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Neurological associations of COVID-19

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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 neuromyopathy) from those caused directly or indirectly by the virus, including infectious, para-infectious, and post-infectious encephalitis, hypercoagulable states leading to stroke, and acute neuropa-thies 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 300000 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 virus 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

See Online for appendix
Table 1: Estimated neurological disease case numbers associated with COVID-19, extrapolated from SARS and MERS data

|                      | SARS case count (n=8096) | MERS case count (n=2228) | COVID-19 worldwide minimum case count (n=4 872 308) | COVID-19 minimum case count in China (n=84 500) | COVID-19 minimum case count in USA (n=1 464 232) | COVID-19 minimum case count in UK (n=246 410) |
|----------------------|--------------------------|--------------------------|----------------------------------------------------|------------------------------------------------|-----------------------------------------------|-----------------------------------------------|
|                      | Extrapolated from SARS   | Extrapolated from MERS   | Extrapolated from SARS                              | Extrapolated from MERS                          | Extrapolated from SARS                        | Extrapolated from MERS                        |
|                      | (95% CI)                 | (95% CI)                 | (95% CI)                                            | (95% CI)                                       | (95% CI)                                      | (95% CI)                                      |
| Patients with CNS    | 3 (0·04% [0·01–0·10])    | 5·0 (0·20% [0·06–0·50])  | 1805 (370–5277)                                     | 967·1 (3143–22539)                              | 31 (6·92)                                     | 168 (55–391)                                  |
| disease (proportion  |                          |                          |                                                   |                                               |                                               |                                               |
| of total coronavirus |                          |                          |                                                   |                                               |                                               |                                               |
| cases [95% CI])      |                          |                          |                                                   |                                               |                                               |                                               |
| Patients with PNS    | 4 (0·05% [0·01–0·13])    | 4·0 (0·16% [0·04–0·41])  | 2407 (658–6163)                                     | 777 (2110–19786)                                | 42 (11–107)                                   | 134 (37–343)                                  |
| disease (proportion  |                          |                          |                                                   |                                               |                                               |                                               |
| of total coronavirus |                          |                          |                                                   |                                               |                                               |                                               |
| cases [95% CI])      |                          |                          |                                                   |                                               |                                               |                                               |
| Total patients with  | 7 (0·09% [0·03–0·18])    | 9·0 (0·36% [0·16–0·68])  | 4213 (1028–11440)                                   | 17 408 (5252–42226)                            | 73 (18–198)                                   | 302 (91–734)                                  |
| neurological disease |                          |                          |                                                   |                                               |                                               |                                               |
| (proportion of total |                          |                          |                                                   |                                               |                                               |                                               |
| coronavirus cases    |                          |                          |                                                   |                                               |                                               |                                               |
| [95% CI])            |                          |                          |                                                   |                                               |                                               |                                               |

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.

For the Johns Hopkins COVID-19 Dashboard see https://coronavirus.jhu.edu/map.html

The estimated incidence of neurological disorders during the 2009 influenza A H1N1 pandemic was 1·2 per 100 000, with children affected more than adults. The 1918 H1N1 influenza pandemic has been associated with post-infectious encephalitis lethargica, although a causative link has not been proven.

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 small proportion could build up to a large number of cases. The minimum prevalence of CNS complications ranged from 0·04% for SARS to 0·20% for MERS, and PNS complications ranged from 0·05% for SARS to 0·16% for MERS, from which we have extrapolated the number of cases with neurological complications of COVID-19 (table 1). Given the 4–8 million cases of COVID-19 globally, these prevalences project to a total of 1805–9671 patients with CNS complications and 2407–7737 with PNS complications. These numbers, which do not include the increasingly important syndromes of stroke-associated COVID-19 infection, will rise as the pandemic continues.

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
Infections, followed by cerebrovascular disease, which is relatively unusual (table 2).

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).

The clinical presentation

SARS-CoV-2 meningitis, encephalitis, myelitis, or CNS vasculitis

**Confirmed**
- A person with laboratory confirmation\(^27\) of SARS-CoV-2 infection, irrespective of clinical signs and symptoms; confirmatory tests include a nucleic acid amplification test (eg, RT-PCR) or validated antibody test; in an area with established circulation of virus, there should be one positive RT-PCR test or identification of virus on sequencing (one or more negative tests do not rule out infection if there is clinical suspicion); and in an area without established circulation of virus, there should be one positive RT-PCR test for two different viral genome targets or one positive result with partial or whole genome sequencing.

**Probable**
- (1) A suspect case for whom testing for the COVID-19 virus is inconclusive; or (2) a suspect case for whom testing could not be done for any reason.

**Suspected**
- (1) A patient with acute respiratory illness (fever and at least one sign or 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 before onset; or (2) a patient with acute respiratory illness who has been in contact with a confirmed or probable case in the last 14 days before symptom onset; or (3) a patient with severe acute respiratory illness that requires hospitalisation, and in the absence of an alternative explanation that fully explains the clinical presentation.

WHO COVID-19 case definitions\(^26\)

**Confirmed**
- A person with laboratory confirmation\(^27\) of SARS-CoV-2 infection, irrespective of clinical signs and symptoms; confirmatory tests include a nucleic acid amplification test (eg, RT-PCR) or validated antibody test; in an area with established circulation of virus, there should be one positive RT-PCR test or identification of virus on sequencing (one or more negative tests do not rule out infection if there is clinical suspicion); and in an area without established circulation of virus, there should be one positive RT-PCR test for two different viral genome targets or one positive result with partial or whole genome sequencing.

**Probable**
- (1) Either SARS-CoV-2 detected in CSF or other sample; or evidence of SARS-CoV-2-specific antibody in serum indicating acute infection; and (2) no other known traditional cardiovascular risk factors\(\|\).

**Possible**
- (1) A suspect case for whom testing for the COVID-19 virus is inconclusive; or (2) a suspect case for whom testing could not be done for any reason.

**Suspected**
- (1) A patient with acute respiratory illness (fever and at least one sign or 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 before onset; or (2) a patient with acute respiratory illness who has been in contact with a confirmed or probable case in the last 14 days before symptom onset; or (3) a patient with severe acute respiratory illness that requires hospitalisation, and in the absence of an alternative explanation that fully explains the clinical presentation.

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 pleocytosis, 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).\(^27\)
| CNS disease | Clinical presentation | SARS-CoV-2 diagnostics | Other pathogen and antibody investigations | Relevant blood tests and radiology findings | Neurological investigations (CSF findings, neuroimaging, neurophysiology) | Management, progress, and outcome |
|-------------|-----------------------|------------------------|--------------------------------------------|---------------------------------------------|--------------------------------------------------------------------------|---------------------------------|
| Encephalitis | Moniguchi et al.,13 one case, Japan | Man aged 24 years, 9 days of fatigue, headache, fever, sore throat; then generalised seizures, reduced consciousness, and meningism | RT-PCR was negative in nasopharyngeal swab; positive in CSF | Serum: anti-HSV-1 and VZV IgM antibodies tests were negative | 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 | CSF: clear, colourless, raised opening pressure (320 mm H2O) and cell count (32/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 | 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) |
| | Sohal et al.,32 one case, USA | 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 | RT-PCR was positive; source not specified | Blood: culture was negative for bacterial growth; influenza PCR was negative | Arterial blood gas test: pH 7.13, PaO2 68 mm Hg, PCO2 78 mm Hg, raised brain natriuretic peptide, troponin, CRP, LDR; hypnoxia, and leucopenia; chest x-ray: normal; chest CT: basilar opacities along with right lower lobe consolidation | Head CT: no acute changes, chronic microvascular ischaemic changes, 24-h EEG: six left temporal seizures and left temporal sharp waves that 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 vancomycin and piperacillin tazobactam; after onset of seizures, treated with levetiracetam and valproate but they were not controlled; died on day 5 of illness |
| | Wong et al.,33 one case, UK | Man aged 40 years developed ataxia, oscillopsia, hiccups, and diarrhoea | RT-PCR was positive in nasopharyngeal swab; CSF RT-PCR was not done | Blood: negative for hepatitis A, B, and C; HIV-1 and HIV-2, and syphilis antibody; CSF: bacterial culture was negative; anti- MOC IgG antibody and anti-aquaporin 4 antibody test results not reported | 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 hypo echoic liver with raised periperal and pericholecystic echogenicity | 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 | Treated with oral amoxicillin, but no other treatment; gradual improvement in neurological symptoms; discharged home after 11 days on gabapentin; oscilposia and ataxia persisted |
| | Dugue et al.,34 one case, USA | Infant aged 6 weeks with cough, fever, and episodes of bilateral leg stiffening and sustained upward gaze | RT-PCR was positive and high-throughput sequencing detected viral RNA in nasopharyngeal and anal swabs; RT-PCR was negative in plasma and CSF | 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 | Leucopenia (5.07 × 10⁹ white blood cells per μL) with a normal differential, and elevated procalcitonin of 0.21 ng/mL, normal urea and electrolytes | CSF: normal; brain MRI: normal; prolonged EEG monitoring showed two polymorphs of temporal sharp transients and intermittent vertex delta, slowing with normal sleep-wake cycling | No specific treatment; no further episodes and discharged home after 1 day |

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).35–38 40 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).58 Two patients had fever only, with no respiratory features.40 The neurological manifestations were typical for encephalitis, with irritability, confusion, and reduced consciousness, sometimes associated with seizures; three patients also had neck stiffness35,36,38 and another had psychotic symptoms.63 A man aged 40 years developed ataxia, oscilposia, hiccups,
### Table 2: Clinical Presentation of 40 Patients with CNS Disease Due to SARS-CoV-2 Infection

| Clinical presentation | SARS-CoV-2 diagnostics | Other pathogen and antibody investigations | Relevant blood tests and radiology findings | Neurological investigations (CSF findings, neuroimaging, neurophysiology) | Management, progress, and outcome |
|-----------------------|------------------------|------------------------------------------|------------------------------------------|-------------------------------------------------|----------------------------------|
| Helms et al,35 16 cases, France | 40 patients had agitation; 26 of the 40 evaluated had confusion, 39 had corticospinal tract signs, 15 had a dysarthric syndrome at discharge, and seven had history of neurological disorders, including transient ischaemic attack, partial epilepsy, and mild cognitive impairment | RT-PCR was positive for all patients’ nasopharyngeal samples; negative RT-PCR in CSF in seven patients | NR | NR | In seven patients who had CSF analysis, none had pleocytosis, two had matched oligodendral bands, and one had raised protein; in 13 patients who had brain MRI, eight had enhancement in leptomeningeal 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 |
| Mao et al,36 16 cases, China | 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 | RT-PCR was positive in all patients’ throat swabs | NR | 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 | NR |
| Poyiadji et al,37 one case, USA | Female patient with cough, fever, and altered mental status; imaging consistent with acute necrotising encephalopathy | RT-PCR was positive in nasopharyngeal swab; CSF RT-PCR not done | CSF: bacterial culture negative after 3 days and tests for HSV, VZV, and WNV were negative | NR | Non-contrast head CT: symmetric hypointensity in bilateral medial thalam; brain MRI: T2 FLAIR hyperintensity in bilateral medial temporal lobes, thalami, and subcortical regions, and evidence of haemorrhage indicated by hypointensity on susceptibility-weighted images and rim enhancement on post-contrast images |
| Paniz-Mondolfi et al,38 one case, USA | Man aged 74 years with history of Parkinson’s disease presented following two falls at home with fever, confusion, and agitation | RT-PCR was positive in nasopharyngeal swab; electron microscopy of brain tissue: viral particles in endothelial and neural cells | 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 | Head CT: no acute changes | Given hydroxychloroquine and low-molecular-weight heparin initially, then tocilizumab; persistently febrile and agitated with episodes of hypotension and increasing hypoxia; developed new onset atrial fibrillation; given fluids and amiodarone, reverting to sinus rhythm, then metoprolol; deteriorated and died |
| Zhou et al,39 one case, China | Patient aged 56 years with COVID-19 pneumonia | SARS-CoV2 detected by sequencing in CSF | NR | NR | NR |

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### Acute disseminated encephalomyelitis

**Zanin et al;** one case, Italy

- **Clinical presentation:** Woman aged 54 years presented with agitation, decreased consciousness, and seizures following several days of anosmia and ageusia.
- **SARS-CoV-2 diagnostics:** RT-PCR was positive in respiratory sample.
- **Other pathogen and antibody investigations:** Blood: cultures were negative; urine: cultures were negative.
- **Relevant blood tests and radiology findings:** 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.
- **Neurological investigations (CSF findings, neuroimaging, neuropsychology):** CSF: normal; brain and spine MRI: periventricular confluent white matter lesions and numerous high signal cord lesions from bulbo-medullary junction to T6 level; no contrast enhancement.
- **Management, progress, and outcome:** Treated with antivirals and hydroxychloroquine; clinically deteriorated becoming hypoxic; requiring intubation and mechanical ventilation; treated with high dose dexamethasone; tracheostomy done on day 7; weaned off ventilator on day 15; discharged and transferred to rehabilitation without sensorimotor deficit about 1 month after admission.

**Zhang et al;** one case, USA

- **Clinical presentation:** Woman in early 40s with a 9-day history of headache and myalgia presented with dysphagia, dysarthria, expressive dysphasia, dysphagia, dysarthria, left-sided facial weakness, fever, and dyspnoea on admission.
- **SARS-CoV-2 diagnostics:** RT-PCR was positive; site not specified (presumed respiratory sample).
- **Other pathogen and antibody investigations:** 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.
- **Relevant blood tests and radiology findings:** Mild leukocytosis with lymphopenia; chest x-ray: patchy consolidation in right lower lung.
- **Neurological investigations (CSF findings, neuroimaging, neuropsychology):** CSF: normal cell count, protein, and glucose; brain MRI: extensive areas of high signal in bilateral frontoparietal white matter, anterior temporal lobes, basal ganglia, external capsules, and thalamus; some foci showed diffusion-weighted imaging changes and corresponding apparent diffusion coefficient changes; brain and neck magnetic resonance angiography: normal; EEG: no evidence of seizures.
- **Management, progress, and outcome:** Treated with hydroxychloroquine, ceftriaxone, and intravenous immunoglobulin; some improvement in dysphagia and dysarthria after 5 days.

### Myelitis

**Zhao et al;** one case, China

- **Clinical presentation:** Man aged 68 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.
- **SARS-CoV-2 diagnostics:** RT-PCR was positive in nasopharyngeal swab.
- **Other pathogen and antibody investigations:** 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.
- **Relevant blood tests and radiology findings:** Lymphopenia (0.55 × 10⁹ cells per L) and raised CRP (217 mg/L) and procalcitonin (43.3 mg/mL); slightly raised alanine aminotransferase (56 U/L) and aspartate aminotransferase (50 U/L); chest CT: bilateral patchy changes.
- **Neurological investigations (CSF findings, neuroimaging, neuropsychology):** Brain CT: lacunar infaracts; spinal imaging not done.
- **Management, progress, and outcome:** On admission, deteriorated rapidly and admitted to ICU; treated with mofloxacain, osefatimavir, liposavitavir-ritonavir, ganciclovir, and meropenem, followed by dexamethasone and intravenous immunoglobulin for neurological symptoms; required oxygen; slight improvement in power in upper and lower limbs following treatment, but still unable to walk; discharged and transferred for rehabilitation.

### Peripheral nervous system disease

**Camdessanche et al;** one case, France

- **Clinical presentation:** Man aged 64 years with 2 days of cough and fever presented following a fall; on day 9 of hospital admission, developed paraesthesia in hands and feet and progressive weakness in all limbs, with areflexia and loss of vibration sense; then developed dysphagia and respiratory insufficiency.
- **SARS-CoV-2 diagnostics:** RT-PCR was positive in nasopharyngeal swab on admission; 9 days before onset of neurological symptoms.
- **Other pathogen and antibody investigations:** Negative for Campylobacter jejuni, M pneumonieae, Salmonella enterica, CMV, EBV, HSV-1, HSV-2, VZV, influenza viruses A and B, HIV, and hepatitis E; serum antiganglioside antibodies not detected.
- **Relevant blood tests and radiology findings:** Chest CT: 10% to 25% ground glass opacities.
- **Neurological investigations (CSF findings, neuroimaging, neuropsychology):** CSF: normal cell count and raised protein (166 mg/dL); nerve conduction study and electromyography: acute inflammatory demyelinating polyneuropathy.
- **Management, progress, and outcome:** Had initially needed 2L to 3L of 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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### GBS variants and other neuropathies

**Toscano et al.**<sup>44</sup> Five cases, Italy

- **Clinical presentation**: Woman aged 71 years with isolated ophthalmoplegia, bilateral ptosis, paresis of the right limbs, facial paralysis, and dysphagia.
- **SARS-CoV-2 diagnostics**: RT-PCR was positive in nasopharyngeal swab.
- **Other pathogen and antibody investigations**: 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.
- **Relevant blood tests and radiology findings**: 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 and CT showed interstitial pneumonia, without parenchymal opacities or alveolar damage.
- **Neurological investigations** (CSF findings, neuroimaging, neurophysiology): CSF analysis: all patients had normal white cell counts, three had elevated proteins; MRI enhancement of caudal nerve roots in two patients; and of facial nerve in one, and no signal change in two patients; nerve conduction study: axonal pattern in three patients and demyelinating in two.
- **Management, progress, and outcome**: 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.

**Zhao et al.**<sup>45</sup> One case, China

- **Clinical presentation**: Man aged 39 years, with fever; unable to abduct his right eye (right abducens palsy).
- **SARS-CoV-2 diagnostics**: RT-PCR was positive in oropharyngeal swab.
- **Other pathogen and antibody investigations**: Laboratory results upon admission were clinically significant for lymphopenia and thrombocytopenia; chest CT: ground glass opacities bilaterally.
- **Relevant blood tests and radiology findings**: Antiganglioside antibody GD1b-IgG detected in serum; normal CSF cytology, sterile cultures, and negative antibody tests.
- **Neurological investigations** (CSF findings, neuroimaging, neurophysiology): CSF: normal cell count and raised protein (124 mg/dL); nerve conduction study: acute inflammatory demyelinating polyneuropathy.
- **Management, progress, and outcome**: All treated with intravenous immunoglobulin for 5 days; given arbidol, lopinavir, and ritonavir; improved neurologically, had normal power and reflexes on discharge at day 30.

**GBS variants and other neuropathies**

**Gutiérrez-Ortiz et al.**<sup>46</sup> One Miller Fisher Syndrome, Spain

- **Clinical presentation**: Man aged 50 years with 5 days of cough, fever, malaise, headache, back pain, anosmia, and ageusia, who developed right internuclear ophthalmoplegias with right fascicular oculomotor palsy, ataxia, and areflexia (preserved plantar responses).
- **SARS-CoV-2 diagnostics**: RT-PCR was positive in ophthalmological swab.
- **Other pathogen and antibody investigations**: Antiganglioside antibody GD1b-IgG detected in serum; normal CSF cytology, sterile cultures, and negative antibody tests.
- **Relevant blood tests and radiology findings**: Lymphopenia; elevated CRP; chest x-ray: normal.
- **Neurological investigations** (CSF findings, neuroimaging, neurophysiology): CSF: normal opening pressure, cell count, raised protein (80 mg/dL), and normal glucose; brain CT with contrast: normal.
- **Management, progress, and outcome**: All treated with intravenous immunoglobulin for 5 days; complete recovery at 2 weeks except for residual anosmia and ageusia.

**Dinkin et al.**<sup>47</sup> One ophthalmoplegia, USA

- **Clinical presentation**: Woman aged 71 years with isolated ophthalmoplegia after a few days of cough and fever; unable to abduct her right eye (right abducens palsy).
- **SARS-CoV-2 diagnostics**: RT-PCR was positive in nasal swab.
- **Other pathogen and antibody investigations**: Leucopenia; chest x-ray: bilateral opacities.
- **Relevant blood tests and radiology findings**: CSF: normal opening pressure; brain MRI: enhancement of optic nerve sheaths and posterior Tenon capsules.
- **Neurological investigations** (CSF findings, neuroimaging, neurophysiology): CSF: normal cell count, but raised protein (62 mg/dL); brain CT: normal.
- **Management, progress, and outcome**: Treated with hydroxychloroquine and oxygen; discharged after 6 days; symptoms improving, although ongoing at 2 weeks after discharge.

**Gutiérrez-Ortiz et al.**<sup>48</sup> One bilateral ophthalmoplegia, Spain

- **Clinical presentation**: 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.
- **SARS-CoV-2 diagnostics**: RT-PCR was positive in ophthalmological swab.
- **Other pathogen and antibody investigations**: Normal CSF cytology, sterile cultures, and negative anti-pathogen antibody tests.
- **Relevant blood tests and radiology findings**: Leucopenia, but blood tests otherwise normal; chest x-ray: normal.
- **Neurological investigations** (CSF findings, neuroimaging, neurophysiology): CSF: normal cell count, but raised protein (62 mg/dL); brain CT: normal.
- **Management, progress, and outcome**: No specific treatment; complete recovery in 2 weeks.

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### Clinical presentation SARS-CoV-2 diagnostics Other pathogen and antibody investigations Relevant blood tests and radiology findings Neurological investigations (CSF findings, neuroimaging, neurophysiology) Management, progress, and outcome

| (Continued from previous page) | Clinical presentation | SARS-CoV-2 diagnostics | Other pathogen and antibody investigations | Relevant blood tests and radiology findings | Neurological investigations (CSF findings, neuroimaging, neurophysiology) | Management, progress, and outcome |
|-------------------------------|-----------------------|------------------------|--------------------------------------------|--------------------------------------------|-------------------------------------------------|----------------------------------|
| Escalada Pellitero et al;48 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 | NR | 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;49 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 (11842 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;50 357 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 | NR | Treated with nasal corticosteroids (8%), oral corticosteroids (3%), and nasal irrigation (17%) |
| Cerebrovascular disease | Ischaemic stroke | Avula et al;51 four cases, USA Four patients (aged 73 to 88 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 droop, 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)
Beyrouti et al,\textsuperscript{52} six cases, UK

Six patients (aged 53 to 83 years; five male and one female), three of whom had hypertension, two ischaemic heart disease, two atrial fibrillation, one a previous stroke and high body-mass index, and one was a smoker with heavy alcohol consumption and diabetes; three had dysarthria, one expressive dysphasia, one aphasia; four had hemiparesis and two had incoordination; one had reduced consciousness, and all had respiratory symptoms at a median of 13 days (range –2 to 24) before or after 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 antibody. 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).

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.

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.

Li et al,\textsuperscript{53} 11 cases, China

11 patients (aged 57 to 91 years; six female and five male), nine of whom had hypertension, six diabetes, three cardiovascular disease, three were smokers, and one with malignancy; five had large-vessel stenosis, three cardioembolic, and three small-vessel disease; all had respiratory symptoms a median of 11 days (range 0 to 30) before neurological symptom onset. All RT-PCRs were 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 chest CT.

Nine had severe disease; six were treated with antiplatelets (aspirin or clopidogrel); five were given anticoagulant therapy (clexane); four died and seven survived.

Morassi et al,\textsuperscript{54} four cases, Italy

Four patients (aged 64 to 82 years), three of whom had hypertension, two had a previous stroke or transient ischaemic attack and aortic valve disease, and one was a smoker with a previous myocardial infarction; all presented with severe acute respiratory illness; three developed neurological manifestations during hospitalisation (two hemiparesis and one inability to rouse when sedation held); one presented with episodes of transient loss of consciousness and confusion.

All RT-PCRs were positive on nasopharyngeal swab.

All had 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).

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.

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.

(Continued from previous page)

| Clinical presentation | SARS-CoV-2 diagnostics | Other pathogen and antibody investigations | Relevant blood tests and radiology findings | Neurological investigations (CSF findings, neuroimaging, neurophysiology) | Management, progress, and outcome |
|-----------------------|-------------------------|------------------------------------------|---------------------------------------------|-------------------------------------------------|----------------------------------|
| Beyrouti et al,\textsuperscript{52} six cases, UK | 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 antibody | 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) | 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 | 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 |
| Li et al,\textsuperscript{53} 11 cases, China | All RT-PCRs were 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 chest CT | NR | Nine had severe disease; six were treated with antiplatelets (aspirin or clopidogrel); five were given anticoagulant therapy (clexane); four died and seven survived |
| Morassi et al,\textsuperscript{54} four cases, Italy | All RT-PCRs were positive on nasopharyngeal swab | NR | All had 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) | 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 | 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 |

(Table 2 continues on next page)
### Table 2: Selected reports of neurological manifestations associated with COVID-19

| Clinical presentation                                                                 | SARS-CoV-2 diagnostics | Other pathogen and antibody investigations | Relevant blood tests and radiology findings | Neurological investigations (CSF findings, neuroimaging, neurophysiology) | Management, progress, and outcome |
|---------------------------------------------------------------------------------------|------------------------|---------------------------------------------|---------------------------------------------|--------------------------------------------------------------------------|---------------------------------|
| (Continued from previous page)                                                        |                        |                                             |                                             |                                                                          |                                 |
| **Intracerebral haemorrhage**                                                         |                        |                                             |                                             |                                                                          |                                 |
| Oxley et al;55 five cases, USA                                                        | 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 | All five had positive RT-PCR (presumed to be upper respiratory samples); no mention of CSF studies | One had thrombocytopenia, one prolonged prothrombin time, one prolonged activated partial thromboplastin time, and three each had raised fibrinogen, increased D-dimer, and raised ferritin; CT angiography reported in one patient: patchy ground glass opacities in lung apices | All had single-territory infarcts on brain CT or MRI | Four had clot retrieval, one of whom had intravenous thrombolysis and hemi-infarction and one had stent insertion; two had apixaban, two aspirin alone, and one dual antiplatelets; one discharged home; two discharged to rehabilitation facilities; two remain in hospital (one in ICU and one in stroke unit) |
| **Cerebral venous sinus thrombosis**                                                  |                        |                                             |                                             |                                                                          |                                 |
| Li et al;53 one case, China                                                           | Man aged 32 years with history of smoking developed neurological features 14 days after initial presentation with COVID-19 | RT-PCR was positive on throat swab | NR | NR | NR | Treated with anticoagulation; survived but remains in hospital |

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=varicella 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. LDDH=lactate dehydrogenase. GCS=Glasgow Coma Scale.

generalised slowing, two had focal abnormalities, and one patient, who presented with psychiatric symptoms followed by a seizure, was found to be in non-convulsive status epilepticus.5 One patient responded quickly to high dose steroids,4 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).6 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).7

The largest study to date,8 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
concerns of all four limbs with or without sensory loss, 43–45,69–74 11 patients had Guillain-Barré syndrome with weakness of all four limbs. 45,68,75 Onset of respiratory symptoms but SARS-CoV-2 on nasopharyngeal swab 168 children hospitalised with COVID-19, 82 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). 41 Two case reports 40,41 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). 44 The other presented with seizures and reduced consciousness, and required intubation for respiratory failure. 46 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. 77 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. 42

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. 46 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. 46,48 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 diarrhea before the onset of neurological disease.

11 patients had Guillain-Barré syndrome with weakness of all four limbs with or without sensory loss. 46–48,76–78 Three had a paraparetic variant with leg weakness only, 46,75 and one had lower limb paraesthesia. 76 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, and 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, and another had an acute vestibular syndrome with horizontal nystagmus and oscillopsia.

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.14,43,44,73,75 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.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.57 Rhabdomyolysis due to COVID-19 has also been reported.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).87 A study of 259 patients, 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,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.89 Subclinical deficits in smell, taste, or both have also been detected.90-92 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.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.92 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.\(^9\) In the Netherlands, three (2%) of 184 patients in intensive care with COVID-19 had ischaemic strokes.\(^9\) In total, 88 patients with ischaemic stroke and eight with haemorrhagic stroke\(^53,54,62,73\) 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.\(^31,34,78\) Younger stroke patients have also been reported.\(^52,53,56,60,95\) 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.\(^9\) 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\(^36\) and five had only cerebrovascular symptoms.\(^53,55,64,65\)

In two patients, ischaemic stroke has been associated with thrombus in the aorta,\(^95,96\) and indeed multiple infarcts have been reported in these and other patients (figure 2E, F).\(^52,77,79\) Sometimes associated with arterial thrombosis and limb ischaemia,\(^77,79\) Concurrent deep vein thrombosis and pulmonary embolism have been found in other stroke patients.\(^55,65\) 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.\(^35\) 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.\(^55,57,72,95\) Positive lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein-1 antibodies have also been reported in COVID-19-associated stroke,\(^57,72\) 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.\(^9\) 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, NCT0406389), 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.\(^9\) In mouse models, following intranasal injection, human coronavirus OC43 invades the CNS by the olfactory route.\(^10\) Alternative entry routes include carriage across the blood–brain barrier, following viraemia, or through infected leukocytes. 7 The angiotensin converting enzyme 2 receptor, to which SARS-CoV-2 binds for entry into cells,\(^10\) is found in brain vascular endothelium and smooth muscle.\(^101\) SARS-CoV-2 replicates in neuronal cells in vitro.\(^102\)

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.\(^9\)

Autopsy material from a patient who developed encephalopathy weeks after presenting with SARS showed oedema, neuronal necrosis, and broad glyco- and plasm-
microvascular and macrovascular complications in the brain, as described systemically.46

Acute ischaemic stroke might also occur through the early inflammatory process, following acute infection, destabilising a carotid plaque or triggering atrial fibrillation.107 A vasculitis process similar to that for varicella zoster virus, in which viral replication in the cerebral arterial wall triggers local inflammation,107 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,108 but cerebral vessels have not yet been investigated.

**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-19.11 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 pleocytosis, 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.109 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.10 Up to 70% of patients with sepsis might develop encephalopathy or polyneuropathy.11 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.36,102

**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.8 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
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, chaired a Siemens Diagnostics clinical advisory board, and advises the WHO Brain Health Unit Forum on Neurology and COVID-19; TS has also previously filed a patent for a test for bacterial meningitis based on a blood test (GB 1606537.7, April 14, 2016). All other authors declare no competing interests.

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Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barre syndrome associated with SARS-CoV-2 infection. J Neurol Neurosurg Psychiatry 2020; published online April 28. https://doi.org/10.1136/jnnp-2020-323522.

Solomon T, Michael BD, Smith PE, et al. Management of suspected viral encephalitis in adults—Association of British Neurologists and British Infection Association National Guidelines. J Infect 2012; 64: 347–73.

Pirotta A, Odolini S, Stefano Masciocchi S, et al. Steroid-responsive encephalitis in Coronavirus disease 2019. Ann Neurol 2020; published online May 17 https://doi.org/10.1002/ana.25783.

Duong L, Xu P, Liu A. Meningoencephalitis without respiratory failure in a young female patient with COVID-19 infection in downtown Los Angeles, early April 2020. Brain Behav Immun 2020; published online April 12 https://doi.org/10.1016/j.bbi.2020.04.024.

Vollono C, Rollo F, Rornozzi M, et al. Focal status epilepticus as a unique clinical feature of COVID-19: a case report. Seizure 2020; 79: 109–12.

Bernard-Valnet R, Pizzarotti B, Anichini A, et al. Two patients with acute meningoencephalitis concomitant to SARS-CoV-2 infection. Eur J Neurol 2020; published online May 7 https://doi.org/10.1111/ene.14298.

Wölflé R, Cormam VM, Gugmemos W, et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020; 581: 465–69.

Lee Y-L, Luu-Darns ME, Benjamin L, et al. Dynamics of anti-SARS-CoV-2 IgM and IgG antibodies among COVID-19 patients. J Infect 2020; published online April 21 https://doi.org/10.1016/j.jinf.2020.04.019.

Jin Y, Wang M, Zuo Z, et al. Diagnostic value and dynamic variance of serum antibody in coronavirus disease 2019. Int J Infect Dis 2020; 94: 45–52.

Liu Y, Yan L-M, Wan L, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis 2020; 20: 565–57.

He X, Lai EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med 2020; 26: 672–75.

Xiang F, Wang X, He X, et al. Antibody detection and dynamic characteristics in patients with COVID-19. Clin Infect Dis 2020; published online April 19 https://doi.org/10.1093/cid/ciaa461.

Abdelnoour L, Eltahir Abdalla M, Babiker S. COVID-19 infection presenting as motor peripheral neuropathy. J Formos Med Assoc 2020; 119: 1119–20.

Galán AV, del Saz Saucedo P, Postigo FP, Paniguea EB. Guillain-Barré syndrome associated with SARS-CoV-2 infection. Neurologia 2020; 35: 268–69.
