Pathophysiology, diagnosis, and management of neuroinflammation in covid-19

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Abstract

Although neurological complications of SARS-CoV-2 infection are relatively rare, their potential long term morbidity and mortality have a significant impact, given the large numbers of infected patients. Covid-19 is now in the differential diagnosis of a number of common neurological syndromes including encephalopathy, encephalitis, acute demyelinating encephalomyelitis, stroke, and Guillain-Barré syndrome. Physicians should be aware of the pathophysiology underlying these presentations to diagnose and treat patients rapidly and appropriately. Although good evidence has been found for neurovirulence, the neuroinvasive and neurotropic potential of SARS-CoV-2 is limited. The pathophysiology of most complications is immune mediated and vascular, or both. A significant proportion of patients have developed long covid, which can include neuropsychiatric presentations. The mechanisms of long covid remain unclear. The longer term consequences of infection with covid-19 on the brain, particularly in terms of neurodegeneration, will only become apparent with time and long term follow-up.

Introduction

In December 2019, clusters of cases of severe pneumonia epidemiologically linked to a seafood and wet market in Wuhan, China were admitted to health facilities.[1] In January 2020, a novel strain of coronavirus, SARS-CoV-2, belonging to the same family of viruses causing, severe acute respiratory syndrome (SARS) in 2002, and Middle East respiratory syndrome (MERS) in 2012, was isolated from respiratory tract samples of affected patients. On 11 March 2020, the World Health Organization declared the SARS-CoV-2 (covid-19) outbreak a global pandemic.[2]

Although the numbers of patients infected were relatively small (SARS 8096, MERS 2591) anecdotal case series documented neurological complications including stroke, seizures, and Guillain-Barré syndrome.[3-6] The death rate was highest for MERS (34.5%), followed by SARS 9.6% and SARS-CoV-2, 1.4%.[4 7] The growth in the total number of covid-19 cases worldwide has been exponential: over 760 million cases and 6.8 million deaths have been recorded, with 13 billion doses of vaccine administered.[8]

The Opensafely study on behalf of NHS England, which used a health analytics platform linked to general practitioners, found that death related to covid-19 was associated with the following risk factors: male sex, greater age, deprivation, and comorbidities including diabetes and severe asthma. Compared with the white population, individuals of black and South Asian ethnicity were also at higher risk of death, even after controlling for other risk factors.[9]

The covid-19 pandemic took the world by surprise. The immediate medical response was confused and bewildering, owing to a lack of precedence and experience of any such previous pandemic. However, the rapid and international coordinated response by the medical community has been outstanding. Within 12 months of the onset of the pandemic, the first vaccines were administered. This review summarizes the evidence on the neurological consequences of covid-19. We provide a summary of the complications encountered by clinicians, propose a pathophysiological basis for them, and discuss potential treatments. This review is for all clinicians and scientists who were, and still are, caring for patients affected by covid-19, both in the acute and chronic clinical setting. The current evidence is that the virus will become endemic in the global population. However, the development of new variants is still a great unknown that only time will reveal.

This review will include a granular understanding of subtypes of syndromes (including acute disseminated encephalomyelitis), a critical review of stroke management in covid-19, and navigate neurological complications in an established vaccine era.

Epidemiology

The first large retrospective case series of 214 patients from Wuhan in 2020 documented neurological manifestations in 36.4%.[10] These manifestations were classified into three categories: central nervous system (headache, impaired consciousness, ataxia, stroke), peripheral nervous system (anosmia, ageusia, nerve pain), and skeletal muscle injury. Neurological complications were more frequent in those with severe covid-19 infection. However, the underlying pathophysiological mechanisms were unclear. Direct viral invasion, associated immune and inflammatory processes, and complications of severe illness including sepsis, hypoxia, ventilation, and extracorporeal membranous oxygenation (ECMO) were all postulated.

An early observational study, describing a highly selected group of 43 inpatients, was able to classify, with some pathophysiological insight, a collection of neurological syndromes associated with covid-19. These syndromes were encephalopathy (presenting with delirium and psychosis but with normal magnetic resonance imaging and cerebrospinal fluid); inflammatory central nervous system syndromes including ADEM (acute disseminated encephalomyelitis), para-infectious and post-infectious encephalitis; myelitis; ischemic stroke often associated with pulmonary thromboembolic disease; and Guillain-Barré syndrome.[11] With increasing experience of the pandemic, these neurological case definitions have been revised.[12]

The global consortium study of neurological dysfunction in covid-19 (GCS-Neuro-COVID) and the European Academy of Neurology neuro-covid registry (ENERGY), representing 28 centers, 13 countries, and four continents between them, documented neurological manifestations (self-reported neurological symptoms or neurological signs or syndromes) in 82% of patients admitted to hospital.[13] The most common symptoms were headache (37%) and anosmia or ageusia (26%). The most prevalent signs or syndromes were acute encephalopathy (49%), coma (17%), stroke (6%), and meningitis/encephalitis (0.5%). In addition, this study reported an increased risk of in-hospital death (adjusted odds ratio 5.99; 95% confidence interval 4.33 to 8.28) in those with neurological signs or syndromes. Pre-existing neurological disorders were associated with an increased risk of developing neurological signs and syndromes or both with covid-19 infection (2.23; 1.80 to 2.75).

An individual patient data meta-analysis of 1979 patients admitted to hospital with covid-19 and acute onset neurological presentations, which included patients from low and middle income countries (LMIC), identified important geographical variance in terms of outcomes in these patients. The death hazard was higher in LMIC WHO regions when compared with high income countries.[14] Such inequities should be at the forefront of consideration in the inclusion, design, and aims of future research and policy globally.

Sources and selection criteria

PubMed and Medline were searched for articles published in English using terms including covid-19 OR"SARS-CoV-2"AND"neuro*"OR"neuropathology" OR "encephalopathy" OR "encephalitis" OR "acute demyelinating encephalomyelitis" OR "ADEM" OR "acute haemorrhagic leukoencephalopathy" OR "AHLE" OR "demyelination" OR "acute necrotising encephalopathy" OR "PIMS-TS" OR "MIS-C" OR "stroke" OR "Guillain-Barré syndrome" OR myopathy OR myasthenia gravis OR "long covid". Articles were also identified through the reference lists of selected publications. We included systematic reviews, large randomized controlled trials, high quality population based observational studies (which we considered at low risk of bias), and clinical guidelines. Where no other literature was identified, we report case series and limit presentations described in case reports to those with multiple reports in more than one geographical location in the narrative review. However, for table 1, which describes all neurological syndromes in covid-19, we included case reports with fewer examples.

Given the recency of the pandemic, that few prospective or longer term follow-up studies have been done is not surprising. Estimates of case frequency are largely linked to hospital admissions, relying upon physician reporting. The incidence of neurological presentations in patients not admitted to hospital is less clear. A lack of standardized definitions across studies complicates the interpretation of many results. For example, cases of ADEM were often included in encephalitis studies. The application of best fit diagnoses to novel presentations and the presence of mixed pathologies complicated interpretation further. While most studies state the evidence for covid-19 for each case, coincidental infection cannot be excluded, and are a consequence of real time learning and observation of a new disease. The neuropathology and pathophysiology of acute covid-19, as well as those of long covid, is an ongoing area of research.

Pathophysiology

The epidemiological data described above suggest that, despite the myriad neurological presentations that have been described in covid-19 infection, SARS-CoV-2 is not a classic neurotropic virus. It does, however, have the potential for neuroinvasion, and clearly has the ability for neurovirulence (box 1).

Angiotensin converting enzyme 2 (ACE2) has been identified as the key receptor for the entry of SARS-CoV-2 into cells.[20] Publicly available brain transcriptomic databases show that although total expression of ACE2 is lower in the brain than in the lungs, some brain regions express relatively high levels. These regions include the paraventricular nuclei of the thalamus, the raphe nuclei (brainstem), and the tuberomamillary nuclei (posterior hypothalamus), as well as the choroid plexus.[21] Bulk and single cell RNA sequencing in human and mouse models show ACE2 expression in the olfactory

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Table 1 | Neurological complications of covid-19 described in the literature[15-18]

Syndrome	Clinical presentation	Postulated mechanism
Central nervous system		
Acute necrotizing encephalopathy*	Acute neurological deterioration, often with seizures and characteristic magnetic resonance imaging appearances related to the deep gray matter	Unclear: possible role of cytokine storm in the context of metabolic, mitochondrial, or genetic factors
Encephalopathy†	Delirium or disordered consciousness, including prolonged wakening from sedation; focal neurological signs, or psychiatric features can be present	Multifactorial: Toxic metabolic, including sepsis, hypoxia–ischemia, and electrolyte disturbances Cytokine driven; a possible role for other immune mechanisms and endotheliopathy
Encephalitis†	Diverse depending upon phenotype; altered mental status; seizures and focal neurological signs or movement disorders can be present	Post-infective immune, likely multi-mechanistic including antibody mediated
ADEM*	Encephalopathy, focal neurological signs, sometimes seizures	Post-infective immune
AHLE*	Encephalopathy, focal neurological signs, and sometimes seizures; can be associated with raised intracranial pressure	Post-infective immune
ADEM-like*	Prolonged awakening following admission to intensive care, variable pyramidal tract signs or seizures; characteristic lesions in deep white matter on magnetic resonance imaging	Unclear; can be multifactorial and include hypoxia, sepsis, coagulopathy, microthrombosis, endotheliopathy, cytokine storm, post-infective/para-infective immune
MOGAD*	Transverse myelitis, ADEM/brain or brainstem lesions, optic neuritis	Post-infective immune
Optic neuritis*	Unilateral or bilateral visual loss with retrobulbar pain worse on eye movement	Post-infective immune; can be related to MOGAD
Transverse myelitis*	Motor and/or sensory symptoms and/or sphincter disturbance; imaging can be normal or show typical lesions and/or leptomeningeal enhancement	Post-infective immune; can be related to MOGAD
PIMS-TS†	Systemic symptoms: fever, rash, gastrointestinal and cardiac. Neurological symptoms (14.8-20.45%) can include encephalopathy, headache or meningism, behavioral change, visual hallucinations, focal neurological signs, seizures	Cytokine driven, in particular interleukin 6 and interleukin 8
PRES*	Encephalopathy, hypertension, seizures, visual disturbances	Multifactorial: hypertension related to severe covid-19, endothelial dysfunction possibly associated with endotheliopathy, drug side effects
Pseudotumor cerebri*	Symptoms or signs of raised intracranial pressure including headache, reduced vision, pulsatile tinnitus, papilledema, oculomotor nerve palsies	Cerebral venous stasis related to pro-inflammatory and pro-thrombotic state; can be associated with PIMS-TS
Parkinsonism*	Tremors, bradykinesia, and rigidity	Multiple possible mechanisms, including: Microvascular injury Neuroinflammation Potential impact of SARS-CoV-2 on α-synuclein protein Post-viral manifestation of subclinical disease
Peripheral nervous system		
Polyneuropathy (Guillain-Barré syndrome)*	Ascending weakness/sensory loss, +/- facial/bulbar weakness, respiratory insufficiency, dysautonomia	Post-infective immune
Mononeuritis multiplex*	Weakness +/- sensory disturbance	Post-infective immune, possible immune–thrombotic
Neuralgic amyotrophy*	Weakness, wasting +/- sensory disturbance neuralgia of the affected nerve(s)	Post-infective immune
Myositis*	Myalgia, myopathy	Post-infective immune or a subclinical trigger by infection
Myasthenia gravis*	Bulbar symptoms, diplopia, muscle weakness, fatiguability	Post-infective immune or a subclinical trigger by infection
Vascular		
Cerebral arterial infarction†	Stroke syndrome	Risk is seen mostly in large vessel occlusion, and the postulated mechanism is an underlying coagulopathy. Rarer complication with vector based vaccine
Venous infarction†	Stroke syndrome, seizure, altered mental status, encephalopathy	The postulated mechanism is an underlying coagulopathy. Rarer complication with vector based vaccine
Spinal cord infarction*	Acute myelopathy typically affects the thoracic region	Presumed to be due to an underlying coagulopathy
Intracerebral hemorrhage†	Stroke syndrome, seizure, altered mental status, encephalopathy	Typically, lobar haemorrhage. Mechanism multifactorial and linked with anticoagulant treatment; some description of hematoma with fluid level owing to anticoagulation use, or possibly underlying RCVS-like mechanisms and hypertension
Complications of prolonged illness/intensive care		
Critical illness polyneuropathy or myopathy†	Weakness, wasting +/- sensory disturbance	Risk correlating with the duration of admission to intensive care
Lower cranial nerve palsies*	Hypophonia, dysphagia (Tapia syndrome)	Presumed to be mechanical owing to prolonged intubation, jugular cannulation
Brachial plexopathy and other compression neuropathies†	Weakness, wasting +/- sensory disturbance, significant neuralgia of the affected nerve(s)	Presumed to be mechanical owing to proning

ADEM=acute-demyelinating encephalomyelitis; AHLE=acute haemorrhagic leukoencephalopathy; MOGAD=myelin oligodendrocyte glycoprotein antibody associated diseases; PIMS-TS=pediatric multisystem inflammatory syndrome; PRES= posterior reversible encephalopathy syndrome; RCVS=reverse cerebral vasoconstriction syndrome. *Evidence limited to case reports and case series, no current evidence of excessive risk due to covid-19. This lack of evidence could be because events are rare, coded as a syndromic rather than pathological diagnosis (ie, seizure rather than ADEM), or the excess risk is small, or no independent risk is associated with covid-19. †Evidence of excessive risk owing to covid-19 compared with a comparative control group.

sustentacular and vascular pericytes, rather than in olfactory sensory and olfactory bulb neurons.[21] Postmortem studies in patients with covid-19 confirmed that the major cellular targets of SARS-CoV-2 replication are the respiratory mucosa ciliated cells and the olfactory mucosa sustentacular cells.

Box 1: Glossary of terms[19]

- Neuroinvasion: The ability of a virus to enter the nervous system (central or peripheral)
- Neurotropism: The ability of a virus to infect and replicate within cells (neural or glial) of the nervous system
- Neurovirulence: The ability of a virus to cause neuropathology and clinical disease. Does not require a virus to enter the nervous system, and can include the effect of systemic processes including a dysregulated inflammatory or immune response, vasculopathy, or hypoxia

Some cases showed viral RNA in the leptomeningeal layers surrounding the olfactory bulb.[22] In theory, therefore, direct viral invasion of the brain parenchyma by hematogenous dissemination via the choroid plexus, an impaired blood-brain barrier, or retrograde invasion from the leptomeningeal regions around the olfactory bulb remain possibilities.

An early neuropathological study detected SARS-CoV-2 in the brains of 21/40 (53%) patients with covid-19.[23] Viral proteins were found in cranial nerves IX (glossopharyngeal) and X (vagus), as well as in individual cells in the medulla oblongata. However, the presence of viral antigen was not associated with severity of neuropathological changes, including astrogliosis, activation of microglia, and infiltration by cytotoxic T lymphocytes. These changes were mainly seen throughout the brainstem, cerebellum, and meninges. In most studies where virus has been identified in the brain, the viral load is reported to be very low, and the findings are subject to limitations, including the possibility of hematogenous spread or viral contamination during autopsy. Another difficulty is distinguishing shed protein from whole virus.[24] Reports of SARS-CoV-2 RNA isolation in cerebrospinal fluid are rare, including in those patients with covid-19 neurological syndromes. Thus, the evidence points to SARS-CoV-2 invading the nervous system (neuroinvasion), but less compelling data suggest neurotropism. The varied neurological presentations are instead a reflection of disparate underlying pathophysiology including inflammatory, immune mediated, and vascular mechanisms (fig 1a and 1b). A recent study in which SARS-CoV-2 was sequenced in autopsy brain tissue of unvaccinated patients during the first wave of the pandemic, up to 200 days after the original diagnosis, raises new questions about a possible sanctuary site in the brain.[25] Although no correlation with neuropathology was indicated, this result warrants further investigation, especially in relation to long covid.

The pathophysiology of covid-19 neurological syndromes is discussed in the sections below. However, it should be noted that neuropathological changes are not limited to patients with neurological syndromes, and can be found in patients with covid-19 without clinical neurological presentations. These changes could reflect the systemic consequences of a complex and mixed pathophysiology of severe SARS-CoV-2 infection, including hypoxia, sepsis, and metabolic derangement, often in the intensive care setting. Many features overlap with other systemic inflammatory syndromes, viral infections of the central nervous system, or critical illness requiring admission to intensive care, invasive ventilation, or ECMO.[24 26 27] In postmortem studies of patients with severe covid-19, the most frequent neuropathological changes included widespread reactive astrocytosis, and microglial activation with neuronal injury or loss attributed to hypoxic ischemic brain injury.[24] The same studies reported innate immune activation with microglial nodule formation and variable neuronophagia, with a particular predilection for the brainstem.[23 24] Some authors suggest that this could contribute to symptoms of brainstem dysfunction, such as tachypnea.[24] Adaptive immunity appears to be less prominent; cytotoxic T lymphocyte infiltration, described in the perivascular regions and brain parenchyma in some patients, was often absent or sparse, while mild meningeal infiltration by cytotoxic T cells was thought to be reactive.[24 26] Perivascular demyelination with some ADEM-like features is described in some small case studies.[28] Pre-existing neuropathology (vascular or neurodegenerative) could contribute to both histological findings and the clinicopathological response to infection.[24 29]

Immune activation is prominent in the pathophysiology of systemic covid-19 infection, and likely contributes to both neuropathology and neurological symptomatology of covid-19. Cytokine storms are central to the pathophysiology of acute severe SARS-CoV-2 infection,[30] Several studies have investigated the association of cytokines with clinical severity and prognosis.[31 32] An early 2020 retrospective study from China showed an association between severity/mortality from covid-19 and increased pro-inflammatory and anti-inflammatory levels of cytokines, including interleukin 2R, interleukin 6, interleukin 8, interleukin 10, and tumor necrosis factor (TNF).[33] A subsequent observational study measured serum levels of interleukin 6, TNF-alfa, and interleukin 1 beta in 1484 patients admitted to hospital with covid-19.[34] After adjusting for disease variables including laboratory inflammation markers, hypoxia, patient demographics, and comorbidities, interleukin 6 and TNF-alfa serum levels remained independent and significant predictors of disease severity and death. Immune directed treatments improve outcomes in severe covid-19 infection; these include tocilizumab (monoclonal antibody blocking interleukin 6 receptor) and dexamethasone.[35 36]

Several studies have attempted to correlate the association between brain injury and markers of immune dysregulation.[37 38] In one observational study of 175 patients with covid-19, sera from patients with covid-19 showed elevations of brain injury biomarkers, including neurofilament light chain and glial fibrillary acidic protein (GFAP), in a severity dependent manner, with evidence of ongoing brain injury after four months of follow-up.[37]

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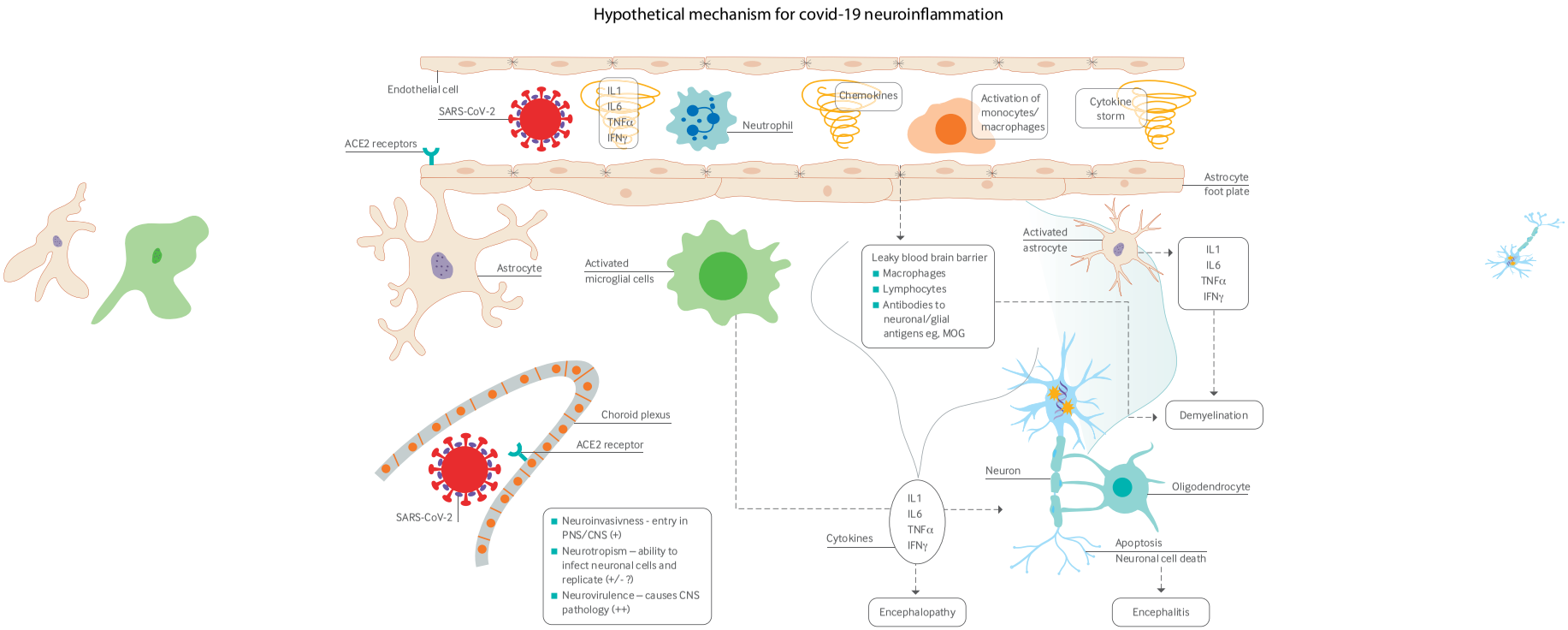

Fig 1a | Hypothetical mechanism for covid-19 neuroinflammation

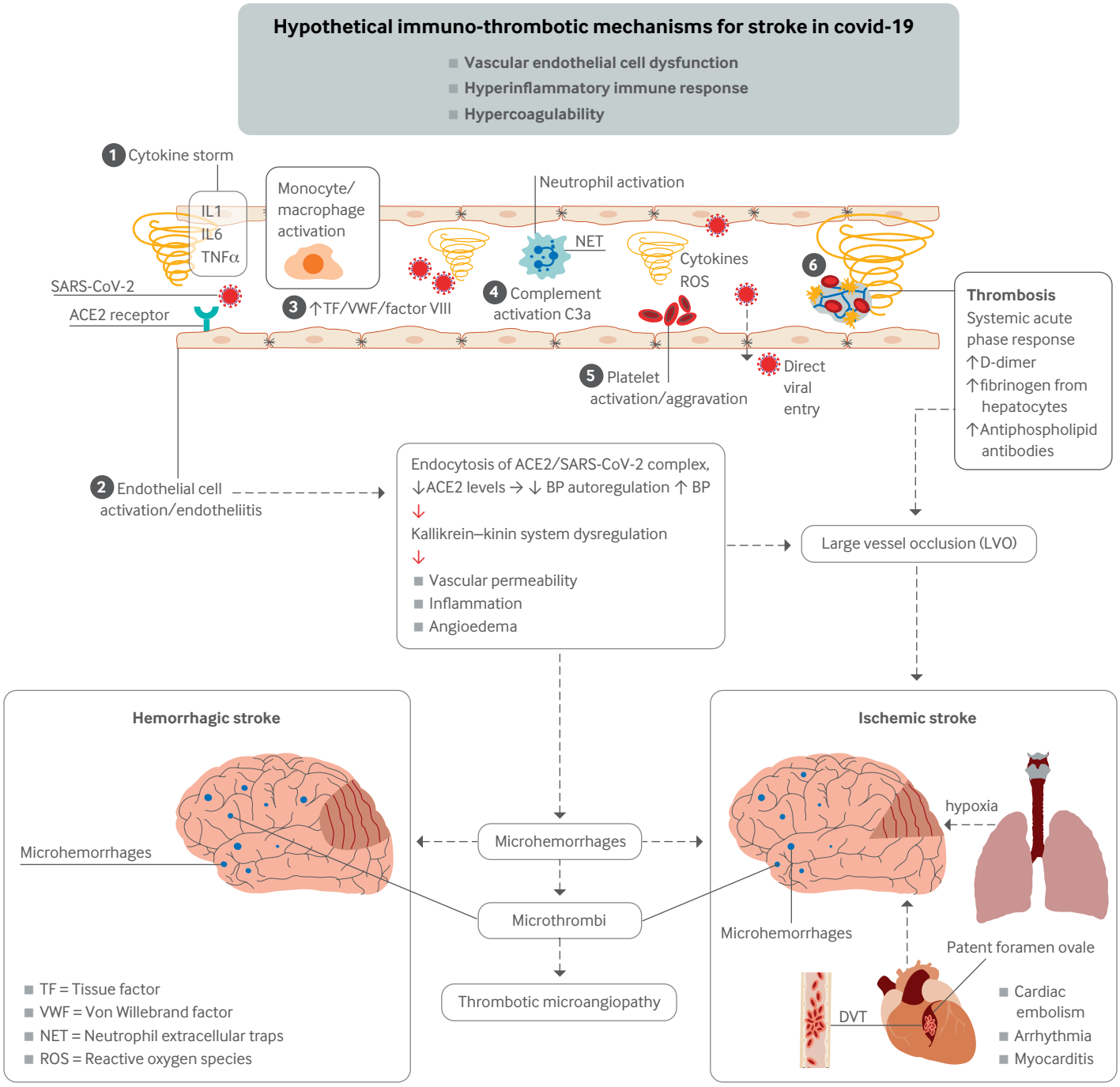

Fig 1b | Hypothetical immuno-thrombotic mechanisms for stroke in covid-19

These markers were associated with elevated levels of pro-inflammatory cytokines and autoantibodies against brain proteins, such as myelin associated glycoprotein. However, the positive correlation between pro-inflammatory cytokines and brain injury biomarkers was also seen in the comparator group of 45 patients with influenza, suggesting that rises could be related to severity, rather than infection with a specific virus.[37] This finding could also have implications for patients with long covid.

Humoral autoimmunity could contribute to the pathophysiology of covid-19 neurological presentations. Molecular mimicry between viral proteins and neuronal antigens, or delayed stimulation of post-viral autoantibodies, is described in a number of viral infections, including herpes simplex virus, Epstein-Barr virus, and HIV.[39] In a limited uncontrolled study of 11 critically ill patients with covid-19 with varied neurological symptoms including myoclonus, delirium, and seizures, one in four specimens of cerebrospinal fluid showed IgA and IgG SARS-CoV-2 antibodies.[40] Intrathecal synthesis is rarely reported, and in most cases, SARS-CoV-2 antibodies derive from sera in the context of blood-brain barrier leakage.[41] Using cell based assays and indirect immunofluorescence techniques

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on unfixed murine brain sections, all 11 patients showed anti-neuronal antibodies in cerebrospinal fluid or serum, or both.[40] Antigens included intracellular and neuronal surface proteins such as Yo and N-methyl-D-aspartate receptor (NMDAR), but also a number of non-specific epitopes. These included vessel endothelium, astrocytic proteins and neuropil of basal ganglia, hippocampi, and olfactory bulb epitopes.

Cerebromicrovascular dysfunction in covid-19 likely contributes to several neurological manifestations, including strokes, headaches, and encephalopathy. Experimental animal models show that the protease of SARS-CoV-2 induces cellular pathways, leading to string vessel formation of the small cerebral vessels, while subunit 1 of SARS-CoV-2 binds to ACE2, triggering pericyte mediated angiotensin evoked constriction of the cerebral capillaries; downstream effects of which are hypoxia and clotting abnormalities.[42 43] Some of these findings are corroborated in human histopathological and radiological examination. For example, evidence of endotheliitis (including subluminal fibrinogen deposition inferring blood-brain barrier permeability, with resulting multifocal microvascular injury and microhemorrhages) has been described.[23 26] However, severe disease, systemic hypoxia, and hemodynamic changes confounded these findings. Some studies have shown biomarkers of endotheliopathy persisting beyond three months, and have hypothesized a role in long covid.[44] However, rigorous profiling of tissue, and peripheral blood biomarkers linking pathophysiology to clearly phenotyped syndromes and outcomes, supporting a causal mechanism, are still lacking.

In contrast, the mechanisms of macrovascular complications resulting in ischemic stroke are less specific, but likely to comprise a combination of microvascular injury, modulating cerebral blood flow, SARS-CoV-2 mediated systemic hypercoagulability, and antiphospholipid syndrome.[45 46] The delay of about one week from the onset of covid-19 symptoms to developing ischemic stroke suggests an immune mediated trigger.[47 48] Thromboembolic complications might also reflect cardiac dysfunction such as myocarditis.[49 50]

The impact of SARS-CoV-2 infection on long term brain health is of great interest. Markers of neuronal and glial injury are reported to be elevated in blood in patients with severe covid-19, and in patients with encephalopathy.[51] A study of 60 inpatients with covid-19 and neurological presentations, including 25 with encephalopathy, found a correlation between cerebrospinal fluid 14-3-3 and levels of neurofilament light chain (both markers of neuronal degeneration) in the acute illness and neurological disability at 18 months, suggesting that neuronal injury is related to outcome (ρ=0.719, p=0.001 and ρ=0.583, p=0.006 for CSF 14-3-3 and CSF neurofilament light, respectively).[52] Longer term trends in cerebrospinal fluid, serum, and imaging biomarkers, and association with neurodegenerative disease, are not yet known. Before covid-19, severe infection (bacterial or viral) requiring hospital admission was reported to increase long term risk of dementia (including vascular dementia and Alzheimer's disease).[53] Whether covid-19 engenders similar or additional individual or population level risk will only be borne out over longer term follow-up studies. The main drivers leading to increased risk of dementia are unclear (possible factors include hypoxia, systemic inflammation, and loss of blood-brain barrier integrity). Alteration of amyloid processing has been suggested, but requires further investigation.[54]

Most outcome studies are in patients admitted to hospital, and how this relates to mild SARS-CoV-2 infection or younger individuals is unclear. A UK Biobank study of 785 participants, including 401 with predominantly mild (not admitted to hospital) SARS-CoV-2 infection, reported reduction in gray matter volume, particularly in the orbitofrontal cortex and para-hippocampal gyrus.[55] Additionally, changes in structures connected to the olfactory cortex, as well as greater reduction in global brain size, were found in individuals following SARS-CoV-2 infection compared with non-infected controls. Since group results cannot be extrapolated to individuals, these data require caution in interpretation.[56] These findings could simply reflect olfactory hypofunction prevalent with the earlier strains of the pandemic. Individuals studied were predominantly older adults, and 56-62% of infected individuals showed volume loss greater than controls. Plasticity with potential reversibility has not yet been explored.

Neurological syndromes

Encephalopathy

Encephalopathy, which includes delirium and a spectrum of disordered levels of consciousness, is the commonest neurological complication reported in patients admitted to hospital with covid-19. In the intensive care setting, encephalopathy can be severe, manifesting as delayed wakening from sedation, agitation, or confusion. An early retrospective observational study of 58 patients in intensive care units with acute respiratory distress syndrome (ARDS) caused by covid-19 found that 49 (84%) had neurological features, including agitation on discontinuing sedation and neuromuscular blockade (n=40, 69%), and confusion (n=26/40, 65%, assessed by confusion assessment method for the intensive care unit (CAM-ICU).[57] Pyramidal tract signs with brisk reflexes, ankle clonus, and extensor plantars were found in 39 (67%), and 15/45 (33%) had ongoing executive dysfunction at the point of discharge from intensive care. Encephalopathy might have a prolonged course in this group. In a study of 795 patients with severe covid-19, 571 patients recovered command following (motor score 6 on the Glasgow coma scale) admission to intensive care, with 25% doing so ≥10 days and 10% doing so ≥23 days after cessation of mechanical ventilation.[58]

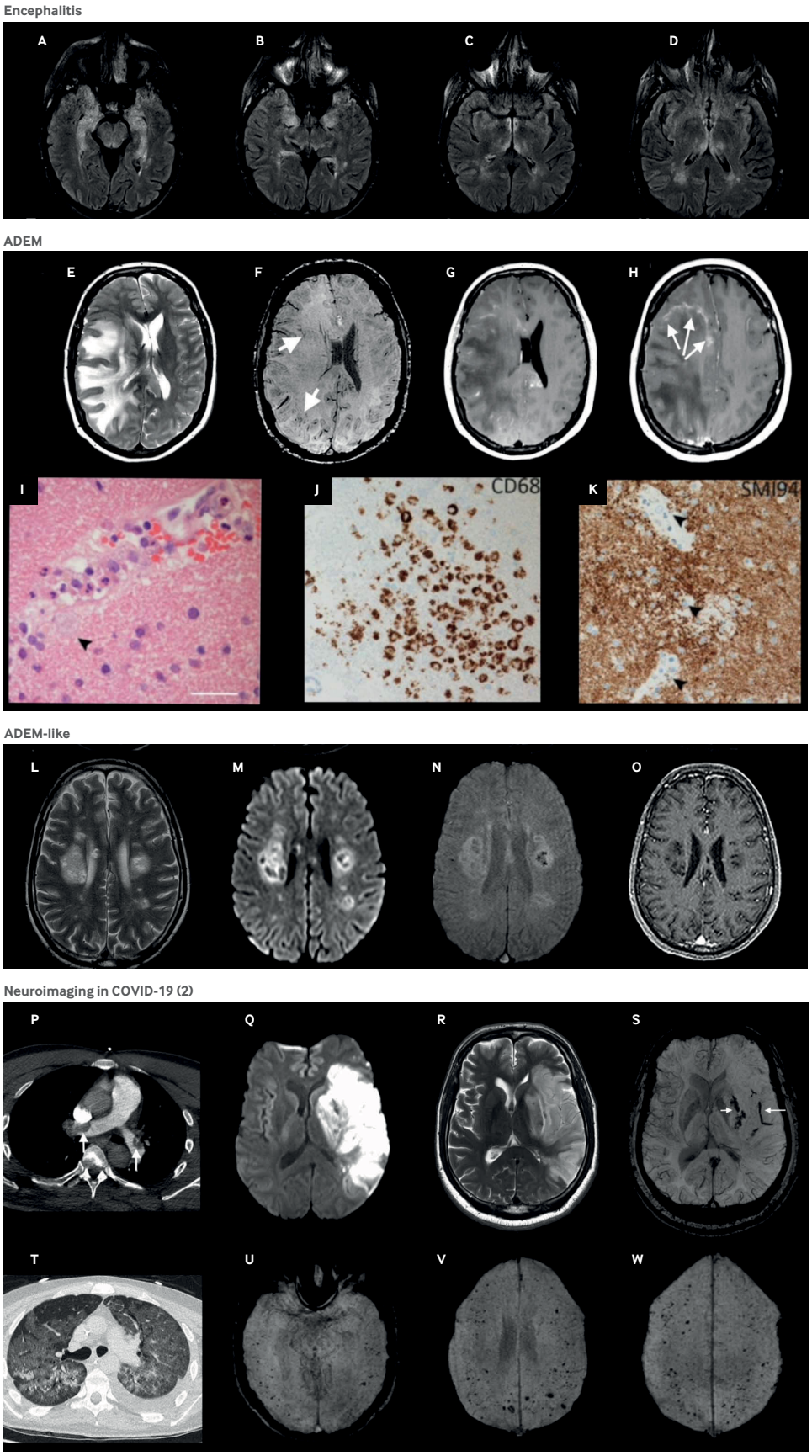

Fig 2 | Neuroimaging in covid-19.[11] A-D show imaging from a patient with limbic encephalitis: axial fluid attenuated inversion recovery (FLAIR) images show bilateral hyperintensity in the mesial temporal lobes (A), hypothalamus (B) and thalamus (C,D); E-H show axial magnetic resonance

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Fig 2 | Continued
images (E-H), and histopathology (I-K) from a patient diagnosed with acute disseminated encephalomyelitis (ADEM): axial T2 weighted (E), susceptibility weighted images (F), post gadolinium (G, H) images show extensive confluent tumefactive lesions involving the white matter of the right cerebral hemisphere, corpus callosum, and corona radiata with mass effect, subfalcine herniation (E), clusters of prominent medullary veins (F, short arrows), and peripheral rim enhancement (H, arrows). The white matter shows scattered small vessels with surrounding infiltrates of neutrophils and occasional foamy macrophages extending into the parenchyma (I, arrow). The endothelium is focally vacuolated but no evidence indicates vasculitis or fibrinoid vessel wall necrosis in any region. The white matter contains a few perivascular T cell but the cortex appears normal (not shown). CD68 stain confirms foci of foamy macrophages in the white matter, mainly surrounding small vessels (J). Myelin basic protein stain (SMI94) shows areas with focal myelin debris in macrophages around vessels in the white matter (arrows) in keeping with early myelin breakdown (K). Bar is equivalent to 45 microns in E, 70 microns in J and K. L-O show imaging from a patient with ADEM-like changes following severe covid-19 and admission to intensive care: axial T2 weighted (L), diffusion weighted imaging (M), susceptibility weighted images (N), and post contrast T1 weighted (O) images show multifocal clusters of lesions involving the deep white matter of both cerebral hemispheres, intralesional cyst-like areas of varied sizes and some peripheral rims of restricted diffusion (M), some hemorrhagic changes (N), and T1 hypointense "black holes" without contrast enhancement (O). P-S show imaging from a patient with cerebral infarction and pulmonary thromboembolism: CT pulmonary angiogram (P) showed large emboli in the right and left pulmonary arteries (arrows). Diffusion weighted imaging (Q), T2 weighted fast spin echo (R), and susceptibility weighted images (S) show restricted diffusion (Q) and T2 hyperintensity (R) in the left basal ganglia and cortical territory of left middle cerebral artery. The susceptibility weighted images (S) show hemorrhagic transformation in the basal ganglia (short arrow) and a long intravascular thrombus in a Sylvian branch of the left middle cerebral artery (long arrow). T-W shows images from a patient with severe covid-19 infection and cerebral microhemorrhages: chest CT (T) shows severe covid-19 pneumonitis. Susceptibility weighted images (U-W) show numerous cerebral microbleeds in the temporal, frontal, and parietal lobes, predominantly located at the grey/white matter junction. Adapted from Paterson, Brown et al,[11] with permission from journal *Brain*

Encephalopathy, especially delirium, is not limited to the intensive care population, and can occur at or before the onset of respiratory symptoms or presentation to hospital and in patients with mild respiratory symptoms.[11 59] Younger adults can also be affected, and rarely, encephalopathy can overlap with acute psychiatric symptoms, including paranoid or delusional beliefs.[11 60] Focal neurological signs including ataxia or long tract signs can also occur in these patients, but imaging is usually normal.[11] Both hyperactive and hypoactive delirium, including akinetic mutism, are reported.

The causes of encephalopathy could be multifactorial, including well established causes of cerebral dysfunction. In a retrospective study of 4491 inpatients with covid-19, 559 (12%) had a toxic metabolic encephalopathy, 435 (78%) of whom had mixed etiology including sepsis, hypoxia, uremia, hyper/hyponatremia, and fever.[59] Patients with toxic metabolic encephalopathy had a more severe course of covid-19 (requiring admission to intensive care, intubation, and also developing acute renal failure). Risk factors for toxic metabolic encephalopathy included older age, diabetes, and premorbid neurological (including neurodegenerative), psychiatric, or cardiovascular disorders. Hypoxia might delay wakening from sedation, with both degree and duration of hypoxemia associated with delayed recovery of command following intubation.[58] Additional factors associated with prolonged recovery include duration of sedating or neuromuscular blocking drugs, use of renal replacement treatment, older age, and male sex.[58] Metabolic disorders such as thiamine deficiency and the precipitation of Wernicke's encephalopathy have also been implicated in covid-19 encephalopathy.[61] In older patients, pre-existing, perhaps subclinical, neurodegenerative pathology including microglial activation related to Alzheimer's might predispose them to delirium.[29]

The role of systemic or central nervous system inflammation and microvascular dysfunction in encephalopathic states is unclear. Phenotypically similar encephalopathies, presenting with dysexecutive syndromes and aphasia, are described in other cytokine driven hyperinflammatory states, such as secondary hemophagocytic lymphocytosis (sHLH) or immune effector cell associated neurotoxicity syndrome (ICANS) following chimeric antigen receptor T cell (CAR-T) treatment.[30 62] Elevated levels of pro-inflammatory cytokines including interleukin 6, interleukin 8, and macrophage inflammatory protein-1 beta (MIP-1β) have been found in the cerebrospinal fluid of some patients with covid-19 encephalopathy, and could correlate with measures of blood-brain barrier integrity.[63] However, both the presence of cytokines and blood-brain barrier disruption are not restricted to specific neurological phenotype or abnormalities on brain imaging, and comparison with control groups, including patients with covid-19 without neurological presentations, is lacking.[52 63 64] Evidence of SARS-CoV-2 in cerebrospinal fluid is sparse.[65]

Some evidence has been found to support a humoral autoimmune mechanistic model. In a short case series, two of three teenagers with SARS-CoV-2 infection and neuropsychiatric complications, not fulfilling the criteria for encephalitis and with normal imaging and standard laboratory investigations, had evidence of intrathecal antibody against SARS-CoV-2 and neuronal autoantibodies on anatomical immunostaining.[66] Antibodies targeting transcription factor 4 were isolated in one patient who responded well to immunotherapy. A further case series reported three patients with severe myoclonus (the commonest movement disorder in covid-19 infection) and somnolence with normal imaging and cerebrospinal fluid.[67] Again, improvement was observed following corticosteroids and plasma exchange, or both.

Brain imaging accompanying encephalopathy is by definition usually normal, or might show leptomeningeal enhancement. However, leukoencephalopathic changes or microhemorrhages

might be found, especially in the intensive care population (fig 2 U-W).[11 64] Cytotoxic lesions in the splenium of the corpus callosum, thought to be caused by cytokine mediated glutamate release, are also reported.[68 69] Functional imaging studies might show abnormal patterns of metabolism or perfusion, particularly in frontoparietal or frontotemporal patterns in patients with neurological symptoms following covid-19 infection.[70 71] In a study of 26 patients, with two or more neurological symptoms, 10/15 patients undergoing ^{18}fluorodeoxyglucose positron emission tomography had predominantly frontoparietal hypometabolism with a high correlation with poor performance on the Montreal cognitive assessment (R^2=0.62).[71] Electroencephalography might show diffuse or focal slowing, with some patients reported to have seizures or non-convulsive status epilepticus. Cerebrospinal fluid is normocellular in encephalopathy; cerebrospinal fluid pleocytosis warrants investigation for SARS-CoV-2 related or post-infective immune mediated encephalitis, or other viral or bacterial co-infection.[12 63 64]

In our experience, encephalopathy tends towards improvement, especially if imaging and laboratory investigations including cerebrospinal fluid parameters are normal. Published longer term outcome data are lacking. Management of encephalopathy includes dealing with contributing factors such as hypoxia, electrolyte imbalance, and sepsis. Anecdotal reports suggest that intravenous immunoglobulin (IVIg) might have a role in management, thus supporting a neuroinflammatory pathophysiological mechanism.[72] The effects of IVIg are pleiotropic, and include binding to Fc receptors on macrophages and microglia, as well suppression of inflammation mediated by cytokines and chemokines. Encephalopathy in covid-19 is associated with a greater risk of death within 30 days, poorer functional outcome, and risk of a dementia at six months.[73 74]

Inflammatory central nervous system syndromes

Acute necrotizing encephalopathy

Acute necrotizing encephalopathy presents with acute, rapid onset neurological deterioration, typically progressing to coma, often with seizures, in the context of a febrile illness.[75 76] Although more common in children, adult cases have been described, including case reports in the context of covid-19.[11 77-79] Magnetic resonance imaging shows bilateral, symmetrical signal abnormalities in the deep gray matter, usually involving the thalami, progressing to necrosis, and often hemorrhage. Cerebrospinal fluid is typically non-cellular but with elevated protein, and histology reveals edema with lack of inflammatory infiltrate.[75] Acute necrotizing encephalopathy is associated with a range of viruses, including influenza A and H1N1. Cytokine storming has been implicated in the pathogenesis, which could be relevant to covid-19, though systemic inflammatory markers might not be significantly raised in some cases.[79] Metabolic or mitochondrial mechanisms are also postulated. A genetic predisposition linked to mutations in the RANBP2 nucleoporin encoding gene is described, and might provide insights into the cellular and metabolic response to infection and inflammation.[76] Treatment targeting the systemic immune response including corticosteroids, intravenous immunoglobulins, and tocilizumab have been used with benefit in some cases, though outcomes are often poor with high case fatality.[76 78]

Encephalitis

Encephalitis is reported rarely in the context of covid-19. Most cases are presumed to be immune mediated, without clear evidence for direct brain infection. A study of 10 384 patients treated for covid-19 at the Mayo clinic identified five (0.05%) patients with definite, probable, or possible autoimmune encephalitis, using the Graus criteria.[80 81] However, three had only possible autoimmune encephalitis, reported as difficult to distinguish from toxic metabolic encephalopathy. Two large multicenter retrospective studies which screened consecutive covid-19 admissions determined incidences of 40 and 50 in 100 000 admissions meeting International Encephalitis Consortium criteria.[82-84] In a retrospective study of 71 904 covid-19 emergency department admissions in Spain, 29 patients met diagnostic criteria for meningoencephalitis, though 32.2% had presumed bacterial etiology, and detailed case descriptions were lacking[82] The ENCOVID study identified 22 patients with encephalitis among 43 139 admissions[84] The range of pathologies and radiological abnormalities described include potential encephalitis mimics, highlighting the need for careful case assessment and use of diagnostic criteria. These mimics could include stroke, reversible posterior leukoencephalopathy (RPLS) syndrome, and reversible cerebral vasoconstriction syndrome (RCVS).

No dominant encephalitis phenotype associated with covid-19 has emerged. Our own experience, reflected by case reports in the literature, included occasional cases of limbic or rhomboencephalitis, responsive to immune suppression. Other presentations reported are highly heterogeneous, including altered mental state with aphasia, seizures, or non-convulsive status epilepticus, movement disorders including opsoclonus myoclonus or parkinsonism, and ataxia.[84] Focal motor signs corresponding with lesions within white matter tracts are also described.[80] Reported imaging features are equally varied, including cases with temporal lobe hyperintensity on magnetic resonance imaging typical of limbic encephalitis, T2 weighted/fluid attenuated inversion recovery (T2/FLAIR) hyperintensities within the cerebral white matter, brainstem or cerebellum, or normal brain imaging (fig 2 A-D).[11]

Timing of onset of encephalitis can vary. In the ENCOVID study, 11 (44%) patients had

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Box 2: Long covid-19; a patient experience

Long covid for me was characterized by severe daily headache, dizziness, nausea, fatigue, and difficulty concentrating. At one stage I experienced word finding difficulties during conversation. I needed six months off work. Two years later, I am progressively much improved. I am still unable to work as hard as I used to due to ongoing problems with mental endurance and frequent headaches following periods of focus. With careful activity pacing, I am on the whole able to function normally at work, and also, socially.

The fatigue associated with long covid for me has been a very different experience from normal tiredness. The physical fatigue is a whole body experience that is like a brick wall exhaustion. That has now settled. The mental fatigue is characterized by an inability to focus, think through complex problems and, sometimes, even have a conversation. It is triggered by long sustained periods of mental activity. I still experience this in a much milder way two years later, but have learnt that I can avoid it with pacing and by taking proper rest breaks at work.

As a doctor myself, I am all too aware of poorly understood clinical presentations. I now carefully frame how I tell a patient that their test results are normal. Instead I tell them that the results don't explain their symptoms. This avoids a misunderstanding that I might think their symptoms are imagined or due to anxiety.

A pandemic with large numbers of patients with the same condition provides a perfect pool for research. I hope this will help patients with myalgic encephalomyelitis/chronic fatigue syndrome too. It is noteworthy that many of these patients report an infective trigger prior to symptom onset.

onset of neurological and respiratory symptoms concomitantly, while 12 (48%) had onset after (median eight days, range 5-12) and two (8%) preceding respiratory symptoms.[84] The variable relation between infection and symptom onset, as well as the phenotypical heterogeneity, suggests a possible range of contributing para-infective or post-infective immune processes and host susceptibilities, including cellular, cytokine, humoral, or other immune factors.[85 86] Associations with known cell surface antibodies including to the NMDAR and voltage gated potassium channel complex have been described, albeit rarely, such that a direct causal link is difficult to establish.[87 88] In some cases, the presence of SARS-CoV-2 could be coincidental or non-specific; however, some of these observations could contribute to the general understanding of neurological autoimmunity and its association with infection and inflammation, rather than of covid-19 as such. More specific biomarkers are needed to identify cases of autoimmune encephalitis among those patients with significant cognitive and neuropsychiatric symptoms.

ADEM

ADEM is an immune mediated inflammatory demyelinating disorder. It usually affects the white matter regions of the brain and spinal cord. ADEM is considered a para-infectious or post-infectious syndrome, usually triggered by viruses. Acute hemorrhagic leukoencephalopathy (AHLE, Weston-Hurst disease) is a rare fulminant form of ADEM. Both have been reported rarely in the context of covid-19, with reporting bias and under-reporting of cases both likely. In a UK nationwide surveillance study, 13 of 267 reported covid-19 neurological presentations, in patients admitted to hospital from March to October 2020, were classified as leukoencephalopathy or demyelination.[60] In a prospective study of 47 572 patients with covid-19 in Singapore, also in the first phase of the pandemic from March to July 2020, one case each of ADEM and AHLE were identified, both in critically unwell male adults.[89]

Outside of the covid-19 setting, ADEM and AHLE are most often described in children. Clinical presentation of ADEM includes encephalopathy, focal neurological symptoms or signs, and sometimes seizures. Magnetic resonance imaging is characterized by diffuse, large, poorly demarcated lesions in the white matter and in some cases in deep gray matter, while histology reveals perivenular inflammatory infiltration and demyelination.[90] Some children might have antibodies to myelin oligodendrocyte glycoprotein.[91] Most respond to immunosuppression with good prognosis and monophasic course. AHLE can cause raised intracranial pressure requiring neurosurgical intervention, with cerebral edema, petechial hemorrhage on magnetic resonance imaging, and high mortality.[92] Histology shows small vessel fibrinoid necrosis, perivascular neutrophil infiltration, hemorrhage, and demyelination.

In both syndromes, the (presumed) precipitating infective agent is frequently not identified; thus, the pandemic, with a prevalent and known agent, provides an unusual scenario. Despite this, the series of events leading from infection to inflammation in both presentations remains poorly delineated and can still only be presumed. Evidence for a preceding SARS-CoV-2 infection in reported cases varies from positive nasopharyngeal polymerase chain reaction (PCR) test, to SARS-CoV-2 antibody seropositivity or clinical symptoms temporally associated with peaks in infection. SARS-CoV-2 PCR has been found to be positive in cerebrospinal fluid in a small number of cases; however, the relevance of this is unclear.[93]

A systematic review comparing 46 covid-19 related ADEM and AHLE cases to typical pre-covid-19 cases, found increased numbers of adult compared with pediatric cases. The authors postulated that this could be related to immunological naivety to SARS-CoV-2 in the general population, and the age related increase in severity of SARS-CoV-2 respiratory infection. Historically, infections relating to ADEM are usually mild.[94] Other differences between pre-covid-19 and post-covid-19 cases identified were more frequent preceding severe respiratory illness

(29/46, 63% ventilated), less frequent myelin oligodendrocyte glycoprotein antibody positivity (1/15, 7% tested), more common hemorrhagic lesions (42%), less frequent response to standard immune suppression, and higher mortality.[94] These differences were suggested to be due in part to disproportionate numbers of AHLE in the cohort (15/46), with delays to diagnosis and treatment owing to ventilation contributing to worse treatment response and outcomes. However co-reporting of ADEM and AHLE, alongside more novel presentations to which these labels are applied as a best fit, or in which there might be mixed (for example vascular/microvascular) pathology, could contribute to some differences, making interpretation difficult.

Most diagnoses of ADEM and AHLE reported in relation to covid-19 were based on pre-existing pediatric diagnostic criteria. We reported the only case to date with fulminant presentation and extensive edema requiring hemicraniectomy (fig 2 E-K).[11] Histological descriptions are limited to the few patients who undergo biopsy. In our case, brain histology showed perivenular inflammation and myelin laden macrophages typical for ADEM.[11] Brain tissue was negative for SARS-CoV-2. Similar histological features were present in another case without preceding respiratory signs but with positive SARS-CoV-2 serology in 2020.[94] Other demyelinating presentations reported as post-infective complications of SARS-CoV-2 infection include myelitis and optic neuritis.[95]

The treatment of ADEM in the context of covid-19 has been extrapolated from the experience of pre-covid-19 cases. This extrapolation has been based on case reports and small case series in adults and children. Treatment consists of immunomodulation, usually with corticosteroids (1 g methylprednisolone for 3-5 days), followed by an oral prednisolone taper. In poor responders, treatment escalation often includes intravenous immunoglobulin and plasma exchange or both.[96]

ADEM-like presentations in the intensive care cohort

Atypical deep white matter lesions, especially in patients "slow to wake" after intubation and ventilation for critical covid-19, have been difficult to classify, and could be included in different studies as ADEM, ADEM-like, or hypoxia-ischemic brain injury.[11 97] Lesions are multifocal and appear hyperintense on FLAIR sequences, with variable degrees of hemorrhagic change, intralesional cyst-like areas, peripheral rim enhancement, and restricted diffusion (fig 2 L-O). Clinical features associated with these changes include abnormal wakefulness after sedation was stopped, confusion, or agitation, with variable pyramidal tract signs and seizures and headache reported in some cases. Given the requirement of magnetic resonance imaging, and the identification of clinical signs only on sedation withdrawal, diagnosis of these lesions is often delayed, and the timing and mechanism of brain injury is unclear. Histological correlation is lacking. While both ADEM and vascular pathologies have been described together, other contributors could include hypoxia, sepsis, coagulopathy, and cytokine storms.[28] In one study, such lesions were correlated with severity of systemic and respiratory illness.[97]

Given the rarity of reporting of these cases, few treatment data are available. Whether inflammation is persistent is unclear. Some reported cases were treated with steroids, and others with supportive management only.[11] In our own experience, these cases tended towards slow recovery with variable persistent cognitive and physical outcomes. On magnetic resonance imaging, we have found these lesions to be largely static over time, in contrast to ADEM, in which lesions typically resolve.

Pediatric inflammatory multisystem disorder temporally associated with SARS-CoV-2 (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C)

While children were less likely to present with severe respiratory symptoms, concerns of a cytokine mediated, pediatric, multisystem inflammatory syndrome were raised early in the covid-19 pandemic.[98 99] This syndrome, termed PIMS-TS or MIS-C, disproportionately affected black, Asian, and Hispanic children, and included older adolescents or young adults under adult neurology services.[100 101 102] Characteristic systemic features include fever, rash, and frequent gastrointestinal symptoms including abdominal pain and diarrhea, with cardiac involvement and hypotension requiring inotropic support in some cases.[99 101] Neurological involvement is reported in 14.8-20.5% cases.[102 103] In a retrospective UK multicenter study including 25 children with PIMS-TS and neurological involvement, encephalopathy was the commonest symptom (88%), followed by headache or meningism (40%), behavioral change (36%), visual hallucinations (24%), focal neurological signs (24%), and seizures (16%).[100] Peripheral neurological symptoms (40%) were mostly attributed to critical illness neuromyopathy, although focal nerve or muscle involvement is also reported.[100 103] Other covid-19 neurological complications, including acute stroke or ADEM, might co-occur.[95 100 102]

Elevated cytokine levels (particularly interleukin 6 and interleukin 8) and infrequent cerebrospinal fluid pleocytosis supported a cytokine driven etiology.[100 101] Additionally, markers of systemic inflammation are significantly elevated or abnormal, including elevated C reactive protein, erythrocyte sedimentation rate, D-dimer, ferritin, lymphopenia, and thrombocytopenia.[99 101] Magnetic resonance imaging abnormalities are common. In a retrospective imaging study including 11 PIMS-TS cases, abnormalities included splenial lesions of the corpus callosum (64%), ADEM-like changes (64%), cranial nerve (18%) or cauda equina (9%) enhancement, myelitis (9%), features suggestive of microthrombi (9%), and enhancing myositis of the facial and neck musculature (36%).[95] Cerebral edema has also been

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rarely reported.[102 104] Splenial lesions are reported to represent cytotoxic edema secondary to cytokine mediated glutamate release, to which the corpus callosum is especially vulnerable. These splenial lesions have previously been described in children and adults with febrile or viral illnesses including influenza.[69 95 100 102 105-107] Most reported cases were treated with various forms of immunomodulation including corticosteroids, IVIg, and in a small number of cases, tocilizumab or anakinra.[100 101] A more recent randomized controlled trial that recruited 75 patients with PIMS-TS to receive either intravenous methylprednisolone or IVIg concluded that intravenous methylprednisolone could be an acceptable first line treatment for children with PIMS-TS.[108] Outcome data are limited to short term only; encephalopathy appears to respond well to treatment in most patients; however, ongoing disability related to neuromyopathy is reported.[100 103]

Stroke

The risk of stroke is more than twofold greater in patients with covid-19 compared with matched controls.[47 48 109 110] Further, the risk appears to peak between 1-2 weeks following primary respiratory covid-19 infection and persists for up to one month; the stroke sometimes occurred 1-3 days before manifestation of the respiratory illness.[47 48 110] Acute stroke has been commonly reported as a neurological complication, but the overall frequency in the covid-19 population is low (1.4%; 95% confidence interval 1.0 to 1.9).[111] A meta-analysis suggested that the absolute incidence of stroke was 0.168%, lower than previously estimated.[112] The most common manifestation was acute ischemic stroke (87.4%); intracerebral hemorrhage was less common (11.6%).[111] Emerging data indicate an association between covid-19 and intracerebral hemorrhage, occurring in patients admitted to hospital and intensive care.[113] Notably, the characteristics of intracerebral hemorrhage in covid-19 differed from historic populations; in lobar location +/- fluid levels, multifocality (often in the presence of coagulopathies or anticoagulation use), and in its association with high rates of mortality.[113]

Similarly, in ischemic stroke, multiple focal large vessel arterial disease, usually in the absence of vasculopathy and often accompanied by systemic venous thrombosis (eg, pulmonary embolism), was characteristic of covid-19 (fig 2 P-S)[60 114 115] Systemic venous thrombosis was likely due to widespread thromboinflammation, with inflammatory markers such as D-dimer and C reactive protein invariably linked to the covid-19 ischemic stroke phenotype.[114 116] Although the exact mechanism is not fully understood, a stroke secondary to a cardiac shunt is less likely to fully explain these observations.

Compared with a historic pre-pandemic stroke cohort, patients with stroke associated with covid-19 were younger (about one third were <60 years old) and had a greater number of conventional, modifiable cerebrovascular risk factors (eg, atrial fibrillation, diabetes, hypertension, dyslipidemia, and congestive cardiac failure).[60 115] Inpatient mortality and morbidity was considerably higher compared with non-covid-19 or historical controls.[111 114-118]

In terms of management, a large individual patient data meta-analysis suggested that anticoagulation could be beneficial in this population.[14] However, no trials have provided definitive guidance. The value of treatment with mechanical thrombectomy and thrombolysis remains unclear. Although small studies suggest a negative impact with mechanical thrombectomy, intravenous thrombolysis was not associated with an increased risk of disability, mortality, or hemorrhagic transformation.[119 120]

Overall, vaccinations appear to reduce covid-19 associated stroke, despite the rare post-vaccine complication of arterial and venous cerebral infarction among those taking vector based vaccines.[121]

Guillain-Barré syndrome

Guillain-Barré syndrome, a disabling post-infectious polyradiculoneuropathy, was an early target of interest for potential neurological complications of SARS-CoV-2. Guillain-Barré syndrome has been described with other viral infections including MERS, and more convincingly with Zika virus, but also established viral infections such as cytomegalovirus and HIV; *Campylobacter jejuni* remains the best characterized and most frequent cause worldwide.[122] Alongside the historical concern from influenza vaccinations, reports of a causative association of Guillain-Barré syndrome with SARS-CoV-2 were therefore inevitable.

The first cautiously worded case report from Wuhan in January 2020[123] was swiftly followed by many reports of cases, clusters, and series of patients with Guillain-Barré syndrome associated with covid-19. These descriptions were retrospective, many with insecure reporting methods, and a paucity of reliable diagnostic confirmation. In addition, the small event numbers even in the larger series resulted in unfeasibly high Guillain-Barré syndrome cases rates. For example, 1.8% of covid-19 cases, a figure reported in one study, would equate to more than 250 000 excess Guillain-Barré syndrome cases in the UK in 2020 and 2021.[124] Questions were therefore appropriately raised to challenge the covid-19-Guillain-Barré syndrome association. Counting cases of Guillain-Barré syndrome independently of the pandemic, through a UK-wide mandatory intravenous immunoglobulin treatment register for Guillain-Barré syndrome without reporting bias, showed fewer than 2300 cases in the UK in 2020 and 2021 combined. In the first six months of the pandemic, no geographical clustering of cases was observed with the recorded geographical spread of covid-19.[125] Similar data were reported from Singapore, and a parallel pandemic of Guillain-Barré syndrome has not materialized.[126] One population based study from the US veterans affairs population,

investigating long term sequalae, suggested a link with covid-19 and Guillain-Barré syndrome beyond six months, but this requires corroboration in other settings.[15]

Guillain-Barré syndrome is a post-infectious disease triggered by molecular mimicry of neural epitopes on invading pathogens, driving a break in immunological tolerance to these epitopes, and targeted attack on axons and myelin mediated by macrophages. To date, and despite a number of different approaches, no linear, non-linear, protein, glycoprotein or carbohydrate epitopes, or immunological responses that might result from such drivers have been found in covid-19.[127]

A greater likelihood of causation exists if an excess of plausible cases can be shown, as well as specific or unique disease features, or a phenotype that makes the cases identifiable from background disease. All case reporting is biased unless one is able to obtain a truly random sample or complete acquisition. However, our own cohort, and the review of all the published case series, found no distinctive features of Guillain-Barré syndrome reported as being related to covid-19, compared with Guillain-Barré syndrome not associated with covid-19.[125 128] The excess morbidity and ventilation of patients in the covid-19 cohort was most likely related to covid-19 lung diseases, rather than neuromuscular complications of Guillain-Barré syndrome.[128]

If any extremely rare cases of Guillain-Barré syndrome are caused by covid-19, since they are not phenotypically different from other spontaneous cases, the treatment remains the same: intravenous immunoglobulin or plasma exchange. Early in the pandemic, an initial shift towards more plasma exchange was performed in some cohorts, as (subsequently unfounded) concerns arose about an adverse effect of IVIg. In the long term, patients have been treated in the same way and had very similar outcomes.

Other neuromuscular syndromes

Anecdotal case reports have described new onset myasthenia gravis in patients infected with covid-19. One explanation for these cases is that, as with any other viral infection, those with subtle symptoms or subclinical disease will become manifest.[129 130]

In the early series from Wuhan, 11% of patients had evidence of muscle injury, defined as having an elevated creatine kinase level and myalgia, or both.[10] More severely ill patients had higher levels of injury. However, many confounding variables were present, including hypoxia, sepsis, drug toxicity, and mechanical ventilation, making it difficult to disentangle the possible underlying mechanisms. A large autopsy study comparing non-covid-19 infected patients and patients with covid-19 who had died found significant signs of muscle inflammation in the covid-19 group.[131] These included upregulation of major histocompatibility complex, endomysial infiltration with leukocytes, and occasionally, abnormal expression of myxovirus resistance protein A on capillaries suggestive of type 1 interferonopathy; which can be seen in dermatomyositis, but also as a tissue response to viral infection.[131 132] Although SARS-CoV-2 RNA was detected by reverse transcriptase PCR, evidence for direct invasion of myofibers was not confirmed using immunohistochemistry and electron microscopy. Occasional cases of rhabdomyolysis in patients with covid-19 have also been described.[133] However, owing to the restrictions imposed during the pandemic, muscle biopsies were not routinely performed.

A number of focal neuropathies, including facial palsy and neuralgic amyotrophy, have been described in the context of SARS-CoV-2 infection.[134 135] Both presentations, however, can occur in the setting of other viral infections such as herpes simplex, herpes zoster, and HIV. Causation is difficult to prove.[136 137]

In a follow-up series of patients who had been severely ill with covid-19 and required mechanical ventilation, a portion (11/69, 16%) presented with multiple mononeuropathies.[138] These were not at the usual sites attributable to compression or traction. The authors postulated a possible vasculitic or immune thrombotic mechanism affecting the peripheral nerves or plexuses, rather than attributing the findings to critical care neuromyopathy. However, nerve biopsies were not performed.

Neurological presentations related to long covid

Long covid refers to prolonged symptoms following infection with SARS-CoV-2 that are not explained by an alternative diagnosis. It includes the National Institute for Health and Care Excellence terms “ongoing symptomatic covid-19” (symptoms lasting 4-12 weeks) and “post-covid syndrome” (symptoms beyond 12 weeks).[139]

In a review of the first year of the post-covid-19 clinic at University College London Hospitals (n=1325; 566 not admitted to hospital), the most common neurological symptoms were headache (17.6%), brain fog (15.1%), disturbed sleep (10.7%), and anosmia (9.2%).[140] Anecdotally, at the Queen Square covid-19 neurology clinic, the most common neurological symptoms are attentional cognitive symptoms (brain fog), chronic daily headache, sensory symptoms, and autonomic symptoms. This list of symptoms is similar to a review of the first 100 patients seen at a neurology covid-19 clinic in Chicago (brain fog 81%, headache 68%, numbness/tingling 60%, anosmia 55%).[141] In an international cohort, an online survey was completed by 3762 patients who had symptoms for more than six months, with onset before June 2020. The most frequent symptoms were fatigue, post-exertional malaise, and cognitive dysfunction. Of those, 85% experienced a relapse in symptoms with physical or mental activity.[142] In a meta-analysis of 51 studies assessing 16 neuropsychiatric symptoms, the most common symptoms were sleep disturbance, fatigue, cognitive impairment, anxiety and post-traumatic stress. Little evidence indicated a relation between

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symptoms and the severity of the acute illness.[143] In the UK post-hospitalization study (1077 adults, multicenter observational study), factors associated with failure to recover were female gender, middle age, ≥2 comorbidities, and a more severe acute illness.[144]

The chronic daily headache phenotype is most consistent with migraine. In the Queen Square cohort, imaging has been normal in the majority; a small number had some non-specific white matter T2 hyperintensities or incidental findings. In a Spanish case-control study, the presence of headache at onset was associated with a higher prevalence of headache and fatigue in the post-infectious phase.[145] The headache had features of migraine and tension headache. Headache at onset was associated with a history of migraine (odds ratio 2.9; 95% confidence interval 1.41 to 5.98) and with development of persistent tension-type headache post-covid-19 (2.65; 1.66 to 4.24). Among those who had a history of migraine, worsening of migraine post infection was seen in 58.6% of those with headache at onset of the acute illness and 34.3% of those who did not have headache acutely (p<0.001). Fatigue was more common in those who had headache acutely (1.55; 1.07 to 2.24).

Cognitive symptoms are common (box 2) and on neuropsychometry assessment, both anecdotally from the Queen Square clinic and other published studies, mainly affect anterior cognitive pathways including executive function, impaired attention, and reduced verbal fluency.[146 147] In one University of California, San Francisco study, patients with cognitive symptoms had a greater median number of pre-existing cognitive risk factors than control patients without cognitive symptoms. A small number of patients also had mildly raised cerebrospinal fluid protein. Matched oligoclonal bands were present, and therefore intrathecal synthesis/inflammation was not indicated.[148]

The syndrome is heterogeneous and the mechanisms behind the neurological manifestations are still poorly understood. Some studies have shown an association between inflammatory markers (elevated D-dimer, C reactive protein, and lymphopenia) and post-covid-19 symptoms,[149] but this is not borne out in other studies.[150-152] Similarities exist with other post-viral syndromes and chronic fatigue syndrome.[153-155] Some patients might also experience somatoform symptoms.[156] Ongoing research could yield further insights into the pathogenesis of post-covid-19 syndrome, and perhaps help unravel the mechanisms behind chronic fatigue syndrome or other post-viral syndromes.

Effect on pre-existing inflammatory neurological disease (central and peripheral)

Initially, concerns were raised that covid-19 or vaccination would worsen disease or precipitate relapse in patients with pre-existing inflammatory central nervous system and neuromuscular disease.[157] Some evidence suggested that more substantial harms resulted from difficult and delayed diagnosis of general neurological disorders, anxiety of the unknown for patients, and reduced disease control resulting from fewer healthcare interactions and alterations in treatment strategies in the first year of covid-19, than resulted from relapses precipitated by infection or vaccination.[157 158]

Early concerns were also raised that immunosuppressants used in neurological and rheumatological disease would affect humoral seroconversion to virus infection or covid-19 vaccination, with subsequent risks and adverse outcomes. A very large prospective national study showed that only mycophenolate mofetil, anti-CD20 monoclonal treatments, and sphingosine 1-phosphate (SIP-1) inhibitors (eg, fingolimod or siponimod) reduced humoral seroconversion.[159]

That the chronic relapsing and remitting peripheral nerve (and some central) diseases, especially chronic inflammatory demyelinating polyneuropathy (CIDP) or multifocal motor neuropathy with conduction block (MMNCB), worsen briefly with any infection through inflammatory decompensation, is well recognized. Early in the pandemic, case reports of recurrent Guillain-Barré syndrome and CIDP were inevitably published, but none has been substantiated by large series. In contrast, the main risk of an adverse outcome to patients with pre-existing multiple sclerosis who contracted covid-19 was not the infection, but previous recent treatment with anti-CD20 agents (rituximab and ocrelizumab), whereas interferons and glatiramer acetate were protective against severe covid-19.[160-162] Patients with multiple sclerosis had normal T cell responses to SARS-CoV-2 infection and covid-19 vaccine in all treated groups compared with controls, and indeed, patients on anti-CD20 treatments with multiple sclerosis had enhanced IFN-γ T cell responses compared with untreated patients.[163] No good studies have been performed on the effects of SIP-1 inhibitors on SARS-CoV-2 infection or vaccination T cell responses, which are much more likely to be associated with deficient T cell function; these studies are urgently needed.

In patients with myasthenia gravis, a global electronic health record database found that compared with the general covid-19 population, patients with myasthenia gravis and covid-19 were at a higher risk of admission to hospital (odds ratio 3; 95% confidence interval 2.4 to 3.8), admission to intensive care (5.2; 3.7 to 7.3), intubation (odds ratio 4.6), and death (4.3; 2.9 to 6.4).[164]

Concerns about antiviral vaccines precipitating relapses of inflammatory diseases are extrapolated from the rare association of influenza vaccine with Guillain-Barré syndrome.[165] However, a study of more than 700 patients with previous Guillain-Barré syndrome found they were at no additional risk of another episode of Guillain-Barré syndrome following vaccination.[166] Recent reassurance that influenza vaccination does not precipitate further episodes of Guillain-Barré syndrome or CIDP

influenced two Dutch studies showing that although 5% of patients with CIDP and MMNCB reported a worsening of symptoms, these were mild, and only half required a modification of treatment.[167-169] This finding was similar for patients with central nervous system diseases (multiple sclerosis, neuromyelitis optic spectrum disorders (NMOSD)).

Management of covid-19 associated neurological disorders

The key to the management of neurological disorders associated with covid-19 is a detailed history, including the time between infection and symptom onset, and examination together with the appropriate interpretation of radiological and laboratory data. This protocol is crucial, as the diagnosis will imply specific disease mechanism(s) which will guide best management (fig 3). At Queen Square, a multidisciplinary input in challenging cases, including complex stroke, has been invaluable.

In most cases, including encephalitis, ADEM, and Guillain-Barré syndrome, the recommended management corresponds with pre-covid-19 guidance. For syndromes with multifactorial causes such as encephalopathy, identification and optimization of contributing factors including hypoxia, sepsis, and metabolic disturbances form an essential part of management. Specific treatment guidelines have been required for the syndromes more particular to covid-19 such as hyperinflammation in PIMS-TS.

Emerging treatments

Emerging treatment data largely highlight the secondary benefit of systemic treatment on neurological complications of covid-19. A recent retrospective UK based observational study of 184 986 adult hospital inpatients (January 2020 to June 2021) showed reduction of neurological events (stroke, seizure, meningitis/encephalitis, or other neurological complication) in patients treated with dexamethasone and remdesivir, compared with standard care.[182] In patients with severe covid-19, neurological events were reduced in patients treated with dexamethasone (odds ratio 0.76, 95% confidence interval 0.69 to 0.90), remdesivir (0.69, 0.51 to 0.90), and dexamethasone and remdesivir combined (0.54, 0.47 to 0.61). In patients with non-hypoxic covid-19, neurological events were reduced in patients treated with dexamethasone (0.78, 0.62 to 0.97), with a trend towards reduced events with dexamethasone and remdesivir combined (0.63, 0.31 to 1.15). The impact on neurological complications of other drugs recommended by NICE with shown efficacy in covid-19, including tocilizumab and baricitinib, nirmatrelvir, and ritonavir, are not yet reported.[183] However, these similarly target either systemic inflammation or viral replication or entry, and thus would be predicted to have a similar effect.

Systemic treatment could either directly or indirectly affect the pathophysiology of neurological complications of covid-19. In subgroup analysis of the above study, incidence of stroke was reduced by use of dexamethasone in both severe and non-hypoxic disease (odds ratio 0.57, 95% confidence interval 0.48 to 0.68 and 0.47, 0.29 to 0.72, respectively), supporting the role of inflammation in stroke related to covid-19.[182 184] The impact on other presentations including seizures (reduced in patients with severe covid-19 treated with dexamethasone (0.41, 0.33 to 0.52), remdesivir (0.28, 0.1 to 0.61), or both (0.37, 0.27 to 0.51)), could be multifactorial. Meningitis/encephalitis events were also reduced in the severe covid-19 groups with dexamethasone or combination treatment, suggesting a potential benefit of reduction in central nervous system inflammatory events. However, further interrogation of this group with detailed phenotyping data is needed. ADEM and other inflammatory events were studied separately, alongside syndromes not expected to respond to immune treatment.

The success of the vaccine programs in reducing the incidence and severity of covid-19 is well documented. Although adenovirus vector based vaccines have been linked to a small number of neurological complications (cerebral venous sinus thrombosis and Guillain-Barré syndrome), self-controlled studies conclude that the risk of neurological events from SARS-CoV-2 infection far outweighs that following vaccination.[121 134] Incidentally, following the introduction of vaccination programs and increasing population immunity, the number of cases of acute neurological syndromes, including stroke and ADEM, has fallen at our institution. However, this finding is yet to be corroborated at a population level. A recent systematic review and meta-analysis showed that vaccination reduces risk of developing long covid; patients who had received two doses of vaccination had significantly lower risk compared with those not vaccinated (odds ratio 0.57, 95% confidence interval 0.43 to 0.76).[185]

Optimization of comorbidities associated with severe covid-19 in reducing risk of neurological complications needs further investigation. In a retrospective cohort study of 10 541 patients admitted to hospital with covid-19 between January and September 2020, outpatient use of statins and hypertensives, or both, reduced the risk of death (adjusted odds ratio 0.68, 95% confidence interval 0.58 to 0.81) or severe disease (0.80, 0.69 to 0.93) in patients with known cardiovascular disease and hypertension, or both.[186] Although incidence of neurological events was not explored in this study, covid-19 severity increases risk of neurological complications. The public health need to catch up on cardiovascular risk modifying treatments missed because of pandemic disruption has also been highlighted, to reduce risk of not just severe covid-19, but also excess cerebrovascular events resulting from missed treatment opportunities.[187]

Guidelines

The Association of British Neurologists and other national and international neurological organizations

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Management strategies for key neurological complications in covid-19

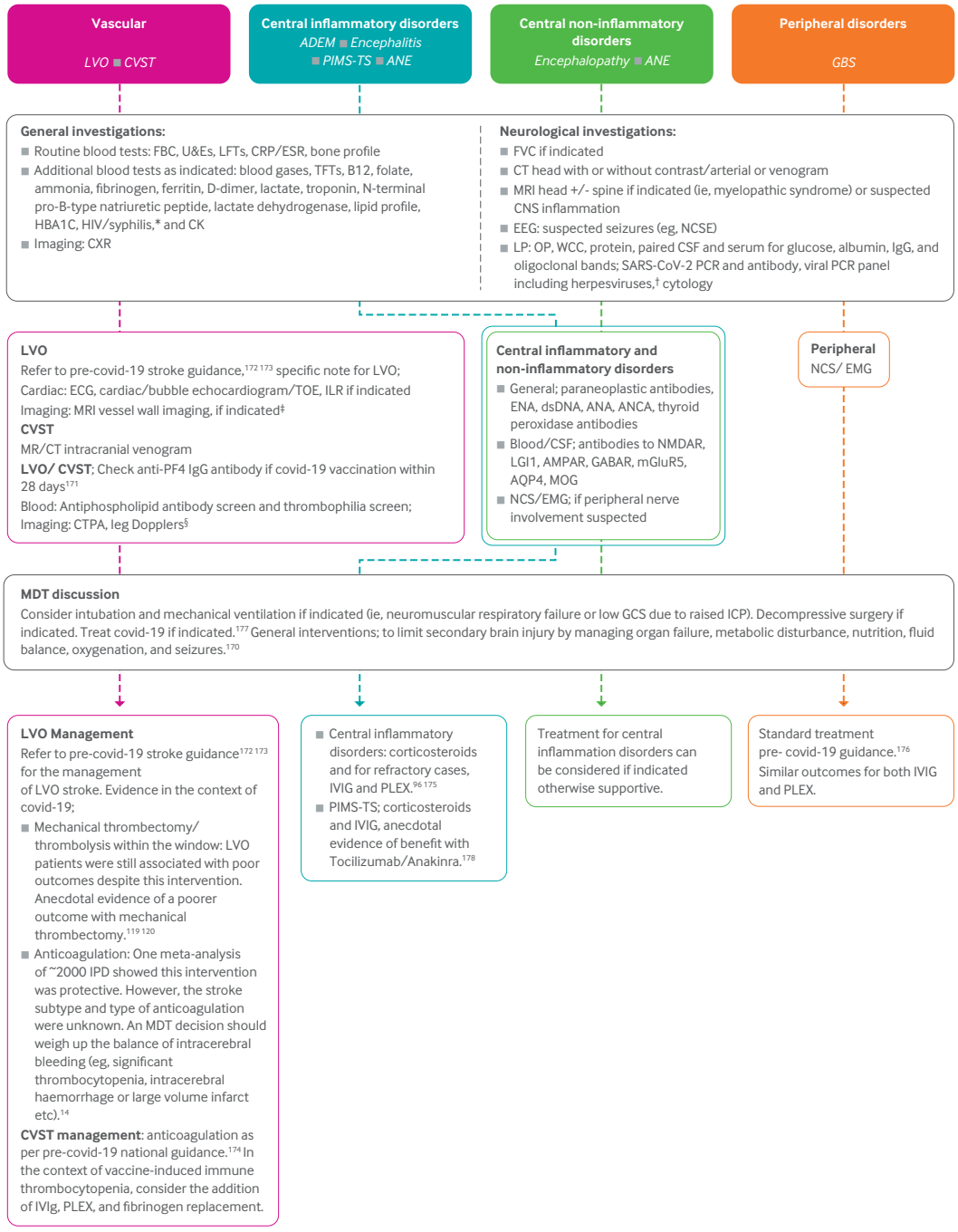

Fig 3 | Management strategies for key neurological complications in covid-19 ADEM=acute-demyelinating encephalomyelitis; AMPAR=alfa-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ANA=antinuclear antibodies; ANCA=antineutrophil cytoplasmic antibodies; ANE=acute necrotizing encephalitis; AQP4=aquaporin 4; MOG=myelin oligodendrocyte glycoprotein; CK=creatinine kinase; CNS=central nervous system; CRP=C reactive protein; CSF=cerebrospinal fluid; CSVT=cerebral sinus venous thrombosis; CXR=chest x ray; dsDNA=double stranded DNA; ECG=electrocardiogram; EEG=electroencephalogram; ENA=extractable nuclear antigen; ESR=electrolyte sedimentation rate; FBC=full blood count; FVC=forced vital capacity; GABA-R= γ-aminobutyric acid receptor; GBS=Guillain-Barré syndrome; GCS=Glasgow coma scale; HBA_{1C}=glycated hemoglobin A_{1C}; HIV=human immunodeficiency virus; ICP=intracranial pressure; MDT=multidisciplinary team; IgG-immunoglobulin G, ILR=implantable loop recorder; IPD=individual patient data; IVIg=intravenous immunoglobulin; LFT=liver function test; LGI1=leucine rich glioma inactivated 1; LP=lumbar puncture; LVO=large vessel arterial occlusion; mGluR5=metabotropic glutamate receptor 5; NCS/EMG=nerve conduction study/electromyography; NCSE=non-convulsive status epilepticus; NMDA-R=N-methyl-D-aspartate receptor; OP=opening pressure; PCR=polymerase chain reaction; PET=positron emission tomography; PF4=platelet factor 4; PIMS-TS =pediatric multisystem inflammatory syndrome-temporally associated with SARS-CoV-2; PLEX=plasma exchange; SARS-CoV-2=severe acute respiratory coronavirus-2; TOE=transesophageal echocardiogram; U&Es=urea and electrolyte; WCC=white cell count. *Reports of increased incidence of secondary syphilis and HIV are risk factors for hospital admission/severe covid-19 and increased mortality.[179 180] †Evidence of reactivation during covid-19 and post vaccination.[181] ‡Indication includes an unexplained intracranial arterial stenosis. §To investigate for evidence of a hypercoagulable state

published regularly updated guidelines throughout the pandemic, for clinicians and patients living with neurological diseases, and their carers.[188 189] These guidelines included guidance on relative risk of severe covid-19 in neurology patients, shielding and reducing risk of infection, information on potential drug interactions in the context of covid-19 and common neurological conditions, and guidance on immune suppression in patients with neuroinflammatory disorders not related to covid-19. Neurological diseases such as multiple sclerosis, motor neuron disease, myasthenia gravis, and Huntington's disease have been highlighted as high risk patient groups warranting early covid-19 treatment in the community, following confirmation of a positive test.[177]

Consensus guidelines have been published for the investigation and management of encephalopathy and PIMS-TS.[170 178] Encephalopathy guidelines recommended investigating and optimizing secondary causes of encephalopathy or central nervous system pathology including encephalitis, ADEM, and posterior reversible encephalopathy syndrome (PRES), when suggestive clinical features are present.[170] Guidelines for PIMS-TS were published in 2020 relating to prescription of steroids, IVIg, and biological treatments, as well as highlighting the need for multidisciplinary input.[178] In the UK, NICE has published guidelines on the management of long covid, and also vaccine induced immune thrombocytopenia and thrombosis.[139 171] More integrated guidelines could emerge as understanding of covid-19 neuropathology evolves. These guidelines are likely to overlap with general preventative and treatment guidelines reducing severity of systemic covid-19, in the expectation that these measures will also reduce neurological burden. The need for increased surveillance and early recognition of neurological injury, especially in the intensive care population, should be highlighted.

Conclusion

The covid-19 pandemic has had seismic global consequences in terms of morbidity and mortality, as well as in overwhelming health systems, even in wealthy settings. Nevertheless, the medical and scientific community has risen to the challenge with impressive results. Although neurological complications in the acute setting are relatively rare in comparison with the total number of infections, the consequences of neurological injury for individual patients are significant. The mechanism of neurovirulence of SARS-CoV-2 appears to be related primarily to immune dysregulation and an immunothrombotic milieu. Treatments therefore need to be focused on this aspect of the pathophysiology. The large numbers of patients now with long covid will be a legacy of the pandemic. Elucidating the mechanism of long covid to manage and treat these patients is vital. Additionally, the unknown long term consequences in relation to neurodegeneration will require longer term study.

QUESTIONS FOR FURTHER RESEARCH

- Can a granular pathophysiological mechanistic model for both acute and long covid-19 be established?
- What are the differing risk factors globally for short term and long term neurological complications of covid-19?
- What are the benefits versus complications of anticoagulation in ischemic stroke associated with covid-19 with consideration of subtypes (ie, large *v* small arterial strokes) on outcome?
- What are the optimal treatment strategies for long covid?
- What are the long term neurological consequences of covid-19 infection?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

The authors are grateful to a patient who reviewed the manuscript and provided a patient account to show the individual patient burden of neurological symptoms following covid-19 (box 2).

GLOSSARY OF ABBREVIATIONS

- SARS: severe acute respiratory syndrome
- MERS: Middle East respiratory syndrome
- ADEM: acute disseminated encephalomyelitis
- ECMO: extracorporeal membranous oxygenation
- LMIC: low and middle income countries
- ACE2: angiotensin converting enzyme 2
- TNF-alfa: tumor necrosis factor
- GFAP: glial fibrillary acidic protein
- NMDAR: N-methyl-D-aspartate receptor
- ARDS: acute respiratory distress syndrome
- sHLH: secondary hemophagocytic lymphocytosis
- ICANS: immune effector cell associated neurotoxicity syndrome
- CAR-T: chimeric antigen receptor T cell
- MIP-1β: macrophage inflammatory protein-1 beta
- IVIg: intravenous immunoglobulin
- RPLS: reversible posterior leukoencephalopathy
- RCVS: reversible cerebral vasoconstriction syndrome
- T2/FLAIR: T2 weighted/fluid attenuated inversion recovery
- AHLE: acute hemorrhagic leukoencephalopathy
- PIMS-TS: pediatric inflammatory multisystem disorder temporally associated with SARS-CoV-2
- MIS-C: multisystem inflammatory syndrome in children
- SIP-1: sphingosine 1-phosphate:
- CIDP: chronic inflammatory demyelinating polyneuropathy
- MMNCB: multifocal motor neuropathy with conduction block
- NMOSD: neuromyelitis optic spectrum disorders
- PRES: posterior reversible encephalopathy syndrome

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1 Zhu N, Zhang D, Wang W, et al, China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;382:727-33. doi:10.1056/NEJMoa2001017
2 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. 2020. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020
3 Ng Kee Kwong KC, Mehta PR, Shukla G, Mehta AR. COVID-19, SARS and MERS: A neurological perspective. *J Clin Neurosci* 2020;77:13-6. doi:10.1016/j.jocn.2020.04.124
4 World Health Organization. Middle East respiratory syndrome (MERS-CoV). 2022. https://www.who.int/health-topics/middle-east-respiratory-syndrome-coronavirus-mers#tab=tab_1
5 Manji H, Carr AS, Brownlee WJ, Lunn MP. Neurology in the time of COVID-19. *J Neurol Neurosurg Psychiatry* 2020;91:568-70.
6 World Health Organization. WHO Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. 2015. https://www.who.int/publications/m/item/summary-of-probable-sars-cases-with-onset- of-illness-from-1-november-2002-to-31-july-2003
7 Sharma A, Ahmad Farouk I, Lal SK. COVID-19: a review on the novel coronavirus disease evolution, transmission, detection, control and prevention. *Viruses* 2021;13:202. doi:10.3390/v13020202
8 World Health Organization. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/
9 Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;584:430-6. doi:10.1038/s41586-020-2521-4
10 Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020;77:683-90. doi:10.1001/jamaneurol.2020.1127
11 Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain* 2020;143:3104-20. doi:10.1093/brain/awaa240
12 Ellul MA, Benjamin L, Ivi B, et al. Neurological associations of COVID-19. *Lancet Neurol* 2020;19:767-83. doi:10.1016/S1474-4422(20)30221-0
13 Chou SHY, Beghi E, Helbok R, et al, GCS-NeuroCOVID Consortium and ENERGY Consortium. Global incidence of neurological manifestations among patients hospitalized with COVID-19—a report for the GCS-NeuroCOVID Consortium and the ENERGY Consortium. *JAMA Netw Open* 2021;4:e2112131. doi:10.1001/jamanetworkopen.2021.12131
14 Singh B, Lant S, Cividini S, et al, Brain Infections Global COVID-Neuro Network Study Group. Prognostic indicators and outcomes of hospitalised COVID-19 patients with neurological disease: An individual patient data meta-analysis. *PLoS One* 2022;17:e0263595. doi:10.1371/journal.pone.0263595
15 Xu E, Xie Y, Al-Aly Z. Long-term neurologic outcomes of COVID-19. *Nat Med* 2022;28:2406-15. doi:10.1038/s41591-022-02001-z
16 Taquet M, Sillett R, Zhu L, et al. Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients. *Lancet Psychiatry* 2022;9:815-27. doi:10.1016/S2215-0366(22)00260-7
17 Knight R, Walker V, Ip S, et al, CVD-COVID-UK/COVID-IMPACT Consortium and the Longitudinal Health and Wellbeing COVID-19 National Core Study. Association of COVID-19 with major arterial and venous thrombotic diseases: a population-wide cohort study of 48 million adults in England and Wales. *Circulation* 2022;146:892-906. doi:10.1161/CIRCULATIONAHA.122.060785
18 Flood J, Shingleton J, Bennett E, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS): Prospective, national surveillance, United Kingdom and Ireland, 2020. *Lancet Reg Health—Eur*. 2021;3:100075.
19 Bauer L, Laksono BM, de Vrij FMS, Kushner SA, Harschnitz O, van Riel D. The neuroinvasiveness, neurotropism, and neurovirulence of SARS-CoV-2. *Trends Neurosci* 2022;45:358-68. doi:10.1016/j.tins.2022.02.006
20 Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271-280.e8. doi:10.1016/j.cell.2020.02.052
21 Chen R, Wang K, Yu J, et al. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in the human and mouse brains. *Front Neurol* 2021;11:573095. doi:10.3389/fneur.2020.573095
22 Brann DH, Tsukahara T, Weinreb C, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *Sci Adv* 2020;6:1-20. doi:10.1126/sciadv.abc5801
23 Matschke J, Lütgehetmann M, Hagel C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. *Lancet Neurol* 2020;19:919-29. doi:10.1016/S1474-4422(20)30308-2
24 Thakur KT, Miller EH, Glendinning MD, et al. COVID-19 neuropathology at Columbia University Irving Medical Center/New York Presbyterian Hospital. *Brain* 2021;144:2696-708. doi:10.1093/brain/awab148
25 Stein SR, Ramelli SC, Grazioli A, et al, NIH COVID-19 Autopsy Consortium. SARS-CoV-2 infection and persistence in the human body and brain at autopsy. *Nature* 2022;612:758-63. doi:10.1038/s41586-022-05542-y
26 Lee M-H, Perl DP, Nair G, et al. Microvascular injury in the brains of patients with covid-19. *N Engl J Med* 2021;384:481-3. doi:10.1056/NEJMc2033369
27 Deigendesch N, Sironi L, Kutza M, et al. Correlates of critical illness-related encephalopathy predominate postmortem COVID-19 neuropathology. *Acta Neuropathol* 2020;140:583-6. doi:10.1007/s00401-020-02213-y
28 Reichard RR, Kashani KB, Boire NA, Constantopoulos E, Guo Y, Lucchinetti CF. Neuropathology of COVID-19: a spectrum of vascular and acute disseminated encephalomyelitis (ADEM)-like pathology. *Acta Neuropathol* 2020;140:1-6. doi:10.1007/s00401-020-02166-2
29 Poloni TE, Medici V, Moretti M, et al. COVID-19-related neuropathology and microglial activation in elderly with and without dementia. *Brain Pathol* 2021;31:e12997. doi:10.1111/bpa.12997
30 Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395:1033-4. doi:10.1016/S0140-6736(20)30628-0
31 Pröbstel A-K, Schirmer L. SARS-CoV-2-specific neuropathology: fact or fiction?*Trends Neurosci* 2021;44:933-5. doi:10.1016/j.tins.2021.10.006
32 Keddie S, Ziff O, Chou MKL, et al. Laboratory biomarkers associated with COVID-19 severity and management. *Clin Immunol* 2020;221:108614. doi:10.1016/j.clim.2020.108614
33 Liu QQ, Cheng A, Wang Y, et al. Cytokines and their relationship with the severity and prognosis of coronavirus disease 2019 (COVID-19): a retrospective cohort study. *BMJ Open* 2020;10:e041471. doi:10.1136/bmjopen-2020-041471
34 Del Valle DM, Kim-Schulze S, Huang HH, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med* 2020;26:1636-43. doi:10.1038/s41591-020-1051-9
35 Abani O, Abbas A, Abbas F, et al, RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021;397:1637-45. doi:10.1016/S0140-6736(21)00676-0
36 Horby P, Lim WS, Emberson JR, et al, RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021;384:693-704. doi:10.1056/NEJMoa2021436
37 Needham EJ, Ren AL, Digby RJ, et al, Cambridge NeuroCOVID Group, CITIID-NIHR COVID-19 BioResource Collaboration, Cambridge NIHR Clinical Research Facility. Brain injury in COVID-19 is associated with dysregulated innate and adaptive immune responses. *Brain* 2022;145:4097-107. doi:10.1093/brain/awac321
38 Paterson RW, Benjamin LA, Mehta PR, et al, UCLH Queen Square COVID-19 Biomarker Study Group. Serum and cerebrospinal fluid biomarker profiles in acute SARS-CoV-2-associated neurological

syndromes. *Brain Commun* 2021;3:b099. doi:10.1093/braincomms/fcab099
39 Armangue T, Spatola M, Vlagea A, et al, Spanish Herpes Simplex Encephalitis Study Group. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. *Lancet Neurol* 2018;17:760-72. doi:10.1016/S1474-4422(18)30244-8
40 Franke C, Ferse C, Kreye J, et al. High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms. *Brain Behav Immun* 2021;93:415-9. doi:10.1016/j.bbi.2020.12.022
41 Alexopoulos H, Magira E, Bitzogli K, et al. Anti-SARS-CoV-2 antibodies in the CSF, blood-brain barrier dysfunction, and neurological outcome: Studies in 8 stuporous and comatose patients. *Neurol Neuroimmunol Neuroinflamm* 2020;7:4-8. doi:10.1212/NXI.0000000000000893
42 Wenzel J, Lampe J, Müller-Fielitz H, et al. The SARS-CoV-2 main protease M^{pro} causes microvascular brain pathology by cleaving NEMO in brain endothelial cells. *Nat Neurosci* 2021;24:1522-33. doi:10.1038/s41593-021-00926-1
43 Rhea EM, Logsdon AF, Hansen KM, et al. The S1 protein of SARS-CoV-2 crosses the blood-brain barrier in mice. *Nat Neurosci* 2021;24:368-78. doi:10.1038/s41593-020-00771-8
44 Ahamed J, Laurence J. Long COVID endotheliopathy: hypothesized mechanisms and potential therapeutic approaches. *J Clin Invest* 2022;132:1-11. doi:10.1172/JCI161167
45 Benjamin LA, Paterson RW, Moll R, et al, UCLH Queen Square COVID-19 Biomarker Study group. Antiphospholipid antibodies and neurological manifestations in acute COVID-19: A single-centre cross-sectional study. *EClinicalMedicine* 2021;39:101070. doi:10.1016/j.eclinm.2021.101070
46 Kakarla V, Kaneko N, Nour M, et al. Pathophysiologic mechanisms of cerebral endotheliopathy and stroke due to Sars-CoV-2. *J Cereb Blood Flow Metab* 2021;41:1179-92. doi:10.1177/0271678X20985666
47 Yang Q, Tong X, George MG, Chang A, Merritt RK. COVID-19 and risk of acute ischemic stroke among medicare beneficiaries aged 65 years or older: self-controlled case series study. *Neurology* 2022;98:e778-89. doi:10.1212/WNL.0000000000013184
48 Katsoularis I, Fonseca-Rodríguez O, Farrington P, Lindmark K, Fors Connolly AM. Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in Sweden: a self-controlled case series and matched cohort study. *Lancet* 2021;398:599-607. doi:10.1016/S0140-6736(21)00896-5
49 Stamm B, Huang D, Royan R, Lee J, Marquez J, Desai M. Pathomechanisms and treatment implications for stroke in COVID-19: a review of the literature. *Life (Basel)* 2022;12:207. doi:10.3390/life12020207
50 Miraclin T A, Aaron DS, Sivadasan A, et al. Management and outcomes of COVID-19 associated cerebral venous sinus thrombosis. *J Stroke Cerebrovasc Dis* 2022;31:106306. doi:10.1016/j.jstrokecerebrovasdis.2022.106306
51 Frontera JA, Boutajangout A, Masurkar AV, et al. Comparison of serum neurodegenerative biomarkers among hospitalized COVID-19 patients versus non-COVID subjects with normal cognition, mild cognitive impairment, or Alzheimer's dementia. *Alzheimers Dement* 2022;18:899-910. doi:10.1002/alz.12556
52 Guasp M, Muñoz-Sánchez G, Martínez-Hernández E, et al, Barcelona Neuro-COVID Study Group. CSF biomarkers in COVID-19 associated encephalopathy and encephalitis predict long-term outcome. *Front Immunol* 2022;13:866153. doi:10.3389/fimmu.2022.866153
53 Sipilä PN, Heikkilä N, Lindbohm JV, et al. Hospital-treated infectious diseases and the risk of dementia: a large, multicohort, observational study with a replication cohort. *Lancet Infect Dis* 2021;21:1557-67. doi:10.1016/S1473-3099(21)00144-4
54 Ziff OJ, Ashton NJ, Mehta PR, et al. Amyloid processing in COVID-19-associated neurological syndromes. *J Neurochem* 2022;161:146-57. doi:10.1111/jnc.15585
55 Douaud G, Lee S, Alfaro-Almagro F, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature* 2022;604:697-707. doi:10.1038/s41586-022-04569-5
56 Kremer S, Jäger HR. Brain changes after COVID-19 - how concerned should we be?*Nat Rev Neurol* 2022;18:321-2. doi:10.1038/s41582-022-00661-6
57 Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med* 2020;382:2268-70. doi:10.1056/NEJMc2008597
58 Waldrop G, Safavynia SA, Barra ME, et al. Prolonged unconsciousness is common in COVID-19 and associated with hypoxemia. *Ann Neurol* 2022;91:740-55. doi:10.1002/ana.26342
59 Frontera JA, Melmed K, Fang T, et al. Toxic metabolic encephalopathy in hospitalized patients with COVID-19. *Neurocrit Care* 2021;35:693-706. doi:10.1007/s12028-021-01220-5
60 Ross Russell AL, Hardwick M, Jeyanantham A, et al, Spectrum, risk factors and outcomes of neurological and psychiatric complications of COVID-19: a UK-wide cross-sectional surveillance study. *Brain Commun* 2021;3:1-15.
61 Branco de Oliveira MV, Irikura S, Lourenço FHB, et al. Encephalopathy responsive to thiamine in severe COVID-19 patients. *Brain Behav Immun Health* 2021;14:100252. doi:10.1016/j.bbih.2021.100252
62 Pensato U, Muccioli L, Cani I, et al. Brain dysfunction in COVID-19 and CAR-T therapy: cytokine storm-associated encephalopathy. *Ann Clin Transl Neurol* 2021;8:968-79. doi:10.1002/acn3.51348
63 Normandin E, Holroyd KB, Collens SI, et al. Intrathecal inflammatory responses in the absence of SARS-CoV-2 nucleic acid in the CSF of COVID-19 hospitalized patients. *J Neurol Sci* 2021;430:120023. doi:10.1016/j.jns.2021.120023
64 Lersy F, Benotmane I, Helms J, et al. Cerebrospinal fluid features in patients with coronavirus disease 2019 and neurological manifestations: correlation with brain magnetic resonance imaging findings in 58 patients. *J Infect Dis* 2021;223:600-9. doi:10.1093/infdis/jiaa745
65 Abenza Abildúa MJ, Atienza S, Carvalho Monteiro G, et al. Encephalopathy and encephalitis during acute SARS-CoV-2 infection. Spanish Society of Neurology COVID-19 Registry. *Neurologia (Engl Ed)* 2021;36:127-34. doi:10.1016/j.nrleng.2020.11.003
66 Bartley CM, Johns C, Ngo TT, et al. Anti-SARS-CoV-2 and autoantibody profiles in the cerebrospinal fluid of 3 teenaged patients with COVID-19 and subacute neuropsychiatric symptoms. *JAMA Neurol* 2021;78:1503-9. doi:10.1001/jamaneurol.2021.3821
67 Rábano-Suárez P, Bermejo-Guerrero L, Méndez-Guerrero A, et al. Generalized myoclonus in COVID-19. *Neurology* 2020;95:e767-72. doi:10.1212/WNL.0000000000009829
68 Edjlali M, Le Gal A, Louvet M, et al, Garches COVID-19 Collaborative Group. Teaching NeuroImages: Cytotoxic lesions of the corpus callosum in encephalopathic patients with COVID-19. *Neurology* 2020;95:1021-2. doi:10.1212/WNL.0000000000010880
69 Starkey J, Kobayashi N, Numaguchi Y, Moritani T. Cytotoxic lesions of the corpus callosum that show restricted diffusion: mechanisms, causes, and manifestations. *Radiographics* 2017;37:562-76. doi:10.1148/rg.2017160085
70 Helms J, Kremer S, Merdji H, et al. Delirium and encephalopathy in severe COVID-19: a cohort analysis of ICU patients. *Crit Care* 2020;24:491. doi:10.1186/s13054-020-03200-1
71 Hosp JA, Dressing A, Blazhenets G, et al. Cognitive impairment and altered cerebral glucose metabolism in the subacute stage of COVID-19. *Brain* 2021;144:1263-76. doi:10.1093/brain/awab009
72 Huo S, Ferse C, Bösl F, et al. Intravenous immunoglobulins for treatment of severe COVID-19-related acute encephalopathy. *J Neurol* 2022;269:4013-20. doi:10.1007/s00415-022-11152-5
73 Liotta EM, Batra A, Clark JR, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. *Ann Clin Transl Neurol* 2020;7:2221-30. doi:10.1002/acn3.51210
74 Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry* 2021;8:416-27. doi:10.1016/S2215-0366(21)00084-5
75 Neilson DE. The interplay of infection and genetics in acute necrotizing encephalopathy. *Curr Opin Pediatr* 2010;22:751-7. doi:10.1097/MOP.0b013e3283402bfe
76 Shukla P, Mandalla A, Elrick MJ, Venkatesan A. Clinical manifestations and pathogenesis of acute necrotizing encephalopathy: the interface between systemic infection and neurologic injury. *Front Neurol* 2022;12:628811. doi:10.3389/fneur.2021.628811
77 Dixon L, Varley J, Gontsarova A, et al. COVID-19-related acute necrotizing encephalopathy with brain stem involvement in a patient with aplastic anemia. *Neurol Neuroimmunol Neuroinflamm* 2020;7:1-8. doi:10.1212/NXI.0000000000000789
78 Delamarre L, Gollion C, Grouteau G, et al, NeuroICU Research Group. COVID-19-associated acute necrotising encephalopathy successfully treated with steroids and polyvalent immunoglobulin with unusual IgG targeting the cerebral fibre network. *J Neurol Neurosurg Psychiatry* 2020;91:1004-6. doi:10.1136/jnnp-2020-323678
79 Virhammar J, Kumlien E, Fällmar D, et al. Acute necrotizing encephalopathy with SARS-CoV-2 RNA confirmed in cerebrospinal fluid. *Neurology* 2020;95:445-9. doi:10.1212/WNL.0000000000010250
80 Valencia Sanchez C, Theel E, Binnicker M, Toledano M, McKeon A. Autoimmune encephalitis after SARS-CoV-2 infection. *Neurology* 2021;97:e2262-8. doi:10.1212/WNL.0000000000012931
81 Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016;15:391-404. doi:10.1016/S1474-4422(15)00401-9
82 Fragiel M, Miró Ò, Llorens P, et al, Spanish Investigators on Emergency Situations TeAm (SIESTA) network. Incidence, clinical characteristics, risk factors and outcomes of meningoencephalitis

in patients with COVID-19. *Eur J Clin Microbiol Infect Dis* 2021;40:1645-56. doi:10.1007/s10096-021-04206-5
83 Venkatesan A, Tunkel AR, Bloch KC, et al, International Encephalitis Consortium. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. *Clin Infect Dis* 2013;57:1114-28. doi:10.1093/cid/cit458
84 Pilotto A, Masciocchi S, Volonghi I, et al, SARS-CoV-2 related encephalopaties (ENCOVID) Study Group. Clinical presentation and outcomes of severe acute respiratory syndrome coronavirus 2-related encephalitis: the ENCOVID Multicenter Study. *J Infect Dis* 2021;223:28-37. doi:10.1093/infdis/jiaa609
85 Siow I, Lee KS, Zhang JJY, Saffari SE, Ng A. Encephalitis as a neurological complication of COVID-19: A systematic review and meta-analysis of incidence, outcomes, and predictors. *Eur J Neurol* 2021;28:3491-502. doi:10.1111/ene.14913
86 Jesuthasan A, Massey F, Manji H, Zandi MS, Wiethoff S. Emerging potential mechanisms and predispositions to the neurological manifestations of COVID-19. *J Neurol Sci* 2021;428:117608. doi:10.1016/j.jns.2021.117608
87 Monti G, Giovannini G, Marudi A, et al. Anti-NMDA receptor encephalitis presenting as new onset refractory status epilepticus in COVID-19. *Seizure* 2020;81:18-20. doi:10.1016/j.seizure.2020.07.006
88 Vasilevska V, Guest PC, Bernstein HG, Schroeter ML, Geis C, Steiner J. Molecular mimicry of NMDA receptors may contribute to neuropsychiatric symptoms in severe COVID-19 cases. *J Neuroinflammation* 2021;18:245. doi:10.1186/s12974-021-02293-x
89 Koh JS, De Silva DA, Quek AML, et al. Neurology of COVID-19 in Singapore. *J Neurol Sci* 2020;418:117118. doi:10.1016/j.jns.2020.117118
90 Krupp LB, Tardieu M, Amato MP, et al, International Pediatric Multiple Sclerosis Study Group. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. *Mult Scler* 2013;19:1261-7. doi:10.1177/1352458513484547
91 Bruijstens AL, Lechner C, Flet-Berliac L, et al, E.U. paediatric MOG consortium. E.U. paediatric MOG consortium consensus: Part 1 - Classification of clinical phenotypes of paediatric myelin oligodendrocyte glycoprotein antibody-associated disorders. *Eur J Paediatr Neurol* 2020;29:2-13. doi:10.1016/j.ejpn.2020.10.006
92 Waak M, Malone S, Sinclair K, et al. Pediatric neurology acute hemorrhagic leukoencephalopathy: pathological features and cerebrospinal fluid cytokine profiles. *Pediatr Neurol* 2019;100:92-6. doi:10.1016/j.pediatrneurol.2019.06.013
93 Novi G, Rossi T, Pedemonte E, et al. Acute disseminated encephalomyelitis after SARS-CoV-2 infection. *Neurol Neuroimmunol Neuroinflamm* 2020;7:e797. doi:10.1212/NXI.0000000000000797
94 Manzano GS, McEntire CRS, Martinez-Lage M, Mateen FJ, Hutto SK. Acute disseminated encephalomyelitis and acute hemorrhagic leukoencephalitis following COVID-19. *Neurol Neuroimmunol Neuroinflamm* 2021;8:e1080. doi:10.1212/NXI.0000000000001080
95 Lindan CE, Mankad K, Ram D, et al, ASPNR PECOBIG Collaborator Group. Neuroimaging manifestations in children with SARS-CoV-2 infection: a multinational, multicentre collaborative study. *Lancet Child Adolesc Health* 2021;5:167-77. doi:10.1016/S2352-4642(20)30362-X
96 Pohl D, Alper G, Van Haren K, et al. Acute disseminated encephalomyelitis: Updates on an inflammatory CNS syndrome. *Neurology* 2016;87(Suppl 2):S38-45. doi:10.1212/WNL.0000000000002825
97 Kremer S, Lersy F, de Sèze J, et al. Brain MRI findings in severe COVID-19: a retrospective observational study. *Radiology* 2020;297:E242-51. doi:10.1148/radiol.2020202222
98 Paediatric Intensive Care Society. PICS Statement: Increased number of reported cases of novel presentation of multi- system inflammatory disease. 2020. https://pccsociety.uk/wp-content/uploads/2020/08/PICS-statement-re-novel-KD-C19-presentation-v2-27042020.pdf
99 Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 2020;395:1771-8. doi:10.1016/S0140-6736(20)31103-X
100 Ray STJ, Abdel-Mannan O, Sa M, et al, CoroNerve study group. Neurological manifestations of SARS-CoV-2 infection in hospitalised children and adolescents in the UK: a prospective national cohort study. *Lancet Child Adolesc Health* 2021;5:631-41. doi:10.1016/S2352-4642(21)00193-0
101 Riollano-Cruz M, Akkoyun E, Briceno-Brito E, et al. Multisystem inflammatory syndrome in children related to COVID-19: A New York City experience. *J Med Virol* 2021;93:424-33. doi:10.1002/jmv.26224
102 LaRovere KL, Riggs BJ, Poussaint TY, et al, Overcoming COVID-19 Investigators. Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. *JAMA Neurol* 2021;78:536-47. doi:10.1001/jamaneurol.2021.0504
103 Abdel-Mannan O, Eyre M, Löbel U, et al. Neurologic and radiographic findings associated with COVID-19 infection in children. *JAMA Neurol* 2020;77:1440-5. doi:10.1001/jamaneurol.2020.2687
104 Becker AE, Chiotos K, McGuire JL, Bruins BB, Alcamo AM. Intracranial hypertension in multisystem inflammatory syndrome in children. *J Pediatr* 2021;233:263-7. doi:10.1016/j.jpeds.2021.02.062
105 Kashiwagi M, Tanabe T, Shimakawa S, et al. Clinico-radiological spectrum of reversible splenial lesions in children. *Brain Dev* 2014;36:330-6. doi:10.1016/j.braindev.2013.05.007
106 Kurahashi H, Azuma Y, Masuda A, et al. MYRF is associated with encephalopathy with reversible myelin vacuolization. *Ann Neurol* 2018;83:98-106. doi:10.1002/ana.25125
107 Li X-F, Ai B, Ye J-W, et al. Clinical characteristics of H1N1 influenza A-associated mild encephalopathy with reversible splenial lesion: 4 pediatric cases. *Curr Med Sci* 2021;41:815-2010.1007/s11596-021-2408-0.
108 Welzel T, Atkinson A, Schöbi N, et al, Methylprednisolone versus intravenous immunoglobulins in children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS): an open-label, multicentre, randomised trial. *Lancet Child Adolesc Health* 2023;12:0-1010.1016/S2352-4642(23)00020-2.
109 Merkler AE, Parikh NS, Mir S, et al. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza. *JAMA Neurol* 2020;77:1-7. doi:10.1001/jamaneurol.2020.2730
110 Tu TM, Seet CYH, Koh JS, et al. Acute ischemic stroke during the convalescent phase of asymptomatic COVID-2019 infection in men. *JAMA Netw Open* 2021;4:e217498. doi:10.1001/jamanetworkopen.2021.7498
111 Nannoni S, de Groot R, Bell S, Markus HS. Stroke in COVID-19: A systematic review and meta-analysis. *Int J Stroke* 2021;16:137-49. doi:10.1177/1747493020972922
112 Nagraj S, Varrias D, Hernandez Romero G, et al. Incidence of stroke in randomized trials of COVID-19 therapeutics: a systematic review and meta-analysis. *Stroke* 2022;53:3410-8. doi:10.1161/STROKEAHA.122.040233
113 Beyrouti R, Best JG, Chandratheva A, Perry RJ, Werring DJ. Characteristics of intracerebral haemorrhage associated with COVID-19: a systematic review and pooled analysis of individual patient and aggregate data. *J Neurol* 2021;268:3105-15. doi:10.1007/s00415-021-10425-9
114 Perry RJ, Smith CJ, Roffe C, et al, SETICOS collaborators. Characteristics and outcomes of COVID-19 associated stroke: a UK multicentre case-control study. *J Neurol Neurosurg Psychiatry* 2021;92:242-8. doi:10.1136/jnnp-2020-324927
115 Qureshi AI, Baskett WI, Huang W, et al. Acute ischemic stroke and COVID-19: an analysis of 27676 patients. *Stroke* 2021;52:905-12. doi:10.1161/STROKEAHA.120.031786
116 Ramos-Araque ME, Siegler JE, Ribo M, et al, SVIN Multinational Registry and Task Force. Stroke etiologies in patients with COVID-19: the SVIN COVID-19 multinational registry. *BMC Neurol* 2021;21:43. doi:10.1186/s12883-021-02075-1
117 Dmytriw AA, Dibas M, Phan K, et al, North American Neurovascular COVID-19 (NAN-C) Consortium & Society of Vascular and Interventional Neurology (SVIN) Investigators. Acute ischaemic stroke associated with SARS-CoV-2 infection in North America. *J Neurol Neurosurg Psychiatry* 2022;93:360-8. doi:10.1136/jnnp-2021-328354
118 Ntaios G, Michel P, Georgiopoulos G, et al. Characteristics and outcomes in patients with COVID-19 and acute ischemic stroke: The Global COVID-19 Stroke Registry. *Stroke* 2020;51:e254-8. doi:10.1161/STROKEAHA.120.031208
119 Sasanejad P, Afshar Hezarkhani L, Arsang-Jang S, et al. Safety and outcomes of intravenous thrombolytic therapy in ischemic stroke patients with COVID-19: CASCADE Initiative. *J Stroke Cerebrovasc Dis* 2021;30:106121. doi:10.1016/j.jstrokecerebrovasdis.2021.106121
120 Zureigat H, Alhusban M, Cobia M. Mechanical thrombectomy outcomes in COVID-19 patients with acute ischemic stroke. *Neurologist* 2021;26:261-7. doi:10.1097/NRL.0000000000000360
121 Hippisley-Cox J, Patone M, Mei XW, et al. Risk of thrombocytopenia and thromboembolism after covid-19 vaccination and SARS-CoV-2 positive testing: self-controlled case series study. *BMJ* 2021;374:n1931. doi:10.1136/bmj.n1931
122 Kim JE, Heo JH, Kim HO, et al. Neurological complications during treatment of middle east respiratory syndrome. *J Clin Neurol* 2017;13:227-33. doi:10.3988/jcn.2017.13.3.227
123 Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or

coincidence?*Lancet Neurol* 2020;19:383-4. doi:10.1016/S1474-4422(20)30109-5
124 Rifino N, Censori B, Agazzi E, et al. Neurologic manifestations in 1760 COVID-19 patients admitted to Papa Giovanni XXIII Hospital, Bergamo, Italy. *J Neurol* 2021;268:2331-8. doi:10.1007/s00415-020-10251-5
125 Keddie S, Pakpoor J, Mousele C, et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. *Brain* 2021;144:682-93. doi:10.1093/brain/awaa433
126 Umapathi T, Er B, Koh JS, Goh YH, Chua L. Guillain-Barré syndrome decreases in Singapore during the COVID-19 pandemic. *J Peripher Nerv Syst* 2021;26:235-6. doi:10.1111/jns.12439
127 Lunn MP. Guillain-Barré syndrome in an era of global infections and 21st century vaccination. *Curr Opin Neurol* 2022;35:571-8. doi:10.1097/WCO.0000000000001086
128 Taga A, Lauria G. COVID-19 and the peripheral nervous system. A 2-year review from the pandemic to the vaccine era. *J Peripher Nerv Syst* 2022;27:4-30. doi:10.1111/jns.12482
129 Restivo DA, Centonze D, Alesina A, Marchese-Ragona R. Myasthenia gravis associated with SARS-CoV-2 infection. *Ann Intern Med* 2020;173:1027-8. doi:10.7326/L20-0845
130 Muralidhar Reddy Y, B SK, Osman S, Murthy JMK. Temporal association between SARS-CoV-2 and new-onset myasthenia gravis: is it causal or coincidental?*BMJ Case Rep* 2021;14:e244146. doi:10.1136/bcr-2021-244146
131 Aschman T, Schneider J, Greuel S, et al. Association between SARS-CoV-2 infection and immune-mediated myopathy in patients who have died. *JAMA Neurol* 2021;78:948-60. doi:10.1001/jamaneurol.2021.2004
132 Manzano GS, Woods JK, Amato AA. Covid-19–associated myopathy caused by type I interferonopathy. *N Engl J Med* 2020;383:2389-90. doi:10.1056/NEJMc2031085
133 Rivas-García S, Bernal J, Bachiller-Corral J. Rhabdomyolysis as the main manifestation of coronavirus disease 2019. *Rheumatology (Oxford)* 2020;59:2174-6. doi:10.1093/rheumatology/keaa351
134 Li X, Raventós B, Roel E, et al. Association between covid-19 vaccination, SARS-CoV-2 infection, and risk of immune mediated neurological events: population based cohort and self-controlled case series analysis. *BMJ* 2022;376:e068373. doi:10.1136/bmj-2021-068373
135 Goh Y, Beh DLL, Makmur A, Somani J, Chan ACY. Pearls & Oy-sters: Facial nerve palsy in COVID-19 infection. *Neurology* 2020;95:364-7. doi:10.1212/WNL.0000000000009863
136 Han CY, Tarr AM, Gewirtz AN, et al. Brachial plexopathy as a complication of COVID-19. *BMJ Case Rep* 2021;14:e237459. doi:10.1136/bcr-2020-237459
137 Mitry MA, Collins LK, Kazam JJ, Kaicker S, Kovanlikaya A. Parsonage-turner syndrome associated with SARS-CoV2 (COVID-19) infection. *Clin Imaging* 2021;72:8-10. doi:10.1016/j.clinimag.2020.11.017
138 Needham E, Newcombe V, Michell A, et al. Mononeuritis multiplex: an unexpectedly frequent feature of severe COVID-19. *J Neurol* 2021;268:2685-9. doi:10.1007/s00415-020-10321-8
139 National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19. 2022. https://www.nice.org.uk/guidance/ng188.
140 Heightman M, Prashar J, Hillman TE, et al. Post-COVID-19 assessment in a specialist clinical service: a 12-month, single-centre, prospective study in 1325 individuals. *BMJ Open Respir Res* 2021;8:e001041. doi:10.1136/bmjresp-2021-001041
141 Graham EL, Clark JR, Orban ZS, et al. Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 "long haulers". *Ann Clin Transl Neurol* 2021;8:1073-85. doi:10.1002/acn3.51350
142 Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine* 2021;38:101019. doi:10.1016/j.eclinm.2021.101019
143 Badenoch JB, Rengasamy ER, Watson C, et al. Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis. *Brain Commun* 2022;4:fcab297.
144 Evans RA, McAuley H, Harrison EM, et al, PHOSP-COVID Collaborative Group. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. *Lancet Respir Med* 2021;9:1275-87. doi:10.1016/S2213-2600(21)00383-0
145 Fernández-de-Las-Peñas C, Gómez-Mayordomo V, Cuadrado ML, et al. The presence of headache at onset in SARS-CoV-2 infection is associated with long-term post-COVID headache and fatigue: A case-control study. *Cephalalgia* 2021;41:1332-41. doi:10.1177/03331024211020404
146 Ceban F, Ling S, Lui LMW, et al. Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. *Brain Behav Immun* 2022;101:93-135. doi:10.1016/j.bbi.2021.12.020
147 Lamontagne SJ, Winters MF, Pizzagalli DA, Olmstead MC. Post-acute sequelae of COVID-19: Evidence of mood & cognitive impairment. *Brain Behav Immun Health* 2021;17:100347. doi:10.1016/j.bbih.2021.100347
148 Apple AC, Oddi A, Peluso MJ, et al. Risk factors and abnormal cerebrospinal fluid associate with cognitive symptoms after mild COVID-19. *Ann Clin Transl Neurol* 2022;9:221-6. doi:10.1002/acn3.51498
149 Mandal S, Barnett J, Brill SE, et al, ARC Study Group. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax* 2021;76:396-8. doi:10.1136/thoraxjnl-2020-215818
150 Moreno-Pérez O, Merino E, Leon-Ramirez JM, et al, COVID19-ALC research group. Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study. *J Infect* 2021;82:378-83. doi:10.1016/j.jinf.2021.01.004
151 Townsend L, Dyer AH, Jones K, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One* 2020;15:e0240784. doi:10.1371/journal.pone.0240784
152 Salmon-Ceron D, Slama D, De Broucker T, et al, APHP COVID-19 research collaboration. Clinical, virological and imaging profile in patients with prolonged forms of COVID-19: A cross-sectional study. *J Infect* 2021;82:e1-4. doi:10.1016/j.jinf.2020.12.002
153 Hickie I, Davenport T, Wakefield D, et al, Dubbo Infection Outcomes Study Group. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *BMJ* 2006;333:575-8. doi:10.1136/bmj.38933.585764.AE
154 Azcue N, Gómez-Esteban JC, Acera M, et al. Brain fog of post-COVID-19 condition and Chronic Fatigue Syndrome, same medical disorder?*J Transl Med* 2022;20:569. doi:10.1186/s12967-022-03764-2
155 Qanneta R. Long COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome: Similarities and differences of two peas in a pod. *Reumatol Clin* 2022;18:626-810.1016/j.reuma.2022.05.003.
156 Kachaner A, Lemogne C, Dave J, Ranque B, de Broucker T, Meppiel E. Somatic symptom disorder in patients with post-COVID-19 neurological symptoms: a preliminary report from the somatic study (Somatic Symptom Disorder Triggered by COVID-19). *J Neurol Neurosurg Psychiatry* 2022;25 Aug:327899. doi:10.1136/jnnp-2021-327899
157 Stojanov A, Bozovic I, Stojanov J, et al. The influence of the COVID-19 pandemic on patients with chronic inflammatory demyelinating polyradiculoneuropathy. *Clin Neurol Neurosurg* 2021;205:106654. doi:10.1016/j.clineuro.2021.106654
158 Zubair AS, Zubair AS, Desai K. Chronic inflammatory demyelinating polyradiculoneuropathy during the COVID-19 pandemic: telemedicine limitations and strategies for improvement. *Cureus* 2021;13:e14146. doi:10.7759/cureus.14146
159 Wieske L, van Dam KPJ, Steenhuis M, et al, T2B! Immunity against SARS-CoV-2 study group. Humoral responses after second and third SARS-CoV-2 vaccination in patients with immune-mediated inflammatory disorders on immunosuppressants: a cohort study. *Lancet Rheumatol* 2022;4:e338-50. doi:10.1016/S2665-9913(22)00034-0
160 Sormani MP, Salvetti M, Labauge P, et al, Musc-19, Covisep study groups. DMTs and Covid-19 severity in MS: a pooled analysis from Italy and France. *Ann Clin Transl Neurol* 2021;8:1738-44. doi:10.1002/acn3.51408
161 Simpson-Yap S, Pirmani A, Kalincik T, et al. Updated Results of the COVID-19 in MS Global Data Sharing Initiative: Anti-CD20 and Other Risk Factors Associated With COVID-19 Severity. *Neurol Neuroimmunol Neuroinflamm* 2022;9:e200021. doi:10.1212/NXI.0000000000200021
162 Reder AT, Centonze D, Naylor ML, et al. COVID-19 in patients with multiple sclerosis: associations with disease-modifying therapies. *CNS Drugs* 2021;35:317-30. doi:10.1007/s40263-021-00804-1
163 Reder AT, Stuve O, Tankou SK, Leist TP. T cell responses to COVID-19 infection and vaccination in patients with multiple sclerosis receiving disease-modifying therapy. *Mult Scler* 2023;29:648-56. doi:10.1177/13524585221134216
164 Roy B, Kovvuru S, Nalleballe K, Onteddu SR, Nowak RJ. Electronic health record derived-impact of COVID-19 on myasthenia gravis. *J Neurol Sci* 2021;423:117362. doi:10.1016/j.jns.2021.117362
165 Lunn MP, Cornblath DR, Jacobs BC, et al. COVID-19 vaccine and Guillain-Barré syndrome: let's not leap to associations. *Brain* 2021;144:357-60. doi:10.1093/brain/awaa444
166 Shapiro Ben David S, Potasman I, Rahamim-Cohen D. Rate of recurrent Guillain-Barré syndrome after mRNA COVID-19 vaccine BNT162b2. *JAMA Neurol* 2021;78:1409-11. doi:10.1001/jamaneurol.2021.3287
167 Kuitwaard K, Bos-Eyssen ME, Blomkwist-Markens PH, van Doorn PA. Recurrences, vaccinations and long-term symptoms in GBS and CIDP. *J Peripher Nerv Syst* 2009;14:310-5. doi:10.1111/j.1529-8027.2009.00243.x
168 Baars AE, Kuitwaard K, de Koning LC, et al. SARS-CoV-2 vaccination safety in Guillain-Barré syndrome, chronic

inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy. *Neurology* 2023;100:e182-91. doi:10.1212/WNL.0000000000201376
169 van Dam KPJ, Wieske L, Stalman EW, et al, T2B! Immunity against SARS-CoV-2 study group. Disease activity in patients with immune-mediated inflammatory diseases after SARS-CoV-2 vaccinations. *J Autoimmun* 2023;135:102984. doi:10.1016/j.jaut.2022.102984
170 Michael BD, Walton D, Westenberg E, et al, Global COVID-19 Neuro Research Coalition. Consensus clinical guidance for diagnosis and management of adult COVID-19 encephalopathy patients. *J Neuropsychiatry Clin Neurosci* 2023;35:12-27. doi:10.1176/appi.neuropsych.22010002
171 National Institute for Health and Care Excellence. COVID-19 rapid guideline: vaccine-induced immune thrombocytopenia and thrombosis (VITT). 2021. https://www.nice.org.uk/guidance/ng200
172 Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. *Stroke* 2021;52:e364-467. doi:10.1161/STR.0000000000000375
173 Royal College of Physicians. National clinical guideline for stroke. 2016. https://www.rcplondon.ac.uk/guidelines-policy/stroke-guidelines
174 Ulivi L, Squitieri M, Cohen H, Cowley P, Werring DJ. Cerebral venous thrombosis: a practical guide. *Pract Neurol* 2020;20:356-67. doi:10.1136/practneurol-2019-002415
175 Venkatesan A, Michael BD, Probasco JC, Geocadin RG, Solomon T. Acute encephalitis in immunocompetent adults. *Lancet* 2019;393:702-16. doi:10.1016/S0140-6736(18)32526-1
176 Leonhard SE, Mandarakas MR, Gondim FAA, et al. Diagnosis and management of Guillain-Barré syndrome in ten steps. *Nat Rev Neurol* 2019;15:671-83. doi:10.1038/s41582-019-0250-9
177 Department of Health and Social Care. Defining the highest risk clinical subgroups upon community infection with SARS-CoV-2 when considering the use of neutralising monoclonal antibodies (nMABs) and antiviral drugs (updated March 2023). 2023. https://www.gov.uk/government/publications/higher-risk-patients-eligible-for-covid-19-treatments-independent-advisory-group-report-march-2023/defining-the-highest-risk-clinical-subgroups-upon-community-infection-with-sars-cov-2-when-considering-the-use-of-neutralising-monoclonal-antibodies
178 Harwood R, Allin B, Jones CE, et al, PIMS-TS National Consensus Management Study Group. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. *Lancet Child Adolesc Health* 2021;5:133-41. doi:10.1016/S2352-4642(20)30304-7
179 Stanford KA, Almirol E, Schneider J, Hazra A. Rising syphilis rates during the COVID-19 pandemic. *Sex Transm Dis* 2021;48:e81-3. doi:10.1097/OLQ.0000000000001431
180 Nomah DK, Reyes-Urueña J, Díaz Y, et al, PISCIS study group. Sociodemographic, clinical, and immunological factors associated with SARS-CoV-2 diagnosis and severe COVID-19 outcomes in people living with HIV: a retrospective cohort study. *Lancet HIV* 2021;8:e701-10. doi:10.1016/S2352-3018(21)00240-X
181 Bhavsar A, Lonnet G, Wang C, et al. Increased risk of herpes zoster in adults ≥50 years old diagnosed with COVID-19 in the United States. *Open Forum Infect Dis* 2022;9:c118. doi:10.1093/ofid/ofac118
182 Grundmann A, Wu CH, Hardwick M, et al, ISARIC4C investigators. Fewer COVID-19 neurological complications with dexamethasone and remdesivir. *Ann Neurol* 2023;93:88-102. doi:10.1002/ana.26536
183 Department of Health and Social Care. Clinical platform trials for coronavirus (COVID-19) treatments. 2023. https://www.gov.uk/guidance/clinical-platform-trials-for-coronavirus-covid-19-treatments#results-of-trials-to-date-effective-and-ineffective-treatments
184 Lee MH, Perl DP, Steiner J, et al. Neurovascular injury with complement activation and inflammation in COVID-19. *Brain* 2022;145:2555-68. doi:10.1093/brain/awac151
185 Tsampasian V, Elghazaly H, Chattopadhyay R, et al. Risk factors associated with post–COVID-19 condition. *JAMA Intern Med* 2023;183:566-80. doi:10.1001/jamainternmed.2023.0750
186 Daniels LB, Ren J, Kumar K, et al. Relation of prior statin and anti-hypertensive use to severity of disease among patients hospitalized with COVID-19: Findings from the American Heart Association's COVID-19 Cardiovascular Disease Registry. *PLoS One* 2021;16:e0254635. doi:10.1371/journal.pone.0254635
187 Dale CE, Takhar R, Carragher R, et al, CVD-COVID-UK Consortium. The impact of the COVID-19 pandemic on cardiovascular disease prevention and management. *Nat Med* 2023;29:219-25. doi:10.1038/s41591-022-02158-7
188 Association of British Neurologists. ABN covid-19 response. 2023. https://www.theabn.org/page/covid19_response
189 American Academy of Neurology. 2023. Covid-19 neurology resource center. https://www.aan.com/tools-resources/covid-19