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Supplementary appendix

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Neurological Associations of COVID-19 - Supplementary Material

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4. Neurological disease associated with COVID-19 (full table)

1. Neurological disease associated with SARS or MERS infection

Virus	First author	Number of patients	Clinical presentation	SARS-CoV-2 diagnostics	Neurological investigations	Therapy for neurological disease and outcome
SARS-CoV	Xu[1] – 1 case, China	1	Encephalopathy	Antibody positive in serum. SARS-CoV detected in brain tissue by RT-PCR and immunohistochemistry.	CSF: not reported. CT brain: cerebral oedema, areas of ischaemia.	Supportive treatment only. Death 35 days after onset.
	Hung[2] – 1 case, China	1	Encephalopathy with seizures	RT-PCR positive in serum and CSF	CSF analysis: normal. CT brain: normal.	Supportive therapy. Seizure free at discharge, no further details of outcome.
	Lau[3] – 1 case, China	1	Encephalopathy with seizures	RT-PCR positive in CSF, stool and peritoneal fluid. Serum SARS-CoV IgG titre <1:25 day 1, 1:1600 day 39.	CSF analysis: normal. MRI brain: normal. EEG: normal.	Supportive therapy.
	Tsai[4] – 4 cases, Taiwan	1	Motor-predominant peripheral neuropathy	RT-PCR positive in throat swab. Serum coronavirus antibody positive	NCS/EMG findings consistent with critical illness polyneuropathy.	Almost complete recovery at 2 months.
		1	Motor-predominant peripheral neuropathy	RT-PCR positive in serum. Serum coronavirus antibody positive.	CSF analysis: normal. NCS: axonal sensorimotor polyneuropathy	No specific treatment. Nearly full return of muscle power at 7 weeks.
		1	Myopathy with peripheral neuropathy	Serum coronavirus antibody positive. RT-PCR negative.	CSF analysis: normal. NCS: axonal sensorimotor polyneuropathy. EMG: early recruitment with fibrillations and positive waves. CK: 9050 U/l	No specific treatment. Modest improvement in strength, no improvement in sensory problems at day 87.
		1	Myopathy	RT-PCR positive in throat swab. Serum coronavirus antibody positive	EMG: normal recruitment with active spontaneous activity and abundant brief small polyphasic waves. NCS: normal. CK: 366 U/l	No specific treatment. Full power at 7 weeks.
MERS-CoV	Algahtani[5] – 2 cases, Saudi Arabia	1	Intracerebral haemorrhage	RT-PCR positive in sputum.	CT brain: right frontal haemorrhage with oedema and midline shift.	Death 2 months after onset.

	1	Polyneuropathy	RT-PCR positive in respiratory secretions	CSF analysis: normal. MRI spine: normal. NCS: length dependent axonal polyneuropathy.	IVIG. Slow improvement after 6 months.
Arabi[6] – 3 cases, Saudi Arabia	1	Encephalopathy/ADEM	RT-PCR positive in tracheal aspirate, negative in CSF	CSF analysis: normal MRI brain: multiple areas of signal abnormality in deep white matter, periventricular areas, midbrain, cerebellum and upper cervical cord.	Death 34 days after onset
	1	Multiple cerebral infarcts	RT-PCR positive in respiratory sample	CSF analysis not reported MRI brain: acute infarction in the parasagittal region and temporal, parietal, and occipital lobes.	Death 9 days after onset
	1	Encephalopathy/ADEM	RT-PCR positive in respiratory samples, negative in CSF	CSF analysis: normal cell count, protein 0.85 g/L MRI brain: confluent T2WI/FLAIR hyperintensity within the white matter of both cerebral hemispheres and along the corticospinal tract.	Discharged home, detailed outcome not reported
Kim[7] – 4 cases, South Korea	1	Bickerstaff's brainstem encephalitis overlapping with GBS (hypersomnolence, quadriparesis, ptosis, ophthalmoplegia mild ataxia, areflexia)	RT-PCR positive in sputum, negative in CSF	CSF analysis: normal, ganglioside antibodies negative. MRI brain: normal, NCS normal on day 46.	IVIG. Full recovery by day 60.
	1	GBS or critical care neuropathy (distal limb weakness and hyporeflexia	"laboratory confirmed MERS infection"	NCS normal.	No specific treatment. Weakness resolved after 53 days. Ongoing sensory symptoms at 7 months.
	1	Peripheral sensory symptoms	"laboratory confirmed MERS infection"	NCS: normal.	No specific treatment. Symptoms gradually improved over 6 months.
	1	Peripheral sensory symptoms	Exposed to MERS and developed respiratory illness. No laboratory confirmation reported.	NCS not performed, CSF not analysed.	No specific treatment. Symptoms resolved over 4 months.

ADEM = acute disseminated encephalomyelitis; CK = creatinine kinase; CSF = cerebrospinal fluid; CT = computed tomography; EEG = electroencephalogram; EMG = electromyography; FLAIR = fluid-attenuated inversion recovery (MRI sequence); GBS = Guillain-Barré syndrome; ICU = intensive care unit; IVIG = intravenous immunoglobulin; NCS = nerve conduction study; MRI = magnetic resonance imaging; RT-PCR = reverse transcription polymerase chain reaction; T2WI= T2-weighted image (MRI sequence)

Table 1. Neurological disease associated with SARS or MERS infection

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

BBB= blood-brain barrier

A) Virus may enter the nervous system across the blood brain barrier, possibly by infected leukocytes, or through retrograde transport along the olfactory or other cranial or peripheral neurons.[8] Viruses can enter neurons to cause cytopathology.

B) Innate immune responses to viral infection and resultant inflammation may cause tissue damage, as is thought to occur in acute encephalopathy syndromes in influenza infection.[9]

C) Pathological adaptive immune responses include damage caused by cytotoxic T cells[10] and antibody mediated response against host tissue, either in the central or peripheral nervous system.[11,12] The latter may be caused by molecular mimicry between the pathogen and host epitopes, or tissue damage may result in failure of tolerance to self-antigens.

D) Viral infection may cause blood vessel damage either by direct infection or immune-mediated vasculitis.[13] Alternatively, the virus may activate the vessel endothelium triggering inflammatory and thrombotic pathways with release of microparticles leading to thrombotic microangiopathy, as part of a secondary haemophagocytic lymphohistiocytosis,[14] a syndrome of excessive inflammation and tissue destruction due to abnormal immune activation, thought to be related to excessive and inadequately regulated lymphocyte and macrophage activity.

3. Case definitions for neurological syndromes

i. Meningitis[1]

<table>
<tr><td>Level 1
Meningitis</td><td>Level 2
Possible meningitis</td><td>Level 3
Meningism</td><td>Level 4
Suspected meningitis</td></tr>
<tr><td colspan="4">Suspected meningitis with no other diagnoses apparent, but does not fulfil level 3 criteria</td></tr>
<tr><td colspan="3">[ ] Absence of an alternative diagnosis for symptoms

AND

[ ] Neck stiffness

OR

[ ] Kernig’s sign positive

OR

[ ] Brudzinsky’s sign positive</td><td rowspan="4"></td></tr>
<tr><td colspan="2">[ ] Fever (≥ 38ºC)</td><td rowspan="3"></td></tr>
<tr><td>[ ] CSF total white cell count > 5 cells/mm^3

OR

[ ] Meningeal enhancement seen on contrast enhanced CT or MRI</td><td></td></tr>
<tr><td>[ ] Level 1
Meningitis</td><td>[ ] Level 2
Possible meningitis</td><td>[ ] Level 3
Meningism</td><td>[ ] Level 4
Suspected meningitis</td></tr>
</table>

ii. Encephalitis[2,3,4]

<table>
<tr><td>Level 1
Encephalitis</td><td>Level 2
Possible encephalitis</td><td>Level 3
Encephalopathy</td><td>Level 4
Suspected encephalopathy</td></tr>
<tr><td colspan="4">[ ] Suspected encephalopathy (an alteration in consciousness, cognition, personality or behaviour) with no other diagnosis apparent, but does not fulfill level 3 criteria</td></tr>
<tr><td colspan="3">[ ] Acute or sub-acute (<4 weeks) alteration in consciousness, cognition (including delirium* or coma^), personality or behaviour persisting for more than 24 hours
AND
[ ] Absence of an alternative diagnosis for symptoms</td><td rowspan="3"></td></tr>
<tr><td colspan="2">[ ] New onset seizure
OR
[ ] New focal neurological signs
OR
[ ] Fever (≥ 38ºC)
OR
[ ] New movement disorder (includes: Parkinsonism, oromotor dysfunction etc.)
OR
[ ] EEG with focal abnormalities</td><td rowspan="2"></td></tr>
<tr><td>[ ] CSF total white cell count > 5 cells/mm^3
OR
[ ] Neuroimaging compatible with encephalitis
OR
[ ] Confirmation of brain inflammation on brain biopsy</td><td></td></tr>
<tr><td>[ ] Level 1
Encephalitis</td><td>[ ] Level 2
Possible encephalitis</td><td>[ ] Level 3
Encephalopathy</td><td>[ ] Level 4
Suspected encephalopathy</td></tr>
</table>

*__Delirium__[4] is defined as a clinical manifestation of encephalopathy, with the following features:

A) Disturbance in attention (reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment);
B) Develops over a short period of time, represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of the day
C) An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).
D) Criteria A & C are not explained by another pre-existing, established, or evolving neurocognitive disorder, and do not occur in the context of a severely reduced level of arousal, like coma.
E) There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal, or exposure to a toxin, or is because of multiple etiologies.

Where a patient has acute cognitive changes that are compatible with delirium but not all of these features are present, this is defined clinically as **subsyndromal delirium**.

^Coma[4] is defined as a state of severely depressed responsiveness defined using diagnostic systems such as the Glasgow Coma Score (GCS) or the Full Outline of UnResponsiveness (FOUR) score

iii. Acute disseminated encephalomyelitis (ADEM)[5,6]

<table>
<tr><td>Level 1
ADEM</td><td>Level 2
Probable ADEM</td><td>Level 3
Suspected ADEM</td></tr>
<tr><td colspan="3">[ ] Suspected ADEM with no other diagnosis apparent, but does not fit level 2 criteria</td></tr>
<tr><td colspan="2">[ ] unifocal or multifocal clinical CNS event

OR

[ ] alteration in consciousness or behavioural change (encephalopathy) unexplained by fever/systemic illness/postictal symptoms

AND

[ ] abnormal brain MRI with typical diffuse, poorly demarcated lesions >1cm</td><td rowspan="2"></td></tr>
<tr><td>[ ] no new clinical or MRI findings 3 months or more after symptom onset

OR

[ ] signs/symptoms/MRI findings consistent with multiphasic ADEM*</td><td></td></tr>
<tr><td>[ ] Level 1
ADEM</td><td>[ ] Level 2
Probable ADEM</td><td>[ ] Level 3
Suspected ADEM</td></tr>
</table>

*Multiphasic ADEM – two episodes of Level 2 ADEM separated by three months but not followed by any further events. The second ADEM event can involve either new or re-emergence of prior neurological symptoms/signs/MRI findings. Beyond a second event, the diagnosis is no longer consistent with multiphasic ADEM

iv. Myelitis [7]

Level 1 Myelitis	Level 2 Possible myelitis	Level 3 Myelopathy	Level 4 Suspected myelopathy
[ ] Weakness or sensory disturbance of upper and/or lower limbs, developing to its worst severity between 4h and 21d following onset of symptoms *			
[ ] Absence of an alternative diagnosis for symptoms **WITH** [ ] Brisk reflexes or extensor plantar response **OR** [ ] Bladder or bowel dysfunction **OR** [ ] Clearly defined sensory level			
[ ] Absence of extra-axial compressive aetiology by neuroimaging (MRI or CT myelography) **AND** [ ] Absence of flow voids on the surface of the spinal cord suggestive of arteriovenous malformation on neuroimaging (MRI)			
[ ] CSF total white cell count >5 cells/mm^3 **OR** [ ] MRI changes consistent with myelitis (gadolinium enhancement or T2 hyperintensity) **OR** [ ] Elevated IgG index			
[ ] Level 1 Myelitis	**[ ] Level 2 Possible myelitis**	**[ ] Level 3 Myelopathy**	**[ ] Level 4 Suspected myelopathy**

*if the patient wakes up with symptoms, symptoms must continue to worsen from the point of waking

v. Guillain-Barré syndrome (GBS)[8]

<table>
<tr><th>Level 1</th><th>Level 2</th><th>Level 3</th><th>Level 4</th></tr>
<tr><td colspan="4">[ ] Suspected GBS with no other diagnosis apparent, but does not fulfil level 3 criteria</td></tr>
<tr><td colspan="3">[ ] Bilateral and flaccid weakness of the limbs

AND

[ ] Absence of an alternative diagnosis for weakness

AND

[ ] Decreased or absent deep tendon reflexes in affected limbs

AND

[ ] Monophasic illness pattern with weakness nadir between 12 hours and 28 days, followed by clinical plateau</td><td rowspan="3"></td></tr>
<tr><td colspan="2">[ ]CSF total white cell count < 50 cells/mm^3

OR

[ ]If CSF results unavailable, electrophysiological findings consistent with GBS</td><td rowspan="2"></td></tr>
<tr><td>[ ]CSF protein level above laboratory normal value AND CSF total white cell count < 50 cells/mm^3

AND

[ ] Electrophysiological findings consistent with GBS</td><td></td></tr>
<tr><td>[ ] Level 1</td><td>[ ] Level 2</td><td>[ ] Level 3</td><td>[ ] Level 4</td></tr>
</table>

vi. Cerebrovascular disease[9,10,11]

Stroke and Transient ischaemic attack (TIA):

	Definitions
Central Nervous System (CNS) infarction	Brain, spinal cord, or retinal cell death attributable to ischemia, based on: [ ] clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded (CNS infarction includes hemorrhagic infarctions, types I and II, see 'Intracerebral hemorrhage') **OR** [ ] pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution
Silent CNS infarction	[ ] Imaging or neuropathological evidence of CNS infarction, without a history of acute neurological dysfunction attributable to the lesion.
Ischemic stroke	[ ] An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.
Intracerebral hemorrhage	[ ] A focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma. (Intracerebral hemorrhage includes parenchymal hemorrhages after CNS infarction, type I - petechiae of blood along the margins of the infarction, and type II - confluent petechiae within the infarction but without a space-occupying effect.)
Silent cerebral hemorrhage	[ ] A focal collection of chronic blood products within the brain parenchyma, subarachnoid space, or ventricular system on neuroimaging or neuropathological examination that is not caused by trauma and without a history of acute neurological dysfunction attributable to the lesion.
Stroke caused by intracerebral hemorrhage	[ ] Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.
Subarachnoid hemorrhage	[ ] Bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord)
Stroke caused by subarachnoid hemorrhage	[ ] Rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma.
Stroke caused by cerebral venous thrombosis	[ ] Infarction or hemorrhage in the brain, spinal cord, or retina because of thrombosis of a cerebral venous structure. Symptoms or signs caused by reversible edema without infarction or hemorrhage do not qualify as stroke.
Stroke, not otherwise specified	[ ] An episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting ≥24 hours or until death, but without sufficient evidence to be classified as one of the above.
Transient ischemic attack (TIA)	[ ] A transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction

Table 7. Cerebrovascular disease case definitions

Central Nervous System Vasculitis:

	Definite	Possible
Central Nervous System (CNS) vasculitis	Clinical presentation compatible with CNS vasculitis with exclusion of alternative possible diagnoses and of primary systemic vasculitic syndrome **AND** Positive CNS histology (biopsy or autopsy) showing CNS angiitis (granulomatous, lymphocytic or necrotising), including evidence of vessel wall damage.	Clinical presentation compatible with CNS vasculitis with exclusion of alternative possible diagnoses and of primary systemic vasculitic syndrome **AND** Laboratory and imaging support for CNS inflammation (elevated levels of CSF protein and/or cells, and/or the presence of oligoclonal bands and/or MR scan evidence compatible with CNS vasculitis), with angiographic* exclusion of other specific entities, but without histological proof of vasculitis.

*Certain disorders, perhaps most particularly moyamoya disease, may require formal contrast angiography for definitive diagnosis.

Table 8. Central nervous system (CNS) vasculitis definition

References for neurological syndrome case definitions

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4. Neurological disease associated with COVID-19 (full table)

First author and number of cases	Clinical presentation	SARS-CoV-2 diagnostics	Other pathogen and antibody investigations	Relevant blood tests and radiology findings	Neurological investigations (cerebrospinal fluid findings, neuroimaging, neurophysiology)	Management, progress and outcome
Central Nervous System						
Encephalitis						
Bernard-Valnet[15] - 2 cases, Switzerland	64-year-old female with a 5-day history of mild asthenia, myalgia and cough developed psychotic symptoms (hyper-religiosity with mystic delusions, visual hallucinations) who developed seizures, and focal status epilepticus. On admission she appeared disoriented with a marked attention deficit, verbal and motor perseverations, and bilateral grasping. 67-year-old female, with a history of mild respiratory symptoms 17 days before, developed headache, confusion, agitation, left hemianopia and neglect	Both RT-PCR positive in nasal swab, negative in CSF.	CSF: Negative for common viral and bacterial pathogens and anti-neuronal antibodies. (Bacterial pathogens: *Neisseria meningitidis, Listeria monocytogenes, Streptococcus pneumoniae, Haemophilus influenza, Escherichia Coli K1, Streptococcus Agalactiae*; Viral pathogens: Enterovirus, HSV-1, HSV-2, VZV, CMV, HHV-6, Parechovirus. Anti-neuronal antibodies: anti-NMDAR, anti-CAPSR2, anti-LGI1, anti-DPPX, anti-GABA B R, anti-AMPAR, anti-lgLON5, anti-mGLUR5, anti-GlyR	Chest radiology results were only reported in the second patient (67-year-old female), who had a chest ultrasound scan: subpleural densities	In the first patient, CSF: raised cell count (17 cells/mm3 [97% lymphocytes]) and slightly raised protein 0.46g/L. Glucose ratio (CSF/serum) of 0.59. MRI brain: normal EEG: non-convulsive status epilepticus (abundant bursts of anterior low-medium voltage irregular spike-and waves superimposed on an irregularly slowed theta background) In the second patient, CSF: Raised cell count (21 cells/mm3 [89% lymphocytes]), and slightly raised protein 0.46g/L. Glucose ratio (CSF/serum) of 0.62. MRI brain: normal	The first patient was given clonazepam and valproate for seizures and markedly improved 96 hours after admission. The second patient was at first treated with ceftriaxone, amoxicillin and acyclovir. Neurological symptoms resolved after 24 hours, except for a mild headache. The patient was discharged 3 days after admission with no symptoms.
Duong[16] - 1 case, USA	41-year-old female with fever, encephalopathy - including agitation, lethargy and disorientation, a single seizure and meningism. History of diabetes and obesity.	"Positive"- details not reported. CSF RT-PCR not available.	CSF: Negative for HSV on PCR testing.	Chest X-ray: normal. White cell count, U+Es and LFTs normal, CK normal.	Raised white cells (70 cells/mm3 [100% lymphocytes], protein 1.0 g/L), glucose ratio (CSF/serum) 0.6 CT brain normal EEG: generalised slowing	Treated with ceftriaxone, vancomycin, and aciclovir, which was stopped when SARS-CoV-2 infection was confirmed, and anti-epileptic medication, which was subsequently stopped. Hydroxychloroquine was also given. He started to improve at day 5 of admission, although had ongoing intermittent hallucinations.
Moriguchi[17] -1 case, Japan	24-year-old male presented 9 days after symptoms of fatigue, headache, fever - followed by a sore throat - with generalised seizures, reduced conscious level and meningism.	RT-PCR negative in nasopharyngeal swab, positive in CSF.	Serum: Anti-HSV 1 and VZV IgM antibodies tests were negative.	Increased blood white cell count, neutrophil dominant, relatively decreased lymphocytes, increased CRP. CT Chest: small ground glass opacity in the right upper zone and bilaterally in lower zones.	CSF: Clear, colourless. Raised opening pressure (320 mmH20) and cell count (12/mm3 - 10 mononuclear and 2 polymorphonuclear cells) CT Head: no brain oedema. MRI brain: hyperintensity along the wall of the right lateral ventricle on diffusion weighted imaging, and hyperintense signal in the right medial temporal lobe and hippocampus on T2 weighted images	Treated empirically for bacterial pneumonia and viral encephalitis. On admission, required intubation and mechanical ventilation due to seizures. Admitted to ICU. Still on intensive care at time of report (day 15)
Pilotto[18] - 1 case, Italy	60-year-old male with akinetic mutism and nuchal rigidity, on examination he had positive palmomental and glabella reflexes. Confusion and irritability preceded cough and fever by 2 days.	RT-PCR positive in nasopharyngeal swab; negative in CSF.	CSF: Negative for anti-neuronal antibodies: anti-NMDAR, anti-LGI1, anti-CASPR2, anti-GABA A R, anti-GABA B R, anti-AMPAR, anti-Ri, anti-Yo, anti-Ma2, anti-Hu, anti-Amphiphysin, anti-MOG.	Normal FBC, increased D-dimer (968 ng/mL), normal CRP, fibrinogen and ferritin. Chest X-ray: bilateral interstitial pneumonia.	Raised cell count (18 cells/μL) and protein (0.69g/L) CT and MRI brain normal EEG: generalised slowing, more prominent in anterior regions with decreased reactivity to acoustic stimuli. Following treatment, EEG showed improvement and normalization of anterior regions slowness.	Treated with lopinavir/ritonavir and hydroxychloroquine, then with ampicillin and aciclovir. Clinical symptoms persisted, and high dose intravenous steroids were started (1g/day for 5 days) - the patient rapidly improved. Oral prednisone was started with progressive tapering. At discharge, eleven days after admission, neurological examination was normal.
Sohal[19] - 1 case, USA	72-year-old man presented with weakness and light headedness following a hypoglycaemic episode. Shortly after admission he had difficulty breathing and was noted to have altered mental status. On day two of admission he started to have seizures.	RT-PCR positive-source not specified	Blood: culture negative for bacterial growth. Influenza PCR: negative.	ABG: pH of 7.13, PaO2 of 68mmHg, PCO2 of 78mmHg. Raised BNP (541 pg/mL), troponin (0.35ng/mL), CRP (61 mg/L), LDH (230 U/L), as well as lymphopenia (0.5 k/cmm) and leukopenia at 4000k/cmm. Chest X-ray: normal. CT chest: bibasilar opacities along with right lower lobe consolidation.	CT head: no acute changes, chronic microvascular ischaemic changes. 24h EEG showed six left temporal seizures and left temporal sharp waves which were epileptogenic	Required intubation and ventilation, and was admitted to ICU. Became hypotensive requiring norepinephrine via central line. Hydroxychloroquine and azithromycin were started in addition to antimicrobials of vancomycin and piperacillin tazobactam. Onset of seizures - treated with levetiracetam and valproate but they were not controlled. Death on day 5 of illness.

	Vollono[20] - 1 case, Italy	78-year-old female with pre-existing post encephalitic epilepsy presented with myoclonus of the right eyelid and upper-lip - diagnosed as a focal status epilepticus; she had HSV encephalitis 2 years earlier with persistent fluent aphasia and mild right-sided limb weakness as a result. She had been on anti-epileptic treatment and seizure free for 2 years. 12 hours after admission she became febrile. Exposure to a contact of a known coronavirus case 'the week before'.	RT-PCR positive in nasopharyngeal and oropharyngeal swabs	Blood cultures and urine culture 'negative for common bacteria, fungi and neurotropic viruses'	Lymphopaenia (560 cells/ mm3) and thrombocytopaenia (125,000/mm3), slightly raised CRP (29 mg/L). Procalcitonin 0.07 ng/mL. Chest X-ray: normal.	MRI brain: extensive gliosis in the left temporal and parietal lobes from previous encephalitis but no acute changes EEG showed semi-rhythmic, irregular, high amplitude delta activity, predominantly lateralised over the left fronto-centro-temporal regions, consistent with focal status epilepticus	Treated with Intravenous midazolam and valproate and had a subsequent resolution of seizures. She was also given lopinavir-ritonavir and hydroxychlorquine. No oxygen was required. She improved clinically and was discharged after 14 days of admission.
	Wong[21] - 1 case, UK	40-year-old male presented with ataxia, diplopia, oscillopsia and bilateral facial weakness, diagnosed with rhombencephalitis. 13 days before he had fever and progressive shortness of breath on exertion, followed 10 days later by a productive cough and diarrhea.	RT-PCR positive in nasopharyngeal swab. CSF RT-PCR not performed.	Blood test: negative for hepatitis A, B, C, HIV 1 and 2, and syphilis antibody. CSF: negative bacterial culture. Sent for Anti MOG-IgG antibody and anti-aquaporin 4 antibody testing but results not reported.	Normal white cell count with lymphopaenia, raised CRP, abnormal LFTs. Chest X-ray: right lower zone consolidation. Liver ultrasound: inflammatory diffusely hypoechoic liver with a raised periportal and pericholecystic echogenicity.	Normal cell count and protein (0.42 g/L) MRI brain: increased signal lesion in the right inferior cerebellar peduncle extending to involve a small portion of the upper cord. The lesion measured 13mm in maximum cross-sectional area and 28mm in longitudinal extent. There was swelling at the affected tissue and associated micro-haemorrhage.	Treated with oral amoxicillin, no other treatment. Gradual improvement in neurological symptoms and he was discharged home after 11 days on gabapentin; oscillopsia and ataxia persisted.
Other Encephalopathies							
	Benussi[22] - 15 cases, Italy	15 patients hospitalised with COVID-19 with delirium. Few specific clinical details.	RT-PCR positive in respiratory specimens (both nasopharyngeal and oropharyngeal swabs performed)	NR	Nothing specific to cases with delirium.	NR	NR
	Chacón-Aguilar[23] - 1 case, Spain	26-day old infant with febrile with nasal discharge, vomiting had 2 episodes of hypertonia - one associated with upward gaze and the other with facial cyanosis. Irritability and hyperreflexia on examination.	RT-PCR positive in nasopharyngeal swab	Blood, urine, stool and CSF cultures were negative for RSV and influenza A and B virus.	Normal FBC, U+Es, LFTs and CRP. Raised CK (380 U/L) and LDH (390 U/L), slightly elevated fibrinogen (418 mg/dL).	CSF: normal Cranial ultrasound: normal 36-hour EEG: no epileptiform activity	Treated with empirical antibiotic therapy until negative culture results. No further episodes. Discharged at six days.
	Dugue[24] - 1 case, USA	6-week-old infant with cough and fever had episodes of bilateral leg stiffening and sustained upward gaze	RT-PCR positive and RNA on high throughput sequencing in nasopharyngeal and anal swab samples. RT-PCR negative in serum/plasma, CSF.	Nasopharyngeal swab: respiratory pathogen PCR panel positive for rhinovirus/enterovirus, high throughput sequencing detected rhinovirus C. CSF: meningitis/ encephalitis pathogen PCR panel negative and culture negative.	Leucopaenia of 5.07 x10^3 white blood cells/µL with a normal differential, and elevated procalcitonin of 0.21 ng/m. Normal U+Es.	CSF: normal MRI brain normal Prolonged EEG monitoring: excess of temporal sharp transients and intermittent vertex delta slowing with normal sleep-wake cycling	No specific treatment. No further episodes and discharged home after one day.
	Filatov[25] - 1 case, USA	74-year-old male presented with fever and cough but not admitted as normal bloods and chest X-Ray, 24 hours later he re-presented to hospital with headache and altered mental status. History of previous stroke and atrial fibrillation	Positive, source not specified	Throat and nasopharyngeal culture negative for strep. Blood cultures and urine culture negative. Influenza A and B negative. CSF negative for HSV, CMV and RSV on RT-PCR.	Following admission: Chest X-ray: small right pleural effusion with ground glass opacities; CT Chest: patchy bibasal consolidation and subpleural opacities	CSF: White cell count normal (4), protein slightly raised (68) CT brain: previous left PCA infarct, no acute changes. EEG: bilateral slowing and focal slowing in the left temporal region with sharply countered waves.	Started on antiepileptic medication, given the possibility of subclinical seizures, antibiotics and aciclovir. Also given hydroxychloroquine and lopinavir/ritonavir. Developed respiratory failure and was admitted to ICU, intubated and mechanically ventilated; patient remained in ICU at time of publication.
	Garazzino[26] - 5 cases, Italy	From a sample of 168 children with confirmed COVID-19, 5 had seizures. Of these, three had a history of epilepsy, one had a past history of febrile seizures and the remaining one had a first episode of febrile seizures as the first symptom of COVID-19.	All RT-PCR positive in nasopharyngeal swab	Not clear from study whether patients who had co-infection were the patients with neurological complications.	No specific description of findings in patients with neurological complications.	In the patient with new onset seizures, it is reported that "SARS-CoV2 encephalitis was ruled out" although no CSF results are reported	No detail given of specific treatment. Outcome not reported.

	Helms[27] - 49 cases, France	40 had agitation, 26 of the 40 who could be evaluated had evidence of confusion, 39 had corticospinal tract signs (enhanced tendon reflexes, ankle clonus, and bilateral extensor plantar reflexes). 15 had a dysexecutive syndrome at discharge (inattention, disorientation, or poorly organized movements in response to command). 7 had a history of neurological disorders, including transient ischemic attack, partial epilepsy, and mild cognitive impairment.	All positive by RT-PCR in nasopharyngeal samples. Negative RT-PCR in CSF in 7 patients.	NR	NR	7 patients had CSF analysis. None had pleiocytosis. 2 patients had matched oligoclonal bands. 1 patient had raised protein. 13 patients had MRI brain. 8 had enhancement in leptomeningeal spaces. 11 patients had perfusion imaging, and all had bilateral frontotemporal hypoperfusion. 2 patients had acute ischaemic stroke. 1 had subacute ischaemic stroke. 8 patients had EEG. 1 had diffuse bifrontal slowing.	All required treatment on ITU for severe COVID-19. 45 had been discharged from ICU at the time of writing.
	Mao[28] - 16 cases, China	16 patients hospitalised with COVID-19 had "impaired consciousness", of which 1 had a seizure characterized by a sudden onset of limb twitching and loss of consciousness, lasting 3 minutes.	All positive by RT-PCR in throat swab.	NR	Patients with 'CNS disease' and severe respiratory disease had lower lymphocyte levels and platelet counts and higher blood urea nitrogen levels compared with those without CNS symptoms.	NR	13 had severe respiratory disease and 3 non-severe according to American Thoracic Society guidelines. No further details.
	Neerland[29] - 1 case, Norway	Female patient in her late eighties with a 1-day history of nasal congestion presented with fever, confusion and dizziness, who had a fall. History of mild cognitive impairment.	RT-PCR positive in nasopharyngeal swab	Nasopharyngeal testing for 'relevant respiratory tract microbes'; urine positive for blood and leukocytes but culture negative.	Normal FBC, U+Es and LFTs. Normal ferritin. Slightly raised CRP (12 mg/L) and ESR (23 mm/h). Chest X-ray: small left sided pleural effusion	NR	No specific treatment. Did not require oxygen. Discharged at ten days with residual vertigo.
	Poyiadji[30] - 1 case, USA	Female patient with cough, fever and altered mental status. Imaging consistent with acute necrotising encephalopathy.	RT-PCR positive in nasopharyngeal swab. CSF RT-PCR unable to be performed.	CSF: bacterial culture negative after 3 days, and 'tests' for HSV, VZV and WNV negative.	NR	Non-contrast CT head: symmetric hypoattenuation within the bilateral medial thalami. Normal CT angiogram and CT venogram. MRI brain: T2 FLAIR hyperintensity within the bilateral medial temporal lobes, thalami and subinsular regions with evidence of hemorrhage indicated by hypointense signal intensity on susceptibility-weighted images and rim enhancement on postcontrast images	IVIG. Outcome not reported
	Paniz-Mondolfi[31] - 1 case, USA	74-year-old male with a background of Parkinson's disease presented following 2 falls at home with fever, confusion and agitation	RT-PCR positive in nasopharyngeal swab. Electron microscopy of frontal lobe specimens at post-mortem: presence of viral particles in endothelial cells and neural cell bodies.	NR	Increased CRP, ferritin, d-dimer and thrombocytopaenia. Initial chest radiology - no changes in lung fields, subsequently developed new changes bilaterally on chest X-ray suggestive of consolidation.	CT head: no acute changes	Given hydroxychloroquine and LMWH initially, then tocilizumab. Persistently febrile, agitated with episodes of hypotension and increasing hypoxia. Developed new onset atrial fibrillation and was given fluids and amiodarone, reverting to sinus rhythm, then continued on metoprolol. Deteriorated and died.
	Ye[32] - 1 case, China	Male patient presented 13 days after onset of fever, shortness of breath, and myalgia with confusion and signs of meningeal irritation (nuchal rigidity, Kernig's and Brudzinski's sign, extensor plantar response).	RT-PCR positive in nasopharyngeal swab; RT-PCR, Anti-SARS-CoV-IgM and IgG negative in CSF	CSF: no evidence of bacterial or tuberculous infection	lymphopaenia (0.8 x 10^9/L), CT Chest: multiple subpleural ground glass opacities	CSF: Normal CT brain normal	Required oxygen. Given umifenovir and mannitol, complete resolution of encephalopathy by day 27 of illness and discharged.
	Zhou[33] - 1 case, China	56-year-old patient with COVID-19 pneumonia	SARS-CoV2 detected by sequencing in CSF	NR	NR	NR	NR

Myelitis						
Zhao[34] -1 case, China	66-year-old man was admitted with fever, dyspnoea and 'asthma'. Five days after respiratory symptom onset he developed acute flaccid paralysis of the lower limbs, urinary and faecal incontinence and a sensory level at T10.	RT-PCR positive in nasopharyngeal swab.	Blood: Negative for EBV, influenza A, influenza B, adenovirus, coxsackievirus, parainfluenza virus, CMV, RSV on serum IgM testing. Negative for Chlamydia pneumoniae, Mycoplasma pneumoniae, and TB.	Lymphopaenia (0.55 ×10^9/L) and raised CRP (277 mg/L) and procalcitonin (4.33 ng/mL). Slightly raised ALT (56 U/L) and AST (50 U/L). CT Chest: bilateral patchy changes.	CT brain showed lacunar infarcts. Spinal imaging not performed	On admission, he deteriorated rapidly and was admitted to ICU. Treated with moxifloxacin, oseltamivir, lopinavir-ritonavir, ganciclovir, and meropenem, followed by dexamethasone and IVIG for his neurological symptoms. Required supplementary oxygen. Slight improvement in power in upper and lower limbs following treatment, but still unable to walk. Discharged and transferred for rehabilitation.
Acute disseminated encephalomyelitis						
Zanin[35] - 1 case, Italy	54-year-old woman presented with agitation, decreased conscious level and seizures following several days of anosmia and ageusia	RT-PCR positive in respiratory sample	Blood: cultures negative; urine: cultures negative.	Lymphopenia (0.3/mm3) with mild elevation of inflammatory markers (CRP 41.3 mg/L, Fibrinogen 520 mg/dL). Chest X-ray: interstitial pneumonia	CSF: Normal MRI brain and spine: periventricular confluent white matter lesions and numerous high signal cord lesions from bulbomedullary junction to T6 level. No contrast enhancement.	Treated with antiretrovirals and hydroxychloroquine. Clinically deteriorated following admission, becoming hypoxic and requiring intubation and mechanical ventilation. Treated with high dose dexamethasone. Tracheostomy was performed at day 7 and she was weaned off the ventilator at day 15. Discharged and transferred to rehabilitation without sensorimotor deficit after approximately 1 month of admission.
Zhang[36] - 1 case, USA	Female patient in her early forties with a 9-day history of headache and myalgia presented with dysphagia, dysarthria, expressive dysphasia and encephalopathy. Left sided facial weakness. Had fever and dyspnoea on admission.	RT-PCR positive- site not specified (presumed respiratory sample)	Negative influenza swab and a negative rapid streptococcus test. CSF: negative PCR test for HSV 1 and 2, HHV 6, VZV, and negative Cryptococcus test, bacterial cultures negative.	Mild leukocytosis with lymphopenia. Chest X-ray: patchy consolidation in the right lower lung	CSF: normal cell count, protein, and glucose. MRI brain: extensive areas of high signal in bilateral frontoparietal white matter, anterior temporal lobes, basal ganglia, external capsules and thalami. Some foci demonstrated diffusion weighted imaging (DWI) changes and corresponding apparent diffusion coefficient (ADC) changes. Magnetic resonance angiography (MRA) brain and neck: normal EEG: no evidence of seizures	Treated with hydroxychloroquine, ceftriaxone and IVIG. Some improvement in dysphagia and dysarthria after 5 days.
Peripheral Nervous System Disease						
Guillain Barré syndrome						
Abdelnour[37] - 1 case, UK	69-year-old male with progressive bilateral proximal lower limb weakness and areflexia. Initial transient (3 hour) period of sensory symptoms. Gait ataxia. 7 days after neurological symptom onset he developed fever and confusion	2 x RT-PCR positive in nasopharyngeal swabs at 3 days and 11 days after neuro symptom onset	NR	Lymphopenia (0.64), raised CRP (14), ferritin (526) and LDH (386), slightly raised LFTs. Normal Hb, platelets, and U+Es. Initial Chest X-ray normal; repeat exam 7 days later showed peripheral right lower lobe consolidation.	MRI brain and cervical/thoracic spine: no evidence of acute pathology; old infarcts in L frontal, parietal and occipital lobes.	No treatment given; made a spontaneous recovery of his muscle power and gait. Discharged home after 18 day of admission
Alberti[38] - 1 case, Italy	71-year-old male with paresthesia in hands and feet, rapidly progressive symmetrical weakness more marked in lower limbs than upper; areflexia, plantar response preserved; lower back pain; autonomic disturbance (hypertension). 'The week before' neurological symptom onset: fever; during admission developed dyspnoea and was hypoxic	RT-PCR positive in nasopharyngeal swab on admission, 3 days after neuro symptom onset	NR	Chest CT: multiple bilateral ground glass opacities and consolidation	CSF: mild leucocytosis (9 cells/ul), raised protein (54 mg/dL), CT Head: normal Nerve conduction study and electromyography: Severe acute inflammatory demyelinating polyneuropathy	Treated with IVIG for 5 days. Required oxygen support (60-80%) and was started on non-invasive ventilation (CPAP). Deteriorated and died.
Camdessanche[39] - 1 case, France	64-year-old male with a 2-day history of cough and fever presented following a fall. On day 9 of hospital admission, he developed paresthesia in his hands and feet, and progressive weakness in all four limbs with areflexia and loss of vibration sense. He developed dysphagia and respiratory insufficiency.	RT-PCR positive in nasopharyngeal swab on admission, 9 days before neuro symptom onset	Negative for Campylobacter jejuni, Mycoplasma pneumoniae, Salmonella enterica, CMV, EBV, HSV1 & 2, VZV, Influenza virus A & B, HIV and hepatitis E. Serum: Anti-ganglioside antibodies not detected.	CT chest: 10–25% ground glass opacities.	CSF: normal cell count, raised protein (166 mg/dl), Nerve conduction study and electromyography: acute inflammatory demyelinating polyneuropathy	He had initially needed 2-3L of oxygen via nasal cannula but had been weaned off it prior to neurological symptom onset. Given lopinavir/ritonavir. Treated with IVIG for 5 days, developed respiratory insufficiency and required admission to ICU for intubation and mechanical ventilation. No other details on outcome given.

Coen[40] - 1 case, Switzerland	Male in his seventies with symmetrical flaccid areflexic paraparesis and loss of upper limb tendon reflexes, distal allodynia, voiding difficulties and constipation. No sensory deficit. 10 days before neurological symptom onset had myalgia, fever, dry cough	RT-PCR positive in nasopharyngeal swab 5 days before admission. CSF tested and was negative.	Serum: no antiganglioside antibodies detected. CSF: Negative for other pathogens in the Meningitis/Encephalitis (ME) Panel testing (BioFire Diagnostics, UT)	Chest X-ray: normal	CSF: normal cell count, raised protein, no intrathecal IgG antibody synthesis MRI spine: normal Nerve conduction study and electromyography: acute inflammatory demyelinating polyneuropathy with a sural sparing pattern	Treated with IVIG for 5 days, improved and by day 11 of admission was discharged and transferred to a rehabilitation facility
El Otmani[41] - 1 case, Morocco	70-year-old female with rapidly progressive bilateral weakness in all four limbs with paresthesia and areflexia. Symptoms initially attributed to her rheumatoid arthritis, but she did not respond to steroid treatment. 3 days before neurological symptom onset: 48 hours of dry cough	RT-PCR positive in oropharyngeal swab 10 days after admission, 12 days after neuro onset. CSF tested and was negative.	NR	Lymphocytopenia (520/ml, normal: 1500 - 5000), otherwise normal. CT chest: ground glass opacities in the left lung.	CSF: normal cell count, raised protein (100 mg/dl), Nerve conduction study and electromyography: Acute motor sensory axonal neuropathy (AMSAN)	Hydroxychloroquine and azithromycin. Treated with IVIG for 5 days, no significant improvement had been seen after a week. No other details on outcome given.
Galán[42] - 1 case, Spain, Spain	43-year-old male with symmetrical progressive weakness in all four limbs and sensory disturbance distally; areflexia; subsequently developed bilateral facial weakness and dysphagia. 10 days before neurological symptom onset: diarrhoea, upper respiratory symptoms	RT-PCR positive during admission, sample tested was not reported.	NR	Chest X-ray: ground glass opacity in the right mid zone.	Nerve conduction study and electromyography: acute inflammatory demyelinating polyneuropathy	Initially given hydroxychloroquine, lopinavir y ritonavir, amoxicillin, steroids. Treated with IVIG for 5 days, and improved. Required oxygen during admission. No other details on outcome given.
Marta-Enguita[43] - 1 case, Spain	76-year-old female with a 10-day history of lower back pain, worst at night and radiating down her legs. 8 days before back pain had cough, tiredness, fever. She developed paresthesia distally in her upper and lower limbs, followed by progressive weakness in all four limbs, worst proximally; areflexia; reduced sensation below the knee.	RT-PCR positive 1 day before onset of backpain, sample tested was not reported.	NR	Thrombocytopaenia (102 × 10^9/L) and increased fibrinogen (470 mg/dL) and D-dimer (773 ng FEU/mL), otherwise normal. CT chest: mild lung involvement	CT head: normal. CT cervical and thoracic spine: evidence of degeneration but no compression	4 hours after admission, developed dysphagia and progressive respiratory failure, required oxygen but not through to be a complication of respiratory disease. Died.
Padroni[44] - 1 case, Italy	70-year-old female developed paresthesia in her hands and feet, and progressive difficultly walking with distal weakness in upper and lower limbs and areflexia; preserved sensation on examination. 24 days before onset of neurological symptoms: fever, dry cough, which had resolved 'in a few days'.	RT-PCR positive in nasopharyngeal swab 23 days before neurological symptom onset	Serum: Negative IgM and IgG tests for mycoplasma and CMV. Urine: negative antigen tests for legionella and strep pneumoniae. CSF: negative for HSV, CMV, EBV, VZV, HIV, borrelia burgdorferi IgM and IgG	Normal white blood cells (10.41 x 10^9), hepatic and renal function, CRP, ESR, D-dimer, creatine phosphokinase, blood glucose, folate and vitamin B12. CT chest: ground glass changes in both lungs.	CSF: normal cell count, slightly raised protein (48 mg/dl), Nerve conduction study and electromyography: acute inflammatory demyelinating polyneuropathy with a sural sparing pattern	Treated with IVIG for 5 days, developed respiratory insufficiency and required oxygen and admission to ICU for intubation and mechanical ventilation. No other details on outcome given.
Toscano[45] - 5 cases, Italy	5 patients, 4 males and 1 female, aged 23-77 years old. 4 patients had flaccid, areflexic limb weakness - 3 with quadriparesis or quadriplegia and 1 with paraplegia - 3 of 4 of these patients had facial weakness, 2 had dysphagia, and 3 developed respiratory failure. 1 patient had facial diplegia and areflexia with limb paresthesia and ataxia. Patients presented a median (range) of 7 (5-10) days after respiratory symptoms: cough in 4, fever in 3, hyposmia/anosmia or ageusia in 3 and pharyngitis in 1.	4 patients RT-PCR positive in nasopharyngeal swab. One positive by serological test. RT-PCR in CSF negative in all patients.	1 patient (patient 5)- negative for *Campylobacter jejuni,* EBV, CMV, HSV, VZV, influenza, and HIV. 3 patients tested for antiganglioside antibodies, but none were detected.	1 - CT scan of the thorax revealed interstitial bilateral pneumonia; 2- no details; 3 - CT scan of the thorax revealed multiple bilateral, ground-glass opacities compatible with interstitial pneumonia; 4- ; chest imaging was 'negative'; 5- X-ray and CT showed interstitial pneumonia, without parenchymal opacities nor alveolar damage;	CSF analysis: all patients had normal WCC, 3 patients had elevated protein. MRI: enhancement of caudal nerve roots in 2 patients, enhancement of facial nerve in one, and no signal change in 2. Nerve conduction study: axonal pattern in 3 patients, demyelinating in 2.	All treated with IVIG, 2 had 2 cycles, one also had plasma exchange. 3 required mechanical ventilation. At 4 weeks: 2 were still ventilated in intensive care, 2 were having physiotherapy and one was discharged.

Virani[46] - 1 case, USA	54-year-old male with progressive weakness in his lower then upper limbs; areflexia. 10 days before onset of neurological symptoms: fever, treated with antibiotics and developed diarrhoea (diagnosed with c. difficile colitis and started on treatment).	RT-PCR positive in nasopharyngeal swab 2 days after neurological symptom onset; also, rhinovirus positive.	Tested for other common respiratory pathogens, positive for rhinovirus.	Normal hemoglobin, white blood cell count, platelet count, procalcitonin and metabolic panel. MRI spine: incidental finding of bilateral basal opacities in lungs.	MRI spine: normal	Developed dyspnoea and weakness progressed to include trunk. Developed new onset urinary retention during course of illness. Treated with IVIG for 5 days, at which point he had developed respiratory insufficiency and was being ventilated. After 4 days of IVIG he came off the ventilator and by day 5 of treatment, upper limb weakness had resolved. Lower limb weakness persisted at the point of discharge to a rehabilitation facility.
Zhao[47] - 1 case, China	61-year-old female with progressive weakness of her lower limbs, then upper limbs, and severe fatigue; areflexia in lower limbs, and decreased sensation distally. 7 days after neurological symptom onset she developed a dry cough and fever.	RT-PCR positive in oropharyngeal swab.	NR	laboratory results on admission were clinically significant for lymphocytopenia (0·52×10^9/L, normal: 1·1–3·2×10^9/L) and thrombocytopenia (113×10^9 /L, normal: 125–300×10^9/L). CT chest: ground glass opacities bilaterally.	CSF: normal cell count, raised protein (124 mg/dL), Nerve conduction study: acute inflammatory demyelinating polyneuropathy	Treated with IVIG for 5 days. Also given arbidol, lopinavir, and ritonavir. Improved neurologically - normal power and reflexes on discharge at day 30.
GBS variants and other neuropathies						
Dinkin[48] – 1 Miller Fisher syndrome, USA	36-year-old male, with a history of infantile strabismus, developed ophthalmoplegia after 4 days of fever, cough, and myalgia. He had a partial left oculomotor palsy and bilateral abducens palsies. Reduced lower limb deep tendon reflexes. Bilateral distal lower limb paresthesia and sensation. Gait ataxia.	RT-PCR positive in nasal swab	Antiganglioside antibodies not detected.	Leucopaenia, blood tests otherwise normal. Chest X-ray: normal.	MRI brain: hyperintensity and enlargement of the left oculomotor nerve on T2 imaging	Treated with hydroxychloroquine. Partial response to IVIG treatment, discharged after 3 days of admission.
Gutiérrez-Ortiz[49] - 1 Miller Fisher Syndrome, Spain	50-year-old man with a 5-day history of cough, fever, malaise, headache, back pain, anosmia and ageusia developed right internuclear opthalmoparesis with right fascicular oculomotor palsy, ataxia and areflexia (preserved plantar responses).	RT-PCR positive in oropharyngeal swab, negative in CSF	Antiganglioside antibody GD1b-IgG detected in serum. Negative for anti-GM1, GM2, GM3, GD1a, GD1b, GD3, GT1a, GT1b, GQ1b, and anti-sulfatide antibodies. Normal CSF cytology, sterile cultures and negative anti-pathogen antibody tests.	Lymphopaenia, elevated CRP. Chest X-ray: normal.	CSF: normal opening pressure, cell count, raised protein (80 mg/dL), normal glucose. CT brain with contrast: normal	Treated with IVIG for 5 days, complete recovery at 2 weeks, except for residual anosmia and ageusia.
Dinkin[48] - 1 ophthalmoplegia, USA	71-year-old female presented with isolated ophthalmoplegia after 'a few days' of cough and fever. Unable to abduct her right eye - right abducens palsy	RT-PCR positive in nasal swab	NR	Leucopaenia Chest X-ray: bilateral opacities	CSF: Normal opening pressure MRI brain: enhancement of the optic nerve sheaths and posterior Tenon capsules	Treated with hydroxychloroquine and oxygen. Discharged after 6 days. Symptoms improving, although ongoing, at 2 weeks post-discharge
Gutiérrez-Ortiz[49] - 1 bilateral ophthalmoplegia, Spain	39-year-old man with 3 days of fever and diarrhoea developed diplopia. He had abduction deficits in both eyes and fixation nystagmus consistent with bilateral abducens palsy. Global areflexia, ageusia.	RT-PCR positive in oropharyngeal swab, negative in CSF	Normal CSF cytology, sterile cultures and negative anti-pathogen antibody tests.	Leucopaenia, blood tests otherwise normal. Chest X-ray: normal.	CSF: normal cell count, raised protein (62 mg/dL) CT brain: normal	No specific treatment. Complete recovery in 2 weeks.
Pellitero[50] - 1 acute vestibular dysfunction, Spain	30-year-old female developed unsteadiness, disequilibrium and nausea, worse on standing. 3 weeks before had 10 days of anosmia and ageusia. Unable to walk without assistance. Horizontal nystagmus with a rapid phase to the right, oscillopsia. Romberg positive.	RT-PCR positive on admission, sample tested was not reported.	NR	Lymphocytopaenia (1000 cells/mm3), D-dimer level of 2270 ng/mL, fibrinogen level of 326 mg/dL, LDH level of 235 U/L, and C-reactive protein level of 1.2 mg/L. Chest CT angiogram: normal	MRI brain with contrast: normal.	Treated with antiemetics and vestibular suppressants, the patient improved.
Rhabdomyolysis and other muscle disease						
Jin[51] – 1 rhabdomyolysis, China	60-year-old man admitted with COVID-19 developed weakness and tenderness in lower limbs 15 days after onset of fever and cough.	RT-PCR positive in throat swab	Urine: blood and protein detected	Leucopaenia, raised CRP and LDH. Normal U+Es, LFTS, CK initially, then raised CK: 11,842 U/L, myoglobin: 12,000 mg/L, AST, ALT. CT Chest: ground glass opacities	NR	Worsening respiratory status following admission. Antibiotics and supportive therapy, the patient's neuromuscular symptoms improved over several days.

Mao[28] - 23 cases, China	23 patients with COVID-19 and 'skeletal muscle injury'	RT-PCR positive in throat swab	NR	Median CK was 400 (range 203-12216)	NR	17 of these had severe respiratory disease. ITU admission and outcome not reported.
Suwanwongse[52] – 1 rhabdomyolysis, USA	88-year-old man with cough and fever developed bilateral proximal weakness and tenderness in his lower limbs. Creatinine kinase raised (13,581 U/L).	RT-PCR positive in nasopharyngeal swab.	Urine: blood detected	Raised CK and LDH. C X-Ray: small left sided pleural effusion (not new)	NR	Treated with hydroxychloroquine and supportive therapy. Became overloaded with fluid and was given furosemide, then developed acute kidney injury. No other details given.
Taste and smell dysfunction						
Beltrán-Corbellini[53] - 31 cases, Spain	86 COVID-19 patients in hospital compared to a historical control group of patients positive for influenza by PCR. Smell and taste dysfunction were more common in COVID-19 than in influenza. Patients with smell or taste dysfunction were younger than those without. Smell and taste loss were often acute in onset.	All RT-PCR positive in respiratory samples	NR	NR	NR	NR
Bénézit[54] - 63 cases, France	Patients tested for SARS-CoV2 were invited to complete a questionnaire. Sample of 68 patients who reported a positive SARS-CoV2 test. Taste dysfunction in 63 patients, smell dysfunction in 51 patients, 43 had both. Smell and taste dysfunction were strongly associated with COVID-19, separately and combined.	All patients reported positive RT-PCR on nasopharyngeal swab	NR	NR	NR	NR
Haehner[55] - 22 cases, Germany	Of 500 patients at a COVID-19 testing centre, 22 positive patients had loss of smell. Among positive patients, those with smell loss were significantly younger with less severe disease. Olfactory loss occurred 1-2 days before other symptoms in 1 patient, at the same time in 4 patients and 1-7 days after in 14 patients. 3 were uncertain.	All RT-PCR positive in respiratory samples	NR	NR	NR	NR
Hornuss[56] - 18 cases, Germany	45 consecutive hospitalised patients with COVID-19 and 45 uninfected controls underwent olfactory testing. No controls had smell dysfunction. 44% of anosmic and 50% of hyposmic patients did not report smelling problems. Smell or taste dysfunction occurred a median of 5 days after first COVID-19 symptoms.	All RT-PCR positive in respiratory samples	NR	NR	NR	None required mechanical ventilation.
Klopfenstein[57] - 54 cases, France	Sample of 114 patients with confirmed COVID-19. 54 patients with smell dysfunction, 46 of these also had taste dysfunction. Mean duration of anosmia was 8.9 days. Median 4.4 days after symptom onset	All RT-PCR positive in respiratory samples	NR	NR NR	NR	5 patients required ITU admission
Lechien[58] - 357 cases from Italy, Belgium, France, Switzerland, Spain	357 (86%) with smell dysfunction; 342 (89%) with taste dysfunction	All RT-PCR positive in respiratory samples			NR	Treated with nasal corticosteroids (8%), oral corticosteroids (2.5%), nasal irrigation (17%)

Moien[59] - 59 cases, Iran	60 hospitalised COVID-19 patients underwent olfactory testing and 59 were found to have deficits - 21 reported smell or taste dysfunction. In the control group of 60 healthy subjects, 11 had mild olfactory dysfunction. All reported that smell or taste dysfunction occurred at the same time or immediately after the onset of their other symptoms	All RT-PCR positive in respiratory samples	NR	NR	NR	6 patients had severe disease, ITU admission not reported
Vaira[60] - 53 cases, Italy	Sample of 72 COVID-19 patients. 53 reported symptoms of smell or taste dysfunction. On objective testing, 60 patients had anosmia and 35 had gustatory dysfunction. Generally, smell and taste dysfunction occurred within 5 days of symptom onset.	All RT-PCR positive in respiratory samples	NR	NR	NR	NR
Cerebrovascular disease						
Ischaemic stroke						
Al Saeigh[61] - 1 case, USA	62-year-old woman with no comorbidities presented with acute-onset hemiparesis and aphasia. Underwent thrombectomy and was discharged for rehabilitation. Re-presented 10 days later with change in mental status. No respiratory symptoms, no fever; nasal swab done on re-presentation with haemorrhagic transformation, not with initial ischaemic stroke	RT-PCR positive in nasal swab. CSF RT-PCR negative on two samples.	NR	Chest X-ray: no evidence of severe respiratory disease	First CT angiogram: left middle cerebral artery occlusion; second CT head: haemorrhagic with midline shift and obstructive hydrocephalus	Thrombectomy for initial left middle cerebral artery occlusion; decompressive hemicraniectomy and external ventricular drain placement for haemorrhagic transformation. Remained intubated post-operatively due to poor mental status. No other treatment/outcome data reported
Avula[62] - 4 cases, USA	Four patients, aged 73-88 years old. All had hypertension, 3 dyslipidaemia, 1 diabetes and neuropathy, 1 carotid stenosis, 1 CKD. Three presented with acute new focal neurological deficit (facial droop, slurred speech; left-sided weakness; right-arm weakness, word finding difficulty), one with altered mental status. One had fever, respiratory distress, nausea, vomiting; one had fever only; one had mild shortness of breath with dry cough; one had no respiratory symptoms nor fever.	All four had positive RT-PCR - presumed to be upper respiratory samples. No mention of CSF studies.	Negative blood and urine cultures in the two patients for which results were reported.	Three patients had lymphopaenia, one with leucopaenia and two with leucocytosis. Two had elevated D-dimer and inflammatory markers. Three had patchy changes bilaterally on Chest X-ray or CT.	All four had evidence of unifocal infarcts: three on CT, one on MRI brain.	All were treated with antiplatelet therapy - none had thrombolysis or thrombectomy. Three required intubation and ventilation and all three died. The forth was discharged to a rehabilitation facility.
Benussi[22] - 35 cases, Italy	35 patients: aged an average of 77 years	All had positive RT-PCR on a respiratory sample.	NR	Patients with cerebrovascular disease and COVID-19 had an increased neutrophil and platelet count, reduced lymphocyte count, higher C-reactive protein, erythrocyte sedimentation rate, lactate dehydrogenase, aspartate and alanine aminotransferase, prothrombin time and fibrinogen levels compared to patients with cerebrovascular disease but without COVID-19. No details specific to ischaemic stroke.	NR	8/35 had endovascular treatment; 2/35 had intravenous fibrinolysis; 3/35 had bridging therapy. Median modified Rankin score on discharge was 5 (severe disability; bedridden).

	Beyrouti[63] - 6 cases, UK	Patients aged 53-83 years, 5 male, 1 female. Three had hypertension, 2 ischaemic heart disease, 2 atrial fibrillation, 1 had a previous stroke and high BMI, another had diabetes, ischaemic heart disease and was a smoker with heavy alcohol consumption. Three had dysarthria, one expressive dysphasia, one aphasia. Four had hemiparesis; two, incoordination. One had reduced consciousness (GCS 13/15). All had respiratory symptoms, four had fever, at a median (range) of 13 (-2 to +24) days either before (in 5) or after (in 1) neurological symptom onset	All six had positive RT-PCR - presumed to be upper respiratory samples. No mention of CSF studies.	One had a medium titre IgM anti-cardiolipin antibody and low titre IgG and IgM aβ2GP1.	One had a leucocytosis, three had lymphopaenia. All had a raised D-dimer and LDH. Five had a raised ferritin, five had a raised CRP. All had bilateral patchy changes on chest X-ray or CT, two had pulmonary emboli - one in a segmental artery, the other with bilateral emboli in segmental and subsegmental arteries.	Initial scans (CT/MRI brain) showed unifocal infarcts in four, one of whom had bilateral infarcts on a follow up MRI brain. Two had bilateral infarcts on initial scans.	One treated with dual antiplatelet and therapeutic low-molecular weight heparin (LMWH) therapy; one had external ventricular drain placement and therapeutic LMWH; another had apixaban; the fourth had therapeutic LMWH; two had intravenous thrombolysis. Three required oxygen therapy, two were admitted to ITU, one died secondary to COVID-19 pneumonia following cardiorespiratory deterioration.
	Gonzáles-Pinto[64] - 1 case, Spain	36-year-old woman without respiratory symptoms presented with 48 hours of aphasia and right hemiplegia.	Positive RT-PCR - presumed to be upper respiratory sample. No mention of CSF studies.	NR	Leucocytosis (23600 cells/µl) and raised CK (8669 U/l), D-dimer (7540 ng/ml) and CRP (156 mg/ml). CT Chest revealed a bilateral pneumonia and bilateral acute pulmonary embolism	CT brain showed left middle cerebral artery (MCA) infarct and mild midline deviation. CT angiography showed occlusion of left internal carotid artery, left MCA and the anterior cerebral artery, and thrombus in the ascending aorta.	No operative intervention due to poor clinical status and severe mass effect; pharmacological therapies not reported. Deteriorated, and died 3 days after admission.
	Helms[27] - 3 cases (also reported in CNS section), France	"unexplained encephalopathic features" while on intensive care unit with COVID-19.	All RT-PCR positive on nasopharyngeal swab	NR		Unclear if the reported CSF and electroencephalography results relate to these three patients MRI brain: Two small unifocal acute ischemic stroke; one unifocal subacute ischemic stroke	All patients admitted to ITU with Acute Respiratory Distress Syndrome (ARDS).
	Klok[65] - 3 cases, The Netherlands	3 patients: "proven COVID-19 pneumonia admitted to the ICU"; no disaggregated clinical details.	NR	NR	NR	CT scans showed ischaemic stroke.	All patients were admitted to ITU with COVID-19 pneumonia.
	Li[66] - 11 cases, China	11 patients: aged 57-91 years old, 9 with hypertension, 6 with diabetes, 3 with cardiovascular disease, 3 smokers, 1 with malignancy; 6 female and 5 males; 5 had large-vessel stenosis; 3 cardioembolic; 3 small-vessel disease. All patients had respiratory symptoms a median (range) of 11 days (range 0-30) before neurological manifestations	All RT-PCR positive on throat swab	NR	No specific detail given on the 11 patients with ischaemic stroke. All patients had evidence of COVID-19 pneumonia on CT chest.	NR	Nine had severe disease. Six were treated with antiplatelet (aspirin or clopidogrel); five were given with anticoagulant therapy (Clexane). Four died; seven survived.
	Lodigiani[67] - 9 cases, Italy	Patients aged 57-76, 6 male and 3 females, two had lung cancer. Six presented with stroke; presumed the other three presented with respiratory illness	"Laboratory-proven COVID-19"	NR	6 patients had a raised D-dimer. One also had a pulmonary embolism confirmed on CT. No additional details given.	NR	One had aspirin only, three had aspirin with treatment dose LMWH, one of who had systemic thrombolysis and one who had mechanical thrombectomy. One had LMWH only. One had LMWH and clopidogrel, one LMWH and systemic thrombolysis, another had LMWH with local lysis and mechanical thrombectomy. One had treatment dose unfractionated heparin. During admission, one patient developed necrotising meningoencephalitis, one disseminated intravascular coagulation. At the time of reporting, three were admitted to ITU, two died, four had been discharged.
	Lushina[68] - 1 case, USA	84-year-old man with a history of hypertension, was admitted with fever, shortness of breath, cough, and abdominal pain, which had started 2 weeks prior to admission. Found to have a nonreactive, pinpoint left pupil incidentally.	Positive RT-PCR - presumed to be upper respiratory sample. No mention of CSF studies.	NR	Lymphopenia, elevated D-dimer of and troponin T. CT chest: diffuse ground-glass opacities and bibasilar consolidations, compatible with severe COVID-19 pneumonia, and bilateral lobar pulmonary emboli. CT abdomen and pelvis: new left renal infarct.	CT head and CT angiography showed occlusion of distal basilar artery and proximal posterior cerebral arteries, with small thrombus in aortic arch	Respiratory condition deteriorated on admission and he was intubated and ventilated. Mechanical thrombectomy was performed; blood flow restored, but died the next day.

Morassi[69] - 4 cases, Italy	4 patients: aged 64-82 years, 3 with hypertension and, 2 with a previous stroke/TIA and aortic valve disease, 1 who was a smoker with a previous myocardial infarction. All presented primarily with severe acute respiratory illness; 3/4 developed neurological manifestations during hospitalization (two hemiparesis, one inability to rouse when sedation held); 1/4 presented with episodes of transient loss of consciousness followed by confusion, in addition to respiratory symptoms.	All RT-PCR positive on nasopharyngeal swab	NR	All had raised CRP, two had a raised d-dimer, two had raised LDH, two had abnormal renal and liver function tests. CT Chest on all patients: bilateral ground glass opacities, one patient also had bilateral pleural effusions and a pulmonary embolism.	One had CSF analysis: normal leukocyte count, protein and IgG index. All had multifocal infarcts on CT/MR brain. The patient presenting with transient loss of consciousness and ensuing confusion had electroencephalography: "normal background in the alpha range (8 Hz), associated with recurrent sharp slow waves over the left temporal region, which occasionally were seen also on the right homologous regions"	One was treated with aspirin, clopidogrel and enoxaparin; another given levetiracetam; treatment not reported for the remaining two. Two were intubated and mechanically ventilated. Two died; of the two survivors, one had coma (GCS 3/15) and one was severely disabled with modified Rankin score of 4.
Moshayedi[70] - 1 case, USA	Male, in 70s, no comorbidities reported; after 5 days of shortness of breath admitted to hospital with ST-elevation myocardial infarction and bilateral ischaemic lower limbs. Developed in-hospital aphasia with right hemiparesis and facial droop.	RT-PCR positive on respiratory specimen	NR	Renal failure and activated PTT >85.5 while on heparin.	MRI brain: acute infarct in the left insular, temporal, parietal, and frontal lobes; smaller acute infarcts in the right caudate and left cerebellar hemisphere; haemorrhagic conversion in the left fronto-temporal territory. MR angiogram: occlusion of left middle cerebral artery proximal M1 segment.	Comfort measures instituted, no other details.
Oxley[71] - 5 cases, USA	33-49 years old; 4/5 male. All had hemiplegia; 4/5 had reduced conscious level. Additionally, three had dysarthria, one global dysphasia, two had a sensory deficit. Three had systemic/respiratory symptoms.	All five had positive RT-PCR - presumed to be upper respiratory samples. No mention of CSF studies.	NR	One had thrombocytopaenia, one prolonged PT, one prolonged APTT, three with raised fibrinogen, three with increased D-dimer, three with raised ferritin. CT angiography reported in one patient: Patchy ground-glass opacities in bilateral lung apices	All had single-territory infarcts on CT or MRI brain	Four had clot retrieval, of whom one had intravenous thrombolysis and hemicraniectomy and one had stent insertion. Two had apixaban; two aspirin-alone; one had dual antiplatelets. One discharged home; two discharged to rehabilitation facilities; two remain in hospital (one ITU, one stroke unit).
Zhang[72] - 3 cases, China	3 patients: aged 65-70 years; one female; three with hypertension, two with previous stroke, one known diabetes and coronary artery disease, and one with emphysema and nasopharyngeal carcinoma. One had ischaemia of lower limbs and a few fingers on the left hand. The other two had "similar findings". Onset of neurological manifestations occurred at 10, 18 and 33 days after COVID-19 symptom onset- all had fever and dyspnoea, two with cough, two with headache and one with diarrhoea.	Stated that infection was confirmed in all patients with RT-PCR serologic testing, but no specific details given.	Antiphospholipid antibodies were detected in all three - anti-cardiolipin IgA antibody and low titre aβ2GP1 IgA and IgM.	All three had a raised CRP and D-dimer. Two had lymphopaenia, two thrombocytopaenia, one had raised LDH. CT Chest: bilateral pulmonary infiltrates in all three, ground glass opacity in two.	Imaging showed multifocal cerebral infarctions.	All patients were admitted to ITU. One was intubated and mechanically ventilated due to hypoxaemic respiratory failure. There is minimal detail about the other two and no information on mortality.
Zhai[73] - 1 case	79-year-old male, no comorbidities reported, with a 6-day history of a slight cough developed right hemiparesis and dysarthria due to tongue deviation	RT-PCR positive on throat swab	Negative for influenza virus, adenovirus, coxsackievirus, CMV and mycoplasma pneumoniae. Does not state what sample was tested, nor the test.	Lymphopaenia and eosinophilic granulocytopenia, raised CRP and ESR. Chest CT: bilateral pulmonary parenchymal ground-glass and consolidative pulmonary opacities, with a peripheral distribution.	CT head: lacunar infarct	Treated with antiviral drugs (oseltamivir; ribavirin) and anti-inflammatory drugs (moxifloxacin and dexamethasone). Clopidogrel (75 mg) and atorvastatin (20 mg) were used to treat acute ischemic stroke. After twelve days of treatment, he could "walk normally and communicate with near fluent language". Discharged.
Intracerebral haemorrhage						
Al Saeigh[61] – 1 case, USA	31-year-old man presented after one week of malaise, mild fever, cough and arthralgia with sudden onset of headache and loss of and loss of consciousness. Some confusion after first operation.	RT-PCR positive in nasal swab. CSF RT-PCR negative on two samples.	NR	NR	CT head: subarachnoid haemorrhage in the posterior fossa; subsequent CT showed hydrocephalus; cerebral angiogram showed ruptured dissecting right posterior– inferior cerebellar artery aneurysm	External ventricular drain inserted initially; then flow-diverting stent placed to treat ruptured aneurysm. Intubated for surgery but did not require ongoing ventilator support. Post-operative confusion resolved; discharged for rehabilitation.

Benussi[22] – 3 cases, Italy	3 patients: no disaggregated clinical details provided.	All had positive RT-PCR on a respiratory sample.	NR	COVID-19 positive cerebrovascular disease patients had an increased neutrophil and platelet count, lymphopaenia, higher CRP, ESR, LDH, AST, ALT, PTT and fibrinogen levels compared to negative cerebrovascular patients.	NR	NR
Li[66] – 1 case, China	62-year-old man with history of smoking developed stroke symptoms 9 days after onset of COVID-19 respiratory/systemic symptoms.	RT-PCR positive on throat swab	NR	NR	NR	Died 22 days after the stroke.
Morassi[69] – 2 cases, Italy	Two patients: both 57-year-old men were admitted to hospital with critical COVID-19. At 7 and 11 days later (14 and 17 days after onset of respiratory symptoms - both had cough and fever, one with dyspnoea) they were found to have bilaterally fixed dilated pupils and coma (GCS 3/15).	Both RT-PCR positive on nasopharyngeal swab	NR	Both had raised CRP, LDH, AST and gamma GT. CT chest showed diffuse bilateral ground glass opacities in both patients.	One had bilateral cerebellar haemorrhages on CT brain, with hydrocephalus. The other had a large frontal haemorrhage with displaced ventricles and multiple smaller haemorrhages.	Both developed respiratory failure, requiring intubation and ventilation and admission to ICU. Both deteriorated neurologically, and imaging confirmed cerebral haemmorhage; both died.
Sharifi-Razavi[74] – 1 case, Iran	79-year-old man had acute loss of consciousness and bilateral extensor plantar reflexes 3 days after onset of fever and cough	RT-PCR positive on oropharyngeal swab		Lymphopaenia, raised CRP and ESR. CT chest: ground-glass opacity in the left lower lobe	CT head: massive intracerebral haemorrhage in the right hemisphere, with intraventricular and subarachnoid haemorrhage	NR
Cerebral venous sinus thrombosis						
Li[66] - 1 case, China	32-year-old man with history of smoking developed neurological features 14 days after initial presentation with COVID-19	RT-PCR positive on throat swab	NR	NR	NR	Treated with anticoagulation; survived but remains in hospital.

ADEM = acute disseminated encephalomyelitis; AF = atrial fibrillation; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP=brain natriuretic peptide. CK = creatinine kinase; CKD= Chronic kidney disease; CRP = C-reactive protein; CSF = cerebrospinal fluid; CT = computed tomography; CVST = cerebral venous sinus thrombosis; EBV = Epstein-Barr virus; EEG = electroencephalogram; EMG = electromyography; ESR = erythrocyte sedimentation rate; FLAIR = fluid-attenuated inversion recovery (MRI sequence); GBS = Guillain-Barré syndrome; Hb = haemoglobin; HSV = Herpes Simplex virus; ICU = intensive care unit; IVIG = intravenous immunoglobulin; LFTs = liver function tests; LDH = lactate dehydrogenase; NCS = nerve conduction study; MRI = magnetic resonance imaging; PTT = prothrombin time; RT-PCR = reverse transcription polymerase chain reaction; T2WI= T2-weighted image (MRI sequence); U+Es= urea and electrolytes; VZV= Varicella Zoster virus; WCC = white cell count

Table 9. Neurological disease associated with COVID-19

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