COVID-19 and neuroinflammation: a literature review of relevant neuroimaging and CSF markers in central nervous system inflammatory disorders from SARS-COV2

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Abstract

Background The literature on neurological manifestations in COVID-19 patients has been rapidly increasing with the pandemic. However, data on CNS inflammatory disorders in COVID-19 are still evolving. We performed a literature review of CNS inflammatory disorders associated with coronavirus disease-2019 (COVID-19).

Methods We screened all articles resulting from a search of PubMed, Google Scholar and Scopus, using the keywords; “SARS-CoV-2 and neurological complication”, “SARS-CoV-2 and CNS Complication” looking for reports of transverse myelitis, longitudinally extensive transverse myelitis, neuromyelitis optica, myelitis, Myelin Oligodendrocyte Glycoprotein Antibody Disorder (MOGAD), Acute Disseminated Encephalomyelitis (ADEM), Acute Hemorrhagic Necrotizing Encephalitis/Acute Hemorrhagic Leukoencephalitis (AHNE/AHLE), Cytotoxic lesion of the Corpus Callosum/Mild Encephalopathy Reversible Splenium Lesion(CLOCC/MERS) and Optic neuritis published between December 01, 2019 and March 15, 2021.

Results Our literature search revealed 43 patients meeting the diagnosis of myelitis, including Transverse Myelitis, ADEM, AHNE/AHLE or CLOCC/MERS and Optic neuritis published between December 01, 2019 and March 15, 2021. Acute myelitis was most commonly associated with non-severe COVID-19 and all reported cases of AHNE/AHLE had severe COVID-19 infection. Based on IDSA/ATS criteria of either requiring vasopressor for septic shock or mechanical ventilation, 49% (n = 18) patients were considered to have a severe COVID infection. There were 7 (n = 19%) fatalities.

Conclusion To our knowledge, this is among the first reviews that includes the clinical features, neuroimaging, CSF findings and outcomes in COVID-19-associated CNS inflammatory disorders. Our observational review study reveals that although rare, myelitis, ADEM, AHNE and CLOCC can be associated with COVID-19 infection. Further studies using MRI imaging and CSF analysis in early diagnosis and intervention of these disorders are warranted.

Keywords COVID-19 · SARS-CoV-2 · ADEM · AHNE · Myelitis
Abbreviations

COVID-19  Coronavirus infectious disease-2019
nCov  Novel coronavirus
SARS-CoV-2  Severe acute respiratory distress syndrome coronavirus 2
MERS  Middle-east respiratory syndrome
Cerebrospinal fluid  CSF
CNS  Central nervous system
PNS  Peripheral nervous system
RT-PCR  Reverse transcription polymerase chain reaction
IDSA/ATS  Infectious Diseases Society of America/American Thoracic Society
AHNE  Acute hemorrhagic necrotizing encephalitis
AHLE  Acute hemorrhagic leukoencephalitis
ADEM  Acute disseminated encephalomyelitis
LETM  Longitudinal extensive transverse myelitis
MRI  Magnetic resonance imaging
CIS  Clinical isolated syndrome
CLOCC  Cytotoxic lesion of the corpus callosum
MOG  Myelin oligodendrocyte glycoprotein
MERS  Mild encephalopathy reversible splenium lesion
MOGAD  Myelin oligodendrocyte glycoprotein antibody disorder
NMO  Neuromyelitis optica
AQP4  Aquaporin 4
IVIG  Intravenous immunoglobulin
PLEX  Plasma exchange/plasmapheresis
IVMP  Intravenous methylprednisolone
Hcq  Hydroxychloroquine

Introduction

The worldwide dashboard of WHO registered more than 97 million confirmed cases and 2.1 million deaths due to COVID-19 as of January 24, 2021, a year after very first identified case [1]. Though it most often presents with symptoms and complications referable the respiratory system, reports of neurological manifestations continue to grow.

Several studies have reported neurological complications patients with COVID-19 [2–4]. Reports from Wuhan, China describe neurological complications frequently in patients with COVID-19. Those studies showed that 36.4% patients had neurological symptoms including acute cerebrovascular events, impaired consciousness and dizziness [4]. Another study showed one-third of patients with COVID-19 had neurological complications [5]. Anosmia and dysgeusia are also common neurological manifestation of COVID patients and is thought to be mediated by viral invasion of the olfactory neuroepithelium and cellular distribution of taste cells via ACE2 receptor [6, 7].

A prospective study by Frontera et al., detected neurologic disorders in 13.5% of patients with COVID-19 and indicated that neurological symptoms were associated with decreased likelihood of discharge to home and increased risk of in-hospital mortality [8]. These manifestations appear to be an amalgamation of systemic disease complications including systemic inflammatory mediators, nervous system and vasculature inflammation, or the effects of direct viral invasion. The neuroinflammation associated with COVID-19 could be either from direct viral neuroinvasion leading to inflammation and cytokine release or from delayed autoimmune dysregulation or molecular mimicry leading to autoimmune/inflammatory syndromes that is parainfectious/postinfectious [9–11]. Currently, there is insufficient knowledge about the effects of SARS-CoV-2 on central nervous system (CNS) inflammation involving brain, optic nerve and spinal cord. In this review, we have retrospectively analyzed the various CNS inflammatory manifestations of COVID-19 reported to date. This includes acute myelitis, acute disseminated Encephalomyelitis (ADEM), acute hemorrhagic necrotizing encephalitis (AHNE), and cytotoxic lesion of the corpus callosum (CLOCC). We also discuss the relevant neuroimaging and cerebrospinal fluid markers (CSF) associated with CNS inflammation and COVID-19.

Methods

Study design

We conducted a thorough literature review in March 2021 using the terms “SARS-CoV-2 and neurological complication”, “SARS-CoV-2 and CNS Demyelination” for reports of myelitis, transverse myelitis (TM), longitudinally extensive transverse myelitis (LETM), neuromyelitis optica (and spectrum disorder; NMO or NMOSD), myelitis, Acute Disseminated Encephalomyelitis (ADEM), Acute Hemorrhagic Necrotizing Encephalitis/Acute Hemorrhagic Leukoencephalitis (AHNE/AHLE), Cytotoxic lesion of the Corpus Callosum (CLOCC) and Optic neuritis (ON).

We searched PubMed, Google Scholar and Scopus databases for identifying case series and case reports published between December 01, 2019 to March 15, 2021. Review articles and consensus statements were excluded from the analysis. We used the preferred reporting items for systematic reviews and meta-analyses (PRISMA) for the display of inclusions and exclusions [12]. Based on our search criteria,
we found articles from PubMed \((n = 189)\), Google Scholar \((n = 1201)\) and Scopus \((n = 55)\). Amongst all, 424 cases were identified as duplicates. Finally, we screened 1021 articles for title and abstracts, and reviewed full-text literatures in accordance with our study objective after removing 918 articles which were either missing clinical information or did not meet our study objective and 70 based on exclusion criteria (Fig. 1). The review was limited to articles in English.

We included 33 publications and 43 cases for review for observational analysis that met our below-mentioned inclusion criteria, out of which 15 were of acute myelitis including transverse myelitis, 10 cases of ADEM, 6 cases of CLOCC, 9 cases of AHNE/AHLE. Apart from these one case of myelitis, considered by the authors to be Clinically isolated syndrome (CIS), and two cases had MOG mediated demyelinating disease. One MOGAD patient presented with optic neuritis and one with optic neuritis and myelitis. We excluded statistical analysis of MOGAD disorders as a separate entity as well as one CIS case due to low sample size although we describe these cases in “Discussion”. Therefore 40 cases of COVID-19 and CNS inflammatory disorder were reviewed for descriptive quantitative analysis.

**Inclusion criteria**

The inclusion criteria for the published studies included: (1) Patient age ≥ 18 years; (2) COVID-19 diagnosis confirmed by RT-PCR nasopharyngeal or serum antibody test; (3) CSF study findings in COVID-19 and MRI imaging performed; (4) CNS specific disorders including ADEM, AHNE/AHLE,
CLOCC, acute myelitis including transverse myelitis and longitudinally extensive myelitis and ON.

**Exclusion criteria**

The exclusion criteria from the published studies include: (1) Patient age < 18 years; (2) Duplicate articles which involved repetition of cases (3) Articles in languages other than English; (4) Studies that had no available individual patient’s data; (5) Editorials; (6) Articles and reported literature on CNS and peripheral nervous system (PNS) disorders other than acute myelitis, ADEM, AHNE/AHLE, CLOCC and ON.

**Quality assessment**

The critical appraisal checklist for case reports provided by the Joanna Briggs Institute (JBI) was used to perform assessment of overall quality of case series and case reports [13].

**Data acquisition**

Two reviewers independently performed the literature search. From the selected articles, we extracted the following data for our analysis: study type, date of publication, age, gender, clinical presentation of COVID-19, diagnostic tests for SARS-CoV-2 infection including RT-PCR nasopharyngeal, CSF SARS-CoV-2 RT-PCR and serum antibodies, CSF markers including cell count, protein, severity of COVID-19 (based on IDSA/ATS criteria), treatment, neuroimaging including MRI findings. Severity of COVID-19 was measured using IDSA/ATS criteria [14].

**Data analysis**

We performed demographic analysis including age, gender, severity of COVID-19 cases and outcome of the cases where provided. Pooled descriptive analyses were conducted to assess differences in these markers among groups including severe vs non-severe, fatal vs non-fatal outcomes.

**Results**

Based on our literature search, we found a total of 40 cases with COVID-19 diagnosed with various CNS inflammatory disorders for the descriptive quantitative analysis. These included 35 case reports and 2 case series published from 16 different countries. Of the 40 cases, 14 were from the USA, 4 cases from France, 3 cases from UK, 2 each from the Italy, Qatar, India, Belgium, Iran and one each from UAE, Australia, Brazil, Germany, Spain, Moldova, Japan, Singapore and Switzerland. Summarized information of these cases is presented in Tables 1, 2, 3 and 4.

The demographic characteristics including severity of COVID-19, outcomes, treatment, MRI abnormality is summarized in Table 5. The main cohorts of CNS inflammatory disorder include acute myelitis including transverse myelitis (TM) /LETM and optic neuritis, ADEM including AHLE/ANHE and CLOCC. Out of the entire cohort, there were 14 patients (35%) with age < 50 years, and the remaining 26 patients (65%) were aged > 50 years. The mean age was 50.7 (SD ± 15.1) years, median age was 52.5 years, with age ranging from 21 to 75 years. Amongst the total of 40 patients in the the statistical analysis, 27 patients were male (68%) and the other 13 were female (32%). Of the 40 cases, 37% (n = 15) had transverse myelitis, 25% (n = 10) ADEM, 15% (n = 6) AHNE/AHLE, and 23% (n = 9) CLOCC/MERS. Based on IDSA/ATS criteria of either requiring vasopressor for septic shock or mechanical ventilation, 49% (n = 18) of patients were considered to have had a severe COVID infection. In our review, 19% (n = 7) were fatal (Table 5).

In terms of medications received, 71% of the patients (n = 25) were given intravenous methylprednisolone (IV MP), 26% (n = 9) were given intravenous immunoglobulin G (IVIG), while 23% of the patients (n = 8) received plasma exchange/plasmapheresis (PLEX) for management of various neurological inflammatory disorders. For management for COVID-19, 6% of the patients (n = 2) were given azithromycin, 9% (n = 3) were given hydroxychloroquine (HCQ), while 14% (n = 5) received a combination of HCQ and azithromycin. No patient received tocilizumab. Abnormal contrast enhancement in MRI imaging of the spine and brain was reported in 10% (n = 4) and 23% (n = 9) respectively (Table 5).

The comparisons of severity, outcomes, and CNS manifestations (acute myelitis, ADEM, AHNE/AHLE, and CLOCC/MERS) against age, gender, CSF protein, and elevated cell count are shown in Table 6. However, a statistically significant difference was observed in the CSF cell count amongst patients with a non-severe compared to patients with severe COVID-19 infection. Seventy nine percent (11/14) of the reported elevated cell counts were in patients with a non-severe as compared to patients with severe COVID-19 infection where only 21% of cases had elevated cell counts (3/14) (p = 0.03), whereas 71% of those with transverse myelitis have elevated cell count. Elevation of the CSF protein levels among the various pathologies also showed a difference that was borderline significant. No significant differences were seen in other variables with regards to age, gender, and CSF characteristics (Table 6).
Table 1  Study Origin, Demographics, CSF, MRI findings, severity and outcomes in COVID-19 and acute transverse myelitis and MOGAD myelitis disorder

| Author/country | Patient age/ gender | Time duration from COVID-19 to neurological symptom onset | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes | *Severity based on IDSA/ATS |
|----------------|---------------------|---------------------------------------------------------|--------------|---------------------------|--------------|-------------------------|-------------|-----------|------------|----------|----------------------------|
| Sarma D et.al. /USA | 28y/F | 7 days | None | Paresthesias in all extremities, as well as numbness to the tip of her tongue and urinary retention | CSF WBC 125/mm³, mononuclear cells, total protein 60 mg/dl, CSF glucose normal, ** | NA | MRI with and without contrast of the cervical, thoracic, and lumbar spine showed elongated signal changes throughout the spinal cord to the conus medullaris. Reported abnormal enhancement | Acute Transverse myelitis | Prednisone and PLEX 2 session | Recovered | Non-Severe |
| Chow C.C.N. et.al/Australia | 60y/M | 16 days | HTN | Bilateral lower limb weakness, urinary retention and constipation | CSF WBC <5/ mm³, protein 79 mg/dl, glucose 58 mg/dl ** | Serum AQP4, MOG Ab negative | MRI scan of thoracic spine showed hyperintense signal from T7 to T10, without abnormal enhancement | Acute transverse myelitis | IVMP 1 g / day for 3 days | Recovered | Non-severe |
| Chakraborty U et. al. / India | 59y/F | 4 days | Obesity | Ascending flaccid paraplegia along with retention of urine and constipation | CSF WBC <5/ mm³, protein 72 mg/dl, glucose 75 mg/dl ** | NA | MRI thoracic spine revealed hyperintensity signal at T6–T7. Post contrast study not reported | Acute transverse myelitis | IVMP 1 g/day | Deceased | Severe |
Table 1 (continued)

| Author/country | Patient age/gender | Time duration from COVID-19 to neurological symptom onset | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes |
|----------------|---------------------|----------------------------------------------------------|--------------|--------------------------|--------------|------------------------|--------------|-----------|------------|----------|
| Valiuddin H et al. /USA | 61y/F | 7 days | NA | Paresthesias over hand and feet followed by severe weakness in lower extremities and constipation and difficulty in voiding urine | CSF WBC 3/mm³, protein 87 mg/dl, glucose 73 mg/dl **, CSF MOG Ab negative, OCB absent | NA | MRI cervical spine hyperintense signal entire length of cervical spine without abnormal contrast enhancement | Acute transverse myelitis | IVMP for 5 days with no improvement and 5 sessions of PLEX | Partial recovery | Non-severe |
| Alkebti R et al./UAE | 32 y/M | 2 days | NA | Bilateral lower limb weakness, difficulty in passing urine | Not done | NA | MRI of cervical, thoracic spine extensive hyperintense signal long segment without abnormal contrast enhancement | Acute transverse myelitis | IVMP for 5 days, Acyclovir and Enoxaparin | Partial recovery | Non-severe |
| Durrani M et al./USA | 24 y/M | 9 days | None | Bilateral lower-extremity weakness, overflow urinary incontinence | CSF lymphocytic pleocytosis, normal glucose and protein levels, OCB absent | AQP4 negative | MRI showed a non-enhancing T2-weighted hyperintense signal T7-T12 level No abnormal enhancement seen | Acute Transverse myelitis | IVMP Partial recovery | Partial recovery | Non-severe |
| Author/country | Patient age/gender | Time duration from COVID-19 to neurological symptom onset | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes |
|---------------|-------------------|----------------------------------------------------------|----------------|--------------------------|---------------|---------------------|-------------|------------|------------|----------|
| Munz M et. al./Germany | 60 y/M | 8 days | HTN | Retention of urine and progressive weakness of the lower limbs | CSF WBC 16/mm³, protein 79.3 mg/dl; glucose not reported | Serum AQP4, and MOG Ab negative | MRI of the spine revealed T2 signal hyper-intensity of the thoracic spinal cord at T-9 level. No abnormal enhancement seen | Acute transverse myelitis | IVMP | Recovered | Non-severe |
| Sotoca J et.al./Spain | 69y/F | 8 days | NA | Neck pain, imbalance, motor weakness and numbness over left hand | CSF WBC 75 cells/mm³, protein 283 mg/dl, glucose normal | NA | MRI spinal cord showed T2-hyper-intensity extending from the medulla oblongata to C7 with patchy enhancement; MRI brain normal | Acute necrotizing myelitis | IVMP 1 g/day for 3 days and PLEX | Partial recovery | Non-severe |
| Zachariadis A et. al./Switzerland | 63 y/M | 12 days | Obesity | Paresthesias over feet, progressive weakness in lower extremities | CSF WBC 16/mm³, protein 57 mg/dl, glucose 62 mg/dl | Serum AQP4 and MOG Ab negative for SARS-CoV-2 positive for IgM and IgG | Brain and spinal cord MRI did not show any abnormality. A second spine MRI, 7 days after admission was again normal | Acute Transverse myelitis | IVIG 0.4 g/kg for 5 days. Followed by corticosteroid therapy IV for 5 days | Partial recovery | Non-severe |
| Author/country | Patient age/gender | Co-morbidity | Time duration from COVID-19 to neurological symptom onset | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes | *Severity based on IDSA/ATS |
|---------------|--------------------|--------------|-------------------------------------------------------------|---------------------------|--------------|------------------------|--------------|-----------|------------|----------|--------------------------------|
| Abdelhady M et al. /Qatar | 52 y/M | DM | 3 days | Inability to pass urine for 3 days, bilateral lower limb weakness | CSF lymphocytic pleocytosis and increased proteins | NA | MRI hyper-intensity signal long segment in the upper and mid-thoracic cord | Acute flaccid myelitis | Patient received steroids and acyclovir | Deceased | Severe |
| Lisnic V et al. /Moldova preprint | 27Y/M | HIV on ART | NA | Paresthesias and bilateral lower extremity weakness in addition to bladder and bowel retention | CSF normal cell and chemistry OCB absent | Serum AQP4 and MOG Ab negative | MRI revealed an extensive C4-T5 hyper-intense lesion without gadolinium enhancement | Acute transverse myelitis | IVMP 1 g/day for 5 days and PLEX | Recovered | Non-severe |
| Escobar M.M et al. /USA | 41Y/M | None | 14 days | Inability to pass urine for 2 days, bilateral lower limb paresthesia and weakness | CSF 230 cells/mm³ with 56% lymphocytes, remaining neutrophil, protein 62 mg/dl, **glucose 44 mg/dl OCB absent | Serum AQP4 and MOG Ab negative | MRI cervical and thoracic spine patchy T2 hyper-intense signals involving C2- C6 and T3-T5 levels, no abnormal enhancement, Brain MRI normal | Acute transverse myelitis | IVMP1g/day for 5 days | Recovered | Non-Severe |
| Author/coun-try | Patient age/gender | Time duration from COVID-19 to neurological symptom onset | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes | *Severity based on IDSA/ATS |
|----------------|---------------------|------------------------------------------------------------|--------------|--------------------------|--------------|--------------------------|--------------|-----------|------------|----------|----------------------------------|
| Memon A. B et al. / USA | 65/F | 2 wks | Diabetes, Obesity | Paraplegia, Constipation, Retention | CSF WBC 20 cells/mm³, lymphocytic predominant, protein 81.6 mg/dl, glucose 58 mg/dl ** | Serum AQP4 and MOG Ab negative | Initial MRI imaging of brain focal restriction right pons and spine normal Repeat MRI brain hyper-intensity in posterior limbs of internal capsules and the pons without associated enhancement. MRI cervical spine multifocal signal abnormality present C2-C6 without abnormal enhancement | Acute Transverse myelitis | IVMP for 5 days, and PLEX | Recovered | Non-sever |

**Note:** CSF WBC = cerebrospinal fluid white blood cells, MOG Ab = Myelin-Oligodendrocyte Glycoprotein Antibody, IVMP = Intravenous Immunoglobulin Mannheim, and PLEX = Plasma Exchange.
| Author/country | Patient age/gender | Time duration from COVID-19 to neurological symptom onset | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes | *Severity based on IDSA/ATS |
|---------------|-------------------|----------------------------------------------------------|--------------|--------------------------|--------------|-------------------------|--------------|-----------|------------|----------|----------------------------|
| Baghbanian S. M et. al. / Iran | 53/F | 3 days | Diabetes, HTN | Paraplegia, Constipation, Retention | CSF WBC 13 cells/mm³, lymphocytic predominant, protein normal, glucose normal ** OCB absent | Serum AQP4 and MOG Ab negative | MRI thoracic longitudinally extensive transverse myelitis in the T8-T10 cord segments. Post contrast study not reported Brain MRI was normal | Brain MRI was normal | Acute transverse myelitis | PLEX | Recovered | Non-sever |
| Fumery T et. al/Belgium | 38/F | 2wks | None | Paraplegia, Constipation, Retention | CSF WBC 337 cells/mm³, lymphocytic predominant, protein 78 mg/dl, glucose NA ** RT-PCR Negative for COVID-19 OCB absent | NA | MRI showed extensive transverse myelitis in involving predominantly the cervical and thoracic regions of the spinal cord, no abnormal enhancement Brain mri normal | Brain mri normal | Acute transverse myelitis | IVMP for 5 days | Recovered | Non-sever |

MOG Myelin Oligodendrocyte Glycoprotein, MOGAD Myelin Oligodendrocyte Glycoprotein Antibody Disorder, AQP4 Ab Aquaporin-4 antibody, IVIG Intravenous Immunoglobulin, PLEX Plasmapheresis, IVMP Intravenous Methylprednisolone, MRI Magnetic Resonance Imaging, CSF Cerebrospinal Fluid, OCB Oligoclonal bands, AQP4 aquaporin 4, MOG myelin oligodendrocyte glycoprotein

*Severity based on Infectious Diseases Society of America IDSA and American Thoracic Society ATS guidelines

**Serum glucose not reported or available
| Author/country | Patient age/gender | Time duration from COVID-19 to neurological symptom onset | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes | *Severity based On IDSA/ATS |
|--------------|-------------------|----------------------------------------------------------|--------------|--------------------------|--------------|-------------------------|-------------|-----------|------------|----------|---------------------------|
| Sawalha et al./USA | 44y/M             | 14 days                                                  | None         | Bilateral eye pain and vision loss | CSF WBC 3 cell/mm3, total protein 50 mg/dl, glucose 88 mg/dl ** | Serum AQP4 Ab negative MOG positive titer of 1:160 | Brain MRI showed enhancement in the right more than the left optic nerve no other abnormalities were noted in brain, cervical, or thoracic spine | MOGAD with optic neuritis | IVMP for 5 days | Recovered | Non-severe |
| Author/country | Patient age/gender | Time duration from COVID-19 to Neurological symptom onset | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes | *Severity based On IDSA/ATS |
|---------------|-------------------|----------------------------------------------------------|--------------|--------------------------|--------------|----------------------|-------------|-----------|------------|----------|----------------------------|
| Zhou S et.al. / USA | 26y/M | 2 days | None | Bilateral, subacute, sequential vision loss, numbness on the soles of his feet | CSF WBC 55 cells/mm3, Lymphocytic predominant, protein 31 mg/dl, glucose 57 mg/dl ** | Mirror OCB in both serum and CSF | MRI of the brain and orbits uniform enhancement and thickening of both optic nerves extending from the globe to their intracranial prechiasmal segments, MRI of the spine patchy hyperintensities in the lower cervical and upper thoracic spinal cord associated with mild gadolinium enhancement | MOGAD with Myelitis, optic neuritis | IVMP for 5 days | Partial improvement | Non-severe |
Discussion

It is now well known that infection with SARS-CoV-2 causes a multi-systemic inflammatory/immunological response. Although the exact mechanism responsible for postinfectious neurological disorders is not fully understood, the diverse neurological presentations of COVID-19 have been attributed to the underlying immunological mechanisms [10, 15, 16]. It is hypothesized that in some instances the T cell and/or antibody immune reaction against the infectious agent is directed against a CNS cell or structure because of similarities between some component of the infectious agent and a protein, lipid or carbohydrate component of the CNS. This which once was called cross-reactivity is now known as molecular mimicry. Even though a strong immune response is essential for protective adaptive immunity, a prolonged and overactive immune response contributes to pathological tissue injury [17]. This immune response has garnered attention towards a phenomenon called “cytokine storm” which is associated with high fever, respiratory distress, multi-organ failure and increased mortality over the first 2 weeks in COVID-19 patients [18, 19]. Currently, little is known about the lasting neurological effects of the “cytokine storm”. In this systematic review of 43 patients, 40 subjected to statistical analysis with a spectrum of CNS inflammatory disorders in COVID-19 patients, the most common presentation was that of acute myelitis, often transverse, followed by ADEM, CLOCC/MERS, and AHNE/AHLE.

The timing of neuroinflammatory complications relative to initial symptoms of COVID-19 infection and the rarity of detection of SARS-CoV-2 in CSF or CNS, suggest that most of these particular CNS syndromes reviewed in this paper are parainfectious/postinfectious disorders [9, 20–22]. The patients in this review exhibited a wide variety of neurological symptoms of which the most common presentation in myelitis was urinary retention and lower limb weakness [22–37]. ADEM mostly presented with decrease level of mentation [21, 38–43], CLOCC/MERS with altered sensorium [44–51] and AHNE/AHLE with reduced consciousness and coma [52–57].

In terms of diagnostic test for COVID-19 in our review all CNS inflammatory disorders were diagnosed with positive nasopharyngeal RT-PCR, whereas CSF RT-PCR SARS-CoV-2 was positive in two cases of ADEM [21, 41]. Serum SARS-CoV-2 IgG and IgM antibodies were positive in a case of TM [32]. It is unknown if the CNS disease is due to the direct invasion. CSF protein was found to be elevated in 11 cases of transverse myelitis including a case of myelitis, 5 cases of ADEM and 4 cases of AHNE/AHLE suggestive of underlying neuroinflammatory process and changes in blood brain or blood meningeal barriers. Similar to our reports, another study also showed increased CSF protein level in

### Table 2 (continued)

| Author/country | Patient age/gender | Time duration from COVID-19 to neurological symptom onset | Neurological presentation | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes |
|---------------|-------------------|----------------------------------------------------------|---------------------------|--------------|---------------------------|--------------|------------------------|-------------|-----------|------------|----------|
| Domingues, R.B et.al. / Brazil | 42y/F | 21 days | NA | Paresthesias of the left upper limb, hemithorax, and hemiface | CSF cell count 1 cell/mm³, protein 32 mg/dl, glucose 68 mg/dl | CSF RT-PCR positive for COVID-19 | MRI C spine hyperintense lesion at C-6, No abnormal enhancement | Normal MRI C spine hyperintense lesion at C-6, No abnormal enhancement | Acute myelitis/CIS | NA | Recovered | Non-severe |

### Abbreviations
- MOG: Myelin-Oligodendrocyte Glycoprotein
- AQP4: Aquaporin-4
- MOGAD: Myelin Oligodendrocyte Glycoprotein Antibody Disorder
- CIS: Clinical Isolated Syndrome
- AQP4 Ab: Aquaporin-4 antibody
- IVIG: Intravenous Immunoglobulin
- PLEX: Plasmapheresis
- IVMP: Intravenous Methylprednisolone
- MRI: Magnetic Resonance Imaging
- CSF: Cerebrospinal Fluid
- AQP4: Aquaporin-4
- MOG: Myelin Oligodendrocyte Glycoprotein
- OCB: Oligoclonal bands

*Severity based on Infectious Diseases Society of America IDSA and American Thoracic Society ATS guidelines
**Serum glucose not reported or available
| Author/country        | Patient age/gender | Time duration from COVID-19 to neurological symptom onset | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes | *Severity based on IDSA/ATS |
|----------------------|--------------------|----------------------------------------------------------|--------------|---------------------------|--------------|------------------------|--------------|-----------|------------|----------|----------------------------|
| McCuddy M et.al/USA  | 37y/F              | 22 days                                                  | DM, HTN, Obesity | Weakness upper extremity and paraplegia | CSF WBC 2/ mm³, total protein 95 mg/dl, glucose 95 mg/dl; ** OCB absent | No serum Autoantibodies or inflammatory markers available | MRI Brain 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 | Severe |
| McCuddy M et.al/USA  | 56y/M              | 20 days                                                  | DM, HTN       | Unresponsive, no spontaneous limb movement | CSF WBC 1/ mm³, protein 55 mg/dl; ** glucose 12 mg/dl; OCB absent | No serum Autoantibodies or inflammatory markers available | MRI Brain hyperintensity and restriction diffusion in deep cerebral white matter and bilateral cerebellum. No hemorrhage | ADEM | IVMP 1 gm for 5 days, IVIG and PLEX | Remains on Ventilator and had tracheostomy | Severe |
| Author/country | Patient age/gender | Time duration from COVID-19 to neurological symptom onset | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes | *Severity based on IDSA/ATS |
|----------------|-------------------|----------------------------------------------------------|--------------|--------------------------|--------------|--------------------------|--------------|-----------|------------|----------|---------------------------------|
| McCuddy M et al./USA (pt3) | 70Y/F | 16 days | DM, HTN, Obesity | Unresponsiveness | CSF WBC 0/mm³, protein 63 mg/dl, glucose 87 mg/dl | No serum Autoantibodies or inflammatory markers available | MRI Brain hyperintense and restriction diffusion in corpus callosum, cerebral deep white matter and minimum enhancement | No cord MRI done | ADEM | IVMP 1 gm for 5 days and IVIG and then PLEX | Partial recovery | Severe |
| Assunção F.B. et al./Brazil | 49y/M | NA | None | Altered consciousness after protracted sedation | CSF WBC, chemistry not reported RT-PCR negative for SARS-COV-2 | No serum Autoantibodies or inflammatory markers available | MRI Brain hyperintensity periventricular and deep white matter, splenium of the corpus callosum, and pons with restricted diffusion on DWI sequences Neither gadolinium enhancement, no hemorrhage | No cord MRI done | ADEM | NA | NA | Severe |
Table 3 (continued)

| Author/country | Patient age/ gender | Time duration from COVID-19 to neurological symptom onset | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes | *Severity based on IDSA/ATS |
|----------------|---------------------|----------------------------------------------------------|--------------|---------------------------|--------------|------------------------|-------------|-----------|------------|----------|----------------------------|
| Parsons T et. al. / USA | 51y/F | NA | NA | Decreased responsiveness | CSF WBC 1/mm³, protein 62 mg/dl, **glucose 56 mg/dl, **; RT-PCR SARS-COV-2 Negative | Mirror OCB in CSF and serum | AQP4 Ab negative | MRI Brain hyperintense lesions in deep white matter and juxta cortical white matter. These lesions show diffusion restriction on weighted imaging (DWI), mild gadolinium enhancement | No cord MRI ADEM IVMP 1gm for 5 days and IVIG | Partial recovery | Severe |
| Langley L et.al. / UK | 53y/M | 59 days | None | Agitation and global hypotonia | CSF cell count, chemistry not reported, mirror OCB in CSF and serum | No serum Autoantibodies or inflammatory markers available | MRI 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 | Severe |
| Author/country       | Patient age/gender | Time duration from COVID-19 to neurological symptom onset | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes | *Severity based on IDSA/ATS |
|---------------------|--------------------|----------------------------------------------------------|--------------|---------------------------|-------------|------------------------|--------------|-----------|------------|----------|--------------------------|
| Zoghi A et al. /Iran| 21 y/M             | 214 days                                                 | None         | Weakness and paresthesia of the lower limbs, urinary retention, increased | CSF WBC 150/ mm3 lymphocyte predominant, protein 281 mg/dl, glucose 34 mg/dl, ** RT-PCR Positive for SARS-COV-2 | AQP4 and MOG antibodies negative | MRI Brain hyperintense signal in internal capsule to the pons and corpus callosum no restriction diffusion, no enhancement. No hemorrhage Cervical and thoracic MRI showed longitudinally extensive transverse myelitis (LETM) | ADEM | PLEX | Partial recovery | Non-severe |
| Author/country | Patient age/ gender | Time duration from COVID-19 to neurological symptom onset | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes | *Severity based on IDSA/ATS |
|---------------|-------------------|---------------------------------------------------------|-------------|--------------------------|--------------|------------------------|--------------|-----------|------------|----------|-----------------------------|
| Utukuri P.S. et al. / USA | 44y/M | 0 day | none | Urinary retention, bilateral lower extremity weakness and numbness | CSF WBC 6/mm3, protein 36 mg/dl, OCB absent | No serum Autoantibodies or inflammatory markers available | MRI Brain periventricular and juxta cortical hyperintense Lesions with associated with Gad enhancement No hemorrhage MRI spine hyperintense lesions throughout the cervical and thoracic spinal cord, no abnormal enhancement | ADEM | IVMP and IVIG | Partial recovery | Non-severe | |
| Novi G et al/ Italy | 64/F | 14 days | HTN | Bilateral vision impairment associated with sensory deficit on her right leg | 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 | AQP4 and MOG Ab negative | MRI Brain evidence of 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 | Non-severe | |
| Reichard R. R et al./USA | 71/M | 11 days | CAD | Respiratory failure | Not done | Not done | Not done | ADEM | NA | Deceased | Severe | |
| Author/country | Patient age/gender | Time duration from COVID-19 to neurological symptom onset | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes | *Severity based on IDSA/ATS |
|---------------|--------------------|---------------------------------------------------------|-------------|--------------------------|-------------|------------------------|-------------|-----------|------------|----------|---------------------------|
| Poyiadji N et.al. / USA | 58y/F | 0 | None | Altered mental status | CSF cell count, chemistry not reported | No serum Autoantibodies or inflammatory markers available | MRI Brain hemorrhagic rim-enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions | AHNE IVIG NA NA |
| Dixon L et.al. / UK | 59y/F | 10 days | Aplastic anemia | Seizures and reduced level of consciousness | CSFWBC 4/mm3, protein 230 mg/dl, glucose not reported and RT-PCR Negative for SARS-COV-2 | No serum Autoantibodies or inflammatory markers available | MRI Brain stem edema with symmetrical hemorrhagic lesions in the brain stem, amygdalae, putamina, and thalamic nuclei | AHNE IV high dose dexamethasone Deceased Severe |
| Author/country | Patient age/gender | Time duration from COVID-19 to neurological symptom onset | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes | *Severity based on IDSA/ATS |
|---------------|-------------------|-----------------------------------------------------------|-------------|--------------------------|--------------|------------------------|-------------|-----------|-----------|---------|--------------------------|
| Delamarre L/et.al./France | 51y/M            | 21 days                                                     | None        | Unresponsive and rapidly comatose | CSF WBC 4/mm³, protein 180 mg/dl, glucose 86.4 mg/dl, **MOG Ab negative, RT-PCR negative for SARS-COV-2 | No serum Autoantibodies or inflammatory markers available | MRI Brain hyperintense lesions in the thalami, cerebellum, brainstem, supratentorial grey and white matters without gadolinium-enhanced lesion with areas of restricted diffusion in thalami, and hemorrhage | AHNE | IVMP 1gm for 3 days and IVIG | Recovered | Severe |
| Yong M.H et.al./Singapore | 61y/M            | 7 days                                                      | Diabetes, HTN | Confusion                 | Not done     | Not done               | MRI 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, PLEX Remdesivir | Partially recovery | Severe |
Table 3 (continued)

| Author/country | Patient age/gender | Time duration from COVID-19 to neurological symptom onset | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes |
|----------------|--------------------|----------------------------------------------------------|--------------|---------------------------|--------------|------------------------|--------------|-----------|------------|----------|
| Varadan B et al./India | 46/M | 35 days | Alcoholic liver disease | Confusion, Left hemiplegia | CSF showed lymphocytic pleocytosis with increased protein, glucose NA ** | Not done | MRI Brain 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 microhemorrhage | AHLE | IVMP1 gm for 5 day | Deceased | Sever |

*Severity based on IDSA/ATS
Table 3 (continued)

| Author/country | Patient age/gender | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes | *Severity based on IDSA/ATS |
|----------------|--------------------|--------------|---------------------------|--------------|------------------------|-------------|-----------|------------|----------|-----------------------------|
| Haqiqi A et al. /UK | 56/M | 7 days | CKD, HTN, Confusion | CSF WBC 1/ mm3, protein 71 mg/dl, glucose 77 mg/dl, serum glucose 154 mg/dl, OCB positive, RT-PCR negative for SARS-COV-2 | Not done | MRI Brain hyperintense lesions in the bilateral cerebral hemisphere, brainstem, and white matter with areas of diffusion restriction were noted within most of the lesions and microhemorrhage. No post contrast report available | AHLE | Supportive | Recovered | Severe |

ADEM Acute Disseminated Encephalomyelitis, AHNE Acute Hemorrhagic Necrotizing Encephalitis, AHLE Acute Hemorrhagic Leukoencephalitis, IVIG Intravenous Immunoglobulin, PLEX Plasmapheresis, IVMP Intravenous Methylprednisolone, MRI Magnetic Resonance Imaging, CSF Cerebrospinal Fluid, OCB, Oligoclonal bands, CAD Coronary artery disease, HTN Hypertension

*Severity based on Infectious Diseases Society of America IDSA and American Thoracic Society ATS guidelines

**Serum glucose not reported or available
| Author/country | Patient age /gender | Time duration from COVID -19 to neurological symptom onset | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | CSF MRI findings | Diagnosis | Management | Outcomes | Severity based on IDSA/ATS |
|---------------|-------------------|----------------------------------------------------------|--------------|--------------------------|-------------|------------------------|-----------------|------------|------------|----------|--------------------------|
| Rasmussen C et.al. / USA | 66y/M | 19 days | DM, HTN | Right-sided weakness decreased alertness, aphasic | Not done | NA | MRI Brain: multiple areas of diffusion restriction within the corpus callosum, corona radiata, and centrum semiovale, with associated hyperintensities on T2. Multiple areas of microhemorrhage were also detected. Enhancement not reported. No cord MRI | CLOCC | Conservative mx for pneumonia and iv heparin azithromycin and hydroxychloroquine | Partial recovery | Severe |
| Elkhaled W et.al. / Qatar | 23y/M | 2 days | None | Altered sensorium with disorientation and delayed verbal | CSF normal cell count and chemistry | NA | Brain MRI revealed an isolated oval-shaped lesion in the splenium of the corpus callosum, with hyperintense and restriction diffusion. Enhancement not reported. No cord MRI | CLOCC | Dexamethasone, and conservative management for pneumonia favipiravir, piperacillin tazobactam, and azithromycin | Deceased | Severe |
| Agarwal N et.al/ Italy | 73y/M | 3 weeks | None | Altered consciousness | CSF WBC 0/ mm3, protein 38 mg/dl, glucose 64 mg/dl; ** OCB absent | NA | MRI brain isolated lesion in the splenium slightly to the left, with a longitudinal morphology along the length of the splenial fibers was seen. No enhance seen. No cord MRI | CLOCC | Darunavir/ Cobicistat, antibiotics and hydroxychloroquine | Partial recovery | Severe |
| Author/country       | Patient age |
|---------------------|-------------|
| Moreau A et. al./Belgium | 26/M        |
| Edjlali M et. al./France (pt 1) | 49/M        |
| Edjlali M et. al./France (pt 2) | 51/M        |
| Kakadia B et. al./USA | 69/M        |

| Time duration from COVID-19 to neurological symptom onset | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes | *Severity based on IDSA/ATS |
|----------------------------------------------------------|--------------|---------------------------|--------------|------------------------|--------------|-----------|------------|----------|-----------------------------|
| 2 days                                                   | None         | Agitation, Confusion      | CSF WBC 3/ mm3, protein normal, glucose NA, ** | Not done    | Brain MRI revealed an isolated oval-shaped lesion in the splenium of the corpus callosum, with hyperintense and restriction diffusion | Enhancement not reported | CLOCC   | NA         | Recovered | Non-severe                  |
| NA                                                       | NA           | Confusion                 | NA           | NA                     | Brain MRI revealed an isolated oval-shaped lesion in the splenium of the corpus callosum, with hyperintense and restriction diffusion | Enhancement not reported | CLOCC   | NA         | NA         | NA                           |
| NA                                                       | AN           | Confusion                 | NA           | NA                     | Brain MRI revealed a non-enhancing region of restricted diffusion and hyperintensity in the splenium of the corpus callosum. Enhancement not reported | MERS     | Supportive | Recovered | Non-severe                  |

**Note:** CSF findings indicate normal cell count and chemistry.
| Author/country      | Patient age /gender | Time duration from COVID-19 to neurological symptom onset | Co-morbidity | Neurological presentation | CSF findings | Serum AQP4, and MOG Ab | MRI findings | Diagnosis | Management | Outcomes | *Severity based on IDSA/ATS |
|---------------------|---------------------|-----------------------------------------------------------|--------------|--------------------------|-------------|-------------------------|-------------|-----------|------------|----------|-----------------------------|
| Misayo H et al. / Japan | 75/M                | NA                                                        | None         | Confusion                | Not done    | Not done                | Brain MRI revealed a non-enhancing region of restricted diffusion and hyperintensity in the splenium of the corpus callosum. Enhancement not reported | MERS       | Favipiravir, corticosteroid pulse, ciclesonide and meropenem | Not recovered | Severe |
| Forestier G et al. / France | 55/M                | NA                                                        | None         | Impaired consciousness   | CSF WBC 0/mm³, protein 46 mg/dl, glucose normal ** | Not done    | Brain MRI revealed a non-enhancing region of restricted diffusion and hyperintensity in the splenium of the corpus callosum. Enhancement not reported | CLOCC      | Supportive | Partially recovered | Severe |

*CLOCC Cytotoxic lesion of the Corpus Callosum, MERS Mild encephalopathy with reversible splenium lesion, MOG Myelin Oligodendrocyte Glycoprotein, AQP4 Ab Aquaporin-4 antibody, MRI Magnetic Resonance Imaging, CSF Cerebrospinal Fluid, OCB Oligoclonal band

*Severity based on Infectious Diseases Society of America IDSA and American Thoracic Society ATS guidelines

** Serum glucose not reported or available
the majority of the COVID-19 patients with neurological manifestations [58]. CSF cell count analysis was reported in 30 patients among which 11 cases had elevated cell count > 5 cells/mm$^3$ with lymphocytic predominance.

**Acute myelitis including LETM plus optic neuritis**

Viral infections of the CNS are uncommon but are important in the differential diagnosis of acute/subacute myelopathy [59]. Acute myelitis was the most common CNS inflammatory disorder noted in our analysis with a total of 15 cases, including cases of TM and LETM. The average latency reported in previous cases of postinfectious myelitis/encephalomyelitis was 3–20 days [11, 60]. The latency period of myelitis in this review was similar from less than 1 week [22, 23, 26–28, 33] to more than 1 week [25, 29–31, 36, 37]. The patients presented with a vast range of neurological symptoms, the most common in myelitis were urinary retention and lower limb weakness. Other less frequent symptoms were weakness in upper limb, quadriplegia; paresthesia of lower limb or upper limb or both. The MRI findings in myelitis were categorized into short segment 2 ($n$ = 15, 13.3%) as described by Chakraborty et. al. and Munz et al. [26, 30], or long segment cord involvement of either cervical, thoracic or cervico-thoracic reported in 12 cases [23, 25, 27–29, 31, 33–35]. Interestingly abnormal enhancement of spinal cord ($n$ = 2, 13.3%) was reported in two publications [23, 31]. Brain MRI studies were reported in 8 cases and were unremarkable in 7 cases [31–35]. One reported case had right pontine restriction diffusion ([36]. Zachariadis et al. reported normal spinal cord MRI in a 63-year-old man who presented with lower limb weakness and paresis where diagnosis for myelitis was based on clinical presentation and CSF elevated protein [32]. A case report by Zhao et al., did not have adequate investigations or their provided findings lacked essential data to fulfill all the inclusion criteria for diagnosis of acute myelitis [61].

Two cases of optic neuritis with positive serum Myelin oligodendrocytes glycoprotein (MOG) antibodies one of whom also had myelitis (MOGAD NMO) were reported by Zhou et al. and Sawalah et al. with MOG antibody titers of 1:1000 and 1:160 respectively with negative serum aquaporin 4 (AQP4) antibodies(Table 2). MOG is a protein expressed in the oligodendrocyte membrane and the outermost layer of myelin sheath. Antibodies against MOG have been involved in the pathogenesis of several neurological conditions as noted in subgroups of patients with ADEM, aquaporin-4 (AQP4) seronegative neuromyelitis optica spectrum disorders (NMOSD), monophasic or recurrent isolated optic neuritis (ON), transverse myelitis, atypical MS and ADEM [62]. The demyelination caused by MOG antibodies is attributed to encephalitogenic T cells, antibody-dependent cell toxicity (ADCC) and complement dependent cytotoxicity (CDC) and encephalitogenic T cells which cause blood brain barrier leakage, inflammation and demyelination [63, 64].

The case described by Domingues et al. 42 years woman patient presenting with hemisensory loss 3 weeks after testing positive for CSF SARS-CoV-2 by RT-PCR. A focal cervical cord lesion at C-6 was demonstrated and normal brain MRI. CSF oligoclonal bands were absent with normal CSF cell count and protein. Testing for MOG and AQP4
Table 6  Comparisons of COVID-19 severity, outcome and CNS inflammatory disorders for different characteristics

| Variables          | Age | Gender | CSF Protein | Elevated Cell Count |
|--------------------|-----|--------|-------------|---------------------|
|                    | > 50| ≤ 50   | Total (n)   | Fisher Test (p value) | Yes (> 5) | No (≤ 5) | Total (n) | Fisher Test (p value) |
| COVID-19 Severity  |     |        |             |                     |           |         |          |                     |
| Non-severe         | 10 (42) | 9 (69) | 19 | 0.17 | 13 (52) | 6 (50) | 19 | 1 | 12 (55) | 6 (67) | 18 | 0.696 | 11 (79) | 6 (38) | 17 | 0.033 |
| Severe             | 14 (58) | 4 (31) | 18 |     | 12 (48) | 6 (50) | 18 |  | 10 (45) | 3 (33) | 13 |       | 3 (21) | 10 (62) | 13 |       |
| Outcomes           |     |        |             |                     |           |         |          |                     |
| Nonfatal           | 19 (79) | 10 (83) | 29 | 1 | 19 (79) | 10 (83) | 29 | 1 | 18 (82) | 8 (89) | 26 | 1 | 11 (79) | 14 (88) | 25 | 0.642 |
| Fatal              | 5 (21) | 2 (17) | 7 |    | 5 (21) | 2 (17) | 7 |  | 4 (18) | 1 (11) | 5 |   | 3 (21) | 2 (12) | 5 |       |
| CNS Manifestation  |     |        |             |                     |           |         |          |                     |
| Transverse Myelitis| 9 (35) | 6 (43) | 15 | 0.83 | 8 (30) | 7 (54) | 15 | 0.39 | 12 (55) | 2 (22) | 14 | 0.051 | 10 (71) | 3 (19) | 13 | 0.012 |
| ADEM               | 6 (23) | 4 (29) | 10 |     | 7 (26) | 3 (23) | 10 |  | 6 (27) | 2 (22) | 8 |   | 3 (21) | 5 (31) | 8 |       |
| AHNE/AHLE          | 5 (19) | 1 (7) | 6 |     | 4 (15) | 2 (15) | 6 |  | 3 (14) | 1 (11) | 4 |   | 1 (7) | 3 (19) | 4 |       |
| CLOCC              | 6 (23) | 3 (21) | 9 |     | 8 (30) | 1 (8) | 9 | 1 (5) | 4 (44) | 5 |   | 0 (0) | 5 (31) | 5 |       |

CNS Central nervous system, ADEM Acute Disseminated Encephalomyelitis, AHNE Acute Hemorrhagic Necrotizing Encephalitis, AHLE Acute Hemorrhagic Leukoencephalitis, CSF Cerebrospinal Fluid
antibodies was not performed. This patient had an acute onset myelopathy, likely myelitis, of unknown cause. While described as case of suspected CNS demyelination as clinically isolated syndrome (CIS) the patient had a prior episode compatible with a cervical myelopathy and therefore might not meet strict criteria for CIS [65] (Table 2).

**ADEM including AHNE/ANLE**

ADEM is an immune-mediated generally, monophasic demyelinating disorder involving the brain and occasionally spinal cord. A number of infectious agents, mainly viruses, have been associated with ADEM [66]. In ADEM, latency periods typically vary from 0 days to 8 weeks [43]. The most common presentations were decreased responsiveness, limb weakness, paresthesia of lower limbs, and urinary retention. The most common finding seen on MRI was hyperintensity and restriction diffusion in the deep cerebral white matter. A peculiar finding of hemorrhages and hyperintense lesions within the subcortical and deep white matter of the frontoparietal lobes was noted by Langley et al. [41] and post autopsy findings of hemorrhagic white matter lesions throughout the cerebral hemispheres with surrounding axonal injury and macrophages by Reichard et al. [67]. The MRI findings of spinal cord involvement were of particular interest in 3 cases. The Zoghi et al. reported longitudinally extensive acute transverse myelitis in the thoracic and cervical segments, while Utukuri et al. reported the presence of mild T2 hyperintensities with minimal foci of non-enhancing T2 hyperintense lesions throughout the cervical and thoracic spinal cord. Novi et al. noted a single spinal cord lesion at T8 with bilateral optic nerve enhancement [21, 41, 42] (Table 3).

Acute necrotizing encephalopathy is a rare complication of influenza and other viral infections and has been related to intracranial cytokine storms, which result in blood–brain barrier breakdown but without direct viral invasion or parainfectious demyelination [68–71]. The similar and overlapping AHLE, which also includes demyelination, can be considered part of a continuum with ADEM based on clinical, pathologic and experimental evidence [67, 72, 73]. Our review revealed six cases of AHNE/AHLE associated with COVID-19. MRI findings in these cases included hyperintense T2 lesions in the thalami, cerebellum, brainstem, supratentorial gray and white matters without gadolinium-enhanced lesions with areas of restricted diffusion and microhemorrhage (Table 3). The patients predominately presented with decreased level of responsiveness. MRI findings showed hemorrhagic lesion lesions in bilateral thalami, medial temporal lobe and sub insular regions [52–57]. Outcome and severity of COVID-19 were not reported in one case [52] but the other 5 cases had severe COVID-19 based on IDSA/ATS guidelines [53–57]. There was two fatal outcome as reported by Dixon et al. [53, 56].

**CLOCC/MERS**

Cytotoxic lesions of the corpus callosum (CLOCC) is a disease entity associated with reversible lesions in the corpus callosum on MRI [74]. The MRI lesions typically resolve within a few days to weeks however the clinical recovery may take longer usually several months [75]. Our review noted 9 cases of CLOCC/MERS in patients with COVID-19 [44–51]. The patients had a varied range of clinical presentations, of which the most common was altered sensorium (n = 8), aphasia (n = 2), bradyphrenia (n = 1) and limb weakness (n = 1). MRI imaging in CLOCC demonstrated diffusion restriction and non-enhancing lesions mainly in the splenium of corpus callosum with variable involvement of remaining corpus callosum and cerebral white matter as noted in our cases as well (Table 4).

Our review has several limitations. Cases included in this review were identified through a comprehensive search of databases using a systematic search strategy. However, despite the set criteria, there is a possibility of missing out new upcoming reports and studies because of the evolving nature of the COVID-19 pandemic. A second limitation associated with any review is the concern that a disproportionate number of acute myelitis and other inflammatory neurological disorders associated with COVID are more likely to be reported in case reports and series which can introduce a bias. With the rapidly growing evidence of COVID-19 and association with neurological disorders, case reports and series of atypical demyelination disorders are more likely to be published. Finally, because of the emerging nature of the pandemic, there are no suitable contemporary non-COVID-19 case studies from the institutions reporting the COVID-19 associated CNS inflammatory variants, which would be the appropriate control for comparing the differences in clinical presentations, outcomes and pathophysiology of these disorders when not associated with COVID-19. We believe further studies and reviews are warranted.

**Conclusion**

In this paper we have reviewed and discussed the clinical features, neuroimaging, CSF findings and outcomes in patients with various manifestations of COVID-19 associated CNS inflammation. The most prevalent CNS inflammatory disorder was acute myelitis followed by ADEM including AHNE/AHLE variant and CLOCC respectively. Our review study reveals that CNS inflammatory disorders are rare but can be associated with COVID-19 infection as
they have been reported with many other viruses. Further research using MRI imaging and CSF analysis in earlier diagnosis and intervention of these disorders is warranted.

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Declarations

Conflicts of interest In the last 2 years Dr. Lisak has participated as a speaker in meetings sponsored by and received consulting fees and/or grant support from: Alexion, Argenx, UCB/Ra Pharmaceuticals, Novartis, Mallinckrodt, Genentech/Roche, Chugai, Janssen, GLG Consulting, Alpha Sites Consulting, Schlesinger Group Consulting, Slingshot Consulting, Health Sources, Adivo Associates, Smart Analyst, Clairview, Clarion and Decision Resources. He served as Chair of the Adjudication Committee for a MS clinical trial for MedDay (Biotin study). He is funded by a R21 grant by NINDS “Molecular Characterization of B Cell Exosomes in Multiple Sclerosis” and as site PI for the NINDS funded study “LP4/Agrin Antibodies in Double Seronegative Adjudication Committee for a MS clinical trial for MedDay (Biotin study). He is funded by a R21 grant by NINDS “Molecular Characterization of B Cell Exosomes in Multiple Sclerosis” and as site PI for the NINDS funded study “LP4/Agrin Antibodies in Double Seronegative Neuroinflammation Gravis”. He has received publication royalties from Oxford University Press (Neuroimmunology, 2019) and Blackwell Wiley (International Neurology, 2nd Edition, 2016). The rest of the authors have no disclosures.

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