Journal of Neurology (2022) 269:1071–1092
https://doi.org/10.1007/s00415-021-10771-8

REVIEW

SARS-CoV-2-associated acute disseminated encephalomyelitis: a systematic review of the literature

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Received: 10 August 2021 / Revised: 22 August 2021 / Accepted: 23 August 2021 / Published online: 30 August 2021

Abstract

The literature on cases of acute disseminated encephalomyelitis (ADEM) associated with SARS-CoV-2 infection has been rapidly increasing. However, the specific clinical features of ADEM associated with SARS-CoV-2 (SARS-CoV-2-ADEM) have not been previously evaluated. We screened all articles resulting from a search of PubMed and Web of Science databases looking for reports of ADEM published between December 01, 2019, and June 5, 2021. Of the 48 ADEM cases identified from 37 studies, 34 (71%) had ADEM while 14 (29%) were of AHLE. RT-PCR for SARS-CoV-2 was positive in 83% ($n = 19$) of patients. 26 patients (54%) were male, and 18 patients (38%) were female, with a male to female sex ratio of 1.4:1; median age was 44 (1.4–71) years. 9 patients (19%, 9/48) were children. Of the 9 children patients, their median age was 9 years (range 1.4–13 years), 6 patients (67%) were female, and 2 patients (22%) were male, with a female to male sex ratio of 3:1.39 patients (81%) was performed CSF analysis. PCR for SARS-CoV-2 tested positive in 3 patients (14%, 3/22) on CSF sample. 31 (64%) of patients had a poor outcome on discharge from hospital. Five (10%) patients died in hospital. Compared to classic ADEM, SARS-CoV-2-ADEM have a more longer duration between the onset of the antecedent infective symptoms and the start of ADEM symptoms, the older age distribution of the patients, relatively poor outcome, a lower full recovery rate, a more frequently brain lesions involved the periventricular white matter and corpus callosum, and less frequently affected the deep gray matter. Taken together, the present comprehensive review reveals that although rare, ADEM can be associated with SARS-CoV-2 infection. SARS-CoV-2-ADEM seems to share most features of classic ADEM, with moderate discrepancies from the classical ADEM.

Keywords COVID-19 · SARS-CoV-2 · Acute disseminated encephalomyelitis · Clinical features

Introduction

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly evolved into a worldwide pandemic. COVID-19 predominantly affects the respiratory system and patients typically present with a cough, sore throat, fever, fatigue and breathing difficulties [1]. However, since Mao for the first time reported there is evidence of neurological involvement in COVID-19 [2], neurologic complications are increasingly recognized in the coronavirus disease 2019 (COVID-19) pandemic [3–6]. In detail, several pieces of evidence suggested potential neurologic complications of SARS-CoV-2 infection include anosmia, ageusia, anorexia, myalgias, headache, dizziness, meningoencephalitis, altered consciousness, Guillain–Barré syndrome, syncope, seizure, and stroke [7, 8].

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As a rare illness, acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disorder of the central nervous system (CNS) that predominantly affects children [9]. However, several studies reported an increased incidence of ADEM after SARS-CoV-2 epidemics around the world. More recently, numerous case report/series have described cases of ADEM linked to SARSCoV-2 infection, which suggests a possible association between ADEM and SARS-CoV-2 infection [10–15].

Until now, no systematic review has conducted to review the available information on the reports of ADEM associated with the COVID-19 infection. This study aims to perform a systematic review of all published studies on SARS-CoV-2-related ADEM and give a comprehensive overview of the demographic characteristics, clinical features, diagnostic investigations, and outcome of SARS-CoV-2-related ADEM patients. At the same time, we also compare the clinical features of SARS-CoV-2-associated ADEM to the classical form of ADEM. The current study may get a better understanding of the acute and post-infectious manifestations of SARS-CoV-2-associated ADEM to guide long-term management and health service reorganization.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [16, 17]. A PRISMA-P checklist has been provided as an online supplementary file. We conducted a thorough literature review in June 2021 using keywords (including all commonly used abbreviations of these terms) used in the search strategy were as follows: ("acute demyelinating encephalomyelitis;" OR "acute haemorrhagic leukoencephalitis") AND ("COVID-19"OR "SARS-CoV-2"). We searched PubMed and Web of Science databases for identifying case series and case reports published between December 1, 2019, to June 5, 2020. Suitable references were also identified in the authors' archives of scientific literature on ADEM. At least two independent reviewers independently screened all publications, including title and abstract, to determine whether studies include cases. Further case reports and case series studies were obtained by reference tracing of retrieved articles. We restricted our search to studies published in English. Publications that were not peer-reviewed were excluded from this study. For each case, we extracted data concerning demographic and clinical variables, results of diagnostic investigations, and outcome. Searches were performed by SAR, AA, and MF. The selection of relevant articles was shared with all authors.

According to our search criteria, we found 246 studies from PubMed and Web of Science. Duplicate studies, studies with missing clinical data, review articles and articles unrelated to our study objective were excluded and 31 full-text literatures were reviewed in accordance with our study objective.

Results

A total of 48 patients with COVID-19 diagnosed with ADEM/AHLE were used for analyses from the 37 case reports and case series published between December 1, 2019, to June 5, 2020. The demographic data, the clinical, laboratory and imaging findings of the 48 patients are detailed in Table 1 and summarised in Tables 2 and 3.

Epidemiological distribution and demographic characteristics of the patients

Of the 48 ADEM cases identified from 37 studies, 26 patients (54%) were male and 18 patients (38%) were female, with a male to female sex ratio of 1.4:1; median age was 44 (1.4–71) years. 9 patients (20%, 9/45) were children. Of the 9 children patients, their median age was 8 years (age range 1.4–13 years), 6 patients (75%, 6/8) were female, and 2 patients (25%, 2/8) were male, with a female to male sex ratio of 3:1. Adult to children ratio is 4:1(36/9), indicating that SARS-CoV-2-related ADEM predominantly affects adults after than children.

Overall, patients were reported from 10 countries but mostly from Europe (43.7%, 21/48) and especially from UK (25.0%). In details, patients were originally from USA ($n=13$), United Kingdom ($n=12$), Italy ($n=5$), Brazil ($n=4$), India ($n=3$), Iran ($n=3$), Singapore ($n=3$), France ($n=3$), Canada ($n=1$), and Greece ($n=1$) (Table 2).

Clinical features of SARS-CoV-2-associated ADEM

Most common manifestations of COVID-19 included fever (66.0%, 23/35),cough (27.0%, 13/35), dyspnoea (24.0%,11/35), anosmia/hyposmia (14.0%, 5/35) (17.0%, 6/35), myalgia (14.0%, 5/35), fatigue (11.0%, 4/35), lethargy(9.0%, 3/35) and rash (6.0%, 2/35). Six patient [18–23] did not present any sign related to COVID-19. The diagnosis of SARS-CoV-2 infection was made by positive RT-PCR of nasopharyngeal swab in 18 (78%) patients (sometimes after repeated tests) and when negative by in 5 (21%) patient. SARS-CoV-2 RT-PCR with sputum exam was positive in 1 (3%) patients, and when positive by serology in 3 (10%) patient.

34 (71.0%) had ADEM while 14 (29.0%) were of AHLE. In all ($n=48$) but one patients [14], ADEM manifestations developed after those of COVID-19. Differently, the temporal relationship between onset of COVID-19 symptoms and ADEM was not reported or not calculable

Table 1 Demographic and clinical characteristics of ADEM and AHNE/AHLE With Evidence of SARS-CoV-2 infection

No	Ref	Age/sex	Initial viral syndrome	Diagnosis of COVID-19	Neurological symptoms/signs	TVN (days)	CSF findings	Abs	MRI results	Diagnosis	Treatment	Outcome status
1	[46]	46/M	Fever,breathlessness	(+) RT-PCR/NPS	Confusion, Left hemiplegia	35	CSF showed lymphocytic pleocytosis with increased protein, glucose NA**	Not tested: Serum AQP4, and MOG Ab	Hyperintense lesions in the bilateral cerebral hemisphere,left thalamus, cerebellum,brainstem, and white matters with areas of diffusion restriction and irregular patchy areas of rim enhancement were noted within most of the lesions and microhemorrha	AHLE	IVMP1gm for 5 day	Deceased
2	[11]	?	NA	NA	Nonne	NA	Not done	NA	Multifocal haemorrhagic lesions predominantly in the white matter	AHLE	Corticosteroid+IVIG	NA
3	[11]	?	NA	NA	Flaccid tetraparesis and facial weakness evolving to areflexia (day 2) and respiratory failure (day 5)	10	Mild pleocytosis (red blood cells 22/μL and white blood cells 6/μl) and raised protein 0.56 g/L; viral culture and CSF SARS-CoV-2 serology were negative	NA	Brain:T2WI, discrete hyperintense foci in the deep and subcortical white matter; DWI and ADC, hyperintensity of the lesions without restricted diffusion on ADC maps; Cervical spine: T2WI, a small linear lesion on the right side of the spinal cord at C1	ADEM	IVIG	NA
4	[14]	52/M	Cough; myalgia; dyspnoea; hypoxia	NA	Low conscious level; withdrawal to pain; hyperreflexia and clonus	22	Normal protein level; WBC 1 cells/μl; glucose (CSF+blood), N; OB(-);NMDA Ab (−); PCR assay for SARS CoV-2(−)	Negative	Brain: multiple clusters of lesions in the deep cerebral white matter. Cystlike areas of varied sizes, some with haemorrhagic foci and peripheral rims of restricted diffusion were shown within these clusters	AHLE	Supportive	Incomplete but ongoing
5	[14]	60/M	Fatigue; myalgia; fever;dyspnoea; hypoxia	NA	Low conscious level; opening eyes to voice; withdrawal to pain; right extensor plantar	27	Normal protein level; WBC 1 cells/μl; glucose (CSF5.5 mM/L↑), N; CSF culture and viral PCR negative including SARSCoV-2	NA	Multifocal and confluent areas of signal change in the cerebral hemispheric white matter with extensive microhaemorrhages in the subcortical regions	AHLE	1 g IVMP 3 days;	Incomplete ongoing

Table 1 (continued)

No	Ref	Age/sex	Initial viral syndrome	Diagnosis of COVID-19	Neurological symptoms/signs	TVN (days)	CSF findings	Abs	MRI results	Diagnosis	Treatment	Outcome status
6	[14]	59/F	Cough; chills; lethargy;myalgia	NA	Recurrent fleeting episodes of vacant staring and speech arrest; generalised tonicclonic seizures; headache; low conscious level; left pupil unreactive at nadir; left extensor plantar	10	Protein(2.34 g/L↑); cell count (4WBC); CSF viral PCR negative including SARS-CoV-2	NA	Brain (day 6): extensive, confluent and largely symmetrical areas throughout brainstem, limbic and insular lobes, superficial subcortical white matter and deep gray matter. Clusters of microhaemorrhages, restricted diffusion and peripheral rim enhancement	AHLE	No response	Died
7	[14]	52/M	Fever; hypoxia	NA	Headache; back pain; vomiting; progressive limb weakness; Flaccid four limb weakness, proximal > distal; facial and neck weakness; areflexia; extensor plantars, normal sensation; ophthalmoplegia day 3	-6	Protein(1.01 g/L↑); CSF viral PCR: negative including SARS-CoV-2	NA	Brain: multifocal confluent lesions in internal and external capsules splenium and deep white matter of cerebral hemispheres. Over 5 days, lesions increased in size and showed multiple microhaemorrhages and extensive prominent medullary veins. Components of brachial and lumbosacral plexus showed increased signal and enhancement	AHLE	1 g IVMP 5 days + IVIG	Incomplete ongoing recovery
8	[14]	47/F	Cough; fever; dyspnoea	NA	Subacute left sided numbness and weakness; headache;vomiting; reduced conscious level; Dense left hemiparesis; reduced sensation on left	8	19 WBC cells/μL (10% polymorphs, 90% lymphocytes); OB(-);CSF viral PCR: not test	Neuronal Abs to AQP4 and MOG (−)	Severe right hemispheric vasogenic oedema with a leading edge on contrast imaging. Smaller areas of T2 hyperintense changes in the left hemisphere. Marked mass effect with 10 mm leftwards midline shift, and mild subfalcine herniation	AHLE(Brain biopsy consistent with ADEM)	Right hemicraniectomy; 1 g IVMP 5 days, then oral prednisolone; IVIG	Incomplete recovery; improving

Table 1 (continued)

No	Ref	Age/sex	Initial viral syndrome	Diagnosis of COVID-19	Neurological symptoms/signs	TVN (days)	CSF findings	Abs	MRI results	Diagnosis	Treatment	Outcome status
9	[14]	54/F	Cough; fever; dysgeusia; truncal rash	NA	Unsteadiness; left sided limb weakness; slurred speech; fatigue; falls; Drowsy; slow to respond; dysarthric; trunk and limb ataxia; broad base standing; unable to walk; leftsided pyramidal weakness; bilateral extensor plantars	23	OB(−);CSF viral PCR: not test	NA	Multiple large lesions with peripheral rim restriction in periventricular white matter of both cerebral hemispheres	ADEM	1 g IVMP 3 days, then oral prednisolone	Incomplete recovery; improving
10	[47]	12/F	Skin rash, and fever	(−) RT-PCR/NPS	Headache, inability to stand, walk, and handle objects	5	18 mg/dL of protein, 74 mg/dL of glucose, no cells, and normal opening pressure; PCR assay for SARS CoV-2(−)	Neuronal Abs to AQP4 and MOG (−)	Brain: DWI–extensive bilateral and symmetric restricted diffusion involving the subcortical and deep whitematter. T2-FLAIR and ADC–focal hyperintense lesion in the splenium of the corpus callosum with restricted diffusion Cervical spine: highlighting longitudinally extensive cervical myelopathy involving both white and gray matter	ADEM	1 g IVMP 5 days	Poor
11	[18]	6/M	None	(+) RT-PCR/NPS	Brief epileptic seizure by generalized tonic–clonic semiology with spontaneous resolution		Absence of cells and proteins; OB(+)	Neuronal Abs to AQP4 and MOG (−)	Brain(day 3): T2-FLAIR–hyperintense lesions in the right cerebellar hemisphere, cortical–subcortical cuneus gyrus of the right parietallobe, left side of the corpus callosum and corona radiata, cortical–subcortical inferior left parietal gyrus;Post-contrast T1WI–signal increase in the inferior left parietal gyrus lesion	ADEM	30 mg/kg/die IVMP 5 days	Good

Table 1 (continued)

No	Ref	Age/sex	Initial viral syndrome	Diagnosis of COVID-19	Neurological symptoms/signs	TVN (days)	CSF findings	Abs	MRI results	Diagnosis	Treatment	Outcome status
12	[48]	53/M	Cough, shortness of breath, fevers, myalgia and malaise	(+) RT-PCR/NPS	Agitation and global hypotonia	59	CSF cell count, chemistry not reported, mirror OCB in CSF and serum	No serum AAbs and IM available	Brain: multiple hyperintense lesions within the subcortical and deep white matter of the frontoparietal lobes. Hemorrhage present No cord MRI	ADEM	IVMP for 3 days	Partial recovery
13	[12]	65/M	NA	NA	Altered mental state with aphasia and focal motor deficit	44	63 mg/L of protein, 2 cells/µl; OB(−)	NA	NA	ADEM	NA	NA
14	[24]	?	NA	NA	NA	NA	PCR assay for SARS CoV-2(+)	NA	Hyperintense lesions on white matter substance in the deep hemispheric and periventricular areas both on FLAIR and ADC map	ADEM	NA	NA
15	[19]	35/F	None	(+) RT-PCR/NPS	Gait instability	60	Time1:1 WBC, 0 RBC, protein of 22 mg/dL, glucose 76 mg/dL, negative meningitis-encephalitis panel	Neuronal Abs to AQP4 and MOG (−)	Brain: extensive diffuse confluent periventricular, temporal, subcortical and midbrain hyperintensities overall mildly progressed since prior MRI with mild patchy diffusion restriction, no contrast enhancement, and no evidence of microhemorrhages on SWI	ADEM	1 mg/kg/die IVMP 5 days + 2 g IVIGP 3 days + PE	Poor: hospital day 48, she had not improved, and was transferred to a long-term care facility
							Time 2: 2 WBC, 51 RBC, protein 19 mg/dL, glucose 70 mg/dL and negative: culture, meningitis-encephalitis panel		Spine: normal			
16	[20]	30/M	None	(−) RT-PCR/NPS	Ataxia and confusion	NA	Glucose: 58 mg/dl, protein: 45.7 mg/dl, WBC: 0, and RBC: 16 (mm^3); OB(+)	Neuronal Abs to AQP4 and MOG (−)	Brain: revealed multiple lesions with simultaneous enhancement Spine: cervical MRI revealed a plaque	ADEM	1 mg/kg/die IVMP 5 days followed by rituximab 1 g IV	Discharged with relative recovery after 7 days

Table 1 (continued)

No	Ref	Age/sex	Initial viral syndrome	Diagnosis of COVID-19	Neurological symptoms/signs	TVN (days)	CSF findings	Abs	MRI results	Diagnosis	Treatment	Outcome status
17	[21]	49/M		(+) RT-PCR/NPS	Delayed recovery of consciousness	NA	PCR assay for SARS CoV-2(−)	NA	Brain: multiple nodular/oval hyperintensities that involve the deep and periventricular cerebral white matter, splenium of the corpus callosum, and pons. all lesions show restricted diffusion on DWI sequences	ADEM	NA	NA
18	[21]	9/?	None	(+) Serologic test for COVID-19	Difficulty walking and speaking, right hemiparesis, and impaired ocular motor function	NA	PCR assay for SARS CoV-2: NA	NA	Brain: multiple large hyperintense oval lesions predominantly affecting the subcortical WM of the cerebral hemispheres, the posterior arm of the right internal capsule, and the infratentorial fossa structures, particularly in the middle cerebellar peduncles. All lesions concurrently demonstrate diffusion restriction observed in the diffusion sequence and gadolinium enhancement in the postcontrast T1 sequence. Most lesions have an open-ring enhancement pattern, best characterized in the right middle cerebellar peduncle	ADEM	NA	NA
19	[32]	21/M	Fever with chills, nonproductive cough, and a sore throat	(−) RT-PCR/NPS; Serologic test for COVID-19:IgG(+)	Weakness and paresthesia of the lower limbs,urinary retention, increased paraparesis severity and weakness in the upper limbs; he also became drowsy	214	CSF WBC 150/ mm^3 Lymphocyte predominant, protein 281 mg/dl, glucose 34 mg/dl, PCR assay for SARS CoV-2(+)	Neuronal Abs to AQP4 and MOG (−)	Brain: hyperintense signal in internal capsule to the pons and corpus callosum no restriction diffusion, no enhancement. No hemorrhage Cervical and thoracic MRI: showed LETM	ADEM	PE	Partial recovery

Table 1 (continued)

No	Ref	Age/sex	Initial viral syndrome	Diagnosis of COVID-19	Neurological symptoms/signs	TVN (days)	CSF findings	Abs	MRI results	Diagnosis	Treatment	Outcome status
20	[29]	61/M	Fever, cough, and anosmia	NA	Confusion	7	Not done	Not done	Brain: hyperintense lesions in the thalami, cerebellum, and white matters with gadolinium-enhanced lesion in thalami with areas of restricted diffusion in thalami, and microhemorrhage	AHLE	IVMP 1gm for 5 days and IVIG, PE, Remdesivir	Partial recovery
21	[49]	17/F	Fever	(+) RT-PCR/NPS; Serologic test for COVID-19:IgG(+)	Progressively worsening weakness, and unsteady gait	13	Mild pleocytosis with lymphocytic predominance: 5WBC/μL (81% lymphocytes, 19% monocytes), 1RBC/μL, glucose of 58 mg/ dL, and protein of 17 mg/ Dl; PCR assay for SARS CoV-2(−)	Neuronal Abs to AQP4 and MOG (−)	Brain: multifocal hyperintense T2-FLAIR signals in bilateral subcortical and periventricular white matter without contrast enhancement Spine: unremarkable	ADEM	IVIG 2 g/kg for 4 days; 30 mg/kg/day IVMP 5 days	Completely normalized
22	[33]	64/F	Influenza-like syndrome	NA	Severe visual loss, sensory deficiton her right leg, pyramidal sign on her left leg, mild behavorial abnormalities, headache	14	CSF cell count 22/μL with Lymphocytes predominant, Protein 45.2 mg/dl, glucose not reported, mirror OCB in CSF and serum CSF RT-PCR Positive for COVID-19	Neuronal Abs to AQP4 and MOG (−)	Brain: multiple Gad enhancing Lesions of the brain, associated with a single spinal cord lesion at the T8 level and with bilateral optic nerve enhancement	ADEM	IVMP and IVIG	Recovered
23	[13]	41/M	Cough, shortness of breath	SARS-CoV-2 RT-PCR: Sputum positive	Slow waking postsedation; Bilateral ulnar neuropathies	NA	Not done	NA	Brain: bilateral symmetrical white matter hyperintensities with microhaemorrhages in the posterior frontal lobes). Subcortical white matter changes were also present in the left occipital lobe with parenchymal haemorrhage	ADEM	Supportive	Improving (day 53)

Table 1 (continued)

No	Ref	Age/sex	Initial viral syndrome	Diagnosis of COVID-19	Neurological symptoms/signs	TVN (days)	CSF findings	Abs	MRI results	Diagnosis	Treatment	Outcome status
24	[22]	58/M	None	(+) RT-PCR/NPS;	Decreased level of consciousness and the inability to walk	NA	CSF examination revealed WBCs: 0/mm^3 (normal range: 0–5/mm^3), Glucose: 105 mg/dL (normal < 80 mg/dL), and protein: 15 mg/dL (normal < 45 mg/dL); PCR assay for SARS CoV-2(−)	NA	Brain: diffuse confluent white matter hyperintensity on FLAIR-weighted MRI, particularly at the left-side without prominent enhancement on T1WI. Moreover, the involvement of cortical as well as deep gray matter, and dorsal midbrain was evident	ADEM	NA	NA
25	[25]	51/F	Dyspnoea, fever, and vomiting	NA	Decreased responsiveness	NA	CSF WBC 1/mm^3,protein 62 mg/dl, **glucose56 mg/dl, **; RT-PCR	AQP4 Ab negative	Brain: hyperintense lesions in deep white matter and juxta cortical white matter. These lesions show diffusion restriction on DWI, mild gadolinium enhancement	ADEM	IVMP 1 g/day for 5 days and IVIG	Partial recovery
							SARS COV-2(−);Mirror OB in CSF and serum		No cord MRI			
26	[30]	71/M	NA	NA	Respiratory failure	11	Not done	Not done	Not done	ADEM	NA	Deceased
27	[15]	54/F	Fever andprogressive dyspnoea	RT-PCR for SARS-CoV-2 was positive	Unconscious	NA	CSF RT-PCR for neurotropic viruses, including SARS-CoV-2, was negative	NA	Brain: alterations of the periventricular white matter, hyperintense in T2WI, without restriction of diffusion nor contrast enhancement. Similar lesions were found at the bulbo-medullary junction and in both the cervical and dorsal spinal cord	ADEM	Dexamethasone 20 mg/die for 10 days and 10 mg/die for 10 days	Transferred to rehabilitation without sensorimotor deficits
28	[23]	44/M	None	(+) RT-PCR/NPS;	Urinary retention, bilateral lower extremity weakness and numbness	0	CSF WBC 6/mm^3,protein 36 mg/dl, OB(−)	No serum Abs orinflammatorymarkers available	Brain: periventricular and juxta cortical hyperintense; Lesions with associated with Gad enhancement; No hemorrhage	ADEM	IVMP and IVIG	Partial recovery: discharged to an acute rehabilitation facility
									Spine: hyperintense lesions throughout the cervical and thoracic spinal cord, no abnormal enhancement			

Table 1 (continued)

No	Ref	Age/sex	Initial viral syndrome	Diagnosis of COVID-19	Neurological symptoms/signs	TVN (days)	CSF findings	Abs	MRI results	Diagnosis	Treatment	Outcome status
29	[31]	12/F	Fever, throat pain, cough	COVID-19 IgG Ab s(+)	Repeated generalized convulsions	37	Not done	Not done	Brain: extensive lesions with altered T2 and FLAIR signals at gray and white matter junction of both cerebral hemispheres with mild associated enhancement, diffuse cortical swelling with diffusion restriction	ADEM + GBS	IVIG	Complete-neurological recovery and was discharged home
30	[26]	65/M	Fatigue, fever, and cough	(+) RT-PCR/NPS;	Altered consciousness after discontinuation of sedation	NA	NA	NA	FLAIR and DWI hyperintense lesions within the periventricular white matter, basal ganglia, cerebellar peduncles and corpus callosum. Patchy enhancement of all lesions in particular globus pallidus bilaterally, with a punctuate pattern in the cerebellum. Microhemorrhage of bilateral globus pallidus	ADEM	NA	NA
31	[50]	54/F	Respiratory distress	(+) RT-PCR/NPS	Altered mental status without focal neurologic deficit	8	Normal CSF SARS-CoV-2 PCR negative	NA	Multiple supratentorial punctiform and tumefactive lesions of white matter, involving corpus callosum: hypersignal on flair and DWI with restricted diffusion. 10 day after: enhancement of all lesions (No lesion in spine MRI)	ADEM	Steroid treatment	NA
32	[34]	13/F	Fever,	(+) RT-PCR/NPS	Altered consciousness, seizures	3	CSF analysis showed 10/mm^3 white cells, being negative for SARS-CoV-2 RNA	MOG IgG antibodies(+)	Brain: bilateral widespread white matter highsignal abnormalities, including the splenium of the corpus callosum with associated diffusion restriction and high signal in the thalami and pons Spine: normal	ADEM	Steroid treatment	Partial recovery

Table 1 (continued)

No	Ref	Age/sex	Initial viral syndrome	Diagnosis of COVID-19	Neurological symptoms/signs	TVN (days)	CSF findings	Abs	MRI results	Diagnosis	Treatment	Outcome status
33	[34]	10/F	Vomiting, lethargy, and pyrexia	(+) RT-PCR/NPS	Ageusia, headache; fluctuating sensorium and urinary incontinence	15	CSF analysis showed a markedly raised white-cell count (WCC) of 6075/mm^3 with 93% lymphocytes and CSF protein of 0.58 g/L. CSF SARS-CoV-2 RNA test was negative	MOG IgG antibodies (−)	Brain: asymmetric bilateral high-signal lesions in the basal ganglia and the subcortical white matter in the frontal and temporal lobes, with involvement of the left internal capsule and left hippocampus	ADEM	IV aciclovir and antibiotics	Good
34	[51]	56/M	Flu-like symptoms	(+) RT-PCR/NPS	Diffusely slow and poorly responsive	7	WBC < 1.0 cell/uL, red blood cells of 6 RBC/uL, CSF protein of 0.71 g/L, and CSF glucose of 4.3 mmol/L with serum glucose of 8.6 mmol/L (normal limit of 3.0–6.0 mmol/L)	NA	Brain: increased symmetrical FLAIR signal throughout the white matter. Diffuse haemosiderin staining throughout the white matter and the genu of the corpus callosum. There are also some cystic haemorrhagic areas containing a fluidblood level within both cerebral hemispheres	AHLE	Supportive	Recovered
35	[52]	48/F	Myalgia, dry cough, shortness of breath, and fever	Positive by SARS-CoV-2 PCR testing	Equal and nonreactive pupils bilaterally with absent cough, gag, and corneal reflexes	14	CSF had 76 × 10^6/L nucleated cells (65% neutrophils) in the presence of 33,000 × 10^6/L erythrocytes. CSF IgG ratio was 0.35 with an IgG index of 1.05; Negative for SARS-CoV-2	NA	Brain: extensive bilateral parietal and occipital intraparenchymal hemorrhage, with surrounding edoema with intraventricular extension and acute hydrocephalus cortical enhancement in MRI	AHLE	Vasopressor and steroids	Residual severe neurological deficit. Recovering and undergoing rehabilitation

Table 1 (continued)

No	Ref	Age/sex	Initial viral syndrome	Diagnosis of COVID-19	Neurological symptoms/signs	TVN (days)	CSF findings	Abs	MRI results	Diagnosis	Treatment	Outcome status
36	[53]	57/M	Fever, dry cough	(+) RT-PCR/NPS	Flaccid and unconscious for more than 48 h until we noticed bilateral extension posturing on painful stimuli	3	CSF was acellular with moderate protein elevation (0.69 g/l). IgG index was 0.51, OB were absent in CSF and serum, and PCR was negative for SARS-CoV-2	NA	Brain: hypointense haemosiderin rims and extensive perilesional oedema. Note sparing of the thalami. T2* sequence documenting haemorrhage. T1 MRI sequence after contrast infusion showing an alternating ring enhancement pattern. FLAIR and T2* MRI sequences 1 month later showing complete resorption of the perilesional oedema and comma-like residual lesions with a haemosiderin rim involving the external capsules and the posterior limb of the internal capsule immediately adjacent to the globus pallidus	AHLE	Azithromycin, hydroxychloroquineand lopinavir/- ritonavir, anakinra	Recovered with moderate tetra paresis
37	[54]	33/M	Fever	(+) RT-PCR/NPS	Acute onset rapidly progressive weakness of both upper and lower limbs since 3 days and altered sensorium since 1 day; episode of generalised tonic–clonic seizures	2	Viral RT-PCR panel negative Normal protein and cell count	NA	Brain: symmetrical FLAIR hyperintensities involving bilateral subcortical fronto-parietal lobes, splenium of corpus callosum, medulla and visualized cervical cord with petechial haemorrhages and evidence of diffusion restriction involving splenium of corpus callosum	AHLE	IVMP 1 g/day for 5 days	Improvement following steroids, death due to respiratory insufficiency and shock

Table 1 (continued)

No	Ref	Age/sex	Initial viral syndrome	Diagnosis of COVID-19	Neurological symptoms/signs	TVN (days)	CSF findings	Abs	MRI results	Diagnosis	Treatment	Outcome status
38	[55]	54/M	NA	(+) RT-PCR/NPS	Impaired consciousness	24	CSF: a normal cell count with protein levels within the reference range; SARS-CoV-2 PCR negative	NA	Brain MRI: multiple nodular FLAIR hyperintense lesions in the subcortical white matter, bilateral corticospinal tracts, and in the right optic nerve. The lesions presented mild contrast enhancement and were predominantly found in both parietal and occipital lobes. They induced mild mass effect on adjacent structures and their presentation was consistent with pseudotumoral inflammatory demyelinating lesions observed in acute disseminated encephalitis	ADEM	IVMP + PE	In a persistent vegetative state
39	[56]	37/F	Cough, chest pain, fever and worsening shortness of breath		Weakness upper extremity and paraplegia	22	CSF WBC 2/mm^3, total protein 95 mg/dl, glucose—85 mg/dl, **OB absent	NA	Brain MRI: hyperintense and restriction Diffusion in corpus callosum, cerebral deep white matter, brainstem including pons, medulla and enhancement in body of corpus callosum. No hemorrhage No cord lesions	ADEM	Decadron 20 mg iv × 5 Days and Convalescent plasma therapy	Partial recovery
40	[56]	56/M	Poor appetite, fever and acute respiratory failure		Unresponsive,no spontaneous Limb movement	20	CSF WBC 1/mm^3, protein 55 mg/dl, **glucose 112 mg/dl, OB absent	NA	Brain MRI: hyperintensity and restriction diffusion in deep cerebral white matter and bilateral cerebellum. No hemorrhage No contrast study done No cord MRI reported	ADEM	IVMP 1gm for 5 days, IVIG and PE	Remains on ventilator and had tracheostomy
41	[56]	70/F	Decreased appetite, fatigue, generalized weakness and lethargy and cough		Unresponsiveness	16	CSF WBC 0/mm^3,protein 63 mg/dl, glucose 87 mg/dl, **	NA	Brain MRI: hyperintense and restriction diffusion in corpus callosum, cerebral deep white matter and minimum enhancement No cord MRI done	ADEM	IVMP 1gm for 5 days and IVIG and then PE	Partial recovery

Table 1 (continued)

No	Ref	Age/sex	Initial viral syndrome	Diagnosis of COVID-19	Neurological symptoms/signs	TVN (days)	CSF findings	Abs	MRI results	Diagnosis	Treatment	Outcome status
42	[57]	5/F	Fever, neck swelling and erythematous skin rash	(−) RT-PCR/NPS; COVID-19 IgG Abs (+)/IgM Abs (+)	Irritable; neck stiffness, muscular weakness and right Babinski sign	5	CSF was acellular with normal protein and glucose. OB absent	NA	Brain MRI: showed two lesions, one in the splenium of the corpus callosum and the other in the subcortical white matter of the left parietal lobe, that exhibit restricted diffusion without contrast enhancement	ADEM	IVMP 1 mg/kg/d for 5 days and IVIG 0.4 mg/kg/d	Recovered
43	[27]	51/F	Fever, diarrhoea	Positive for COVID-19	Incontinence, and aphasia	NA	NA	NA	Brain autopsy: histologic features of ADEM	ADEM	NA	Deceased
44	[27]	64/M	Fever	Positive for COVID-19	Collapsed and was non-responsive with a fixed and dilated right pupil	NA	NA	NA	Brain autopsy: histologic features of AHLE	AHLE	NA	Deceased
45	[28]	59/M	NA	Positive for COVID-19	Impaired conscious level, complex ophthalmoplegia, and hyperreflexia	NA	Not done	NA	Brain MRI: peripheral low signal on T2*, abnormal diffusion, high T1, and increased attenuation (D) within the corpus callosum splenium. Confluent high FLAIR and T2 abnormality are noted within the deep cerebral white matter	AHLE	Steroid treatment	Recovered
46	[58]	59/M	Minimal symptoms	Positive for COVID-19	Progressive right sided hemiparesis and persistent, progressive encephalopathy	28	CSF: cell count of 7, protein of 48, and glucose of 65	MOG Ab and AQP-4 Ab (−)	Brain MRI: progressive multi-focal large ovoid T2-FLAIR hyperintensities, consistent with tumefactive demyelinating disease	ADEM	NA	NA
47	[59]	64/M	Shortness of breath, congestion	Positive for COVID-19	Acute mental status change	NA	CSF: lymphocytic pleocytosis, normal protein, glucose; COVID was negative		Brain MRI: wide-spread diffusion restriction in white matter and cerebellum with corresponding T2 Flair hyper-intensities signal not following a vascular pattern	ADEM	IVMP 1 g every 24 h × 5 doses	Poor: comfort care

Table 1 (continued)

No	Ref	Age/sex	Initial viral syndrome	Diagnosis of COVID-19	Neurological symptoms/signs	TVN (days)	CSF findings	Abs	MRI results	Diagnosis	Treatment	Outcome status
48	[60]	5/M	NA	(+) RT-PCR/NPS	Headaches, blurry vision, and emesis	NA	CSF: lymphocytic pleocytosis	MOG Ab and AQP-4 Ab (−)	Brain MRI: supratentorial and infratentorial enhancing lesions, with vasogenic edoema and punctate hemorrhage foci, and bilateral optic nerve swelling Spine MRI: d longitudinally extensive myelitis Brain biopsy: foci of lymphohistiocytic perivascular inflammation consistent with a meningoencephalitis. ADEM	ADEM	IVMP	Poor

Onset refers to days before (negative values) or after (positive values) the onset of SARS CoV-2 respiratory symptoms. 0 indicates concomitant onset of neurological symptoms.

Ref. reference, *NA* not-available, *M* male, *F* female, (+) Positive, *TVC* Time between reported viral syndrome and confirmed COVID-19, *TVN* Time between reported viral syndrome and onset of neurological symptoms (days), *ADC* apparent diffusion coefficient, *ADEM* acute demyelinating encephalomyelitis, *AHLE* acute haemorrhagic leukoencephalitis, *AAbs* Autoantibodies, *IM* inflammatory markers, *GTCS* generalized tonic–clonic seizure, *IVIG* intravenous immunoglobulin, *IVMP* intravenous methylprednisolone,*LETM*longitudinally extensive transverse myelitis, *LOC* loss of consciousness, *LP* lumbar puncture, *N* normal, *PE* plasma exchange, *WNV* West Nile virus, *SWI* susceptibility-weighted image

Table 2 Clinical and demographic characteristics of the 48 patients with SARS-CoV-2 and ADEM/AHLE

Characteristic	Value ($n=48$)
ADEM—no. (%)	34 (71)
AHLE—no. (%)	14 (29)
Median age (range)—yr	43.7 (1.4–71)
Male sex—no. (%)	26 (54.2)
Famale sex—o. (%)	18 (37.5)
Adult—no./total no. (%)	36/45 (80)
Children—o./total no. (%)	9/45 (20)
Country—no./total no. (%)	
USA	13/48 (27)
UK	12/48 (25)
Italy	5/48 (10)
Brazil	4/48 (8)
India	3/48 (7)
Iran	3/48 (6)
Singapore	3/48 (6)
France	3/48 (6)
Canda	1/48 (2)
Greece	1/48 (2)
General symptoms before the onset of the ADEM—no./total no. (%)	35/48 (73)
Cough	13/35 (37)
Fever	23/35 (66)
Dyspnoea/hypoxia/Short of breath	11/35 (31)
Myalgia	5/35 (14)
Lethargy	3/35 (9)
Fatigue	4/35 (11)
Anosmia/hyposmia	6/35 (17)
Rash	2/35 (6)
SARS-CoV-2 infection diagnostic categor —no./total no. (%)	31/48 (64.5)
Nasopharyngeal swab/PT-PCR	23/31 (74)
Positive	18/23(78)
Negative	5/23 (21)
Sputum/PT-PCR	1/31 (3)
SARS-CoV-2 IgG (serum)	3/31 (10)

in 16 patients (24.4%) [8, 11, 13, 15, 18, 20, 22, 24–28]. COVID-19 symptoms began concurrent in one case [23]. The mean interval between onset of COVID-19 and ADEM symptoms in the remaining 31 patients was a mean 24.7 days (range 1–214 days).The most prominent reported clinical features are those of acute meningoencephalitis, including encephalopathy (59%), headache (15%), seizures (11%) and fever (66%) (Table 3). Other clinical manifestations at onset included sensory symptoms (11%, 5/46), hemiplegia (8.7%, 4/46),leg weakness (8%, 3/46), tetraparesis (4%, 2/46), arm weakness (4%, 2/46),facial weakness (4%, 2/46), hyporeflexia or areflexia (4%, 2/46).Gait ataxia is the most another commonly reported clinical features of SARS-CoV-2-related ADEM (13%, 6/46).

Results of CSF, biochemical, and neuroimaging investigations

CSF was examined in all (81.0%, 39/48) except six of the patients [11, 13, 29–31], and was not reported in three patients [26, 27]. Increased protein level were present in 15 patients (38%, 15/39), and normal protein level were present in 13 patients (33%, 13/39) with a median CSF protein of 376.0 mg/dl (min: 15, max: 2340 mg/dl) (Tables 1 and 3).The pleocytosis was evident in 12/31 cases (39%). The search for the viral RNA in CSF was positive in three patients (14.0%, 3/22) [24, 32, 33]out of all 22 cases in whom was done. AQP4 antibodies were tested in 19 patients, being negative in all. MOG antibodies were searched in 19 patients, being positive in one case [34]. Furthermore, CSF SARS-CoV-2 RNA was not reported or not calculable in 23 patients.

In 44 patients (92%, 44/48), head MRI was performed. The deep white matter is the most frequently involved (43%, 19/44), followed by corpus callosum (32%, 14/44) and subcortical white matter (23%, 10/44). Brainstem is another frequently involved (20%, 9/44). The brain lesions occurring in SARS-CoV-2-ADEM involve the periventricular white matter relatively frequently (18%, 8/44). The cerebellum is less frequently involved (14%, 6/44) (Tables 1 and 2), often symmetrically [9], while deep gray matter are present to a lesser extent (5%, 2/39). Contrast enhancement was reported in 17 cases (89%, 17/19). Spinal MRI scans were performed in a minority of the patients (12.5%, 6/48).

Management of SARS-CoV-2-ADEM and patient outcomes

All the patients except ten [12, 21, 22, 24, 26, 27, 30] were treated with specific treatment (79.0%, 38/48). 23 patients were treated with intravenous methylprednisolone (IVMP) (61%, 23/38) 0.13 patients were treated with intravenous immunoglobulin (IVIg) (34%, 13/38); and five received plasma exchange (13%, 5/38). Eleven received combined IVMP and IVIg (29%, 11/38). 31 (64%) of patients had a poor outcome on discharge from hospital. Five (10.4%) patients died in hospital.

Discussion

In current analysis, we identified and reviewed a total of 48 cases of ADEM with COVID-19 from 37 studies identified worldwide through different case series and reports. The cases were categorized into two groups for further statistical

Table 3 Clinical and Laboratory Findings in the 48 Patients with SARS-CoV-2 and ADEM/AHLE

Characteristic	Value ($n=48$)
Subtype of ADEM—no./total no. (%)	
ADEM	34/48 (71)
AHLE	14/48 (29)
Duration, median (range), days	37 (84)
Time between reported viral syndrome and onset of neurological symptoms ($n=31$)	25 (1–214)
Signs and symptoms of neurologic illness—no./total no. (%)	46/48 (96)
Low conscious level	27/46 (59)
Headache	7/46 (15)
Gait ataxia	6 /46 (13)
Seizure	5 /46 (11)
Abnormal sensation	5/46 (11)
Hemiplegia	4/46 (9)
Leg weakness	3/46 (7)
Urinary disturbance	4/46 (9)
Tetraparesis	2/46 (4)
Facial weakness	2 /46 (4)
Arm weakness	2/46 (4)
Hyporeflexia or areflexia	2/46 (4)
Facial paresthesia	1/46 (2)
Results of CSF analysis—no./total no. (%)	39/48 (81)
Increased protein level—no./total no. (%)	15/39 (38)
Nromal protein level—no./total no. (%)	13/39 (33)
Proteins (mg/dL) (range)	376 (15–2340)
Increased white-cell count level—no./total no. (%)	12/31 (39)
Normal white-cell count level—no./total no. (%)	18/31 (58)
PCR for SARS-CoV-2 on CSF (Positive)—no./total no. (%)	3/22 (14)
PCR for SARS-CoV-2 on CSF (Negative)—no./total no. (%)	19/22 (86)
AQP4 Antibodies	
Negative—no./total no. (%)	13/19 (68)
Positive—no./total no. (%)	0/19 (0)
MOG Antibodies	
Negative—no./total no. (%)	12/19 (63)
Positive—no./total no. (%)	1/19 (5)
MRI abnormalities	
Brain—no./total no. (%)	44/48(92)
Deep white matter	19/44 (43)
Subcortical white matter	10/44 (23)
Periventricular white matter	8/44 (18)
Corpus callosum	14/44 (32)
Deep gray matter	2/44 (5)
Brainstem	9/44 (20)
Cerebellum	6/44 (14)
Microhemorrhage	12/44 (27)
Spinal cord—no./total no. (%)	6/10 (60)
Cervical	6/10 (60)
Thoracic	1/10 (10)
Gadolinium enhancement— no./total no. (%)	17/19 (89)
Treatment modality of SARS-CoV-2-ADEM/AHLE	
IVMP— no./total no. (%)	23/38 (61)
IVIg—no./total no. (%)	13/38 (34)
PE—no./total no. (%)	5/38 (13)

Table 3 (continued)

Characteristic	Value ($n=48$)
IVIg + IVMP—no./total no. (%)	11/38 (29)
IVIg + IVMP + PE—no./total no. (%)	4/38 (11)
Not-available—no./total no. (%)	10/48 (21)
Outcome and prognosis	
Good—no. (%)	7/48 (15)
Poor—no. (%)	31/48 (64)
Dead— no. (%)	5/48 (10.4)
Not-available—no./total no. (%)	11/48 (23)

PE plasma exchange; *IVIg* intravenous immunoglobulin

analysis, "ADEM" versus "AHLE". The novel addition to our review was for the first time reviewed clinical features, results of diagnostic investigations, and outcome in 48 cases of COVID-19-associated ADEM spectrum.

Classic ADEM is an immune-mediated, inflammatory demyelinating disease of the central nervous system (CNS) that usually affects children and young adults after an infection or vaccination [9, 35]. The mean age of onset of classic ADEM is between 3.6 and 7 years [36]. We found significant differences between COVID-19-associated ADEM and classic ADEM in age at onset; the mean age for COVID-19-associated ADEM was 44 years. In the present study, mean age at onset in patients with COVID-19-associated ADEM largely older that of classic ADEM subjects, indicating that an adult age range might be affected (Table 4). Although ADEM has no obvious gender predominance, a slight male prevalence is reported in a few paediatric series [37]. We found a slightly higher prevalence of COVID-19-associated ADEM in males compared to females (male:female ratio is 1.4:1), which is consistent with the literature in general.

In the typical presentation of ADEM, neurological symptoms develop 7–14 days following an infection and may involve headache, emesis, meningismus, and alterations in behaviour and level of alertness s [35]. Common neurological exam findings include altered mental status, ataxia, and extremity weakness. A latency period between the onset of the ADEM symptoms and onset of COVID-19 has been reported in different papers (Table 1). The present cohort has shown an average latency of 25 days from the onset of COVID symptoms to the presentation of ADEM. The mean latency ranged between a duration of 0 to 214 days. We did not found significant differences between COVID-19-associated ADEM vs. classic ADEM in neurological symptoms and signs at onset.

The diagnosis of ADEM is based on a combination of clinical features, supported by MRI findings. Brain MRI T2-weighted and fluid-attenuated inversion recovery (FLAIR) images typically demonstrate multiple hyperintense bilateral, asymmetric patchy and poorly marginated lesions [37], which typically involve the subcortical and deep white matter [9, 37–40]. The brain lesions occurring in ADEM more frequently affect the deep gray matter and cortex [41] and less frequently involve the periventricular white matter [42] and corpus callosum [41].The deep gray matter is frequently involved (40–60%), often symmetrically [43]. In our population, most common brain lesions resemble those of classic ADEM, i.e. the distribution of lesions more frequently affect subcortical and deep white matter (Tables 3 and 4). Compared to the lesions observed in classic ADEM, the brain lesions occurring in COVID-19-associated ADEM more frequently involve the periventricular white matter (18%) and corpus callosum (32%), and less frequently affect the deep gray matter (5% vs. 40–60%). The reported frequency of gadolinium-enhancing lesions in classic ADEM is highly variable between studies (10–95%) [43], largely overlapping with the percentages in our cohort (89%).

CSF examination reveals inflammatory findings in most ADEM patients [44], consisting of elevated protein levels (15–60%) and lymphocytic pleocytosis (25–65%). In our population, increased protein level was present in 38% patients, and normal protein level were present in 33% patients. The pleocytosis was evident in 39% cases. These results indicated that we did not found an obvious discrepancy concerning CSF findings between classic ADEM and COVID-19-associated ADEM. First-line acute treatment of classic ADEM generally consists of IVMP at a dose of 30 mg/kg/day (maximum 1000 mg/day) for 3–5 days, followed by an oral prednisone taper for 4–6 weeks [9]. 61% patients were treated with IVMP, which overlapping with the percentages in classic ADEM [43]. The use of IVIg is usually considered a second-line treatment option for ADEM patients who do not respond to or who deteriorate after intravenous steroids, which has proven effective in about 40–50% of steroid-resistant patients [43]. 34% of patients were treated with IVIg, indicating that a high percentage use of IVIg for the treatment of COVID-19-associated ADEM.

Patients with classic ADEM usually have a good outcome with a complete recovery. The outcome seems to be better in children than in young adults, especially for the disease

Table 4 Comparation of clinical characteristics of SARS-CoV-2-ADEM with typical ADEM

Characteristic	SARS-CoV-2-ADEM	Typical ADEM
Onset age preponderance	Predominantly adult, median age 44 yr (1.4–71 yr)	More commonly affects children
Male:female ratio	1.4:1	1:1
Prodromal symptoms	Fever, cough, dyspnoea, anosmia/hyposmia, myalgia, fatigue	Fever, headache, malaise, nausea, and vomiting
Duration(days)	25	7–14
Symptoms/signs of acute phase		
Encephalopathy	59%	100% [45]
Seizures	11%	12–50% [45]; 13–46% [43]
Cranial nerve deficits	15%	18–39% [45]
Pyramidal signs	5%	18–60% [45]
Sensory deficits	13%	0–9% [45]; 28–65% [43]
Cerebellar signs/ataxia	15%	36–47% [45]
Urinary disturbance	8%	6–25% [45]
MRI brain		
Brain—no./total no. (%)	92%	60–100% [43]
Deep/Subcortical white matter	43%/23%	Typically, lesions occur in the deep and subcortical white matter while sparing periventricular white matter
Periventricular white matter	18%	Less frequently involve the periventricular white matter [42], and more frequently affect the deep gray matter and cortex [42]
Corpus callosum	32%	Less frequently involve corpus callosum [41]
Deep gray matter	5%	40–60%,often symmetrically [43]
Brainstem	20%	17–63% [43]
Cerebellum	14%	27–41% [43]
Microhemorrhage	27%	Not reported
Gadolinium-enhancing lesions	89%	0–95% [43]
Spinal cord involvement	60%	10–100% [43]
Outcome and prognosis	64% poor with a dead rate of 10%	Good: usually have a good outcome with a complete recovery. The outcome seems to be better in children than in young adults
CSF analysis		
Increased protein level	38%	16–97% [43]
Increased white-cell count level	39%	25–65% [43]
OB(+)	35%	~29% [43]
Steroid treatment	61%	46–95% [43]
IVIG	34%	Second-line treatment option for ADEM patients who do not respond to or who deteriorate after intravenous steroids [61]. has proven effective in about 40–50% of steroid-resistant patients [43]
PE	13%	Occasionally been used as a second-line therapy in severe cases. The effectiveness of PE is estimated at around 40% [62], which is comparable to the effectiveness of IVIg
ICU management	50%	15% [63]
Mortality	10%	~5% [43]
Full recovery	15%	47–89% [43]

course, recovery, and mean duration of hospitalization [45]. Unlike typical ADEM, most of COVID-19-related ADEM have a relatively poor outcome, with mortality rates of 10% (Table 4). In analogy to classic ADEM, only 15% COVID-19-associated ADEM subjects have a full recovery (15% VS 47–89%). In this regard, cases with COVID-19-associated ADEM need a higher rate of ICU management.

Our study had several strengths. Major strengths of our review are the inclusion of a high number of patients, together with an in-depth analysis of the clinical features of COVID-19-associated ADEM for the first time. This is among the first studies focused on comparing the clinical presentation, management and outcomes in COVID-19 patients who were diagnosed with ADEM, highlighting on

differences with classic ADEM. Our study should be considered in light of several limitations. First, cases included in this review were identified through a comprehensive search of databases using a systematic search strategy. There is a possibility of missing out new upcoming studies because of the evolving nature of the COVID-19 pandemic. Second limitation associated with this systematic review is the concern notably restriction of the search to the PubMed and Web of Science, inclusion of articles published only in English, and heterogeneity of included studies.

Conclusion

In conclusion, based on the systematic review of 48 cases, we showed the clinical picture of COVID-19-associated ADEM, and revealed that although rare, ADEM can be associated with SARS-CoV-2 infection. SARS-CoV-2-ADEM seems to share most features of classic ADEM, with a moderate discrepancies from the classical ADEM. In analogy to classic ADEM, COVID-19-associated ADEM have a more longer duration between the onset of the antecedent infective symptoms and the start of ADEM symptoms, the older age distribution of the patients, relatively poor outcome, a lower full recovery rate, a more frequently brain lesions involved the periventricular white matter and corpus callosum, and less frequently affected the deep gray matter.

Acknowledgements This work was supported in part by the National Natural Science Foundation of China (61971011), Science Foundation of AMHT (2020YK02), Science Foundation of CASIC (2020-LCYL-009), Science Foundation of ASCH(YN202104), Cultivation plan of Scientific Research Committee for health development of Haidian District of Beijing (HP2021-19-50701), Natural Science Foundation of Inner Mongolia Autonomous Region(IMAR) (2018MS08046; 2020MS08175; 2021MS08131), and Program for Young Talents of Science and Technology in Universities of IMAR (NJYT-17-B23).

Author contributions Conceptualization: all authors; methodology, formal analysis, and investigation: YW HW; writing-original draft preparation: YW and HW; writing-review and editing: all authors; supervision: YW and Hongquan Wang.

Declarations

Conflicts of interest The authors declare no financial or other conflicts of interest.

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