




Neurological implications of COVID-19: a review of the science and clinical guidance

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ABSTRACT

COVID-19 is a significant global health burden. The pulmonary morbidity and mortality of COVID-19 is well described, however, there is mounting evidence of neurological manifestations of SARS-CoV-2, which may be of prognostic significance. This paper summarises the available evidence in order to provide clinicians with a concise summary of the peripheral and central neurological manifestations of COVID-19, discusses specific issues regarding the management of chronic neurological disease in the context of the pandemic, and provides a summary of the thrombotic implications of the disease for the neurologist.

INTRODUCTION

Officially declared as a global pandemic by WHO on 11 March 2020, the COVID-19 outbreak has radically affected the social, political and medical landscape.¹ At the time of writing, there have been in excess of 43 million cases globally, and more than 27 000 within Australia.^{2,3}

Although the most common symptoms are cough, dyspnoea and fever, the disease is heterogeneous in presentation and severity, and many extrapulmonary manifestations have been noted.^{4,5} The neurological manifestations of COVID-19 were initially highlighted by Mao's series of 214 patients in Wuhan, who reported a 36.4% prevalence of neurological symptoms, increasing to 45.5% in those with severe respiratory compromise.⁶ Beyond good patient care, it now appears that identification of neurological complications is of prognostic significance.^{4,5}

This review summarises the rapidly evolving literature of the neurological manifestations of COVID-19, to aid both the recognition of significant extrapulmonary manifestations of the disease among attending front-line clinicians and consulting neurologists, and explores the pandemic's broader impact on chronic disease management.

METHODS

A narrative review was performed by searching electronic databases (Medline, PubMed) in July 2020, repeated in August 2020 to identify relevant articles. Key search terms included: 'COVID-19', 'coronavirus', 'SARS-CoV-2', 'neurological', 'neurology', 'stroke', 'thromboembolism', 'thrombosis' and search terms relating to neurology subspecialties. Owing to the rapidly evolving literature base, we supplemented electronic searches with extensive eclectic searching using references lists, review articles and suggestive applications in PubMed (ie, similar articles).

DISCUSSION

Neurological manifestations of COVID-19

The neurological manifestations of COVID-19 can manifest either during the acute phase, or as a later, postinfectious phenomena. The variously implicated neuropathological effects of SARS-CoV-2 infection that are discussed include: (1) direct viral injury, (2) neural or vascular pathology arising secondary to a hyperinflammatory state; (3) vasculopathy/coagulopathy; (4) postinfectious autoimmune and (5) neurological consequence of severe illness (sepsis, hypoxia).⁷

Both central (CNS) and peripheral nervous system (PNS) manifestations have been described in COVID-19 (table 1). A meta-analysis on neurological symptoms in COVID-19 undertaken by Wang *et al*, divided symptoms into commonly reported (>10 studies, >1500 reports), or sporadically reported. The most commonly reported neurological symptoms included fatigue in 33.2%, dyspnoea in 26.9%, myalgia in 16.0%, headache in 9.2% and nausea in 5.1%. Sporadically reported symptoms included anorexia in 30%, malaise in 26.7%, dizziness in 10% and confusion in 5.2%.⁸ The authors' attribution of



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Table 1 Examples of central nervous system and peripheral nervous system neurological manifestations of COVID-19 reported in the literature

Central nervous system	Peripheral nervous system
Dizziness	Hypoguesia and hyposmia
Headache	Guillain-Barre syndrome and other polyneuropathies
Cerebrovascular disease	Myalgia
Encephalopathy/Delirium	Brachial plexopathy
Encephalitis	
Acute disseminated encephalomyelitis	
Acute necrotising haemorrhagic encephalopathy	
Seizures	

dyspnoea as a neurological symptom in this case is perhaps presumptive, however, as discussed below, neurological differentials of dyspnoea should be considered in patients with persistent dyspnoea and neurophysiological correlation may be of benefit.

CNS manifestations of COVID-19

The neuroinvasive potential of SARS-CoV-2

SARS-CoV-2 is in the same betaCoV class as MERS-CoV (Middle East respiratory syndrome coronavirus) and SARS-CoV-1, infections which are known to be associated with neurological injury.^{6,9} ACE2 has been identified as the functional receptor for SARS-CoV-2.⁶ This is present in multiple human organs including the nervous system, vascular endothelium and respiratory system, making them potential targets of SARS-CoV-2.^{8,9}

Biologically, several putative mechanisms have been suggested by which SARS-CoV-2 may directly affect the CNS. Direct invasion of the CNS has been proposed via the olfactory nerve, the vascular endothelium at the blood–brain barrier given an abundance of ACE2 receptors in the vascular endothelium, or via leucocyte migration across the blood–brain barrier.¹⁰ Of interest, in light of the high prevalence of hypoguesia and hyposmia are case reports demonstrating frontal lobe diffusion restriction on MRI,^{8,11} as well as transient oedema of the olfactory cleft.¹² While this would be supportive of olfactory nerve involvement, hyposmia is a common finding in respiratory illness.

Clinically, despite the number of cases worldwide, few cases of neuroinvasive SARS-CoV-2 have been described. Only two cases of cerebrospinal fluid (CSF) SARS-CoV-2 PCR positive encephalitis and a case of CSF SARS-CoV-2 sequence positive demyelinating disease have been published.^{5,13} On the available evidence, it appears that neurological disease associated with COVID-19 is not likely to be a direct viral effect.^{5,14}

Cerebrovascular disease and COVID-19

One of the most debilitating neurological complication of COVID-19 is ischaemic stroke, which is likely a consequence of the prothrombotic phenotype associated with the disease. The estimated incidence of cerebrovascular

disease (CVD) in patients with SARS-CoV-2 admitted to hospital is as high as 5%, with a greater prevalence of large vessel occlusion, although, haemorrhagic strokes and cerebral sinus thrombosis have also been reported.^{10,15}

Evidence of hypercoagulability as the aetiology of stroke in COVID-19 patients is supported by observational data. Several case reports have demonstrated raised inflammatory markers in patients presenting with ischaemic stroke.^{15,16} Additionally, disturbed coagulation profiles have been observed with raised D-dimer levels, elevated fibrinogen levels, moderate thrombocytopenia and prolongation of the partial thromboplastin (PT) time and activated partial thromboplastin time (aPTT), which correlate with a hypercoagulable state.^{5,10,14} Moreover, it has been suggested that transient antiphospholipid antibody production might also play a role in mediating the prothrombotic phenotype, however, the significance of transient antiphospholipid antibodies in the acute inflammatory state remains to be elucidated.¹⁴ As expected, patients with more severe disease were at increased risk of stroke, and accordingly inflammatory markers and D-dimer correlated with stroke risk.^{10,14}

A second postulated mechanism of stroke in COVID-19 is that of endothelial dysfunction. Endothelial dysfunction may account for some of the increased haemorrhagic and ischaemic stroke risk observed in COVID-19 given SARS-CoV-2 can bind to, and invade, vascular endothelial cells via endothelial expressed ACE2, which in turn triggers endothelial inflammatory cell death (pyroptosis).^{10,14} The clinical implications of this possible mechanism requires clinical correlation.

Other CNS pathology in COVID-19

The remaining reported CNS syndromes reported in the literature include encephalopathy, encephalitis mimicking ‘limbic encephalitis’ without identifiable antibodies, acute demyelinating encephalomyelitis with and without haemorrhage and transverse myelitis. As previously mentioned, CSF SARS-CoV-2 PCR positivity is exceedingly rare, and these conditions were treated as per standard local practice.

PNS manifestations of COVID-19

The most common PNS syndromes that have been described with COVID-19 include Guillain-Barre syndrome (GBS), brachial plexopathy, polycranial neuropathies and myopathies, with symptom onset occurring from a week prior to nearly a month following the respiratory symptoms of the disease.^{4,7}

Parainfectious and postinfectious mechanisms are postulated to be the cause for several of the central and peripheral neurological complications of SARS-CoV-2. These include a cytokine storm caused by exaggerated recruitment and activation of immune cells in response to the infection. In particular innate immune cells such as macrophages, neutrophils and natural killer cells secrete cytokines including IL-1, IL-6, IL-17, TNF-alpha, CCL2 and IL-2 which can result in a proinflammatory cascade with collateral damage.^{5,14} The second mechanism, which has been described in GBS, is molecular mimicry of COVID-19

surface antigens resulting in antibodies against ganglioside components of peripheral nerves.¹⁴ Molecular mimicry is also speculated in postinfectious encephalomyelitis with cross-reaction against myelin autoantigens.⁵

Non-COVID-related complications of critical illness

In addition to direct neurological complications of the virus, neurologists must also be aware of pertinent neurological complications of critical care management of COVID-19. All clinicians will be responsible for identifying and providing rehabilitation for postintensive care syndrome, manifesting as worsened physical, cognitive and/or mental health impairments in patients with severe COVID-19 who are discharged from hospital.¹⁷

Early research indicated that one in five infected individuals are admitted to hospital and 1 in 10 may be admitted to the intensive care unit (ICU), highlighting the number of patients potentially at risk of complications of critical illness and prolonged ICU care.¹⁷ There is also a greater use of prone positioning as a critical treatment to improve oxygenation in patients with COVID-related acute respiratory distress syndrome which compounds the risk for neurological complications of critical illness. Closed nerve injuries in immobile and unconscious patients resulting in plexopathy (most commonly brachial plexopathy) occur due to compression and traction. National guidelines 'recommend a 'swimmer's position' with one arm (alternating) abducted and adducted with the head toward the abducted arm' and the UK guidelines suggest resting the shoulder slightly forward of the anterior capsule of the shoulder joint. These guidelines do not completely prevent neuropathies and the main method to prevent injury is frequent, careful and deliberate changing of position; somatosensory evoked potential are not a sensitive method to identify impending insult.¹⁸

Prone positioning may also increase rates of ocular complications, varying from ocular injury, exposure keratopathy, conjunctival chemosis, acute angle closure, ischaemic optic neuropathy, orbital compartment syndrome and vascular occlusions. Neurologists are most likely to be consulted for potential ischaemic optic neuropathy, which may present as a relative afferent pupillary defect.¹⁹

Discussion of neurological manifestations of COVID-19

From our review of the literature, it is evident that the neurological manifestations of SARS-CoV-2 are common, varied and contribute significantly to the morbidity of the disease. While complications such as encephalopathy predictably affect the older population, inflammatory and thromboembolic complications affects younger patients and do not completely correlate with the severity of disease.⁷

In addition to the immediate neurological manifestations of the disease, there are increasing reports of post-infectious fatigue and cognitive 'fog'. Postviral fatigue has been reported in other viral infections, including the coronaviridae such as SARS.²⁰ In a pandemic, this illness may contribute to significant morbidity and economic burden. Ongoing international collaboration to characterise the

extrapulmonary manifestations of SARS-CoV-2 are required in order to best frame the long-term care of patients as we recover from the pandemic.²¹

Indirect implications of the pandemic for neurologists

To quote Charles Hummel, 'your greatest danger is letting the urgent things crowd out the important'. As neurologists, especially in Australia, we have played a minor direct role in front-line patient care. However, the indirect effect on the management of chronic disease is also profound, with significant reallocation of healthcare resources and altered patient consulting patterns. This section summarises the current guidance of management of neurological disease in the era of the pandemic.

In considering the management of chronic disease, individual patient preferences and circumstances must take precedence. As such, the following sections should be considered as general guidelines only. In all patients with chronic neurological conditions, an adequate supply of regular and rescue medications should be maintained, and telehealth consultations considered where appropriate. In-person visits and elective hospitalisation should be reduced and deferred whenever possible. As the primary treating clinicians, advanced care planning should be discussed with patients and their families and clearly communicated with all care providers.

The most significant change in providing neurological care has been the widespread adoption of telemedicine. The American Academy of Neurology has resources available from www.aan.com/tools-and-resources/covid-19-neurology-resource-center/ and comprehensive advice on conducting remote neurological examinations can be found at <https://n.neurology.org/content/94/24/1077.abstract>^{22 23}

Specific considerations including suggestions from The Thoracic Society of Australia and New Zealand and Australian and New Zealand Society of Respiratory Sciences and The Royal Australian and New Zealand College of Radiologists in investigation of neurological patients during the pandemic are addressed in table 2.²⁴⁻²⁷ The investigation of neurology patients will vary depending on the rate of community transmission, risk and yield of the test for an individual patient, however general recommendations are summarised in table 2.

Multiple sclerosis

On the basis of consensus agreement which can be found at MS Australia and Korsukewitz *et al.*,^{28 29} patients who have multiple sclerosis (MS) in general should not stop immunotherapy. Self-injected therapies such as glatiramer acetate and beta-interferon are not immunosuppressive, and while regular MS therapies such as natalizumab, fingolimod dimethyl fumarate and teriflunomide are mildly immunosuppressive there is no evidence of increased SARS-CoV-2 infection risk, and patients are advised to observe standard COVID-19 infection prevention advice.

Pulsed immunosuppressive therapies such as rituximab, ocrelizumab, alemtuzumab and cladribine have variable

Table 2 Managing investigations for neurology patients

Investigations	Impact/suggestion for neurology service
Testing of respiratory function	As of 7 July 2020, The Thoracic Society of Australia and New Zealand and Australian and New Zealand Society of Respiratory Sciences suggest all pulmonary function testing can be performed in patients who are afebrile, have no symptoms of a viral illness and staff can perform it with appropriate personal protective equipment. There is a concern that spirometry creates the potential for droplet formation and aerosolisation. ²⁶
Nerve Conduction Studies and EMG	Consider limiting testing to those patients in whom the test will make a considerable and immediate impact on management, for example, in cases where there is clinical suspicion of acute inflammatory neuropathies, neuromuscular junction disorders, vasculitis and/or myositis. Typical presentations of GBS or myasthenia may not require routine neurophysiology testing prior to initiating treatment. ²⁷
EEG testing	<ul style="list-style-type: none"> ▶ Consider changing from cup or disc electrodes to needle electrodes which have their own limitations but can be applied rapidly. ▶ Brief, reduced montages that screen for generalised status epilepticus with video recording are recommended by Gelisse <i>et al</i> ▶ Hyperventilation is discouraged ▶ PPE measures as per institution guidelines²⁴
Imaging	The Royal Australian and New Zealand College of Radiologists has listed advice regarding reintroduction of services as restrictions ease. ²⁵ As specialists who request these investigations, we must take in to consideration the risk posed to patients from attending hospital and also the likely reduction in availability of these services.

EEG, electroencephalography; EMG, electromyography; GBS, Guillain-Barre syndrome; PPE, personal protective equipment.

levels and periods of immunosuppression, however, due to their nature have options to delay and time therapy courses, which should be discussed with the treating neurologist. Specific advice for MS and related disorders is available from MS Australia.²⁹

Parkinson's disease

There is no evidence that Parkinson's disease itself increases the risk of COVID-19, however, patients with the disease represent an 'at-risk' group within society. In patients with complex devices, we recommend providing a contingency plan in the event of device malfunction (eg, pump failure for continuous levodopa/carbidopa continuous gel or apomorphine infusion administration) and to teach patients to check deep brain stimulation device battery charge and change device settings which can be dictated by the neurologist remotely. Specific advice for the management of advanced therapies in Parkinson's disease have been published by Fasano *et al* and can be accessed here.³⁰

Neuromuscular disease

While there is no epidemiological data, it is intuitive that patients with neuromuscular and motor neuron disease are at an increased risk of experiencing complications from COVID-19. An alternative method to face-to-face physiotherapy and exercise sessions is encouraged to maintain strength in patients. Furthermore, the risk of COVID-19 should be recognised by treating neurologists and any parameters for monitoring for COVID-19 or deterioration in neuromuscular disease developed. Any non-invasive ventilation (NIV) equipment is aerosolising, and Solé *et al* have proposed measures to limit this.²⁷ Prior to initiating or discontinuing NIV, the patient's mask must be in place with a tight seal, antibacterial filters used and PPE donned by

carers. It is also good practice to regularly clean the device, monitor for pressure sores and rotate masks as required.

Intermittent therapies such as plasma exchange or intravenous immunoglobulins have a minimal impact on immune function, and the general advice is to continue these therapies and that patients continue to observe standard COVID-19 infection prevention. Related immunosuppressive therapies including prednisolone, methotrexate, azathioprine, mycophenolate and cyclophosphamide have variable levels of immunosuppression depending on the dosage and concomitant treatment. Due to the substantial risk of relapse with cessation, the general advice is to continue therapy.

Specific advice regarding the management of genetic neuromuscular disease can be accessed here,³¹ and regarding general neuromuscular disease can be accessed here.³² Specific advice on the management of immunotherapies are available here.²⁸

Epilepsy

There is no evidence that epilepsy increases the risk of COVID-19. We recommend that neurologists counsel patients, families and caregivers on how to provide emergency care for patients and in what circumstances they should present to the emergency department for seizures.

Other neurological disorders

Other neurological disorders do not increase the risk of SARS-CoV-2; however, their morbidity should be considered by the treating neurologist. For example, patients with cognitive impairment may have particular challenges in social distancing, and patients with migraine may have increased morbidity and utilisation of healthcare resources.

Table 3 National COVID-19 clinical evidence Taskforce recommendations for chemoprophylaxis in patients with COVID-19⁴²

Population	Chemoprophylaxis recommendation
Adults with moderate COVID-19	<ul style="list-style-type: none"> ▶ Prophylactic anticoagulants, preferably low molecular weight heparins for example, enoxaparin 40 mg or dalteparin 5000 IU once daily ▶ If contraindicated, unfractionated heparin or renally adjusted doses of low-molecular-weight heparins may be used for example, enoxaparin 20 mg or dalteparin 2500 IU once daily
Severe or critical COVID-19, without contraindications	<ul style="list-style-type: none"> ▶ Consider increased prophylactic dosing, preferably low molecular weight heparins, for example, enoxaparin 40 mg or dalteparin 5000 IU two times per day ▶ In presence of acute kidney injury (creatinine clearance <30 mL/min), unfractionated heparin or renally adjusted doses of low-molecular-weight heparins may be used, for example, enoxaparin 40 mg or dalteparin 5000 IU once daily
All patients	<ul style="list-style-type: none"> ▶ Chemoprophylaxis should be combined with non-pharmacological measures such as rehydration ▶ Where VTE chemoprophylaxis is contraindicated, mechanical prophylaxis like intermittent pneumatic compression should be used

VTE, venous thromboembolism.

Specific guidelines for aiding in managing migraine in the era of COVID-19 may be found here.³³

Management implications of CVD and COVID-19

Clot retrieval and thrombolysis within appropriate time frames and as per best practice in patients with COVID-19 presenting with stroke is recommended. Given increased turnover of SARS-CoV-2 PCR testing (<8 to 24 hours in our centre) and risk of undetected SARS-CoV-2 positive status especially in cases requiring inter-hospital or regional transfer for acute stroke or neurosurgery intervention with general anaesthetic, SARS-CoV-2 testing of patients presenting with stroke should strongly be considered. A separate section on thrombotic phenomena, venous thromboembolism (VTE) prophylaxis and treatment in COVID-19 follows later in this review.

Therefore, we recommend standard institutional protocols, as well as personal protective equipment including N95 masks, with a low threshold for intubation of stroke thrombectomy COVID-19 positive patients prior to transport to the angiography suite, ideally in a negative pressure environment, to reduce risk of exposure to neurointervention staff.³⁴

Thrombosis in COVID-19

Thrombosis is of particular importance to the neurologist. As noted above, CVD is the leading cause of neurological comorbidity in COVID-19. Furthermore, VTE is a leading complication of most neurological conditions that require inpatient treatment such as GBS. The interaction and pathophysiology of COVID-19 and thrombosis are, therefore, discussed and summarised below.

Table 4 Recommendations for patient on pre-existing thrombotic therapy from the global COVID-19 thrombosis Collaborative group^{37 38 41}

Population	Recommendation
Patients with mild COVID-19 (outpatient) ³⁸	<ul style="list-style-type: none"> ▶ Mild COVID-19 is not a known risk of anti-thrombotic agents; continue taking antithrombotic agents as recommended for patients on antithrombotics for prior known thrombotic disease
Patients with moderate to severe COVID-19 with suspected or confirmed DIC without overt bleeding on chronic therapeutic anticoagulation ³⁸	<ul style="list-style-type: none"> ▶ Weigh anticoagulation indication against bleeding risk, consider dose adjustment or discontinuation ▶ Majority of the authors recommend reducing anticoagulation intensity barring exceedingly high thrombosis risk
Patients with moderate to severe COVID-19 without overt bleeding on dual antiplatelet therapy ³⁸	<ul style="list-style-type: none"> ▶ Individualised decisions for antiplatelet therapy ▶ In general, consider continuing dual antiplatelet therapy for platelet counts >50 000; reduce to single antiplatelet for platelet count 25 000–50,000; discontinue antiplatelets if platelet count <25 000
Patients with moderate to severe COVID-19 on existing anticoagulation for other diseases, for example, atrial fibrillation	<ul style="list-style-type: none"> ▶ Consider changes to therapeutic low-molecular-weight heparins while an inpatient for safer monitoring profile and less interactions with other drugs³⁷ ▶ If breakthrough VTE occurs while on oral anticoagulants recommend changing over to low molecular weight heparins^{37 41} ▶ If significant renal dysfunction present, consider unfractionated heparin

VTE, venous thromboembolism.

Pathophysiology of thrombosis in COVID-19

The thrombotic response is a highly evolutionary conserved arm of the innate immune system that is activated by invading organisms thereby serving to limit pathogen spread. Unchecked, however, the widespread activation of this ‘thromboinflammatory’ response can result in sepsis induced coagulopathy, multi organ dysfunction and death. SARS-CoV-2 can invade vascular endothelial cells, causing the loss of the normal anticoagulant function of the endothelium.³⁵ Loss of anticoagulant function combines with platelet hyperactivity, enhanced leucocyte tissue factor expression and complement activation release of neutrophil extracellular traps associated with the pro-inflammatory state to result in thrombosis formation in COVID-19 patients.³⁶

Characteristics of thrombotic events and coagulopathy

The key features of COVID-19 associated thrombosis are the relatively increased incidence in younger patients, and propensity for multiterritory thrombotic events.³⁷ In a series of 184 critically ill patients, 31% were found to have thrombotic complications.³⁸ Both micro and macrovascular venous and arterial thrombosis have been described, resulting in stroke and myocardial infarction.^{6 10 38}

Utility of markers of thrombosis

Changes in coagulation parameters are common in hospitalised patients with COVID-19. Due to the observed abnormalities in coagulation profiles, plasma D-dimer, PT, aPTT, fibrinogen and platelet counts are recommended to be measured on admission.^{37 39–41} Although elevations of the D-dimer are common in COVID-19 and appear to be a prognostic marker, there remains a lack of robust clinical data to support the routine intervention with anticoagulation in patients with a rising D-dimer without clinical or radiological evidence of thrombosis.^{38 40}

VTE prophylaxis

Consensus recommendations endorsed by the International Society of Thrombosis and Haemostasis recommend VTE prophylaxis in all hospitalised COVID-19 patients with low-molecular-weight heparin (LMWH), due to the elevated thrombotic risk.³⁷ VTE prophylaxis was associated with a mortality benefit at 28 days in a retrospective study.³⁹ Table 3 summarises the National COVID-19 Clinical Evidence Taskforce recommendations for chemoprophylaxis in patients with COVID-19.⁴² Table 4 lists the Global COVID-19 Thrombosis Collaborative Group recommendations, as well as those from Gavioli *et al* and Zhai *et al*, for patients on pre-existing thrombotic therapy.^{37 38 41}

Treatment of VTE and pulmonary embolism

The anticoagulant of choice is LMWH due to ease of administration and stability in moderate organ dysfunction.^{37 38} Direct-acting oral anticoagulants were associated with six times higher plasma levels in COVID-19 patients compared with pre-morbid levels, possibly from multiple drug–drug interactions including antiviral drugs.^{37 38}

Future of management of COVID-19

The management of COVID-19 is generally supportive including oxygenation and ventilatory support. Remdesivir has recently been shown to reduce hospitalisation duration and is the first medication to be approved by the Therapeutic Goods Administration for the treatment of COVID-19.⁴³ Numerous trials are underway for treatment of COVID-19 with multiple studies currently recruiting on the Australian New Zealand Clinical Trials Registry. The Cochrane Library’s Special Collections on COVID-19 provides current evidence in COVID-19 critical care.

CONCLUSION

The impact of the COVID-19 extends beyond the pulmonary morbidity and mortality of the disease. The neurological manifestations related with SARS-CoV-2 are varied, and their presence has prognostic significance. Neurologists should be aware of the possible manifestations of the disease that they may encounter, in order to provide appropriate guidance to primary treating clinicians.

The impact of the pandemic on chronic neurological conditions should also be recognised, and proactive steps taken by treating clinicians with each patient in order to help minimise the interruption of the pandemic on their care, alleviate the concerns of patients and caregivers and where required, advocate for their care. Finally, as the focus of healthcare shifts from the ‘crisis’, diligence and advocacy will be required to ensure ongoing international collaboration in maintaining registries to monitor for complications of the disease.

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