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

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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].
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 SARS-CoV-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 | MRI results | Diagnosis | Treatment | Outcome status |
|----|-----|---------|-------------------------|-----------------------|----------------------------|------------|--------------|-------------|------------|------------|----------------|
| 1  | [46] | 46/M    | Fever, breathlessness (+) RT-PCR/NPS | Confusion, Left hemiplegia | CSF showed lymphocytic pleocytosis with increased protein, glucose NA** | 35 | 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 microhemorrhages | AHLE | IVMP 1 gm for 5 day | Deceased |
| 2  | [11] | ? NA    | NA | NA | None | NA | Not done | NA | Multifocal haemorrhagic lesions predominantly in the white matter | AHLE | Corticosteroid + IVIG | NA |
| 3  | [11] | ? NA    | 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 | 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; OR(-);NMDA Ab (-); PCR assay for SARS CoV-2(-) | 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 (CSF:5.5 mM↑); N; CSF culture and viral PCR negative including SARS CoV-2 | 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 |
| 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 tonic-clonic seizures; headache; low conscious level; left pupil unreactive at nadir; left extensor plantar | 10         | Protein(2.34 g/L↑); 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 lumbar 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          | 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 hemiconractomy; 1 g IVMP 5 days, then oral prednisolone; IVIG | Incomplete recovery; improving |
| 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 plantar | 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 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 white matter; 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 parietal lobe, 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 |
| 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 | 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 | Time 1: 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 |
| 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 (mm³); OB(+) | Neuronal Abs to AQP4 and MOG (−) | Brain: revealed multiple lesions with simultaneous enhancement | ADEM | 1 mg/kg/die IVMP 5 days followed by rituximab 1 g IV | Discharged with relative recovery after 7 days |
| 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                    | 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 paraparesis of the lower limbs, urinary retention, increased paraparesis severity and weakness in the upper limbs; he also became drowsy | 214 | CSF WBC 150/mm³; 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 |
| 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 | [89] | 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 | 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 deficit on her right leg, pyramidal sign on her left leg, mild behavioral abnormalities, headache | 14 | CSF cell count 22μL 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 | CSF examination revealed WBC: 0/ mm³ (normal range: 0–5/mm³), 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 | Decreased responsiveness | CSF WBC: 1/ mm³; protein 62 mg/dl, **glucose 56 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 |
| 26 | [30] | 71/M | NA | Respiratory failure | Not done | Not done | 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 | Deceased | Transferred to rehabilitation without sensorimotor deficits |
| 27 | [15] | 54/F | Fever and progressive dyspnoea | RT-PCR for SARS-CoV-2 was positive | Unconscious | Not done | Brain: periventricular and juxta cortical hyperintense; Lesions with associated with Gad enhancement; No hemorrhage Spine: hyper intense lesions throughout the cervical and thoracic spinal cord, no abnormal enhancement | ADEM | IVMP and IVIG | Partial recovery; discharged to an acute rehabilitation facility |
| 28 | [23] | 44/M | None (+) RT-PCR/ NPS; Urinary retention, bilateral lower extremity weakness and numbness | CSF WBC: 6/ mm³; protein 36 mg/dl, OB(−) | No serum Abs or inflammatory markers available | Brain: periventricular and juxta cortical hyperintense; Lesions with associated with Gad enhancement; No hemorrhage Spine: hyper intense lesions throughout the cervical and thoracic spinal cord, no abnormal enhancement | ADEM | IVMP and IVIG | Partial recovery; discharged to an acute rehabilitation facility |
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 punctate pattern in the cerebellum. Microhemorrhage of bilateral globus pallidus | ADEM | NA | NA |
| 31 | [30] | 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/mm³ 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 |
| 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 | 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/μL, red blood cells of 6 RBC/μL, 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) | 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 fluid blood 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 | Brain: extensive bilateral parietal and occipital intraparenchymal hemorrhage, with surrounding edema 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 | TVN (days) | CSF findings | MRI results | Diagnosis | Treatment | Outcome status |
|----|------|---------|------------------------|-----------------------|------------|--------------|-------------|-----------|-----------|----------------|
| 36 | [53] | 57/M    | Fever, dry cough (+)   | (+) RT-PCR/ NPS       | 3          | Flaccid and unconscious for more than 48 h until we noticed bilateral extension posturing on painful stimuli | | | | Recovered |
| 37 | [54] | 33/M    | Fever                 | (+) RT-PCR/ NPS       | 2          | 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 | | | | 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 pseudonodular 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/mm³, 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 | 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/mm³, protein 55 mg/dl, **glucose 112 mg/dl, OB absent | NA | Brain MRI: hyperintensity and restriction diffusion in deep cerebrospinal white matter and bilateral cerebellum. No hemorrhage | 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/ mm³, 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 | ADEM | IVMP 1gm for 5 days and IVIG and then PE | Partial recovery |
| No | Ref | Age/sex | Initial viral syndrome | Diagnosis of COVID-19 | Neurological symptoms/signs | TVN (days) | CSF findings | MRI results | Diagnosis | Treatment | Outcome status |
|----|-----|---------|------------------------|-----------------------|-----------------------------|-----------|--------------|-------------|------------|-----------|----------------|
| 42 | [57] | 51/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 edema 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     | 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.
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. (%)                                         |                |
| Increased protein level—no./total no. (%)                                        | 15/39 (38)     |
| Normal 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)      |
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 [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% of patients, and normal protein level were present in 33% of 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 PE plasma exchange; IVIg intravenous immunoglobulin

| 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) |
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

| 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] |
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, the extent to which the findings from this review can be applied to the general ADEM population is uncertain due to limitations in the included studies. In analogy to classic ADEM, COVID-19-associated ADEM have a more heterogeneous nature, where symptoms, treatment, and outcomes vary depending on the individual patient.

**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 discrepancy from the classical ADEM. In analogy to classic ADEM, COVID-19-associated ADEM have a more duration between the onset of the antecedent infective symptoms and the start of ADEM symptoms, the older age distribution of cases, and the more frequently affected the deep gray matter. The involvement of the periventricular white matter and corpus callosum, and less frequently affected the deep gray matter.

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**Declarations**

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

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