagnosis and treatment of all the non-emergent conditions, which were put away in the wake of this pandemic.

Role of Neurologists

We are still at an early stage to completely discern the heterogenous nature of this disease. By and large, it is a disorder involving the respiratory tract most often. However, growing evidences of extra-pulmonary conditions cannot be taken lightly. It is of prime importance that neurological features are examined and worked up thoroughly and more large-scale studies conducted to get a clearer picture. Reports distinguishing between the direct effects of the virus on the nervous system and the effects of systemic illness on the nervous system (hypoxia, sepsis, hypercoagulable states and disseminated intravascular coagulation) are still nebulous. The role of telemedicine comes forward in a big way in the care of those already living with a neurological disorder. However, a wide spectrum of issues is expected with up-trending telemedicine. Most prominent disadvantages are lack of accessibility, affordability, decay of doctor–patient relationship, and lack of interpersonal communication leading to misadventures. It is of paramount value that chronic patients continue to get an undisrupted supply of medications and personal protective equipment to preclude the worsening of their conditions and curb the growing curve of infection. Emergency therapeutic interventions should be ensured to run in a smooth manner to prevent increases in mortality and morbidity of cerebrovascular events.

Of the several critical situations faced by neurologists in this present situation, the diciest remains the management of acute stroke. In the context of COVID-19, the ability to provide timely and efficacious care needs to be weighed against the risk of exposure to infection, and this becomes especially crucial in patients of acute stroke, given that specific treatment therapies within specified time windows (thrombolysis/thrombectomy/medical therapy) are known to affect the functional recovery and long-term outcome of these patients. Stroke patients may have symptomatic as well as asymptomatic COVID-19 infection or may develop fever during an hospital stay due to urinary tract infection or aspiration pneumonia as a complication of stroke, thus necessitating rapid evaluation for COVID-19 infection. Quite expectedly, these will burden the already overstressed healthcare system. Healthcare providers involved in providing care to patients of acute stroke with COVID-19 infection do have a risk of contracting the infection from them, although the exact risk is yet to be ascertained. Under these circumstances, it therefore becomes essential that recommendations and guidelines on stroke care be modified as per emergency medical

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situations, and neurologists follow what may be aptly termed as a "protected stroke code" instead of the regularly practised stroke codes.[131–135]

Recommendations for Managing Stroke During Covid-19[131–140]

First, apart from the regular screening methods used by paramedics before transferring the patient to appropriate centres, COVID-19 pandemic mandates the use of additional screening protocol, including that of an infection control screen and a travel history screen for all patients, based on the recommendations of WHO or CDC.[1,141,142] They must complete screening the patient for infection, assessing for features such as fever, cough, chest pain, headache, myalgia, shortness of breath and gastrointestinal symptoms like vomiting or diarrhea.[141] Travel history includes any recent (≤14 d) travel abroad or contact with someone who has travelled abroad, bearing in mind that as the pandemic unfolds worldwide, travel history becomes less and less important. The protected stroke code should be activated in any confirmed or suspect cases of COVID-19, as per WHO or CDC definitions.[1,141,142] One of the challenges faced at this step is the inability to extract relevant information from the patient or relatives concerned. Approximately 10–12% of stroke patients are known to suffer from cognitive dysfunction, dysarthria, aphasia or the absence of near relatives.[136,137] Moreover, acute stroke patients may also be in the prodromal phase of infection or being asymptomatic carriers. The paramedics should be instructed to activate institutionally and regionally recognised protected stroke code systems for such patients also and continue with such protocols until screening can be reliably completed or COVID-19 ruled out with formal testing. Efficient communication across transfer sites and adherence to local screening procedures needs to be highlighted at this point.

Second, once this modified stroke code is activated, it alerts the stroke care team of the receiving institution. Members of the stroke team must make certain that basic measures to stop disease transmission are donned at the earliest. This includes wearing of personal protective equipment and maintaining a safe distance (at least 2 m) from the patient unless necessary. Given the acute shortages of personal protective equipment in most regions, the use of filtering face-piece respirator should be advocated to the ones most in need. Stroke evaluation often does not expose the healthcare professional to aerosol-generating procedures. In such instances, the use of filtering face-piece respirator may be reconsidered based on availability, regional prevalence of SARS-CoV-2 infection and institutional practices. As a routine, full-sleeved gown, extended cuff gloves overlapping the sleeves of the gown, eye protection (either in the form of face shield or goggles) and surgical mask, in the least, should be worn by the involved healthcare professional. Aerosol-generating procedures, for example, intubation, oropharyngeal/nasal suctioning, bag-valve-mask ventilation, proving cardiopulmonary resuscitation, non-invasive ventilation or nebulisation, will require upgrading the personal protective equipment to include a filtering face-piece respirator. A surgical mask must also be placed on the patient and should always remain so during transportation. Supplemental oxygen may be provided as required via nasal prongs, placed below this mask.

Third, the number of members on the stroke team evaluating a patient should be kept as minimum as possible, keeping in mind that those at risk of contracting infection are best kept back. The fruitful use of tele-stroke must be optimized at present to reduce exposure to the patient as much as possible. One bright side is that most aspects of stroke evaluation can be completed using tele-stroke.

Fourth, it is indispensable to maintain suitable precautionary measures even during conveyance of the patient to and from the imaging facility, not only to avoid contamination of the patient and the related healthcare professional, but also to protect the sanitization of the environment. Separate pathways may be assumed for patients with COVID-19 infection. Creation of a stroke greenway while transporting the patient to consultation suites, imaging rooms or angiographic suites may be a viable option. A suspect or confirmed case must be admitted in an isolation ward afterwards, keeping suspects apart from confirmed cases.

Fifth, while considering all these above precautionary measures, it is of prime importance that patient management does not take a backhand, and that appropriate therapies be delivered to those who arrive within the correct time windows. Besides stroke evaluation, the attending healthcare professional should also assess the patient for other underlying comorbidities, other organ damage and their general condition. A quick but helpful tool in assessing these is the Sequential Organ Failure Assessment (SOFA) score.[143] This is essential because it is already a known fact that underlying illnesses and multi-organ damage worsen prognosis in COVID-19 patients, and stroke care needs to be modified accordingly. Both COVID-19 and stroke increase the risk of renal insufficiency and adversely affect their outcome. Before sending a patient for imaging studies, which require contrast administration, neurologists must consider the plausibility of development of contrast-induced nephropathy, and contrast use may be avoided altogether if not necessary. In case of suspected COVID-19 cases, it may be reasonable to carry out a CT scan of the chest in conjunction with brain CT. Whenever possible, negative pressure isolators should be utilized during imaging procedures.

Sixth, Mao et al.[4] showed that patients with severe SARS-CoV-2 infection, as well as those with neurologic complications, had leucocytosis, higher C-reactive protein and D-dimer levels. Previous studies have shown that the use of rt-PA in patients with ischemic stroke and higher levels of inflammatory markers has foreseen a greater risk of ICH and poorer prognosis.[138–140] The presence of hepatic dysfunction may further add to the potential threat of ICH, as rt-PA is metabolised in the liver,[144] and any dysfunction will lead to decreased clearance of the drug. Apart from a detailed coagulation profile, other tools like thromboelastography go a long way in helping neurologists weigh the risks against the benefits of rt-PA administration.

Seventh, being an invasive procedure, mechanical thrombectomy, on the other hand, will pose greater challenges. Rapid transfer between different places, even within the same hospital, may be difficult at present, given the stringent protocols that need to be followed. After measuring out pros and cons of thrombectomy, and if the patient meets all the usual inclusion criteria, thrombectomy may be considered as a therapeutic option, given that it can be performed with appropriate safety precautions

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assuming the patient to be a case of COVID-19. Consent from relatives may be obtained via digital communication media. Patients undergoing mechanical thrombectomy often require mechanical ventilation during or after the procedure, and more so in the setting of COVID-19. A low threshold for using general anesthesia and mechanical ventilation is advocated during these times. A tracheobronchial aspirate may be sent for SARS-CoV-2 detection at the same time. Given that several steps in introducing endotracheal intubation are aerosol-generating procedures, it may be considered favorable to intubate the patient prior to arrival at an angiographic suite.

Eighth, institutions must frame their own policies regarding decontamination and disinfection of angiographic suites and surrounding zones. Modifications of usual distinctions between critical, semi-critical and non-critical items and high-touch or low-touch surfaces must be put to order. A protocol for terminal cleaning to avoid contamination to the next patient must be followed. It is best to use a negative pressure angiographic suite, but it is not always feasible, especially in resource-crunched countries already reeling under the threats of a looming economic crisis.

Ninth, it is still debatable as to whether antiplatelets or anticoagulants are preferred in acute stroke patients with COVID-19. Due to a lack of any definite studies, it is recommended to follow the existing guidelines to administer single or dual antiplatelet agents to such patients, and to withhold these drugs for 24 h post-thrombolysis or thrombectomy. Superiority of one antiplatelet agent over another is yet to be defined.

Tenth, having said all these, we must keep in mind that it is easier said than done. Economically backward countries will undoubtedly face the heat in keeping up to more stringent protocols. The cracks on healthcare resources are already well visible and the hollowness of civilization shining through. It is therefore of supreme importance that the general preventive measures laid down by the WHO are fostered strictly by the general population,[141] and more so by the people more at a risk of stroke, so that viral transmission can be nipped off at the bud.

Recommendations for Care of Patients With Seizure Disorders

There are diverse predicaments faced by those with epilepsy, those caring for them as well as those treating them during these trying-and-testing times. Most studies have evinced that epilepsy does not increase the risk of SARS-CoV-2 infection, lest the patient also has associated comorbidities.[145,146] There are however a few exceptions – autoimmune epilepsies, for instance, which make the person more susceptible to infection both due to the disease process itself and as an effect of immunomodulatory therapy for the underlying autoimmune process.[145,146] It is of paramount importance to communicate to patients with epilepsy the consequences of discontinuation of medication. It is essential that they stock up medicines for a few months in advance taking into consideration the effects prolonged periods of lockdowns and empty pharmacy shelves are going to have. Non-compliance with therapy can have dangerous consequences. Additionally, the threshold to administer emergency rescue medications (benzodiazepines via nasal, rectal or buccal route) may be lowered in such crisis situations. The objective is to reduce visits to healthcare facilities as much as possible in order to reduce exposure to infection, prevent acute attacks of seizures/status epilepticus, to minimize visits to the emergency department and to prevent unnecessary utilization of ventilator machines in these times of crises. Caregivers should be instructed to give as much care as possible at home. Introduction of telemedicine practices will mitigate needless visits to the clinics and avoiding crowded places. While it is important to ensure compliance to medication, it should also be kept in mind that most of these antiepileptic drugs interact with many commonly used drugs. Many patients hospitalized with severe COVID-19 require antiepileptic drugs either as prophylaxis or as part of therapy, and it is irrefutable that severe infection is often associated with underlying cardiovascular comorbidities. Certain combinations are not recommended, and certain ones require extra vigilance to prevent adverse effects and avoidable drug interactions. Furthermore, some drugs used for symptomatic therapy like antihistamines are capable of lowering seizure thresholds.[145] For certain conditions like Dravet syndrome, where fever control is crucial to allay seizures, acetaminophen can be used.[145,146] Patients with tuberous sclerosis or autoimmune epilepsy syndromes receiving corticosteroids or everolimus, among others, are potential candidates of a dysregulated immune response because of these drugs make them more susceptible to infections.[145–147] Nevertheless, some studies have shown everolimus to prevent viral infections.[147,148] A major drawback in the treatment of epilepsies and seizures is the limited use of electroencephalography (EEG) and other imaging procedures at present for fear of transmission of infections. The use of video monitoring EEG for the assessment of intractable seizures can be a useful alternative. Given this extraordinary reduction in healthcare facilities and strategies to reduce transmission of SARS-CoV-2, it is prudent to delay diagnostic EEG/non-emergent investigation procedures. Moreover, neurologists may consider postponement of any changes in treatment (such as weaning off or change in therapies, elective epilepsy surgeries, etc.) at present unless dictated by exigent reasons. Key advice on lifestyle issues like need for regular sleep, healthy eating habits and avoidance of alcohol and other recreational drugs must be reinforced on the patients. Anxiety and depression are of frequent occurrence in epilepsy patients, which heighten expectedly during periods of stress and must be appropriately attended to.

Recommendations for Managing Alzheimer's and Parkinson's Disease[149–151]

On the flip side, we have patients suffering from Alzheimer's disease, Parkinson's disease or other types of dementia and movement disorders, most of whom belong to the geriatric population and are more susceptible to SARS-CoV-2 infection, and sadly are often seen to not understand the measures of hygiene and social distancing laid down by the authorities. Sometimes, even if they understand, they fail to remember them or are unable to implement them effectively. It thus becomes the responsibility of caregivers to continuously reinforce these rules and practices in a soothing and empathizing manner. These patients should be kept informed about the ongoing situation, keeping in mind their vulnerability. With the advent of

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modernization and growing urbanization, as more and more nuclear families are coming up, older generations are frequently found to be living alone or in residential accommodations, nursing homes and old age care facilities away from their near and dear ones. Currently, when the authorities are enforcing orders of lockdowns and social isolation, it is only natural for these people to feel more distant and isolated from their loved ones. Modes of tele-communication can serve a "modus operandi" in keeping in touch with their family members as well as provide self-help guidance like meditation and relaxation exercises and psychological counselling. Furthermore, nursing homes and long-term stay facilities must restrict the number of visitors and outsiders and prohibit group activities to contain the spread of infection.

Time and again, we have stressed on the importance of continued medication during these times, and it is advisable to keep a stock of medicines in advance to allay acute shortages. It is recommended to continue medications for Alzheimer's or Parkinson's disease even in the setting of COVID-19 infection to prevent further complications of the underlying illness. The use of telemedicine to examine patients has been validated in several studies, and neurologists must make the finest use of it. Direct contact with the patient is best avoided unless outright emergencies arise. Certain non-emergent procedures, like botulinum toxin injection, also mandate hospital visits and face-to-face interactions. Appropriate personal protection should be taken in such situations. However, considering the ongoing emergency, elective operations like deep brain stimulation may be deferred.

Recommendations for Patients With Demyelinating Disorders[152]

First, all general measures of personal protection and self-hygiene as advised by WHO and CDC must be practised strictly to prevent infection.[141,142]

Second, in those suffering from mild SARS-CoV-2 infection, it may be reasonable to continue treatment. Considerations for stopping treatment may be undertaken in those taking drugs with greater immunosuppressive effects, having risk factors for severe disease, or in those already suffering from severe infection. Treatment can be restarted after 4 weeks or after complete resolution of symptoms, keeping in mind the risk of rebound MS activity with sphingosine-1-phosphate modulators and natalizumab.

Third, fever care is of great importance in MS.

Fourth, a higher threshold should be assumed before offering corticosteroid treatment to MS patients during COVID-19 pandemic, and it is advisable to test the patient for COVID-19 before starting steroids.

Fifth, some of the drugs used in MS therapy (interferon-β, glatiramer acetate) do not increase the risk of infection, and hence they can be considered during therapy initiation and can be continued as well. Drugs with a low risk of systemic immunosuppression (dimethyl fumarate, teriflunomide) can be safe to start, but treatment continuation requires regular monitoring of leukocyte count, which may be difficult during an ongoing pandemic.

Sixth, extended interval dosing of drugs with a moderate risk of immunosuppression (S-1-P modulators, anti-CD20 antibodies) has been shown to be effective and is recommended.

Seventh, drugs causing a high degree of immunosuppression (cladribine, alemtuzumab) mandate delaying further courses of treatment based on disease status, patient factors as well as drug factors. It is also unadvisable to start therapy with these drugs at present.

Eighth, patients of neuromyelitis optical spectrum disorders should continue treatment to prevent relapses, including corticosteroids, azathioprine, mycophenolate mofetil, tocilizumab, rituximab or eculizumab. If at all drugs need to be stopped, moderate-dose corticosteroids may be given as rescue therapy to allay attacks on a short-term basis.

Ninth, it should be borne in mind that routine check-ups and laboratory investigations may always not be possible during this pandemic.

Lastly, it is always advised to provide individualized treatment based on patient factors, disease status and drug effects.

COVID-19 and its Psychological Aftermath

As most of us speculate the potential neurological manifestations of COVID-19, a rather hideous aftermath of a medical, social and economic cataclysm is slowly but rearing its ugly head. Jim E. Wallis rightly said, "sometimes it takes a natural disaster to reveal a social disaster", and, truly enough, mental health issues in the wake of this pandemic are on the rise everywhere across the world, spanning all ages and economic strata of the society. There is an increasing prevalence of depression, anxiety, sleep and stress disorders among medical as well as non-medical healthcare personnel, children, older individuals and the general population as a whole, and as the WHO puts it, "a substantial investment is needed to avert a mental health crisis".[141]

A study from Ethiopia showed a threefold increase in the prevalence of depression in April 2020.[141] Surveys across China have reported soaring rates of depression (50%), anxiety (45%) and insomnia (34%) among healthcare personnel.[153] Similar studies from Canada recorded a mighty 47% of healthcare workers in need of psychological support.[141] Additionally, at-risk groups include patients contracting the disease and their relatives, children confined to their homes/quarantine centers for prolonged periods, elderly individuals, especially those in need of caregiver support or otherwise, women juggling between home-schooling, working from home and household tasks, and people already suffering from an underlying psychiatric problem. Apart from the pandemic-related psychological distress, the direct effects of SARS-CoV-2 itself and the resulting host immune response on the CNS and its neuropsychiatric sequelae should not be overlooked.

A multitude of factors can be held responsible for such emotional turmoil being faced by the greater part of the world at this point of time. Social isolation, fear of contracting infection, loss of near and dear ones, enforcement of strict public health measures curbing personal freedom, growing insecurities regarding loss of income and employment and incurring financial losses are major stressors accountable for this psychological upheaval.[154–156] Within a week of lockdowns, India registered a 20% increase in overall mental health issues.[154] Moreover, frontline health workers – bearing the brunt of excessive workload, uncertainties of prognoses, shortages of resources for testing, treatment and personal protection, feelings of quandary,

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dilemmas about the health of self and family, discrimination, prejudice and stigmatisation – are at a greater risk of coming down with mental health issues. Research conducted by Lai et al.[153] has shown women and nurses to be more vulnerable to psychological predicaments. 76.7% of all the participants were women, and 60.8% of them were nurses (90.8% being females).[153] Probably, a continuous close contact with affected patients and longer working hours place them at a higher risk. 71.5% of them carried junior titles, lacking experience and necessary expertise to handle crisis situations.[153] These findings are very much comparable to those during the SARS outbreak in 2003.[157,158]

What is disheartening is to see children and young adolescents succumbing to stress and anxiety in the wake of this adversity.[155,156] In view of forestalling further spread of this highly infectious disease, countries around the world have been forced to push a majority of their population into quarantine, which includes many children as well. While this has effectively slowed the progression of the disease, this dramatic change in their environment seems to have quite a distressing effect on everyone, and children are no exception. They are being exposed to widespread fear propelled by the rapid spread of the virus, compounded by constant news chatter about death and disease, which creates an environment of uncertainty around them. Million children worldwide are stuck in limbo, with their schools shut down indefinitely and outdoor activities stalled.[155] While for those staying at home with their parents this strain may have been reduced to some extent, it is equally difficult for those separated from their caregivers/parents. Being confined to their homes for prolonged periods increases irritability, restlessness, nervousness and lack of concentrating abilities among children.[155] High incidences of acute stress disorders, adjustment issues and grief among children isolated or quarantined during a pandemic have been reported.[159,160] Parental loss during childhood does go a long way in the development of mood disorders, psychosis and increased suicidal rates in the future. There are growing evidences of household violence and child abuse in view. Children with disabilities, those staying in crowded settings and living on streets are deemed particularly vulnerable. For an entire generation, to grow up in these conditions, with no clear answers for the foreseeable future, is unprecedented and will inevitably have a significant impact on their outlook.

Any calamity of this magnitude is known to shake up the extremes of age to a greater degree than the rest of the population. In addition to the growing concerns regarding SARS-CoV-2 infection and its precariousness faced by the general population, older individuals face some other specific worries. Elderly people suffering from multiple comorbidities require regular visits to the physician for health check-ups and getting prescriptions for underlying conditions. Public transport being halted in most places has reduced visits to the clinics, and more and more use of online and telemedicine is being encouraged. Older adults have limited access to the internet and smartphones, and consequently most are unable to benefit from such provisions. Besides, many countries are facing acute shortages of drugs because of interruption of manufacture, transport and business. Likewise, people already living with a chronic psychiatric problem are unable to access care they would normally require to function in a stable way. Undoubtedly, mental health services have been suppressed to a large extent under present circumstances. In many regions, mental healthcare facilities have been converted to care facilities serving patients with COVID-19; face-to-face services that are of utmost importance in psychiatric treatments have been stopped. People already living with an existing mental illness are more vulnerable to continuous media reporting about the wavering situation. Inability to acquire their maintenance medicines, being coerced into a confined situation, lack of psychological counselling sessions, shut down of outpatient departments and reduced visits from caregivers have put those most in need at risk of falling through the cracks and have inflicted on countless others new-found grief, anxiety and depression and inclination towards self-harm. 32% of known psychiatric patients from UK have been reported worsened psychiatric symptoms during this phase.[141]

Other potential psychiatric problems that need to be addressed are the rising incidences of addiction and substance abuse. Canada has reported an increase in alcohol intake in about 20% of adults in the age group of 15–49 years.[141] On the other hand, social distancing, limited celebrations and unavailability of addictive substance can lead to alarming withdrawal symptoms in many. While outdoor activities have been discontinued in most regions, a sizeable proportion of the population are resorting to binge watching of television and spending a large part of the day on electronic gadgets, laying a substrate for the development of behavioural problems in the long run.

On the other end of the spectrum lies the acute neuropsychiatric problems among those infected with COVID-19 and having neurologic complications. The wide gamut of neurological problems has already been discussed, and it is noteworthy that strokes and encephalopathies often have acute and subacute neuropsychiatric sequelae. Nearly one-third of patients admitted in the ICU are expected to develop delirium.[161] In an observational study by Helms et al.[55] from France, among the 14% of COVID-19 patients who developed neurologic complications, 33% were discharged with various executive dysfunctions, notably inattention, disorientation or poorly organised movements in response to commands. Long-term neuropsychiatric deficits following acute neurologic disorders are also not uncommon. Salluh et al.[161] also found persistent neurocognitive deficits in patients with delirium even after 18 months post discharge. A multitude of studies have indicated that exposure to viral infections *in utero*, childhood or even adulthood placed individuals at an increased risk of schizophrenia later in life.[162,163] Severance et al.[164] established an increased prevalence of antibodies against four HCoV strains in patients with psychosis. Contemplating such evidence, it is not practicable to completely shut one's eyes to these conceivable problems of SARS-CoV-2 infection in the long run.

So how do we terminate this relentless turn of events? Or are we going to be dragged into this unfathomable abyss of destruction eventually? It is what we do today that will reflect in our future. The need of the hour is to identify these potential problems and prepare us to combat them in the face. Timely mental healthcare is necessary. Mental health professionals are facing overwhelming challenges due to a lack of sufficient resources, proper protocols and guidelines and are in quandary as to how to provide mental healthcare in isolation units and hospitals. The integration of mental health crisis interventions with the general disposition of disease prevention and treatment is of indispensable value. Multidisciplinary mental health teams, both at

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regional and national levels, should be able to provide care to patients and health workers. Clear and accurate information regarding COVID-19 should be communicated to both patients and healthcare personnel to allay their fears and anxiety to some extent. Regular screening of suspected patients, confirmed cases and health workers for mental illness should be made a norm rather than exception. On 27 January 2020, the central health authority of China issued the "Principles for Emergency Psychological Crisis Intervention for COVID-19 Pneumonia Epidemic".[165] More than 20 specific guidelines and expert consensus were made available to frontline healthcare professionals in China at the end of February 2020.[166] Extensive adoption of online education systems, psychological counselling and hotline services were set up for those in need. Consequently, two surveys conducted in China, one at the end of January and the other towards the end of February, showed remarkable improvement in mental health status among frontline healthcare professionals following dramatic changes in approaches to provisions of mental healthcare and psychological support.[153,167] Considering these recent events, it is imperative that China shares its protocol of emergency mental health services with the rest of the world. As it stands today, it is indeed the collective responsibility of governments and the civil society with the support of the whole United Nations system to fight this growing concern. International academic organisations such as the World Psychiatric Association and Pacific Rim College of Psychiatrists should aim at developing updated guidelines. Large-scale studies need to be conducted and references taken from previous experiences of pandemics to guide appropriate action. It is critical that people continue to have access to treatment and be provided with the correct information to reduce discrimination and social stigmatization. The real need is to build community-based capacities that strengthen social cohesion and reduce loneliness and aim to build resilience among adolescents and young children. Laying out newer guidelines and imposing such large-scale reforms is inevitably associated with drawbacks and limitations. Despite all these measures, it is highly probable that older individuals are unable to access the internet effectively, or healthcare professionals are faced with time constraints to avail of these services. Nevertheless, unless this pandemic is attended to at this critical hour itself, the post-COVID-19 landscape will be a fertile breeding ground for an increase in chronic stress, anxiety, depression, alcohol dependence[168] and self-harm.

Conclusion

Neurological manifestations in SARS-CoV-2 are diverse and heterogeneous, ranging from mild symptoms such as anosmia and hypogeusia/ageusia to more severe pictures such as stroke, seizures, ataxia, polyradiculoneuropathy, encephalopathy and movement disorders. However, it is yet to be established that whether these are only associations or having an etiological relationship with COVID-19. Studies are in the pipeline to unfurl the pathological and etiological relationship between COVID-19 and various documented neurological manifestations. Possible proposed pathological mechanisms range from a direct neuroaxial invasion to aberrant immunomodulation, endotheliitis and microthrombus generation.

Apart from SARS-CoV-2-related neurological manifestations, other neurological disorders requiring treatment with IST/IMT must be dealt with great caution. The availability of drugs, especially antiepileptic drugs, interferons and other immunomodulators, which need to be continued on a regular or cycle basis, should be handled with great compassion during this pandemic. Neurological disorders should be better managed as per recommendations available for any particular disease rather than an individual approach especially amidst pandemic.

Finally, a myriad of psychiatric or psychological aspects like depression, panic, phobia, bereavement, anxiety, stress and burnout during this pandemic would further complicate diagnostic and treatment perspectives.

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DR and RG wrote the first draft which was critically reviewed and improved by SD, MJD, JBL and BKR.

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