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SHORT COMMENTARY

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. 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

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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
MOG	Myelin oligodendrocyte glycoprotein
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-hospial 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,

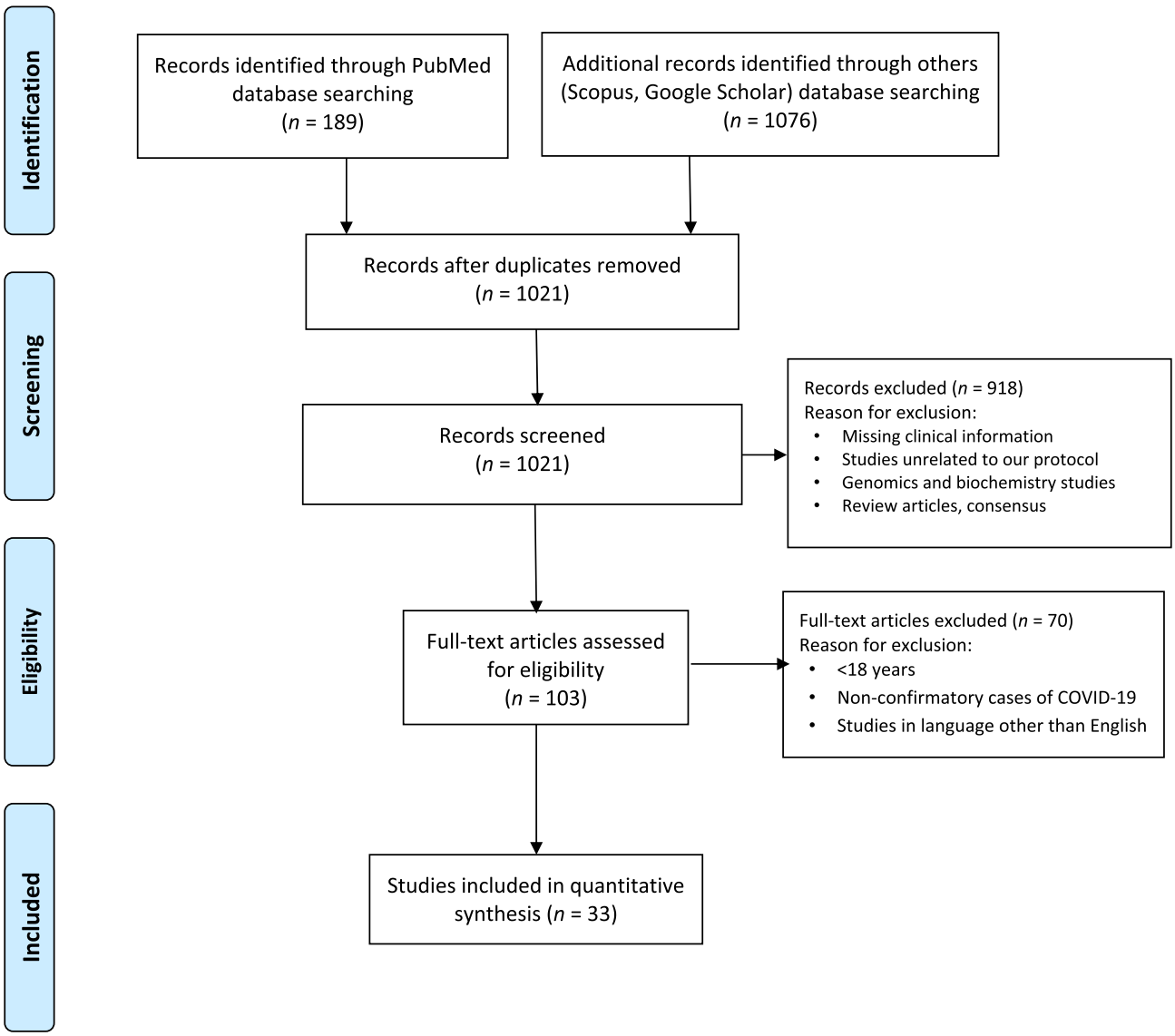

Fig. 1 Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) Flow Diagram

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	*Severitybased 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/mm^3, 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	*Severitybased on IDSA/ATS
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	Non-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	*Severitybased on IDSA/ATS
Munz M et. al. / Germany	60 y/M	8 days	HTN	Retention of urine and and progressive weakness of the lower limbs	CSF WBC 16/mm3; protein 79.3 mg/dl; glucose not reported OCB absent	Serum AQP4, and MOG Ab negative	MRI of the spine revealed T2 signal hyperintensity 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 CSF RT-PCR for SARS-COV-2 negative	NA	MRI spinal cord showed T2-hyperintensity 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 CSF RT-PCR negative for COVID-19	Serum AQP4 and MOG Ab negative 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

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	*Severitybased on IDSA/ATS
Abdelhady M et.al. /Qatar	52 y/M	3 days	DM	Inability to pass urine for 3 days, bilateral lower limb weakness	CSF lymphocytic pleocytosis and increased proteins CSF RT-PCR negative for COVID-19	NA	MRI hyperintensity signal long segment in the upper and mid-thoracic cord No abnormal enhancement seen Brain MRI normal	Acute flaccid myelitis	Patient received steroids and acyclovir	Deceased	Severe
Lisnic V et.al. /Moldova preprint	27Y/M	NA	HIV on ART	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 hyperintense lesion without gadolinium enhancement Brain MRI normal	Acute transverse myelitis	IVMP 1 g/day for 5 days and PLEX	Recovered	Non-severe
Escobar M.M et.al. / USA	41Y/M	14 days	None	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 hyperintense 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

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	*Severitybased on IDSA/ATS
Memon A. B et. al. / USA	65/F	2 wks	Diabetes, Obesity	Paraplegia, Constipation, Retention	CSF WBC 20cells/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 for5 days, and PLEX	Recovered	Non- sever

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	*Severitybased on IDSA/ATS
Baghbanian S. M et. al. / Iran	53/F	3 days	Diabetes, HTN	Paraplegia, Constipation, Retention	CSF WBC 13cells/mm3, lymphocytic predominant, protein normal, glucose normal ** OCB absent	Serum AQP4 and MOG Ab negative	MRI thoracic spine longitudinally extensive transverse myelitis in the T8-T10 cord segments. Post contrast study not reported 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 337cells/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	Acute transverse myelitis	IVMP for5 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

Table 2 Study Origin, Demographics, CSF, MRI findings, severity and outcomes in COVID-19 and MOG disorder with optic neuritis and CIS

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 K 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

Table 2 (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
Zhou S et.al. / USA	26y/M	2 days	None	Bilateral, subacute, sequential vision loss, numbness on the soles of his feet	CSF WBC 55cells/mm3, Lymphocytic predominant, protein 31 mg/dl, glucose 57 mg/dl ** Mirror OCB in both serum and CSF CSF RT-PCR Negative for COVID-19	Serum AQP4 Ab Negative; MOG-IgG positive titer of 1:1000	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

Table 2 (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
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	NA	Brain MRI normal MRI C spine hyperintense lesion at C-6. No abnormal enhancement	Acute myelitis/CIS	NA	Recovered	Non-severe

MOG Myelin Oligodendrocyte Glycoprotein, *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

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 staitical 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 3 Study Origin, Demographics, CSF, MRI findings, severity and outcomes in COVID-19 and ADEM and AHNE/AHLE

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-85 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 No cord lesions	ADEM	Decadron 20 mg iv×5 Days and Convalescent plasma therapy	Partial recovery	Severe
McCuddy M et.al/USA (pt2)	56y/M	20 days	DM, HTN	Unresponsive, no spontaneous limb movement	CSF WBC 1/mm3, protein 55 mg/dl, **glucose 112 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 No contrast study done No cord MRI reported	ADEM	IVMP 1gm for 5 days , IVIG and PLEX	Remains on Ventilator and had tracheostomy	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
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 1gm 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	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

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
Zoghi A et.al. /Iran	21y/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

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
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

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
Poyiadji N et.al. / USA	58y/F	0	None	Altered mental status	CSF cell count, chemistry not reported	No serum Autoanti bodies 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 Autoanti bodies 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

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
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 Autoanti bodies or inflamm atory 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	61/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	Sever

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
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	IVMP1gm for 5 day	Deceased	Sever

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
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 matters 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

Table 4 Study Origin, Demographics, CSF, MRI findings, severity and outcomes in COVID-19 and CLOCC

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
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

Table 4 (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
Moreau A et. al./ Belgium	26/M	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 No cord MRI	CLOCC	NA	Recovered	Non- sever
Edjlali M et.al. / France (pt 1)	49/M	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
Edjlali M et.al. / France (pt 2)	51/M	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
Kakadia B et.al/ USA	69/M	Acutely	HTN	Disorientation, bradyphrenia	Normal CSF cell count and chemistry	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	Supportive	Recovered	Non- severe

Table 4 (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
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

Table 5 General characteristics of SARS-CoV-2 patients with CNS inflammatory disorder ($n=40$)

Characteristics	*N* (%)
Age	
Median (range), in years	52.5 (21–75)
Mean (SD), in years	50.7 (15.1)
Age > 50	26 (65)
Age ≤ 50	14 (35)
Gender	
Male	27 (68)
Female	13 (33)
Clinical cohort	
Transverse myelitis	15 (38)
ADEM	10 (25)
AHNE/AHLE	6 (15)
CLOCC/MERS	9 (23)
*Severity	
Severe	18 (49)
Non-severe	19 (51)
#Outcomes	
Fatal	7 (19)
Non-fatal	29 (81)
$Treatment	
IV Methylprednisolone	25 (71)
IVIG	9 (26)
PLEX	8 (23)
Azithromycin	2 (6)
Hydroxychloroquine	3 (9)
Azithromycin + Hydroxychloroquine	5 (14)
Remdesivir	1 (3)
MRI abnormal enhancement	
Abnormal enhancement of spinal cord on MRI	4 (10)
Abnormal enhancement of brain on MRI	9 (23)

ADEM Acute Disseminated Encephalopathy, *CLOCC* Cytotoxic lesion of the Corpus Callosum, *AHNE* Acute Hemorrhagic Necrotizing Encephalopathy, *AHLE* Acute Hemorrhagic Leukoencephalopathy, *IVIG* Intravenous Immunoglobulin, *PLEX* Plasmapheresis, *IVMP* Intravenous Methylprednisolone, *MRI* Magnetic Resonance Imaging

*3 cases severity data not available

#4 cases outcome not available

$5 cases treatment not 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 paresthesia 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)	Male	Female	Total (*n*)	Fisher Test (*p* value)	High (> 45)	Low (≤ 45)	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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Availability of data and materials Data was extracted from the articles published in PUBMED, Google Scholar, Scopus. This will be provided on request.

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 NINDS funded study "LP4/Agrin Antibodies in Double Seronegative Myasthenia 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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