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COVID-19-Associated Encephalopathy: Systematic Review of Case Reports

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Background and Purpose Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) primarily attacks the respiratory system, but there are also several reports of the involvement of the central nervous system, with one of the manifestations being encephalopathy. The relatively new emergence of COVID-19 means that few studies have investigated the clinical profile of encephalopathy associated with this disease. This study aimed to determine the clinical profile, laboratory, and imaging results of encephalopathy associated with COVID-19.

Methods Three databases, namely PubMed/MEDLINE, Embase, and Scopus, were systematically searched for case reports and case series related to COVID-19-associated encephalopathy published from January 1, 2019 to July 20, 2020.

Results This review included 24 studies involving 33 cases. The most-reported neurological symptoms were disorientation/confusion (72.72%), decreased consciousness (54.54%), and seizures (27.27%). Laboratory examinations revealed increases in the C-reactive protein level (48.48%), the lactate dehydrogenase level (30.30%), and lymphopenia (27.27%). Brain imaging did not produce any pathological findings in 51.51% of the cases. Electroencephalography showed generalized slowing in 45.45% of the cases. Elevated protein (42.42%) and lymphocytosis (24.24%) were found in the cerebrospinal fluid. Fifteen patients were reportedly discharged from the hospital in a stable condition, while four cases of mortality were recorded.

Conclusions The clinical, laboratory, and imaging findings in this review support the hypothesis that cerebral damage in COVID-19-associated encephalopathy is caused by cytokine-immune-mediated inflammation rather than by direct invasion.

Keywords COVID-19; encephalopathy; encephalitis; neuro immune; nerve inflammation; SARS-CoV-2.

INTRODUCTION

In January 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified as the cause of an outbreak of pneumonia that developed into respiratory failure in Wuhan, China.[1] The spread of SARS-CoV-2 subsequently expanded and led to an increase in the number of fatalities, with it being declared a pandemic by the World Health Organization in March 2020.[2] As of July 2020, there were 15 million confirmed cases and more than 600,000 deaths.[3]

SARS-CoV-2 commonly attacks the respiratory system, causing a type of pneumonia called coronavirus disease 2019 (COVID-19), which has the initial symptoms of upper respiratory tract infection that rapidly develops into respiratory failure.[4,5] While respiratory disorder is the main clinical manifestation of COVID-19, some studies have found that most patients also experience neurological symptoms.[6,7] Helms et al.[7] found neurological symptoms in 84% of the patients who entered an intensive care unit (ICU) without sedation and

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neuromuscular blockers, with symptoms of central nervous system (CNS) dysfunction such as agitation (69%) and confusion (65%). A systematic review by Ghannam et al.[8] found that 23% of patients also had complications of encephalopathy. The results of both of these previous studies indicated the possibility of CNS involvement in the course of COVID-19, with the presence of SARS-CoV-2 neurotropism.[8]

The relatively new emergence of COVID-19 means that few studies have investigated the clinical profile of encephalopathy associated with this disease. There have been some reported cases of encephalopathy related to COVID-19, with varying clinical appearance and laboratory and imaging findings. The present study performed a systematic review with the aim of identifying the clinical profile and findings from laboratory and imaging investigations on encephalopathy associated with COVID-19.

METHODS

This review conformed to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement (Fig. 1).[9]

Search strategy

Two authors (V.P. and A.P.) searched three databases: PubMed/MEDLINE, Embase, and Scopus. Eligible titles and abstracts were marked for further review and screening. The articles included were only those published in English from January 1, 2019 to July 20, 2020. The search terms used were "COVID-19," "SARS-CoV-2," and "encephalopathy." If a publication could not be accessed physically or digitally, the authors were contacted by email. The agreement between two of the present authors in selecting case reports was calculated using the Cohen's kappa (κ) statistic, which was reported with the 95% CI. The risk of bias were calculated using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-1) assessment tool.[10]

Study selection

The studies included in this review were prospective or retrospective case reports or case series of encephalopathy patients related to COVID-19, while experimental studies were excluded. All potentially relevant articles were screened for eligibility. Publications that were not in English were excluded.

Data extraction

Data were extracted from all eligible reports by two authors (V.P. and A.P.). The extracted data included bibliographic information, demographic information, symptom onset, clinical symptoms (respiratory and neurological), investigation results (laboratory, imaging, and electroencephalography), therapy, and outcome. All disagreements were resolved by discussion between two authors [V.P. and A.P.].) with supervision by a third author (Y.M.T.S.). The collected data were entered into a Microsoft Excel worksheet. General data values were expressed as the percentage and number of patients.

RESULTS

Twenty-four studies involving 33 patients with encephalopathy

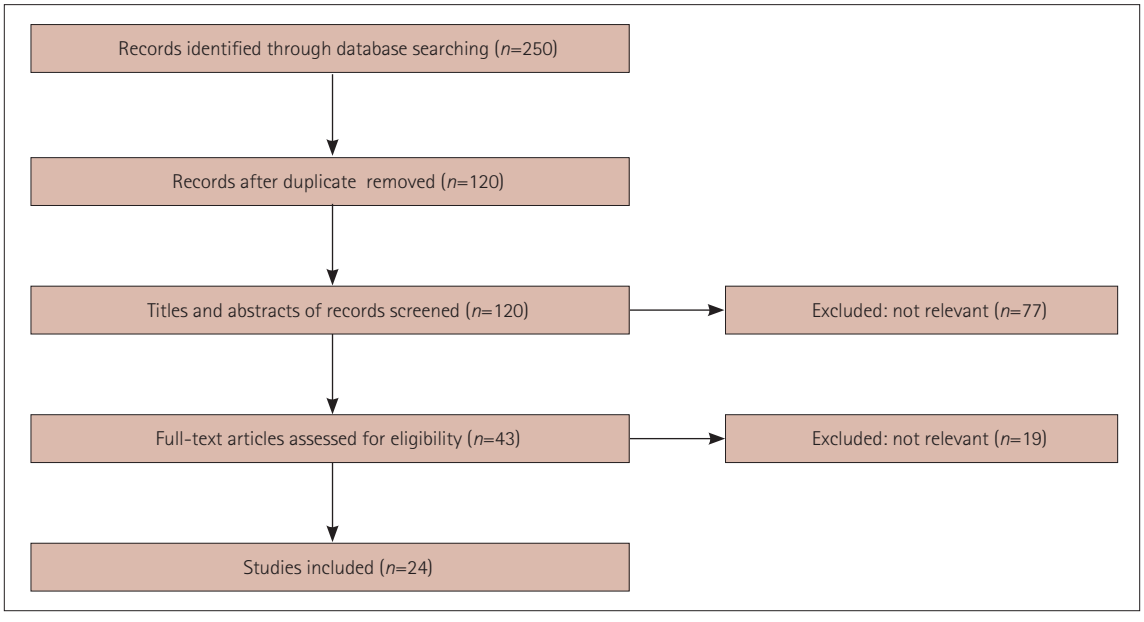

Fig. 1. Flow chart of study selection.

and COVID-19 were collected from the 3 databases (PubMed/MEDLINE, Scopus, and Embase).[11-34] The patients comprised 11 females and 22 males aged 47.90±16.65 years (mean±SD). The onset of respiratory or systemic symptoms occurred 6.0±4.3 days after respiratory/systemic symptoms, while CNS disorders appeared after 11.10±7.85 days; however, in two cases the neurological symptom appeared 1−3 days earlier than the respiratory symptoms. Demographic data are provided in Table 1. The agreement in selecting case reports between the two authors was excellent, as shown by a Cohen's κ statistic of 0.95 (95% CI=0.93−0.98). Assessments performed using the ROBINS-I assessment tool showed a low risk of bias.

The most-common respiratory/systemic symptoms (Table 2) were fever (54.54%), fatigue/myalgia (48.48%), cough (42.42%), and shortness of breath (30.30%). The most-prominent symptoms of the CNS were disorientation/confusion (72.72%), loss of consciousness (54.54%), and seizures (27.27%). Physical examinations revealed a extensor plantar response, the meningeal irritation sign, and motor weakness in 18.18%, 12.12%, and 12.12% of the cases, respectively. In laboratory examinations, the most frequently recorded findings were increases in the C-reactive protein (CRP) level (48.48%), the lactate dehydrogenase (LDH) level (30.30%), and lymphopenia (27.27%).

Chest imaging was reported for 22 studies, with ground-glass opacities (72.72%) as the predominant finding, which is a typical finding in COVID-19 cases. Brain imaging did not produce pathological findings in 51.51% of the cases. Hyperintensity in the white matter was found in 24.24% of the cases. Electroencephalography (EEG) was carried out in 11 cases, with the most-common finding of generalized slowing (45.45%). The most-common findings in analyses of the cerebrospinal fluid (CSF) were elevated protein (42.42%) and lymphocytosis (24.24%). Significant increases in proinflammatory cytokines were found in all five studies (100%) that performed these analyses of the CSF: interleukin (IL)-6,[18,24,27,33,34] IL-1β,[27] IL-8,[18,24] and TNF-α (tumor necrosis factor alpha).[18] Antineuronal autoantibodies were only found in one (N-methyl-D-aspartate receptor [NMDA-R])[33] out of the eight examined cases[2,18,27,29,31-33] (12.5%). Polymerase chain reaction (PCR) examination of the CSF for SARS-CoV-2 was carried out in 28 cases, with positive results in 3 cases.[19,20,30] PCR examinations of the CSF for other viruses such as herpes simplex virus (HSV), human herpes virus 6, cytomegalovirus, and varicella-zoster virus produced negative results.

The most commonly used pharmacological agents (Table 3) were hydroxychloroquine (48.48%), azithromycin (27.27%), and favipiravir (24.24%). Intravenous steroids were given in 8 cases (methylprednisolone in 5,[18,26,29,31,32] dexamethasone in 2,[28,33] and unspecified in 1[21]), while immunotherapies such as plasmapheresis and intravenous immunoglobulin (IVIg) were given to 10 patients (plasmapheresis to 6[34] and IVIg to 4[18,26,29,32]). Fifteen patients (65.21%) were reportedly discharged from the hospital in a stable condition, while four mortality cases (17.39%)[17,23,28] were recorded.

DISCUSSION

Analysis of systematic reviews

The main target of organ damage by SARS-CoV-2 is the respiratory system, but there are several reports of affected patients also experiencing neurological problems ranging from mild manifestations (e.g., headaches and dizziness) to life-threatening complications (e.g., cerebrovascular disorders and encephalitis).[6] Helms et al.[7] found that agitation (69%) was a common complaint in COVID-19 patients receiving treatment in the ICU.

This review found that the common symptoms in encephalopathy patients were disorientation or confusion (72.72%), decreased consciousness (54.54%), and seizures (27.27%). These symptoms indicate damage in the CNS, especially the cerebral cortex, which is typically found in acute encephalopathy. This result was consistent with the clinical manifestations of encephalopathy, where disorientation was the most-common symptom reported in patients with positive HSV PCR (92%).[35] Manifestations of seizures and headaches were found in 27.27% and 30.30% of the cases of COVID-19-associated encephalopathy, while HSV encephalitis seizures were found in 56% of the cases and headaches in 83% of the cases.[35] Abnormal behavior that is characteristically found in HSV is rarely found in COVID-19 encephalopathy. The clinical appearance of COVID-19-associated encephalopathy was similar to that of encephalopathy associated with MERS-CoV-2 (Middle East respiratory syndrome coronavirus 2), with symptoms of upper respiratory tract infection (fever, cough, and fatigue), a decrease in mental status, and rapid respiratory failure.[36] The meningeal irritation sign was only found in four cases (12.12%), which indicated that the pathological process was more dominant in the cortex than in the meninges. This also indicated that the involvement of the meninges in COVID-19-associated encephalopathy was less common than that of HSV, since the meningeal irritation sign appeared in 29% of HSV cases.[35] However, these results can also be attributed to the loss of meningeal irritation in severe states of consciousness. CSF examinations predominantly showed elevated protein and pleocytosis, suggesting an inflammatory process in the brain that could be caused by an infection such as viral encephalitis, or an autoimmune condition such as limbic encephalitis or Guillain-Barré syndrome (GBS).

The laboratory results showed that the inflammatory markers CRP and LDH as well as lymphopenia were increased in

Table 1. Clinical profile and demographic data of the 24 studies including 33 cases

Author	Country	Age and sex	Respiratory/ systemic symptom onset	Symptoms	Onset	Method of COVID-19 diagnosis	CSF profile	Brain imaging (CT/MRI)	EEG	Cytokines profile
Duong et al.[11]	USA	41 years, female	NR	Seizure	NR	RT-PCR	Lymphocytic pleocytosis, increased RBC	Normal brain CT with contrast	Generalized slowing with no epileptic discharge	NR
Bernard-Valnet et al.[12]	Switzerland	64 years, female	5 days	Tonic-clonic seizures, disorientation, psychosis	Acute (not specified)	RT-PCR	Lymphocytic pleocytosis, increased protein	Normal brain MRI	Nonconvulsive focal status epilepticus	NR
		67 years, female	17 days	Headache, confused	Few hours before admission	RT-PCR	Lymphocytic pleocytosis, increased protein	Normal brain MRI	NR	NR
Ye et al.[13]	China	Male (age NR)	4 days	Altered consciousness, confusion	Acute (not specified)	RT-PCR	Normal	Normal brain CT	NR	NR
McAbee et al.[14]	USA	11 years, male	2 days	Status epilepticus	Acute (not specified)	RT-PCR	Neutrophilic pleocytosis, increased protein and RBC	Normal brain CT	Frontal intermittent delta activity	NR
Andriuta et al.[15]	France	Middle-aged female	7 days	Gait disturbance, hypopallesthesia, bladder and bowel incontinence	Progressively developed on day 16 of admission	RT-PCR	NR	Brain MRI: medial mesencephalic hyperintensity	Normal	NR
		Middle-aged male	NR	Altered consciousness, flaccid tetraparesis	NR	RT-PCR	NR	Brain MRI: bilateral diffuse white-matter hyperintensities	NR	NR
Chaumont et al.[16]	France	69 years, male	7 days	Confusion, headache	1 day before admission	RT-PCR/CT	Lymphocytic pleocytosis, increased protein	Normal brain MRI	Bilateral slowing	NR

Table 1. Clinical profile and demographic data of the 24 studies including 33 cases (continued)

Author	Country	Age and sex	Respiratory/ systemic symptom onset	Symptoms	Onset	Method of COVID-19 diagnosis	CSF profile	Brain imaging (CT/MRI)	EEG	Cytokines profile
Sohal and Mansur[17]	USA	72 years, male	NR	Weakness, lightheadedness, seizure	Day 3 of admission	RT-PCR	NR	Brain CT: chronic microvascular changes	Six left temporal seizures	NR
Pilotto et al.[18]	Italy	60 years, male	2 days	Altered consciousness	5 days before admission	RT-PCR	Lymphocytic pleocytosis, increased protein	Normal brain CT	Generalized slowing with reduced reactivity to acoustic stimuli	Increased IL-6, IL-8, TNF-α, and β2-microglobulin
Al-Olama et al.[19]	UAE	36 years, male	2 days	Drowsy, headache	4 days after respiratory symptom	RT-PCR	NR	Brain CT: right frontal intracerebral hematoma with subarachnoid hemorrhage in ipsilateral sylvian fissure and frontal and temporal lobes suggestive of viral encephalitis	NR	NR
Moriguchi et al.[20]	Japan	24 years, male	1 day	Generalized seizure, unconsciousness	9 days after respiratory symptom	CT/RT-PCR CSF	Increased opening pressure, mononuclear pleocytosis	Right lateral ventriculitis and encephalitis in right mesial lobe and hippocampus	NR	NR
Vandervorst et al.[21]	Belgium	29 years, male	7 days	Generalized weakness, disorientation	10 days after respiratory symptom	RT-PCR	Normal	Hyperintensity in the left medial temporal lobe with mild gyral expansion	General excess beta rhythm with left temporal delta activity	NR
Wong et al.[22]	UK	40 years, male	10 days	Unsteady gait	Day 3 of admission	RT-PCR	Normal	Suggestive of inflammatory rhombencephalitis/ myelitis	NR	NR

Table 1. Clinical profile and demographic data of the 24 studies including 33 cases (continued)

Author	Country	Age and sex	Respiratory/ systemic symptom onset	Symptoms	Onset	Method of COVID-19 diagnosis	CSF profile	Brain imaging (CT/MRI)	EEG	Cytokines profile
Zandifar and Zandifar[23]	Iran	49 years, male	2 days	Tonic-clonic seizure, altered consciousness	Acute (not specified)	Clinical, imaging, and exclusion of other possibilities	Pleocytosis, increased protein	Diffuse brain edema	NR	NR
		39 years, male	5 days	Tonic seizure, altered consciousness, disorientation	Day 3 of admission	RT-PCR	NR	NR	NR	NR
Farhadian et al.[24]	USA	78 years, female	2 days	Uncontrolled limb movements	3 days before admission	RT-PCR		Brain MRI: atrophy and patchy periventricular and subcortical white-matter hyperintensities	Mild generalized slowing	Increased IL-6, IL-8, and IFN-γ-induced protein 10
Chalil et al.[25]	Canada	48 years, female	14 days	Altered consciousness	Day 15 of admission	RT-PCR+CT	Neutrophilic pleocytosis	Brain CT: extensive bilateral parietal and occipital intraparenchymal hemorrhage and interventricualr extension with hydrocephalus	NR	NR
Afshar et al.[26]	Iran	39 years, female	9 days	Altered consciousness, tonic-clonic seizure	1 day after respiratory symptom	Clinical, imaging, and serology	Normal	Brain MRI: hyperintensities in bilateral thalami, medial temporal lobe, and pons	NR	NR
Bodro et al.[27]	Spain	25 years, male	1 day	Confusion and agitation	12 hours after respiratory symptom	RT-PCR	Lymphocytic pleocytosis, increased protein	Normal brain CT and MRI	NR	NR
		49 years, male	7 days	Disorientation	Few hours after admission	RT-PCR	Lymphocytic pleocytosis, increased protein	Normal brain CT and MRI	NR	NR

Table 1. Clinical profile and demographic data of the 24 studies including 33 cases (continued)

Author	Country	Age and sex	Respiratory/ systemic symptom onset	Symptoms	Onset	Method of COVID-19 diagnosis	CSF profile	Brain imaging (CT/MRI)	EEG	Cytokines profile
Abdi et al.[28]	Iran	58 years, male	No complaint	Altered consciousness	1 month, progressive over 2 days	RT-PCR	Increased glucose	Brain MRI: diffuse confluent white-matter hyperintensities	NR	NR
Delamarre et al.[29]	France	51 years, male	10 days	Altered consciousness	11 days after respiratory symptom	RT-PCR	Albumin-cytological dissociation	Brain MRI: bilateral hyperintensities in bilateral thalami	Low-voltage symmetrical delta activity	
Huang et al.[30]	USA	40 years, female	NR	Syncope and altered mental status	NR	RT-PCR	Normal	NR	NR	NR
Khoo et al.[31]	UK	65 years, female	Respiratory symptoms at 2 weeks before admission	Involuntary movements, diplopia, cognitive decline	7 days before admission	RT-PCR	Normal	Normal brain MRI	Normal	NR
Zambreanu et al.[32]	UK	66 years, female	NR	Altered consciousness, confusion	Few hours before admission	RT-PCR	Increased protein	Hyperintensities in mesial temporal lobes and medial thalami	NR	NR
Panariello et al.[33]	Italy	23 years, male	NR	Psychosis	3 days	RT-PCR	Normal	Normal	6 Hz theta activity	Increased IL-6
Dogan et al.[34]	Turkey	49 years, male	NR	Altered consciousness	NR	RT-PCR	Increased protein	Suggestive of encephalitis	NR	Increased IL-6
		59 years, male	NR	Altered consciousness	NR	RT-PCR	Increased protein	Suggestive of encephalitis	NR	Increased IL-6
		59 years, male	NR	Altered consciousness	NR	RT-PCR	Increased protein	Normal	NR	Normal
		51 years, female	NR	Altered consciousness	NR	RT-PCR	Increased protein	Normal	NR	Normal
		55 years, male	NR	Altered consciousness	NR	RT-PCR	Increased protein	Normal	NR	Normal
		22 years, male	NR	Altered consciousness	NR	RT-PCR	Increased protein	Suggestive of encephalitis	NR	Increased IL-6

COVID-19, coronavirus disease 2019; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalography; IFN-γ, interferon gamma; NR, not reported; RBC, red blood cells; RT-PCR, reverse-transcription PCR.

Table 2. Summary of the case reports and case series findings

Variable	Cases (*n*=33)
Comorbidities	
HT	7 (21.21)
DM	4 (12.12)
Obesity	3 (9.09)
CAD	1 (3.03)
ESKD	1 (3.03)
Kidney transplant	1 (3.03)
Dyslipidemia	1 (3.03)
AD	1 (3.03)
OA	1 (3.03)
GERD	1 (3.03)
Closed-angle glaucoma	1 (3.03)
Autism	1 (3.03)
Substance abuse	1 (3.03)
COVID-19 systemic/respiratory symptoms	
Fever	18 (54.54)
Cough	14 (42.42)
Nasal congestion	3 (9.09)
Sore throat	1 (3.03)
Dyspnea	10 (30.30)
Fatigue/myalgia	16 (48.48)
Headache	10 (30.30)
Anosmia	3 (3.03)
Ageusia	2 (6.06)
Diarrhea	4 (12.12)
Neurological symptoms	
Loss of consciousness	18 (54.54)
Disorientation/confusion	24 (72.72)
Hallucination	4 (12.12)
Psychotic	2 (6.06)
Stiff neck	1 (3.03)
Insomnia	1 (3.03)
Aphasia	2 (6.06)
Seizure	
Tonic–clonic	5 (15.15)
Tonic	1 (3.03)
Myoclonic	1 (3.03)
Unspecified	2 (6.06)
Involuntary movements	3 (9.09)
Unsteadiness	3 (9.09)
Diplopia	2 (6.06)
Dysphagia	1 (3.03)
Incontinence bowel/bladder	1 (3.03)
Neurological signs	
Meningeal irritation sign	4 (12.12)
Pupil anisocoria	2 (6.06)
Akinetic mutism	3 (9.09)
Motor weakness	
Tetraplegia	1 (3.03)
Paraplegia	1 (3.03)
Hemiplegia	2 (6.06)
Sensory deficit	2 (6.06)
Extensor plantar response	6 (18.18)
Photophobia	1 (3.03)
Visual field defect	1 (3.03)
Facial weakness	1 (3.03)
Tongue weakness	1 (3.03)
Nystagmus	1 (3.03)
Loss of brainstem reflexes	3 (9.09)
Sensory hemineglect	1 (3.03)
Ataxia	2 (3.03)
Laboratory findings	
Lymphopenia	9 (27.27)
Leukocytosis	8 (24.24)
Leukopenia	3 (9.09)
Thrombocytosis	3 (9.09)
Thrombocytopenia	3 (9.09)
Elevated CRP	16 (48.48)
Elevated LDH	10 (30.3)
Elevated procalcitonin	3 (9.09)
Elevated ESR	1 (3.03)
Elevated D-dimer	6 (18.18)
Elevated CK	3 (9.09)
Elevated AST/ALT	2 (6.06)
Elevated LDH	1 (3.03)
Chest imaging (*n*=22)	
GGO+consolidation (CT)	4 (18.18)
GGO without consolidation (CT)	12 (54.54)
Infiltrate/consolidation (X-ray)	3 (13.63)
Subpleural condensation (USG)	1 (4.54)
Normal	2 (9.09)
Brain imaging	
Normal	17 (51.51)
Diffuse edema	1 (3.03)
Hyperintensities	
Thalamus	3 (9.09)
Cerebellar	2 (6.06)
Periventricular	2 (6.06)
Mesencephalic	3 (9.09)
Pons	3 (9.09)
White matter	8 (24.24)
Temporal lobe	3 (9.09)
Hemorrhagic	
Pallidum	1 (3.03)
Lobar	2 (6.06)
Sulcus (SAH)	4 (12.12)
Contrast enhancement	4 (12.12)

Table 2. Summary of the case reports and case series findings (continued)

Variable	Cases (*n*=33)
CSF studies	
Elevated WBC	9 (27.27)
Elevated neutrophils	1 (3.03)
Lymphocytosis	8 (24.24)
Elevated RBC	5 (15.15)
Elevated protein	14 (42.42)
Decreased glucose	1 (3.03)
Elevated pressure	2 (6.06)
Antineuronal autoantibodies (*n*=8)	
Positive	1 (12.50)
Negative	7 (87.50)
Inflammatory cytokines (*n*=7)	7 (100)
CSF PCR (*n*=28)	
Positive	3 (10.71)
Negative	25 (89.28)
EEG (*n*=11)	
Background slowing	7 (63.30)
Focal focus	
Frontal	1 (9.09)
Temporal	2 (18.18)
Normal	1 (9.09)
Outcomes (*n*=23)	
Discharged	15 (65.21)
Death	4 (17.39)
Still in treatment	4 (17.39)

AD, Alzheimer's disease; ALT, alanine transaminase; AST, aspartate transaminase; CAD, coronary artery disease; CRP, C-reactive protein; CSF, cerebrospinal fluid; CK, creatinine kinase; DM, diabetes mellitus; EEG, electroencephalography; ESKD, end-stage kidney disease; ESR, erythrocyte sedimentation rate; GERD, gastroesophageal reflux disease; GGO, ground-glass opacity; HT, hypertension; LDH, the lactate dehydrogenase; NR, not reported; OA, osteoarthritis; PCR, polymerase chain reaction; SAH, subarachnoid hemorrhage; USG, ultrasonography; WBC, white blood cells

48.48%, 30.30%, and 27.27% of the cases, respectively. These proportions are higher than those found in the general systematic review of COVID-19 studies conducted by Rodriguez-Morales et al.,[37] where increases in CRP and LDH were found in 22.2% and 6.3% of the cases, respectively. These differences are attributable to frequent and severe inflammatory reactions in COVID-19-associated encephalopathy. Wang[38] found that CRP levels were significantly higher in patients with severe symptoms than in those with moderate or mild symptoms (54.15 mg/dL vs. 16.76 mg/dL vs. 1.52 mg/dL, $p<0.05$). The presence of lymphopenia indicated the involvement of T cells, which caused the depletion of CD4 and CD8 cells.[37,39] Lymphopenia can occur due to lymphocyte sequestration in specific target organs such as the lungs, gastrointestinal tract, and lymphoid tissue via the activation of angiotensin-converting enzyme 2 (ACE_2) receptors by SARS-CoV-2. Other hypotheses are that the phenotype and mechanism of SARS-CoV-2 are similar to those of acute respiratory syndrome coronavirus (SARS-CoV), including the tendency for direct bone-marrow suppression, the immune-mediated destruction of lymphocytes,[40-43] and lymphopenia manifestation.[40]

Brain imaging studies did not show significant pathological features in 51.51% of the cases. The most-common patho-

Table 3. Pharmacological agents used in studies

Classification	Pharmacological agent	Cases (*n*=33)
Antiviral	Acyclovir	9* (27.27)
	Atazanavir	1 (3.03)
	Arbidol	1 (3.03)
	Oseltamivir	1* (3.03)
	Darunavir/cobicistat	1 (3.03)
	Lopinavir	2 (6.06)
	Ritonavir	2 (6.06)
	Favipiravir	8 (24.24)
Antibiotic	Ceftriaxone	6 (4*; 18.18)
	Vancomycin	3 (1*; 9.09)
	Levofloxacin	1 (3.03)
	Linezolid	1 (3.03)
	Piperacillin-tazobactam	1 (3.03)
	Amoxicillin	2 (1*; 6.06)
	Ampicillin	3* (9.09)
	Meropenem	1 (3.03)
	Azithromycin	9 (27.27)
Antiepileptic	Levetiracetam	6 (18.18)
	Clonazepam	2 (12.12)
	Valproate	3 (9.09)
	Midazolam	2 (6.06)
Other	Hydroxychloroquine	16 (48.48)
	Mannitol	1 (3.03)
	Norepinephrine	1 (3.03)
	Methylprednisolone	5 (15.15)
	Dexamethasone	2 (6.06)
	Nebivolol	1 (3.03)
	Amlodipine	1 (3.03)
	Quetiapine	2 (6.06)
	Aripiprazole	1 (3.03)
	Haloperidol	2 (6.06)
	Promazine	1 (3.03)
	Paracetamol	1 (3.03)
	Tocilizumab	2 (6.06)
	Heparin, protamine sulfate	1* (3.03)
	Vitamins B and C	1 (3.03)
	Plasmapheresis	6 (18.18)
	IVIg	4 (12.12)

Data are presented as *n* (%).
*Administration was stopped before full course completed.

logical finding was diffuse hyperintensity in T2-weighted/fluid-attenuated inversion recovery imaging, most frequently in the white matter (24.24%). These findings were consistent with those of the systematic review conducted by Katal et al.,[44] where the proportion of normal magnetic resonance imaging (MRI) images was most frequently found (41%) in COVID-19 patients. Therefore, the neuroimaging results for encephalopathy associated with COVID-19 in the present review resembled those of encephalopathy/encephalitis found in the previous coronavirus outbreak. Two cases of SARS-CoV accompanied by severe neurological symptoms in the form of decreased consciousness and seizures had normal neuroimaging results.[44,45] Arabi et al.[36] reported on three Middle Eastern respiratory syndrome coronavirus (MERS-CoV) patients, whose MRI evaluations revealed that hyperintense lesions in T2-weighted images were spread widely and bilaterally in the white matter and subcortical areas, frontal lobes, temporal, parietal, and basal ganglia, as well as in the corpus callosum. These neuroimaging findings suggest similarities in the pathomechanism of CNS involvement in SARS-CoV-2, SARS-CoV,[46] and MERS-CoV.

EEG examinations were performed in 11 cases, with the results showing nonspecific generalized slowing in 7 cases (63.30%) and epileptiform foci in 3 cases (27.27%): 2 in the temporal lobe and 1 in the frontal lobe. This was consistent with Canham et al.[47] reporting that the predominant EEG feature in patients with severe COVID-19 was generalized slowing. These findings indicate that COVID-19 exerts diffuse and widespread effects in the CNS, in contrast to encephalitis caused by HSV, where atypical 2–3 Hz periodic lateralized epileptiform discharges originate from the temporal lobes.[48] The CSF analysis showed increased levels of protein (42.42%), white blood cells (27.27%), and lymphocytes (24.24%). The negative results from the PCR analysis of the CSF for SARS-CoV-2 argue against direct invasion of the virus as an underlying mechanism of COVID-19 encephalopathy.

There is a large variety of pharmacological agents administered due to the dynamic changes in COVID-19 guidelines and protocols at each center. Acyclovir and ceftriaxone were generally given as empirical therapy, and stopped when there was no evidence of a bacterial infection or HSV. There was an increase in proinflammatory cytokines in the CSF,[18,24,27,33,34] indicating a possible role of intravenous steroids and immunotherapy (IVIg and plasmapheresis) in the management of encephalopathy associated with COVID-19. Methylprednisolone and IVIg therapy given in the four cases of COVID-19-associated encephalopathy[18,26,29,32] produced positive responses, with three patients discharged in a stable conditions[18,29,32] and the fourth still receiving care but with significant improvement.[26] Dogan et al.[34] reported that plasmapheresis therapy produced dramatic improvements in both clinical and laboratory findings. This positive result supported the theory of a cytokine-mediated hyperinflammatory response as the basis for the pathomechanism of COVID-19-associated encephalopathy.[18]

Cytokine-immune-mediated inflammation as the underlying pathomechanism in SARS-CoV-2-associated inflammation

While the mechanism of encephalopathy in COVID-19 remains unclear, previous studies have indicated the presence of neurotropism of SARS-CoV-2 that allows it to invade the CNS. There are two pathways that allow this invasion: 1) through the systemic circulation and 2) through the cribriform plate of ethmoid bone.[49] SARS-CoV-2 binds with the ACE_2 receptor via spike protein S1, allowing the attachment of virions to cell membranes.[49,50] The systemic dissemination results from the attachment of SARS-CoV-2 to the ACE_2 receptor in the capillary endothelium.[50] ACE_2 expression in glia cells and neurons is the pathway mechanism for cerebral damage.[49,50] The occurrence of hyposmia or anosmia due to the spread of the virus in the olfactory bulb via the cribriform plate is an alternative pathway for invading the CNS.[49]

The findings of the present study do not support the pathomechanism of CNS damage in COVID-19-associated encephalopathy involving direct invasion by the virus. EEG findings indicate diffuse cerebral abnormalities, possibly resulting from severe and extensive inflammation. CSF analyses have shown an inflammatory process (denoting elevated protein) mediated by cytokines, supported by the results of increased proinflammatory cytokines in the CSF. The predominantly negative CSF PCR (89%) against SARS-CoV-2 does not support the hypothesis that direct viral invasion of the brain is the cause of encephalopathy. However, it should be noted that the negative PCR result for SARS-CoV-2 in the CSF does not imply the absence of the virus, because PCR in the CSF has a rather low sensitivity.[37] The possibility of an autoimmune mechanism was considered based on several previous studies linking COVID-19 with GBS.[51] There were two reported cases with autoimmune features: 1) NMDA-R[33,52] and 2) limbic encephalitis, with T2-weighted hyperintense signal abnormalities in the limbic lobes, bilateral medial thalamus, and frontal white matter.[32] The positive response exhibited by COVID-19 patients to intravenous steroid therapy and immunotherapy (IVIg and plasmapheresis) commonly used in autoimmune conditions such as myasthenia gravis and GBS suggest that an immune process plays a role in the occurrence of encephalitis.[53]

Fig. 2 illustrates the pathomechanism of immune-mediated cerebral damage in COVID-19-associated encephalopa-

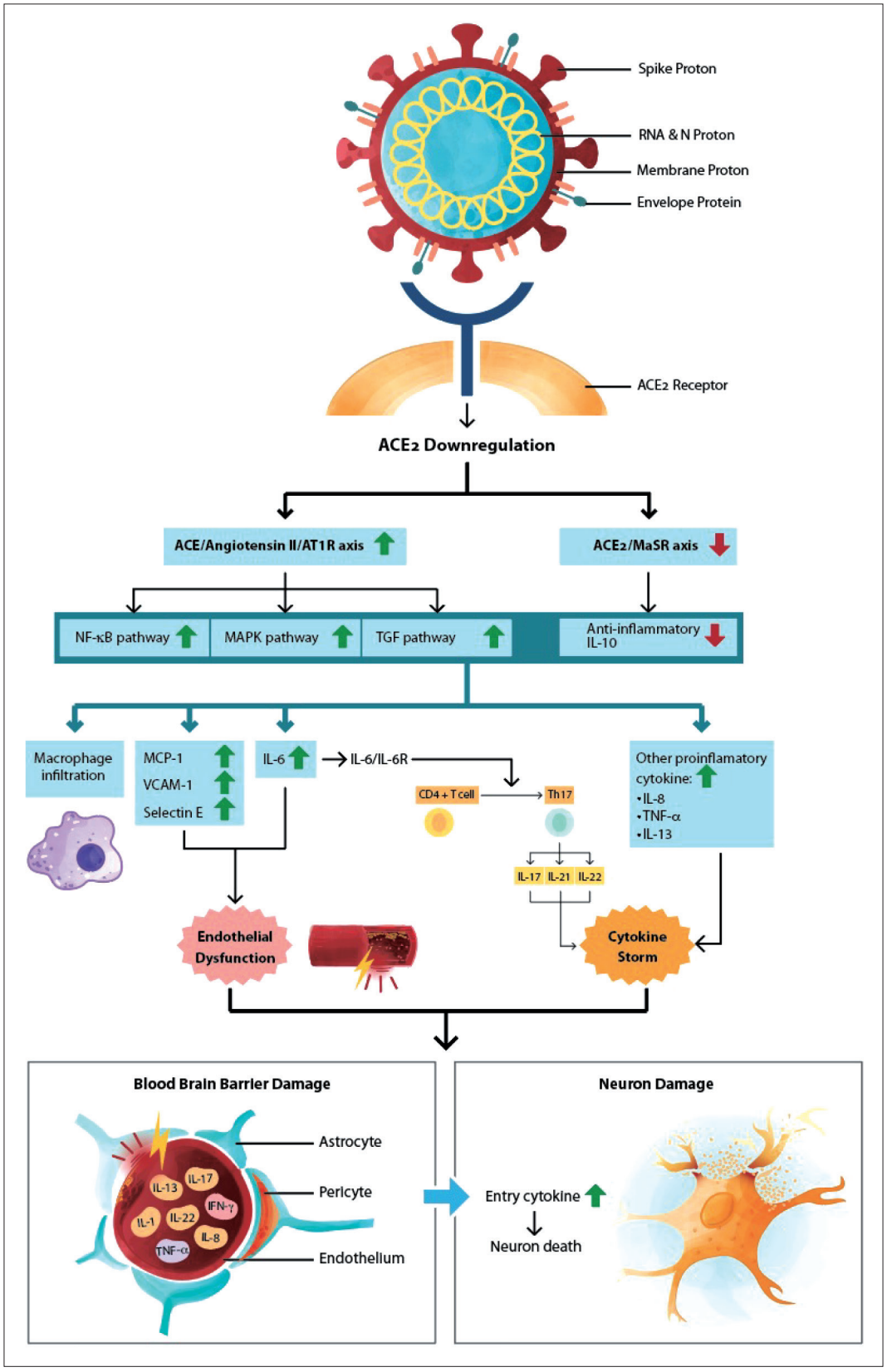

Fig. 2. Cytokine-immune-mediated inflammation and pathomechanism in COVID-19-associated encephalitis. ACE_2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemotactic protein 1; NF-κB, nuclear factor kappa B; TGF, tumor growth factor; VCAM-1, vascular cell adhesion molecule 1; Th17, T helper 17.

thy based on the theories from previous studies.[54-56] The binding of SARS-CoV-2 to ACE_2 receptor via spike protein causes ACE_2 downregulation,[50,54] followed by an increase in the ACE/angiotensin II/AT1R axis and a decrease in the MaSR (ACE_2/Mas receptor) axis.[54] These processes consequently result in the activation of the NF-κB (nuclear factor kappa B) and MAPK (mitogen-activated protein kinase) pathways, upregulation of TGF-β (tumor growth factor beta), and downregulation of the anti-inflammatory cytokine IL-10.[54,55] These excitations of proinflammatory pathways increase the levels of MCP-1 (monocyte chemotactic protein 1), VCAM-1 (vascular cell adhesion molecule 1), selectin-E, and IL-6.[55] IL-6 was found to be the core part of the cytokine storm.[54-56] IL-6 activates CD4 and T cells into Th17 (T helper 17) cells, which aggravate the proinflammatory cytokines IL-17, IL-21, and IL-22.[57] The cytokine storm and the endothelial dysfunction causing damage to the blood–brain barrier make it easier for proinflammatory cytokines to enter the brain parenchyma and also cause further neural damage.[56] The pathomechanism underlying COVID-19 encephalopathy has been suggested to be a cytokine-immune-inflammatory process,[18,34,56] but further research is needed to explain and confirm this hypothesis.

The main limitation in this study was the large variety of case reports and the findings of certain techniques such as EEG and PCR not being reported for all studies. Inflammatory markers and antineuronal autoantibodies were only assessed in a few studies, and so whether the cytokine-immune-mediated inflammatory process is the cause of COVID-19 encephalopathy remains inconclusive.

In conclusion, The clinical, laboratory, and imaging findings in this review support the hypothesis that cerebral damage in COVID-19-associated encephalopathy is caused by cytokine-immune-mediated inflammation rather than by direct invasion. There have been several reports on the benefits of intravenous steroid therapy and immunotherapy in COVID-19-associated encephalopathy. Cytokine-immune-mediated inflammation may cause encephalopathy, but this remains inconclusive due to the inadequate data. Therefore, further examinations and research are needed to confirm this hypothesis.

Availability of Data and Material

All data generated and analyzed during this study are included in this published article.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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