Global uncertainty in the diagnosis of neurological complications of SARS-CoV-2 infection by both neurologists and non-neurologists: An international inter-observer variability study

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Supplementary Material 1

Case definitions for neurological syndromes associated with SARS-CoV-2 infection

Encephalopathy or delirium: Alteration in consciousness, behaviour, personality, and/or cognition, without evidence of brain parenchymal involvement or CNS inflammation. This includes:

- Encephalopathy attributable to metabolic disturbance
- Encephalopathy attributable to fever/sepsis
- Encephalopathy attributable to hypoxia-ischaemia
- **Posterior reversible encephalopathy syndrome (PRES)** – encephalopathy characterised by white matter oedema affecting posterior parietal and occipital lobes.
- Malignant cerebral oedema

Encephalitis: New-onset encephalopathy with **evidence of inflammation in the CNS** (cerebrospinal fluid white cell count >4/ml, protein >0.45g/dL, or MRI consistent with parenchymal inflammation) and/or clinical or electrophysiological **evidence of brain parenchymal involvement** (such as focal neurological deficit, new-onset seizure, or focal changes on EEG).
This includes:

- Viral encephalitis due to SARS-CoV-2 (e.g. CSF or tissue positive by PCR or synthesis of intrathecal antibody)
- Viral encephalitis due to other viral pathogens (e.g. CSF PCR positive Herpes simplex virus)
- **Acute Disseminated Encephalomyelitis (ADEM)-** encephalitis characterised by multiple, asymmetric, poorly demarcated T2-hyperintense lesions on the MRI
- **Acute Haemorrhagic Leukoencephalitis**- characterised by inflammation of the venules and haemorrhagic changes

Hypoxic brain injury: evidence of hypoxic damage to the brain on imaging, resulting from generalised body hypoxia. May be associated with hypoxic encephalopathy

Meningitis: One or more of headache, fever, meningism (neck stiffness, photophobia, positive Kernig's or Brudzinski's signs) in the absence of significant encephalopathy; with **evidence of inflammation in the CNS** (such as cerebrospinal fluid white cell count >4/ml, protein >0.45g/dL, or MRI consistent with meningeal inflammation). Meningitis with evidence of brain parenchymal involvement indicates meningoencephalitis.

Central demyelination: Acute neurological symptoms and signs associated with typical neuroimaging features on MRI best attributed to demyelination in the central nervous system (e.g. T2-hyperintense lesions), with or without oligoclonal bands in CSF/serum

Myelitis: Weakness and/or sensory disturbance of the limbs, attributable to a spinal cord lesion, with **evidence of inflammation in the CNS** (cerebrospinal fluid white cell count >4/ml, protein >0.45g/dL, oligoclonal bands, or MRI consistent with spinal inflammation – e.g. T2-hyperintense lesions). Supporting symptoms and signs include brisk reflexes or extensor plantar response, bladder or bowel dysfunction or clearly defined sensory level.

Seizures: New-onset convulsive or non-convulsive seizures thought to be attributable to COVID-19. (Not typically seizures provoked by infection in someone with pre-existing epilepsy – unless their epilepsy presentation is radically novel- e.g. refractory status epilepticus)

Cerebrovascular disease and stroke: Symptoms, signs, and neuroimaging consistent resulting from occlusion or injury of blood vessels supplying the central nervous system. Includes:

- Transient ischaemic attack (symptoms/signs <24 hours)
- **Ischaemic stroke** – occlusion of large or small arteries (lacunar stroke)
- **Intracerebral haemorrhage** – bleeding into brain parenchyma
- **Subarachnoid haemorrhage** – bleeding into subarachnoid space
- **Cerebral vasculitis/ vasculitic stroke** – evidence of angiographic beading and/or inflammation in CSF and/or clinical suspicion of vasculitis
- **Cerebral venous sinus thrombosis** – occlusion of cerebral venous system
- **Cerebral microangiography** – damage and/or occlusion of smallest arteries, arterioles, capillaries and venules of the brain

Headache: New-onset headache disorder not attributable to an exacerbation of chronic disorder (e.g. migraine) or an alternative neurological diagnosis (e.g. meningitis)**.**

Movement Disorder/ Parkinsonism: New onset movement disorder, such as parkinsonism (rigidity, bradykinesia, pill-rolling rest tremor), chorea, dystonia, myoclonus, athetosis and others.

Cranial nerve palsy: symptoms and signs resulting from dysfunction of one or more cranial nerves, not attributable to another neurological disease. This does not include simple anosmia associated with COVID-19.

Anosmia/ ageusia: loss of smell and/or taste not attributable to another neurological disease

Guillain-Barre syndrome and variants: symptoms and signs attributable to peripheral nerve pathology of immune origin. In Guillain-Barré syndrome this usually manifests as ascending, areflexic sensorimotor flaccid paralysis; in Miller-Fisher syndrome as ophthalmoplegia, ataxia, and areflexia.

Compression or critical illness neuropathy: sensory and/or motor symptoms and signs attributable to peripheral nerve damage secondary to critical illness (e.g. prolonged ITU admission) and not to specific neurological disease

Neuromuscular junction disorder: Primarily fatigable weakness disorder with supportive electrophysiology, antibody-status, or convincing clinical diagnosis. This includes Myasthenia gravis (e.g. neurophysiological evidence of decremental responses, jitter on single-fibre EMG, and/or positive acetylcholine receptor/MUSK antibody) and Lambert-Eaton syndrome (e.g. neurophysiological evidence of incremental responses and/or positive voltage-gated calcium channel antibody).

Myopathy or myositis: Motor symptoms and/or signs attributable to muscle damage (myopathy) and/or inflammation (myositis) with elevation of peripheral muscle enzymes (e.g. creatinine kinase-CK).

Autonomic dysfunction: signs or symptoms of autonomic nervous system dysfunction, such us labile blood pressure or heart rate, or dysfunction of bladder or bowel emptying

Psychiatric syndromes: A new presentation of a significant mental health symptom, such as psychosis, or a significant change in someone with an existing mental health disorder. This includes: psychosis, major depression, mania, anxiety, obsessive-compulsive or related syndrome, tics, catatonia, impulse control syndrome, neurocognitive (dementia-like) syndrome, personality change, apathy, chronic fatigue, post-traumatic stress disorder, functional neurological disorder, other dissociative syndromes.

Dysexecutive syndrome: dysfunction in processing and response to stimuli and commands, in patient off-sedation

Neurocognitive changes: new onset deficit in cerebral higher function, such as, but not limited to perception, judgement, cognition, memory, decision-making, and not attributed to another neurological syndrome

Neuroleptic malignant syndrome: syndrome of fever, tachycardia, rigidity and confusion in association with antipsychotic medication.

Abbreviations:
CSF= cerebrospinal fluid, CNS= central nervous system, EEG= electroencephalogram, EMG= electromyography, ITU= intensive care unit, MRI= magnetic resonance imaging

Case definitions for association ranks between neurological syndromes and SARS-CoV-2 infection

	Confirmed	Probable	Possible	Unlikely
Temporal Relationship	Neurological syndrome in temporal relationship with SARS-CoV-2 infection	Neurological syndrome in temporal relationship with SARS-CoV-2 infection	Neurological syndrome in temporal relationship with SARS-CoV-2 infection	No temporal relationship between neurological syndrome and SARS-CoV-2 infection
	AND	AND	AND	OR
Evidence of SARS-CoV-2 infection	SARS-CoV-2 virus detected in cerebrospinal fluid or brain tissue or SARS-CoV-2-specific intrathecal antibody	SARS-CoV-2 virus detected in respiratory or other non-CNS sample or evidence of SARS-CoV-2-specific antibody in serum indicating acute infection	Clinical or radiological suspicion of SARS-CoV-2 infection without laboratory evidence	No laboratory, radiological or clinical suspicion of SARS-CoV-2 infection
	AND	AND	OR	
Evidence of alternative aetiology	Absence of alternative aetiologies and/or risk factors	Absence of alternative aetiologies and/or risk factors	Presence of alternative aetiologies and/or risk factors	

Supplementary material 2

Case vignettes

Case 1
A 54-year-old man presented with a one-week history of sore throat, dysgeusia, and hyposmia, followed by a language disturbance that developed earlier in the morning and manifested as a word-finding difficulty. He had a past medical history of hypertension and dyslipidaemia, managed with irbesartan and simvastatin. He worked as a hospital clerk and lived with his wife. His vital signs revealed a temperature of 37.5°C, respiratory rate of 22 breaths per minute and oxygen saturation of 93%. Neurological examination revealed expressive aphasia and mild ideomotor slowing without further cognitive alterations. His speech was slow, effortful, and contained phonological and neological paraphasias. He was able to follow commands and was oriented to time, but not to the place. His Glasgow Coma Scale was M6, V4, E4. The remainder of the neurological examination was normal with no focal neurological signs. The patient underwent a multimodal CT assessment, which was unrevealing. Electroencephalogram (EEG) and brain MRI were also unremarkable. Arterial blood gas analysis and blood tests showed hypocapnic hypoxemia. Laboratory results were notable of an elevated D-dimer level, lymphopenia, and elevated inflammatory markers. COVID-19 was diagnosed on the basis of bilateral interstitial pneumonia on a chest computed tomography (CT) scan. Cerebrospinal fluid (CSF) examination showed a normal protein, glucose and nucleated cells 2/mm2. Microbiology and virology analysis of CSF was unremarkable, including negative RT-PCR for SARS-CoV-2. *Modified from: Pensato U, Muccioli L, Pasini E, et al. Frontiers in neurology. 2020 Oct 19;11:1123.*
Case 2
A 60-year-old man presented with a three-day history of acute onset right eye ptosis and diplopia. He also complained of a right hemicranial headache. There was no eye pain, fever or respiratory symptoms. Two months earlier he had developed right facial weakness that was treated with antivirals. He had diabetes mellitus for ten years which was well controlled with oral hypoglycaemic medications. He did not have any other comorbidity. At admission, his vitals were stable with a blood pressure of 130/86 mmHg. Neurological examination revealed a non-fatigable right eye ptosis. Right eye abduction was normal, but the rest of the right eye movements were limited. Pupils were 2mm each and reactive to light bilaterally. The left eye had normal movements. There was an associated right eye altitudinal field defect and a right lower motor neuron facial weakness. Facial sensation, taste sensation and bulbar movements were normal and so was the limb examination. Investigations revealed a positive nasopharyngeal swab for SARS-CoV-2. Fasting and postprandial blood sugars were raised, in keeping with his diagnosis of diabetes mellitus. Complete blood count, renal and hepatic function tests, lipid profile and d-dimer were normal. Cerebrospinal fluid analysis showed no cells, normal protein, and glucose. MRI brain was also within normal range.
Case 3
A 32-year-old man with a history of a tension-type migraine presented with headache, generalized weakness, dizziness, nausea, and vomiting that started in the morning the previous day. The patient described a severe, sudden-onset headache located over the left temple and sudden acute vertigo. His headache was constant and more severe than his normal migraine headaches. He denied fever, changes in vision, rash, or neck stiffness. He had no shortness of breath or cough. He was not on any regular medications. He lived with his parents who had both tested positive for SARS-Co-V2. His vital signs were unremarkable, and he was alert and oriented. His neurologic examination was notable for decreased sensation over the left temple, left upper extremity ataxia and dysmetria, and rotary nystagmus. Gait and the remainder of the neurological examination were normal.

Laboratory work revealed lymphopenia and elevated d-dimer of 2443 ng/mL (normal range 0–230 ng/mL). C-reactive protein was elevated to 1.7 mg/dL (range 0.0–0.9 mg/dL). He had mildly elevated glucose at 121 mg/dL (normal range 70–110 mg/dL). Urine and drugs screen and remainder of the biochemical profile were unremarkable. The PCR on the nasopharyngeal swab was positive for SARS-CoV-2. CT head without contrast showed a geographic hypoattenuation throughout the left inferior cerebellar hemisphere. A magnetic resonance imaging (MRI) brain with and without contrast was performed shortly thereafter and confirmed these results.

Modified from: Quenzer F, Smyres C, Tabarez N, et al. The Journal of emergency medicine. 2021 Feb 9.

Case 4

A 59-year-old female healthcare worker whose only co-morbidity was obesity presented with acute-onset progressive flaccid paraplegia of both lower limbs along with retention of urine and high-grade fever for four days. She had no shortness of breath or cough.

On admission, she was febrile and tachycardic with oxygen saturation of 95% on room air. She had paraplegia with profound hypotonia of both lower limbs. Her deep tendon reflexes of lower limbs were absent with bilateral mute plantar response. All modalities of sensation were diminished below the T10 segmental level. Higher function tests and cranial nerve examination revealed no abnormality and neurological examination including the deep tendon reflexes of the upper limbs were within normal limits.

Her complete blood count was within normal limits. Viral serology for hepatitis B, hepatitis C and HIV were negative. Her renal and liver function tests and chest X-ray were normal. Nasopharyngeal and oropharyngeal swab for SARS-CoV-2 was positive. MRI T2-weighted imaging of the dorsal spine revealed hyperintensity in the spinal cord at T6–T7 vertebral level. A cerebrospinal fluid (CSF) revealed white cell count of 5x10^6 (normal < 5x10^6), protein of 71.4mg/dL (normal 15-45 mg/dL), normal glucose, negative bacterial culture and virology panel, including negative RT-PCR for SARS-CoV-2.

Modified from: Chakraborty U, Chandra A, Ray AK, et al. BMJ Case Reports CP. 2020 Aug 1;13(8):e238668.

Case 5

A 35-year-old man presented with a 2-hour history of sudden-onset dysphasia, mild confusion and right arm incoordination. On arrival to the hospital, severe expressive and receptive dysphasia remained evident. No symptoms were noted in other systems. The patient had a medical history of migraines only, no regular medication and was a current smoker. An initial CT brain showed no abnormalities and the patient received thrombolysis for a suspected ischaemic stroke. His symptoms resolved over approximately two hours following thrombolysis and he was admitted to the stroke ward for observation. A routine nasopharyngeal swab on admission was positive for SARS-CoV-2.

On day three, the patient again developed sudden-onset expressive and receptive dysphasia, alongside amnesia, right arm weakness and headache. Later the same day, he developed pyrexia of 39.7°C, but had no respiratory symptoms and signs. Repeated blood tests showed lymphopenia. Chest radiograph showed no evidence of infection. An MRI brain was performed which was reported as normal.

On day four, a lumbar puncture was performed which had a raised opening pressure of 24cm/H2O with a clear appearance of cerebrospinal fluid (CSF). CSF white cell count was 134 x10^6/L (99% lymphocytes; normal <5), protein of 0.52 g/L (normal 0.15-0.45 g/L), and CSF: serum glucose ratio of 0.73 (normal). CSF bacterial culture was negative and so was polymerase chain reaction for Neisseria meningitides, Streptococcus pneumoniae and several viruses including herpes simplex virus, varicella-zoster virus, enterovirus and parechovirus. However, PCR of the CSF was positive for SARS-CoV-2 RNA. An MR angiogram was performed which was normal. The electroencephalography demonstrated excess slow waves, which was not explained by

medications or systemic disease On day five the patient had ongoing amnesia and pyrexia but by eight days was deemed to have made a full recovery and discharged.

Case 6

A 6-week-old term male infant presented for evaluation after one day of cough, fever, and brief episodes of sustained upward gaze associated with bilateral leg stiffening. There was no shaking, breathing change, or pallor during this episode. The infant had two siblings with cough and fever at the time of presentation.

Vital signs were notable for fever of 38.4°C and mild hypertension (114/57 mmHg) with a mottled appearance. The anterior fontanel was soft and non-bulging, and neurologic examination was unremarkable. However, the patient had a witnessed episode of sustained upward gaze associated with bilateral leg stiffening and decreased responsiveness lasting 10 seconds with subsequent return to baseline and no hypoxia or vital signs change.

Laboratory results were notable for leukopenia with a normal differential and elevated procalcitonin. Electrolytes were normal. The respiratory pathogen PCR panel was positive for rhinovirus/enterovirus. A SARS-CoV-2 PCR was also positive. A chest radiograph was not performed. A lumbar puncture had an unremarkable cerebrospinal fluid (CSF) profile. CSF meningitis/encephalitis PCR panel and bacterial culture were negative. CSF testing did not detect SARS-CoV-2.

The patient was connected to long-term EEG monitoring which showed an excess of temporal sharp transients for age and intermittent vertex delta slowing with normal sleep-wake cycling. MRI of the brain with and without contrast to rule out a corresponding structural lesion was normal. The patient was discharged home after one day of admission without further fever or events on follow-up 1 week later.

Modified from: Dugue R, Cay-Martínez KC, Thakur KT, et al. Neurology. 2020 Jun 16;94(24):1100-2.

Case 7

A 32-year-old man with no past medical history suffered from flu-like symptoms for ten days, having tested positive for SARS-CoV-2. He presented to hospital with generalized aches and severe headaches for two days, which were worse on lying flat and on coughing. He also had mild tinnitus with no visual obscurations. On examination, the patient had left upper limb numbness and slurred speech. The cranial nerves and the motor examination were intact and normal coordination was observed. There was no fever and no signs of meningeal irritation.

Brain imaging showed poor contrast opacification with filling defect in the straight sinus, right transverse, and sigmoid sinus with associated right thalamus venous infarction. General laboratory blood tests were unremarkable. A lumbar puncture was not undertaken.

Case 8

A 47-year-old woman developed headache, cough and lethargy, followed by tingling and numbness of all extremities three days later. This ascended to the waist from lower limbs and up to elbows in upper limbs symmetrically. On day five, she got weakness of all four limbs and on day seven, she developed difficulty swallowing and was admitted to hospital. She had a past medical history of multinodular goitre. Her only medication was thyroxine.

On admission, she had a low-grade fever. The remainder of her vitals were normal, with Glasgow Coma Scale of 15. Her chest X-ray on admission revealed bilateral lower zone ground-glass opacifications. The admission blood test showed raised white cell count, raised neutrophil count, CRP of 95 mg/L (normal < 5) and D-dimer of 5.05 ug/L (normal 0-0.5). Lumbar puncture showed: normal opening pressure, raised protein at 100 mg/dL (normal range 35 – 45 mg/dL), glucose 65% of blood glucose (within range), no white cells and normal cytology.

During the course of admission, the patient had bilateral facial palsy, bulbar palsy requiring nasogastric tube feeding, areflexic quadriparesis with limb power 2-3/5 and autonomic dysfunction evidenced by hypertension, tachycardia and urinary retention. On day 2, her oxygen saturations dropped to 92% and she was given oxygen 5 L/minute via a face mask. She did not require ventilatory support or admission to a higher care setting. She was at her peak for three more days and then gradually improved. Her nerve conduction studies done on day 16 showed demyelination.

Case 9

A 37-year-old female, with prior history of episodic migraine and peptic ulcer disease presented with a change in her usual headache. She described an increase in the frequency, which tended to occur twice per month to a near-daily headache, with no clear circadian pattern. The headache was pressure-like, bilateral, located in the forehead and around the eyeballs. On a 0-10 scale, the intensity was around 8, with severe interference in her daily activities. Together with the headache, she had mild photophobia and nausea, but no neck stiffness.

She attributed the worsening to the lockdown and the COVID-19 illness of her sister. When she was specifically questioned, she described concomitant arthralgia, myalgia, dry cough, and anosmia. She had not examined herself for fever. On the examination, she had borderline tachypnoea and pyrexia, with a temperature of 37.7ºC. Her general exam and neurological exam were both normal, including fundus examination. Her blood tests showed lymphopenia of 500 x 109 / L lymphocytes (Normal range >1500 x 109 / L), mildly raised D-dimer of 750 U (normal <500 U), and mildly raised C-Reactive Protein of 15 mg/L (Normal range <5mg/L). Her chest X-ray was normal, and a cranial MRI with contrast was also within the normal range.

Her headache persisted for one week, without any other neurological symptoms or signs. It then gradually improved and two weeks after the onset of the symptoms, she became asymptomatic.

Case 10

A 37-year-old married man with two young children experienced a 5-day history of fever, cough, breathlessness, and myalgia. This was accompanied by severe insomnia and anxiety that he may infect his family with SARS-CoV-2. The patient worked as a mental health nurse and had recently lost several patients to COVID-19. He had no notable medical or psychiatric history and took no regular medications.

On day 5, he became increasingly confused and began acting bizarrely. He reported that he had both seen and heard the devil and was also observed responding to auditory hallucinations. In a phone call with a family member, he was reported as being ‘paranoid’. He was also incontinent of urine. The next day, he went to the bathroom, stating he would wash to avoid infecting his family. On investigating loud noises, his wife found that the patient had lacerated his neck and jumped from an upstairs window. Emergency service attended the scene; the patient was sedated, intubated, resuscitated and transferred to a trauma centre.

CT imaging of the patient’s neck and chest confirmed a tracheal injury and ground glass opacification and consolidation in keeping with moderate COVID-19. A CT of the head revealed no intracranial pathology. Laboratory results revealed an elevated white cell count with lymphopenia. The remainder of blood tests, including the toxicology screen, were all negative. A SARS-CoV-2

PCR test was positive. During his subsequent intensive care admission, a repeat CT of the head, cerebrospinal fluid (CSF) studies (lactate, glucose, protein, microscopy, cytology, flow cytology and NMDA receptor antibodies) and serology tests (CASPPR2, LGI1, voltage-gated potassium channel and NMDA receptor antibodies, HIV and syphilis) were all negative.

Following a tracheal and orthopaedic surgery, the patient had a prolonged hospital stay. He eventually made a good recovery but had limited recollection of the events leading up to admission, other than recalling severe worry about SARS-CoV-2 infection and insomnia. He showed no further suicidality or signs of disease recurrence.

Modified from Gillett G & Jordan I. BMJ Case Reports CP 13.10 (2020): e239191.