Brain dysfunction in COVID-19 and CAR-T therapy: cytokine storm-associated encephalopathy

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Abstract

Objective: Many neurological manifestations are associated with COVID-19, including a distinct form of encephalopathy related to cytokine storm, the acute systemic inflammatory syndrome present in a subgroup of COVID-19 patients. Cytokine storm is also associated with immune effector cell-associated neurotoxicity syndrome (ICANS), a complication of chimeric antigen receptor T-cell (CAR-T) therapy, a highly effective treatment for refractory hematological malignancies. We investigated whether COVID-19-related encephalopathy, ICANS, and other encephalopathies associated with cytokine storm, share clinical and investigative findings.

Methods: Narrative literature review.

Results: Comparisons between COVID-19-related encephalopathy and ICANS revealed several overlapping features. Clinically, these included dysexecutive syndrome, language disturbances, akinetic mutism and delirium. EEG showed a prevalence of frontal abnormalities. Brain MRI was often unrevealing. CSF elevated cytokine levels have been reported. A direct correlation between cytokine storm intensity and severity of neurological manifestations has been shown for both conditions. Clinical recovery occurred spontaneously or following immunotherapies in most of the patients. Similar clinical and investigative features were also reported in other encephalopathies associated with cytokine storm, such as hemophagocytic lymphohistiocytosis, sepsis, and febrile infection-associated encephalopathies.

Interpretation: COVID-19-related encephalopathy and ICANS are characterized by a predominant electro-clinical frontal lobe dysfunction and share several features with other encephalopathies associated with cytokine storm, which may represent the common denominator of a clinical spectrum of neurological disorders. Therefore, we propose a unifying definition of cytokine storm-associated encephalopathy (CySE), and its diagnostic criteria.

Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), predominantly characterized by respiratory symptoms. The condition encompasses a broad spectrum of severity,1 associated in a subgroup of patients with cytokine storm, an acute systemic inflammatory syndrome that may lead to multiorgan failure.2 Both central and peripheral nervous system manifestations have been reported.3,4 COVID-19-related encephalopathy has been described as a distinct clinical condition whose biological underpinnings have not been wholly unveiled.5–6 Although it was initially attributed to CNS invasion by SARS-CoV-2, based on evidence from other coronavirus neuroinvasive and neurotropic properties,7,8 SARS-CoV-2 RNA is almost invariably undetectable in the cerebrospinal fluid (CSF) of patients with neurological manifestations.3,9 Additionally, CSF analysis, neuroimaging, and neuropathological findings, as well as the clinical
response to various immunotherapies, are not consistent with an infectious disease targeting the brain but rather with an immune-mediated pathogenesis.4,9–11 Therefore, a cytokine-mediated neuroinflammatory process, associated with cytokine storm, has been suggested as the underlying pathogenic mechanism.5,10,12–14

Chimeric antigen receptor T-cell (CAR-T) therapy is a novel and highly effective treatment for refractory hematological malignancies, whose most common complication is cytokine release syndrome, a cytokine storm disorder.14,15 Its therapeutic benefit is also limited by neurotoxicity, namely immune effector cell-associated neurotoxicity syndrome (ICANS), which may accompany cytokine storm.15–17 Notably, encephalopathy has been described as a recurrent manifestation also in other cytokine storm disorders, such as hemophagocytic lymphohistiocytosis and sepsis.14

Herein, we aimed to (i) briefly review different cytokine storm disorders (for a comprehensive description, we suggest a recently published review14); (ii) provide a detailed comparison between COVID-19-related encephalopathy and neurotoxicity related to CAR-T therapy to show that these conditions are characterized by overlapping clinical and investigative features; (iii) describe neurological manifestations in other hyperinflammatory syndromes, suggesting that these may belong to the same spectrum of cytokine storm-associated encephalopathy disorders.

Cytokine Storm Disorders

The cytokine storm umbrella encompasses several disorders at the intersection of hematology, oncology, rheumatology, and virology. Cytokine storm is characterized by a dysregulated immune response to various triggers and is defined by elevated circulating cytokine levels, acute systemic inflammatory symptoms, and secondary organ dysfunction, including the brain.14 Activated macrophages and monocytes appear to be responsible for the pathological hyperinflammation, regardless of the triggers.14,18 Several cytokine storm disorders have been described, including COVID-19-associated cytokine storm,18 cytokine release syndrome,15 hemophagocytic lymphohistiocytosis (HLH),19 macrophage activation syndrome,20 and multicentric Castleman disease.21 Although their primum movens differ, they share several laboratory abnormalities and clinical features, including encephalopathy (Table 1)14,18; diagnostic criteria exist to discriminate between these hyperinflammatory disorders.15,18,22,23

In COVID-19, SARS-CoV-2 invades macrophages/monocytes via the ACE2 receptor, leading to their activation.24 As a result, a subgroup of COVID-19 patients develop cytokine storm that may exacerbate lung damage and lead to multiorgan failure.2 Cytokine release syndrome is a supraphysiological response observed in oncological patients treated with CAR T-cells or other immune effector cell-engaging therapies.15 Activated T-cells directed against tumor antigens release interferon-gamma, which stimulates macrophages, resulting in cytokine storm.25 A hyperinflammatory state coupled with a dysregulated immune system is also considered the underlying mechanism of HLH.26 Various triggers, usually an acute viral infection, may lead to macrophage activation, resulting in hypercytokinemia in subjects unable to suppress these cells.26 Predisposing conditions to HLH include malignancies and immunodeficiency disorders.27 MAS is a condition observed in patients affected by rheumatological disorders with overlapping laboratory features with HLH, and is therefore frequently referred to as rheumatological HLH.14

Table 1. Features of interest in selected cytokine storm disorders.

| Trigger                  | COVID-19-associated cytokine storm | Cytokine release syndrome | Macrophage activation syndrome | Hemophagocytic lymphohistiocytosis |
|--------------------------|-----------------------------------|---------------------------|---------------------------------|------------------------------------|
| Encephalopathy           | ++                                | +++                       | ++                              | ++                                 |
| Fever                    | ++                                | ++                        | +                               | +                                 |
| Lymphopenia              | +++                               | +++                       | +                               | +++                                |
| Ferritin                 | ++                                | +++                       | +                               | +                                 |
| Lactate                  | +++                               | +++                       | +++                             | +                                 |
| dehydrogenase            | +++                               | +++                       | +                               | +                                 |
| D-dimer                  | +++                               | ++                        | +                               | +                                 |
| Hypofibrinogenemia       | None                              | +++                       | +                               | +                                 |
| IL-6                     | ++                                | +++                       | +                               | +                                 |

Modified from Webb et al. Lancet Rheum 2020.18
Sepsis is defined as an overwhelming inflammatory response to an infection, where it is still unclear which immune cell types and cytokines may be responsible for propagating the pathological hyperinflammation. Notably, a subgroup of septic patients develop a macrophage activation-like syndrome.

**Comparison of COVID-19-Related Encephalopathy and ICANS**

**Clinical features**

COVID-19-related encephalopathy and ICANS are two neuropsychiatric syndromes with varying degrees of severity, ranging from mildly altered mental status to coma. Delirium is one of the most common and earliest symptoms of COVID-19-related encephalopathy, present in up to 85% of COVID-19 patients in ICU, and is also reported in up to 66% of patients with ICANS. Language disturbances, notably expressive aphasia, are a frequent finding in both conditions, and may represent the first manifestation of CNS dysfunction, which may develop into a more severe form of encephalopathy. Akinetic mutism is an uncommon neurological presentation resulting from frontal-subcortical dissociation that has been described as a specific feature of ICANS. This peculiar manifestation has also been observed in several case reports of COVID-19-related encephalopathy, and might help discriminate these conditions from other encephalopathies.

Frontal release signs and dysexecutive symptoms represent a common finding in patients with COVID-19-related encephalopathy and are commonly encountered in ICANS, further suggesting a frontal lobe dysfunction. Transitory motor deficits have been described for both conditions, while corticospinal tract signs have been observed in up to 67% cases with severe SARS-CoV-2 infection and various other case reports of COVID-19-related encephalopathy, potentially representing a recurrent feature of this condition. Movement disorders, such as tremor and myoclonus of varying severity, have also been observed in both disorders. Seizures represent a relatively frequent manifestation of ICANS, and their occurrence is a defining feature of severe neurotoxicity. Patients with COVID-19-related encephalopathy may also present with new-onset seizures, either focal or generalized, convulsive or non-convulsive, including status epilepticus. Headache is another frequently reported symptom in COVID-19 and ICANS, occurring in 28% and 55% of patients, respectively. Even though this is a non-specific manifestation and its features have been poorly described in both disorders, it may represent an early manifestation of CNS involvement.

**EEG**

Since the outbreak of SARS-CoV-2, several reports of EEG findings in COVID-19 patients have been published. Diffuse background slowing is the most frequent abnormality, reported in approximately two-thirds of patients. Other diffuse EEG features include generalized rhythmic delta activity and periodic discharges with triphasic morphology. Notably, many studies describe a preponderance of frontal lobe abnormalities, including frontal focal slowing and intermittent rhythmic delta activity (FIRDA), sharp waves, epileptiform discharges, and status epilepticus.

Similarly, diffuse slowing in the theta-delta range occurs in most ICANS patients, and FIRDA represents the most common rhythmic pattern, followed by generalized periodic discharges with triphasic morphology. In both conditions, EEG abnormalities correlate with the severity of the encephalopathy and might improve following immunotherapy.

**Neuroimaging**

Neuroradiological features of COVID-19-related encephalopathy are heterogeneous. Most patients present with an unremarkable examination, but a few recurring radiological features have been reported, including multifocal white matter hyperintensities, diffuse microbleeds, cortical diffusion restriction, and leptomeningeal enhancement.

Brain MRI in ICANS is also often unrevealing, but radiological abnormalities similar to those in COVID-19 have been described. Interestingly, lesion of the splenium of the corpus callosum and posterior reversible encephalopathy syndrome (PRES) and posterior reversible encephalopathy have been observed in both COVID-19 patients and CAR T-cell therapy recipients.

FDG-PET and perfusion studies in COVID-19-related encephalopathy showed frontal lobe hypometabolism and hypoperfusion, consistent with the observed electro-clinical frontal lobe dysfunction. In ICANS, FDG-PET shows variable patterns of cortical hypometabolism, often colocalized with EEG abnormalities.

**Pathophysiology**

Several studies have shown a direct correlation between cytokine storm intensity and severity of neurological manifestations in COVID-19-related encephalopathy and
The average lower serum cytokine load detected in COVID-19-associated cytokine storm compared with cytokine release syndrome may explain the lower incidence of encephalopathy observed in the former (Table 1). In COVID-19-related encephalopathy, CSF SARS-CoV-2 RNA remains almost invariably undetectable, making a pathogenic role of CNS viral invasion unlikely. Similarly, neurotoxicity grade in ICANS correlates with CSF cytokine levels but not with CAR T-cells in CSF. In both conditions, CSF investigations revealed normal or mildly elevated cell counts with variable protein levels and elevated cytokine levels with molecular consistency across conditions. Therefore, a cytokine-mediated neuroinflammatory process has been suggested as the underlying pathogenic mechanism.

Evidence suggests that peripheral inflammation may lead to endothelial activation and blood–brain barrier (BBB) disruption, resulting in microglia and astrocyte activation. This induces a neuroinflammatory process that promotes CNS cytokine production, oxidative stress, and immune-cell trafficking, further contributing to BBB disruption, resulting in a vicious circle (Fig. 1).

Accordingly, glial (CSF GFAP) and BBB disruption (serum S100B) markers have been found elevated in both ICANS and COVID-19-related encephalopathy. Neuropathological findings in COVID-19 patients revealed mild abnormalities with pronounced inflammation due to diffuse astrocyte and microglia activation and infiltration of lymphocytes, similar to patients with sepsis. Additionally, the presence of SARS-CoV-2 RNA was not associated with the severity of neuropathological changes.

Preclinical models demonstrated that frontal lobes are most susceptible to cytokine-induced inflammation via the NF-kB signaling pathway, potentially explaining the frontal-predominant dysfunction observed in both conditions.

Outcome and treatment

Spontaneous clinical recovery has been reported for various patients with COVID-19-related encephalopathy. However, a subgroup of patients may develop severe neurological manifestations (e.g., impairment of consciousness) lasting up to several weeks. High-dose corticosteroids, intravenous immunoglobulin, and plasmapheresis have shown efficacy in treating COVID-19-related encephalopathy, promoting recovery even in patients with a severe, persistent encephalopathy. Clinical responses may occur as soon as the first day following immunotherapy and may be
accompanied by a dramatic decrease of circulating and CSF cytokines. 84,37 However, considering the absence of reliable response biomarkers, treatment duration should be primarily based on clinical response.

In ICANS, most symptoms are transient and fully reversible, with sparse reports of persistent abnormalities. 17,77 In rare cases, encephalopathy may progress to coma and lead to death as a consequence of diffuse cerebral edema. 16 Corticosteroids represent the first-line therapy for ICANS but are typically employed only in severe cases, as there is a potential concern of their interference with CAR T-cells anti-tumor action. 77,79 Tocilizumab, an anti-IL-6 receptor antibody, is the standard of care in cytokine release syndrome 15 and has also shown efficacy in COVID-19. 79 Yet, its role in the management of associated neurological manifestations remains controversial, as it may lead to increased IL-6 levels in the CSF, which may exacerbate neurotoxicity. 15 In both conditions, the overall prognosis is strongly influenced by the course of systemic disease and not only by CNS involvement, which is linked to preexisting comorbidities. 80–83

Other Encephalopathies Associated With Systemic Hyperinflammation

Neurological manifestations of hemophagocytic lymphohistiocytosis

CNS involvement has been reported in up to 70% of HLH patients, either during the disease or presentation. 84,85 Most of the data are derived from a pediatric population, while comparably few studies investigated neurological manifestations in adults. 84,86,87 Clinical presentation is very heterogeneous, yet seizures and altered mental status represent the most common manifestations, with the former being more prevalent in pediatric patients. 86,88 In an adult HLH case series with neurological involvement, encephalopathy and language disturbances were present in all patients and were variably associated with seizures, pyramidal dysfunction, and myoclonus. 84 CSF analysis usually shows normal or mildly elevated cell counts and variable protein levels, while several brain MRI abnormalities have been described, including T2/FLAIR hyperintensities, restricted diffusion, and gadolinium enhancement in multiple areas of the brain and meninges. 84,86,87 Most of the neurological symptoms were present during highly active systemic disease; hence a cytokine-mediated neuroinflammatory process has been suggested as the main pathogenic mechanism, 87,88 even though CSF cytokine levels have not been, to our knowledge, investigated. HLH-related encephalopathy is treated with immunotherapies with conflicting results, likely reflecting the severity of disease. 84

Febrile infection-associated encephalopathy disorders

Mild encephalopathy with a reversible splenial lesion (MERS), acute necrotizing encephalopathy (ANE), and febrile infection-related epilepsy syndrome (FIRES) are three neurological disorders that typically occur following an infectious febrile illness in otherwise healthy children and, more rarely, in adults. 89–94

Patients with MERS may present with seizures, mildly altered level of consciousness, delirium, and language disturbances, and mostly have a complete recovery after a short disease course. 89,90 The neuroradiological hallmark of MERS is a transitory lesion of the splenium of the corpus callosum, a finding that has also been reported in COVID-19-related encephalopathy, 5,57 ICANS, 17 ANE, 95 and FIRES. 96

ANE is a life-threatening condition with similar manifestations yet much greater severity, where altered consciousness rapidly progresses to coma; survivors often retain neurological sequelae. 91,92 Brain MRI shows multifocal, symmetric lesions involving the thalamus and other regions, including cerebral white matter, basal ganglia, brainstem, and cerebellum. 91,92 Interestingly, and radiological features of ANE have been described for several patients with HLH 87–89 and COVID-19, 95,100,101 as well as in CAR T-cell therapy recipients. 17

FIRES is a devastating epilepsy syndrome with poor outcome, currently regarded as a subcategory of new-onset refractory status epilepticus (NORSE). 94,102 Specifically, it shares several features with cryptogenic NORSE, including prodromal fever. 103 Patients with FIRES commonly have T2/FLAIR hyperintensities in the mesial temporal lobe and other brain structures, notably the claustrum in adult patients (so-called "claustrum sign"). 93,103,104 This latter finding is frequently encountered also in familial ANE 105 and has been reported in COVID-19-related encephalopathy. 106,107 Additionally, HLH has been described in patients with FIRES. 108

Although the exact pathogenesis remains unclear, it is likely that abnormal host response to the pathogen leads, in predisposed subjects, to cytokine storm and then to cytokine-mediated neuroinflammation due to BBB disruption and microglia activation. This hypothesis is supported by several findings, including (i) the biphasic clinical course, where encephalopathy follows systemic inflammation, (ii) the presence of upregulated proinflammatory cytokines with elevated CSF/blood ratio, (iii) the absence of concomitant findings suggestive of infectious brain disease (absence of marked pleocytosis and pathogens in CSF), (iv) the variable responses reported to immunotherapies, including anti-cytokine drugs in FIRES, as well as (v) the associations mentioned above with well-
defined cytokine storm disorders and related encephalopathies.91,92,109–112 Many other febrile infection-associated encephalopathy disorders showing overlapping clinical-radiological features and, presumably, similar pathogenesis have been described. These include acute infantile encephalopathy predominantly affecting the frontal lobes,113 acute encephalopathy with fulminant cerebral edema,114 acute encephalopathy with early biphasic seizures and late reduced diffusion,115 hemorrhagic shock and encephalopathy syndrome,116 hemiconvulsion-hemiplegia-epilepsy syndrome,117 and Reye-like syndrome.118

**Sepsis-associated encephalopathy (SAE)**

Septic patients frequently present with altered mental status, ranging from mild confusion to coma, which may be one of the earliest clinical manifestations and has been included in the diagnostic criteria of sepsis.119,120 SAE is defined in the presence of sepsis when other potential causes of encephalopathy, including infectious brain disease, are reasonably excluded.120 EEG is often characterized by diffuse background slowing but may also reveal a non-convulsive status epilepticus.121 Notably, EEG abnormalities have been observed in half of the septic patients without clinical evidence of SAE.121 CSF findings are usually unremarkable, except CSF proteins, which may be elevated, reflecting increased permeability of the BBB.120 Neuroimaging is commonly unrevealing, although vasogenic edema, severe leukoencephalopathy, and PRES-like features may be observed.61,122

The underlying pathophysiology is likely multifactorial, as several mechanisms have been proposed, including neuroinflammatory mechanisms similar to the abovementioned cytokine storm-associated conditions.120,123–125 The cornerstone of SAE treatment consists in resolving the underlying sepsis with antibiotic therapy and supporting failing organs.123 Immuno-therapies targeting proinflammatory mediators have been investigated in sepsis,126 but not specifically in SAE.123

**Figure 2.** The spectrum of Cytokine Storm-associated Encephalopathy Disorders (CySED). The yellow circle relates to different triggers responsible for cytokine storm disorders (orange circle). Cytokine storm-associated encephalopathy disorders are shown in the red circle.

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### Discussion

The overwhelming wave of neurological complications observed during COVID-19 pandemic warrants an unmet need to understand the underlying pathophysiological mechanisms to inform treatment. COVID-19-related encephalopathy represents a distinct condition characterized by a predominant electro-clinical frontal lobe dysfunction; strong evidence argues for a cytokine-mediated neuroinflammatory process. As ICANS is a well-defined syndrome that shares the same pathogenic mechanism, we compared these encephalopathy disorders. We report a remarkable overlap of clinical, EEG, neuroradiological, and laboratory features, including the response to immunotherapies.

From these observations, we expanded our focus on neurological manifestations of other conditions associated with cytokine storm, HLH- and sepsis-associated encephalopathy, or where a common neurological mechanism is likely, febrile infection-associated encephalopathies. We found, perhaps surprisingly, that all these disorders have similar features suggesting a common overarching mechanism leading to encephalopathy.

Dysregulated cytokine networks in the CNS are implicated in the pathophysiology of a wide range of other neurological diseases, including autoimmune, infectious, and degenerative conditions. However, the association with cytokine storm observed in the encephalopathies reviewed herein suggests a primary role of proinflammatory cytokines in their pathogenesis.

To date, many of the neurological disorders discussed above have been defined based on clinical presentation associated with specific investigative findings, irrespective of the pathogenic mechanisms. In fact, the encephalopathies presented here have been previously described and named as distinct entities since they exhibit a wide range of clinical-radiological features, and the associated cytokine storm may have different causes. While acknowledging the presence of several differences among these conditions, we suggest that a uniform and comprehensive term may be useful to summarize phenotypic and pathophysiological similarities (Fig. 2). We, therefore, propose a unifying definition of cytokine storm-associated encephalopathy (CySE) based on the following criteria: encephalopathy with acute or subacute onset, association with cytokine storm (as defined by Fajgenbaum et al.), and exclusion of other causes that might independently account for the severity of neurological manifestations. These criteria, as well as supportive findings, are presented in Table 2. In a recent work by Leisman et al., a meta-analysis was performed to investigate the pathological ranges of blood cytokines and biomarkers across different conditions, including disorders often characterized by cytokine storm-associated encephalopathy. This paper makes abundantly clear that an extreme variability exists across different centers and conditions, making it all but impossible at this stage to report a cut-off level for any of the molecular players involved. The absence of recognized diagnostic cut-offs for biomarkers of cytokine storm may limit the applicability of our proposed criteria in patients with milder systemic inflammation. Future studies are warranted to address this issue, to support clinicians in diagnosing cytokine storm and related complications, including CySE. This spectrum of neurological conditions likely includes other encephalopathies associated with

### Table 2. Proposed criteria for cytokine storm-associated encephalopathy (CySE).

| Encephalopathy | -Acute or subacute onset  
|----------------|-------------------------------|
|                | -Severity ranging from mildly altered mental status to coma  
|                | -Common manifestations include: delirium, language disturbances, seizures, and dysexecutive syndrome  
| Association with cytokine storm\(^1\) | -Cytokine storm criteria proposed by Fajgenbaum et al.\(^1\)  
|                | -Elevated circulating cytokine levels  
|                | -Acute systemic inflammatory symptoms  
|                | -Secondary organ dysfunction beyond that which could be attributed to a pathogen, if a pathogen is present  
| Exclusion of other causes\(^2\) | -Including, but not limited to:  
|                | -Metabolic disturbances  
|                | -Definite infectious brain disease  
|                | -Autoantibody-mediated brain disease  
| Supportive findings | -CSF analysis: absence of marked pleocytosis, elevated cytokine CSF/serum ratio  
|                | -EEG: frontal predominant abnormalities  
|                | -Brain MRI\(^3\): diffuse microbleeds, cortical diffusion restriction, and leptomeningeal enhancement; T2/FLAIR hyperintensities of the splenium of the corpus callosum, thalami, or claustrum; PRES-like findings  
|                | -FDG-PET/MRI perfusion: frontal predominant hypometabolism/hypoperfusion  
|                | -Response to immunotherapies  

\(^1\)Cytokine storm may occur concomitantly or precede neurological manifestations.  
\(^2\)This may include brain dysfunction.  
\(^3\)The presence of one or more concomitant conditions potentially contributing to encephalopathy should not be considered as an absolute exclusion criteria if these are not sufficient to account for clinical severity.  
\(^4\)Most of the patients present with unrevealing neuroradiological examinations. It is confusing to use number for references and notes in the same table. Would it be possible to use letters for table notes?
systemic hyperinflammation. We suggest that recognizing a spectrum of cytokine storm-associated encephalopathy disorders may facilitate the cross-translation of knowledge acquired from individual conditions, with potentially relevant clinical implications, such as targeted therapeutic approaches.

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–1720.
2. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033–1034.
3. Pezzini A, Padovani A. Lifting the mask on neurological manifestations of COVID-19. Nat Rev Neurol 2020;16(11):636–644. https://doi.org/10.1038/s41582-020-0398-3
4. Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. Lancet Neurol 2020;19:767–783.
5. Perrin P, Collongues N, Baloglu S, et al. Cytokine release syndrome-associated encephalopathy in patients with COVID-19. Eur J Neurol 2020;28(1):248–258. https://doi.org/10.1111/ene.14491
6. Garg RK, Paliwal VK, Gupta A. Encephalopathy in patients with COVID-19: a review. J Med Virol 2020;93(1):206–222. https://doi.org/10.1002/jmv.26207
7. Gu J, Gong E, Zhang B, et al. Multiple organ infection and the pathogenesis of SARS. J Exp Med 2005;202:415–424.
8. Xu J, Zhong S, Liu J, et al. Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine MIG in pathogenesis. Clin Infect Dis 2005;41:1089–1096.
9. Solomon T. Neurological infection with SARS-CoV-2 — the story so far. Nat Rev Neurol 2021;17(2):65–66. https://doi.org/10.1038/s41582-020-00453-w
10. Piotto A, Masciocchi S. SARS-CoV-2 encephalitis is a cytokine release syndrome: evidences from cerebrospinal fluid analyses. Clin Infect Dis 2021;ciaa1933. https://doi.org/10.1093/cid/ciaa1933
11. Muccioli L, Pensato U, Bernabe G, et al. Intravenous immunoglobulin therapy in COVID-19-related encephalopathy. J Neurol 2020;8:1–3. https://doi.org/10.1007/s00415-020-10248-0
12. Muccioli L, Pensato U, Cani I, et al. Covid-19-associated encephalopathy and cytokine-mediated neuroinflammation. Ann Neurol 2020;88:860–861.
13. Remsk J, Wilcox JA, Rabady NE, et al. Inflammatory leptomeningeal cytokines mediate COVID-19 neurologic symptoms in cancer patients. Cancer Cell 2021;39:276–283.e3.
14. Faigenbaum DC, June CH. Cytokine storm. N Engl J Med 2020;383:2255–2273.
15. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625–638.
16. Rubin DB, Danish HH, Ali AB, et al. Neurological toxicities associated with chimeric antigen receptor T-cell therapy. Brain 2019;142:1334–1348.
17. Santomasso BD, Park JH, Salloum D, et al. Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. Cancer Discov 2018;8:958–971.
18. Webb BJ, Peltan ID, Jensen P, et al. Clinical criteria for COVID-19-associated hyperinflammatory syndrome: a cohort study. Lancet Rheumatol 2020;2(12):e754–e763.
19. Brisse E, Wouters CH, Matthys P. Hemophagocytic lymphohistiocytosis (HLH): a heterogeneous spectrum of cytokine-driven immune disorders. Cytokine Growth Factor Rev 2015;26:263–280.
20. Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic Juvenile idiopathic arthritis: a European League against Rheumatism/American College of Rheumatology/Paediatric rheumatology international trials organisation collaborative initiative. Ann Rheum Dis 2016;75:481–489.
21. Fajgenbaum DC, Uldrick TS, Bagg A, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood 2017;129:1646–1657.
22. Henter JJ, Horne A, Arico M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124–131.
23. Davi S, Consolaro A, Guseinova D, et al. An international consensus survey of diagnostic criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. J Rheumatol 2011;38:764–768.
24. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20:355–362.
25. Wang Z, Han W. Biomarkers of cytokine release syndrome and neurotoxicity related to CAR-T cell therapy. Biomark Res 2018;6:4.
26. Filipovich A, McClain K, Grom A. Histiocytic disorders: recent insights into pathophysiology and practical guidelines. Biol Blood Marrow Transplant 2010;16:S82–S89.

27. Hayden A, Park S, Giustini D, et al. Hemophagocytic syndromes (HSPs) including hemophagocytic lymphohistiocytosis (HLH) in adults: a systematic scoping review. Blood Rev 2016;30:411–420.

28. Karakike E, Giamarellos-Bourboulis EJ. Macrophage activation-like syndrome: a distinct entity leading to early death in sepsis. Front Immunol 2019;10:55.

29. Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain 2020;143:3104–3120.

30. Beach SR, Praschan NC, Hogan C, et al. Delirium in COVID-19: a case series and exploration of potential mechanisms for central nervous system involvement. Gen Hosp Psychiatry 2020;65:47–53.

31. Benussi A, Pilotto A, Premi E, et al. Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy, Italy. Neurology 2020;95:e910–e920.

32. 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.

33. Gust J, Hay KA, Hanafi LA, et al. Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. Cancer Discov 2017;7:1404–1419.

34. Muccioli L, Pensato U, Cani I, et al. COVID-19-related encephalopathy presenting with aphasia resolving following tocilizumab treatment. J Neuroimmunol 2020;349:577400.

35. Pensato U, Muccioli L, Pasini E, et al. Encephalopathy in COVID-19 presenting with acute aphasia mimicking stroke. Front Neurol 2020;11:1123.

36. Arnts H, van Erp WS, Lavrijsen JCM, et al. On the pathophysiology and treatment of akineti mutism. Neurosci Biobehav Rev 2020;112:270–278.

37. Pilotto A, Odolini S, Masiccioli S, et al. Steroid-responsive encephalitis in coronavirus disease 2019. Ann Neurol 2020;88(2):423–427. https://doi.org/10.1002/ana.25783

38. Cani I, Barone V, D’Angelo R, et al. Frontal encephalopathy related to hyperinflammation in COVID-19. J Neurol 2021;268:16–19.

39. Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med 2020;382:2268–2270.

40. Ye M, Ren Y, Lv T. Encephalitis as a clinical manifestation of COVID-19. Brain Behav Immun 2020;88:945–946.

41. Yin R, Feng W, Wang T, et al. Concomitant neurological symptoms observed in a patient diagnosed with coronavirus disease 2019. J Med Virol 2020;92:1782–1784.

42. Muccioli L, Rondelli F, Ferri L, et al. Subcortical myoclonus in COVID-19: comprehensive evaluation of a patient. Mov Disord Clin Pract 2020;7(8):971–973. https://doi.org/10.1002/mdc3.13046

43. Rabano-Suarez P, Bermejo-Guerrero L, Mendez-Guerrero A, et al. Generalized myoclonus in COVID-19. Neurology 2020;95:e767–e772.

44. Hwang ST, Ballout AA, Mirza U, et al. Acute seizures occurring in association with SARS-CoV-2. Front Neurol 2020;11:576329.

45. Le Guennec L, Devianne J, Jalin L, et al. Orbitofrontal involvement in a neuroCOVID-19 patient. Epilepsia 2020;61:e90–e94.

46. Santos de Lima F, Issa N, Seibert K, et al. Epileptiform activity and seizures in patients with COVID-19. J Neurol Neurosurg Psychiatry 2020;324337. https://doi.org/10.1136/jnnp-2020-324337

47. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77(6):683–690. https://doi.org/10.1001/jamaneurol.2020.1127

48. Antony AR, Haneef Z. Systematic review of EEG findings in 617 patients diagnosed with COVID-19. Seizure 2020;83:234–241. https://doi.org/10.1016/j.seizure.2020.10.014

49. Galanopoulou AS, Ferastraouaru V, Correa DJ, et al. EEG findings in acutely ill patients investigated for SARS-CoV-2/COVID-19: a small case series preliminary report. Epilepsia Open 2020;5:314–324.

50. Pasini E, Bisulli F, Volpi L, et al. EEG findings in COVID-19 related encephalopathy. Clin Neurophysiol 2020;131:2265–2267.

51. Vellieux G, Rouvel-Tallec A, Jaquet P, et al. COVID-19 associated encephalopathy: is there a specific EEG pattern? Clin Neurophysiol 2020;131:1928–1930.

52. Vespiagnani H, Colas D, Lavin BS, et al. Report on electroencephalographic findings in critically ill patients with COVID-19. Ann Neurol 2020;88:626–630.

53. Rice J, Nagle S, Randall J, Hinson HE. Chimeric antigen receptor T cell-related neurotoxicity: mechanisms, clinical presentation, and approach to treatment. Curr Treat Options Neurol 2019;21:40.

54. Herlopian A, Dietrich J, Abramson JS, et al. EEG findings in CAR T-cell therapy-related encephalopathy. Neurology 2018;91:227–229.

55. Kandemirli SG, Dogan I, Sarikaya ZT, et al. Brain MRI findings in patients in the intensive care unit with COVID-19 infection. Radiology 2020;297(1):E232–E235. https://doi.org/10.1148/radiol.2020201697
56. Kremer S, Lersy F, de Seze J, et al. Brain MRI findings in severe COVID-19: a retrospective observational study. Radiology 2020;297(2):E242–E251. https://doi.org/10.1148/radiol.2020202222

57. Hayashi M, Sahashi Y, Baba Y, et al. COVID-19-associated mild encephalitis/encephalopathy with a reversible splenial lesion. J Neurol Sci 2020;415:116941.

58. Dixon L, Varley J, Gontsaraova A, et al. COVID-19-related acute necrotizing encephalopathy with brain stem involvement in a patient with aplastic anemia. Neurrol Neuroimmunol Neuroinflamm 2020;7(5):e789. https://doi.org/10.12112/NXI.00000000000000789

59. Poyiadji N, Shahin G, Noujaim D, et al. COVID-19-related acute hemorrhagic necrotizing encephalopathy: imaging features. Radiology 2020;296:E119–E120.

60. Anand P, Lau KHV, Chung DY, et al. Posterior reversible encephalopathy syndrome in patients with coronavirus disease 2019: two cases and a review of the literature. J Stroke Cerebrovasc Dis 2020;29:105212.

61. Bartynski WS, Boardman JF, Zeigler ZR, et al. Posterior reversible encephalopathy syndrome, sepsis, and shock. Am J Neuroradiol 2006;27:2179–2190.

62. D’Amore F, Vinacci G, Agosti E, et al. Pressing issues in COVID-19: probable cause to seize SAR-CoV-2 for its preferential involvement of posterior circulation manifesting as severe posterior reversible encephalopathy syndrome and posterior strokes. Am J Neuroradiol 2020;41:1800–1803.

63. Delorme C, Paccoud O, Kas A, et al. COVID-19-related encephalopathy: a case series with brain FDG-positron-emission tomography/computed tomography findings. Eur J Neurol 2020;27:2651–2657.

64. Cao A, Rohaut B, Le Guennec L, et al. Severe COVID-19-related encephalitis can respond to immunotherapy. Brain 2020;143(12):e102. https://doi.org/10.1093/brain/awaa337

65. Hooiland RL, Stukas S, Cooper J, et al. Amelioration of COVID-19-related cytokine storm syndrome: parallels to chimeric antigen receptor-T cell cytokine release syndrome. Br J Haematol 2020;190:e130–e134.

66. Bodro M, Compta Y, Llanos L, et al. Increased CSF levels of IL-1beta, IL-6, and ACE in SARS-CoV-2-associated encephalitis. Neurrol Neuroimmunol Neuroinflamm 2020;7(5):e821. https://doi.org/10.12112/NXI.0000000000000821

67. Huang X, Hussain B, Chang J. Peripheral inflammation and blood-brain barrier disruption: effects and mechanisms. CNS Neurosci Ther 2021;27:36–47.

68. Gust J, Finney OG, Li D, et al. Glial injury in neurotoxicity after pediatric CD19-directed chimeric antigen receptor T cell therapy. Ann Neurol 2019;86:42–54.

69. Aceti A, Margarucci LM, Scaramucci E, et al. Serum S100B protein as a marker of severity in Covid-19 patients. Sci Rep 2020;10:18665.

70. Matschke J, Lutgehetmann M, Hagel C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. Lancet Neurol 2020;19:919–929.

71. Fabbri VP, Foschini MP, Lazzarotto T, et al. Brain ischemic injury in COVID-19-infected patients: a series of 10 post-mortem cases. Brain Pathol 2021;31(1):205–210. https://doi.org/10.1111/bpa.12901

72. Deigendesch N, Sironi L, Kutza M, et al. Correlates of critical illness-related encephalopathy predominate postmortem COVID-19 neuropathology. Acta Neuropathol 2020;140:583–586.

73. Young AM, Campbell EC, Lynch S, et al. Regional susceptibility to TNF-alpha induction of murine brain inflammation via classical IKK/NF-kappaB signalling. PLoS One 2012;7:e39049.

74. Chaumont H, San-Galli A, Martino F, et al. Mixed central and peripheral nervous system disorders in severe SARS-CoV-2 infection. J Neurol 2020;267:3121–3127.

75. Dogan I, Kaya D, Sarikaya T, et al. Plasmapheresis treatment in COVID-19-related autoimmune meningoencephalitis: case series. Brain Behav Immun 2020;87:155–158.

76. Pugin D, Vargas MI, Thieffry C, et al. COVID-19-related encephalopathy responsive to high doses glucocorticoids. Neurology 2020;95(12):543–546. https://doi.org/10.1212/WNL.00000000000010534

77. Santomasso B, Bachier C, Westin J, et al. The other side of CAR T-cell therapy: cytokine release syndrome, neurologic toxicity, and financial burden. Am Soc Clin Oncol Educ Book 2019;39:433–444.

78. Gardner R, Leger KJ, Annesley CE, et al. Decreased rates of severe CRS seen with early intervention strategies for CD19 CAR-T cell toxicity management. Blood 2016;128:586.

79. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with covid-19 pneumonia. N Engl J Med 2021;384:20–30.

80. Zhou Y, Yang Q, Chi J, et al. Comorbidities and the risk of severe or fatal outcomes associated with coronavirus disease 2019: a systematic review and meta-analysis. Int J Infect Dis 2020;99:47–56.

81. Romagnolo A, Balestrino R, Imbalzano G, et al. Neurological comorbidity and severity of COVID-19. J Neurol 2021;268:762–769.

82. Kittai AS, Huang Y, Gordon M, et al. Comorbidities predict inferior survival in patients receiving chimeric antigen receptor T cell therapy for diffuse large B cell lymphoma: a multicenter analysis. Biol Blood Marrow Transplant 2021;27:46–52.

83. Del Valle DM, Kim-Schulze S, Huang HH, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med 2020;26:1636–1643.

84. Gratton SM, Powell TR, Theeler BJ, et al. Neurological involvement and characterization in acquired
hemophagocytic lymphohistiocytosis in adulthood. J Neurol Sci 2015;357:136–142.
85. Deiva K, Mahlauoi N, Beaudonnet F, et al. CNS involvement at the onset of primary hemophagocytic lymphohistiocytosis. Neurology 2012;78:1150–1156.
86. Cai G, Wang Y, Liu X, et al. Central nervous system involvement in adults with hemophagocytic lymphohistiocytosis: a single-center study. Ann Hematol 2017;96:1279–1285.
87. Song Y, Pei RJ, Wang YN, et al. Central nervous system involvement in hemophagocytic lymphohistiocytosis in adults: a retrospective analysis of 96 patients in a single center. Chin Med J (Engl) 2018;131:776–783.
88. Horne A, Wickstrom R, Jordan MB, et al. How to treat involvement of the central nervous system in hemophagocytic lymphohistiocytosis? Curr Treat Options Neurol 2017;19:3.
89. Yuan J, Yang S, Wang S, et al. Mild encephalitis/encephalopathy with reversible splenial lesion (MERS) in adults—a case report and literature review. BMC Neurol 2017;17:103.
90. Zhu Y, Zheng J, Zhang L, et al. Reversible splenial lesion syndrome associated with encephalitis/encephalopathy presenting with great clinical heterogeneity. BMC Neurol 2016;16:49.
91. Wu X, Wu W, Pan W, et al. Acute necrotizing encephalopathy: an underrecognized clinicoradiologic disorder. Mediators Inflamm 2015;2015:792578.
92. Lin YY, Lee KY, Ro LS, et al. Clinical and cytokine profile of adult acute necrotizing encephalopathy. Biomed J 2019;42:178–186.
93. Kramer U, Chi CS, Lin KL, et al. Febrile infection-related epilepsy syndrome (FIRES): pathogenesis, treatment, and outcome: a multicenter study on 77 children. Epilepsia 2011;52:1956–1965.
94. Hirsch LJ, Gaspard N, van Baalen A, et al. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. Epilepsia 2018;59:739–744.
95. Nakano Y, YukiKuni M, Mizuguchi M, et al. Acute encephalopathy with callosal, subcortical and thalamic lesions. Neurology Asia 2015;20:85–89.
96. Nozaki F, Kumada T, Miyajima T, et al. Reversible splenic lesion in a patient with Febrile Infection-Related Epilepsy Syndrome (FIRES). Neuropediatrics 2013;44:291–294.
97. Radmanesh F, Rodriguez-Pla A, Pincus MD, Burns JD. Severe cerebral involvement in adult-onset hemophagocytic lymphohistiocytosis. J Clin Neurosci 2020;76:236–237.
98. Akiyoshi K, Hamada Y, Yamada H, et al. Acute necrotizing encephalopathy associated with hemophagocytic syndrome. Pediatr Neurol 2006;34:315–318.
99. Dai D, Wen F, Liu S, Zhou S. Brain damage resembling acute necrotizing encephalopathy as a specific manifestation of haemophagocytic lymphohistiocytosis - induced by hypersensitivity. Ital J Pediatr 2016;42:79.
100. Virhammar J, Kumlien E, Fallmar D, et al. Acute necrotizing encephalopathy with SARS-CoV-2 RNA confirmed in cerebrospinal fluid. Neurology 2020;95:445–449.
101. Delamarre L, Gollion C, Grouteau G, et al. 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;91:1004–1006.
102. van Baalen A, Hausler M, Boor R, et al. Febrile infection-related epilepsy syndrome (FIRES): a nonencephalitic encephalopathy in childhood. Epilepsia 2010;51:1323–1328.
103. Yanagida A, Kanazawa N, Kaneko J, et al. Clinically based score predicting cryptogenic NORSE at the early stage of status epilepticus. Neurol Neuroimmunol Neuroinflamm 2020;7:e849.
104. Meletti S, Slonkova J, Mareckova I, et al. Claustrum involvement in hemophagocytic lymphohistiocytosis - acute necrotizing encephalopathy as a specific manifestation of haemophagocytic lymphohistiocytosis - induced by hypersensitivity. Ann Neurol 2012;78:1150–1156.
105. Neilson DE, Adams MD, Orr CM, et al. Infection-triggered familial or recurrent cases of acute necrotizing encephalopathy caused by mutations in a component of the nuclear pore, RANBP2. Am J Hum Genet 2009;84:44–51.
106. Ayatollahi P, Tarazi A, Wennberg R. Possible autoimmune encephalitis with claustrum sign in case of acute SARS-CoV-2 infection. Can J Neurol Sci 2020;1–3. https://doi.org/10.1017/cjn.2020.209
107. Zuhorn F, Omaimen H, Ruprecht B, et al. Parainfectious encephalitis in COVID-19: “The Claustrum Sign”. J Neurol 2020;1–4. https://doi.org/10.1007/s00415-020-10185-y
108. Farias-Moeller R, LaFrance-Corey R, Bartolini L, et al. Fueling the FIRES: hemophagocytic lymphohistiocytosis in febrile infection-related epilepsy syndrome. Epilepsia 2018;59:1753–1763.
109. Sakuma H, Tanuma N, Kuki I, et al. Intrathecal overproduction of proinflammatory cytokines and chemokines in febrile infection-related refractory status epilepticus. J Neurol Neurosurg Psychiatry 2015;86:820–822.
110. Kenney-Jung DL, Vezzani A, Kahoud RJ, et al. Febrile infection-related epilepsy syndrome treated with anakinra. Ann Neurol 2016;80:939–945.
111. Ito Y, Ichiyama T, Kimura H, et al. Detection of influenza virus RNA by reverse transcription-PCR and
proinflammatory cytokines in influenza-virus-associated encephalopathy. J Med Virol 1999;58:420–425.
112. Miyata R, Tanuma N, Hayashi M, et al. Oxidative stress in patients with clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS). Brain Dev 2012;34:124–127.
113. Yamanouchi H, Mizuguchi M. Acute infantile encephalopathy predominantly affecting the frontal lobes (AIEF): a novel clinical category and its tentative diagnostic criteria. Epilepsia Res 2006;70(Suppl 1):S263–S268.
114. Krishnan P, Glenn OA, Samuel MC, et al. Acute fulminant cerebral edema: a newly recognized phenotype in children with suspected encephalitis. J Pediatric Infect Dis Soc 2020;piaa063. https://doi.org/10.1093/jpids/piaa063
115. Takanashi J, Oba H, Barkovich AJ, et al. Diffusion MRI abnormalities after prolonged febrile seizures with encephalopathy. Neurology 2006;66:1304–1309; discussion 291.
116. Levin M, Hjelm M, Kay JD, et al. Haemorrhagic shock and encephalopathy: a new syndrome with a high mortality in young children. Lancet 1983;2:64–67.
117. Salih MA, Kabiraj M, Al-Jarallah AS, et al. Hemiconvulsion-hemiplegia-epilepsy syndrome. A clinical, electroencephalographic and neuroradiological study. Childs Nerv Syst 1997;13:257–263.
118. Mizuguchi M, Yamanouchi H, Ichiyama T, Shiomi M. Acute encephalopathy associated with influenza and other viral infections. Acta Neurol Scand 2007;115:45–56.
119. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801–810.
120. Gofton TE, Young GB. Sepsis-associated encephalopathy. Nat Rev Neurol 2012;8:557–566.
121. Young GB, Bolton CF, Archibald YM, et al. The electroencephalogram in sepsis-associated encephalopathy. J Clin Neurophysiol 1992;9:145–152.
122. Sharshar T, Carlier R, Bernard F, et al. Brain lesions in septic shock: a magnetic resonance imaging study. Intensive Care Med 2007;33:798–806.
123. Robba C, Crippa IA, Taccone FS. Septic encephalopathy. Curr Neurol Neurosci Rep 2018;18:82.
124. Jacob A, Brorson JR, Alexander JJ. Septic encephalopathy: inflammation in man and mouse. Neurochem Int 2011;58:472–476.
125. Wu L, Feng Q, Ai ML, et al. The dynamic change of serum S100B levels from day 1 to day 3 is more associated with sepsis-associated encephalopathy. Sci Rep 2020;10:7718.
126. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. Semin Immunopathol 2017;39:517–528.
127. Becher B, Spath S, Goverman J. Cytokine networks in neuroinflammation. Nat Rev Immunol 2017;17:49–59.
128. Calsolaro V, Edison P. Neuroinflammation in Alzheimer’s disease: current evidence and future directions. Alzheimers Dement 2016;12:719–732.
129. Magliozzi R, Howell OW, Nicholas R, et al. Inflammatory intrathecal profiles and cortical damage in multiple sclerosis. Ann Neurol 2018;83:739–755.
130. Fortuna D, Hooper DC, Roberts AL, et al. Potential role of CSF cytokine profiles in discriminating infectious from non-infectious CNS disorders. PLoS One 2018;13:e0205501.
131. Leisman DE, Ronner L, Pinotti R, et al. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. Lancet Respir Med 2020;8:1233–1244.