

Neurology and COVID-19: Acting now. Preparing for Future

Annu Aggarwal, Tanu Singhal¹, Mohit Bhatt

Centre for Neurosciences, Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute (KDAH), ¹Departments of Infectious Diseases and Pediatrics, KDAH, Mumbai, Maharashtra, India

Abstract

COVID-19 has a wide-ranging and multimodal neurological impact. First, several neurological symptoms and complications are commonly observed in patients with COVID-19. Second, medications and vaccinations used to counter the disease can have secondary neurological effects. Third, patients with pre-existing neurological disorders bear an increased health-risk due to COVID-19. And finally, the pandemic has disrupted the delivery of neurological and vaccination services, and associated educational and research programs. In this article we review the various channels through which the pandemic is known or projected to effect individual patients or the practice of neurology. We also provide recommendations to manage its immediate effects and prepare for the longer-term fall-out.

Keywords: Anosmia, coronavirus, neurological, pandemic, SARS-CoV-2, stroke

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported from Wuhan, China in December 2019 and within a few months has developed into a pandemic, raging across the continents, disrupting human life as no other event in the living memory. In most cases, COVID-19 results in an asymptomatic or mild respiratory illness but in some, it can lead to severe respiratory distress, and even death. As of mid-July 2020, over 13 million people have had a confirmed SARS-CoV-2 infection and over 580,000 have died.^[1]

While COVID-19 is primarily a respiratory disease, with common symptoms of fever, dry cough, fatigue, and myalgias, it also can have secondary effects on neurological, haematological, renal, cardiac, and gastrointestinal systems. In this report we focus on the neurological aspects of the illness. In the next section we review the common neurological features of COVID-19 while in the Section 3, we discuss the impact of COVID-19 on patients with pre-existing neurological disorders. The drugs used to treat COVID-19 and the potential vaccines can also affect the neurological system, as discussed in Section 4. In the subsequent section, we discuss how the pandemic has affected the practice of neurology, and finally present a few concluding remarks. In addition to reviewing the acute and the potential long-term neurological implications of COVID-19, we provide some related recommendations relevant to practicing neurologists, treatment centers and public health authorities [Tables 1 and 2].

NEUROLOGICAL EFFECTS OF COVID-19

A wide spectrum of neurological features has been observed in patients with COVID-19, involving different parts of the neuroaxis including the peripheral and the central

nervous systems [Table 1]. Among the hospitalized COVID-19 patients, 30–80% exhibit neurological problems. These are particularly common among patients with pre-existing comorbidities (hypertension, obesity, diabetes, and others; see Table 3) or those with severe COVID-19.^[2-5] While in most patients, neurological effects are seen concurrently or within a few days of the classical COVID-19 symptoms, in some the neurological features predate or develop significantly later than the initial febrile illness.^[3,6,7] Some neurological issues may persist beyond the resolution of the infection and, it is feared, that COVID-19 may leave the patients susceptible to delayed-onset neurological disorders. Therefore, it is essential that, (i) a higher degree of clinical suspicion for COVID-19 be maintained in patients presenting with neurological problems during this pandemic, and (ii) all COVID-19 patients be monitored for neurological signs during, and even following, their recovery from the acute stage of the illness.

Impairment in sense of smell and taste

Perhaps the most frequent neurological symptom among patients with COVID-19 is new-onset impairment of the sense of smell (anosmia) and/or taste (dysgeusia). These signs have

Address for correspondence: Dr. Annu Aggarwal,
Centre for Neurosciences, Kokilaben Dhirubhai Ambani Hospital and
Medical Research Institute, 4 Bungalows, Andheri West, Mumbai,
Maharashtra - 400 053, India.
E-mail: annu.aggarwal@gmail.com

Submitted: 25-May-2020 **Revised:** 09-Jun-2020 **Accepted:** 18-Jun-2020

Published: 14-Aug-2020

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

DOI: 10.4103/aian.AIAN_513_20

Table 1: Known and anticipated neurological complications of COVID-19

	Peripheral nervous system	Central nervous system
Acute	New loss of smell (anosmia)*,† New loss of taste (dysgeusia)*,† Neuropathy Fatigue* Myalgia*,† Myositis	Headache* Giddiness* Strokes* Symptomatic and asymptomatic Ischemic and hemorrhagic Small and large vessel occlusions Cerebral venous thrombosis related Seizures* Confusion ‡ Inability to wake or stay awake ‡ Aseptic meningitis Viral encephalitis (focal) Acute necrotizing hemorrhagic encephalitis Posterior reversible encephalopathy Generalized stimulus sensitive myoclonus Encephalopathy
Sequelae	Fatigue Myalgias Paresthesia or dysesthesia Bone-breaking pain Chronic pain Critical illness neuropathy-myopathy Difficulty in weaning from ventilator	Mental dullness Confusion, delirium, hallucinations Cognitive problems Dysexecutive syndrome Anxiety Panic attacks Depression
Drug-induced	Varies by drug §	Varies by drug
Delayed¶	Immune mediated syndromes caused by SARS-CoV-2 infection Vaccination	Immune-mediated syndromes caused by SARS-CoV-2 infection Vaccination Neurodegeneration leading to Parkinsonism Cognitive problems
Disruption of vaccination programs	Polio Diphtheria	Tetanus Rabies Subacute sclerosing panencephalitis

*Symptoms predating or concurrent with classical COVID-19 symptoms. †Symptoms suggestive of COVID-19. ‡Warning signs suggesting need for emergency medical care. §For instance, steroids, hydroxychloroquine or antiviral drug can induce neuropathy-myopathy. ¶Based on experience with influenza virus pandemic and other (non-SARS-CoV-2) human coronaviruses

been widely reported although estimates of their incidence range from 5% to 80%.^[3,8-12] The estimates have been higher in the more recent prospective studies of patients with milder symptoms in Europe compared to early retrospective studies of patients with more severe COVID-19 in China. This variation in incidence could thus reflect differences in study design, severity of disease, or could be a regional population based variation.^[3,8-13] The incidence of these symptoms in India remains unknown. Rhinorrhoea (blocked nose) is not sufficient to explain a majority of cases of anosmia.^[8,11] The onset of anosmia and dysgeusia, predates, is concurrent with, or follows other typical symptoms of COVID-19.^[3,8,9,11,12] In most patients, anosmia, and dysgeusia are self-remitting and resolve independently at varying rates, usually in a matter of weeks.^[8,11,12] In patients with mild disease, anosmia, and dysgeusia were strong predictor of SARS-CoV-2 infection,^[10] and these have been added by CDC as indicators of COVID-19. Thus, anosmia and dysgeusia are of diagnostic value for COVID-19 and, as discussed later, provide a

window into a mechanism through which the virus affects the nervous system.

Stroke

COVID-19 is known to induce a prothrombotic state and strokes (ischemic and hemorrhagic) have been reported in 2–5% of patients hospitalized with severe COVID-19.^[3,5] Conversely, cerebrovascular disease has been associated with about a 2.5-fold increased odds of developing severe COVID-19 illness.^[14] Of particular concern are the initial reports of young persons with COVID-19 but without any pre-existing vascular risk factors, developing severe strokes due to large cerebral vessel occlusions, at times involving multiple arterial territories.^[3,5,15,16] Also observed are small asymptomatic ischemic and hemorrhagic strokes that are possibly related to small cerebral vessel disease or small emboli.^[2,3,15] Cerebral venous sinus thrombosis has been described as well.^[17] Strokes have developed both before the classical symptoms of COVID-19, or 7–10 days into

Table 2: Projected medium and long-term impact of COVID-19 on the wider population and the healthcare system

Population
Increase in morbidity and all-cause mortality due to decreased accessibility of medical services
Increase in mental-health problems due to quarantine measures
Resurgence of polio, measles etc., due to disruption of universal childhood vaccination programs
Healthcare system
Disruption of routine out-patient, in-patient and surgical services
Health care workers experiencing;
Nosocomial infections and deaths due to COVID-19
Increased stress and burn-out due to exposure to increased number of patient and deaths
Disruption of medical education and research programs

Table 3: Risk factors for more severe COVID-19 illness in patients with pre-existing neurological disorders

Age ≥ 60 years
Pre-existing neurological disorders
Long-term facility or nursing home residents
Swallowing or breathing difficulty
Immunosuppressants-drugs
Comorbidities
Stroke
Chronic lung disease
Asthma
Serious heart diseases
Obesity
Diabetes
Hypertension
Renal disease
Liver disease
Immunocompromised

the illness.^[3,5,15] The strokes may be related to the several hematological and thrombotic complications associated with COVID-19, although the exact mechanism is yet to be traced.^[3,18] Whether CNS vasculitis is occurring as part of a virus-induced inflammatory storm and the role, if any, of anti-inflammatory drugs, is presently unclear. Standard acute stroke therapies such as tissue-plasminogen activator, mechanical clot retrieval and antiplatelets have been used with mixed outcomes in patients with COVID-19.^[15,19,20] Due to the close association between COVID-19 and cerebrovascular disease, all patients presenting with stroke need to be screened for SARS-CoV-2 infection, while patients with COVID-19 should be monitored for development of ischemic and hemorrhagic strokes. Further studies are required to establish measures for primary and secondary stroke prevention in patients with COVID-19, and to establish short and long-term safety and efficacy of current acute stroke therapies.

Other CNS syndromes

In addition to strokes, several other CNS symptoms and syndromes have been observed in patients with COVID-19.

Of the patient-reported symptoms, headaches, and giddiness are seen in 10–34% of admitted patients.^[3,21–25] A majority of patients admitted in ICU with severe COVID-19 develop encephalopathy (confusion, agitation, and altered sensorium), and global cerebral hypoperfusion has been observed on brain MRI scans in such patients.^[2,5] New-onset confusion and inability to wake or stay awake are listed by CDC as warning signs that patients with COVID-19 need urgent medical care. Seizures can occur at the beginning or during the course of the illness.^[2,3,5] Focal encephalitis, aseptic meningitis, acute necrotizing hemorrhagic encephalitis, posterior-reversible encephalopathy, and generalized stimulus-sensitive myoclonus have also been reported.^[2,3,5–7,22,26,27]

Interestingly, many patients with COVID-19 do not experience dyspnoea (discomfort while breathing) even when their blood oxygenation levels are low. Though impairment of respiratory centers in the brainstem have been proposed as an explanation for this “silent-hypoxia”, the mechanisms are more likely related to preserved lung compliance in early stages of the acute respiratory distress syndrome associated with COVID-19.^[28,29] Irrespective of the cause, the possibility of such silent hypoxia suggests that the decision to admit and ventilate patients should be based on level of blood oxygenation rather than the more conventional parameter of subjective discomfort while breathing. Additionally, for patients with mild COVID-19 who are self-isolated at home or elsewhere, it would be useful to track blood oxygenation levels using relatively inexpensive and readily available home pulse oximeters.

Muscle and nerve injury

Myalgias and muscle injury, evidenced by elevated muscle enzymes (CPK) in the blood, is noted in 20–36% of patients with COVID-19, and is worse in patients with severe forms of the disease.^[3,21,24,25] Muscle pain has been added to the warning symptoms of COVID-19 by CDC. Rhabdomyolysis and increased circulating muscle enzymes, in turn, contribute to renal injury in those with severe illness. Respiratory muscle weakness from ongoing or critical care myopathy-neuropathy can result in difficulty in weaning patients from ventilators.^[3,5,21] Acute inflammatory Miller-Fischer syndrome, polyneuritis cranialis, optic neuritis, and peripheral neuropathy (Guillain-Barré syndrome) have also been reported.^[5,23,30] The true extent of peripheral nervous system affection is probably being under-estimated due to limited availability of EMG-NCV studies.^[3,23,24]

Mechanisms of neurological complications

A number of different mechanisms might be responsible for the neurological problems in patients with SARS-CoV-2 infection. The systemic cytokine (immune-mediated) inflammatory storm that is triggered, especially in cases of severe COVID-19, may affect the nervous system leading to the various neurological complications.^[3,31,32] Secondly, the infection induced hypercoagulable state and embolisms resulting from COVID-19-related myocarditis may both result in strokes and encephalopathies.^[18,33] In patients with severe

COVID-19 disease, hypoxia, multiorgan failure, and various treatments themselves (or, their withdrawal as in the case of cessation of sedation in ventilated patients) may contribute to additional neurological impairment.^[2]

Direct virus invasion of the nervous system is another possible mechanism, which, if verified would have significant and wide-ranging consequences. Among the reasons to entertain this possibility are:

- In one study, SARS-CoV-2 viral particles were seen in brain capillary endothelial cells on electron microscopy and PCR tests confirmed multiple viral proteins in frozen brain sections.^[34] Since endothelial cells lining the blood-vessels express the ACE2 receptor, which SARS-CoV-2 binds to, the electron microscopy observation also suggests a possible route for entry of the virus into the brain.^[32,34]
- Some other human coronaviruses, for instance, SARS-CoV-1 have been shown to be neuro-invasive.^[35]
- In laboratory studies using mice inoculated in the noses by SARS-CoV-1 and MERS-CoV, the virus crossed the BBB by binding to the ACE2 receptors in the olfactory receptors and nerves of these animals.^[36,37]
- The frequent occurrence of anosmia and dysgeusia, especially early in the disease course, suggests that SARS-CoV-2 could be neurotropic, infect the olfactory and gustatory neuroepithelium and then ascend to the brain through these cranial nerves. Although human olfactory receptors and nerves do not themselves express ACE2 receptors the enzyme receptors are present in some non-neuronal cells that support the olfactory receptors and neurons. Thus, invasion of these non-neuronal cells could both disrupt the sense of smell and taste, and provide a pathway for the virus to enter the brain.^[38,39]

Given the presence of SARS-CoV-1 in the brainstem, another route of entry of SARS-CoV-2 would be through the ACE2 receptors in the lower respiratory tract, and through the vagus nerve into the brainstem.^[26] Once real-time PCR for detection of SARS-CoV-2 in the cerebrospinal fluid has been validated, CSF studies would help confirm or refute CNS invasion as a general phenomenon and in particular patients.

Long-term neurological problems

Long-term neurological effects following COVID-19 are a distinct possibility, given preliminary accounts of patient-experience during the current pandemic and observations following previous pandemics.

While the observation period has been necessarily limited, and the accounts largely anecdotal at this stage, several patients have reported disabling fatigue, myalgia, bone-breaking pain, dysesthesia, panic attacks, mental dullness, and confusion extending for months, after mild to moderate COVID-19.^[40] After weaning off ventilator, some patients with severe COVID-19 have had prolonged periods of impaired consciousness, suggesting diffuse cerebral dysfunction.

Furthermore, many patients have required extended ventilatory care and this itself has previously been associated with cognitive impairment and poor long-term neurological outcomes.^[41-43] Dysexecutive syndrome has been noted in around 30% of patients who have survived severe life-threatening COVID-19. It remains to be seen how these patients recover on long-term follow-up.^[2]

Besides the immediate neurological sequelae of COVID-19, delayed neurological consequences, such as post-infection immune-mediated syndrome or neurodegeneration may also occur. Post-infection acute disseminated encephalomyelitis, brain stem encephalitis and Guillain-Barré syndrome have previously been reported with various human coronaviruses.^[44] Both SARS-CoV-1 and MERS-CoV have been shown to enter the brain and cause neuronal death (without encephalitis), particularly targeting the brainstem, striatum, and thalamus.^[35-37] The 1918 Spanish flu (Influenza A; H1N1 influenza) pandemic was followed by increased incidence of encephalitis lethargica (post-infection Parkinsonism) that was characterized by substantia nigral degeneration. The temporal association of the two events suggested H1N1 influenza virus as one of the causes of the Parkinsonism, though this was never conclusively established.^[45] Anosmia, which is an early and frequent feature of COVID-19, is a prodrome for diseases such as Parkinson disease, wherein the pathology starts in the olfactory nerve and spreads across various brain-networks to involve the basal ganglion and brainstem.^[46] It is unclear which, if any, part the neuroaxis or brain networks would be susceptible to degeneration in the long-term, after acute COVID-19 illness. Long-term population follow-up studies are needed to monitor for increased incidence of neurodegenerative problems including cognitive impairment and Parkinsonism.

If the long-term COVID-19-related neurological problems prove to be widespread and significant, treatment plans for dealing with the effects will need to be developed and the neurology health-services geared to deliver them at scale.

COVID-19 IN PATIENTS WITH PRE-EXISTING NEUROLOGICAL DISORDERS

Patients with pre-existing neurological disorders face a heightened health-risk due to COVID-19.^[25] A review of 17.5 million NHS patient records in England found that patients with strokes, dementia, and neurological disorders had a hazard ratio of COVID-19 related hospital death of about 2 to 3, even after adjusting for age, sex, ethnicity, and other co-morbidities.^[47] Secondly, as a population, patients with neurological disorders are older, more likely to have one or more cardiovascular co-morbidities, and more likely to be on immunomodulator therapies. Additionally, patients with chronic debilitating neurological diseases, especially those with respiratory or bulbar weakness or those on immunosuppressant medications, are generally at a greater risk of any infection, particularly respiratory illnesses, and this may be true for COVID-19 too. Patients resident in nursing-home

and hospice (and the health-care workers attending to them) are particularly vulnerable to infection, and such facilities are themselves at risk of becoming reservoirs for the virus. Due to all these factors, patients with pre-existing neurological disorders may see a greater prevalence of, and morbidity and mortality due to, COVID-19.

To counter this greater vulnerability, public health measures to prevent infections in this population need to be emphasized. This too, however, raises some specific concerns since measures such as self-isolation, social-distancing, and frequent hand washing are challenging for patients with significant physical or cognitive impairment, or behavioral issues. Public health measures need to be adapted to ensure safety of this patient population and their caregivers, with possibly more frequent screening and more tailored quarantine facilities. And given the increased risk of COVID-19-related hospital deaths among neurology patients, they may need to be prioritized to receive ICU care.

Apart from the direct effects of the virus itself, changes in daily-routine and the additional personal, familial, and social stress that the pandemic has caused have led to increased prevalence of anxiety, depression, and obsessive-compulsive disruptive behaviors in the general population.^[48,49] These problems are likely to be more severe in patients with pre-existing neurological and psychiatric disorders. Recognition of these problems, education and counselling services, and, if warranted, pharmaceutical interventions are required to address the mental health burden placed on neurological patients and their caregivers.^[50-52]

NEUROLOGICAL IMPLICATIONS OF COVID-19 INTERVENTIONS

Several therapies are in use, being considered, or under development for COVID-19. In parallel, there are also concerted efforts to develop safe and effective vaccines to prevent further spread of the infection and to control the pandemic.

Given the urgency, many of these medications are being used based on prior experience, or on an experimental basis, but without the benefit of the full gamut of preclinical and clinical trials to test for efficacy or to detect the adverse effects they may cause. On the positive side, since most of the initial drugs being considered for COVID-19 have been previously used to treat other disorders, there is an existing knowledge base of their safety profile and pharmacological effects. Practitioners need to leverage this knowledge to anticipate and then monitor for adverse effects, including possible neurological effects, when the drugs are used to treat COVID-19. For example, of the antiviral drugs currently in use for treatment for COVID-19, lopinavir, ritonavir, chloroquine, and azithromycin have been associated with neuropathies and muscle injuries. And, dexamethasone, which has recently been suggested for treatment of patients with

severe respiratory complications can cause insomnia, muscle weakness and behavioral changes.^[53]

Tens of thousands of drugs in use for various diseases are being tested for efficacy against SARS-CoV-2 and have potential for being repurposed in the fight against the virus. These include drugs in use for treatment of neurological disorders, for instance antiepileptics (valproic acid), anti-Parkinson drugs (entacapone), antipsychotics (haloperidol, chlorpromazine, fluphenazine), antidepressants (clomipramine), anti-inflammatories (indomethacin), anti-hypertensives (captopril) and others.^[54,55] If any of these drugs are eventually moved to general clinical use against COVID-19, the treated patients will need to be monitored for the relevant neurological effects, guideline developed to choose the appropriate patient population for which these can be safely used, and measures introduced to counteract any ill-effects. Secondly, repurposing of any of these drugs for COVID-19 would, at least in the short-term, strain the supply for patients who need them for their original purpose.

Vaccinations, including the influenza vaccines, have been associated with various immune-mediated neurological complications such as acute neuropathies, myelitis, encephalopathies and others.^[56-60] Such diseases would also be of concern with the SARS-CoV-2 vaccinations that are under development. While rigorous testing before they are recommended for use outside clinical trials would be ideal, and the practice followed in regular course, it is probable that the testing-cycle of any SARS-CoV-2 vaccine would be shortened. Therefore, health services would need to actively monitor for and be vigilant about any adverse-effect reports following population-wide introduction of any COVID-19 vaccine.

PRACTICE OF NEUROLOGY

In addition to the direct physical effects of the virus in individuals, the pandemic has also caused great social upheaval, which has affected the practice of neurology [Table 3].^[61] And this disruption has even had a deleterious effect on patients who do not have COVID-19. For instance, all-cause-deaths have increased significantly relative to comparable period pre-dating the pandemic, even after accounting for deaths directly attributable to COVID-19. In particular, deaths classified as due to Alzheimer disease and dementia have shown a marked increase (about 14,000 excess deaths in USA between February and June 2020). While some of this excess mortality is likely explained by mis-classification of deaths among patients who have undiagnosed or unrecorded COVID-19, in other cases, the disruption and inaccessibility of routine health-care services probably played a role.^[25,62-64]

Out-patient services for non-COVID-19 patients have been crippled by public health-care related travel restrictions, patients' fear of venturing to medical centers where they may face a greater risk of being infected with SARS-Cov-2, and re-allocation of medical services to care for COVID-19 patients.^[65] In response, some hospitals and individual physicians have rapidly adopted tele-medicine

for routine patient visits and adjustment of medications. Guidelines for examination of patients and overall conduct of tele-consultations have been formulated by various neurology societies.^[66,67] However, patients' access to the technology is still limited and most routine neuro-diagnostic services (for instance, neuroimaging, neuro-electrophysiological and neuropsychological assessments) and day-care procedures (e.g., parenteral immunomodulator therapies, DBS programming, and emergencies) do require in-person visits.^[66,68,69] More considered re-organization of neurology services is needed to triage those requiring in-person visits, to supervised home care systems or near-by primary-care centers. If implemented with due thought, the development of tele-medicine infrastructure and the experience gained in its use could be of lasting value beyond the current pandemic.

Access and availability of medication has also suffered. Maintaining drug manufacturing and associated supply chains for all the commonly used and COVID-19 related drugs is essential to minimize the knock-on effects of the pandemic. Developing e-pharmacies would also help ease patients' access to medicines.

A worrying fall-out of the SARS-CoV-2 pandemic is the global disruption of various routine new-born, early childhood and other population-based vaccination programs.^[70] If this continues for a significant period, it may result in re-emergence or surge in neurological illnesses such as polio, diphtheria, and sub-acute-sclerosing-panencephalitis. Therefore, even after the current acute phase of the pandemic is past, the vaccination status of all children should be checked when they visit a medical facility.

Health care workers have been particularly hard-hit by the pandemic. In addition to their susceptibility to nosocomial SARS-Cov-2 infection, they also face mental health issues due to the additional stress caused by this vulnerability, limited availability of PPEs, long-working hours, and interacting with patients with COVID-19. This has even resulted in higher rates of suicides in this population.^[71,72] As seen with the SARS-CoV-1 epidemic, these mental health problems may outlast the current pandemic and would require longer-term care and support services.^[50-52]

Training of future doctors and scientific research unrelated to COVID-19 have also being impacted. The medical and neurology resident and fellowship programs have been disrupted as health-care workers are reallocated to care of COVID-19 patients, traditional in-person clinics and grand-rounds are on hold. and key international and national medical conferences are deferred or abridged. Collaborations among institutes to restructure the training programs and increase online courses are underway. The public health related restrictions have disrupted clinical drug trials, and other academic-studies. The anticipated global financial recession and uncertainty of timelines for normalization will possibly adversely impact future research funding.

While the current attention is naturally focused on dealing with the patient-centric effects of COVID-19, in the medium-term the disruption to the medical, educational, and research personnel and practices will also need to be addressed.

CONCLUSION

In the few months since the SARS-CoV-2 virus was first identified, researchers and clinicians have traced its wide-ranging impact on both the nervous system and patients with neurological disorders. Measures to detect and counter these effects have also been introduced, and several mechanisms for its action proposed. The pandemic's indirect impact on the practice of neurology is also recognized. Our knowledge of the disease is constantly and rapidly expanding with it being estimated that over 23,000 scientific papers on COVID-19 were published by mid-May and the number is doubling every three weeks.^[73]

The available knowledge needs to be translated into clinical practice, which will need to be regularly updated as we learn more. The longer-term neurological impact of COVID-19, and the medications and vaccinations introduced to treat or prevent it, won't be known for some time. In the meantime, doctors need to anticipate, monitor for, and be ready to treat these delayed effects. Similarly, we need to simultaneously deal with the current pandemic-led changes to neurological practice while working to pre-empt, or minimize, future damage brought on by the disruption to medical education, research, and delivery and to vaccination programs.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis* 2020;20:533-4.
- Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, *et al.* Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med* 2020;382:2268-70.
- Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, *et al.* Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020;77:683-90.
- Mahajan N, Singla M, Singh B, Sajja V, Bansal P, Paul B, *et al.* 2019-NCov: What every neurologist should know? *Ann Indian Acad Neurol* 2020;23(Suppl 1):S28-32.
- Romero-Sanchez CM, Diaz-Maroto I, Fernandez-Diaz E, Sanchez-Larsen A, Layos-Romero A, Garcia-Garcia J, *et al.* Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOV registry. *Neurology* 2020;10.1212/WNL.0000000000009937. doi: 10.1212/WNL.0000000000009937.
- Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology* 2020;201187. doi: 10.1148/radiol.2020201187.
- Yin R, Feng W, Wang T, Chen G, Wu T, Chen D, *et al.* Concomitant neurological symptoms observed in a patient diagnosed with coronavirus disease 2019. *J Med Virol* 2020;10.1002/jmv. 25888. doi: 10.1002/jmv. 25888.

8. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, *et al.* Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): A multicenter European study. *Eur Arch Otorhinolaryngol* 2020;6:1-11.
9. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, *et al.* Self-reported olfactory and taste disorders in SARS-CoV-2 patients: A cross-sectional study. *Clin Infect Dis* 2020:ciaa330. doi: 10.1093/cid/ciaa330.
10. Menni C, Valdes A, Freidin M, Ganesh S, Moustafa J, Visconti A, *et al.* Loss of smell and taste in combination with other symptoms is a strong predictor of COVID-19 infection. *medRxiv* 2020:1-23. doi: 10.1101/2020.04.05.20048421.
11. Spinato G, Fabbri C, Polesel J, Cazzador D, Borsetto D, Hopkins C, *et al.* Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. *JAMA* 2020;323:2089-90.
12. Levinson R, Elbaz M, Ben-Ami R, Shasha D, Levinson T, Chosen G, *et al.* Anosmia and dysgeusia in patients with mild SARS-CoV-2 infection. *medRxiv* 2020:1-12. doi: 10.1101/2020.04.11.20055483.
13. Benny R, Khadilkar SV. COVID 19: Neuromuscular Manifestations. *Ann Indian Acad Neurol* 2020;23(Suppl 1):S40-2.
14. Aggarwal G, Lippi G, Michael Henry B. Cerebrovascular disease is associated with an increased disease severity in patients with Coronavirus Disease 2019 (COVID-19): A pooled analysis of published literature. *Int J Stroke* 2020;15:385-9.
15. Oxley T, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, *et al.* Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med* 2020;382:e60.
16. Jain R, Young M, Dogra S, Kennedy H, Nguyen V, Jones S, *et al.* COVID-19 related neuroimaging findings: A signal of thromboembolic complications and a strong prognostic marker of poor patient outcome. *J Neurol Sci* 2020;414:116923.
17. Hughes C, Nichols T, Pike M, Subbe C, Elghenzai S. Cerebral venous sinus thrombosis as a presentation of COVID-19. *Eur J Case Rep Intern Med* 2020;7:001691.
18. Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, *et al.* Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020;191:145-7.
19. Bhatia R, Sylaja PN, Srivastava MVP, Khurana D, Pandian JD, Suri V, *et al.* Consensus statement-suggested recommendations for acute stroke management during the COVID-19 pandemic: Expert Group on Behalf of the Indian Stroke Association. *Ann Indian Acad Neurol* 2020;23(Suppl 1):S15-23.
20. Escalard S, Maier B, Redjem H, Delvoye F, Hebert S, Smajda S, *et al.* Treatment of acute ischemic stroke due to large vessel occlusion with COVID-19: Experience from Paris. *Stroke* 2020:STROKEAHA120030574. doi: 10.1161/STROKEAHA.120.030574.
21. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;323:1061-9.
22. Filatov A, Sharma P, Hindi F, Espinosa PS. Neurological complications of coronavirus disease (COVID-19): Encephalopathy. *Cureus* 2020;12:e7352.
23. Gutierrez-Ortiz C, Mendez A, Rodrigo-Rey S, San Pedro-Murillo E, Bermejo-Guerrero L, Gordo-Manas R, *et al.* Miller Fisher Syndrome and polyneuritis cranialis in COVID-19. *Neurology* 2020:10.1212/WNL.0000000000009619. doi: 10.1212/WNL.0000000000009619.
24. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, *et al.* Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708-20.
25. Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, Felix SEB, *et al.* Coronavirus disease 2019 case surveillance-United States, January 22–May 30, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:759-65.
26. Papa SM, Brundin P, Fung VSC, Kang UJ, Burn DJ, Colosimo C, *et al.* Impact of the COVID-19 pandemic on Parkinson's disease and movement disorders. *Mov Disord* 2020;35:711-5.
27. Rabano-Suarez P, Bermejo-Guerrero L, Mendez-Guerrero A, Parra-Serrano J, Toledo-Alfocea D, Sanchez-Tejerina D, *et al.* Generalized myoclonus in COVID-19. *Neurology* 2020:10.1212/WNL.0000000000009829. doi: 10.1212/WNL.0000000000009829.
28. Bertran Recasens B, Martinez-Llorens JM, Rodriguez-Sevilla JJ, Rubio MA. Lack of dyspnea in patients with Covid-19: Another neurological conundrum? *Eur J Neurol* 2020: 10.1111/ene. 14265. doi: 10.1111/ene. 14265.
29. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol* 2020;92:552-5.
30. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, *et al.* Guillain-Barré syndrome associated with SARS-CoV-2. *N Engl J Med* 2020;382:2574-6.
31. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, *et al.* COVID-19: Consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395:1033-4.
32. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, *et al.* Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020;395:1417-8.
33. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, *et al.* Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020:e201017. doi: 10.1001/jamacardio. 2020.1017.
34. Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon RE, Reidy J, Lednický J, *et al.* Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). *J Med Virol* 2020;92:699-702.
35. Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, *et al.* Multiple organ infection and the pathogenesis of SARS. *J Exp Med* 2005;202:415-24.
36. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol* 2008;82:7264-75.
37. Li K, Wohlford-Lenane C, Perlman S, Zhao J, Jewell AK, Reznikov LR, *et al.* Middle East respiratory syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4. *J Infect Dis* 2016;213:712-22.
38. Fodoulian L, Tuberosa J, Rossier D, Boillat M, Kan C, Pauli V, *et al.* SARS-CoV-2 receptor and entry genes are expressed by sustentacular cells in the human olfactory neuroepithelium. *bioRxiv* 2020:1-16. doi: 10.1101/2020.03.31.013268.
39. Brann DH, Tsukahara T, Weinreb C, Lipovsek M, Van den Berge K, Gong B, *et al.* Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *bioRxiv* 2020:1-47. doi: 10.1101/2020.03.25.009084.
40. Yong E. COVID-19 Can Last for Several Months. *The Atlantic*; 2020.
41. Sevin CM, Bloom SL, Jackson JC, Wang L, Ely EW, Stollings JL. Comprehensive care of ICU survivors: Development and implementation of an ICU recovery center. *J Crit Care* 2018;46:141-8.
42. Zangrillo A, Beretta L, Scandroglio AM, Monti G, Fominskiy E, Colombo S, *et al.* Characteristics, treatment, outcomes and cause of death of invasively ventilated patients with COVID-19 ARDS in Milan, Italy. *Crit Care Resusc* 2020:Inprint.
43. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, *et al.* Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306-16.
44. Nath A. Neurologic complications of coronavirus infections. *Neurology* 2020;94:809-10.
45. McCall S, Vilensky JA, Gilman S, Taubenberger JK. The relationship between encephalitis lethargica and influenza: A critical analysis. *J Neurovirol* 2008;14:177-85.
46. He R, Yan X, Guo J, Xu Q, Tang B, Sun Q. Recent advances in biomarkers for Parkinson's disease. *Front Aging Neurosci* 2018;10:305.
47. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, *et al.* OpenSAFELY: factors associated with COVID-19 death in 17 million patients. *Nature*. 2020 doi: 10.1038/s41586-020-2521-4.
48. Mackolil J, Mackolil J. Addressing psychosocial problems associated with the COVID-19 lockdown. *Asian J Psychiatr* 2020;51:102156.
49. Prasad S, Holla VV, Neeraja K, Suriseti BK, Kamble N, Yadav R, *et al.* Parkinson's disease and COVID-19: Perceptions and implications in patients and caregivers. *Mov Disord* 2020;35:912-4.

50. Pfefferbaum B, North CS. Mental health and the Covid-19 pandemic. *N Engl J Med* 2020. doi: 10.1056/NEJMp2008017.
51. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, *et al.* Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. *JAMA Netw Open* 2020;3:e203976.
52. Zhang WR, Wang K, Yin L, Zhao WF, Xue Q, Peng M, *et al.* Mental health and psychosocial problems of medical health workers during the COVID-19 epidemic in China. *Psychother Psychosom* 2020;89:242-50.
53. Guidon AC, Amato AA. COVID-19 and neuromuscular disorders. *Neurology* 2020;94:959-69.
54. Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, *et al.* A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* 2020. doi: 10.1038/s41586-020-2286-9.
55. Riva L, Yuan S, Yin X, Martin-Sancho L, Matsunaga N, Burgstaller-Muehlbacher S, *et al.* A large-scale drug repositioning survey for SARS-CoV-2 antivirals. *bioRxiv* 2020:1-43. doi: 10.1101/2020.04.16.044016.
56. Haber P, DeStefano F, Angulo FJ, Iskander J, Shadomy SV, Weintraub E, *et al.* Guillain-Barré syndrome following influenza vaccination. *JAMA* 2004;292:2478-81.
57. Galeotti F, Massari M, D'Alessandro R, Beghi E, Chio A, Logroscino G, *et al.* Risk of Guillain-Barré syndrome after 2010-2011 influenza vaccination. *Eur J Epidemiol* 2013;28:433-44.
58. Persson I, Granath F, Askling J, Ludvigsson JF, Olsson T, Feltelius N. Risks of neurological and immune-related diseases, including narcolepsy, after vaccination with Pandemrix: A population- and registry-based cohort study with over 2 years of follow-up. *J Intern Med* 2014;275:172-90.
59. Shoji H, Kaji M. The influenza vaccination and neurological complications. *Intern Med* 2003;42:139.
60. Sarkanen TO, Alakuijala APE, Dauvilliers YA, Partinen MM. Incidence of narcolepsy after H1N1 influenza and vaccinations: Systematic review and meta-analysis. *Sleep Med Rev* 2018;38:177-86.
61. Gupta P, Muthukumar N, Rajshekhar V, Tripathi M, Thomas S, Gupta SK, *et al.* Neurosurgery and neurology practices during the novel COVID-19 pandemic: A consensus statement from India. *Neurol India* 2020;68:246-54.
62. Centers for Disease Control and Prevention. Excess Deaths Associated with COVID-19. 2020 [cited 2020 Jun 10]. Available from: https://www.cdc.gov/nchs/nvss/vsrr/covid19/excess_deaths.htm.
63. Office of National Statistics. Analysis of death registrations not involving coronavirus (COVID-19), England and Wales: 28 December 2019 to 1 May 2020 UK2020 [cited 2020 Jun 05]. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/analysisofdeathregistrationsnotinvolvingcoronaviruscovid19englandandwales28december2019to1may2020/technicalannex>.
64. Docherty K, Butt J, de Boer R, Dewan P, Koeber L, Maggioni A, *et al.* Excess deaths during the Covid-19 pandemic: An international comparison. *medRxiv* 2020:1-22. doi: 10.1101/2020.04.21.20073114.
65. Garg D, Dhamija RK. The challenge of managing Parkinson's disease patients during the COVID-19 pandemic. *Ann Indian Acad Neurol* 2020;23(Suppl 1):S24-7.
66. American Academy of Neurology. Telemedicine and COVID-19 implementation guide. 2020 [cited 2020 Jun 16]. Available from: <https://www.aan.com/siteassets/home-page/tools-and-resources/practicing-neurologist-administrators/telemedicine-and-remote-care/20-telemedicine-and-covid19-v103.pdf>.
67. International Parkinson and Movement Disorder Society. Telemedicine in Your Movement Disorders Practice. 2020 [cited 2020 Jun 16]. Available from: <https://www.movementdisorders.org/MDS/About/Committees--Other-Groups/Telemedicine-in-Your-Movement-Disorders-Practice-A-Step-by-Step-Guide.htm>.
68. Kassardjian CD, Desai U, Narayanaswami P; AANEM Quality and Patient Safety Committee of the AANEM. Practical guidance for managing emg requests and testing during the COVID-19 pandemic. *Muscle Nerve* 2020;62:30-3.
69. Bhatia R, Srivastava MVP, Khurana D, Pandit L, Mathew T, Gupta S, *et al.* Consensus statement on immune modulation in multiple sclerosis and related disorders during the COVID-19 pandemic: Expert Group on Behalf of the Indian Academy of Neurology. *Ann Indian Acad Neurol* 2020;23(Suppl 1):S5-14.
70. Strategic Advisory Group of Experts on Immunization. The Global Vaccine Action Plan 2011-2020: Review and Lessons Learned. Geneva: World Health Organization (WHO/IVB/1907); 2019. p. 1-44.
71. Epstein D, Andrawis W, Lipsky AM, Ziad HA, Matan M. Anxiety and suicidality in a hospitalized patient with COVID-19 infection. *Eur J Case Rep Intern Med* 2020;7:001651.
72. Kawohl W, Nordt C. COVID-19, unemployment, and suicide. *Lancet Psychiatry* 2020;7:389-90.
73. Brainard J. Scientists are drowning in COVID-19 papers. Can new tools keep them afloat? *Science* 2020.