ORIGINAL ARTICLE

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.[3–6] 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 review[14]); (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.

	COVID-19-associated cytokine storm	Cytokine release syndrome	Macrophage activation syndrome	Hemophagocytic lymphohistiocytosis
Trigger	SARS-CoV-2 infection	CAR T-cell therapy	Autoimmune disorders	Viral infections, hematological cancers, inherited and acquired immunodeficiencies
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.[14] Notably, a subgroup of septic patients develop a macrophage activation-like syndrome.[28]

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,[29–31] present in up to 85% of COVID-19 patients in ICU,[32] and is also reported in up to 66% of patients with ICANS.[33]

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.[10,16,17,29,34] Aphasia usually develops over hours/days but may also present acutely, mimicking stroke.[16,35] Akinetic mutism is an uncommon neurological presentation resulting from frontal-subcortical dissociation[36] that has been described as a specific feature of ICANS.[15] This peculiar manifestation has also been observed in several case reports of COVID-19-related encephalopathy,[10,11,30,37,38] and might help discriminate these conditions from other encephalopathies.[15]

Frontal release signs and dysexecutive symptoms represent a common finding in patients with COVID-19-related encephalopathy[11,37,39] and are commonly encountered in ICANS,[16,17] 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[32,39] and various other case reports of COVID-19-related encephalopathy,[11,29,40,41] 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.[6,17,30,42,43] Seizures represent a relatively frequent manifestation of ICANS, and their occurrence is a defining feature of severe neurotoxicity.[15,17] Patients with COVID-19-related encephalopathy may also present with new-onset seizures, either focal or generalized, convulsive or non-convulsive, including status epilepticus.[44–46]

Headache is another frequently reported symptom in COVID-19 and ICANS, occurring in 28% and 55% of patients, respectively.[16,47] 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.[48] Other diffuse EEG features include generalized rhythmic delta activity and periodic discharges with triphasic morphology.[48] 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.[10,32,45,49–52]

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.[16,53] In both conditions, EEG abnormalities correlate with the severity of the encephalopathy and might improve following immunotherapy.[11,37,48,54]

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.[55,56]

Brain MRI in ICANS is also often unrevealing, but radiological abnormalities similar to those in COVID-19 have been described.[16,17,33] Interestingly, lesion of the splenium of the corpus callosum[5,17,57] and neuroradiological findings resembling acute necrotizing encephalopathy[17,58,59] and posterior reversible encephalopathy syndrome (PRES)[17,60–62] 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.[38,39,63] In ICANS, FDG-PET shows variable patterns of cortical hypometabolism, often colocalized with EEG abnormalities.[16]

Pathophysiology

Several studies have shown a direct correlation between cytokine storm intensity and severity of neurological manifestations in COVID-19-related encephalopathy and

ICANS.[11,32,33,39,64] 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).[18,65] In COVID-19-related encephalopathy, CSF SARS-CoV-2 RNA remains almost invariably undetectable,[3,9] 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.[17] 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.[10,13,16,17,37,38,66] Therefore, a cytokine-mediated neuroinflammatory process has been suggested as the underlying pathogenic mechanism.[5,10,12,14]

Evidence suggests that peripheral inflammation may lead to endothelial activation and blood–brain barrier (BBB) disruption, resulting in microglia and astrocyte activation.[9,67] 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).[5,9,67]

Accordingly, glial (CSF GFAP) and BBB disruption (serum S100B) markers have been found elevated in both ICANS and COVID-19-related encephalopathy.[5,10,68,69]

Neuropathological findings in COVID-19 patients revealed mild abnormalities with pronounced inflammation due to diffuse astrocyte and microglia activation and infiltration of lymphocytes,[9,70,71] similar to patients with sepsis.[72] Additionally, the presence of SARS-CoV-2 RNA was not associated with the severity of neuropathological changes.[9,70]

Preclinical models demonstrated that frontal lobes are most susceptible to cytokine-induced inflammation via the NF-kB signaling pathway,[73] 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.[10,29,30] However, a subgroup of patients may develop severe neurological manifestations (e.g., impairment of consciousness) lasting up to several weeks.[11,64] 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.[10,11,37,64,74–76] Clinical responses may occur as soon as the first day following immunotherapy and may be
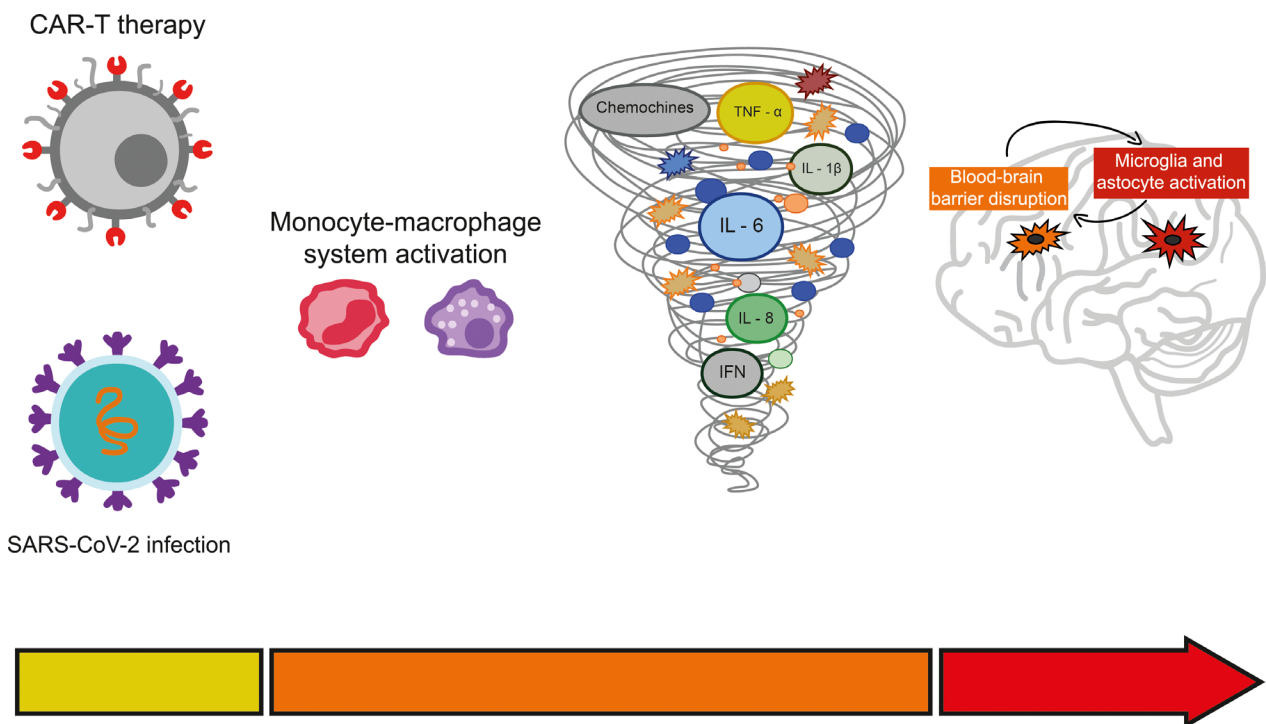

Figure 1. Schematic representation of the mechanisms underlying cytokine-mediated neuroinflammation. Different triggers, including CAR T-cell therapy and SARS-CoV-2 infection, may lead to a massive release of cytokines via activation of the monocyte/macrophage system. Peripheral cytokines promote blood–brain barrier disruption and microglia/astrocyte activation, which may act synergistically.

accompanied by a dramatic decrease of circulating and CSF cytokines.[11,37] 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.[77,78] 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 fewer 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, clinical and radiological features of ANE have been described for several patients with HLH[97–99] and COVID-19,[58,100,101] 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] Immunotherapies targeting proinflammatory mediators have been investigated in sepsis,[126] but not specifically in SAE.[123]
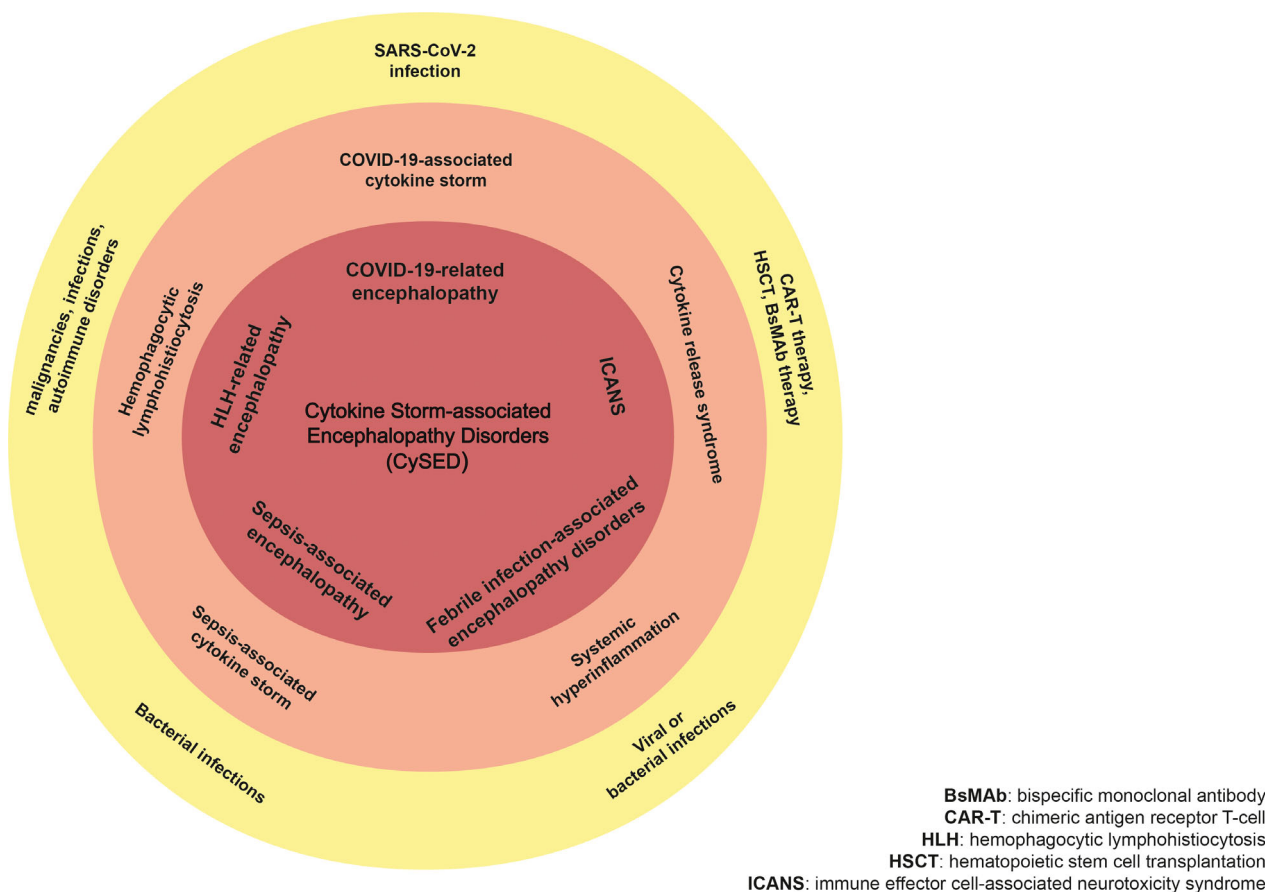

Figure 2. The spectrum of Cytokine Storm-associated Encephalopathy Disorders (CySED). The yellow circle relates to different triggers responsible for cytokine storm disorders (orange circle). Cytokine storm-associated encephalopathy disorders are shown in the red circle.

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.[127–130] 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.,[131] a meta-analysis was performed to investigate the pathological ranges of blood cytokines and biomarkers across different conditions, including disorders often characterized

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[2] beyond that which could be attributed to a pathogen, if a pathogen is present
Exclusion of other causes[3]	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[4]: 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 confounding to use number for references and notes in the same table. Would it be possibles to use letters for table notes?

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

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.

Acknowledgments

Conflict of Interest

The authors declare no conflict of interest.

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