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Neurological associations of COVID-19

Mark A Ellul, Laura Benjamin, Bhagteshwar Singh, Suzannah Lant, Benedict Daniel Michael, Ava Easton, Rachel Kneen, Sylviane Defres, Jim Sejvar, Tom Solomon

Summary

Background The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (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. On the basis of knowledge of other coronaviruses, especially those that caused the severe acute respiratory syndrome and Middle East respiratory syndrome epidemics, cases of CNS and peripheral nervous system disease caused by SARS-CoV-2 might be expected to be rare.

Recent developments A growing number of case reports and series describe a wide array of neurological manifestations in 901 patients, but many have insufficient detail, reflecting the challenge of studying such patients. Encephalopathy has been reported for 93 patients in total, including 16 (7%) of 214 hospitalised patients with COVID-19 in Wuhan, China, and 40 (69%) of 58 patients in intensive care with COVID-19 in France. Encephalitis has been described in eight patients to date, and Guillain-Barré syndrome in 19 patients. SARS-CoV-2 has been detected in the CSF of some patients. Anosmia and ageusia are common, and can occur in the absence of other clinical features. Unexpectedly, acute cerebrovascular disease is also emerging as an important complication, with cohort studies reporting stroke in 2–6% of patients hospitalised with COVID-19. So far, 96 patients with stroke have been described, who frequently had vascular events in the context of a pro-inflammatory hypercoagulable state with elevated C-reactive protein, 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 (eg, hypoxic encephalopathy and critical care neuroopathy) from those caused directly or indirectly by the virus, including infectious, para-infectious, and post-infectious encephalitis, hypercoagulable states leading to stroke, and acute neuropathies such as Guillain-Barré syndrome. Recognition of neurological disease associated with SARS-CoV-2 in patients whose respiratory infection is mild or asymptomatic might prove challenging, especially if the primary COVID-19 illness occurred weeks earlier. The proportion of infections leading to neurological disease will probably remain small. However, these patients might be left with severe neurological sequelae. With so many people infected, the overall number of neurological patients, and their associated health burden and social and economic costs might be large. Health-care planners and policy makers must prepare for this eventuality, while the many ongoing studies investigating neurological associations increase our knowledge base.

Introduction

As of May 19, 2020, the COVID-19 pandemic, caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in more than 4·8 million confirmed cases worldwide and more than 300 000 deaths.1 It is the largest and most severe pandemic since the 1918 influenza pandemic.2 Although the most common and important presentation is with respiratory disease, reports of neurological features are increasing. These features appear to be a combination of non-specific complications of systemic disease, the effects of direct viral infection, or inflammation of the nervous system and vasculature, which can be para-infectious or post-infectious. In this Rapid Review, we consider which neurological manifestations might be expected for COVID-19, given what is known about related coronaviruses and respiratory viruses more broadly. We summarise the evidence to date for COVID-19, examine putative disease mechanisms, and finally suggest a framework for investigating patients with suspected COVID-19-associated neurological disease to support clinico-epidemiological, disease mechanism, and treatment studies.

Evidence from other viruses

Before identification of SARS-CoV-2, six coronaviruses were known to infect humans. Four of these coronaviruses cause seasonal, predominantly mild respiratory illness, and have a high incidence globally, accounting for 15–30% of upper respiratory tract infections.3 The other two coronaviruses have led to major epidemics with deaths principally from respiratory disease; severe acute respiratory syndrome (SARS) was caused by SARS-CoV in 2002–03, and Middle East respiratory syndrome (MERS) by MERS-CoV in 2012.4,5 Both the more innocuous coronavirus and these epidemic strains have been associated with occasional disease of the CNS and peripheral nervous system (PNS).

Both CNS and PNS disease were reported following SARS (appendix pp 2–3). SARS-CoV was detected in CSF by RT-PCR in two of three cases of encephalopathy with seizures,6,7 and was cultured from brain tissue at autopsy.
Table 1: Estimated neurological disease case numbers associated with COVID-19, extrapolated from SARS and MERS data

<table>
<thead>
<tr>
<th></th>
<th>SARS case count (n=8096)</th>
<th>MERS case count (n=2228)</th>
<th>COVID-19 worldwide minimum case count (n=4872308)</th>
<th>COVID-19 minimum case count in China (n=84500)</th>
<th>COVID-19 minimum case count in USA (n=1464232)</th>
<th>COVID-19 minimum case count in UK (n=246410)</th>
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<td></td>
<td>Extrapolated from SARS (95% CI)</td>
<td>Extrapolated from MERS (95% CI)</td>
<td>Extrapolated from SARS (95% CI)</td>
<td>Extrapolated from MERS (95% CI)</td>
<td>Extrapolated from SARS (95% CI)</td>
<td>Extrapolated from MERS (95% CI)</td>
</tr>
<tr>
<td>Patients with CNS disease (proportion of total coronavirus cases [95% CI])</td>
<td>3 (0·04% [0·01–0·10])</td>
<td>5 (0·20% [0·06–0·50])</td>
<td>1805 (370–5277)</td>
<td>9671 (3143–22539)</td>
<td>31 (6–92)</td>
<td>168 (55–391)</td>
</tr>
<tr>
<td>Patients with PNS disease (proportion of total coronavirus cases [95% CI])</td>
<td>4 (0·05% [0·01–0·13])</td>
<td>4 (0·16% [0·04–0·41])</td>
<td>2407 (658–6165)</td>
<td>7717 (2110–19786)</td>
<td>42 (11–107)</td>
<td>134 (37–343)</td>
</tr>
<tr>
<td>Total patients with neurological disease (proportion of total coronavirus cases [95% CI])</td>
<td>7 (0·09% [0·03–0·18])</td>
<td>9 (0·36% [0·16–0·68])</td>
<td>4213 (1028–11440)</td>
<td>17408 (5252–42266)</td>
<td>73 (18–198)</td>
<td>302 (91–734)</td>
</tr>
</tbody>
</table>

Calculated using data available up to May 19, 2020. COVID-19 cases based on Johns Hopkins COVID-19 Dashboard. 95% CI calculated with Clopper-Pearson exact method for proportions using Ausvet Epitools.

SARS = severe acute respiratory syndrome. MERS = Middle East respiratory syndrome. PNS = peripheral nervous system.

Clinical features of COVID-19-associated neurological disease

As the COVID-19 pandemic progresses, reports of neurological manifestations are increasing; to date, 901 patients have been reported. These manifestations can be considered as direct effects of the virus on the nervous system, para-infectious or post-infectious immune-mediated disease, and neurological complications of the systemic effects of COVID-19 (appendix p 4). In one national registry of 125 patients with COVID-19 and neurological or psychiatric disease reported over a 3-week period, 39 (31%) patients had altered mental status, which included 16 (13%) with encephalopathy (of whom seven [6%] had encephalitis), and 23 (18%) with a neuropsychiatric diagnosis, including ten (8%) with psychosis, six (5%) with neurocognitive (dementia-like) syndrome, and four (3%) with an affective disorder. Notably, 77 (62%) patients had a cerebrovascular event: 57 (46%) ischaemic strokes, nine (7%) intracerebral haemorrhages, one (<1%) CNS vasculitis, and ten (8%) other cerebrovascular events. The challenges in managing patients with a highly contagious infection, and
the overwhelming number of cases, have meant that many early reports did not have sufficient detail, few included comprehensive description of CSF analysis, imaging, or follow-up, and they often appear on non-peer-reviewed websites. Most are not reported using standard case definitions (panel; appendix pp 5–12). In what follows, we review the CNS and PNS infectious and inflammatory complications that are well recognised for viral respiratory infections, followed by cerebrovascular disease, which is relatively unusual (table 2).

Encephalitis

Encephalitis is the inflammation of the brain parenchyma, usually caused by an infection or the body’s immune defences. Although it is 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 EEG. Detection of virus in the CSF per se does not provide a diagnosis of encephalitis if there is no evidence of brain inflammation (panel; appendix p 6).27
As of May 19, 2020, eight adults aged 24–78 years (median 62 [IQR 40–70]), including four women, have been described with encephalitis associated with COVID-19, mostly diagnosed through a nasal or nasopharyngeal swab (table 2; appendix pp 13–14).56–58 Neurological features mostly started from the time of respiratory symptom onset to 17 days afterwards, although in one man aged 60 years, confusion preceded cough and fever by two days (figure 1).59 Two patients had fever only, with no respiratory features.59,60

The neurological manifestations were typical for encephalitis, with irritability, confusion, and reduced consciousness, sometimes associated with seizures; three patients also had neck stiffness and another had psychic symptoms.61 A man aged 40 years developed ataxia, oscillopsia, hiccup, and Ramsay Hunt syndrome; in these instances, it is possible that patients may have been previously infected with SARS-CoV-2, and that they may lose both serological and RT-PCR positivity in the context of encephalitis.

(Table 2 continues on next page)

### Clinical presentation

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<tr>
<th>CNS disease</th>
<th>SARS-CoV-2 diagnostics</th>
<th>Other pathogen and antibody investigations</th>
<th>Relevant blood tests and radiology findings</th>
<th>Neurological investigations (CSF findings, neuroimaging, neurophysiology)</th>
<th>Management, progress, and outcome</th>
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<tr>
<td>Encephalitis</td>
<td>Man aged 24 years, 9 days of fatigue, headache, fever, sore throat; then generalised seizures, reduced consciousness, and meningism</td>
<td>RT-PCR was negative in nasopharyngeal swab; positive in CSF</td>
<td>Increased white blood cell count, neutrophil dominant, relatively decreased lymphocytes; increased CRP; chest CT: small ground glass opacity in right upper zone and bilaterally in lower zones</td>
<td>CSF: clear, colourless, raised opening pressure (320 mm H2O); cell count (22/mm³), ten mononuclear and two polymorphonuclear cells; head CT: no brain oedema; brain MRI: hyperintensity along wall of right lateral ventricle on diffusion-weighted imaging, and hyperintense signal in right medial temporal lobe and hippocampus on T2-weighted images</td>
<td>Treated empirically for bacterial pneumonia and viral encephalitis; on admission, required intubation and mechanical ventilation because of seizures, admitted to ICU; still on intensive care at time of report (day 15)</td>
</tr>
<tr>
<td>Sohal et al.</td>
<td>Man aged 72 years with weakness and light headedness following a hypoglycaemic episode; shortly after admission he had difficulty breathing and altered mental status; on day 2 of admission he started to have seizures</td>
<td>RT-PCR was positive; source not specified</td>
<td>Blood: culture was negative for bacterial growth; influenza PCR was negative</td>
<td>Arterial blood gas test: pH 7.13, PaO2 68 mm Hg, PCO2 78 mm Hg, raised brain natriuretic peptide, troponin, CRP, LDI; lymphopenia, and leucopenia; chest x-ray: normal; chest CT: bilateral opacities along with right lower lobe consolidation</td>
<td>Head CT: no acute changes, chronic microvascular ischaemic changes; 24-h EEG: six left temporal seizures and left temporal sharp waves that were epileptogenic</td>
</tr>
<tr>
<td>Wong et al.</td>
<td>Man aged 40 years with ataxia, diplopia, and bilateral facial weakness (rhombencephalitis); 13 days before he had fever and progressive shortness of breath on exertion, followed 10 days later by a productive cough and diarrhoea</td>
<td>RT-PCR was positive in nasopharyngeal swab; CSF RT-PCR was not done</td>
<td>Blood: negative for hepatitis A, B, and C, HIV-1 and HIV-2, and syphilis antibody; CSF: bacterial culture was negative; anti-MOG-IgG antibody and anti-aquaporin 4 antibody test results not reported</td>
<td>Normal white cell count but lymphopenia, raised CRP and abnormal raised liver function tests; chest x-ray: right lower zone consolidation; liver ultrasound: inflammatory diffusely hypoechoic liver with raised portal and pericholecystic echogenicity</td>
<td>Normal cell count and protein (0.42 g/L); brain MRI: increased signal lesion in right inferior cerebellar peduncle extending to involve a small portion of the upper cord (lesion 13 mm in maximum cross-sectional area and 28 mm in longitudinal extent); swelling at the affected tissue and associated micro-haemorrhage</td>
</tr>
<tr>
<td>Other encephalopathies</td>
<td>Infant aged 6 weeks with cough, fever, and episodes of bilateral leg stiffening and sustained upward gaze</td>
<td>RT-PCR was positive and high-throughput sequencing detected viral RNA in nasopharyngeal and anal swabs; RT-PCR was negative in plasma and CSF</td>
<td>Nasopharyngeal sample tested for respiratory pathogen; PCR panel positive for rhinovirus–enterovirus; high-throughput sequencing was positive for rhinovirus C; CSF: meningitis–encephalitis pathogen PCR panel was negative; culture negative</td>
<td>Leucopenia (5.07 × 10^9 white blood cells per μL) with a normal differential, and elevated procalcitonin of 0.21 ng/mL; normal urea and electrolytes</td>
<td>CSF: normal; brain MRI: normal; prolonged EEG monitoring of temporal sharp transients and intermittent vertex delta, slowing with normal sleep–wake cycling</td>
</tr>
<tr>
<td>Dugue et al.</td>
<td>One case, Japan</td>
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<td>One case, USA</td>
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(www.thelancet.com/neurology  Vol 19  September 2020)
and bilateral facial weakness. CSF analysis was reported for six patients; it showed a pleiocytosis in five, mostly lymphocytic, and was normal in one patient. Four patients had CSF PCR done for SARS-CoV-2, of whom one was positive: a man aged 24 years with encephalitis, minor respiratory symptoms, and ground glass changes on chest CT, who had a PCR negative respiratory sample. Few publications reported comprehensive investigation for other causes of encephalitis (table 2; appendix pp 13–14). 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 (figure 2A, B); the patient with ataxia had a cerebellar lesion that extended into the spinal cord. EEG was done in five patients. Two had

<table>
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<th>Clinical presentation</th>
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<tr>
<td>Helms et al, 11 49 cases, France</td>
<td>40 patients had agitation; 26 of the 40 evaluated had confusion, 39 had corticospinal tract signs, 15 had a dysesthetic syndrome at discharge, and seven had history of neurological disorders, including transient ischaemic attack, partial epilepsy, and mild cognitive impairment</td>
<td>RT-PCR was positive for all patients’ nasopharyngeal samples; negative RT-PCR in CSF in seven patients</td>
<td>NR</td>
<td>In seven patients who had CSF analysis, none had pleiocytosis, two had matched oligodendral bands, and one had raised protein; in 13 patients who had brain MRI, eight had enhancement in leptomeningal spaces; in 11 patients who had perfusion imaging, all had bilateral frontotemporal hypoperfusion; two patients had acute ischaemic stroke, and one had subacute ischaemic stroke; in eight patients who had EEG, one had diffuse bifrontal slowing</td>
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<td>Mao et al, 16 cases, China</td>
<td>16 patients were hospitalised with COVID-19 and had impaired consciousness; one had a seizure characterised by a sudden onset of limb twitching and loss of consciousness, lasting 3 min</td>
<td>RT-PCR was positive in all patients’ throat swabs</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Poyiadji et al, 17 one case, USA</td>
<td>Female patient with cough, fever, and altered mental status; imaging consistent with acute necroising encephalopathy</td>
<td>RT-PCR was positive in nasopharyngeal swab; CSF RT-PCR not done</td>
<td>CSF: bacterial culture negative after 3 days and tests for HSV, VZV, and WNV were negative</td>
<td>Patients with CNS disease and severe respiratory disease had lower lymphocyte levels and platelet counts and higher blood urea nitrogen levels than those without CNS symptoms</td>
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<tr>
<td>Paniz-Mondolfi et al, 18 one case, USA</td>
<td>Man aged 74 years with history of Parkinson’s disease presented following two falls at home with fever, confusion, and agitation</td>
<td>RT-PCR was positive in nasopharyngeal swab; electron microscopy of brain tissue: viral particles in endothelial and neural cells</td>
<td>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</td>
<td>Head CT: no acute changes</td>
<td></td>
</tr>
<tr>
<td>Zhou et al, 19 one case, China</td>
<td>Patient aged 56 years with COVID-19 pneumonia</td>
<td>SARS-CoV2 detected by sequencing in CSF</td>
<td>NR</td>
<td>NR</td>
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### Acute disseminated encephalomyelitis

**Zanin et al.**
- One case, Italy

Woman aged 54 years presented with agitation, decreased consciousness, and seizures following several days of anosmia and ageusia.

- CT-PCR was positive in respiratory sample
- Blood: cultures were negative; urine: cultures were negative
- Lymphopenia (0.3 × 10⁹ cells per L) with mild elevation of inflammatory markers (CRP 41.3 mg/L, fibrinogen 520 mg/dL); chest x-ray: interstitial pneumonia
- CSF: normal; brain and spine MRI: periventricular confluent white matter lesions and numerous high signal cord lesions from bulbomedullary junction to T6 level; no contrast enhancement

**Zhao et al.**
- One case, China

Woman in early 40s with a 9-day history of dyspnoea on admission.

- RT-PCR was positive; site not specified (presumed respiratory sample)
- Negative influenza swab and negative rapid streptococcus test; CSF: negative; PCR test for HSV-1 and HSV-2, HHV-6, and VZV, and negative Cryptococcus test; bacterial cultures were negative
- Mild leukocytosis with lymphopenia; chest x-ray: patchy consolidation in right lower lung
- CSF: normal cell count, protein, and glucose; brain MRI: extensive areas of interstitial pneumonia

**Zhang et al.**
- One case, USA

Man aged 66 years admitted with fever, dyspnoea, and asthma; 5 days after respiratory symptom onset, developed acute flaccid paralysis of lower limbs, urinary and faecal incontinence, and a sensory level at T10.

- RT-PCR was positive in nasopharyngeal swab
- Blood: negative for EBV, influenza A, influenza B, adenovirus, coxsackievirus, parainfluenza virus, CMV, and RSV on serum IgM testing; negative for Chlamydia pneumoniae, Mycoplasma pneumoniae, and tuberculosis
- Lymphopenia (0.55 × 10⁹ cells/L) and raised CRP (217 mg/L) and procalcitonin (4.33 ng/mL); slightly raised CRP (277 mg/L)
- Brain CT: Lacomycin infarcts; spinal imaging not done

### Myelitis

**Zhao et al.**
- One case, China

Man aged 64 years with 2 days of cough and fever presented following a fall; on day 9 of hospital admission, developed paresthesia in hands and feet and progressive weakness in all limbs, with areflexia and loss of vibration sense; then developed dysphagia and respiratory insufficiency.

- RT-PCR was positive in nasopharyngeal swab on admission, 9 days before onset of neurological symptoms
- Negative for Campylobacter jejuni, M pneumoniae, Salmonella enterica, CMV, EBV, HSV-1, HSV-2, VZV, influenza virus A and B, HIV, and hepatitis E; serum: antinuclear antibodies not detected
- Chest CT: 10% to 25% ground glass opacities
- CSF: normal cell count and raised protein (166 mg/dL); nerve conduction study and electromyography: acute inflammatory demyelinating polyneuropathy

### Peripheral nervous system disease

**Camdessanche et al.**
- One case, France

Man aged 64 years with 2 days of cough and fever presented following a fall; on day 9 of hospital admission, developed paresthesia in hands and feet and progressive weakness in all limbs, with areflexia and loss of vibration sense; then developed dysphagia and respiratory insufficiency.

- RT-PCR was positive in nasopharyngeal swab on admission
- Negative for Campylobacter jejuni, M pneumoniae, Salmonella enterica, CMV, EBV, HSV-1, HSV-2, VZV, influenza virus A and B, HIV, and hepatitis E; serum: antinuclear antibodies not detected
- Chest CT: 10% to 25% ground glass opacities
- CSF: normal cell count and raised protein (166 mg/dL); nerve conduction study and electromyography: acute inflammatory demyelinating polyneuropathy

- Had initially needed 2L to 3L oxygen via nasal cannula but had been weaned off it before onset of neurological symptoms; given lopinavir-ritonavir; treated with intravenous immunoglobulin for 5 days; developed respiratory insufficiency and required admission to ICU for intubation and mechanical ventilation; no other details given

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<tr>
<td>Toscano et al; 54 five cases, Italy</td>
<td>Five patients (four men and one woman), aged 23 to 77 years, four patients had flaccid, areflexic limb weakness (three with quadriparesis and one with paraparesis), three of whom had facial weakness, two had dysphagia, and three developed respiratory failure; one had facial diplegia, areflexia, limb paresis, and ataxia; patients presented a median of 7 (range 5 to 10) days after respiratory symptoms; four had cough, three had fever, three had hypoxia, anosmia, or ageusia, and one had pharyngitis</td>
<td>RT-PCR was positive in nasopharyngeal swab of four patients; one patient was positive by serological test; RT-PCR in CSF was negative in all patients</td>
<td>One patient (patient 5) was negative for C. jejuni, EBV, CMV, HSV, VZV, influenza, and HIV; three patients were tested for antiganglioside antibodies, but none was detected</td>
<td>Patient 1: CT scan of thorax showed interstitial bilateral pneumonia; patient 2: no details; patient 3: CT scan of thorax showed multiple bilateral, ground glass opacities compatible with interstitial pneumonia; patient 4: chest imaging was negative; patient 5: chest, x-ray and CT showed interstitial pneumonia, without parenchymal opacities or alveolar damage</td>
<td>All treated with intravenous immunoglobulin; two had two cycles, and one also had plasma exchange; three required mechanical ventilation; at 4 weeks, two patients were still ventilated in intensive care, two were having physiotherapy, and one was discharged</td>
</tr>
<tr>
<td>Zhao et al; 55 one case, China</td>
<td>Woman aged 61 years with progressive weakness of lower and then upper limbs and severe fatigue, areflexia in lower limbs and decreased sensation distally; 7 days after neurological symptoms, she developed dry cough and fever</td>
<td>RT-PCR was positive in oropharyngeal swab</td>
<td>NR</td>
<td>Laboratory results on admission were clinically significant for lymphopenia and thrombocytopenia; chest CT: ground glass opacities bilaterally</td>
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<tr>
<td>GBS variants and other neuropathies</td>
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<tr>
<td>Gutiérrez-Ortiz et al; 56 one Miller Fisher Syndrome, Spain</td>
<td>Man aged 50 years with 5 days of cough, fever, malaise, headache, back pain, anosmia, and ageusia, who developed right internuclear ophthalmoplegia with right fasicular oculomotor palsy, ataxia, and areflexia (preserved plantar responses)</td>
<td>RT-PCR was positive in oropharyngeal swab, negative in CSF</td>
<td>Antiganglioside antibody GD1b-IgG detected in serum; normal CSF cytology, sterile cultures, and negative antibody tests</td>
<td>Lymphopenia; elevated CRP; chest x-ray: normal</td>
<td>Treated with intravenous immunoglobulin for 5 days; given arbidol, lopinavir, and ritonavir; improved neurologically, had normal power and reflexes on discharge at day 30</td>
</tr>
<tr>
<td>Dinkin et al; 57 one ophthalmoplegia, USA</td>
<td>Woman aged 71 years with isolated ophthalmoplegia after a few days of cough and fever, unable to abduct her right eye (right abducens palsy)</td>
<td>RT-PCR was positive in nasal swab</td>
<td>NR</td>
<td>Leucopenia; chest x-ray: bilateral opacities</td>
<td>Treated with hydroxychloroquine and oxygen; discharged after 6 days; symptoms improving, although ongoing at 2 weeks after discharge</td>
</tr>
<tr>
<td>Gutiérrez-Ortiz et al; 58 one bilateral ophthalmoplegia, Spain</td>
<td>Man aged 39 years, with 3 days of fever and diarrhoea, developed diplopia; abduction deficits in both eyes and fixation nystagmus consistent with bilateral abducens palsy, global areflexia and ageusia</td>
<td>RT-PCR was positive in oropharyngeal swab and negative in CSF</td>
<td>Normal CSF cytology, sterile cultures, and negative anti-pathogen antibody tests</td>
<td>Leucopenia, but blood tests otherwise normal; chest x-ray: normal</td>
<td>No specific treatment; complete recovery in 2 weeks</td>
</tr>
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### Clinical presentation

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#### Escalada Pellitero et al; one acute vestibular dysfunction, USA

Woman aged 30 years had nausea, unsteadiness, and disequilibrium that was worse on standing; 3 weeks before, she had 10 days of anosmia and ageusia; horizontal nystagmus with rapid phase to the right, oscillopsia, and Romberg positive

RT-PCR was positive on admission; sample tested not reported

Lymphopenia, and raised D-dimer, fibrinogen, and CRP; chest CT angiogram: normal

Brain MRI with contrast: normal

Treated with antiemetics and vestibular suppressants; improved

#### Rhabdomyolysis and other muscle disease

Jin et al; one case of rhabdomyolysis, China

Man aged 60 years admitted with COVID-19 developed weakness and tenderness in lower limbs 15 days after onset of fever and cough

RT-PCR was positive in throat swab

Urine: blood and protein detected

Leucopenia, and raised CRP and LDH; normal urea, electrolytes, liver function tests, and creatine kinase initially; then raised creatine kinase (11 842 U/L), myoglobin (12 000 mg/L), aspartate aminotransferase and alanine aminotransferase; chest CT: ground glass opacities

NR

Worsening respiratory status following admission; received antibiotics and supportive therapy; neuromuscular symptoms improved over several days

#### Taste and smell dysfunction

Lechien et al; 357 cases, Belgium, France, Italy, Spain, and Switzerland

357 (86%) of 417 patients had smell dysfunction; 342 (82%) had taste dysfunction

All RT-PCR were positive in respiratory samples

NR

NR

Treated with nasal corticosteroids (8%), oral corticosteroids (3%), and nasal irrigation (27%)

#### Cerebrovascular disease

Ischaemic stroke

Avula et al; four cases, USA

Four patients (aged 73 to 91 years) with hypertension; three had dyslipidaemia, one diabetes and neuropathy, one carotid stenosis, and one chronic kidney disease; three presented with acute new focal neurological deficit (facial drop, slurred speech; left-sided weakness; and right-arm weakness and word finding difficulty), and one with altered mental status; one had fever, respiratory distress, nausea, and vomiting; one had fever only; one had mild shortness of breath with dry cough; one had no respiratory symptoms or 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 whom results were reported

Three patients had lymphopenia, one with leucopenia 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 brain MRI

All were treated with antiplatelet therapy; none had thrombolysis or thrombectomy; three required intubation and ventilation, all of whom died; fourth patient discharged to rehabilitation facility

(Table 2 continues on next page)
<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>SARS-CoV-2 diagnostics</th>
<th>Other pathogen and antibody investigations</th>
<th>Relevant blood tests and radiology findings</th>
<th>Neurological investigations (CSF findings, neuroimaging, neurophysiology)</th>
<th>Management, progress, and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beyrouti et al; 52 six cases, UK</td>
<td>All six had positive RT-PCR (presumed to be upper respiratory samples); no mention of CSF studies</td>
<td>One had a medium titre IgM anti-cardiolipin antibody and low titre IgG and IgM aβ2GP1 antibody</td>
<td>One had leucocytosis and three had lymphopenia; all had raised D-dimer and LDH; five had raised ferritin and five had raised CRP; all had bilateral patchy changes on chest x-ray or CT, and two had pulmonary emboli (one in a segmental artery and one with bilateral emboli in segmental and subsegmental arteries)</td>
<td>Initial scans (CT and brain MRI) showed unifocal infarcts in four patients, one of whom had bilateral infarcts on a follow-up brain MRI, two had bilateral infarcts on initial scans</td>
<td>One treated with dual antiplatelet and therapeutic low-molecular weight heparin therapy; one had external ventricular drain placement and therapeutic low-molecular weight heparin; two had intravenous thrombolysis; three required oxygen therapy; two were admitted to ICU; one died secondary to COVID-19 pneumonia following cardiorespiratory deterioration</td>
</tr>
<tr>
<td>Li et al; 53 11 cases, China</td>
<td>All RT-PCRs were positive on throat swab</td>
<td>NR</td>
<td>No specific detail given on the 11 patients with ischaemic stroke; all patients had evidence of COVID-19 pneumonia on chest CT</td>
<td>NR</td>
<td>Nine had severe disease; six were treated with antiplatelets (aspirin or clopidogrel); five were given anticoagulant therapy (clexane); four died and seven survived</td>
</tr>
<tr>
<td>Morassi et al; 54 four cases, Italy</td>
<td>All RT-PCRs were positive on nasopharyngeal swab</td>
<td>NR</td>
<td>All raised CRP levels, two each had raised D-dimer, raised LDH, and abnormal renal and liver function tests; chest CT on all patients: bilateral ground glass opacities (one patient also had bilateral pleural effusions and a pulmonary embolism)</td>
<td>One had CSF: normal leukocyte count, protein, and IgG index; all had multifocal infarcts on brain CT or MRI; the patient presenting with transient loss of consciousness and ensuing confusion had EEG: normal background in the alpha range (8 Hz), associated with recurrent sharp slow waves over left temporal region, which occasionally were seen also on the right homologous regions</td>
<td>One patient treated with aspirin, clopidogrel, and enoxaparin; one 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</td>
</tr>
</tbody>
</table>

(Continued from previous page)
Intracerebral haemorrhage

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Age</th>
<th>Symptoms</th>
<th>Investigations</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxley et al.55</td>
<td>Five cases, USA</td>
<td></td>
<td>Five patients (aged 33 to 49 years, four male and one female); all had hemiplegia, four had reduced consciousness; three had dysarthria, one global dysphasia, two had a sensory deficit, and three had systemic or respiratory symptoms</td>
<td>All five had positive RT-PCR (presumed to be upper respiratory samples); no mention of CSF studies</td>
<td>NR</td>
</tr>
</tbody>
</table>

Cerebral venous sinus thrombosis

<table>
<thead>
<tr>
<th>Study</th>
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<th>Age</th>
<th>Symptoms</th>
<th>Investigations</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al.53</td>
<td>One case, China</td>
<td></td>
<td>Man aged 32 years with history of smoking developed neurological features 14 days after initial presentation with COVID-19</td>
<td>RT-PCR was positive on throat swab</td>
<td>NR</td>
</tr>
</tbody>
</table>

A full version of this table is provided in the appendix (pp 13–23); the studies included here are those that more comprehensively reported patient data or reported novel findings. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. HSV=herpes simplex virus. VZV=vaccinia zoster virus. CRP=C-reactive protein. ICU=intensive care unit. PaO2=partial pressure of oxygen. PCO2=partial pressure of carbon dioxide. LDH=lactate dehydrogenase. MOG=myelin oligodendrocyte glycoprotein. NR=not reported. WNV=West Nile virus. FLAIR=fluid-attenuated inversion recovery. HHV=human herpes virus. EBV=Epstein-Barr virus. CMV=cytomegalovirus. RSV=respiratory syncytial virus. LDH=lactate dehydrogenase. GCS=Glasgow Coma Scale.

Table 2: Selected reports of neurological manifestations associated with COVID-19

generalised slowing, two had focal abnormalities, and one patient, who presented with psychotic symptoms followed by a seizure, was found to be in non-convulsive status epilepticus.5 One patient responded quickly to high dose steroids, but for the other seven no specific treatment was reported beyond anticonvulsants, antiviral, and antibiotic medication.

No specific treatment exists for SARS-CoV-2 encephalitis. As for other forms of encephalitis, questions will emerge concerning the relative contributions of viral damage and host inflammatory response, and whether corticosteroids might be useful. Clinical trials seem unlikely, given the current low number of cases.

Other encephalopathies

Encephalopathy is a pathobiological process in the brain that usually develops over hours to days and can manifest as changed personality, behaviour, cognition, or consciousness (including clinical presentations of delirium or coma).5 In patients with encephalopathy and COVID-19, in whom brain inflammation has not been proven, the wide range of other causes to consider includes hypoxia, drugs, toxins, and metabolic derangements (appendix pp 2–3).

The largest study to date,52 from Wuhan, China, retrospectively described 214 patients with COVID-19, of whom 53 (25%) had CNS symptoms, including dizziness (36 [17%] patients), headache (28 [13%]), and impaired
consciousness (16 [7%]). 27 (51%) of the patients with CNS symptoms had severe respiratory disease, but there was little further detail (table 2; appendix pp 14–15). In a French series of 58 intensive care patients with COVID-19, 49 (84%) had neurological complications, including 40 (69%) with encephalopathy and 39 (67%) with corticospinal tract signs. MRI in 13 patients showed leptomeningeal enhancement for eight and acute ischaemic change for two; CSF examination for seven patients showed no pleocytosis. 15 (33%) of 45 patients who had been discharged had a dyselective syndrome. Additionally, some case reports have appeared, including a woman with encephalopathy with imaging changes consistent with acute necrotising encephalopathy (figure 2C, D) and a fatal case in which viral particles were found in endothelial cells and neural tissue, although there was no indication of whether this was associated with inflammation.

Several reports have described 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, 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.

Acute disseminated encephalomyelitis and myelitis
Acute disseminated encephalomyelitis is a syndrome of multifocal demyelination, typically occurring weeks after an infection, which generally presents with focal neurological symptoms, often with encephalopathy (appendix p 7). Two case reports describe middle-aged women with acute disseminated encephalomyelitis and SARS-CoV-2 detected on respiratory swabs (table 2; appendix p 16). One developed dysphagia, dysarthria, and encephalopathy 9 days after the onset of headache and myalgia (figure 1). The other presented with seizures and reduced consciousness, and required intubation for respiratory failure. Both patients had normal CSF and high signal intensities on MRI, typical of acute disseminated encephalomyelitis. They both improved after treatment, one with intravenous immunoglobulin and one with steroids. To date, a single report exists of myelitis (inflammation of the spinal cord; appendix p 8) associated with COVID-19. A man aged 66 years in Wuhan, China, developed fever, fatigue, and then acute flaccid paraparesis with incontinence. Examination showed hyporeflexia and a sensory level at T10. He was treated with dexamethasone and intravenous immunoglobulin, and was discharged for rehabilitation.

Acute disseminated encephalomyelitis 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 might need to be more cautious, especially if the virus is detected in the CSF, because such treatment might diminish the patient’s immune response to the virus.

Peripheral nervous system and muscle disease
Guillain-Barré syndrome is an acute polyradiculopathy characterised by rapidly progressive, symmetrical limb weakness, areflexia on examination, sensory symptoms, and, in some patients, facial weakness, although several variants exist (appendix p 9). To date, 19 patients (six female) with Guillain-Barré syndrome or its variants and COVID-19 have been reported, with a median age of 63 years (range 23 to 77; table 2; appendix pp 16–18). Given the number of SARS-CoV-2 infections worldwide, the incidence is not particularly higher than what might be expected. Neurological symptoms started at a median of 7 days (range –7 to 24) after respiratory or systemic features (figure 1), although two patients developed febrile illness 7 days after the onset of Guillain-Barré syndrome on hospital admission, one had a positive swab for SARS-CoV-2 and the other had lymphocytopenia and thrombocytopenia, which are characteristic for SARS-CoV-2 infection. Three patients had diarrhoea before the onset of neurological disease.

11 patients had Guillain-Barré syndrome with weakness of all four limbs with or without sensory loss, three had a paraparetic variant with leg weakness only, and one had lower limb paraesthesia. 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 were done in 12 patients and were consistent with demyelinating disease in eight and axonal disease in four patients.

Two patients had the Miller Fisher variant of Guillain-Barré syndrome, with ophthalmoplegia, ataxia, and areflexia,\textsuperscript{46,47} one also had loss of smell and taste, and was positive for anti-GD1b-IgG. One patient had bilateral and one patient unilateral abducens palsy,\textsuperscript{46,47} and another had an acute vestibular syndrome with horizontal nystagmus and oscillopsia.\textsuperscript{48}

For 16 patients, SARS-CoV-2 was detected in a respiratory swab, and for two, the sample was not specified; one patient was also positive for rhinovirus. One patient was diagnosed by a blood antibody test. Lumbar puncture was done in 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 Guillain-Barré syndrome was reported for only four patients.\textsuperscript{43,44,73,75} 15 patients were treated with intravenous immunoglobulin, and eight (all with classical Guillain-Barré syndrome) were admitted to intensive care for ventilatory support, two of whom died.\textsuperscript{70,71} 12 improved, and five had ongoing disability at discharge.

Muscle injury associated with raised creatine kinase affected 23 (11%) of 214 patients in the Wuhan series.\textsuperscript{57} Rhabdomyolysis due to COVID-19 has also been reported.\textsuperscript{85,86}

Loss of smell (anosmia) and taste (ageusia) have emerged as common symptoms of COVID-19, either with other features or in isolation, suggesting that they might be useful diagnostic markers (appendix p 19).\textsuperscript{87} A study of 259 patients,\textsuperscript{88} including 68 who were positive for SARS-CoV-2, found that abnormal smell and taste were both strongly associated with COVID-19. In a European study,\textsuperscript{50} olfactory dysfunction was reported for 357 (86%) of 417 COVID-19 patients; 342 (82%) reported gustatory disorders. These symptoms were reported more frequently for COVID-19 patients than for a historical cohort of influenza patients.\textsuperscript{89} Subclinical deficits in smell, taste, or both have also been detected.\textsuperscript{90,91} Although these symptoms can occur in any respiratory infection because of coryza, the fact they occur in isolation of other symptoms suggest that there is involvement of the olfactory nerve.

Cerebrovascular manifestations

As COVID-19 has spread around the world, evidence has grown for an association with cerebrovascular disease, as well as with other forms of vascular disease. Cerebrovascular manifestations were reported for 13 (6%) of 221 COVID-19 patients in an early retrospective case series from Wuhan.\textsuperscript{53} 11 (5%) patients developed ischaemic stroke, one (<1%) had intracerebral haemorrhage, and one (<1%) had cerebral venous sinus thrombosis. In Milan, Italy, nine (2%) of 388 retrospectively identified hospital patients with laboratory-confirmed COVID-19 had a stroke.\textsuperscript{54} Another
centre in Italy reported that 43 (77%) of 56 SARS-CoV-2-positive patients admitted to one neurology unit had cerebrovascular disease; 35 had ischaemic stroke and three haemorrhagic stroke, and five had transient ischaemic attacks. In the Netherlands, three (2%) of 184 patients in intensive care with COVID-19 had ischaemic strokes. In total, 88 patients with ischaemic stroke and eight with haemorrhagic stroke have been reported, 18 (19%) of whom died (table 2; appendix pp 20–23).

Most patients were older than 60 years, and many had known risk factors for cerebrovascular disease, especially hypertension, diabetes, hyperlipidaemia, and vascular disease. Younger stroke patients have also been reported. In one hospital in New York, NY, USA, five patients younger than 50 years with stroke and SARS-CoV2 were admitted in just 2 weeks, whereas the average number of admissions for young patients with stroke per 2 weeks in the preceding year was 0.73. Two patients had no other symptoms of COVID-19. All had large vessel ischaemic strokes.

Cerebrovascular symptoms began at a median of 10 days (range 0–33) after the onset of respiratory illness (figure 1), although in one patient the stroke preceded respiratory features and five had only cerebrovascular symptoms. In two patients, ischaemic stroke has been associated with thrombus in the aorta, and indeed multiple infarcts have been reported in these and other patients (figure 2E, F). Sometimes associated with arterial thrombosis and limb ischaemia. Concurrent deep vein thrombosis and pulmonary embolism have been found in other stroke patients. 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. Blood D-dimer concentration was raised in many patients with COVID-19, consistent with a pro-inflammatory, coagulopathic state in the setting of critical illness. Blood D-dimer concentration was raised in many patients with COVID-19, consistent with a pro-inflammatory, coagulopathic state in the setting of critical illness. Positive lupus anticoagulant, anticardiolipin, and anti-beta2-glycoprotein-1 antibodies have also been reported in COVID-19-associated stroke, although these can be raised in other critical illnesses, including infections.

Immediate anticoagulation with low-molecular-weight heparin has been recommended for patients with COVID-19, to reduce the risk of thrombotic disease. This approach 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 trials are looking at the role of anticoagulation in patients with COVID-19 (NCT04362085, NCT04345848, NCT04406389), including the effect on stroke incidence.

Disease mechanisms
Infection and inflammation of the central and peripheral nervous systems
As with other neurotropic viruses, key questions for SARS-CoV-2 infection concern the routes of entry into the nervous system and the relative contribution of viral infection versus host response to the subsequent damage (appendix p 12).

Viral entry to the brain through 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 entry route is thought to be used by the herpes simplex virus, the most common cause of sporadic viral encephalitis. In mouse models, following intranasal injection, human coronavirus OC43 invades the CNS by the olfactory route. Alternative entry routes include passage across the blood–brain barrier, following viraemia, or through infected leukocytes. The angiotensin converting enzyme 2 receptor, to which SARS-CoV-2 binds for entry into cells, is found in brain vascular endothelium and smooth muscle. SARS-CoV-2 replicates in neuronal cells in vitro.

Damage within the CNS or PNS might be caused directly by the 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.

Autopsy material from a patient who developed encephalopathy weeks after presenting with SARS showed oedema, neuronal necrosis, and broad gliocyte hyperplasia. Immunohistochemical staining showed that SARS-CoV in the brain was associated with elevated expression of the cytokine, monokine induced by gamma interferon (known as MIG or CXCL9), and with infiltration of monocytes and macrophages plus T cells. These findings are consistent with viral CNS entry triggering the infiltration of immune cells and the release of cytokines and chemokines, which contribute to tissue damage.

Little work has been done on disease mechanisms for coronavirus PNS disease. By comparison with other viruses, it would not be surprising to see immune-mediated disease, such as Guillain-Barré syndrome, and direct anterior horn cell viral damage, which causes acute flaccid myelitis, might also be expected.

Cerebrovascular disease
Early indicators suggest that cerebrovascular disease in COVID-19 might be due to a coagulopathy. SARS-CoV-2 can cause damage to endothelial cells, activating inflammatory and thrombotic pathways. Endothelial cell infection or monocyte activation, upregulation of tissue factors, and the release of microparticles, which activate the thrombotic pathway and cause microangiopathy, might occur for SARS-CoV-2 as for other viruses. Monocyte activation is postulated to constitute part of the secondary haemophagocytic lymphohistiocytosis described in severe COVID-19. Thrombocytopenia with elevated D-dimer and C-reactive protein in severe COVID-19 and stroke are consistent with a virus-associated microangiopathic process. Endothelial dysfunction can potentially lead to
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-associated neurological disease, and must systematically consider the evidence for viral infection and the presenting clinical diagnosis, using definitions that distinguish confirmed, probable, and possible cases (panel; appendix pp 5–12).

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 might be infected coincidentally with the virus, including in hospital through nosocomial transmission. A full investigation, which is absent in many reports to date, is needed to rule out other established causes of brain infections before attributing disease to COVID-19.108 Distinguishing between nasopharyngeal SARS-CoV-2 infection and nervous system infection is also key.

For patients with altered consciousness or agitation, all causes of encephalopathy must be considered, including hypoxia, drugs, toxins, and metabolic derangement; encephalitis should be diagnosed only if clinical evidence exists of brain inflammation, such as a CSF pleiocytosis, imaging changes, focal seizures, or histological changes (appendix p 6).57 Even if virus is detected in the CSF, encephalitis should not be diagnosed unless evidence exists of brain inflammation. For patients with possible peripheral nerve disease, clinicians should aim to do CSF examination, looking for evidence of albuminocytological dissociation (an elevated CSF protein level with a normal CSF cell count), nerve conduction studies, and electromyography during recovery, even if they cannot be done acutely.

In patients with neuropathy, cerebrovascular disease, or acute disseminated encephalomyelitis, in whom the damage is probably caused by the host’s response to viral infection, establishing causality is even more challenging, especially if patients present after the virus has been cleared from the nasopharynx. Clinical case definitions for COVID-19 that are based on the history and typical findings for chest imaging and blood investigations will be useful (panel). For patients with stroke, clinicians should consider cerebral angiography, intracranial vessel wall imaging, and, if necessary, brain biopsy, looking for vasculitis. The apparently 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 that it is hard to be sure about causation. The link with SARS-CoV-2 will ultimately need to be proven by careful case-control studies.

In investigating patients with limb weakness and sensory change, it is crucial to distinguish between disease of the peripheral nerves (eg, Guillain-Barré syndrome) and inflammation of the spinal cord, which can present with flaccid paralysis if the anterior horn cells are involved.108 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 might be particularly challenging; no reliable markers exist for neurological disease caused by critical illness, although it tends to occur after several weeks.9 Up to 70% of patients with sepsis might develop encephalopathy or polyneuropathy.111 In the Wuhan series, neurological complications were more common in those with severe disease, suggesting that some of the neurological manifestations were related to critical illness.10,112

Conclusion and future directions

Given existing knowledge of other coronaviruses and respiratory viruses, the wide range of CNS and PNS associations with COVID-19 is not surprising, and this is the focus of most current reports. However, neurological disease is also likely to be seen increasingly in patients who are SARS-CoV-2-positive but with few or no typical features of COVID-19, based on knowledge of other epidemic viral infections and cases reported so far.9 Case-control studies will be needed to help establish whether SARS-CoV-2 is causal or coincidental in such patients. Hypercoagulable states and cerebrovascular disease, which have been seen rarely for some acute viral infections, are an important neurological complication of COVID-19.

Overall, the proportion of patients with neurological manifestations is small compared with that with respiratory disease. However, the continuing pandemic, and the expectation that 50–80% of the world’s population might be infected before herd immunity develops, suggest that the overall number of patients with neurological disease could become large. Neurological complications, particularly encephalitis and stroke, can cause lifelong disability, with associated long-term care needs and
We searched PubMed and Scopus for articles on COVID-19 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 the search tool of each database. We reviewed the references of relevant studies for additional articles and consulted experts in the field to ensure that we did not miss important preprints and unpublished studies. Articles were included on the basis of relevance and originality with regards to the topics covered in this Rapid Review.

potentially large health, social, and economic costs. Health-care planners and policy makers 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 work will involve the collaboration of a range of clinical and research expertise, and harmonised approaches across regions; smaller case series and registries should be combined into meta-analyses such as that of the COVID-19 Neuro Network run through Brain Infections Global, which is also providing standardised case record forms and case definitions.

Contributors
MAE, BDM, JS, and TS devised the idea for this Rapid Review. 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.

Declaration of interests
TS was an adviser to the GlaxoSmithKline Ebola Vaccine programme, chairing a Siemens Diagnostics clinical advisory board, and advises the WHO Brain Health Unit Forum on Neurology and COVID-19; TS has chaired a Siemens Diagnostics clinical advisory board, and advises the TS was an adviser to the GlaxoSmithKline Ebola Vaccine programme, chairing a Siemens Diagnostics clinical advisory board, and advises the WHO Brain Health Unit Forum on Neurology and COVID-19; TS has chaired a Siemens Diagnostics clinical advisory board, and advises the

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References

For more on the COVID-19 Neuro Network of Brain Infections Global see https://braininfectionsglobal.tghn.org/covid-neuro-network/
Rapid Review


