THE CNS/PNS & SARS-COV-2

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Rapid Review

Neurological associations of COVID-19

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Summary

Background The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is of a scale not seen since the 1918 influenza pandemic. Although the predominant clinical presentation is with respiratory disease, neurological manifestations are being recognised increasingly. On the basis of knowledge of other coronaviruses, especially those that caused the severe acute respiratory syndrome and Middle East respiratory syndrome epidemics, cases of CNS and peripheral nervous system disease caused by SARS-CoV-2 might be expected to be rare.

Recent developments A growing number of case reports and series describe a wide array of neurological manifestations in 901 patients, but many have insufficient detail, reflecting the challenge of studying such patients. Encephalopathy has been reported for 93 patients in total, including 16 (7%) of 214 hospitalised patients with COVID-19 in Wuhan, China, and 40 (69%) of 58 patients in intensive care with COVID-19 in France. Encephalitis has been described in eight patients to date, and Guillain-Barré syndrome in 19 patients. SARS-CoV-2 has been detected in the CSF of some patients. Anosmia and ageusia are common, and can occur in the absence of other clinical features. Unexpectedly, acute cerebrovascular disease is also emerging as an important complication, with cohort studies reporting stroke in 2–6% of patients hospitalised with COVID-19. So far, 96 patients with stroke have been described, who frequently had vascular events in the context of a pro-inflammatory hypercoagulable state with elevated C-reactive protein, D-dimer, and ferritin.

Where next? Careful clinical, diagnostic, and epidemiological studies are needed to help define the manifestations and burden of neurological disease caused by SARS-CoV-2. Precise case definitions must be used to distinguish non-specific complications of severe disease (eg, hypoxic encephalopathy and critical care neuropathy) from those caused directly or indirectly by the virus, including infectious, para-infectious, and post-infectious encephalitis, hyper-

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- Before identification of SARS-CoV-2, **six** coronaviruses were known to infect humans.
- **Four of these coronaviruses** :

-Seasonal, predominantly mild respiratory illness, and have a high incidence globally, accounting for 15–30% of upper respiratory tract infections.

- **The other two coronaviruses :**

Major epidemics with deaths principally from respiratory disease; severe acute respiratory syndrome (SARS) was caused by SARS-CoV in 2002–03, and Middle East respiratory syndrome (MERS) by MERS-CoV in 2012 .

- Both associated with occasional disease of the **CNS** and **PNS** Both CNS and PNS disease were reported following SARS.
- SARS-CoV was detected in CSF by RT-PCR in two of three cases of encephalopathy with seizures and was cultured from brain tissue at autopsy.

NEUROLOGICAL CASES PER COUNTRY

	SARS case count (n=8096)	MERS case count (n=2228)	COVID-19 worldwide minimum case count (n=4 872 308)		COVID-19 minimum case count in China (n=84 500)		COVID-19 minimum case count in USA (n=1 464 232)		COVID-19 minimum case count in UK (n=246 410)	
			Extrapolated from SARS (95% CI)	Extrapolated from MERS (95% CI)	Extrapolated from SARS (95% CI)	Extrapolated from MERS (95% CI)	Extrapolated from SARS (95% CI)	Extrapolated from MERS (95% CI)	Extrapolated from SARS (95% CI)	Extrapolated from MERS (95% CI)
Patients with CNS disease (proportion of total coronavirus cases [95% CI])	3 (0·04% [0·01–0·10])	5 (0·20% [0·06–0·50])	1805 (370–5277)	9671 (3143–22539)	31 (6–92)	168 (55–391)	543 (111–1586)	2906 (944–6774)	91 (19–267)	489 (159–1140)
Patients with PNS disease (proportion of total coronavirus cases [95% CI])	4 (0·05% [0·01–0·13])	4 (0·16% [0·04–0·41])	2407 (658–6163)	7737 (2110–19786)	42 (11–107)	134 (37–343)	723 (198–1852)	2325 (634–5946)	122 (33–312)	391 (107–1001)
Total patients with neurological disease (proportion of total coronavirus cases [95% CI])	7 (0·09% [0·03–0·18])	9 (0·36% [0·16–0·68])	4213 (1028–11440)	17408 (5252–42326)	73 (18–198)	302 (91–734)	1266 (309–3438)	5231 (1578–12720)	213 (52–579)	880 (266–2141)

Calculated using data available up to May 19, 2020. COVID-19 cases based on Johns Hopkins COVID-19 Dashboard. 95% CI calculated with Clopper-Pearson exact method[14] for proportions using Ausvet Epitools. SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. PNS=peripheral nervous system.

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

CONT

- Given the 4·8 million cases of COVID-19 globally, these prevalences project to a total of **1805–9671 patients with CNS complications** and **2407–7737 with PNS complications**.

- These numbers, which do not include the increasingly important syndromes of stroke-associated COVID-19 infection, will rise as the pandemic continues.

CASE DEFINITION FOR COVID 19 AND NEUROL. DISEASES

Panel: Provisional case definitions for the association of COVID-19 with neurological disease

WHO COVID-19 case definitions[15]

Confirmed

A person with laboratory confirmation[21] of SARS-CoV-2 infection, irrespective of clinical signs and symptoms; confirmatory tests include a nucleic acid amplication test (eg, RT-PCR) or validated antibody test; in an area with established circulation of virus, there should be one positive RT-PCR test or identification of virus on sequencing (one or more negative tests do not rule out infection if there is clinical suspicion); and in an area without established circulation of virus, there should be one positive RT-PCR test for two different viral genome targets or one positive result with partial or whole genome sequencing

Probable

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

Suspected

(1) A patient with acute respiratory illness (fever and at least one sign or symptom of respiratory distress) and history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days before onset; or (2) a patient with acute respiratory illness who has been in contact with a confirmed or probable case in the last 14 days before symptom onset; or (3) a patient with severe acute respiratory illness that requires hospitalisation, and in the absence of an alternative explanation that fully explains the clinical presentation

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

Confirmed

(1) SARS-CoV-2 detected in CSF or brain tissue† or evidence of SARS-CoV-2-specific intrathecal antibody; and (2) no other explanatory pathogen or cause found

Probable

(1) SARS-CoV-2 detected in respiratory or other non-CNS sample,‡ or evidence of SARS-CoV-2-specific antibody in serum indicating acute infection;§ and (2) no other explanatory pathogen or cause found

Possible

Patient meets suspected case definition of COVID-19 according to national or WHO guidance on the basis of clinical symptoms and epidemiological risk factors; in the context of known community SARS-CoV-2 transmission, supportive features include the following: the new onset of at least one of cough, fever, muscle aches, loss of smell, or loss of taste; lymphopenia or raised D-dimer level; and radiological evidence of abnormalities consistent with infection or inflammation (eg, ground glass changes)

Acute disseminated encephalomyelitis* associated with SARS-CoV-2 infection, Guillain-Barré syndrome,* and other acute neuropathies associated with SARS-CoV-2 infection

Probable association

(1) Neurological disease onset within 6 weeks of acute infection; and (2) either SARS-CoV-2 RNA detected in any sample or antibody evidence of acute SARS-CoV-2 infection; and (3) no evidence of other commonly associated causes

Possible association

(1) Neurological disease onset within 6 weeks of acute infection; and (2) either SARS-CoV-2 RNA detected in any sample or antibody evidence of acute SARS-CoV-2 infection; and (3) evidence of other commonly associated causes¶

Stroke* associated with SARS-CoV-2 infection

Probable association

(1) Either SARS-CoV-2 detected in CSF or other sample,‡ or evidence of SARS-CoV-2-specific antibody in serum indicating acute infection; and (2) no other known traditional cardiovascular risk factors‖

Possible association

(1) Either SARS-CoV-2 detected in CSF or other sample, or evidence of SARS-CoV-2-specific antibody indicating acute infection; and (2) other traditional cardiovascular risk factors‖

These case definitions are suggestions based on published information to date; they are likely to need refining as more data emerge. The terms confirmed, probable, and suspected are used in the WHO COVID-19 case definitions; the terms confirmed, probable, possible, probable association, and possible association reflect the terminology used for the different syndromes in the original publications from which this panel derives.[15,20] SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *Definitions for the different neurological diseases and syndromes are in the appendix (pp 5–12). †Detection in CSF or brain tissue by PCR, culture, or immunohistochemistry, as appropriate. ‡Detection in non-CNS sample by PCR or culture. §Serological evidence of acute infection can be defined as detection of IgM, IgG seroconversion, or an increase of four times in antibody titres in paired acute and convalescent serum samples. ¶These include infection with one of Campylobacter jejuni, Mycoplasma pneumoniae, Cytomegalovirus, Epstein-Barr virus, hepatitis E virus, Zika virus, or HIV, or vaccination in the last 6 weeks. Associated causes might differ depending on geographical location. ‖Traditional cardiovascular risk factors include hypertension, current smoker, diabetes, hypercholesterolaemia, and atrial fibrillation.

ENCEPHALITIS

- Clinical evidence of brain inflammation is accepted : a CSF pleocytosis, imaging changes, or focal abnormalities on EEG.
- Detection of virus in the CSF per se does not provide a diagnosis of encephalitis if there is no evidence of brain inflammation.

CASES RECORDED : ENCEPHALITIS

	Clinical presentation	SARS-CoV-2 diagnostics	Other pathogen and antibody investigations	Relevant blood tests and radiology findings	Neurological investigations (CSF findings, neuroimaging, neurophysiology)	Management, progress, and outcome
CNS disease						
Encephalitis						
Moriguchi et al;[31] one case, Japan	Man aged 24 years, 9 days of fatigue, headache, fever, sore throat; then generalised seizures, reduced consciousness, and meningism	RT-PCR was negative in nasopharyngeal swab; positive in CSF	Serum: anti-HSV-1 and VZV IgM antibodies tests were negative	Increased blood white cell count, neutrophil dominant, relatively decreased lymphocytes, increased CRP; chest CT: small ground glass opacity in right upper zone and bilaterally in lower zones	CSF: clear, colourless, raised opening pressure (320 mm H_20) and cell count (12/mm^3; ten mononuclear and two polymorphonuclear cells); head CT: no brain oedema; brain MRI: hyperintensity along wall of right lateral ventricle on diffusion-weighted imaging, and hyperintense signal in right medial temporal lobe and hippocampus on T2-weighted images	Treated empirically for bacterial pneumonia and viral encephalitis; on admission, required intubation and mechanical ventilation because of seizures; admitted to ICU; still on intensive care at time of report (day 15)

CASES CONT.

Sohal et al;[32] one case, USA	Man aged 72 years with weakness and light headedness following a hypoglycaemic episode; shortly after admission he had difficulty breathing and altered mental status; on day 2 of admission he started to have seizures	RT-PCR was positive; source not specified	Blood: culture was negative for bacterial growth; influenza PCR was negative	Arterial blood gas test: pH 7·13, PaO_2 68 mm Hg, PCO_2 78 mm Hg, raised brain natriuretic peptide, troponin, CRP, LDH; lymphopenia, and leucopenia; chest x-ray: normal; chest CT: bibasilar opacities along with right lower lobe consolidation	Head CT: no acute changes, chronic microvascular ischaemic changes; 24-h EEG: six left temporal seizures and left temporal sharp waves that were epileptogenic	Required intubation and ventilation and was admitted to ICU; became hypotensive requiring norepinephrine via central line; hydroxychloroquine and azithromycin were started in addition to vancomycin and piperacillin tazobactam; after onset of seizures, treated with levetiracetam and valproate but they were not controlled; died on day 5 of illness
Wong et al;[33] one case, UK	Man aged 40 years with ataxia, diplopia, oscillopsia, and bilateral facial weakness (rhombencephalitis); 13 days before he had fever and progressive shortness of breath on exertion, followed 10 days later by a productive cough and diarrhoea	RT-PCR was positive in nasopharyngeal swab; CSF RT-PCR was not done	Blood: negative for hepatitis A, B, and C, HIV-1 and HIV-2, and syphilis antibody; CSF: bacterial culture was negative; anti-MOG-IgG antibody and anti-aquaporin 4 antibody test results not reported	Normal white cell count but lymphopenia; raised CRP and abnormal raised liver function tests; chest x-ray: right lower zone consolidation; liver ultrasound: inflammatory diffusely hypoechoic liver with raised periportal and pericholecystic echogenicity	Normal cell count and protein (0·42 g/L); brain MRI: increased signal lesion in right inferior cerebellar peduncle extending to involve a small portion of the upper cord (lesion 13 mm in maximum cross-sectional area and 28 mm in longitudinal extent); swelling at the affected tissue and associated micro-haemorrhage	Treated with oral amoxicillin, but no other treatment; gradual improvement in neurological symptoms; discharged home after 11 days on gabapentin; oscillopsia and ataxia persisted

CASES CONT.

	Clinical presentation	SARS-CoV-2 diagnostics	Other pathogen and antibody investigations	Relevant blood tests and radiology findings	Neurological investigations (CSF findings, neuroimaging, neurophysiology)	Management, progress, and outcome
(Continued from previous page)						
Helms et al;[35] 49 cases, France	40 patients had agitation; 26 of the 40 evaluated had confusion, 39 had corticospinal tract signs, 15 had a dysexecutive syndrome at discharge, and seven had history of neurological disorders, including transient ischaemic attack, partial epilepsy, and mild cognitive impairment	RT-PCR was positive for all patients' nasopharyngeal samples; negative RT-PCR in CSF in seven patients	NR	NR	In seven patients who had CSF analysis, none had pleiocytosis, two had matched oligoclonal bands, and one had raised protein; in 13 patients who had brain MRI, eight had enhancement in leptomeningeal spaces; in 11 patients who had perfusion imaging, all had bilateral frontotemporal hypoperfusion, two patients had acute ischaemic stroke, and one had subacute ischaemic stroke; in eight patients who had EEG, one had diffuse bifrontal slowing	All patients required treatment on ICU for severe COVID-19; 45 had been discharged from ICU at the time of writing

CASES CONT.

Mao et al;[36] 16 cases, China	16 patients were hospitalised with COVID-19 and had impaired consciousness; one had a seizure characterised by a sudden onset of limb twitching and loss of consciousness, lasting 3 min	RT-PCR was positive in all patients' throat swabs	NR	Patients with CNS disease and severe respiratory disease had lower lymphocyte levels and platelet counts and higher blood urea nitrogen levels than those without CNS symptoms	NR	13 patients had severe respiratory disease and three had non-severe respiratory disease, according to American Thoracic Society guidelines; no further details
Poyiadji et al;[37] one case, USA	Female patient with cough, fever, and altered mental status; imaging consistent with acute necrotising encephalopathy	RT-PCR was positive in nasopharyngeal swab; CSF RT-PCR not done	CSF: bacterial culture negative after 3 days and tests for HSV, VZV, and WNV were negative	NR	Non-contrast head CT: symmetric hypoattenuation in bilateral medial thalami; brain MRI: T2 FLAIR hyperintensity in bilateral medial temporal lobes, thalami, and subinsular regions, and evidence of haemorrhage indicated by hypointensity on susceptibility-weighted images and rim enhancement on post-contrast images	Treated with intravenous immunoglobulin; outcome not reported

MYELITIS

Myelitis						
Zhao et al;[42] one case, China	Man aged 66 years admitted with fever, dyspnoea, and asthma; 5 days after respiratory symptom onset, developed acute flaccid paralysis of lower limbs, urinary and faecal incontinence, and a sensory level at T10	RT-PCR was positive in nasopharyngeal swab	Blood: negative for EBV, influenza A, influenza B, adenovirus, coxsackievirus, parainfluenza virus, CMV, and RSV on serum IgM testing; negative for *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and tuberculosis	Lymphopenia ($0{\cdot}55 \times 10^9$ cells per L) and raised CRP (277 mg/L) and procalcitonin (4·33 ng/mL); slightly raised alanine aminotransferase (56 U/L) and aspartate aminotransferase (50 U/L); chest CT: bilateral patchy changes	Brain CT: lacunar infarcts; spinal imaging not done	On admission, deteriorated rapidly and admitted to ICU; treated with moxifloxacin, oseltamivir, lopinavir–ritonavir, ganciclovir, and meropenem, followed by dexamethasone and intravenous immunoglobulin for neurological symptoms; required oxygen; slight improvement in power in upper and lower limbs following treatment, but still unable to walk; discharged and transferred for rehabilitation

PERIPHERAL NERVOUS SYSTEM

	Clinical presentation	SARS-CoV-2 diagnostics	Other pathogen and antibody investigations	Relevant blood tests and radiology findings	Neurological investigations (CSF findings, neuroimaging, neurophysiology)	Management, progress, and outcome
(Continued from previous page)						
Toscano et al;[44] five cases, Italy	Five patients (four men and one woman), aged 23 to 77 years; four patients had flaccid, areflexic limb weakness (three with quadriparesis and one with paraparesis), three of whom had facial weakness, two had dysphagia, and three developed respiratory failure; one had facial diplegia, areflexia, limb paraesthesia, and ataxia; patients presented a median of 7 (range 5 to 10) days after respiratory symptoms; four had cough, three had fever, three had hyposmia, anosmia, or ageusia, and one had pharyngitis	RT-PCR was positive in nasopharyngeal swab of four patients; one patient was positive by serological test; RT-PCR in CSF was negative in all patients	One patient (patient 5) was negative for *C jejuni*, EBV, CMV, HSV, VZV, influenza, and HIV; three patients were tested for antiganglioside antibodies, but none was detected	Patient 1: CT scan of thorax showed interstitial bilateral pneumonia; patient 2: no details; patient 3: CT scan of thorax showed multiple bilateral, ground glass opacities compatible with interstitial pneumonia; patient 4: chest imaging was negative; patient 5: x-ray and CT showed interstitial pneumonia, without parenchymal opacities or alveolar damage	CSF analysis: all patients had normal white cell counts, three had elevated protein; MRI: enhancement of caudal nerve roots in two patients and of facial nerve in one, and no signal change in two patients; nerve conduction study: axonal pattern in three patients and demyelinating in two	All treated with intravenous immunoglobulin; two had two cycles, and one also had plasma exchange; three required mechanical ventilation; at 4 weeks, two patients were still ventilated in intensive care, two were having physiotherapy, and one was discharged

Guillain-Barré syndrome						
Camdessanche et al;[43] one case, France	Man aged 64 years with 2 days of cough and fever presented following a fall; on day 9 of hospital admission, developed paraesthesia in hands and feet and progressive weakness in all limbs, with areflexia and loss of vibration sense; then developed dysphagia and respiratory insufficiency	RT-PCR was positive in nasopharyngeal swab on admission, 9 days before onset of neurological symptoms	Negative for *Campylobacter jejuni, M pneumoniae, Salmonella enterica*, CMV, EBV, HSV-1, HSV-2 , VZV, influenza virus A and B, HIV, and hepatitis E; serum: antiganglioside antibodies not detected	Chest CT: 10% to 25% ground glass opacities	CSF: normal cell count and raised protein (166 mg/dL); nerve conduction study and electromyography: acute inflammatory demyelinating polyneuropathy	Had initially needed 2L to 3L oxygen via nasal cannula but had been weaned off it before onset of neurological symptoms; given lopinavir–ritonavir; treated with intravenous immunoglobulin for 5 days; developed respiratory insufficiency and required admission to ICU for intubation and mechanical ventilation; no other details given

CVAs

Cerebrovascular disease						
Ischaemic stroke						
Avula et al;[51] four cases, USA	Four patients (aged 73 to 88 years) with hypertension; three had dyslipidaemia, one diabetes and neuropathy, one carotid stenosis, and one chronic kidney disease; three presented with acute new focal neurological deficit (facial droop, slurred speech; left-sided weakness; and right-arm weakness and word finding difficulty), and one with altered mental status; one had fever, respiratory distress, nausea, and vomiting; one had fever only; one had mild shortness of breath with dry cough; one had no respiratory symptoms or fever	All four had positive RT-PCR (presumed to be upper respiratory samples); no mention of CSF studies	Negative blood and urine cultures in the two patients for whom results were reported	Three patients had lymphopenia, one with leucopenia and two with leucocytosis; two had elevated D-dimer and inflammatory markers; three had patchy changes bilaterally on chest x-ray or CT	All four had evidence of unifocal infarcts: three on CT, one on brain MRI	All were treated with antiplatelet therapy; none had thrombolysis or thrombectomy; three required intubation and ventilation, all of whom died; fourth patient discharged to rehabilitation facility

Acute Disseminated Encephalomyelitis

- Multi focal demyelination - occurring weeks after an infection, which generally presents with focal neurological symptoms, often with encephalopathy
- He was treated with dexamethasone and intravenous immunoglobulin, and discharged for rehabilitation.

PERIPHERAL NERVOUS SYSTEM AND MUSCLE DISEASE GUILLAIN-BARRÉ SYNDROME

- An acute polyradiculopathy characterised by rapidly progressive, symmetrical limb weakness, areflexia on examination, sensory symptoms, and, in some patients, facial weakness.

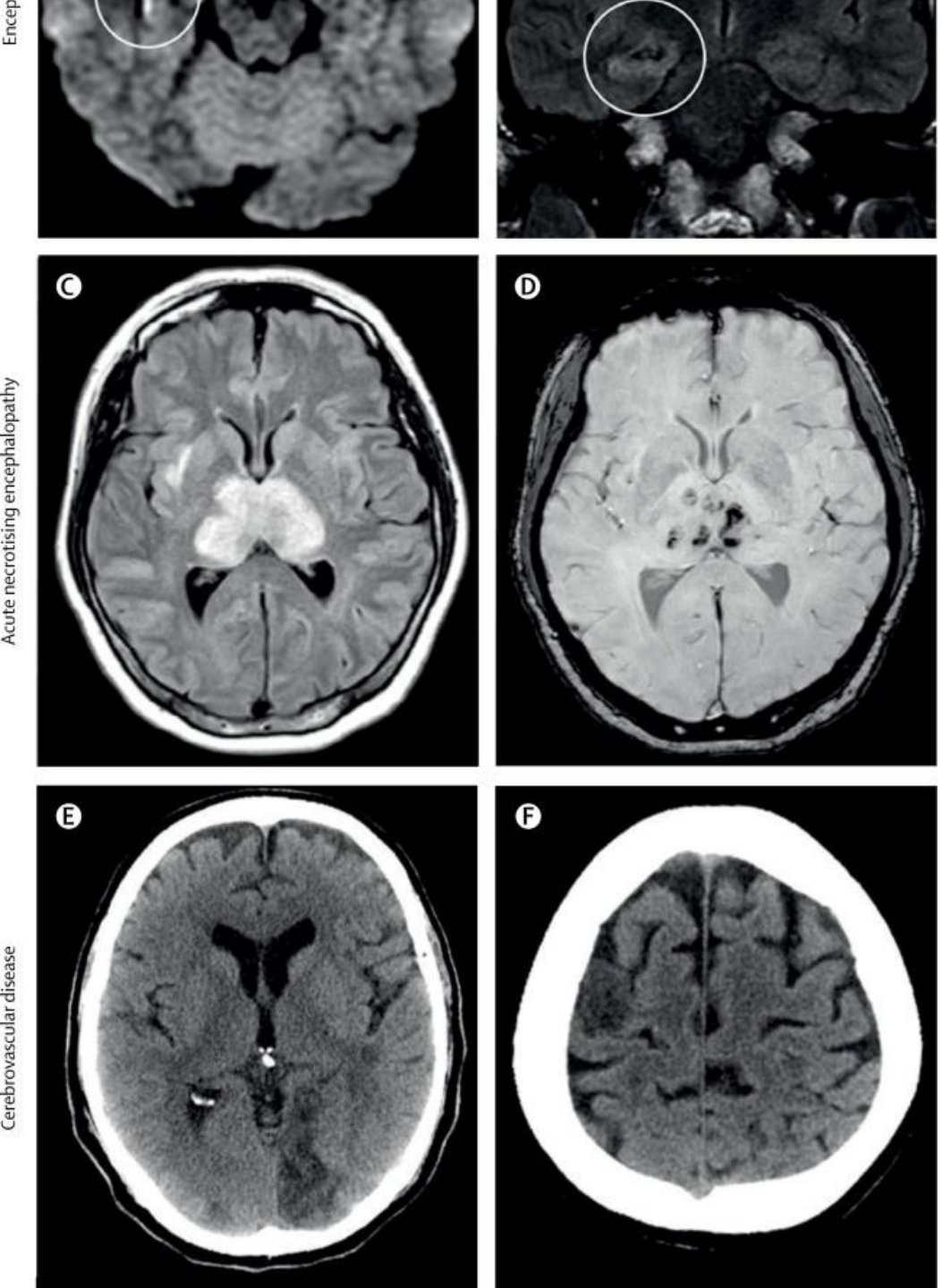
- Neurological symptoms started at a median of 7 days (range –7 to 24) after respiratory or systemic features .

CEREBROVASCULAR ACCIDENTS

- Reported for 13 (6%) of 221 COVID-19 patients in an early retrospective case series from Wuhan:
- **5%** patients developed ischaemic stroke
- **<1%** had intracerebral haemorrhage,
- **<1%** had cerebral venous sinus thrombosis.

CONTIUED

- Cerebrovascular symptoms began at a median of 10 days
- Blood D-dimer concentration was raised in many patients with COVID-19, consistent with a pro-inflammatory, coagulopathic state in the setting of critical illness.
- This approach might also reduce COVID-19-associated ischaemic stroke, but it must be balanced against the risk of intracranial haemorrhage, including haemorrhagic transformation of an acute infarct.



(A) Hyperintensity along the wall of inferior horn of right lateral ventricle on diffusion-weighted imaging, indicating ventriculitis.

(B) hyperintense signal changes in the right mesial temporal lobe and hippocampus with slight hippocampal atrophy on FLAIR MRI, consistent with encephalitis, in a patient with COVID-19.

(C) Hyperintensity within the bilateral medial temporal lobes and thalami on T2/FLAIR MRI.

(D) Evidence of haemorrhage, indicated by hypointense signal on susceptibility-weighted images, consistent with acute necrotising encephalopathy in a patient with confirmed COVID-19.

(E) CT showing ischaemic lesions involving the left occipital lobe.

(F) Right frontal precentral gyrus of the brain in a man aged 64 years who deteriorated neurologically after admission to hospital with COVID-19 and was diagnosed with acute stroke.

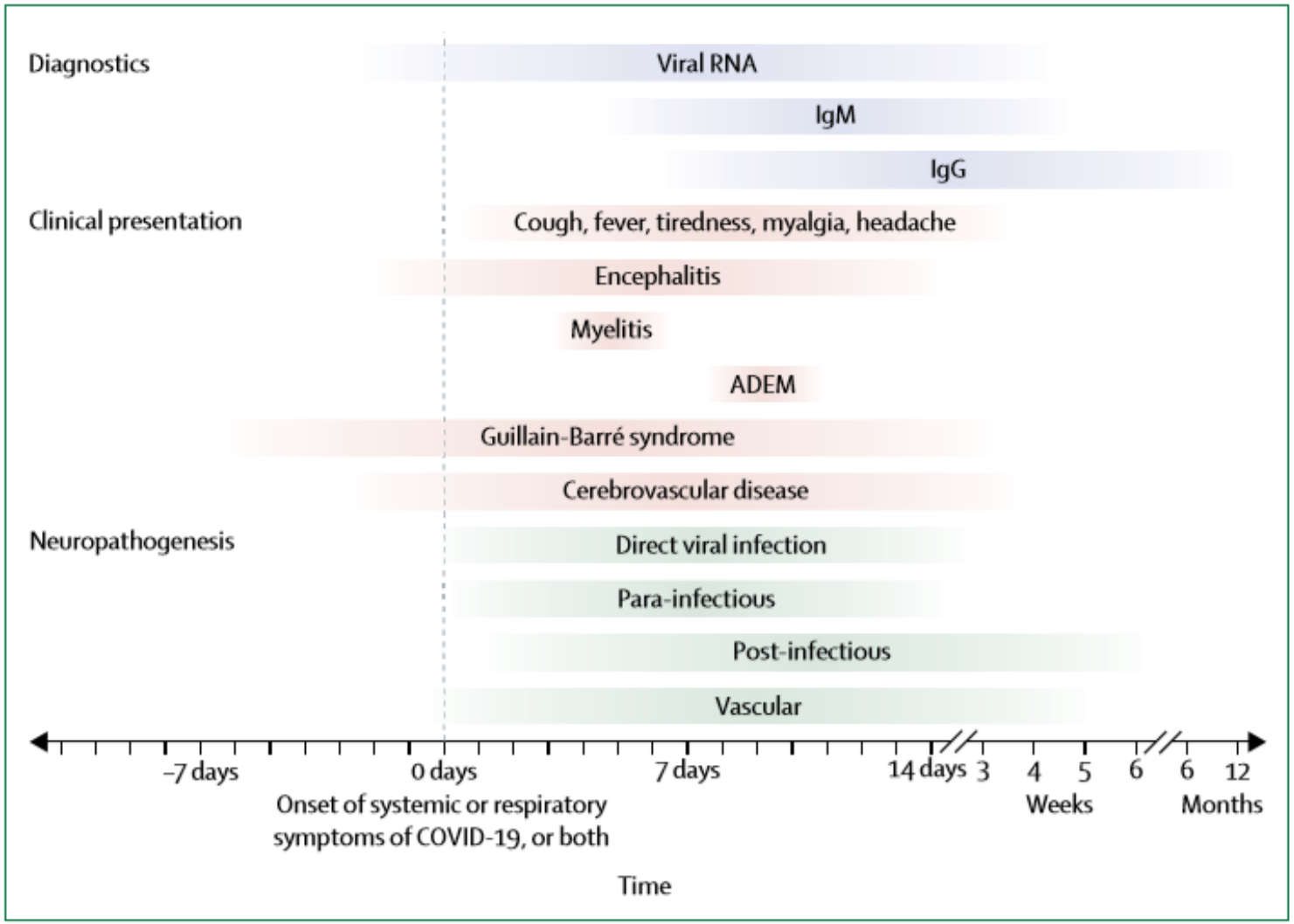


Figure 1: **Approximate timeline for positive diagnostic tests, clinical presentation, and pathogenesis in**

- POINTERS – IT'S A BORROWED SLIDE

- Given that SARS-CoV-2 causes a large number of asymptomatic or mildly symptomatic infections, it is crucial to remember that patients with neurological disease from other causes might be infected coincidentally with the virus, including in hospital through nosocomial transmission.
- **A full investigation, which is absent in many reports to date, is needed to rule out other established causes of brain infections before attributing disease to COVID-19**
- Distinguishing between naso pharyngeal SARS-CoV-2 infection and nervous system infection is also key. For patients with altered consciousness or agitation, all causes of encephalopathy must be considered, including hypoxia, drugs, toxins, and metabolic derangement; encephalitis should be diagnosed only if clinical evidence exists of brain inflammation, such as a CSF pleiocytosis, imaging changes, focal seizures, or histological changes
- **Even if virus is detected in the CSF, encephalitis should not be diagnosed unless evidence exists of brain inflammation. For patients with possible peripheral nerve disease, clinicians should aim to do CSF examination, looking for evidence of albuminocytological dissociation**
- , nerve conduction studies, and electromyography during recovery, even if they cannot be done acutely. In patients with neuropathy, cerebrovascular disease, or acute disseminated encephalomyelitis, in whom the damage is probably caused by the host's response to viral infection, establishing causality is even more challenging, especially if patients present after the virus has been cleared from the nasopharynx. Clinical case definitions for COVID-19 that are based on the history and typical
- **findings for chest imaging and blood investigations will be useful (panel). For patients with stroke, clinicians should consider cerebral angiography, intracranial vessel wall imaging, and, if necessary, brain biopsy, looking for vasculitis. The apparently high incidence of cerebrovascular disease in patients with COVID-19, with predominantly large vessel disease and markers of a highly prothrombotic state, suggest a causal relationship. However, the high prevalence of the virus during the pandemic, and the fact that most stroke patients have other risk factors, mean that it is hard to be sure about causation.**
- The link with SARS-CoV-2 will ultimately need to be proven by careful case-control studies. In investigating patients with limb weakness and sensory change, it is crucial to distinguish between disease of the peripheral nerves (eg, Guillain-Barré syndrome) and inflammation of the spinal cord, which can present with flaccid paralysis if the anterior horn cells are involved.
- **CSF examination, neurophysiological studies, and spinal imaging are essential. For patients on intensive care, determining whether neuropathy, myopathy, encephalopathy, or cerebrovascular disease are non-specific manifestations of critical illness or are specific to the virus itself might be particularly challenging; no reliable markers exist for neurological disease caused by critical illness, although it tends to occur after several weeks.10 Up to 70% of patients with sepsis might develop encephalopathy or polyneuropathy.111 In the Wuhan series, neurological complications were more common in those with severe disease, suggesting that some of the neurological manifestations were related to critical illness.36,**