

Neurological Associations of COVID-19

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Author Statement

MAE, BDM, JS and TS devised the idea for the study. MAE, LB, BS, SL, BDM, RK, SD, JS and TS contributed to the literature search. MAE, LB, BS, SL, BDM and TS designed and drafted the figures. MAE, LB, BS, SL, BDM, RK, SD, JS and TS prepared the initial manuscript draft. All authors contributed to, reviewed and approved the final draft of the paper.

Summary

Background

The COVID-19 pandemic, caused by SARS-CoV-2, is of a scale not seen since the 1918 influenza pandemic. Although the predominant clinical presentation is with respiratory disease, neurological manifestations are being recognised increasingly. Based on knowledge of other coronaviruses, especially those that caused the SARS and MERS epidemics, we might expect to see rare cases of central nervous system (CNS) and peripheral nervous system (PNS) disease caused by SARS-CoV-2.

Recent developments

A growing number of case reports and series describe a wide array of neurological manifestations, but many lack detail, reflecting the challenge of studying such patients. Encephalopathy is relatively common, being reported for 16 (7.5%) of 214 hospitalised COVID-19 patients in Wuhan, China, and 40 (69%) of 58 in intensive care with COVID-19 in France. Encephalitis has been described in 8 patients to date, and Guillain-Barré syndrome in 19 patients. SARS-CoV-2 is detected in the cerebrospinal fluid of some patients. Anosmia and ageusia are common and may occur in the absence of other clinical features. Unexpectedly, acute cerebrovascular disease is also emerging as an important complication, reported for 88 patients, mostly with ischaemic stroke, and possibly due to a pro-inflammatory hypercoagulable state with elevated CRP, D-dimer, and ferritin.

Where next?

Careful clinical, diagnostic and epidemiological studies are needed to help define the manifestations and burden of neurological disease caused by SARS-CoV-2. Precise case definitions must be used to distinguish non-specific complications of severe disease, such as hypoxic encephalopathy and critical care neuropathy, from those caused directly or indirectly by the virus; these include infectious, para- and post-infectious encephalitis, hypercoagulable states leading to stroke, and acute neuropathies such as Guillain-Barré syndrome. Recognising SARS-CoV-2 neurological disease in patients whose respiratory infection is mild or asymptomatic may prove challenging, especially if the primary COVID-19 illness occurred weeks earlier. The proportion of infections leading to neurological disease will remain small. However, these patients may be left with severe neurological sequelae. With so much of the population infected, the overall number of neurological patients, and their associated health, social and economic costs, may be large. Healthcare planners and policymakers must prepare for this eventuality.

Introduction

As of 19th May 2020, the COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has resulted in more than 4.8 million confirmed cases worldwide, and more than 300,000 deaths. It is the largest and most serious pandemic since the 1918 influenza pandemic. Whilst the most common and important presentation is with respiratory disease, there are increasing reports of neurological features. These appear to be a combination of non-specific complications of systemic disease, or infection and/or inflammation of the nervous system and vasculature, which may be para- or post-infectious. In this rapid review, we consider which neurological manifestations might be expected for COVID-19, given what we know about related coronaviruses and respiratory viruses more broadly; we summarize the evidence to date for COVID-19, and examine putative disease mechanisms; finally, we suggest a framework for investigating patients with suspected COVID-19 neurological disease to support clinico-epidemiological, disease mechanism and treatment studies.

Evidence from other viruses

Before SARS-CoV-2, six coronaviruses were known to infect humans. Four that cause seasonal, predominantly mild respiratory illness have a high incidence globally, accounting for about 15-30% of upper respiratory tract infections.¹ Two have led to major epidemics with deaths principally from respiratory disease; Severe Acute Respiratory Syndrome (SARS) was caused by SARS-CoV in 2002-3 and Middle East Respiratory Syndrome (MERS) by MERS-CoV in 2012.^{2,3} Both the more innocuous coronaviruses and these epidemic strains have been associated with occasional disease of the central nervous system (CNS) and peripheral nervous system (PNS).

Both CNS and PNS disease were reported following SARS (appendix, page 10-11). SARS-CoV was detected in CSF by RT-PCR in two of three cases of encephalopathy with seizures;^{4,5} it was cultured from brain tissue at autopsy in the third.⁶ Four patients with severe SARS developed neuromuscular disease, predominantly motor neuropathy, myopathy, or both,⁷ which may have been SARS-specific or secondary to critical illness.⁸ CNS involvement was described for five adults with MERS; two had acute disseminated encephalomyelitis (ADEM), two had cerebrovascular disease, and one had Bickerstaff's brainstem encephalitis.⁹⁻¹¹ Neuropathy was described for 3 patients.^{9,11} HCoV-OC43, a seasonal coronavirus, has caused encephalitis in an infant with severe combined immunodeficiency,¹² and ADEM in an older immunocompetent child.¹³ Headache, neck stiffness, and seizures were described among 22 children (median age 36 months) with suspected CNS infection and coronavirus IgM antibodies in serum and/or CSF.¹⁴ Ten had a CSF pleiocytosis, and eight had brain imaging abnormalities. All 22 made a full recovery.¹⁴

Neurological complications have been described for other respiratory viruses, particularly seasonal and pandemic influenza.¹ These include acute necrotising encephalopathy associated with mutations in the RANBP2 gene, acute infantile encephalopathy, and acute haemorrhagic leukoencephalopathy and myelopathy in adults.^{15,16} The estimated incidence of neurological disorders during the 2009 H1N1 influenza pandemic was 1.2 per 100,000, with children affected more than adults.¹⁷⁻²⁰ The 1918 H1N1 "Spanish" influenza pandemic was associated with post-infectious encephalitis lethargica.²¹

Projected epidemiology of COVID-19 -associated neurological disease

Although neurological complications are rare in SARS, MERS and COVID-19, the scale of the current pandemic means that even a very small proportion could build up to a large number of cases. Table 1 shows that for SARS and MERS, the minimum prevalence of CNS complications ranged from 0.04% to 0.2% and for PNS complications from 0.05% to 0.16%; the extrapolated number of cases with neurological complications of COVID-19, based on these related viruses, is also shown. Given the 4.8 million cases of COVID-19 globally as of 19th May 2020, this projects to a total of 1805-9671 patients with CNS, and 2407-7737 with PNS complications. These numbers, which don't include the increasingly important syndromes of stroke-associated COVID-19 infection, will rise as the pandemic continues.

RECENT DEVELOPMENTS

COVID-19 and neurological disease

As the COVID-19 pandemic progresses there are increasing reports of neurological manifestations (Table 2). These can be considered as direct effects of the virus on the nervous system, para- or post-infectious immune mediated disease, and neurological complications of the systemic effects of COVID-19. The challenges in managing patients with a highly contagious infection, and the overwhelming numbers of cases mean that many early reports lack detail, have limited CSF analysis, imaging or follow up, and appear on non-peer-reviewed websites.

Encephalitis

Encephalitis is inflammation of the brain parenchyma, usually caused by an infection, or the body's immune defences. Although strictly speaking a pathological diagnosis, for practical purposes clinical evidence of brain inflammation is accepted, such as a CSF pleiocytosis, imaging changes or focal abnormalities on electroencephalogram (EEG). Detection of virus in the CSF *per se* does not diagnose encephalitis if there is no evidence of brain inflammation (Table 3; appendix, page 3).²²

As of 19th May 2020, eight adults (four women) aged 24-78 (median 62) years have been described who had encephalitis associated with COVID-19, mostly diagnosed through a nasal/nasopharyngeal swab.²³⁻²⁹ Neurological features mostly started from the time of respiratory symptom onset to 17 days after, though in one 60-year-old man confusion preceded cough and fever by two days (Figure 2a);²⁵ two patients had fever only, with no respiratory features.^{26,29} The neurological manifestations were typical for encephalitis, with irritability, confusion and reduced consciousness, sometimes associated with seizures; three patients also had neck stiffness²⁴⁻²⁶ and another had psychotic symptoms.³⁰ A 40-year-old man developed ataxia, oscillopsia, hiccups and bilateral facial weakness.²⁷ CSF, reported for six patients showed a pleiocytosis in five, mostly lymphocytic, and was normal in one. Four had CSF PCR performed for SARS-CoV-2, of whom one was positive – a 24-year-old man with encephalitis, minor respiratory symptoms and “ground glass” changes on chest CT, who had a PCR negative respiratory sample.²⁴ Few publications reported a comprehensive work up for other causes of encephalitis.³⁰ Brain imaging was normal or had no acute changes for six patients, and showed high signal intensity in two, including temporal lobe changes in one;²³ the patient with ataxia had a cerebellar lesion that extended into the spinal cord.²⁷ Electroencephalography was performed in five patients. Two had generalised slowing, two had focal abnormalities; one, who presented with psychotic symptoms followed by a seizure, was found to be in non-convulsive status

epilepticus.³⁰ One patient responded quickly to high dose steroids,²⁵ but for most there was no specific treatment beyond anticonvulsants, antiviral and antibiotic medication.

There is no specific treatment for SARS-CoV-2 encephalitis. As for other forms of encephalitis, there will be questions around the relative contributions of viral damage and host inflammatory response, and whether corticosteroids might be useful. Clinical trials seem unlikely, given current numbers.

Other encephalopathies

Encephalopathy is the syndrome of altered mental status, which can manifest as changed personality, behaviour or consciousness. In encephalopathic SARS-CoV-2 patients, in whom brain inflammation has not been proven, the wide range of other causes to consider includes hypoxia, drugs, toxins, and metabolic derangements (appendix, page 3).²²

The largest study to date, from Wuhan where the pandemic began, described retrospectively 214 patients with COVID-19, of whom 53 had CNS symptoms including dizziness (36 patients, 46.1%), headache (28,35.9%), and impaired consciousness (16, 20.5%), 27 had severe respiratory disease but there was little further detail.³¹ In a French series of 58 intensive care patients with COVID-19, 49 had neurological complications, including 40 (69%) with encephalopathy, and 39 (67%) with corticospinal tract signs.³² MRI in 13 patients showed leptomeningeal enhancement for eight and acute ischemic change for two (see below); CSF examination for 7 patients showed no pleiocytosis. Fifteen (33%) of 45 who had been discharged had a dysexecutive syndrome. In addition to these series, there has been a handful of case reports, including an encephalopathic woman with imaging changes consistent with acute necrotising encephalopathy²³ (Figure 1a) and a fatal case in which viral particles were found in endothelial cells and neural tissue, though there was no indication of whether this was associated with inflammation.³³

There have been several reports of seizures in children with SARS-CoV-2 infection. Paroxysmal episodes consistent with seizures were described in two infants with no respiratory symptoms but SARS-CoV-2 on nasopharyngeal swab.^{34,35} Both made a good recovery. In one series of 168 children hospitalised with COVID-19, seizures were described for five (3%) children, of whom three had pre-existing epilepsy and one had previous febrile seizures.³⁶

Acute disseminated encephalomyelitis (ADEM) and myelitis

ADEM is a syndrome of multifocal demyelination, typically occurring weeks after an infection, which generally presents with focal neurological symptoms often with encephalopathy.³⁷ Two case reports describe middle-aged women with ADEM and SARS-CoV-2 detected on respiratory swabs. One developed dysphagia, dysarthria and encephalopathy 9 days after onset of headache and myalgia.³⁸ The other presented with seizures and reduced consciousness and required intubation for respiratory failure.³⁹ Both had normal CSF and high signal intensities on MRI typical of ADEM. They both improved after treatment, the first with IVIG, the second with steroids. To date there is just a single report of myelitis (inflammation of the spinal cord) associated with COVID-19. A 66-year-old man in Wuhan, China developed fever, fatigue and then acute flaccid paraparesis with incontinence. Examination demonstrated hyporeflexia and a sensory level at T10. He was treated with dexamethasone and IVIG and was discharged for rehabilitation.⁴⁰

ADEM and myelitis, usually considered post-infectious diseases, are treated typically with corticosteroids or other immunotherapies. In these para-infectious cases, with SARS-CoV-2 detectable at presentation, clinicians may need to be more cautious, especially if virus is detected in the CSF.

Cerebrovascular disease

As COVID-19 has spread around the world, evidence has grown for an association with cerebrovascular disease, as well as other forms of vascular disease. There were cerebrovascular manifestations for 13 (5.9%) of 221 COVID-19 patients in an early retrospective case series from Wuhan: 11 (5%) developed ischaemic stroke, one (0.5%) had intracerebral haemorrhage, and one (0.5%) cerebral venous sinus thrombosis.⁴¹ In Brescia, Italy 43 (77%) of 56 SARS-CoV-2 positive patients admitted to one neurology unit had cerebrovascular disease: 35 ischaemic and three haemorrhagic stroke, and five with transient ischaemic attacks.⁴² In total 88 patients with ischaemic and 8 with haemorrhagic stroke⁴¹⁻⁴⁵ have been reported, 18 (19%) of who died (Table 2; appendix, pages 12-22)

Most patients were over 60 years old, many with known risk factors for cerebrovascular disease, especially hypertension, diabetes mellitus, hyperlipidaemia, and vascular disease.^{41,45-48} Younger stroke patients have also been reported.^{43,47,49-51} In one New York hospital, five young stroke patients with SARS-CoV2 were admitted in just two weeks, whereas the average number of young stroke admissions per two weeks in the preceding year was 0.73.⁵¹ Two had no other symptoms of COVID-19. All had large vessel ischaemic strokes. Cerebrovascular symptoms began a median (range) of 9.5 (0-33) days after the onset of respiratory illness, though in one patient the stroke preceded reparatory features,³¹ and in five there were only cerebrovascular symptoms.^{43,48,49,51}

In a couple of patients, ischaemic stroke has been associated with thrombus in the aorta,^{49,52} and indeed multiple infarcts have been reported for these and other patients,^{46,47,53} sometimes associated with arterial thrombosis and limb ischaemia.^{46,53} Concurrent deep vein thrombosis and pulmonary embolism has been found for other stroke patients.^{47,49} Arterial and venous imaging is clearly essential for COVID-19 patients with acute cerebrovascular events. Small asymptomatic infarcts identified on MRI only have also been described.³² Blood D-dimer concentration was raised in many COVID-19 stroke patients, consistent with a pro-inflammatory, coagulopathic state in the setting of critical illness.^{41,45-52} Positive lupus anticoagulant, anticardiolipin and anti- β 2-glycoprotein-1 antibodies have also been reported in COVID-19 associated stroke,^{46,47} though these can be raised in other critical illness, including infections.

Immediate anticoagulation with low molecular weight heparin has been recommended for COVID-19 patients, to reduce the risk of thrombotic disease.⁵⁴ This might also reduce COVID-19-associated ischaemic stroke, but it must be balanced against the risk of intracranial haemorrhage, including haemorrhagic transformation of an acute infarct. Several randomised controlled trials are looking at the role of anticoagulation in COVID-19 patients, including the impact on stroke incidence.

Peripheral nervous system and muscle disease

Guillain-Barré syndrome (GBS) is an acute polyradiculopathy characterized by rapidly progressive symmetrical limb weakness, with sensory symptoms, and areflexia, with or without facial weakness, though there are several variants. To date, 19 patients (six female) with GBS or its variants and SARS-CoV-2 infection have been reported, with a median (range) age of 62.5 (23-77) years. For the number of SARS-CoV-2 infections world-wide, incidence is not particularly above what might be expected.⁵⁵ Neurological symptoms started typically 7 (range -7-24) days after respiratory or systemic features (Figure 2a), although two patients developed febrile illness 7 days after the onset of GBS,^{56,57} on hospital admission one had a positive swab for SARS-CoV-2, and the other had lymphocytopenia and thrombocytopenia, characteristic for SARS-CoV-2 infection. Three patients had diarrhoea before the onset of neurological disease.

Eleven patients had classical GBS with weakness of all four limbs with or without sensory loss,^{56,58–65} three had a paraparetic variant with leg weakness only,^{57,65,66} and one had lower limb paraesthesia.⁶⁵ Four of these patients had facial nerve involvement, five had dysphagia, and eight developed respiratory failure. Three had autonomic complications, one with hypertension and two with sphincter dysfunction. Electrophysiological studies, performed in 12 patients, were consistent with demyelinating disease in eight, and axonal disease in four.

Two patients had the Miller Fisher variant of GBS with ophthalmoplegia, ataxia and areflexia;^{67,68} one also had anosmia and ageusia (see below), and was positive for anti-GD1b-IgG. One patient had bilateral, and one patient unilateral, abducens palsy,^{67,68} and another had an acute vestibular syndrome with horizontal nystagmus and oscillopsia.⁶⁹

For 16 patients, SARS-CoV-2 was detected in a respiratory swab, for two the sample was not specified; one patient was also positive for rhinovirus. One patient was diagnosed by a blood antibody test. A lumbar puncture was performed for 13 patients, and showed albuminocytological dissociation in 11. SARS-CoV-2 was not detected in any CSF samples. Testing for other pathogens commonly associated with GBS was reported for just four patients.^{60,63,65,66} Fifteen patients were treated with intravenous immunoglobulin; eight, all with classical GBS, were admitted to intensive care for ventilatory support, two of these died.^{59,61} Twelve improved and five had ongoing disability at discharge.

Muscle injury association with raised creatine kinase affected 23 (11%) of the 214 patients in the Wuhan series.²⁵ Rhabdomyolysis due to COVID-19 has also been reported.^{70,71}

Loss of smell (anosmia) and taste (ageusia) have emerged as common symptoms of COVID-19, either with other features or in isolation, suggesting they may be useful diagnostic markers.⁷² A study of 259 patients, including 68 positive for SARS-CoV-2, found abnormal smell and taste were both strongly associated with COVID-19.⁷³ In a European study, olfactory dysfunction was reported for 357 (86%) of 417 COVID-19 patients; 342 (89%) reported gustatory disorders.⁷⁴ These symptoms were reported more frequently for COVID-19 patients than for a historical cohort of influenza patients.⁷⁵ Subclinical deficits in smell and/or taste have also been detected.^{76,77} Although these symptoms can occur in any respiratory infection due to coryza, the fact they occur in isolation of other symptoms suggest there is involvement of the olfactory nerve.

Disease mechanisms

Infection and inflammation of the central and peripheral nervous system

As for other neurotropic viruses, there are critical questions for SARS-CoV-2 around routes of entry into the nervous system, and the relative contribution of virus infection versus host response in the subsequent damage (Figure 2b).

Viral entry to the brain via the olfactory bulb, the only part of the CNS not protected by dura, is one plausible route for SARS-CoV-2, especially given the anosmia in COVID-19. This is thought to be a route of entry for herpes simplex virus, the most common cause of sporadic viral encephalitis.⁷⁸ In mouse models, following intranasal injection HCoV-OC43 invades the CNS by the olfactory route.⁷⁹ Alternative entry routes include carriage across the blood brain barrier, following viraemia, or via infected leukocytes.¹ The angiotensin converting enzyme 2 (ACE-2) receptor, which SARS-CoV-2 binds to for entry into cells,⁸⁰ is found in brain vascular endothelium and smooth muscle.⁸¹ SARS-CoV-2 replicates in neuronal cells in vitro.⁸²

Damage within the CNS or PNS may be caused directly by virus or by the body's innate and adaptive immune responses to infection. Data so far do not suggest that SARS-CoV-2 or related coronaviruses are highly neurovirulent, unlike herpes simplex virus, some enteroviruses and some arthropod-borne viruses, which can cause rampant destruction of neurons.⁷⁸

Autopsy material from a patient who developed encephalopathy weeks after presenting with SARS showed oedema, neuronal necrosis and broad gliocyte hyperplasia.⁶ Immunohistochemical staining demonstrated SARS-CoV in the brain was associated with elevated expression of monokine induced by interferon-g (Mig) and infiltration of monocytes/macrophages plus T lymphocytes. These findings are consistent with viral CNS entry triggering infiltration of immune cells and cytokine/chemokine release, which contributed to tissue damage.

There has been little work on disease mechanisms for coronavirus PNS disease. By comparison with other viruses, it would not be surprising to see immune-mediated disease, e.g. GBS; direct anterior horn cell viral damage causing acute flaccid myelitis might also be expected.⁸³

Cerebrovascular disease

Early indicators suggest cerebrovascular disease in COVID-19 may be due to a coagulopathy. SARS-CoV-2 can cause damage to endothelial cells activating inflammatory and thrombotic pathways.⁸⁴ Endothelial cell infection and/or monocyte activation, upregulation of tissue factors, and the release of microparticles activating the thrombotic pathway and causing microangiopathy may occur for SARS-CoV-2, as for other viruses.^{85,86} The latter is postulated to represent part of the secondary haemophagocytic lymphohistiocytosis spectrum described in severe COVID-19.⁸⁷ Thrombocytopenia with elevated D-dimer and CRP in severe COVID-19 and stroke are consistent with a virus-associated microangiopathic process.⁴¹ Endothelial dysfunction can potentially lead to micro- and macro-vascular, arterial and potentially venous complications in the brain, as described systemically.⁸⁸

Acute ischaemic stroke may also occur through the early inflammatory process following acute infection destabilising a carotid plaque or triggering atrial fibrillation.⁸⁹ A vasculitis process similar to that for varicella zoster virus, where viral replication in the cerebral arterial wall triggers local inflammation,⁹⁰ is also plausible: endothelial infection by SARS-CoV-2 with inflammation and apoptosis of endothelial cells has been shown in kidney, heart, bowel and lung at autopsy,⁸⁴ but cerebral vessels have not yet been investigated.

WHERE NEXT?

Investigating for neurological disease

As SARS-CoV-2 continues to spread, and patients with neurological symptoms are seen increasingly, it is essential that the desire to publish quickly is balanced with the need for careful clinical, diagnostic and epidemiological studies. Clinicians must adopt a methodical approach to investigating patients with possible COVID-19 neurological disease, and systematically consider the evidence for viral infection, and the presenting clinical diagnosis, using definitions that distinguish confirmed, probable, and possible cases (Table 3; appendix, page 2-8).

Given that SARS-CoV-2 causes a large number of asymptomatic or mildly symptomatic infections, it is crucial to remember that patients with neurological disease from other causes may be infected coincidentally with the virus, even in hospital through nosocomial transmission. A full work-up, lacking for many reports to date, is needed to rule out other established causes of brain infections

before attributing disease to COVID-19.^{22,91} Distinguishing between nasopharyngeal SARS-CoV-2 infection and nervous system infection is also critical (Table 3).

For patients with altered consciousness or agitation, consider all causes of encephalopathy, including hypoxia, drugs, toxins, and metabolic derangement; only diagnose encephalitis if there is clinical evidence of brain inflammation such as a CSF pleiocytosis, imaging changes, focal seizures, or histological changes (appendix, page 3).²² Even if virus is detected in the CSF, encephalitis should not be diagnosed unless there is evidence of brain inflammation. For patients with possible peripheral nerve disease, aim to perform CSF examination including albuminocytologic ratio, nerve conduction studies and electromyography during recovery, even if they cannot be done acutely.

In patients with neuropathy, cerebrovascular disease or ADEM, where the damage is likely caused by host response to viral infection, establishing causality is even more challenging, especially if patients present after virus has cleared from the nasopharynx. Clinical case definitions for COVID-19, based on the history and typical findings for chest imaging and blood investigations (Table 3) will be useful. For stroke patients, consider cerebral angiography, intracranial vessel wall imaging and, if necessary, brain biopsy, looking for vasculitis. The apparent high incidence of cerebrovascular disease in patients with COVID-19, with predominantly large vessel disease and markers of a highly prothrombotic state, suggest a causal relationship. However, the high prevalence of the virus during the pandemic, and the fact that most stroke patients have other risk factors, mean it is hard to be sure about causation. The link with SARS-CoV-2 may ultimately need to be proven by careful case-control studies.

In investigating patients with limb weakness and sensory change it is critical to distinguish between disease of the peripheral nerves such as GBS, and inflammation of the spinal cord, which can present with flaccid paralysis if the anterior horn cells are involved.⁸³ CSF examination, neurophysiological studies and spinal imaging are essential.

For patients on intensive care, determining whether neuropathy, myopathy, encephalopathy or cerebrovascular disease are non-specific manifestations of critical illness or are specific to the virus itself may be especially challenging; there are no reliable markers for critical illness, though it tends to occur after several weeks.⁸ Up to 70% of patients with sepsis may develop encephalopathy or polyneuropathy.⁹² In the Wuhan series, neurological complications were more common in those with severe disease, suggesting some of the neurological manifestations were related to critical illness.^{93,94}

Conclusion and future directions

Given knowledge of other coronaviruses and respiratory viruses, the wide range of CNS and PNS associations with COVID-19 is not surprising. Currently the focus is on neurological complications of patients with obvious COVID-19 respiratory disease; however, we are likely to see neurological disease in patients with few or no typical features of COVID-19, based on knowledge of other epidemic viral infections and cases reported so far.⁹⁵ Hypercoagulable states and cerebrovascular disease, which have been seen rarely for some acute viral infections, are emerging as an important neurological complication of COVID-19.

Overall, the proportion of patients with neurological manifestations is small compared with respiratory disease. However, the continuing pandemic, and expectation that 50-80% of the world's population may be infected before herd immunity develops, suggest that the overall number of patients with neurological disease may become large. Neurological complications, particularly

encephalitis and stroke can cause lifelong disability with associated long-term care needs, and associated health, social and economic costs, may be considerable. Healthcare planners and policymakers need to be aware of the growing burden.

Careful clinical, diagnostic and epidemiological studies are needed to help define the neurological disease manifestations and burden. This will involve collaboration of a range of clinical and research expertise, and harmonised approaches across regions, using standardised case record forms such as on <https://braininfectionsglobal.tghn.org/covid-neuro-network/>.

Search Strategy and selection criteria

We searched PubMed and Scopus for articles on COVID-19 and neurological disease published in English from database inception to May 19, 2020 without language restrictions, using the terms “COVID-19”, “Novel coronavirus”, “SARS-CoV-2”, or “coronavirus” in combination with “neurological”, “nervous system”, “encephalitis”, “encephalopathy”, “seizure”, “ataxia”, “myelopathy”, “Guillain-Barré syndrome”, “myopathy”, “peripheral neuropathy”, “neuritis”, “cerebrovascular”, “stroke”, “neuromuscular”, or “brain”, modified as per requirements for each database’s search tool. We reviewed references of relevant studies for additional articles that might have been missed in the initial search. Experts in the field were consulted to ensure important preprints and unpublished studies were not missed. Articles were included on the basis of relevance and originality with regards to the topics covered in this Rapid Review.

Declaration of Interests:

TS was an adviser to the GlaxoSmithKline Ebola Vaccine programme and chaired a Siemens Diagnostics clinical advisory board. All other authors report no competing interests.

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Table 1. Estimated neurological disease case numbers associated with SARS, MERS and COVID-19

Total number of cases reported*	SARS 8096	MERS 2228	COVID-19 Worldwide 4872308		COVID-19 China 84500		COVID-19 USA 1464232		COVID-19 UK 246410	
			Extrapolated from		Extrapolated from		Extrapolated from		Extrapolated from	
			SARS	MERS	SARS	MERS	SARS	MERS	SARS	MERS
			<i>minimum case count [lower and upper 95% CI bound]</i>	<i>minimum case count [lower and upper 95% CI bound]</i>	<i>minimum case count [lower and upper 95% CI bound]</i>	<i>minimum case count [lower and upper 95% CI bound]</i>	<i>minimum case count [lower and upper 95% CI bound]</i>	<i>minimum case count [lower and upper 95% CI bound]</i>	<i>minimum case count [lower and upper 95% CI bound]</i>	<i>minimum case count [lower and upper 95% CI bound]</i>
CNS disease, no. of patients [95% CI] (percentage of total coronavirus cases [95% CI])	3 (0.04 [0.01-0.10])	5 (0.20 [0.06-0.5])	1805 [370-5277]	9671 [3143-22539]	31 [6-92]	168 [55-391]	543 [111-1586]	2906 [944-6774]	91 [19-267]	489 [159-1140]
PNS disease, no. of patients [95% CI] (percentage of total coronavirus cases [95% CI])	4 (0.05 [0.01-0.13])	4 (0.16 [0.04-0.41])	2407 [658-6163]	7737 [2110-19786]	42 [11-107]	134 [37-343]	723 [198-1852]	2325 [634-5946]	122 [33-312]	391 [107-1001]
Total neurological disease, no. of patients [95% CI] (percentage of total coronavirus cases [95% CI])	7 (0.09 [0.03-0.18])	9 (0.36 [0.16-0.68])	4213 [1028-11440]	17408 [5252-42326]	73 [18-198]	302 [91-734]	1266 [309-3438]	5231 [1578-12720]	213 [52-579]	880 [266-2141]

*calculated based on available data up until 19th May 2020; COVID-19 cases from <https://coronavirus.jhu.edu/map.html>
95% confidence interval (CI) calculated with Clopper-Pearson exact method⁹⁶ for proportions, to 6dp using <https://epitools.ausvet.com.au/ciproportion>

Table 1. Estimated neurological disease case numbers associated with COVID-19 extrapolated from SARS and MERS

Table 2. Selected reports of neurological disease associated with COVID-19 (abbreviated version – full table in the appendix)

First author and number of cases	Clinical presentation	SARS-CoV-2 diagnostics	Other pathogen and antibody investigations	Relevant blood tests and radiology findings	Neurological investigations (cerebrospinal fluid findings, neuroimaging, neurophysiology)	Management, progress and outcome
Central Nervous System						
Encephalitis						
Moriguchi ²⁴ -1 case	24-year-old male presented 9 days after symptoms of fatigue, headache, fever - followed by a sore throat - with generalised seizures, reduced conscious level and meningism.	RT-PCR negative in nasopharyngeal swab, positive in CSF.	Serum: Anti-HSV 1 and VZV IgM antibodies tests were negative.	Increased blood white cell count, neutrophil dominant, relatively decreased lymphocytes, increased CRP. CT Chest: small ground glass opacity in the right upper zone and bilaterally in lower zones.	CSF: Clear, colourless. Raised opening pressure (320 mmH2O) and cell count (12/mm ³ - 10 mononuclear and 2 polymorphonuclear cells) CT Head: no brain oedema. MRI brain: hyperintensity along the wall of the right lateral ventricle on diffusion weighted imaging, and hyperintense signal in the right medial temporal lobe and hippocampus on T2 weighted images	Treated empirically for bacterial pneumonia and viral encephalitis. On admission, required intubation and mechanical ventilation due to seizures. Admitted to ICU. Still on intensive care at time of report (day 15)
Sohal ²⁸ - 1 case	72-year-old man presented with weakness and light headedness following a hypoglycaemic episode. Shortly after admission he had difficulty breathing and was noted to have altered mental status. On day two of admission he started to have seizures.	RT-PCR positive-source not specified	Blood: culture negative for bacterial growth. Influenza PCR: negative.	ABG: pH of 7.13, PaO ₂ of 68mmHg, PCO ₂ of 78mmHg. Raised BNP (541 pg/mL), troponin (0.35ng/mL), CRP (61 mg/L), LDH (230 U/L), as well as lymphopenia (0.5 k/cmm) and leukopenia at 4000k/cmm. Chest X-ray: normal. CT chest: bibasilar opacities along with right lower lobe consolidation.	CT head: no acute changes, chronic microvascular ischaemic changes. 24h EEG showed six left temporal seizures and left temporal sharp waves which were epileptogenic	Required intubation and ventilation, and was admitted to ICU. Became hypotensive requiring norepinephrine via central line. Hydroxychloroquine and azithromycin were started in addition to antimicrobials of vancomycin and piperacillin tazobactam. Onset of seizures - treated with levetiracetam and valproate but they were not controlled. Death on day 5 of illness.
Wong ²⁷ - 1 case	40-year-old male presented with ataxia, diplopia, oscillopsia and bilateral facial weakness – diagnosis: rhombencephalitis. 13 days before he had fever and progressive shortness of breath on exertion, followed 10 days later by a productive cough and diarrhea.	RT-PCR positive in nasopharyngeal swab. CSF RT-PCR not performed.	Blood test: negative for hepatitis A, B, C, HIV 1 and 2, and syphilis antibody. CSF: negative bacterial culture. Sent for Anti MOG-IgG antibody and anti-aquaporin 4 antibody testing but results not reported.	Normal white cell count (7.0 × 10 ⁹ /L) with lymphopenia (1.2 × 10 ⁹ /L), raised CRP (50 mg/L), abnormal LFTs (raised GGT 628 U/L, ALT 542 U/L, bilirubin 28 μmol/L, ALP 132 u/L). Chest X-ray: right lower zone consolidation. Liver ultrasound: inflammatory diffusely hypoechoic liver with a raised periportal and pericholecystic echogenicity.	Normal cell count and protein (0.42 g/L) MRI brain: increased signal lesion in the right inferior cerebellar peduncle extending to involve a small portion of the upper cord. The lesion measured 13mm in maximum cross-sectional area and 28mm in longitudinal extent. There was swelling at the affected tissue and associated micro-haemorrhage.	Treated with oral amoxicillin, no other treatment. Gradual improvement in neurological symptoms and he was discharged home after 11 days on gabapentin; oscillopsia and ataxia persisted.
Other Encephalopathies						
Dugue ³⁵ - 1 case	6-week-old infant with cough and fever had episodes of bilateral leg stiffening and sustained upward gaze	RT-PCR positive in nasopharyngeal swab and anal swab. High-throughput sequencing showed SARS-CoV2 RNA in nasopharyngeal samples and anal swab samples. RT-PCR negative in plasma and CSF.	Nasopharyngeal swab: respiratory pathogen PCR panel positive for rhinovirus/enterovirus, high throughput sequencing positive for rhinovirus C. CSF: meningitis/ encephalitis pathogen PCR panel was negative and culture negative.	Leucopaenia of 5.07 x10 ³ white blood cells/μL with a normal differential, and elevated procalcitonin of 0.21 ng/m. Normal U+Es.	CSF: normal MRI brain normal Prolonged EEG monitoring: excess of temporal sharp transients and intermittent vertex delta slowing with normal sleep-wake cycling	No specific treatment. No further episodes and discharged home after one day.
Helms ³² - 49 cases	40 had agitation, 26 of the 40 who could be evaluated had evidence of confusion, 39 had corticospinal tract signs (enhanced tendon reflexes, ankle clonus, and bilateral extensor plantar reflexes). 15 had a dysexecutive syndrome at discharge (inattention, disorientation, or poorly organized	All positive by RT-PCR in nasopharyngeal samples. Negative RT-PCR in CSF in 7 patients.	NR	NR	7 patients had CSF analysis. None had pleiocytosis. 2 patients had matched oligoclonal bands. 1 patient had raised protein. 13 patients had MRI brain. 8 had enhancement in leptomeningeal spaces. 11 patients had perfusion imaging, and all had bilateral frontotemporal hypoperfusion. 2 patients had acute ischaemic stroke. 1 had subacute ischaemic stroke. 8 patients had EEG. 1 had diffuse bifrontal slowing.	All required treatment on ITU for severe COVID-19. 45 had been discharged from ICU at the time of writing.

movements in response to command). 7 had a history of neurological disorders, including transient ischemic attack, partial epilepsy, and mild cognitive impairment.

Mao ³¹ - 16 cases	16 patients hospitalised with COVID-19 had "impaired consciousness", of which 1 had a seizure characterized by a sudden onset of limb twitching and loss of consciousness, lasting 3 minutes.	All positive by RT-PCR in throat swab.	NR	Patients with 'CNS disease' and severe respiratory disease had lower lymphocyte levels and platelet counts and higher blood urea nitrogen levels compared to those without CNS symptoms.	NR	13 had severe respiratory disease and 3 non-severe according to American Thoracic Society guidelines. No further details.
Poyiadji ²³ - 1 case	Female patient with cough, fever and altered mental status. Imaging consistent with acute necrotising encephalopathy.	RT-PCR positive in nasopharyngeal swab. CSF RT-PCR unable to be performed.	CSF: bacterial culture negative after 3 days, and 'tests' for HSV, VZV and WNV negative.	NR	Non-contrast CT head: symmetric hypoattenuation within the bilateral medial thalami. Normal CT angiogram and CT venogram. MRI brain: T2 FLAIR hyperintensity within the bilateral medial temporal lobes, thalami and subinsular regions with evidence of hemorrhage indicated by hypointense signal intensity on susceptibility-weighted images and rim enhancement on postcontrast images	IVIG. Outcome not reported
Paniz-Mondolfi ³³ - 1 case	74-year-old male with fever, confusion and agitation who had two falls at home	RT-PCR positive in nasopharyngeal swab. Electron microscopy of frontal lobe specimens at post-mortem: presence of viral particles in endothelial cells and neural cell bodies. No indication of if this was associated with inflammation.	NR	Increased CRP, ferritin, d-dimer and thrombocytopenia. Initial chest radiology - no changes in lung fields, subsequently developed new changes bilaterally on chest X-ray suggestive of consolidation.	CT head: no acute changes	Given hydroxychloroquine and LMWH initially, then tocilizumab. Persistently febrile, agitated with episodes of hypotension and increasing hypoxia. Developed new onset atrial fibrillation and was given fluids and amiodarone, reverting to sinus rhythm, then continued on metoprolol. Deteriorated and died.
Zhou - 1 case	56-year-old patient with COVID-19 pneumonia	SARS-CoV2 detected by sequencing in CSF	NR	NR	NR	NR

Acute disseminated encephalomyelitis

Zanin ³⁹ - 1 case	54-year-old woman presented with agitation, decreased conscious level and seizures following several days of anosmia and ageusia	RT-PCR positive in respiratory sample	Blood: cultures negative; urine: cultures negative.	Lymphopenia (0.3/mm ³) with mild elevation of inflammatory markers (CRP 41.3 mg/L, Fibrinogen 520 mg/dL). Chest X-ray: interstitial pneumonia	CSF: Normal MRI brain and spine: periventricular confluent white matter lesions and numerous high signal cord lesions from bulbomedullary junction to T6 level. No contrast enhancement.	Treated with antiretrovirals and hydroxychloroquine. Clinically deteriorated following admission, becoming hypoxic and requiring intubation and mechanical ventilation. Treated with high dose dexamethasone. Tracheostomy was performed at day 7 and she was weaned off the ventilator at day 15. Discharged and transferred to rehabilitation without sensorimotor deficit after approximately 1 month of admission.
Zhang ³⁸ - 1 case	Female patient in her early forties with a 9-day history of headache and myalgia presented with dysphagia, dysarthria, expressive dysphasia and encephalopathy. Left sided facial weakness. Had fever and dyspnoea on admission.	RT-PCR positive- site not specified (presumed respiratory sample)	Negative influenza swab and a negative rapid streptococcus test. CSF: negative PCR test for HSV 1 and 2, HHV 6, VZV, and negative Cryptococcus test, bacterial cultures negative.	Mild leukocytosis with lymphopenia. Chest X-ray: patchy consolidation in the right lower lung	CSF: normal cell count, protein, and glucose. MRI brain: extensive areas of high signal in bilateral frontoparietal white matter, anterior temporal lobes, basal ganglia, external capsules and thalami. Some foci demonstrated diffusion weighted imaging (DWI) changes and corresponding apparent diffusion coefficient (ADC) changes. Magnetic resonance angiography (MRA) brain and neck: normal EEG: no evidence of seizures	Treated with hydroxychloroquine, ceftriaxone and IVIG. Some improvement in dysphagia and dysarthria after 5 days.

Myelitis

Zhao ⁴⁰ - 1 case	66-year-old man was admitted with fever, dyspnoea and 'asthma'. Five days after respiratory symptom onset he developed acute flaccid paralysis of the lower limbs, urinary and faecal incontinence and a sensory level at T10.	RT-PCR positive in nasopharyngeal swab.	Blood: Negative for EBV, influenza A, influenza B, adenovirus, coxsackievirus, parainfluenza virus, CMV, RSV on serum IgM testing. Negative for Chlamydia pneumoniae, Mycoplasma pneumoniae, and TB.	Lymphopaenia (0.55 ×10 ⁹ /L) and raised CRP (277 mg/L) and procalcitonin (4.33 ng/mL). Slightly raised ALT (56 U/L) and AST (50 U/L). CT Chest: bilateral patchy changes.	CT brain showed lacunar infarcts. Spinal imaging not performed	On admission, he deteriorated rapidly and was admitted to ICU. Treated with moxifloxacin, oseltamivir, lopinavir-ritonavir, ganciclovir, and meropenem, followed by dexamethasone and IVIG for his neurological symptoms. Required supplementary oxygen. Slight improvement in power in upper and lower limbs following treatment, but still unable to walk. Discharged and transferred for rehabilitation.
Cerebrovascular disease						
Ischaemic stroke						
Avula ⁴⁸ - 4 cases	Four patients, aged 73-88 years old. All had a history of hypertension, 3 dyslipidaemia, 1 diabetes and neuropathy, 1 carotid stenosis, 1 chronic kidney disease. Three presented with acute new focal neurological deficit (facial droop and slurred speech; left-sided weakness; right-arm weakness and word finding difficulty). One presented with altered mental status. Of these patients, one had fever, respiratory distress, nausea, and vomiting; one had fever only; another had mild shortness of breath with a dry cough; and a fourth had no respiratory symptoms nor fever.	All four had positive RT-PCR - presumed to be upper respiratory samples. No mention of CSF studies.	Negative blood and urine cultures in the two patients for which results were reported.	Three patients had lymphopaenia, one with leucopaenia and two with leucocytosis. Two had elevated D-dimer and inflammatory markers. Three had patchy changes bilaterally on Chest X-ray or CT.	All four had evidence of unifocal infarcts: three on CT, one on MRI brain.	All were treated with antiplatelet therapy - none had thrombolysis or thrombectomy. Three required intubation and ventilation and all three died. The fourth was discharged to a rehabilitation facility.
Benussi ⁴² - 35 cases	35 patients: aged an average of 77 years	All had positive RT-PCR on a respiratory sample.	NR	Patients with cerebrovascular disease and COVID-19 had an increased neutrophil and platelet count, reduced lymphocyte count, higher C-reactive protein, erythrocyte sedimentation rate, lactate dehydrogenase, aspartate and alanine aminotransferase, prothrombin time and fibrinogen levels compared to patients with cerebrovascular disease but without COVID-19. No details specific to ischaemic stroke.	NR	8/35 had endovascular treatment; 2/35 had intravenous fibrinolysis; 3/35 had bridging therapy. Median modified Rankin score on discharge was 5 (severe disability; bedridden).
Beyrouti ⁴⁷ - 6 cases	Patients aged 53-83 years, 5 male, 1 female. Three had hypertension, 2 ischaemic heart disease, 2 atrial fibrillation, 1 had a previous stroke and high BMI, another had diabetes, ischaemic heart disease and was a smoker with heavy alcohol consumption. Three had dysarthria, one expressive dysphasia, one aphasia. Four had hemiparesis; two had incoordination. One had reduced consciousness (GCS 13/15). All had respiratory symptoms, four had fever, at a median (range) of 13 (-2 to +24) days either before (in 5) or after (in 1) neurological symptom onset	All six had positive RT-PCR - presumed to be upper respiratory samples. No mention of CSF studies.	One had a medium titre IgM anti-cardiolipin antibody and low titre IgG and IgM aβ2GP1.	One had a leucocytosis, three had lymphopaenia. All had a raised D-dimer and LDH. Five had a raised ferritin, five had a raised CRP. All had bilateral patchy changes on chest X-ray or CT, two had pulmonary emboli - one in a segmental artery, the other with bilateral emboli in segmental and subsegmental arteries.	Initial scans (CT/MRI brain) showed unifocal infarcts in four, one of whom had bilateral infarcts on a follow up MRI brain. Two had bilateral infarcts on initial scans.	One treated with dual antiplatelet and therapeutic low-molecular weight heparin (LMWH) therapy; one had external ventricular drain placement and therapeutic LMWH; another had apixaban; the fourth had therapeutic LMWH; two had intravenous thrombolysis. Three required oxygen therapy, two were admitted to ITU, one died secondary to COVID-19 pneumonia following cardiorespiratory deterioration.

Gonzales-Pinto ⁴⁹ - 1 case	36-year-old woman without respiratory symptoms presented with 48 hours of aphasia and right hemiplegia.	Positive RT-PCR - presumed to be upper respiratory sample. No mention of CSF studies.	NR	Leucocytosis (23600 cells/ μ l) and raised CK (8669 U/l), D-dimer (7540 ng/ml) and CRP (156 mg/ml). CT Chest revealed a bilateral pneumonia and bilateral acute pulmonary embolism	CT brain showed left middle cerebral artery (MCA) infarct and mild midline deviation. CT angiography showed occlusion of left internal carotid artery, left MCA and the anterior cerebral artery, and thrombus in the ascending aorta.	No operative intervention due to poor clinical status and severe mass effect; pharmacological therapies not reported. Deteriorated, and died 3 days after admission.
Helms ³² - 3 cases (also reported in CNS section)	"unexplained encephalopathic features" while on intensive care unit with COVID-19.	All RT-PCR positive on nasopharyngeal swab	NR		Unclear if the reported CSF and electroencephalography results relate to these three patients MRI brain: Two small unifocal acute ischemic stroke; one unifocal subacute ischemic stroke	All patients admitted to ITU with Acute Respiratory Distress Syndrome (ARDS).
Li ⁴¹ - 11 cases	11 patients: aged 57-91 years old, 9 with hypertension, 6 with diabetes, 3 with cardiovascular disease, 3 smokers, 1 with malignancy; 6 female and 5 males; 5 had large-vessel stenosis; 3 cardioembolic; 3 small-vessel disease. All patients had respiratory symptoms a median (range) of 11 days (range 0-30) before neurological manifestations	All RT-PCR positive on throat swab	NR	No specific detail given on the 11 patients with ischaemic stroke. All patients had evidence of COVID-19 pneumonia on CT chest.	NR	Nine had severe disease. Six were treated with antiplatelet (aspirin or clopidogrel); five were given with anticoagulant therapy (Clexane). Four died; seven survived.
Lodigiani ⁵⁰ - 9 cases	Patients aged 57-76, 6 male and 3 females, two had lung cancer. Six presented with stroke; presumed the other three presented with respiratory illness	"Laboratory-proven COVID-19"	NR	6 patients had a raised D-dimer. One also had a pulmonary embolism confirmed on CT. No additional details given.	NR	Four received aspirin, three were also given treatment dose LMWH, of who one received systemic thrombolysis and one a mechanical thrombectomy. Four received treatment dose LMWH, three had additional treatment - one with clopidogrel, one with systemic thrombolysis, another with local lysis and mechanical thrombectomy. One had treatment dose unfractionated heparin. During admission, one patient developed necrotising meningoencephalitis, another had disseminated intravascular coagulation. Three were admitted to ITU, two died and, at the time of reporting, four had been discharged.
Morassi ⁴⁵ - 4 cases	4 patients: aged 64-82 years, 3 with hypertension and, 2 with a previous stroke/TIA and aortic valve disease, 1 who was a smoker with a previous myocardial infarction. All presented primarily with severe acute respiratory illness; 3/4 developed neurological manifestations during hospitalization (two hemiparesis, one inability to rouse when sedation held); 1/4 presented with episodes of transient loss of consciousness followed by confusion, in addition to respiratory symptoms.	All RT-PCR positive on nasopharyngeal swab	NR	All had raised CRP, two had a raised d-dimer, two had raised LDH, two had abnormal renal and liver function tests. CT Chest on all patients: bilateral ground glass opacities, one patient also had bilateral pleural effusions and a pulmonary embolism.	One had CSF: normal leukocyte count, protein and IgG index. All had multifocal infarcts on CT/MR brain. The patient presenting with transient loss of consciousness and ensuing confusion had electroencephalography: "normal background in the alpha range (8 Hz), associated with recurrent sharp slow waves over the left temporal region, which occasionally were seen also on the right homologous regions"	One was treated with aspirin, clopidogrel and enoxaparin; another given levetiracetam; treatment not reported for the remaining two. Two were intubated and mechanically ventilated. Two died; of the two survivors, one had coma (GCS 3/15) and one was severely disabled with modified Rankin score of 4.
Moshayedi ⁵³ - 1 case	Male, in 70s, no comorbidities reported; after 5 days of shortness of breath was admitted to hospital with ST-elevation myocardial infarction and bilateral ischaemic lower limbs. Developed in-hospital aphasia with right hemiparesis and facial droop.	RT-PCR positive on respiratory specimen	NR	Renal failure and activated PTT >85.5 while on heparin.	MRI brain: acute infarct in the left insular, temporal, parietal, and frontal lobes; smaller acute infarcts in the right caudate and left cerebellar hemisphere; haemorrhagic conversion in the left fronto-temporal territory. MR angiogram: occlusion of left middle cerebral artery proximal M1 segment.	Comfort measures instituted, no other details.

Oxley ⁵¹ - 5 cases	33-49 years old; 4/5 male. All had hemiplegia; 4/5 had reduced conscious level. Additionally, three had dysarthria, one global dysphasia, two had a sensory deficit. Three had systemic/respiratory symptoms.	All five had positive RT-PCR - presumed to be upper respiratory samples. No mention of CSF studies.	NR	One had thrombocytopenia, one prolonged PT, one prolonged APTT, three with raised fibrinogen, three with increased D-dimer, three with raised ferritin. CT angiography reported in one patient: Patchy ground-glass opacities in bilateral lung apices	All had single-territory infarcts on CT or MRI brain	Four had clot retrieval, of whom one had intravenous thrombolysis and hemicraniectomy and one had stent insertion. Two had apixaban; two aspirin-alone; one had dual antiplatelets. One discharged home; two discharged to rehabilitation facilities; two remain in hospital (one ITU, one stroke unit).
Zhang ⁴⁶ - 3 cases	3 patients: aged 65-70 years; one female; three with hypertension, two with previous stroke, one known diabetes and coronary artery disease, and one with emphysema and nasopharyngeal carcinoma presented with symptoms of infection. One required invasive ventilation, at which point he had ischaemia of lower limbs and a few fingers on the left hand. The other two patients had "similar findings". Onset of neurological manifestations occurred at 10, 18 and 33 days after COVID-19 symptom onset- all had fever and dyspnoea, two with cough, two with headache and one with diarrhoea.	"Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was confirmed in all the patients by reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay or serologic testing."	Antiphospholipid antibodies were detected in all three - anti-cardiolipin IgA antibody and low titre aβ2GP1 IgA and IgM.	All three had a raised CRP and D-dimer. Two had lymphopaenia, two thrombocytopenia, one had raised LDH. CT Chest: bilateral pulmonary infiltrates in all three, ground glass opacity in two.	Imaging showed multifocal cerebral infarctions.	All patients were admitted to ITU. One was intubated and mechanically ventilated due to hypoxaemic respiratory failure. There is minimal detail about the other two and no information on mortality.

Intracerebral haemorrhage

Al Saeigh ⁴³ - 1 case	31-year-old man presented after one week of malaise, mild fever, cough and arthralgia with sudden onset of headache and loss of and loss of consciousness. Some confusion after first operation.	RT-PCR positive in nasal swab. CSF RT-PCR negative on two samples.	NR	NR	CT head: subarachnoid haemorrhage in the posterior fossa; subsequent CT showed hydrocephalus; cerebral angiogram showed ruptured dissecting right posterior-inferior cerebellar artery aneurysm	External ventricular drain inserted initially; then flow-diverting stent placed to treat ruptured aneurysm. Intubated for surgery but did not require ongoing ventilator support. Post-operative confusion resolved; discharged for rehabilitation.
Benussi ⁴² - 3 cases	3 patients: no disaggregated clinical details provided.	All had positive RT-PCR on a respiratory sample.	NR	Patients with cerebrovascular disease and COVID-19 had an increased neutrophil and platelet count, reduced lymphocyte count, higher CRP, ESR, LDH, AST, ALT, PTT and fibrinogen compared to non-COVID-19 patients.	NR	NR
Li ⁴¹ - 1 case	62-year-old man with history of smoking developed stroke symptoms 9 days after onset of COVID-19 respiratory/systemic symptoms.	RT-PCR positive on throat swab	NR	NR	NR	Died 22 days after the stroke.
Morassi ⁴⁵ - 2 cases	Two patients: both 57-year-old men were admitted to hospital with critical COVID-19. At 7 and 11 days later (14 and 17 days after onset of respiratory symptoms - both had cough and fever, one with dyspnoea) they were found to have bilaterally fixed dilated pupils and coma (GCS 3/15).	Both RT-PCR positive on nasopharyngeal swab	NR	Both had raised CRP, LDH, AST and gamma GT. CT chest showed diffuse bilateral ground glass opacities in both patients.	One had bilateral cerebellar haemorrhages on CT brain, with hydrocephalus. The other had a large frontal haemorrhage with displaced ventricles and multiple smaller haemorrhages.	Both developed respiratory failure, requiring intubation and ventilation and admission to ICU. Both deteriorated neurologically, and imaging confirmed cerebral haemorrhage; both died.
Sharifi-Razavi ⁴⁴ - 1 case	79-year-old man had acute loss of consciousness and bilateral extensor plantar reflexes 3 days after onset of fever and cough	RT-PCR positive on oropharyngeal swab		Lymphopaenia, raised CRP and ESR. CT chest: ground-glass opacity in the left lower lobe	CT head: massive intracerebral haemorrhage in the right hemisphere, with intraventricular and subarachnoid haemorrhage	NR

Cerebral venous sinus thrombosis						
Li ⁴¹ - 1 case	32-year-old man with history of smoking developed neurological features 14 days after initial presentation with COVID-19	RT-PCR positive on throat swab	NR	NR	NR	Treated with anticoagulation; survived but remains in hospital.
Peripheral Nervous System Disease						
Guillain Barré syndrome						
Alberti ⁶¹ - 1 case	71-year-old male with paresthesia in hands and feet, rapidly progressive symmetrical weakness more marked in lower limbs than upper; areflexia, plantar response preserved; lower back pain; autonomic disturbance (hypertension) 'The week before' neurological symptom onset: fever; during admission developed dyspnoea and was hypoxic	RT-PCR positive in nasopharyngeal swab on admission, 3 days after neuro symptom onset	NR	Chest CT: multiple bilateral ground glass opacities and consolidation	CSF: mild leucocytosis (9 cells/ul), raised protein (54 mg/dL), CT Head: normal Nerve conduction study and electromyography: Severe acute inflammatory demyelinating polyneuropathy	Treated with IVIG for 5 days. Required oxygen support (60-80%) and was started on non-invasive ventilation (CPAP). Deteriorated and died.
Camdessanche ⁶⁰ - 1 case	64-year-old male with a 2-day history of cough and fever presented following a fall. On day 9 of hospital admission, he developed paresthesia in his hands and feet, and progressive weakness in all four limbs with areflexia and loss of vibration sense. He developed dysphagia and respiratory insufficiency.	RT-PCR positive in nasopharyngeal swab on admission, 9 days before neuro symptom onset	Negative for <i>Campylobacter jejuni</i> , <i>Mycoplasma pneumoniae</i> , <i>Salmonella enterica</i> , CMV, EBV, HSV1 & 2, VZV, Influenza virus A & B, HIV and hepatitis E. Serum: Anti-ganglioside antibodies not detected.	CT chest: 10–25% ground glass opacities.	CSF: normal cell count, raised protein (166 mg/dl), Nerve conduction study and electromyography: acute inflammatory demyelinating polyneuropathy	He had initially needed 2-3L of oxygen via nasal cannula but had been weaned off it prior to neurological symptom onset. Given lopinavir/ritonavir. Treated with IVIG for 5 days, developed respiratory insufficiency and required admission to ICU for intubation and mechanical ventilation. No other details on outcome given.
Toscano ⁶⁵ - 5 cases	5 patients, 4 males and 1 female, aged 23-77 years old. 4 patients had flaccid, areflexic limb weakness - 3 with quadriparesis or quadriplegia and 1 with paraplegia - 3 of 4 of these patients had facial weakness, 2 had dysphagia, and 3 developed respiratory failure. 1 patient had facial diplegia and areflexia with limb paraesthesia and ataxia. Patients presented a median (range) of 7 (5-10) days after respiratory symptoms: cough in 4, fever in 3, hyposmia/anosmia or ageusia in 3 and pharyngitis in 1.	4 patients RT-PCR positive in nasopharyngeal swab. One positive by serological test. RT-PCR in CSF negative in all patients.	1 patient (patient 5)- negative for <i>Campylobacter jejuni</i> , EBV, CMV, HSV, VZV, influenza, and HIV. 3 patients tested for antiganglioside antibodies, but none were detected.	1 - CT scan of the thorax revealed interstitial bilateral pneumonia; 2- no details; 3 - CT scan of the thorax revealed multiple bilateral, ground-glass opacities compatible with interstitial pneumonia; 4 - ; chest imaging was 'negative'; 5- X-ray and CT showed interstitial pneumonia, without parenchymal opacities nor alveolar damage;	CSF analysis: all patients had normal WCC, 3 patients had elevated protein. MRI: enhancement of caudal nerve roots in 2 patients, enhancement of facial nerve in one, and no signal change in 2. Nerve conduction study: axonal pattern in 3 patients, demyelinating in 2.	All treated with IVIG, 2 had 2 cycles, one also had plasma exchange. 3 required mechanical ventilation. At 4 weeks: 2 were still ventilated in intensive care, 2 were having physiotherapy and one was discharged.
Zhao ⁵⁶ - 1 case	61-year-old female with progressive weakness of her lower limbs, then upper limbs, and severe fatigue; areflexia in lower limbs, and decreased sensation distally. 7 days after neurological symptom onset she developed a dry cough and fever.	RT-PCR positive in oropharyngeal swab.	NR	laboratory results on admission were clinically significant for lymphocytopenia ($0.52 \times 10^9/L$, normal: $1.1-3.2 \times 10^9/L$) and thrombocytopenia ($113 \times 10^9/L$, normal: $125-300 \times 10^9/L$). CT chest: ground glass opacities bilaterally.	CSF: normal cell count, raised protein (124 mg/dL), Nerve conduction study: acute inflammatory demyelinating polyneuropathy	Treated with IVIG for 5 days. Also given arbidol, lopinavir, and ritonavir. Improved neurologically - normal power and reflexes on discharge at day 30.
GBS variants and other neuropathies						
Gutierrez Ortiz ⁶⁸ - 1 Miller Fisher Syndrome	50-year-old man with a 5-day history of cough, fever, malaise, headache, back pain, anosmia and ageusia developed right internuclear ophthalmoparesis with right fascicular oculomotor palsy,	RT-PCR positive in oropharyngeal swab, negative in CSF	Antiganglioside antibody GD1b-IgG detected in serum. Negative for anti-GM1, GM2, GM3, GD1a, GD1b, GD3, GT1a, GT1b, GQ1b, and anti-sulfatide antibodies. Normal CSF cytology, sterile cultures	Lymphopaenia, elevated CRP. Chest X-ray: normal.	CSF: normal opening pressure, cell count, raised protein (80 mg/dL), normal glucose. CT brain with contrast: normal	Treated with IVIG for 5 days, complete recovery at 2 weeks, except for residual anosmia and ageusia.

ataxia and areflexia (preserved plantar responses).

and negative anti-pathogen antibody tests.

Dinkin ⁶⁷ - 1 ophthalmoplegia	71-year-old female presented with isolated ophthalmoplegia after 'a few days' of cough and fever. Unable to abduct her right eye - right abducens palsy	RT-PCR positive in nasal swab	NR	Leucopaenia Chest X-ray: bilateral opacities	CSF: Normal opening pressure MRI brain: enhancement of the optic nerve sheaths and posterior Tenon capsules	Treated with hydroxychloroquine and oxygen. Discharged after 6 days. Symptoms improving, although ongoing, at 2 weeks post-discharge
Gutierrez Ortiz ⁶⁸ - 1 bilateral ophthalmoplegia	39-year-old man with 3 days of fever and diarrhoea developed diplopia. He had abduction deficits in both eyes and fixation nystagmus, consistent with bilateral abducens palsy, global areflexia and ageusia.	RT-PCR positive in oropharyngeal swab, negative in CSF	Normal CSF cytology, sterile cultures and negative anti-pathogen antibody tests.	Leucopaenia, blood tests otherwise normal. Chest X-ray: normal.	CSF: normal cell count, raised protein (62 mg/dL) CT brain: normal	No specific treatment. Complete recovery in 2 weeks.
Pellitero ⁶⁹ - 1 acute vestibular dysfunction	30-year-old female developed unsteadiness, disequilibrium and nausea, worse on standing. 3 weeks before, she reported 10 days of anosmia and ageusia. She was unable to walk without assistance. Horizontal nystagmus with a rapid phase to the right, oscillopsia. Romberg positive.	RT-PCR positive on admission, sample tested was not reported.	NR	Lymphocytopenia (1000 cells/mm ³), D-dimer level of 2270 ng/mL, fibrinogen level of 326 mg/dL, LDH level of 235 U/L, and C-reactive protein level of 1.2 mg/L. Chest CT angiogram: normal	MRI brain with contrast: normal.	Treated with antiemetics and vestibular suppressants, the patient improved.

Rhabdomyolysis and other muscle disease

Jin ⁷⁰ - 1 case of rhabdomyolysis	60-year-old man admitted with COVID-19 developed weakness and tenderness in lower limbs 15 days after onset of fever and cough.	RT-PCR positive in throat swab	Urine: blood and protein detected	Leucopaenia, raised CRP and LDH. Normal U+Es and LFTS and CK initially, then raised CK: 11,842 U/L, myoglobin: 12,000 mg/L, AST and ALT. CT Chest: ground glass opacities	NR	Worsening respiratory status following admission. Antibiotics and supportive therapy, the patient's neuromuscular symptoms improved over several days.
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Taste and smell dysfunction

Lechien ⁷⁴ - 357 cases	357 (86%) with smell dysfunction; 342 (89%) with taste dysfunction	All RT-PCR positive in respiratory samples		NR	NR	Treated with nasal corticosteroids (8%), oral corticosteroids (2.5%), nasal irrigation (17%)
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ADEM = acute disseminated encephalomyelitis; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatinine kinase; CRP = C-reactive protein; CSF = cerebrospinal fluid; CT = computed tomography; CVST = cerebral venous sinus thrombosis; EBV = Epstein-Barr virus; EEG = electroencephalogram; EMG = electromyography; ESR = erythrocyte sedimentation rate; FLAIR = fluid-attenuated inversion recovery (MRI sequence); GBS = Guillain-Barré syndrome; Hb = haemoglobin; HSV = Herpes Simplex virus; ICU = intensive care unit; IVIG = intravenous immunoglobulin; LFTs = liver function tests; LDH = lactate dehydrogenase; NCS = nerve conduction study; MRI = magnetic resonance imaging; PTT = prothrombin time; RT-PCR = reverse transcription polymerase chain reaction; T2WI= T2-weighted image (MRI sequence); U+Es= urea and electrolytes; VZV= Varicella Zoster virus; WCC = white cell count

Table 2. Neurological manifestations associated with COVID-19

Table 3. Provisional case definitions for neurological diseases associated with COVID-19, based on previously established principles^{95,97,98}

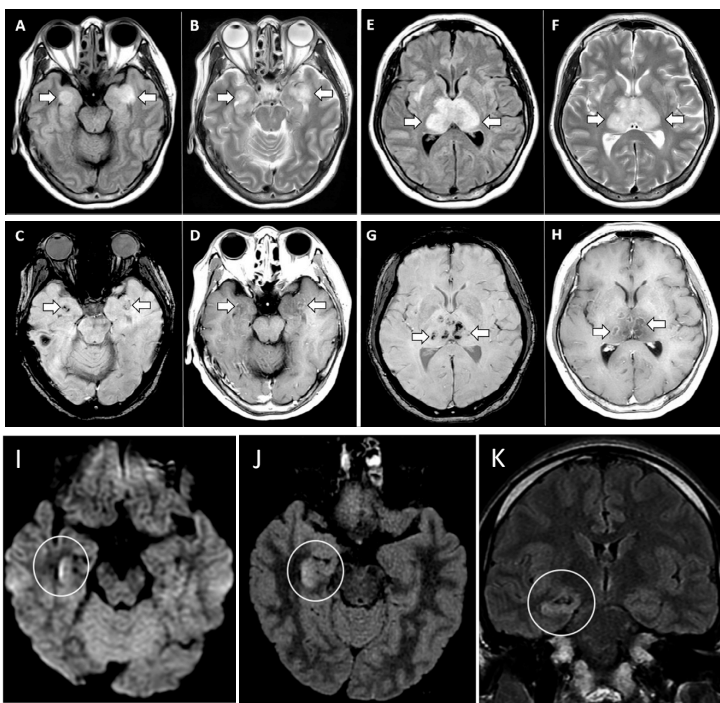
	Confirmed	Probable	Suspected
WHO COVID-19 case definitions⁹⁹	<p>A person with laboratory confirmation¹⁰⁰ of SARS-CoV-2 infection, irrespective of clinical signs and symptoms.</p> <p>Confirmatory tests include a nucleic acid amplification test (e.g. RT-PCR) or validated antibody test,</p> <ul style="list-style-type: none"> •In an area WITH established circulation of virus: one positive RT-PCR test or identification of virus on sequencing. One or more negative tests do not rule out infection if clinical suspicion. •In an area WITHOUT established circulation of virus: one positive RT-PCR test for two different viral genome targets, OR one positive result with partial or whole genome sequencing 	<p>A suspect case, for whom testing for the COVID-19 virus is inconclusive</p> <p>OR</p> <p>A suspect case, for whom testing could not be performed for any reason</p>	<p>A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory distress) AND history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to onset</p> <p>OR</p> <p>A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory distress) AND having been in contact with a confirmed or probable case in the last 14 days prior to symptom onset</p> <p>OR</p> <p>A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory distress AND requiring hospitalisation) AND in the absence of an alternative explanation that fully explains the clinical presentation</p>
SARS-CoV-2 meningitis, encephalitis, myelitis/myelopathy**	<p>SARS-CoV-2 detected in CSF/ brain tissue †,</p> <p>OR</p> <p>Evidence of SARS-CoV-2-specific intrathecal antibody;</p> <p>AND</p> <p>No other explanatory pathogen or cause found</p>	<p>SARS-CoV-2 detected in respiratory or other non-CNS sample ‡,</p> <p>OR</p> <p>Evidence of SARS-CoV-2-specific antibody in serum indicating acute infection+§;</p> <p>AND</p> <p>No other explanatory pathogen or cause found</p>	<p>Patient meets suspected case definition of COVID-19 according to national or WHO guidance (as below), based on clinical symptoms and epidemiological risk factors.</p> <p>In the context of known community SARS-CoV-2 transmission, supportive features* include: <i>Clinical:</i> new onset of least one of: cough, fever, muscle aches, loss of smell, loss of taste; <i>Laboratory:</i> lymphopenia, raised d-dimer; <i>Radiological:</i> evidence of abnormalities consistent with infection or inflammation (e.g. ground glass changes)</p>

	Strong association	Probable association	Possible association
Acute disseminated encephalomyelitis** (ADEM) associated with SARS-CoV-2 infection		Neurological disease onset <= 6 weeks after acute infection, AND SARS-CoV-2 RNA detected in any sample, OR Antibody evidence of acute SARS-CoV-2 infection; AND No evidence of other commonly associated causes	Neurological disease onset <= 6 weeks after acute infection, AND SARS-CoV-2 RNA detected in any sample; OR Antibody evidence of acute SARS-CoV-2 infection; AND Evidence of other commonly associated causes
Guillain-Barré syndrome** and other acute neuropathies associated with SARS-CoV-2 infection		Neurological disease onset <= 6 weeks after acute infection, AND SARS-CoV-2 RNA detected in any sample; OR Antibody evidence of acute SARS-CoV-2 infection; AND No evidence of other commonly associated causes ¶	Neurological disease onset <= 6 weeks after acute infection, AND SARS-CoV-2 RNA detected in any sample; OR Antibody evidence of acute SARS-CoV-2 infection; AND Evidence of other commonly associated causes ¶
CNS vasculitis** associated with SARS-CoV-2 infection	SARS-CoV-2 detected in CSF/brain tissue [†] ; OR Evidence of SARS-CoV-2-specific intrathecal antibody; AND The presence of histopathological features of angiitis within the brain		SARS-CoV-2 detected in CSF/brain tissue [†] ; OR Evidence of SARS-CoV-2-specific intrathecal antibody; AND Laboratory and imaging support for brain inflammation (MR scan evidence compatible with CNS vasculitis with characteristic angiographic changes; elevated levels of

	<p>AND</p> <p>No other explanatory pathogen or cause found</p>	<p>cerebrospinal fluid protein and/or cells, and/or the presence of oligoclonal bands)</p> <p>AND</p> <p>No other explanatory pathogen or cause found</p>
Stroke** associated with SARS-CoV-2 infection	<p>SARS-CoV-2 detected in CSF or other sample‡; OR Evidence of SARS-CoV-2-specific antibody in serum indicating acute infection;</p> <p>AND</p> <p>No other known traditional cardiovascular risk factors¥</p>	<p>SARS-CoV-2 detected in CSF or other sample; OR Evidence of SARS-CoV-2-specific antibody indicating acute infection;</p> <p>AND</p> <p>Other traditional cardiovascular risk factors¥</p>
<p>*These case definitions are suggestions based on published information to date; they are likely to need refining as more data emerge. **See Supplementary Material for case definitions of meningitis, encephalitis, myelitis/myelopathy, acute disseminated encephalitis, Guillain-Barré Syndrome, and stroke, TIA and central nervous system vasculitis. † detection in CSF or brain tissue by PCR, culture, or immunohistochemistry, as appropriate; ‡ detection in non-CNS sample by PCR or culture. § Serological evidence of acute infection can be defined as i) detection of IgM, or ii) IgG seroconversion or iii) >=4-fold rise in antibody titres in paired acute and convalescent serum samples. ¶ These include: infection with one of Campylobacter jejuni, Mycoplasma pneumoniae, Cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis E virus, Zika virus, or HIV; or vaccination in the last 6 weeks. Associated causes may differ depending on geographical location. ¥ traditional cardiovascular risk factors include; hypertension, current smoker, diabetes, hypercholesterolemia, and atrial fibrillation. The terms ‘confirmed’, ‘probable’ and ‘suspected’ are used in the WHO COVID-19 case definition. The terms ‘confirmed’, ‘probable’ and ‘possible’ for COVID-19 meningitis, encephalitis or myelitis and ‘strong association’, ‘probable association’, ‘possible association’ reflect the terminology used for the different syndromes in the original publications from which this table derives (see table references).</p>		
<p>Table 3. Provisional case definitions for neurological diseases associated with COVID-19, based on previously established principles^{95,97,98}</p>		

figures

1. a) Brain imaging in two patients with central nervous system disease associated with COVID-19



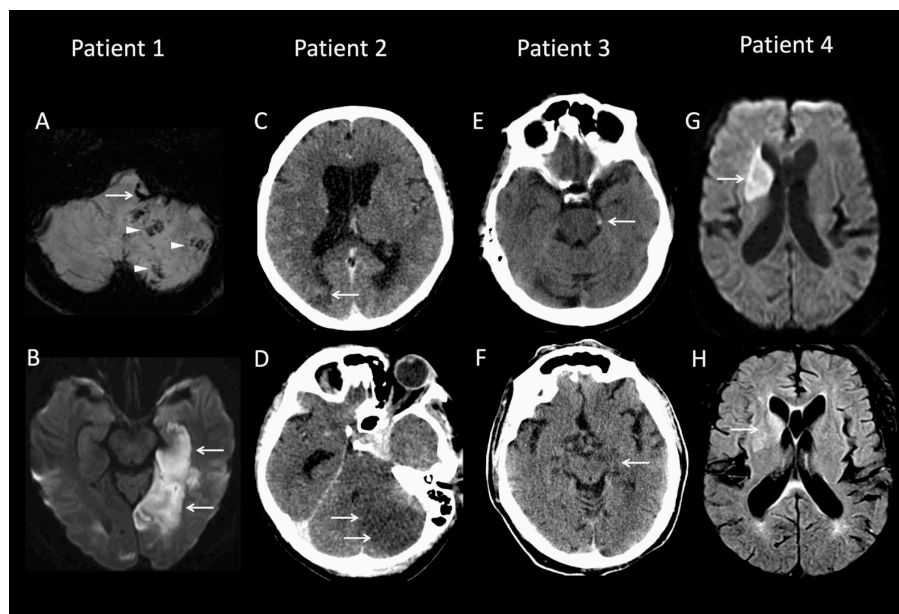
A-H) Patient 1 - Acute Necrotising Encephalopathy associated with SARS-CoV2 infection²³

Magnetic resonance images demonstrate T2 Fluid-attenuated inversion recovery (FLAIR) hyperintensity within the bilateral medial temporal lobes and thalami (A, B, E, F) with evidence of haemorrhage indicated by hypointense signal intensity on susceptibility-weighted images (C, G) and rim-enhancement on postcontrast images (D, H).

I-K) Patient 2 - Encephalitis associated with SARS-CoV2 infection²⁴

Diffusion weighted images (DWI) showed hyperintensity along the wall of inferior horn of right lateral ventricle (I); FLAIR images showed hyperintense signal changes in the right mesial temporal lobe and hippocampus with slight hippocampal atrophy (J, K). These findings indicated right lateral ventriculitis and encephalitis mainly on right mesial lobe and hippocampus.

b) Brain imaging in four patients with COVID-19 and acute cerebrovascular disease⁴⁷



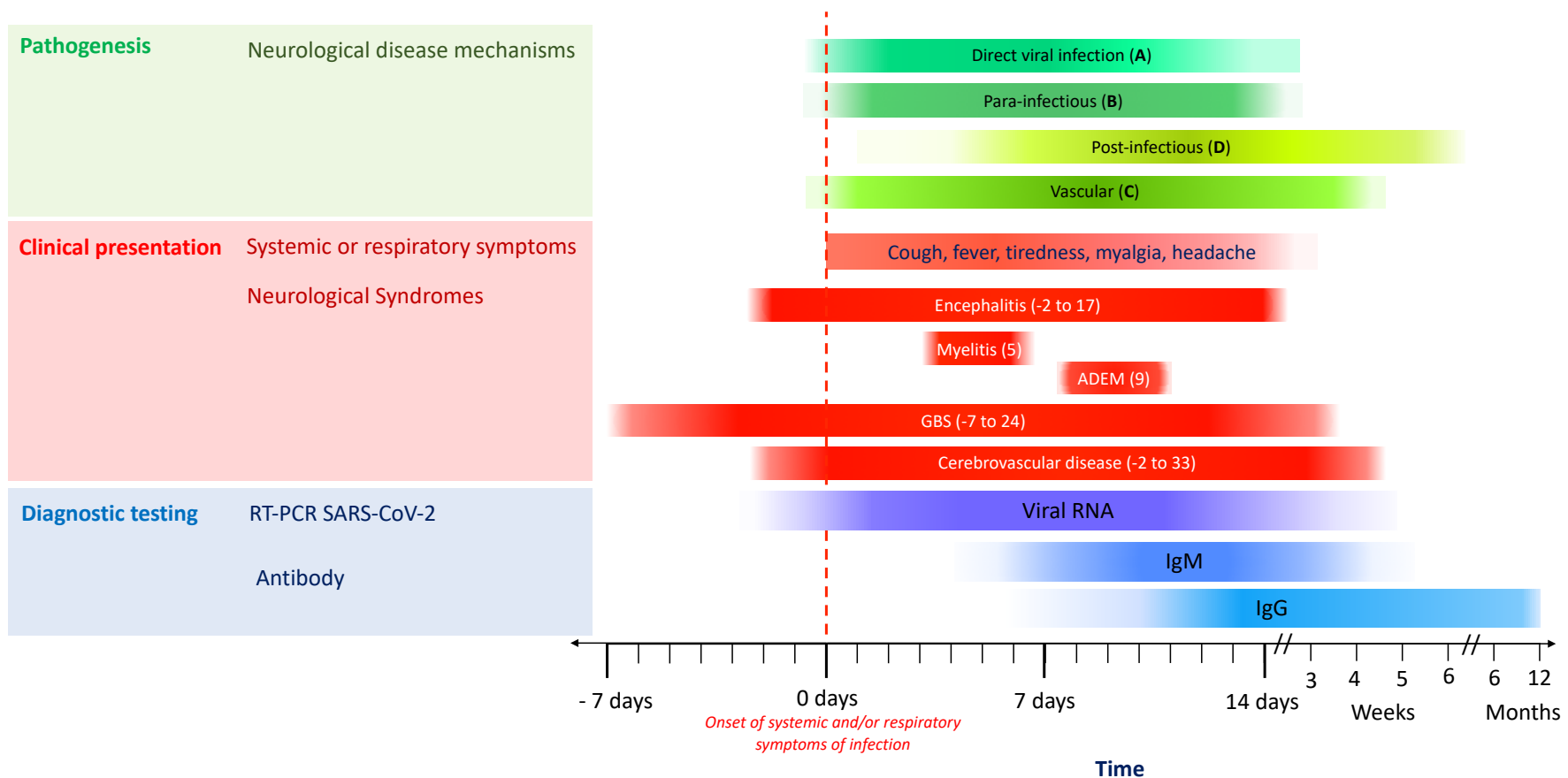
A, B) Patient 1 – A 64-year-old male with COVID-19 developed mild left arm weakness and incoordination on day 15 of illness, followed by acute bilateral incoordination and right homonymous hemianopia a week later. **A)** MRI brain (day 15) shows intradural left vertebral artery occlusion and acute left posterior inferior cerebellar artery territory infarct with petechial haemorrhage; **B)** MRI brain (day 22) shows extensive acute posterior cerebral artery territory infarction.

C, D) Patient 2 - 53-year-old female, on anticoagulation for atrial fibrillation (AF), presented 24 days after respiratory symptom onset with acute confusion, incoordination and drowsiness; **C and D)** CT brain imaging shows acute large left cerebellar and right parieto-occipital infarcts.

E, F) Patient 3 - 85-year-old male presented 10 days after COVID-19 symptom onset with dysarthria and right hemiparesis. He had AF, hypertension and ischaemic heart disease. **E and F)** CT brain shows left posterior cerebral artery occlusion and infarction.

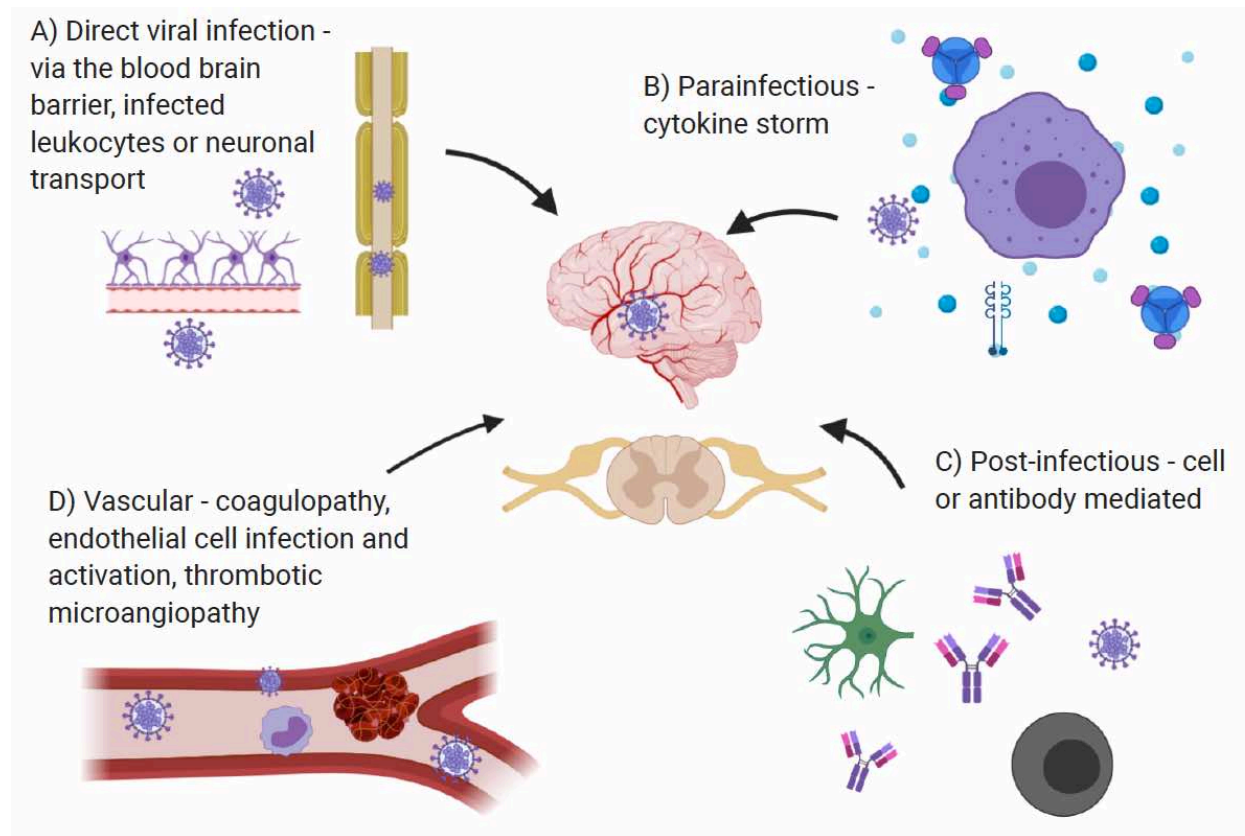
G, H) Patient 4 - 61-year-old male with a history of previous stroke presented with dysarthria and left hemiparesis two days before respiratory symptom onset; SARS-Cov-2 was detected on PCR testing. **G and H)** MRI brain shows an acute right striatal infarct

2. a) Diagnostic testing, clinical presentation and pathogenesis in COVID-19 and neurological disease.



Blue bars represent the time period over which SARS-CoV-2, anti-SARS-CoV-2 IgM or IgG antibodies are detectable on either reverse transcriptase polymerase chain reaction (RT-PCR) or antibody testing. Red bars represent the time of clinical presentation, including the duration of systemic/respiratory symptoms of COVID-19, or when patients have presented with suspected COVID-19-associated neurological disease relative to onset of COVID-19 symptoms. Green bars represent pathological mechanisms that may result in neurological disease in COVID-19, as in other viruses; (A), (B), (C), and (D) refer to figure 2b. Approximate values are based on currently published data. Bars are faded to indicate lack of certainty over specific ranges. The dynamics of anti-SARS-CoV-2 IgG antibody production are not known beyond a few weeks, although by analogy with other viruses, immunity might be expected for months to years.

b) Potential mechanisms of COVID-19 neurological disease based on knowledge of other viruses.



BBB= blood-brain barrier

- A) Virus may enter the nervous system across the blood brain barrier, possibly by infected leukocytes, or through retrograde transport along the olfactory or other cranial or peripheral neurons.⁷⁸ Viruses can enter neurons to cause cytopathology.
- B) Innate immune responses to viral infection and resultant inflammation may cause tissue damage, as is thought to occur in acute encephalopathy syndromes in influenza infection.¹⁵
- C) Pathological adaptive immune responses include damage caused by cytotoxic T cells¹⁰¹ and antibody mediated response against host tissue, either in the central or peripheral nervous system.^{55,102} The latter may be caused by molecular mimicry between the pathogen and host epitopes, or tissue damage may result in failure of tolerance to self-antigens.
- D) Viral infection may cause blood vessel damage either by direct infection or immune-mediated vasculitis.¹⁰³ Alternatively, the virus may activate the vessel endothelium triggering inflammatory and thrombotic pathways with release of microparticles leading to thrombotic microangiopathy, as part of a secondary haemophagocytic lymphohistiocytosis,⁸⁶ a syndrome of excessive inflammation and tissue destruction due to abnormal immune activation, thought to be related to excessive and inadequately regulated lymphocyte and macrophage activity.

