The Journal of Neuropsychiatry and Clinical Neurosciences

Consensus clinical guidance for diagnosis and management of adult COVID-19 encephalopathy patients

Journal:	*The Journal of Neuropsychiatry and Clinical Neurosciences*
Manuscript ID	APPI-JN-22-01-0002.R1
Manuscript Type:	Special Article
Date Submitted by the Author:	01-Feb-2022
Complete List of Authors:	Michael, Benedict; The Walton Centre NHS Foundation Trust, Department of Neurology Walton, Dean; Walton Centre for Neurology and Neurosurgery, Westenberg, Erica; Technical University of Munich, Department of Neurology García-Azorín, David; Hospital Clínico Universitario de Valladolid, Department of Neurology Singh, Bhagteshwar; University of Liverpool Department of Clinical Infection Microbiology and Immunology; Royal Liverpool University Hospital Tropical and Infectious Diseases Unit; Christian Medical College Vellore, Department of Infectious Diseases Tamborska, Arina ; NIHR Health Protection Research Unit in Emerging and Zoonotic Infections at University of Liverpool; University of Liverpool Department of Clinical Infection Microbiology and Immunology Netravathi, M; National Institute of Mental Health and Neurosciences Chomba, Mashina; University of Zambia University Teaching Hospital, Neurology, Department of Medicine; Columbia University Irving Medical Center, Department of Neurology Wood, Greta; NIHR Health Protection Research Unit in Emerging and Zoonotic Infections at University of Liverpool; The Walton Centre NHS Foundation Trust; University of Liverpool Department of Clinical Infection Microbiology and Immunology Easton, Ava; University of Liverpool Department of Clinical Infection Microbiology and Immunology; Encephalitis Society Siddiqi, Omar; University of Zambia University Teaching Hospital; Beth Israel Deaconess Medical Center Department of Neurology, Global Neurology Program; Beth Israel Deaconess Medical Center, Center for Vaccines and Virology Research, Department of Internal Medicine Jackson, Thomas; University of Birmingham Institute of Inflammation and Ageing; University Hospitals Birmingham NHS Foundation Trust, Department of Geriatric Medicine Pollak, Thomas; Institute of Psychiatry Psychology and Neuroscience Division of Academic Psychiatry, Social, Genetic and Developmental Psychiatry Centre Nicholson, Timothy; Institute of Psychiatry, Psychological Medicine Nair, Shalini; Christian Medical College Vellore Breen, Gerome; Institute of Psychiatry Psychology and Neuroscience Division of Academic Psychiatry, Social, Genetic and Developmental Psychiatry Centre; South London and Maudsley NHS Foundation Trust,

	NIHR Maudsley Biomedical Research Centre Prasad, Kameshwar; All India Institute of Medical Sciences, Department of Neurology; Rajendra Institute of Medical Sciences, Department of Neurology & Chief Executive Office Thakur, Kiran; Columbia Presbyterian Medical Center, Department of Neurology Chou, Sherry; Northwestern University - Chicago, Division of Neurocritical Care Schmutzhard, Erich; Medical University Innsbruck Clinic of Neurology, Neurocritical Care Unit Frontera, Jennifer; NYU Grossman School of Medicine Helbok, Raimund; Medical University Innsbruck Clinic of Neurology, Neurocritical Care Unit Padovani, Alessandro; University of Brescia Department of Clinical and Experimental Sciences, Institute of Neurology Menon, David; University of Cambridge, Division of Anaesthesia Solomon, Tom; NIHR Health Protection Research Unit in Emerging and Zoonotic Infections at University of Liverpool; The Walton Centre NHS Foundation Trust, Department of Neurology; University of Liverpool Department of Clinical Infection Microbiology and Immunology Winkler, Andrea; Technical University of Munich, Department of Neurology, Center for Global Health, Faculty of Medicine; University of Oslo Faculty of Medicine, Centre for Global Health, Institute of Health and Society
Keywords:	Neurology - JNP0920, Neuropathology - JNP0940

Word count: 4873
Figures: 4
Tables: 2
References: 141

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Benedict D Michael, PhD, MRCP[#1,2,3], Dean Walton, MBBCh, BSc[#2], Erica Westenberg, MSc[4], David García-Azorín, MD, PhD[5], Bhagteshwar Singh, MRCP[3,6,7], Arina A Tamborska, MRCP[1,2,3], M Netravathi, DM[8], Mashina Chomba, MBChB, MMed[9,10], Greta K Wood, MRes[1,2,3], Ava Easton, PhD[3,11], Omar K Siddiqi, MD[9,12,13], Thomas A Jackson, PhD, MRCP[14,15], Thomas A Pollak, PhD, MRCPsych[16], Timothy R Nicholson, PhD, MRCP[17], Shalini Nair, MD, DNB[18], Gerome Breen, PhD[17,19], Kameshwar Prasad, DM[20], Kiran T Thakur, MD[10], Sherry H-Y Chou, MD[21,22,23], Erich Schmutzhard, MD[24], Jennifer A Frontera, MD[25], Raimund Helbok, MD, PhD[24], Alessandro Padovani, MD, PhD[26], David K Menon, MD, PhD*[27], Tom Solomon, PhD, FRCP*[1,2,3], Andrea S Winkler, MD, PhD*[4,28]. **On behalf of the Global COVID-19 Neuro-Research Coalition**

* Joint senior author

[#] Joint first author

Corresponding author:

Benedict D Michael, PhD, MRCP

Institute of Infection, Veterinary and Ecological Sciences

University of Liverpool, Liverpool, United Kingdom

Email: Benmic@liv.ac.uk

https://orcid.org/0000-0002-8693-8926

Affiliations

1. NIHR Health Protection Unit for Emerging and Zoonotic Infections, Liverpool, UK

2. Department of Neurology, The Walton Centre NHS Foundation Trust, Liverpool, UK

3. Clinical Infection Microbiology and Immunology, Institute for Infection, Veterinary and Ecological Sciences, University of Liverpool, UK

4. Department of Neurology, Center for Global Health, Faculty of Medicine, Technical University of Munich, Germany

5. Department of Neurology, Hospital Clínico Universitario de Valladolid, Spain

6. Tropical and Infectious Diseases Unit, Royal Liverpool University Hospital, Liverpool, UK

7. Department of Infectious Diseases, Christian Medical College, Vellore, India

8. National Institute of Mental Health & Neurosciences, Bangalore, India

9. Neurology, Department of Medicine, University Teaching Hospital, Lusaka, Zambia

10. Department of Neurology, Columbia University Irving Medical Center/New York Presbyterian Hospital, New York, NY, US

11. Encephalitis Society, Malton, UK

12. Global Neurology Program, Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA, US

13. Center for Vaccines and Virology Research, Department of Internal Medicine, Beth Israel Deaconess Medical Center, Boston, MA, US

14. Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, UK

15. Department of Geriatric Medicine, University Hospitals Birmingham, UK

16. Department of Psychosis Studies, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, UK

17. Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, UK

18. Department of Neurological Sciences, Christian Medical College, Vellore, Tamil Nadu, India

19. NIHR Maudsley Biomedical Research Centre, South London & Maudsley NHS Trust and King's College London, UK

20. Department of Neurology & Chief Executive Office, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India

21. Departments of Critical Care Medicine, Neurology, and Neurosurgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, US

22. Safar Center for Resuscitation Research, University of Pittsburgh School of Medicine, Pittsburgh, PA, US

23. Department of Neurology, Northwestern Feinberg School of Medicine, Chicago, IL, US

24. Department of Neurology, Neurocritical Care Unit, Medical University Innsbruck, Austria

25. NYU Grossman School of Medicine, New York, NY, US

26. Institute of Neurology, Department of Clinical and Experimental Sciences, University of Brescia, Italy

27. Division of Anaesthesia, University of Cambridge, UK

28. Centre for Global Health, Institute of Health and Society, Faculty of Medicine, University of Oslo, Norway

Financial Support information

BDM, GB and TS are supported to conduct COVID-19 neuroscience research by the UKRI/MRC (MR/V03605X/1); BDM is also supported for additional neurological

inflammation research due to viral infection by grants from the MRC/UKRI (MR/V007181//1), MRC (MR/T028750/1) and Wellcome (ISSF201902/3). TS is supported by the National Institute for Health Research (NIHR) Health Protection Research Unit in Emerging and Zoonotic Infections (Grant No. NIHR200907), NIHR Global Health Research Group on Brain Infections (No. 17/63/110), and the UK Medical Research Council's Global Effort on COVID-19 Programme (MR/V033441/1). The Global COVID-19 Neuro Research Coalition is supported by the School of Medicine, Technical University of Munich, Grant Number H.40001.1.7-08.

Abstract

Encephalopathy is a common complication in patients hospitalised with COVID-19 that can both be a challenge to manage and also negatively impacts prognosis. While encephalopathy may present clinically as delirium, subsyndromal delirium, or coma and be due to systemic causes, such as hypoxia, COVID-19 has also been associated with more prolonged encephalopathy due to less common but nevertheless severe complications, such as inflammation of the brain parenchyma with or without cerebrovascular involvement, demyelination and/or seizures, which may be disproportionate to COVID-19 severity and which require specific management. Given the large denominator of those hospitalised with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, even these relatively unlikely complications are increasingly recognised and are particularly important as they require specific management. Therefore, the aim of this review is to provide pragmatic guidance on the management of COVID-19 encephalopathy through consensus agreement of the Global COVID-19 Neuro-Research Coalition. A systematic literature search of Medline, MedRxiv, and BioRxiv was conducted between 1st January 2020 and 21st June 2021 with additional review of references cited within the identified bibliographies. A modified Delphi-approach was then undertaken to develop recommendations along with a parallel approach to score the strength of both the recommendation and the supporting evidence. This manuscript presents analysis of contemporaneous evidence for definition, epidemiology, and pathophysiology of COVID-19 encephalopathy and practical guidance for clinical assessment, investigation, and both acute and long-term management.

Introduction

While several neurological manifestations of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection have been reported, in those hospitalised with COVID-19 the most common is encephalopathy, which may be present in 2.3-28% of cases in large observational studies or even more commonly in some settings, such as intensive care.[1-11]

The identification of encephalopathy in association with COVID-19 is of considerable importance, particularly as it confers a negative impact on both mortality and morbidity that can be independent of COVID-19 disease severity.[3,6,9,10] Moreover, whilst the longer-term sequelae of encephalopathy associated with COVID-19 are still to be determined, it is likely that individuals affected will require increased medical support and neuro-rehabilitation at a substantial individual and public health burden.[10,12,13]

Description

Encephalopathy is a broad term that encompasses a wide range of presentations and aetiologies. The term is often used in a heterogeneous manner, and conformity to strict definitions and confirmation of the pathophysiology can be lacking.[14] Early in the pandemic, several papers highlighted the necessity for clear and consistent definitions to categorise neurological complications of COVID-19 and also suggested specific clinical case definitions.[1,12,15]

In early 2020, prior to our more complete appreciation of the pandemic, ten societies largely representing North American and Northern European clinicians in the fields of neurology, neurointensive care and delirium published a position statement on encephalopathy and delirium terminology.[16] This statement defined acute encephalopathy as “a rapidly developing pathobiological process in the brain,” which usually evolves over less than 4 weeks, and usually within hours to a few days.[16] They proposed a nomenclature by which the clinical presentation (i.e., symptoms and signs) of encephalopathy could be labelled as “delirium” and

"subsyndromal delirium," or "coma," based on certain diagnostic criteria and level of alertness respectively.[16] In addition to semantic precision in the use of labels to describe clinical manifestations of encephalopathy, sufficient clinical evaluation and investigation are required to make clinically-relevant diagnostic and treatment decisions.

Consequently, a diagnosis of COVID-19 encephalopathy must: 1) include a robust diagnosis of COVID-19 (ideally through confirmation of SARS-CoV-2 by a validated method or in reference to the World Health Organization (WHO) COVID-19 criteria for 'probable' or 'possible' disease);[17] 2) document a plausible temporal relationship between infection and symptom onset, such as those proposed by the Brighton Collaboration;[18] 3) exclude alternative aetiologies unrelated to SARS-CoV-2, such as primary organ dysfunction, intoxication, or primary autoimmune disease and; 4) distinguish those cases presenting with brain dysfunction which is proportionate and secondary to systemic COVID-19 severity from those with a primary brain disease which may have a variable degree of systemic COVID-19 features through robust clinical examination and investigation.[1,6,7,9,12-16]

The epidemiological picture of COVID-19 encephalopathy

While anosmia, ageusia and headache are common symptoms of COVID-19, encephalopathy is the most common neurological complication in hospitalised COVID-19 patients.[19] In a report of more than 20,000 UK patients hospitalised with COVID-19 nearly 25% had confusion.[20] In a US electronic health record analysis of 12,601 patients hospitalised with COVID-19, 8.7% developed acute encephalopathy.[9] This estimate was similar (12%) among 4,491 patients hospitalised with COVID-19 at four New York hospitals, of whom the majority developed encephalopathy immediately prior to the admission.[14] Moreover, acute encephalopathy was the most prevalent neurological complication, present in 49% of more than 3,500 consecutive hospitalised COVID-19 patients and in 17% and 25% of those who received a formal neurological consultation in the CoroNerve and GCS-COVID/ENERGY cohorts

respectively.[21,23] The prevalence of encephalopathy is higher in older patients and those requiring intensive support, with two critical care-based studies reporting encephalopathy in greater than 80% of patients.[22,23] Encephalopathy may also be more common in those with acute respiratory distress syndrome (ARDS) secondary to SARS-COV-2, for example this was present in 54.9% of 2,088 such patients referred to critical care in one multi-country study.[24] However, encephalopathy has also been reported at presentation to emergency departments in 28% of 817 adults aged >65 years, making for the 6th most common presenting feature in this age group.[25] Overall, these broad patterns of prevalence reflect the largest risk factors associated with COVID-19 encephalopathy: advancing age and COVID-19 illness severity.[9,14,26]

One study estimated that being older than 75 years increases the risk of encephalopathy by 51% (relative risk [95% CI] 1.51, [1.17-1.95]).[25] In another study the incidence of encephalopathy increased steadily with age, from 33% in those younger than 40 years to 74% in those older than 80 years.[3] Patients with COVID-19 encephalopathy are also more likely to be male[9,14,24] and have co-morbidities, for example hypertension, obesity, diabetes mellitus, coronary artery disease and chronic kidney or liver disease.[9,14] The risk of encephalopathy is also increased in patients with pre-existing neurological conditions, including Parkinson's disease and other movement disorders,[9,14,25] history of ischaemic stroke,[9,14,25] dementia,[14,25,27] and history of a mental health disorder.[14,25]

However, encephalopathy disproportionate age, premorbid health, and the systemic severity of COVID-19 disease has also been reported and can be due to cerebrovascular, demyelinating, and other inflammatory pathophysiology.[2,8,10-13,15] For example, in the CoroNerve UK-wide surveillance study, while 25 (9%) of hospitalised adults met the criteria for delirium, an additional 13 (5%) had a severe encephalopathy which was beyond the criteria for delirium due to significantly impaired conscious level and/or new-onset seizures.[2]

Given the high incidence of encephalopathy in patients with COVID-19, the association with poor outcome and the complexities in diagnosis, investigation, and management, we conducted a systematic collation of the literature to inform the development of pragmatic clinical management guidance of utility in high, medium, and low-income settings through the Global COVID-19 Neuro Research Coalition.[28] We set out to provide practical guidance to answer the following clinical questions:

- What is the pathophysiology of COVID-19 encephalopathy?
- Which clinical features suggest COVID-19 encephalopathy?
- Which clinical features suggest a primary Central Nervous System (CNS) pathology?
- What investigations should be performed to establish these CNS diagnoses?
- How should patients suffering from COVID-19 encephalopathy be managed?
- What is the prognosis for patients with COVID-19 encephalopathy?
- What is the role of rehabilitation for these patients?

Search strategy and methods

A Medline search was conducted between 1st January 2020 and 21st June 2021 using the following search terms: (COVID-19 OR SARS-CoV2 OR SARS-CoV-2) AND (neurol* OR neuropath* OR nervous system OR brain OR encephal* OR meningit* OR stroke OR Guillain-Barré syndrome OR cerebr* OR psych* OR mania OR psycho* OR functional OR catatonia OR cognit* OR depress* OR anxi* OR obsessive OR post-traum* OR postraum* OR PTSD OR behaviour OR epilep* OR seizure OR headache* OR migraine OR crani* OR cloza* OR deliri*. A MedRxiv and BioRxiv search was conducted during the same time window for the following search terms: COVID-19 OR SARS-CoV2 OR SARS-CoV-2 in 'neurology' and/or 'psychiatry' categories. We conducted a hand review of references cited within the identified bibliographies and additional publications and pre-prints identified by the Expert Panel within the consortium were accessed.

A modified Delphi-approach was undertaken by the Global COVID-19 NeuroResearch Coalition to resolve conclusions along with a parallel approach to score the consensus strength of both the recommendation and the supporting evidence, as used in previous guidelines.[29,30]

The Global COVID-19 NeuroResearch Coalition is a consortium of clinical academic neurologists/neuropsychiatrists, including patient and public involvement, in both high and low/middle income settings spanning the spectrum of sub-speciality interest.[28] The central secretariat of the Coalition are also members of the WHO Brain Health Unit's Expert Forum on Neurological and Neuropsychiatric Complications of COVID-19. The Coalition undertook a virtual scoping exercise to identify key clinical questions in the pathophysiology, diagnosis and management of encephalopathy in COVID-19 patients. These questions were initially assigned to a partnership of one high and one middle/low-income clinician in sub-categories reflecting clinical and academic experience. After a systematic literature review leveraging the Neurology and Neuropsychiatry of COVID-19 database these sub-groups drafted answers to these questions (https://neuropsychcovid.net). These were then circulated to the key co-authorship group for review and comment as to the grading of recommendations. After iterative review within the key authorship group, the manuscript was circulated to the wider stakeholder authorship for critical review of the nature and strength of the recommendations. At each stage of iterative review discrepancies in opinion were resolved through discussion and the Coalition consensus conclusion was included in the submitted manuscript.

The authors acknowledge that in this fast-moving field recommendations and their underlying supporting evidence are likely to change rapidly for SARS-CoV-2 specific complications; indeed there are some general points applicable to encephalopathy due to other systemic perturbations during other infections. However, in part due to the rapid and large scale clinical trials in COVID-19 treatment, we are actually able to provide more supporting

evidence than for encephalopathy generically. We consider that those components that are more specific to COVID-19 are the para- and post-infectious direct CNS complications of SARS-CoV-2 infection, such as cerebrovascular complications, acute disseminated encephalomyelitis (ADEM), and acute necrotizing encephalitis (ANE), among others. Whilst, at least the demyelinating conditions, have been reported in other infections in small numbers, the sheer scale of the denominator of people infected with SARS-CoV-2 infection have resulted in these relatively unlikely complications being common and have allowed for clinico-epidemiologic studies not previously possible to guide clinical management.

What is the pathophysiology of COVID-19 encephalopathy?

The Consortium elected not to provide recommendations for this section as, following consideration, there were no clinically actionable conclusions. Nevertheless, the pertinent literature to guide clinicians is summarized here (Figure 1).

[INSERT FIGURE 1 ABOUT HERE]

Primary Systemic Pathophysiology

The pathophysiology of COVID-19 encephalopathy is often multifactorial in approximately 4 in 5 hospitalised patients affected.[14]

Hypoxemia and hypotension

Low oxygen saturations (typically <88%) and hypotension are significantly related to encephalopathy in COVID-19 patients.[14] Prolonged hypoxia accompanied by glutamate excitotoxicity results in oligodendrocyte cell injury, blood brain barrier (BBB) disruption, and microhaemorrhages.[31-33] Neuropathological evidence of acute hypoxic injury in COVID-19 patients whose clinical course was complicated by encephalopathy has been reported in multiple autopsy cohorts, and was present in 28% in the largest systematic review.[34-40] Multiple magnetic resonance imaging (MRI) studies have also identified evidence of hypoxic-ischemic brain injury including watershed, cortical, or deep grey restricted diffusion,

leukoencephalopathy and microhaemorrhages.[31,41-48] Additionally, several have described SARS-CoV-2 delayed post-hypoxic leukoencephalopathy (DPHL), characterised by a lucid interval following hypoxia and delayed progressive encephalopathy leading to coma, with necrosis of oligodendrocytes and demyelination.[47-50] It is possible that several reported MRI cases of "COVID leukoencephalopathy," when present with microhaemorrhages, are actually due to hypoxic brain injury and iatrogenic complications of the treatment of hypoxia, in addition to metabolic disturbances; or indeed these factors combined with a viral endotheliopathy.[51]

Electrolyte disturbance

Hyponatraemia has been reported in 10-50% of patients and may be related to IL-6-mediated vasopressin release.[52-55] Also, hypernatraemia, hypokalaemia, hypocalcaemia, and acid-base disturbances have been reported and may contribute to metabolic encephalopathy.[14,54-57] Nevertheless, hyponatraemia can also be seen in primarily CNS disorders reflecting the syndrome of inappropriate antidiuretic hormone release or cerebral salt-wasting syndrome.

Multi-system organ dysfunction

In severe COVID-19, multisystem organ dysfunction, including renal failure, are frequent causes of encephalopathy. Overall, acute kidney injury has been reported in 8-81% of patients with COVID-19, particularly in those requiring intensive care,[14,35,47,58] potentially due to cytokine storms, thrombotic events and/or direct renal cellular viral injury.[59] Secondary metabolic effects, including acidosis and electrolyte disturbance, can further compound uraemic encephalopathy.

Sepsis

Septic encephalopathy occurs in up to 70% of patients with bacteraemia/viraemia, mediated by inflammatory cytokines, BBB breakdown, microthromboses, and alteration of

neurotransmitters.[60-62] SARS-CoV-2 sepsis is likely, at least in part, mediated by a cytokine storm, including interleukin (IL)-1, IL-6, and tumour necrosis factor alpha (TNFα).[63,64]

Abnormal haemostasis

In COVID-19, inflammatory mediators can trigger hypercoagulability resulting in increased D-dimer, thrombocytopenia, and prolonged prothrombin time.[65] This predisposes to microthromboses and thromboembolic events in multiple organs, including the brain, which has been a common neuropathological finding in COVID-19 encephalopathy.[66]

Cytokine storm

This is the hallmark of ARDS and multi-organ dysfunction with severe COVID-19 and has been associated with interleukins (e.g. IL-6, IL-1β), interferons, and TNFα; in particular IL-6 correlates with COVID-19 severity, perhaps through BBB dysfunction.[63,65,67-69] Endothelial inflammation, microhaemorrhages, and extravasation of fibrinogen reflecting BBB breakdown have been reported in neuropathological studies.[14,70-72] Moreover, C-reactive protein (CRP), procalcitonin, D-dimer, and ferritin correlate with CNS damage and poor prognosis.[64,65] In addition, reduced natural killer cell counts and elevated soluble CD25 have also been reported rarely.[73,74]

Primary CNS Pathophysiology

Endotheliitis/Vascular disease

Brain MRI of 31 encephalopathic patients without a systemic cause identified vessel wall enhancement, particularly of the vertebral arteries, and cerebrospinal fluid (CSF) and post-mortem studies have further demonstrated evidence of BBB disruption which could contribute to encephalopathy.[14,70-72,75] Cerebrovascular complications, including ischaemic and haemorrhagic stroke, as well as cerebral venous sinus thromboses are widely recognised.[1,2] In addition, whilst cerebrovascular complications do not necessarily reflect systemic COVID-19

severity in all cases; they may still be associated with conventional cerebrovascular risk factors.[2]

Acute disseminated encephalomyelitis/acute necrotising encephalopathy

Cases with MRI evidence of both ADEM and ANE have been reported and are thought to reflect a cytokine-storm and or adaptive host responses, as CSF evidence of SARS-CoV-2 has only been reported in one case.[43,57] Autopsy studies have confirmed ADEM-like pathology and sometimes haemorrhagic white matter lesions with axonal injury.[35]

Encephalitis

While evidence for direct viral encephalitis is lacking, para/post-infectious encephalitis has been reported.[1,2] Some of these cases may represent autoimmune encephalitis triggered by infection, although specific autoantibodies including N-methyl-D-aspartate receptor (NMDA-R), contactin-associated protein-like 2 (Caspr2) and anti-Purkinje/striatal or hippocampal antibodies have only been identified in a handful of patients.[76] Angiotensin converting enzyme 2-receptor (ACE2-R) expression, which is essential for viral cell entry, has been reported in olfactory epithelial cells. However, single cell sequencing for ACE2-R expression (which eliminates contamination) did not detect expression in olfactory neurons.[77] While some have reported SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR) in neural tissue, most have reported low ribonucleic acid (RNA) copies or not reported levels, therefore the positive result and may simply reflect blood contamination from within cerebral vessels or due to a leaky BBB; in such cases SARS-CoV-2 may enter the CNS as an innocent bystander, rather than through neurotropism.[34,35,78-80] Moreover, *in situ* hybridization studies did not detect SARS-CoV-2 in any neural tissue in two separate studies.[79,81]

Seizures

There are reports of *de novo* seizures including some patients with non-convulsive status epilepticus with resultant prolonged altered mental status, although this may be mechanistically

heterogenous.[61] In some this may represent decompensation in older patients with underlying neurological degenerative disease, but in some younger patients new-onset seizures and status epilepticus have been identified.[2]

Posterior reversible encephalopathy syndrome (PRES)

While PRES is driven by systemic processes, the primary clinical presentation reflects cerebral dysfunction. MRI studies have confirmed classical posterior appearances of PRES in the context of severe hypertension and presenting with symptoms of encephalopathy and often with seizures and visual cortex impairment.[60]

Which clinical features suggest COVID-19 encephalopathy?

Recommendations

- Encephalopathy manifests clinically as delirium, sub-syndromal delirium, and coma *[Strongly recommended; Evidence from non-randomised studies]*
- Premorbid factors associated with risk of developing COVID-19 encephalopathy due to systemic processes, include age and prior neurological diagnoses, especially dementia *[Recommended; Evidence from non-randomised studies]*
- In this group, risk increases with duration of hospital stay and may be most common at approximately two weeks into respiratory symptom onset *[Recommended, but other alternatives may be acceptable; Evidence from non-randomised studies]*
- However, patients may also present with symptoms of encephalopathy predating respiratory symptoms *[Recommended; Evidence from non-randomised studies]*
- Hypoxia and/or hypercapnia is strongly associated with risk of COVID-19 encephalopathy *[Recommended; Evidence from non-randomised studies]*

Clinical approach

Clinically, encephalopathy presents with delirium, sub-syndromal delirium, and coma.[16] In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) of the

American Psychiatric Association, delirium is defined as a transient disturbance of consciousness presenting with change in cognition and predominantly decreased attention.[84] The presentation is usually waxing and waning with fluctuating levels of consciousness. The patient is generally disoriented and may have illusions, hallucinations, or delusions, along with autonomic nervous system symptoms such as tachycardia, diaphoresis, and mydriasis.[85,86]

Taking a history may require the presence of an informant that is either a family member or caregiver (e.g., the nursing home or hospital). A high index of suspicion is required, since a change in orientation or cognitive function may either be gradual or sudden. Some patients may be aggressive or agitated and may be at risk of harm to themselves or others, termed "hyper-active delirium." However, the patient may also be thought to be depressed due to inactivity or withdrawing from daily tasks, termed "hypoactive delirium."[84] Symptoms specific to the aetiology of encephalopathy may also be present. These may include fever, headache, polyuria, polydipsia, and seizures. Standardised tools for assessment such as the confusion assessment method (CAM) and 4AT can also be used to screen patients for delirium and therefore evidence of acute encephalopathy.[87,88] We would recommend that clinicians be alert to the potential for COVID-19 to cause encephalopathy/delirium and have a low-threshold for using tools such as 4AT and CAM to screen patients, especially those at high risk such as those in intensive care units or high dependency units and potentially those requiring oxygen on a general ward. However, the authors consider that, outside of an observational study, it is a challenge to ask that potentially over-stretched clinicians screen all patients.

Highest at risk of encephalopathy are COVID-19 patients with older age, underlying neurological disease such as dementia and stroke, as well as other systemic diseases.[75,90-92] Elderly patients are particularly vulnerable with risk increasing with length of hospital stay, with a median of 14 days from respiratory symptom onset in one national surveillance study.[92,93]

However, while neurological abnormalities commonly follow respiratory symptoms of COVID-19, they may precede them.[75,94]

Which clinical features suggest a primary Central Nervous System (CNS) pathology?

Recommendations

- Clinical features suggestive of a primary CNS disease include new-onset headache (especially if 'thunder-clap', worse lying flat, or otherwise unusual for the patient), focal neurological deficits, symptoms/signs of raised intracranial pressure, seizures, movement disorders, and/or a Glasgow Coma Scale (GCS) <13/15 *[Recommended; Evidence from non-randomised studies]*
- Encephalopathy in COVID-19 patients without clear symptoms, signs, and systemic parameters highly suggestive of a peripheral perturbation causing a secondary encephalopathy, such as hypoxia, hypercapnia, hyponatremia/hypernatraemia, hypoglycemia/hyperglycemia, shock, iatrogenic (e.g., shortly after extubation/ventilation), should be investigated for primary CNS complications of SARS-CoV-2 infection, especially if CNS symptoms and signs are identified (Table 1; Figure 2) as these would be less common in delirium due to systemic perturbations *[Recommended; Evidence from non-randomised studies]*

[INSERT TABLE 1 ABOUT HERE]

[INSERT FIGURE 2 ABOUT HERE]

Clinical approach

It is critical that a diagnosis of encephalopathy is considered in all patients with COVID-19, and basic neurological assessment should be part of the evaluation of every patient. As a minimum, this should include recording of the Glasgow coma score (GCS) or FOUR score at admission and more complete neurological assessment, as well as serial monitoring using these instruments if the patient's neurological function is compromised or if intensive care unit support is required.[95,96]

Clinical evidence from the history and/or examination which may point to a primary CNS disease as a consequence of SARS-CoV-2 infection, such as cerebrovascular pathology, demyelination, and other CNS inflammatory complications, include new-onset headache (especially if "thunder-clap" in character, worse lying flat, or otherwise unusual for the patient), focal neurological features (such as hemiparesis, hemi-sensory disturbance, diplopia, or cortical blindness), symptoms/signs of raised intracranial pressure (such as transient visual obscuration or papilloedema), meningism, seizures (including subtle-motor and non-convulsive status epilepticus), movement disorders (such as opsoclonus-myoclonus), and/or a GCS <13 (Table 1).[1,2,75,92,97-99]

What investigations should be performed to establish these CNS diagnoses?

Recommendations

- Patients with symptoms and signs of encephalopathy should be evaluated for systemic causes, including hypoxia/hypercapnia, metabolic disturbance, organ dysfunction, coagulation disturbance, and iatrogenic contributing factors *[Strongly recommended; Evidence from non-randomised studies]*
- Patients without a clear systemic cause and/or with symptoms and/or signs suggestive of direct CNS pathology should be investigated with neuroimaging *[Recommended; Evidence from non-randomised studies]*
- The optimal neuroimaging modality for CNS inflammatory disorders, leukoencephalopathy, PRES and demyelinating disorders such as ADEM is brain MRI; including contrast-enhanced MR angiography in those with suspected vasculitis *[Strongly recommended; Evidence from non-randomised studies]*
- MRI should include imaging of the spine if myelopathic features are present, such as symmetrical upper motor neuron signs and/or bowel/bladder involvement *[Recommended; Evidence from non-randomised studies]*

- In patients with acute focal neurological deficits, symptoms/signs of raised intracranial pressure (ICP), a thunderclap headache, and/or a rapid decline in conscious level an urgent computerised tomography (CT) brain scan should be performed, including CT venography in those with suspected cerebral venous sinus thrombosis (CVST) *[Recommended; Evidence from non-randomised studies]*
- CSF studies including SARS-CoV-2 PCR and antibody testing (matched to serum and CSF:serum albumin ratio) should be performed in patients in whom MRI is non-diagnostic, including investigation for other CNS pathogens *[Recommended; Evidence from non-randomised studies]*
- Anti-CNS autoantibodies should be assessed in patients with refractory encephalopathy, especially in those with new-onset status epilepticus and/or movement disorders *[Recommended; Evidence from non-randomised studies]*
- Electroencephalogram (EEG) should be performed in patients with otherwise unexplained encephalopathy, especially in those with features suggestive of subtle-motor or non-convulsive status epilepticus, such as focal twitching, posturing, and/or fluctuating consciousness or those with prior clinical seizures *[Recommended; Evidence from non-randomised studies]*

Clinical approach

Irrespective of whether the underlying pathology is of a cerebral or a more systemic nature, the potential aetiologies must be identified as soon as possible and treated appropriately, and there is a particularly important role for neuroimaging and CSF analysis in patients without an obvious systemic cause.[30]

The differential diagnosis of encephalopathy is extensively and, in areas of high incidence of SARS-CoV-2 infection, even relatively low frequency complications may occur in significant numbers of patients. Therefore, in the absence of obvious systemic explanations

for encephalopathy, the work-up of patients must be extended for less frequent causes.[30] Nevertheless, when it comes to more sophisticated investigations, it is important to consider which patient would benefit from specific investigation, especially where healthcare resources are limited (Table 2; Figure 2).

[INSERT TABLE 2 ABOUT HERE]

Neuroimaging

In the appropriate clinical context, CT scanning may identify or confirm evidence of an acute cerebrovascular event and/or evidence of brain shift reflecting cerebral oedema. CT venography is indicated for those in who a cerebral venous sinus thrombosis is suspected. However, MRI is optimal to identify the recognised neuroimaging substrates of CNS complications of SARS-CoV-2 infection including encephalitis, leukoencephalopathy, stroke and demyelinating syndromes such as ADEM, and MR angiography for CNS vasculitis (Figure 3).[2]

[INSERT FIGURE 3 ABOUT HERE]

Examination of CSF for SARS-CoV-2 and antiviral antibodies

Among 430 patients from 242 publications, of whom 321 had cerebral symptoms/signs, and 304 had CSF PCR for SARS-CoV-2 performed, only 17 (6%) were positive.[76] Clinical features included combinations of encephalopathy, coma, seizures, headache, cerebellar features, paraesthesia and visual loss. A further, seven patients tested had intrathecal synthesis of anti-SARS-CoV-2 antibodies. Only 4 (5%) of 77 tested had autoimmune antibodies in the CSF. Overall, the CSF white blood cell count was reported in 409 cases and was 21-100 cells/μL in 28 (7%) and >100 cells/uL in 8 (2%). CSF protein concentration was 'increased' in 40%, >200 mg/dL in 28 (7%), and >1000 mg/dL in 5 (1.2%) of 397 cases in which it was reported.[76]

In another study of CSF analysis from 6 patients, of whom four had encephalopathy, one with meningism and one with fatigue and disorientation, SARS-CoV-2 was detected in plasma

and CSF in three.[103] None had a pleocytosis, the albumin ratio did not support BBB impairment and there was no intrathecal immunoglobulin G (IgG) synthesis but there was an increase of neopterin and beta-2 microglobulin. In one intensive care unit study of eight patients with prolonged encephalopathy, all had high levels of anti-SARS-CoV-2 IgG antibodies in serum and CSF, with a 1:10 dilution.[104] In three cases, the BBB was disrupted, and one case had intrathecal synthesis. PCR was negative for SARS-CoV-2 in all cases and 14-3-3 protein was elevated in four.

Anti-CNS autoantibody detection

Autoantibodies have been reported in some small series, including a series of 11 patients with negative SARS-CoV-2 PCR in CSF, but autoantibodies, including those directed against NMDA-R, cardiolipin, beta-2 glycoprotein, myelin, annexin, and Yo; which may have contributed to encephalopathy, myoclonus, and/or seizures.[105] In large case series of patients with various neurological manifestations, most tested cases were negative for SARS-CoV-2 PCR, but a few showed altered albumin ratios and a minority demonstrated oligoclonal bands.[106,107]

How should patients suffering from COVID-19 encephalopathy be managed?

Recommendations

- Assessment to detect neurological complications is mandatory, and ongoing monitoring is indicated in patients who show abnormalities; including consideration of EEG monitoring if available. *[Recommended; Evidence from non-randomised studies]*
- The use of advanced cardiorespiratory monitoring should be calibrated to the severity of systemic illness *[Strongly recommended; Evidence from non-randomised studies]*
- An acute priority is avoidance of secondary brain injury by earliest possible initiation of intensive care management aiming at preventing or treating organ dysfunction,

metabolic disturbances and hypoxia, and ensuring sufficient energy supply to the CNS *[Recommended; Evidence from non-randomised studies]*

- Fever should be managed, in particular avoiding hyperpyrexia *[Recommended; Evidence from non-randomised studies]*
- Seizures and non-convulsive status epilepticus should be identified promptly and managed with standard anti-epileptic drug protocols *[Recommended; Evidence from non-randomised studies]*
- Corticosteroids are indicated in those with severe systemic COVID-19 which may correlate with severity of encephalopathy in some patients *[Strongly Recommended; Evidence from randomised trials]*
- Tocilizumab or sarilumab are indicated in those with severe systemic COVID-19. Patients with high CRP or IL-6 levels may show particular benefit, although their role for COVID-19 encephalopathy is not established *[Recommended; Evidence from randomised trials]*
- Corticosteroids, Intravenous Immunoglobulin (IVIG), and/or Plasma Exchange (PLEX) are indicated as an immunomodulatory intervention where encephalopathy is thought to be primarily CNS immune-mediated based on clinical, CSF and MRI findings (e.g. ADEM, ANE, encephalitis), and considered in *de novo* seizures in patients without prior CNS disease *[Recommended; Evidence from non-randomised studies]*
- Corticosteroids, IVIG, and/or PLEX may be considered in patients with encephalopathy not adequately explained by systemic parameters or medications in the absence of clear evidence of a CNS immune-mediated cause based on clinical, CSF and imaging findings or where these investigations are not available *[Recommended other alternatives are acceptable; Expert opinion only]*

- Blood pressure should be controlled using established protocols in patients with PRES

  [Recommended; Evidence from non-randomised trials]

Clinical approach

Prevention of encephalopathy is vital and utilisation of multicomponent, non-pharmacological interventions is crucial to avoid the development of COVID-19 encephalopathy when due to systemic perturbations. Once encephalopathy is present these interventions can continue alongside comprehensive management analogous to the urgency of treatment for sepsis to detect and reduce further insults to the critically ill brain.[109-115]

Monitoring

Systemic monitoring should be calibrated to the severity of systemic disease with invasive blood haemodynamic monitoring when needed and available. In addition, specific neurological monitoring should include intermittent, or preferably continuous, EEG monitoring where indicated and available. Seizures are well-recognised in COVID-19, and may be non-convulsive (especially in patients who are sedated for mechanical ventilation) and are an often treatable cause for encephalopathy including in many Low-to-Middle-Income Country (LMIC) settings (Figure 4). While experience from other diseases suggests that more advanced measures (intracranial pressure and brain chemistry monitoring) might provide additional information in some patients,[116] there is limited experience and no evidence of benefit in COVID-19 encephalopathy.

[INSERT FIGURE 4 ABOUT HERE]

General supportive care

Management should target organ dysfunction identified by clinical, laboratory and imaging evidence, including the correction of hypoxia and hypotension.[111-115] Despite recent concerns about liberal oxygen saturation (Sp02) targets in critical illness, there is no evidence that very conservative targets (SpO2 <90%) show benefit, and SpO2 targets of 93-96% are

probably most appropriate.[117] In patients with severe ARDS, careful clinical judgment is needed to balance the protective lung ventilation against optimal blood gas levels. Blood pressure management should generally target normotension with a lower limit of 60-65 mmHg, but particular attention to tight blood pressure control may be needed in patients with PRES. Other aims include aggressive treatment of pyrexia and hyperpyrexia (>40°C), aiming at a liberally defined normothermia (<38°C),[118] restoration of metabolic homeostasis (including renal replacement therapy where appropriate), and addressing additional organ dysfunction. Whilst hypothermia has been employed in some cases, there is not currently sufficient evidence to support this in routine care.[119] Other concerns include controlling for hypoglycaemia and severe hyperglycaemia; and the avoidance of rapid changes in sodium levels, which may precipitate osmotic demyelination, which has been reported in COVID-19.[120,121]

Iatrogenic insults

Encephalopathy may also be due, at least in part, to medication both specific to COVID-19, and agents used more generally in critical illness.[122] The general critical care literature suggests the need for care with sedatives and drugs with anticholinergic effects.[96] While high dose corticosteroids may be life-saving in severe COVID-19, they may precipitate or contribute to acute psychotic effects in some individuals. If possible, pre-COVID-19 steroid therapy should probably be continued but in some instances, this may not be possible.

Systemic immunomodulation

There is increasing recognition that the host response is a critical mediator of severe COVID-19, and there is now good evidence of benefit for a range of immunomodulatory interventions. While the available evidence is dynamic, interventions that are currently thought to show benefit in WHO-grade severe COVID-19 include corticosteroids (dexamethasone and hydrocortisone), and IL-6 inhibitors (tocilizumab and sarilumab), and Janus Kinase (JAK) inhibitors (baricitinib).[123] While evidence of the impact of these interventions on neurological

complications is unclear, the modulation of the host immune response might be expected to mitigate the effects of cytokine excess generally, and also affect immune-mediated CNS diseases more specifically.

Specific CNS therapy

In cases with well-characterised CNS syndromes (such as ADEM, ANE, encephalitis, and also perhaps *de novo* seizures) immunomodulation is indicated regardless of COVID-19 disease severity, including corticosteroids, plasma exchange (PLEX), and/or intravenous immunoglobulin (IVIG), although the latter may increase the risk of thrombosis (Figure 2).[124] Nevertheless, supporting data are largely from case reports and case series and mechanisms of action remain unclear. In addition to well-defined CNS syndromes, these immunomodulatory approaches may also be useful in some patients, especially when a potential inflammatory CNS process driving encephalopathy is supported by clinical, CSF and/or MRI features. The use of other immunomodulatory interventions (e.g. IL-1 or IL-6 antagonists) will depend on local experience and availability, and whether the drug is indicated based on the systemic severity of COVID-19 regardless of CNS manifestations. Trials are currently underway for interferons, and inhibitors of multiple inflammatory mediators including for IL-1, IL-6, TNFa, and JAK, as well as neutralising antibodies, which have been granted Emergency Use Authorisation in some countries.[125,126]

What is the prognosis for patients with COVID-19 encephalopathy?

The Consortium elected not to provide recommendations for this section as, following consideration, there were no clinically actionable conclusions. Nevertheless, the pertinent literature to guide clinicians is summarised here.

Acute COVID-19 encephalopathy is associated with increased mortality and morbidity, with varying estimates of effect size based on different case definitions and patient populations. In the older population, encephalopathy at COVID-19 onset is associated with an up to fourfold

increase in mortality and unfavourable outcome.[23,127-131] In one of the largest multicentre cohort studies of 3,055 hospitalised COVID-19 patients from the United States, those with acute encephalopathy had a 5.5-fold increased risk for death during hospitalisation even after adjusting for age, sex, race, ethnicity, and study site.[3] For patients with coma, the adjusted risk for in-hospital death was 7.7 times higher. A large study from Brazil found 55% of in-hospital death occurred in patients with manifestations of encephalopathy, which was 1.75 times higher than those without encephalopathy.[128] In those who survive beyond hospitalisation, acute encephalopathy is associated with up to 3-fold higher 30-day mortality and worse physical function at 4 weeks post-admission.[4,9,129] The impact of acute encephalopathy on long-term neurological, cognitive, and psychiatric outcome after COVID-19 remains unknown at this time, but early clinical experience suggests that sequelae, such as post-traumatic stress disorder (PTSD), may not be uncommon.

The association between the causal pathophysiology of encephalopathy and poor outcome in acute COVID-19 remains unclear and requires further investigation. Impaired consciousness at hospital admission is a key risk factor for developing critical illness with COVID-19.[132] In cases with encephalopathy reflecting systemic COVID-19 disease severity common risk factors, such as older age, higher intensive treatment unit/ventilator requirements, and more pre-existing conditions, are more common and these same factors may also negatively impact mortality and long-term outcome.[3,4,9,128] Future longitudinal studies using standardised ascertainment methods, case and control definitions, and comprehensive cognitive, psychiatric and neurological assessment are underway to further understand the prognosis of COVID-19 patients who experienced acute encephalopathy.[133]

What is the role of rehabilitation for these patients?

Recommendations

- Patients experiencing ongoing issues post-COVID-19 encephalopathy should be referred to rehabilitation services operated by multi-disciplinary teams *[Recommended; Expert opinion only.*
- Given the scale of the pandemic, thought should be given to rehabilitation interventions that are scalable (both nationally and internationally) (e.g. simple screening processes, remote assessment and treatment options, home rehabilitation, and public-private collaborations) *[Recommended but other alternatives acceptable; Expert opinion only]*
- Research into the long-term outcomes of COVID-19 encephalopathy should be undertaken in order to develop patient-centred pathways and rehabilitation guidelines that will maximise quality of life *[Strongly recommended; Expert opinion only]*
- Self-management programs and non-profit third sector organisations have important roles to play in supporting traditional rehabilitation, along with providing patient information and education on how to maximise recovery *[Recommended but other alternatives acceptable; Expert opinion only]*

Clinical approach

Patients who have recovered from COVID-19 may suffer neurological, psychiatric, physical, and psycho-social difficulties, although we do not yet fully understand the long-term implications to guide rehabilitation.[134] Nevertheless, these may reflect both physiological and psychological impacts (e.g., PTSD), even in patients who did not require intensive care unit admission. Following discharge, many report fatigue, cognitive symptoms, depression, anxiety, and adjustment disorders, and follow-up assessment is likely to be beneficial for many, perhaps the majority, for both independence and return to education and work.[135-138]

Those who have suffered encephalopathy and an acute primary CNS complication, such brain inflammation and stroke, are likely to experience multiple physical symptoms and may well require significant rehabilitation investment.[139] Moreover, as many of the most severely

affected patients with COVID-19 encephalopathy may have comorbid conditions, rehabilitation needs and goal-setting can be even more challenging.[134] There is currently no evidence of encephalitis lethargica presentations as was seen in the epidemic of the late 1800s and early 1900s, although clinicians seeing patients for rehabilitation should be alert to the possibility of delayed emergent phenotypes in patients during rehabilitation and follow-up.

In conclusion, given the large number of patients hospitalised with COVID-19 encephalopathy and the complexity of their rehabilitation needs, these services for survivors must be prioritised, have a long-term focus, be innovative and scalable, and be delivered by multi-disciplinary teams.[134,140,141]

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Table 1: Common systemic causes of encephalopathy in patients with COVID-19 and associated investigations

Pathology	Systemic cause	Investigations
Organ dysfunction	Hypercapnia /hypoxia; Hepatic failure; Acute kidney injury; Thyroid disorders; Cardiac failure	Pulse oximetry, Blood gas; ALT, AST, GGT, ALP, ammonia; Creatinine, urea; TSH, T4; ECG, Echo, clinical examination
Metabolic	Hyper/hyponatremia; Hyper/hypocalcaemia; Hypomagnesemia; Hyper/hypoglycaemia; Hypothermia; Fever/ Hyperpyrexia; Cytokine Storm	Plasma Na^{+}; Corrected plasma Ca^{2+}; Plasma Mg^{2+}; Plasma/finger-prick glucose; Temperature/ observations; IL-1, IL-6, TNF□□(guided by local expertise)
Toxic	Sedatives, corticosteroids, hydroxychloroquine, lopinavir, ritonavir, tocilizumab, drugs/alcohol	Patient history; Treatment review; Blood alcohol level; Urinary drug screen
Septic	Superinfection (typically bacterial or fungal)	Blood/Urine/Sputum cultures; Serology/PCR
Vascular	Hypertensive encephalopathy; Severe hypotension	Non-invasive or invasive blood pressure monitoring
Nutritional	Wernicke encephalopathy	B12/thiamine

pCO_2: carbon dioxide partial pressure; pO_2: oxygen partial pressure; ALT: alanine aminotransferase, AST: aspartate aminotrasferase, GGT: gamma-glutamyl transferase, ALP: alkaline phosphatase; TSH: thyroid stimulating hormone; T4: thyroxine (thyroid hormone); Echo: echocardiography; ECG: electrocardiogram, PCR: polymerase-chain reaction; CRP: C-reactive protein; PCT: procalcitonin; Na^{+}: natrium; Ca^{2+}: calcium, Mg^{2+}: magnesium IL-1; Interleukin-1; IL-6: Interleukin-6; TNF: Tumour Necrosis Factor.

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Table 2: Main indications for evaluation for primary CNS causes of encephalopathy in the context of SARS-CoV-2 and recommended investigations

Investigation	Indication	Investigations
CT	Altered level of consciousness; Headache with red flags*; Altered behaviour; Focal neurological signs/symptoms; Unexplained generalised seizures; Focal/generalised seizures; Suspected stroke; Suspected CVST	CT with and without contrast enhancement; CT angiography +/- CT perfusion in case of sudden-onset symptoms; CT venography
MRI [100]	Same as CT, in case of unclear cause	T1; T2; DWI; FLAIR; Arterial Time-of-Flight; Gradient echo/SWI; T1 + gadolinium; T2 + gadolinium
EEG [99,101,102]	Suspected non-convulsive status epilepticus; Suspected subtle motor status epilepticus; If unclear if psychiatric cause or encephalopathy	EEG; VideoEEG may improve the localisation of the seizures; Consider prolonged monitoring
LP [76,103-107]	In case of suspected encephalitis (including ADEM, and ANE), as soon as possible; In the absence of another clear explanation for encephalopathy; Unexplained seizures or status epilepticus (once stable); Suspected autoimmune encephalitis or Bickerstaff encephalopathy	WBC; RBC; Protein concentration; Paired serum/CSF glucose; Paired CSF Albumin / plasma albumin; Paired oligoclonal bands; Paired SARS-CoV-2 PCR and antibody
Autoantibody tests [108]	Unexplained encephalopathy, particularly if associated with psychiatric features, encephalomyelitis, memory decline, seizures, cerebellar syndrome, movement disorder, or sensory neuronopathy which may suggest autoimmune encephalitis	Auto-antibodies against the following receptors: e.g. NMDA-R, LGI-1, CASPR2, AMPAR, GABA-A/B, mGluR5, DPPX; CRP; ANA; ENA; dsDNA; ANCA; Thyroperoxidase autoantibodies; Antiganglioside antibodies

**Symptoms/signs of raised ICP: Headache and/or transient visual obscuration worse on lying flat/waking from sleep/Valsalva manoeuvres, nausea and vomiting, papiloedema, false-localising signs (e.g. VI palsy). Abbreviations: CT: computed tomography; ADEM: acute demyelinating encephalomyelitis; MRI: magnetic resonance imaging with T1 and T2 representing specific weighting of the images; DWI: diffusion-weighted imaging; FLAIR: fluid-attenuated inversion recovery; SWI: susceptibility weighted imaging; LP: lumbar puncture, WBC: white blood cells; RBC: red blood cells; CSF: cerebrospinal fluid; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; NMDA: N-methyl-d-aspartate; AMPAR: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; GABAR: gamma-aminobutyric acid receptor; mGluR5: metabotropic glutamate receptor 5; CRP: C-reactive protein; ANA: antinuclear antibodies; ENA: extractable nuclear antigen; dsDNA: double stranded DNA; ANCA: antineutrophil cytoplasmic antibodies.*

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Figure 1. Potential pathophysiological mechanisms causing encephalopathy in patients infected with SARS-CoV-2

ADEM: Acute Disseminated Encephalomyelitis; ANE: Acute Necrotising Encephalopathy; NCSE: Non-Convulsive Status Epilepticus; PRES: Posterior Reversible Encephalopathy Syndrome (Figure produced in BioRender © 2021)

Figure 2. Algorithm for the diagnosis and management for adult patients with encephalopathy due to COVID-19.

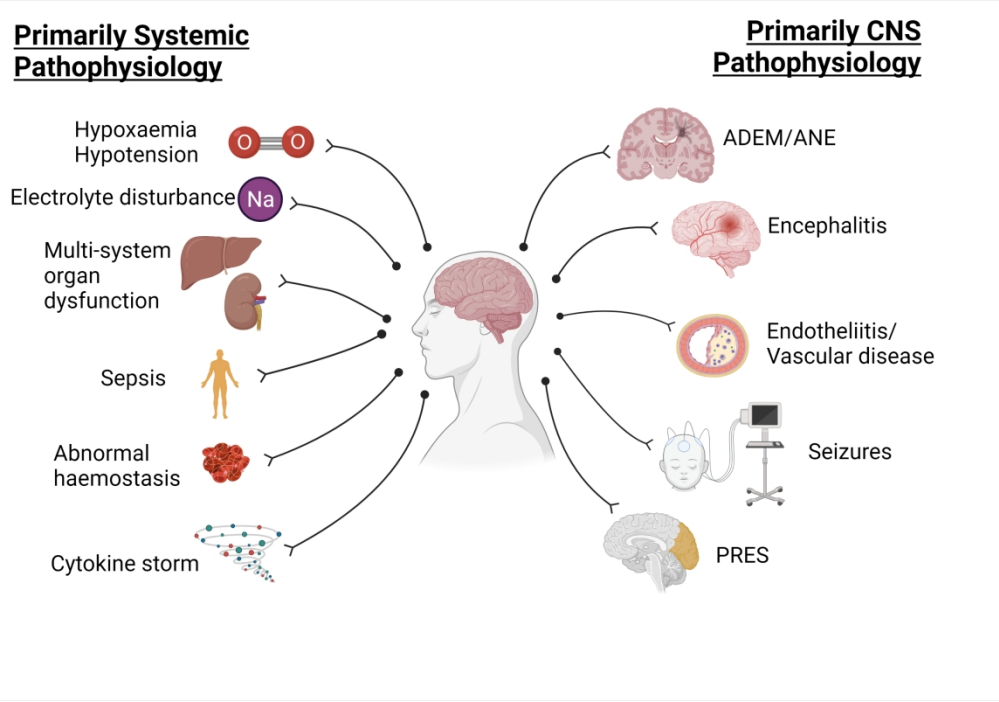
Figure 3. Examples of MRI and CT imaging identifying CNS complications of SARS-CoV-2 infection presenting with encephalopathy.

(A-C; patient 1) - Axial T2-weighted image on day two of symptoms in a patient with acute disseminated encephalomyelitis associated with SARS-CoV-2. It demonstrates an ill-defined hyperintensity in the posterior limb of the internal capsule and thalamus. (B) - There is facilitated diffusion in the ADC map in the core of the lesion, whilst the periphery is isointense with the brain. (C) - Post-gadolinium, T1-weighted imaging of the lesion on day five from symptom onset demonstrates incomplete ring enhancement in the medial and posterior aspect consistent with acute demyelination. (D-E; patient 2) - Axial T2-weighted MRI demonstrating a large area of hyperintensity in the right frontal lobe. (E) - Evidence of diffusion restriction consistent with an acute infarction. (F-G; patient 3) - MRI Head with contrast in a patient with encephalopathy and focal neurology in the context of SARS-CoV-2 infection, suspected to have acute encephalitis, demonstrating high intensity within the right thalamus on axial T2-weighted images. (G) - Evidence of restricted diffusion. (H; patient 4) - Head CT of patient with profound anoxic brain injury and superimposed intracranial haemorrhages while on therapeutic dosed heparin. (I; patient 5) – CT head imaging demonstrating multi-compartmental haemorrhages in

a COVID-19 ARDS patient who was not anticoagulated and had no history of trauma. (J; patient 6) - MRI susceptibility-weighted images of a COVID-19 ARDS patient with multiple microhaemorrhages at the grey-white junction. (K-N; patient 7) - MRI with diffusion weighted imaging demonstrating restricted diffusion consistent with hypoxic ischemic brain injury affecting the purkinje cells of the cerebellum. (L) Striatal neurons of basal ganglia. (M) Cortex, and (N) late hypoxic changes seen in white matter tracts.

Figure 4. Examples of the electroencephalographic findings which have been reported in COVID-19 encephalopathy

A. Electroencephalographic appearances of non-convulsive status epilepticus (NCSE); B. Electroencephalographic appearances of non-specific encephalopathy showing generalised slowing through both hemispheres.



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ADEM: Acute Disseminated Encephalomyelitis; ANE: Acute Necrotising Encephalopathy; NCSE: Non-Convulsive Status Epilepticus; PRES: Posterior Reversible Encephalopathy Syndrome (Figure produced in BioRender © 2021)

254x177mm (300 x 300 DPI)

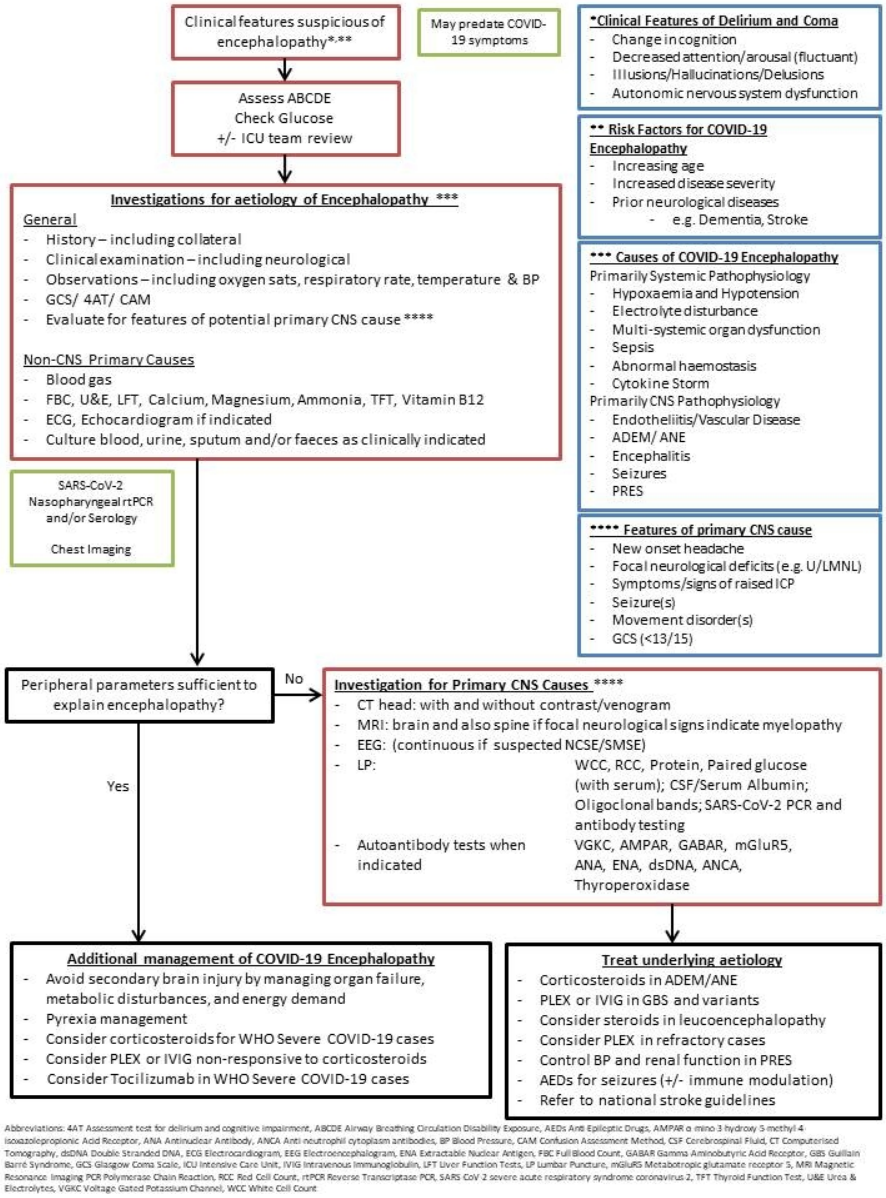
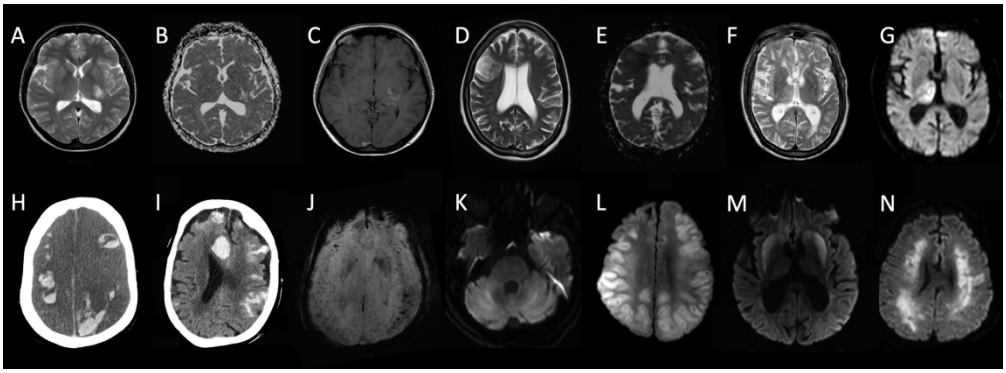


Figure 2. Algorithm for the diagnosis and management for adult patients with encephalopathy due to COVID-19.

190x254mm (96 x 96 DPI)



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(D-E; patient 2) - Axial T2-weighted MRI demonstrating a large area of hyperintensity in the right frontal lobe. (E) - Evidence of diffusion restriction consistent with an acute infarction.

(F-G; patient 3) - MRI Head with contrast in a patient with encephalopathy and focal neurology in the context of SARS-CoV-2 infection, suspected to have acute encephalitis, demonstrating high intensity within the right thalamus on axial T2-weighted images. (G) - Evidence of restricted diffusion.

(H; patient 4) - Head CT of patient with profound anoxic brain injury and superimposed intracranial haemorrhages while on therapeutic dosed heparin.

(I; patient 5) – CT head imaging demonstrating multi-compartmental haemorrhages in a COVID-19 ARDS patient who was not anticoagulated and had no history of trauma.

(J; patient 6) - MRI susceptibility-weighted images of a COVID-19 ARDS patient with multiple microhaemorrhages at the grey-white junction.

(K-N; patient 7) - MRI with diffusion weighted imaging demonstrating restricted diffusion consistent with hypoxic ischemic brain injury affecting the purkinje cells of the cerebellum. (L) Striatal neurons of basal ganglia. (M) Cortex, and (N) late hypoxic changes seen in white matter tracts.

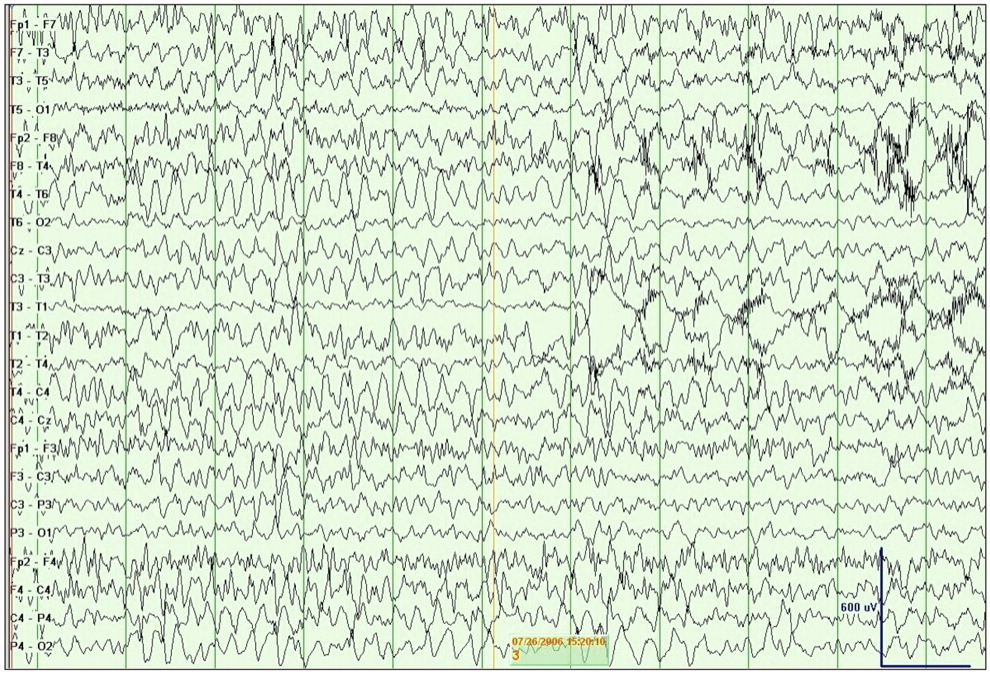
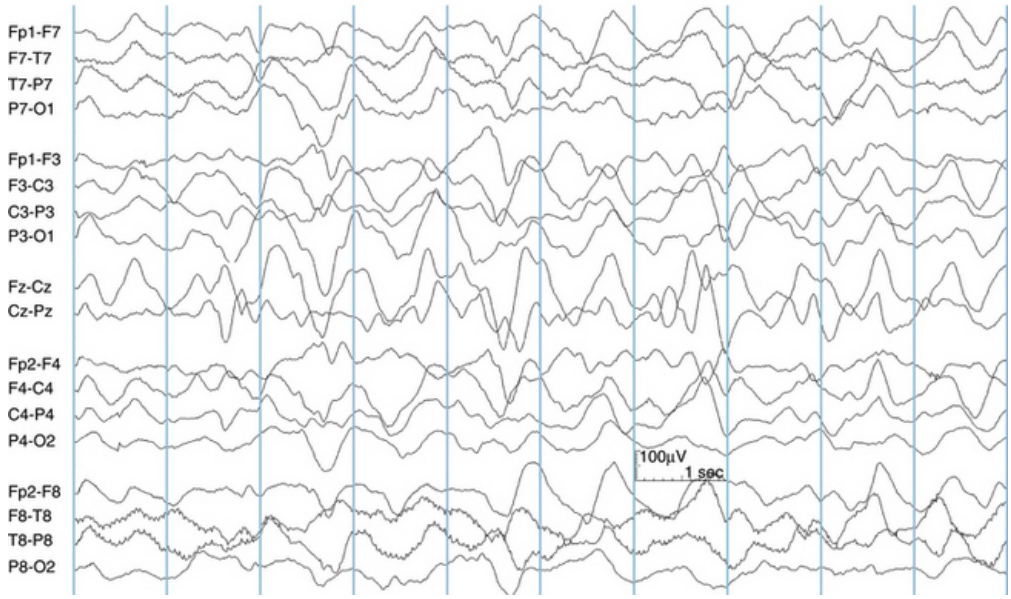


Figure 4. Examples of the electroencephalographic findings which have been reported in COVID-19 encephalopathy

A. Electroencephalographic appearances of non-convulsive status epilepticus (NCSE);



B. Electroencephalographic appearances of non-specific encephalopathy showing generalised slowing through both hemispheres.