Clinical Features, Laboratory, and Radiological Findings of Patients With Acute Inflammatory Myelopathy After COVID-19 Infection

A Narrative Review

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Abstract: The objective of this review was to analyze the existing data on acute inflammatory myelopathies associated with coronavirus disease 2019 infection, which were reported globally in 2020. PubMed, CENTRAL, MEDLINE, and online publication databases were searched. Thirty-three acute inflammatory myelopathy cases (among them, seven cases had associated brain lesions) associated with coronavirus disease 2019 infection were reported. Demyelinating change was seen in cervical and thoracic regions (27.3% each, separately). Simultaneous involvement of both regions, cervical and thoracic, was seen in 45.4% of the patients. Most acute inflammatory myelopathy disorders reported sensory motor and bowel bladder dysfunctions. On cerebrospinal fluid analysis, pleocytosis and increased protein were reported in 56.7% and 76.7% of the patients, respectively. Cerebrospinal fluid severe acute respiratory syndrome coronavirus 2 reverse transcriptase–polymerase chain reaction was positive in five patients. On T2-weighted imaging, longitudinally extensive transverse myelitis and short-segment demyelinating lesions were reported in 76% and 21%, respectively. Among the patients with longitudinally extensive transverse myelitis, 61% reported "moderate to significant" improvement and 26% demonstrated "no improvement" in the motor function of lower limbs. Demyelinating changes in the entire spinal cord were observed in three patients. Most of the patients with acute inflammatory myelopathy (including brain lesions) were treated with methylprednisolone (81.8%) and plasma-exchange therapy (42.4%). An early treatment, especially with intravenous methylprednisolone with or without immunoglobulin and plasma-exchange therapy, helped improve motor recovery in the patients with acute inflammatory myelopathy associated with coronavirus disease 2019.

Key Words: Acute Inflammatory Myelopathy, Acute Transverse Myelitis, COVID-19 Infection, SARS-CoV-2 Virus, Spinal Cord

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Coronavirus disease 2019 (COVID-19) is mainly a respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Recently, many studies have shown that SARS-CoV-2 virus infection can also affect multiple organ systems of the body, including the central nervous system.[2]

Acute inflammatory myelopathy (AIM) is a heterogeneous group of inflammatory spinal cord disorders, which includes multiple demyelinating conditions of the spine, like acute transverse myelitis (ATM), neuromyelitis optica (NMO), acute disseminated encephalomyelitis (ADEM), multiple sclerosis, and clinically isolated syndrome.[3] Acute transverse myelitis is an immune-mediated central nervous system disorder that primarily affects the spinothalamic and pyramidal tracts, posterior columns, and the anterior funiculus of the spinal cord at one or more levels.[4] Longitudinally extensive transverse myelitis (LETM) is a variant of ATM, where inflammatory (demyelinating) lesions extend over three or more vertebral segments.[5] Longitudinally extensive transverse myelitis is associated with NMO and ADEM,[5] whereas short-segment demyelinating lesions are usually seen in multiple sclerosis and clinically isolated syndrome. Neuromyelitis optica is an inflammatory demyelinating condition, which involves the optic nerve along with the spinal cord.[5,6] Acute disseminated encephalomyelitis results in diffuse demyelination of the cerebral white matter along with the involvement of the spinal cord.[7] Magnetic resonance imaging (MRI) is essential in evaluating AIM, especially to visualize the intraparenchymal spinal lesions and differentiate them from other compressive and noncompressive spinal lesions.[3,7,8] Radiologically, AIM is characterized by enhancement of the lesions (demyelinating) after contrast (gadolinium) administration.[5,9]

Acute inflammatory myelopathies and their different variants have a very unpredictable disease course.[3,7] If diagnosed, treated, and rehabilitated early, patients with AIM can significantly improve functional outcomes.[8] The purpose of this review is to provide a synopsis of the information regarding the clinical features, including laboratory findings, neuroimaging findings, and acute management and treatment outcomes of patients with AIM after COVID-19 infection. To determine the short- and long-term rehabilitation goals for these patients, especially at admission, it is essential for the rehabilitation physician to know about their clinical features, laboratory, neuroimaging findings, acute management, and expected outcome.

METHODS

The review was performed according to the PRISMA-P 2015 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[10]

Literature Search

A systematic electronic literature search was conducted in PubMed, CENTRAL, and MEDLINE with a strategy "Coronavirus" OR "coronavirus" OR SARS-Cov-2 OR COVID-19 AND "transverse myelitis" OR "Myelitis" OR "Postinfectious Myelitis" OR "Demyelinative Myelitis" OR "Neuromyelitis Optica" OR "Devic's Disease" OR "Devic's Neuromyelitis Optica" OR "Acute Disseminated Encephalomyelitis" OR "Encephalomyelitis" OR "Acute Disseminated Encephalomyelitis" OR "Multiple Sclerosis" OR "Clinically Isolated Syndrome" from December 1, 2019, to January 31, 2021. Two authors independently evaluated the titles and abstracts of each article for screening and inclusion. Articles evaluating COVID-19 infection–associated AIM were reviewed in full text. A manual search was also conducted from the relevant references of identified articles.

Inclusion Criteria and Study Selection

Studies were deemed eligible for the inclusion if the studies (1) were case series, case reports, or observational studies; (2) included patients with radiological (MRI) evidence of myelopathy, with or without brain lesion, diagnosed during or immediately after COVID-19 infection; (3) included patients with no previous history of any diagnosed neurological illness; (4) had confirmed the SARS-CoV-2 infection either with reverse transcriptase–polymerase chain reaction (RT-PCR) and/or with support of radiological evidence of COVID-19 pneumonia; and (5) reported clinical, laboratory, neuroimaging findings, diagnostic criteria, acute management, and treatment outcomes of AIM. In addition, correspondences or letters that were fulfilling the criteria mentioned previously were included in this review.

The exclusion criteria were as follows: the studies that included (1) patients with suspected COVID-19 infection, in whom COVID-19 infection was not confirmed by RT-PCR test, serological or by radiological test; (2) patients with suspected myelopathy, with no evidence of demyelination (MRI) in the spinal cord; (3) patients with brain lesion (MRI), but no evidence of spinal cord involvement (MRI); (4) patients with myelopathy due to connective tissue disease or infections other than COVID-19 infection; (5) history of radiation exposure, trauma, or malignancy; and (6) patients with structural abnormalities of the spine. Articles not presenting the original data (meta-analyses, review articles, consensus documents, comments, opinion articles, and letters), duplicate studies, abstract-only studies, and articles written in languages other than English were not included in this review.

Selection of Studies

Titles and abstracts of the retrieved studies were screened by two reviewers (AB, AV) independently and were identified as included, excluded, or uncertain. In case of uncertainty, the full-text article was obtained and reviewed for eligibility based on inclusion criteria. Any discrepancies during the selection were resolved by discussion and consensus.

Outcome Measures

Depending on the improvement of motor power or function of the bilateral lower limbs, motor recovery of a patient was categorized into (1) "moderate to significant" improvement, (2) "marginal to a slight" improvement, and (3) "no improvement." Motor recovery was reported as "moderate to significant" improvement if the study reported either (*a*) moderate to significant improvement of motor function in lower limbs, or (*b*) improvement in muscle power more than one grade on the Medical Research Council scale for muscle strength, or (*c*) the affected patient has progressed to "walking with or without support" from "nonambulant" condition. Motor recovery was categorized into "marginal to slight" improvement if the study reported that (*a*) there is minimal/marginal to slight improvement or (*b*) improvement in muscle power of affected lower limb one grade or less on the Medical Research Council scale. The motor recovery was classified as "no improvement" if it mentioned no lower limb muscle power improvement.

Motor recovery/neurological outcome from the included study was assessed at the end of treatment or at the time of follow-up visit, whichever was later.

Data Extraction

Two reviewers (AB and SR) extracted the data independently with a standardized data collection form, including (1) demographic characteristics (age and sex); (2) basic information regarding COVID-19 infection; (3) clinical symptoms related to myelopathy; (4) autoimmune profiles, viral markers, and cerebrospinal fluid (CSF) analysis; (5) MRI findings; (6) acute management; and (7) neurological outcomes or motor recovery.

Data Analysis

Data were presented with descriptive statistics. Any discrepancies in data acquisition or interpretation were resolved during the data extraction process through discussion or consultation with the third reviewer (JS). The total number of events and participants was extracted for dichotomous outcomes. For continuous outcomes, data were presented in mean (SD). If mean and SD were not reported in the particular study, it was calculated manually from the reported indicators. If data were not available or written in an unusable way, the specific research was excluded from analysis, and then, the data were presented descriptively.

RESULTS

The Outcome of the Electronic Search

A total of 4051 articles were identified from electronic databases. After removing duplicate and irrelevant (not matching the inclusion and exclusion criteria) articles, 31 case reports (33 patients) with AIM[11–41] were included in this review. Among them ($N = 33$), 26 patients (24 case reports)[11–31,38,40,41] had only spinal cord involvement with no brain involvement. Seven cases had both spinal cord and brain involvement.[32–37,39] The PRISMA flow diagram, including the reasons for excluding studies, is presented in Figure 1.

Demographic and Descriptive Data of Post-COVID AIM

Thirty-three patients fulfilled the inclusion criteria (Table 1).[11–41] All patients ($N = 33$) were admitted and treated at an acute care hospital. Two patients[15,29] received inpatient rehabilitation after discharge. The mean (SD) age of the included patients was 47 (17.7) yrs. The youngest patient was a 3-yr-old female child.[16] The male-to-female ratio was 16:17.

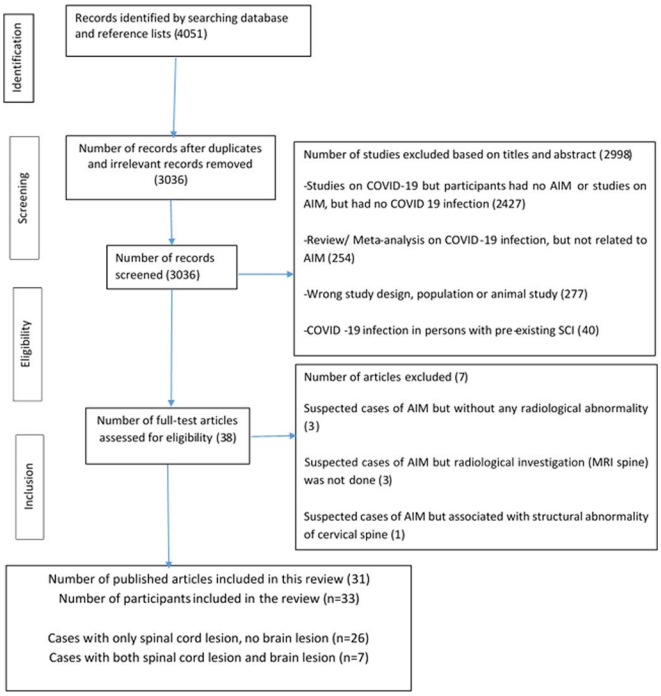

FIGURE 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for the study selection process.

Of the 33 patients[11–41] with AIM, 82% (n = 27) [11–15,17–20,22–27,30–33,35–41] presented with COVID-associated symptoms (cough, fever, dyspnea, myalgia, fatigue, chills, anosmia, and rhinorrhea). The latency period (mean time between the onset of COVID-19 infection to first symptom of inflammatory myelopathy) of AIM varied from 2 days[22] to 3 wks.[31,33] Six patients[16,21,26,28,29,34] did not report any COVID-19 symptoms previously, presented directly with neurological symptoms (either urinary symptoms or sudden weakness).

Autoimmune profiles, viral markers, and CSF analysis were done in all cases. Laboratory findings (autoimmune profiles, viral markers, and CSF analysis) of these patients (N = 33) are presented in Table 1. The CSF analysis was done in 30 cases. Five patients[16,23,30,34,35] (17%) were CSF SARS-CoV-2 RT-PCR positive.

Detailed neuroimaging findings of each patient are presented in Table 1. On MRI of the spine, nine patients had demyelinating changes in the "cervical region only."[18,26–28,30–32,35,36] Demyelinating change in "thoracic region only" was seen in nine patients.[11–13,17,19–21,25,33] Simultaneous and/or overlapping involvement of both regions, "cervical and thoracic," were seen in 15 patients.[14–16,22–26,29,34,37–41] Based on the length of the longitudinal (demyelinating) lesions, it was categorized into two groups. An LETM (lesions extending ≥3 vertebral segments) were seen in 25 patients (76%) [11,12,14–20,22–28,30,32,34,37–41] and short-segment spinal demyelinating lesions (lesions extending <3 vertebral segments) were seen in 7 patients (21%).[13,21,24,29,31,33,36] Extent (exact length) of spinal (cervical) segment involvement (demyelination) was not reported in one patient.[35] Among the patients with LETM lesions (n = 25), demyelinating lesions in the entire spinal cord (upper cervical to conus) were seen in three patients.[14,15,40]

Clinical, Laboratory, and Radiological Findings and Outcome of Patients With "AIM Without Any Brain Lesion"

The group, "AIM without any brain lesion," includes 26 patients (3–70 yrs of age).[11–31,38,40,41] The clinical features of these 26 patients are summarized in Table 1.

Clinical Features (AIM Without Any Brain Lesion)

Motor deficits in lower limbs were reported in 23 patients (88.5%).[11–13,15–20,22–30,38,40,41] One had hemiplegia,[28] and 22 had motor deficits in both lower limbs (symmetrical involvement). The evolution of paralysis varied from patient to patient, from abrupt onset (few hours) [25,26,28] to 7 days.[18]

Sensory deficits (abnormal sensation) were reported in 21 patients.[11–15,18,19,21,23–29,31,38,40,41] Definite clear sensory level (sensory loss below particular level) was reported in 66.7% of the patients,[11–14,23–27,29,38,40,41] whereas altered sensations (in form of tingling, numbness, and/or paraesthesia but without sensory level) were reported in 33.3% of the patients.[15,18,19,21,26,28,31] Six patients[12,14,17,23,25,26] reported low back pain.

Bowel bladder dysfunctions were reported in 23 patients.[11–15,17–27,29,30,38,40,41] Common bladder dysfunctions were urinary retention, urinary overflow incontinence, and urinary urgency (Table 1).

Two patients[14,21] presented with sensory and bladder involvement but without any motor involvement.

Laboratory Findings (AIM Without Any Brain Lesion)

On CSF analysis, pleocytosis[11–18,20,21,23,26,27] was seen in 13 patients, and elevated protein[11–19,23,26–30,40,41] was seen in

TABLE 1. Clinical features, laboratory, and radiological findings of the patients with AIM after COVID-19 infection

					Clinical Features		Laboratory Findings	
SL No.	Study	Age, Yr/ Sex	Comorbidities	Latency Period (Time Since SARS-CoV-2 Infection)	At the Time of Diagnosis	At the Time of Hospital Discharge	Autoimmune Profiling and Viral Markers	CSF Analysis
1	Munz et al.[11]	60/M	HTN, fatty liver, ureterolithiasis	8 d	Sensory: hypoesthesia below T9 level Motor: spastic paraparesis, unable to walk, Babinski sign (B/L) (+Ve) (Evolution of weakness: NR) Bladder/bowel: bladder dysfunction	Sensory: hypoesthesia below T9 level Motor: slight spastic paraparesis, able to walk Bladder: normal bladder function	Autoimmune profile: anti-AQP4 (−Ve), anti-MOG (−Ve), ANA (−Ve), antineuronal Ab (−Ve) Viral markers: HHV-6, EBV, Hep E, HSV, VZV: (−Ve)	Lymphocytic pleocytosis (27/μl), elevated protein levels (1177 mg/l) OCB: (−Ve) SARS-CoV-2 PCR: (−Ve)
2	Baghbanian and Namazi[12]	53/F	T2DM, HTN, IHD	2 wks	Sensory: sensory level at T10 and low back pain Motor: flaccid paraparesis (power: right lower limb: 3/5 and left lower limb: 0/5), lower limb areflexia (Evolution of weakness: 2 d) Bladder/bowel: urinary incontinence	Sensory: NR Motor: paresis recovered to a certain degree Bladder/bowel: NR	Autoimmune profile: anti-NMO (−Ve), anti-MOG (−Ve)	Lymphocytic pleocytosis, IgG index (higher normal limits = 0.71) OCB: (−Ve) SARS-CoV-2 PCR: (−Ve)
3	Chakraborty et al.[13]	59/F	Obesity	NR	Sensory: decreased sensation below T10 level Motor: symmetric flaccid paraplegia, power: 0/5 in both LL, B/L lower limb areflexia (Evolution of weakness: 4 d) Bladder/bowel: urinary retention and constipation	Death	Autoimmune profile: NR Viral markers: hepatitis B, C, HIV: (−Ve)	Lymphocytic pleocytosis, increased protein level (71.4 mg/dl)
4	Sarma and Bilello[14]	28/F	Hypothyroidism	1 wk	Sensory: decreased sensation below T5 Motor: WNL Bladder/bowel: urinary retention	Sensory: decreased sensation in lower limbs up to midthigh bilaterally Motor: WNL Bladder/bowel: WNL	Autoimmune profile: anti-MOG: (−Ve), ANA: (−Ve)	Lymphocytic pleocytosis, increased protein OCB: −Ve Antibody (SARS-CoV-2): (−Ve)
5	Valiuddin et al.[15]	61/F	NR	7 d	Sensory: tingling/ numbness in B/L hands and from the abdomen to B/L feet Motor: power: 4/5 power in B/L upper limb and 3/5 in B/L lower limbs Bladder/bowel: urinary retention and constipation	Sensation: significant improvement (details: NR) Motor: paraplegia (no improvement) Bladder/bowel: neurogenic bladder and bowel	Autoimmune profile: autoimmune encephalopathy panel including anti-MOG: (−Ve)	Pleocytosis, increased protein level, IgG index (higher normal limits = 0.7) OCB: (−Ve)

Radiological Findings												Treatment Outcome
Abnormal Radiological Findings		Spinal Involvement			Region/ Area Involvement			Demyelinating Pattern				
Lesion at Spinal Cord	Lesion at Brain	LETM	Short	Swelling Focal	1	2	≥3	Continuous	Patchy	Clinical Diagnosis	Treatment Received	Motor Recovery
"T3–T5" and " T9–T10"	NAD	+	−	−	+	−	−	−	+	ATM	IV-MPS, acyclovir, ceftriaxone	Motor recovery: "moderate to significant improvement" Outcome assessment: day 13
T8–T10	NAD	+	−	−	+	−	−	+	−	LETM	PLEX	Motor recovery: "marginal to sight improvement" Day of assessment: at time of discharge
T6–T7	NAD	−	+	−	+	−	−	+	−	ATM	IV-MPS, PCM	Death
Entire spinal cord	NAD	+	−	−	−	−	+	+	−	ATM	IV-MPS, PLEX	Motor recovery: motor deficits were absent Categorization: not done Outcome assessment: day 8
Entire spinal cord	NAD	+	−	+	−	−	+	−	+	ATM	IV-MPS, PLEX	Motor recovery: "no improvement" Outcome assessment: day 10

(Continued on next page)

TABLE 1. *(Continued)*

SL No.	Study	Age, Yr/ Sex	Comorbidities	Latency Period (Time Since SARS-CoV-2 Infection)	Clinical Features		Laboratory Findings	
					At the Time of Diagnosis	At the Time of Hospital Discharge	Autoimmune Profiling and Viral Markers	CSF Analysis
6	Kaur et al.[16]	3/F	NR	NR	Sensory: NR Motor: flaccid quadriplegia (Evolution of weakness: 12 hrs) Bowel/bladder: NR	Sensory: NR Motor: flaccid quadriplegia Bowel/bladder: NR	Autoimmune profile: anti-AQ4: (−Ve), anti-MOG: (−Ve), RF: (−Ve) Viral markers: HSV, HIV, EBV, CMV, etc.: (−Ve)	Pleocytosis, elevated protein SARS-CoV-2 RT-PCR: (+Ve)
7	Abdelhady et al.[17]	52/M	T2DM, G6PD deficiency	3 d	Sensory: WNL, abdominal pain Motor: flaccid paraplegia, weakness B/L lower limbs (Evolution of weakness: 3 d) Bladder/bowel: urinary retention	Death	Autoimmune profile: ANCA (−Ve), ANA (−Ve) TB PCR (−Ve) Viral markers: (−Ve) SARS-CoV-2 RT-PCR (CSF): +Ve	Lymphocytic pleocytosis, increased protein
8	Sotoca and Rodríguez-Álvarez[18]	69/F	Not mentioned	1 wk	Sensory: hypoesthesia in (R) face and (L) hand. Motor: paraparesis (Evolution of weakness: 7 d) Bladder/bowel: bladder incontinence	Sensory: details (NR) Motor: improved, able to walk with assistance Bladder/bowel: details: NR	Autoimmune profile: anti-MOG: (−Ve), anti-AQP4: (−Ve), antineuronal surface antibody: (−Ve)	Lymphocytic pleocytosis, increased protein, IgG index: WNL OCB: (−Ve) Culture (bacteria/ virus): (−Ve)
9	Chow et al.[19]	60/M	HTN, dyslipidemia	2 wks	Sensory: paraesthesia below the level of umbilicus Motor: spastic paraparesis, B/L LL weakness, hyperreflexia (Evolution of weakness: 2 d) Bladder/bowel: urinary retention and constipation	Sensory: paraesthesia completely resolved Motor: regained full LL motor power Bowel/bladder: normal	Autoimmune profile: anti-MOG: (−Ve), anti-NMO: (−Ve), ACE (−Ve) Viral markers: mycoplasma, EBV, CMV, HIV, Hep B and C: (−Ve)	Elevated protein
10	Durrani et al.[20]	24/M	Not mentioned	12 d	Sensory: normal Motor: flaccid paraplegia, areflexia (Evolution of weakness: NR) Bladder/bowel: overflow urinary incontinence	Sensory: normal Motor: significant improvement in B/L lower limb (details: NR) Bladder/bowel: NR	Autoimmune profile: anti-AQP4 (−Ve), ANA (−Ve) Viral markers: HIV, infectious diseases: (−Ve)	Lymphocytic pleocytosis OCB: (−Ve)
11	Rodríguez de Antonio et al.[21]	40/F	Venous insufficiency, migraine, and past H/O splenectomy	NR	Sensory: hypoesthesia in perineum and distal third of both the legs and feet Motor: no motor symptoms (Evolution of weakness: NA) Bladder/bowel: mild urinary urgency	Sensory: mild recovery of sensory function Motor: no motor symptoms Bladder/bowel: complete recovery of bladder function	Autoimmune profile: anti-GD2/GD3 IgM antibody (+Ve), anti-MOG (−Ve), anti-AQP4 (−Ve), ANA (−Ve), ANCA (−Ve), ACE (−Ve), antiphospholipid (−Ve)	Lymphocytic pleocytosis OCB: (−Ve)

Radiological Findings												Treatment Outcome
Abnormal Radiological Findings		Spinal Involvement			Region/ Area Involvement			Demyelinating Pattern				
Lesion at Spinal Cord	Lesion at Brain	LETM	Short	Swelling Focal	1	2	≥3	Continuous	Patchy	Clinical Diagnosis	Treatment Received	Motor Recovery
C1–T6	NAD	+	−	+	−	+	−	+	−	LETM	IV-MPS, PLEX, IVIG, rituximab	Motor recovery: "no improvement" Outcome assessment: NR
T3–T6	NAD	+	−	−	+	−	−	+	−	ATM	IV-MPS, acyclovir.	Death
C1–C7	NAD	+	−	+	−	+	−	+	−	ATM	IV-MPS, PLEX	Motor recovery: "moderate to significant improvement" Outcome assessment: end of 4 wks
T7–T10	NAD	+	−	−	+	−	−	+	−	ATM	IV-MPS	Motor recovery: "moderate to significant improvement" Outcome assessment: day 11
T7–T12	NAD	+	−	−	+	−	−	+	−	ATM	IV-MPS	Motor recovery: "moderate to significant improvement" Outcome assessment: at the end of treatment
T5–T6	NAD	−	+	−	+	−	−	−	+	ATM	IV-MPS	Motor recovery: motor deficits were absent Categorization: not done Outcome assessment: at the end of treatment

(Continued on next page)

TABLE 1. *(Continued)*

SL No.	Study	Age, Yr/ Sex	Comorbidities	Latency Period (Time Since SARS-CoV-2 Infection)	Clinical Features		Laboratory Findings	
					At the Time of Diagnosis	At the Time of Hospital Discharge	Autoimmune Profiling and Viral Markers	CSF Analysis
12	AlKetbi et al.[22]	32/M	Nil	2 d	Sensory: normal Motor: flaccid paraplegia (power: upper limb: distal muscles: 3–4/5, proximal muscles: 5/5; lower limbs: both distal and proximal: 0/5) (Evolution of weakness: 24 hrs) Bladder/bowel: urinary retention	Sensory: normal Motor: U/L power: 4/5, B/L LL power: 4/5 Bladder/bowel: on bladder training	Autoimmune profile: anti-LA: (+Ve), ANCA: (−Ve), RF: (−Ve), anticardiolipin: (−Ve), anti–β-2 glycoprotein: (−Ve) Viral markers: PCR (HSV-1, HSV-2, adenovirus, EBV, CMV, HIV, etc.) (−Ve), serology (bacteria/other viruses): (−Ve)	NR
13	Hazrati et al.[23]	63/M	T2DM, CRF, IHD	4 d	Sensory: decreased sensation below T8, lower thoracic pain Motor: flaccid paraparesis, power: 1/5 in B/L LL, areflexia in lower limbs (Evolution of weakness: NR) Bladder/bowel: urinary retention and constipation	Sensory: complete recovery Motor: significant improvement, able to walk without assistance Bladder/bowel: significant improvement (details: NR)	Autoimmune profile: anti-MOG (−Ve), anti-AQP4 (−Ve), anti-NMO: (−Ve), ANA: (−Ve), antiphospholipid (−Ve), anticardiolipin: (−Ve), anticentromere: (−Ve), anti-scl70: (−Ve), anti-ds DNA: (−Ve), anti-Sm: (−Ve), anti–SS-A/SS-B: (−Ve), antinucleosome: (−Ve)	Lymphocytic pleocytosis, increased protein, IgG index: elevated OCB: (−Ve) CSF culture: (−Ve) SARS-CoV-2 RT-PCR: (+Ve)
14	Masuccio et al.[24]	70/F	Obesity, HTN	15 d	Sensory: decreased sensation in LL Motor: flaccid paralysis (power: upper limb: 3/5, lower limb: 0/5) (Evolution of weakness: 5 d) Bladder/bowel: urinary retention	Sensory: details NR Motor: power lower limbs, improved to 1/5 (details: NR) Bladder/bowel: NR	Autoimmune profile: anti-GD1b IgM: (+Ve) Viral markers: antibody (EBV, CMV, HSV, HZV, HIV, etc.): (−Ve)	Normal protein OCB: (+Ve)
15	Khedr et al.[25]	60/F	Hypothyroidism	10 d	Sensory: loss of sensation below T4, girdle-like pain Motor: complete flaccid lower limb paralysis, areflexia (Evolution of weakness: 2 d) Bladder/bowel: urinary retention and fecal constipation	Death	Autoimmune profile: NR	NR

Radiological Findings												Treatment Outcome
Abnormal Radiological Findings		Spinal Involvement			Region/ Area Involvement			Demyelinating Pattern				
Lesion at Spinal Cord	Lesion at Brain	LETM	Short	Swelling Focal	1	2	≥3	Continuous	Patchy	Clinical Diagnosis	Treatment Received	Motor Recovery
Cervical, thoracic, and lumbar	NAD	+	−	+	−	−	+	+	−	ATM	IV-MPS, acyclovir, enoxaparin	Motor recovery: "moderate to significant improvement" as muscle power improved" Outcome assessment: day 6
C7–T12	NAD	+	−	+	−	−	+	+	−	ATM	IV-MPS, IVIG, HCQ, AZM, ritonavir, hemodialysis	Motor recovery: "moderate to significant improvement" Outcome assessment: day 6
C7–T1	NAD	−	+	−	−	+	−	−	+	ATM	PLEX, IVIG	Motor recovery: "marginal to slight improvement" Day of assessment: day 25
T4–T8	NAD	+	−	−	+	−	−	+	−	ATM	IV-MPS, PLEX, heparin	Death

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TABLE 1. *(Continued)*

SL No.	Study	Age, Yr/ Sex	Comorbidities	Latency Period (Time Since SARS-CoV-2 Infection)	Clinical Features		Laboratory Findings	
					At the Time of Diagnosis	At the Time of Hospital Discharge	Autoimmune Profiling and Viral Markers	CSF Analysis
16	Khedr et al.[25]	21/F	Nil	10 d	Sensory: loss of sensory below C4 Motor: flaccid quadriplegia, more weakness in B/L lower limbs, areflexia (Evolution of weakness: few hours) Bladder/bowel: urinary retention and fecal incontinence	Sensory: no improvement (details: NR) Motor: power in the upper limb: mild improvement, the lower limb: no improvement Bladder/bowel: no improvement (details: NR)	Autoimmune profile: NR	NR
17	Advani et al.[26]	47/M	NR	10 d	Sensory: loss of sensation below T10, dull pain in the abdomen Motor: flaccid paraplegia (power bilateral lower limbs: 0/5, areflexia) (Evolution of weakness: abrupt onset) Bladder/bowel: urinary retention	Sensory: no improvement (details: NR) Motor: no improvement (details: NR) Bladder/bowel: no improvement (details: NR)	Autoimmune profile: anti-AQP4: (−Ve); ANCA (−Ve); anticardiolipin: (−Ve), lupus anticoagulant, protein S, C (−Ve); anti–β-2 glycoprotein: (−Ve) Culture (viral/ bacteria): (−Ve) Viral markers: EBV, HSV, VZ, etc.: (−Ve)	Neutrophilic pleocytosis, increased protein
18	Advani et al.[26]	67/F	NR	NR	Sensory: no sensory loss, only paraesthesia at the chest. Motor: spastic paraparesis, weakness of the bilateral lower limbs with power: 4−/ 5, hyperreflexia Duration of evolution of weakness: NR Bladder/bowel: increased frequency	Sensory: complete recovery Motor: muscle power improved to 4+/5, fully ambulatory Bladder/bowel: NR	Autoimmune profile: anti-AQP4: (−Ve); ANCA (−Ve); anticardiolipin (−Ve); lupus anticoagulant, protein S, C negative; anti–β-2 glycoprotein: (−Ve) Culture (viral/ bacteria): (−Ve) Viral markers: EBV, HSV, VZ, etc.: −Ve	No cell, normal protein IgG index: high OCB: +Ve
19	Fumery et al.[27]	38/F	NR	2 wks	Sensory: hypoesthesia below T4 level Motor: motor paraparesis (power: 4/5), hyperreflexia Duration of evolution of weakness: NR Bladder/bowel: urinary retention	Sensory: status improved (details: NR) Motor: status improved (details: NR) Bladder/bowel: status improved (details: NR)	Autoimmune profile: anti-AQP4: (−Ve), MOG: (−Ve) Viral markers: HTLV-1, West Nile, CMV, EBV, EBV, HIV: (−Ve)	Lymphocytic pleocytosis, elevated protein OCB (−Ve) Viral markers: HSV, VZ: (−Ve) SARS-CoV-2 RT-PCR: (−Ve)

Radiological Findings												Treatment Outcome
Abnormal Radiological Findings		Spinal Involvement			Region/ Area Involvement			Demyelinating Pattern				
Lesion at Spinal Cord	Lesion at Brain	LETM	Short	Swelling Focal	1	2	≥3	Continuous	Patchy	Clinical Diagnosis	Treatment Received	Motor Recovery
"C5–T7"	NAD	+	−	+	−	+	−	+	−	ATM	IV-MPS, IVIG, rivaroxaban	Motor recovery: "no improvement" (as no improvement was reported in bilateral lower limbs) Outcome assessment: after 2 mos
"C2–T2"	NAD	+	−	−	−	+	−	+	−	ATM	PLEX, acyclovir, ceftriaxone, vancomycin	Motor recovery: "no improvement" Outcome assessment: at the end of treatment/ 5 sessions of PLEX
C3–C6	NAD	+	−	−	+	−	−	+	−	ATM	IV-MPS, PLEX	Motor recovery: "moderate to significant improvement" Outcome assessment: at the end of treatment/5 sessions of PLEX
Cervical and thoracic spine, starting from "C3 to C4"	NAD	+	−	−	−	+	−	+	−	LETM	IV-MPS	Motor recovery: "moderate to significant improvement" Outcome assessment: at the end of treatment

(Continued on next page)

TABLE 1. *(Continued)*

SL No.	Study	Age, Yr/ Sex	Comorbidities	Latency Period (Time Since SARS-CoV-2 Infection)	Clinical Features		Laboratory Findings	
					At the Time of Diagnosis	At the Time of Hospital Discharge	Autoimmune Profiling and Viral Markers	CSF Analysis
20	Güler et al.[28]	14/F	NR	NR	Sensory: neuropathic pain Motor: asymmetric paraparesis (right hemiplegia), unable to walk Duration of evolution of weakness: sudden onset Bladder/bowel: NR	Sensory: improved (details: NR) Motor: improved, started to walk unsupported (details: NR) Bladder/bowel: NR	Autoimmune profile: anti-NMO (−Ve), anti-Sm/RNP (−Ve), anti SS-A (−Ve), anti–SS-B (−Ve), anti-ds DNA (−Ve), ANA (−Ve), P-ANCA (−Ve), C-ANCA (−Ve) Viral markers: EBV, VCA, CMV, HSV-1, HSV-2, VZ, etc.: (−Ve)	No WBC cells, elevated protein OCB: (−Ve) SARS-CoV-2 RT-PCR: (−Ve)
21	Gracia et al.[29]	72/M	HTN	NR	Sensory: dysesthesia, sensory loss below T9 Motor: spastic paraparesis (power: upper limb 3+/5, lower limb 1+/5) hyperreflexia Duration of evolution of weakness: 3 d Bladder/bowel: urinary retention	Sensory: status (details: NR) Motor: spastic paraparesis (power: upper limb 4+/5, lower limb 1+/5, spasticity increased) Bladder/bowel: urinary retention (no change)	Autoimmune profiling: anti-MOG (−Ve), anti-AQP4: (−Ve), anti-MOG: (−Ve), ANA (−Ve), ANCA (−Ve), antiphospholipid (−Ve), anticardiolipin (−Ve), C3 and C4 (−Ve) Viral markers: VDRL, HIV (−Ve)	No WBC cells, elevated protein OCB: (+Ve), meningitis CSF panel (bacteria/ virus/yeast): (−Ve) Gram stain/acid-fast bacilli/ fungus stain: (−Ve)
22	Saberi et al.[30]	60/M	DM, hyperlipidemia, HTN	2 wks	Sensory: status (details: NR) Motor: lower limb (power: lower limb 1/5) Duration of evolution of weakness: 3 d Bladder/bowel: urinary retention, constipation	Sensory: status (details: NR) Motor: paraparesis (power: lower limb 1/5) Bladder/bowel: status: NR	Autoimmune profile: anti-NMO: (−Ve)	Cell count: not done, elevated protein SARS-CoV-2 RT-PCR: suspicious
23	Domingues et al.[31]	42/M	Similar H/O neurological episode 3 yrs before. Recovered completely without evaluation and treatment.	3 wks	Sensory: paraesthesia and hypoesthesia of left upper limb, hemithorax, and hemiface Motor: WNL Duration of evolution of weakness: NA Bladder/bowel: NR	Sensory: normal (full recovery) Motor: WNL Bladder/bowel: NR	Autoimmune profile: ANA (−Ve), anti-SSA (−Ve), anti-SSB (−Ve)	Cell: 1 WBC/ mm^3, protein: WNL (32 mg/ dl), OCB (−Ve) SARS-CoV-2 RT-PCR: (+Ve)

Radiological Findings												Treatment Outcome
Abnormal Radiological Findings		Spinal Involvement			Region/ Area Involvement			Demyelinating Pattern				
Lesion at Spinal Cord	Lesion at Brain	LETM	Short	Swelling Focal	1	2	≥3	Continuous	Patchy	Clinical Diagnosis	Treatment Received	Motor Recovery
C2–C5	NAD	+	−	−	+	−	−	+	−	ATM	IV-MPS, IVIG, fentanyl, and gabapentin (for neuropathic pain)	Motor recovery: "moderate to significant improvement" Outcome assessment: day 16
"C4–C5" and "T3–T4"	NAD	−	+	+	−	+	−	−	+	ATM	IV-MPS, IVIG	Motor recovery: "no improvement" Outcome assessment: day 40
"C1–C4"	NAD	+	−	−	+	−	−	+	−	ATM	IV-MPS, IVIG, PLEX, HCQ, oseltamivir, enoxaparin	Motor recovery: "no improvement" Day of assessment: day 16
Small central lesion at cervical region (details: NR)	NAD	−	+	−	+	−	−	−	+	CIS	NR	Motor status: motor deficits were absent Categorization: not done

(Continued on next page)

TABLE 1. *(Continued)*

SL No.	Study	Age, Yr/ Sex	Comorbidities	Latency Period (Time Since SARS-CoV-2 Infection)	Clinical Features		Laboratory Findings	
					At the Time of Diagnosis	At the Time of Hospital Discharge	Autoimmune Profiling and Viral Markers	CSF Analysis
24	Nemtan et al.[38]	27/M	HIV infection for the past 1 yr, on ART	NR	Sensory: paraesthesia, numbness B/L lower limbs and right arm, sensory loss below C6 Motor: power B/L lower limbs 1–2/5 Duration of evolution of weakness: 15 hrs Bladder/bowel: urinary retention, constipation	Sensory: details NR Motor: power B/L lower limbs significant improvement (details: NR) Bladder/bowel: sphincter disturbance less severe (details: NR)	Autoimmune profiling: ANA: (−Ve), ANCA: (−Ve), anti-AQ4: (−Ve), anti-MOG: (−Ve) Viral markers: HSV-1, HSV-2, HSV-6, CMV, EBV, hepatitis, etc.: (−Ve)	Cells: no WBC cells, protein: WNL OCB: (−Ve) PCR (HSV-1, HSV-2, HSV-6, CMV, EBV, *Borrelia burgdorferi*, etc.): (−Ve) SARS-CoV-2 RT-PCR: (−Ve)
25	Batum et al.[40]	50/F	Nil	NR	Sensory: sensory loss below T4, numbness, paraesthesia Motor: weakness bilateral lower limbs, areflexia (Evolution of weakness: 1 d) Bowel/bladder: urinary retention	Sensory: improvement (details: NR) Motor: no improvement (details: NR) Bowel/bladder: urinary (details: NR)	Autoimmune profile: RF (−Ve), ANA (−Ve), ANCA (−Ve), anti-SMA (−Ve), anti-Ro (−Ve), anti-ds DNA (−Ve), anti-mRNA (−Ve), antihistone (−Ve), anti-AQP4 (+Ve), anti-MOG (−Ve)	Microprotein 159 mg/dl, OCB: (−Ve)
26	Maideniuc and Memon[41]	61/F	HTN, hyperlipidemia, hypothyroidism	1 wk	Sensory: sensory loss below C3 tingling Motor: weakness in all 4 limbs, unable to walk, DTR increased, Babinski positive (Evolution of weakness: 3 d) Bowel/bladder: urinary retention/constipation	Sensory: NR Motor: started walking with walker Bowel/bladder: NR	Autoimmune profile: ANA (−Ve), C-ANCA (−Ve), P-ANCA (−Ve), anti-ds DNA (−Ve), anti-AQP4(−Ve), anti-MOG (−Ve)	Normal cells, elevated protein, IgG index: WNL OCB: (−Ve) SARS-CoV-2 RT-PCR: (−Ve) CSF paraneoplastic panel: (−Ve)
27	Zoghi et al.[32]	21/M	NA	17 d	Sensory: paraesthesia, loss of sensation T8 Motor: tetraparesis (power: upper limb 4+/5, lower limb 2/5) (Evolution of weakness: 24 hrs) Bowel/bladder: urinary retention, incontinence	Sensation: details: NR Motor: tetraparesis (power: upper limb: WNL, lower limb 3+/5) Bowel/bladder: NR	Autoimmune profile: anti-NMDAR (−Ve); anti-AQP4 (−Ve); anti-MOG (−Ve); ACE (−Ve); antiphospholipid (−Ve); ANA (−Ve); HLA B5, B51 (−Ve)	Lymphocytic pleocytosis, elevated protein, IgG index: raised OCB: −Ve SARS-CoV-2 RT-PCR: (−Ve) Viral markers: PCR (virus/ bacteria/ fungus): (–Ve)
28	Novi et al.[33]	64/M	HTN, vitiligo, and monoclonal gammopathy of undetermined significance	3 wks	Sensory: sensory loss below the right abdomen, visual impairment Motor: WNL Duration of evolution of weakness: NA Bowel/bladder: NR	Sensory: significant improvement in visual acuity Motor: WNL Bowel/bladder: NR	Autoimmune profile: anti-AQP4: (−Ve), anti-MOG: (−Ve)	Lymphocytic pleocytosis, hyperproteinorrachia OCB: (+Ve) Anti–SARS-CoV-2 IgG: (+Ve)

Radiological Findings												Treatment Outcome
Abnormal Radiological Findings		Spinal Involvement			Region/ Area Involvement			Demyelinating Pattern				
Lesion at Spinal Cord	Lesion at Brain	LETM	Short	Swelling Focal	1	2	≥3	Continuous	Patchy	Clinical Diagnosis	Treatment Received	Motor Recovery
C4–T5	NAD	+	−	−	−	+	−	+	−	ATM	IV-MPS, PLEX	Motor recovery: "moderate to significant improvement" Outcome assessment: at 2 mos
C3 to conus	NAD	+	−	+	−	−	+	+	−	NMO	IV-MPS, PLEX, HCQ, AZM, oseltamivir, favipiravir PCM, ceftriaxone, heparin	Motor recovery: "no improvement" Outcome assessment: day 30
C1–T1	NAD	+	−	+	+	−	−	+	−	ATM	IV-MPS, PLEX	Motor recovery: "moderate to significant improvement" Day of assessment: after 5 wks
Both brain and cervical region	+ (Posterior medial cortical surface of temporal lobe)	+	−	−	+	−	−	+	−	ADEM/NMO	Acyclovir, vancomycin, meropenem	Motor recovery: "moderate to significant improvement" Outcome assessment: day 15
Brain with B/L optic nerves and thoracic level (T8)	+ (Periventricular white matter)	−	+	−	+	−	−	−	+	ADEM	IV-MPS, IVIG	Motor recovery: motor deficits were absent Categorization: not done

(Continued on next page)

TABLE 1. *(Continued)*

SL No.	Study	Age, Yr/ Sex	Comorbidities	Latency Period (Time Since SARS-CoV-2 Infection)	Clinical Features		Laboratory Findings	
					At the Time of Diagnosis	At the Time of Hospital Discharge	Autoimmune Profiling and Viral Markers	CSF Analysis
29	Utukuri et al.[34]	44/M	NA	NR	Sensory: numbness B/L lower limbs Motor: B/L lower limb weakness, inability to walk Duration of evolution of weakness: 2 d Bowel/bladder: urinary retention	Sensory: NR Motor: NR Bladder/bowel: NR	Autoimmune profile: anticardiolipin IgM: mildly elevated, ACE: WNL	Lymphocytic pleocytosis, elevated protein IgG index: normal OCB: −Ve SARS-CoV-2 RT-PCR: (+Ve) Culture (bacteria/ virus): (−Ve)
30	Otluoglu et al.[35]	48/M	NR	NR	Sensory: anosmia, pain (myalgia) Motor: WNL Duration of evolution of weakness: NA Bowel/bladder: WNL	Sensory: NR Motor: WNL Bowel/bladder: NR	NR	Cells: absent (no cells detected), elevated protein Culture (bacteria/ virus): (−Ve) SARS-CoV-2 RT-PCR: (+Ve)
31	Wong et al.[36]	40/M	HTN, glaucoma	2 wks	Cranial nerves: diplopia, oscillopsia, nystagmus, B/L facial weakness Cerebellar sign: ataxia Sensory: no deficit Motor: WNL duration of evolution of weakness: 24 hrs Bladder/bowel: no dysfunction	Cranial nerves: nystagmus improved. Oscillopsia persisted. Cerebellar sign: ataxia persisted	Autoimmune profile: anti-MOG: NR, anti-AQ4: NR	Normal protein Culture (bacteria): (−Ve)
32	Zanin et al.[37]	54/F	Past H/O surgery for anterior communicating artery	NR	Sensory: no deficit Motor: WNL Bladder/bowel: no dysfunction Duration of evolution of weakness: NA Others: unconsciousness, anosmia, ageusia, seizure	Sensory: no deficit Motor: WNL Bladder/bowel: no dysfunction	NR	NAD

Radiological Findings											Treatment Outcome
Abnormal Radiological Findings		Spinal Involvement			Region/ Area Involvement			Demyelinating Pattern			
Lesion at Spinal Cord	Lesion at Brain	LETM	Short	Swelling Focal	1	2	≥3	Continuous	Patchy	Clinical Diagnosis	Treatment Received	Motor Recovery
Cervical and thoracic spinal cord Slight expansion of conus medullaris	+ (Parietal lobe, periventricular, and juxtacortical)	+	−	+	−	+	−	+	−	ADEM	IV-MPS, IVIG	Motor recovery: "moderate to significant improvement" Outcome assessment: at the end of treatment
Temporal lobe and upper cervical spinal cord	+ (Temporal lobe)	NR	NR	−	+	−	−	−	+	ADEM	IV-MPS, HCQ, acyclovir, favipiravir, piperacillin with tazobactam, levetiracetam	Motor recovery: motor deficits were absent Categorization: not done
Brain stem and upper cervical cord	+ (Right inferior cerebellar peduncle)	−	+	−	+	−	−	−	−	Rhombencephalitis with associated cervical myelopathy	Amoxicillin, PCM, gabapentin	Motor recovery: motor deficits were absent Categorization: not done
T2WI numerous focal intramedullary signal hyperintensity at bulbomedullary junction and at C2 and from C3T6	+ (Periventricular white matter)	+	−	−	−	+	−	−	+	ADEM	IV-dexamethasone, antiretroviral, HCQ, glycosamide, levetiracetam, phenytoin	Motor recovery: motor deficits were absent Categorization: not done

(Continued on next page)

TABLE 1. *(Continued)*

SL No.	Study	Age, Yr/ Sex	Comorbidities	Latency Period (Time Since SARS-CoV-2 Infection)	Clinical Features: At the Time of Diagnosis	Clinical Features: At the Time of Hospital Discharge	Laboratory Findings: Autoimmune Profiling and Viral Markers	Laboratory Findings: CSF Analysis
33	Corrêa et al.[39]	51/F	NA	2 wks	Sensory: dysesthetic abdominal band at T6–T10, lower limb numbness, proprioceptive deficits Motor: left lower limb weakness Duration of evolution of weakness: 2 d Bladder/bowel: urinary retention	Sensory: remarkable improvement (details: NR) Motor: remarkable improvement (details: NR) Bladder/bowel: remarkable improvement (details: NR)	Autoimmune profile: ANA (+Ve), anti-AQP4: (+Ve)	Lymphocytic pleocytosis, proteinorrachia, IgG index: positive SARS-CoV-2 RT-PCR: (−Ve)

AMAN, acute motor axonal neuropathy; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; AQP4, aquaporin 4; AZM, azithromycine; B/L, bilateral; C, cervical; CIS, clinically isolated syndrome; CMV, cytomegalovirus; CRF, chronic renal failure; DTR, deep tendon reflex; EBV, epstein-barr virus; F, female; F/U, follow-up; GB syndrome, Guillain-Barré syndrome; G6PD, glucose-6-phosphate dehydrogenase; HCQ, hydroxychloroquine; HSV, herpes simplex virus; HTLV-1, human T-lymphotropic virus type 1; HTN, hypertension; HZV, herpes zoster virus; IgM, immunoglobulinM; IHD, ischemic heart disease; IVIG, intravenous immunoglobulin; L, left; LL, lower limbs; M, male; MOG, myelin oligodendrocyte glycoprotein; NA, not applicable; NAD, no abnormality detected; NMDA R, anti-N-methyl-D-aspartate receptor; NR, not reported; PCM, paracetamol (antipyretics); R, right; RF, rheumatoid factor; SMA, smooth muscle antibody; SSA, Sjögren's syndrome-related antigen A; SSB, Sjögren's syndrome-related antigen B; T, thoracic; TB, tuberculosis; T2DM, type 2 diabetes mellitus; T2WI, T2-weighted image; VCA, viral capsid antigen; VDRL, venereal disease research laboratory; Ve, test report; VZ, varicella zoster; VZV, varicella-zoster virus; WNL, within normal limit.

18 patients (Table 1). Cells (white blood cells) were not detected in CSF of four patients.[26,28–30,38] Protein amount was normal in three patients.[24,26,38] Oligoclonal bands (OCBs) were identified in three patients.[24,26,33] Two patients were SARS-CoV-2 RT-PCR positive.[16,31]

Radiological Findings (AIM Without Any Brain Lesion)

Eight patients (30.8%)[11–13,17,19–21,25] presented demyelinating changes in "thoracic region only." Demyelinating change in "cervical region only" was seen in six patients (23.1%).[18,26–28,30,31] Another 12 patients (46.1%)[14–16,22–26,29,38,40,41] showed demyelinating changes in both the cervical and thoracic regions.

Radiological details of each patient are presented in Table 1. The mean length of the spinal lesion (signal changes) was 6.15 segments (vertebrae). Longitudinally extensive transverse myelitis (≥3 vertebral segments) was detected in 22 patients (84.6%).[11,12,14–20,22,23,25–28,30,38,40,41] Among them (n = 22), three had demyelinating changes in the entire spinal cord.[14,15,40]

Treatment Outcome (AIM Without Any Brain Lesion)

Sixty-seven percent of the patients[11,13–23,25,26,28–30,38,40,41] were treated with intravenous (IV) methylprednisolone (MPS), 39%[12,14–16,18,24–26,30,38,40,41] with plasma-exchange therapy (PLEX), and 21%[16,23–25,28–30] were treated with IV immunoglobulin. Antiviral medications were given to 27% of the patients (n = 7).[11,17,22,23,26,30,40]

After acute hospital treatment, 42.3% of the patients (n = 11) had "moderate to significant" improvement[11,18–20,22,23,26–28,38,41] and 18.2% (n = 2) had "marginal to slight" improvement[12,24] in lower limb motor functions. Seven patients (27%)[15,16,25,26,29,30,40] did not report any improvement in lower limb motor function.

Among the patients with LETM (n = 21), 20 reported motor deficits in lower limbs. One patient[14] (with LETM) did not report any kind of motor deficit in the lower limb. Of the 20 patients with motor deficits, two died. After acute treatment, "moderate to significant" improvement in lower limb motor function was seen in 55% of the patients, and "marginal to slight" improvement was seen in one patient. Six patients (30%) did not report any improvement in lower limbs.

Short-segment demyelinating changes were seen in five patients.[13,21,24,29,31] Among them (n = 5), three[13,24,29] reported motor deficits in the lower limb, and two did not report any motor deficits. Among the three patients with motor deficits, one death[13] was reported and one showed "marginal to slight" improvement in the lower limb.[24] One patient[29] did not report improvement in the lower limb.

Clinical, Laboratory, and Radiological Findings and Treatment Outcome of Patients With "AIM With a Brain Lesion"

The group, "AIM with a brain lesion," included seven patients[32–37,39] (male/female: 5/2) with a mean age of 46.6 (12.74) yrs. Clinical features of these patients are summarized in Table 1.

Radiological Findings												Treatment Outcome
Abnormal Radiological Findings		Spinal Involvement			Region/ Area Involvement			Demyelinating Pattern				
Lesion at Spinal Cord	Lesion at Brain	LETM	Short	Swelling Focal	1	2	≥3	Continuous	Patchy	Clinical Diagnosis	Treatment Received	Motor Recovery
T2WI and FLAIR hyperintensity in the fornix and subfornical organ with contrast and LETM on spine MRI	+ (Fornix and in the subfornical organ)	+	−	−	−	+	−	+	−	ADEM	IV-MPS, PLEX, azathioprine	Motor: recovery: "moderate to significant improvement" Outcome assessment: day 6

Clinical Features (AIM With a Brain Lesion)

Of 7 patients, 42.8% had lower limb weakness[32,34,39] and 85.7% had sensory symptoms.[32–36,39] Bowel bladder dysfunction was seen in 42.8% of the patients.[32,34,39] Visual impairment was seen in two patients.[33,36] One patient reported episodes of seizure.[37]

Laboratory Findings (AIM With a Brain Lesion)

On CSF analysis, four patients[32–34,39] had pleocytosis and five had elevated protein.[32–35,39] Oligoclonal bands were seen in one patient.[33] Two patients were SARS-CoV-2 RT-PCR positive.[34,35] Anti–SARS-CoV-2 immunoglobulin G (IgG) antibody was detected in one patient.[33]

Radiological Findings (AIM With a Brain Lesion)

Among the patients with "AIM with a brain lesion," LETM was seen in four patients,[32,34,37,39] and short-segment demyelinating lesion was found in two patients.[33,36] Extent (exact length) of the demyelinating lesion (in cervical region) was not reported in one patient.[35]

Treatment Outcome (AIM With a Brain Lesion)

Five patients[33–35,37,39] were treated with MPS, One[39] with PLEX and two[33,34] were treated with IV immunoglobulin treatment. Three patients[32,35,37] received antiviral medications.

No deaths were reported in patients with "AIM with a brain lesion." After receiving treatments, all patients (including patients with motor deficits) reported "moderate to significant improvement."

DISCUSSION

This review suggests that the SARS-CoV-2 virus, like other viral diseases[28] (eg, Herpesviridae, Flaviviridae, Paramyxoviridae, Orthomyxoviridae), can affect the spinal cord and can result in AIM. In 2020, 33 cases of AIM (7 patients with brain and spinal cord involvement) had been reported after SARS-CoV-2 infection.

The exact mechanism of spinal cord involvement after COVID-19 infection has not yet been determined. However, it has been suggested that SARS-CoV-2 can damage the spinal cord through the angiotensin-converting enzyme (ACE) 2 receptors present in the cell surface[23,26,29] or through the mechanism of cytokine storm or post–infectious inflammatory or immune-mediated mechanism.[13,23,29,42,43]

A significant number of cases (86.4%)[11,12,14,15,18–20,24–27,30–33,36,39,41] in this review reported a longer latency period (≥7 days), which suggests post–infective immunological disorder is likely the cause of spinal cord damage. It has been postulated that the altered immune response (immune reaction against the agent), due to an imbalance between the proinflammatory and anti-inflammatory cytokines in COVID-19, initiates the demyelinating process silently in genetically susceptible persons.[40,43] Cytokine storm is the proinflammatory state characterized by increased release of interleukin 1, interleukin 6, and tumor necrosis factor α.[12,43] It is a well-known complication of COVID-19 infection and can cause activation of the glial cells

with subsequent demyelination of the spinal cord.[42–44] Late and insufficient release of the interferons (interferon α and interferon β) in COVID-19 infection further facilitates the spread of the virus in the human body.[40,43]

Acute inflammatory myelopathies usually, at their peak, cause paraplegia (50%), bladder dysfunction (100%), and sensory deficits (80%–94%).[45] In this review, we also observed similar findings. Besides this, we also found six patients,[12,14,17,23,25,26] with low back pain, two with visual problems,[33,36] and one patient[37] with episodes of seizure.

Lymphocytic pleocytosis and increased protein count in CSF have been reported as essential characteristics of acute inflammation of the spinal cord.[7] However, in CSF study, cell counts and protein amount can be found normal in few subsets of AIMs (e.g., multiple sclerosis and ADEM).[5] In this review, we observed pleocytosis and increased protein count in 56.7% and 76.7% of the patients, respectively.

Similar to the observations,[8] made by many of the included studies,[14,31,33,35–37] this review also could not find any specific relationship with the neurological level of injury (sensory and/or motor level, on clinical examination) and site of lesions, seen on MRI (at the time of admission). Even in patients with AIM who had a weakness, their neurological levels (sensory and/or motor level) did not match their radiological lesions (on MRI spine). Therefore, it is essential to have MRI screening of the entire spine and brain irrespective of their neurological level (sensory and/or motor level) if they are suspected of inflammatory myelopathy. This review observed two patients with LETM[14,37] and four patients with short-segment demyelination at the spinal cord,[31,33,35,36] which had not presented with the typical acute symptom onset of motor weakness.

Cree[9] identified several clinical features, which could predict a better prognosis after AIM. These favorable factors included older age at symptom onset, hyperreflexia, and posterior column sensation, Babinski signs at the peak of the deficit. In this review, we found 10 patients with hyperreflexia[11,18,19,24,26,27,29,33,38,41] during the peak of the attack; among them, eight patients (80.0%)[11,18,19,26,27,33,38,41] improved significantly ("moderate to significant improvement") in motor function.

In the treatment of AIM, several drugs have been tried to reduce spinal cord inflammation and prevent further damage to the spinal cord. These drugs included IV-MPS, plasma-exchange therapy, immunosuppressive drugs like cyclophosphamide, azathioprine, immunoglobulin, and treatment with monoclonal antibody rituximab.[46] Of all medications, IV-MPS is used most frequently in these cases, especially immediately after diagnosis.[8,46] In this review, 13 patients (50%, of 26) reported significant motor recovery in both lower limbs after corticosteroid/MPS injection. Similar to our observation, many studies[47–51] reported significant motor improvement after MPS therapy.

Patients with AIM usually experience multiple disabilities, including motor deficits, sensory impairments, bowel bladder dysfunction, and sexual problems. Many studies[8,52,53] have reported significant functional recovery after inpatient rehabilitation. After an acute attack of inflammatory myelopathy, one third of patients achieve almost full motor recovery, one third experience a moderate degree of permanent disability, and one third of patients fail to improve (severe disability) or do not survive.[7,45] Patients who eventually achieve full motor recovery (100%) can have persistent bladder dysfunction (50%–86%), bowel deficits (36%–77%), and sexual dysfunction (82%).[54] However, it has to be remembered that these data have come from patients of AIMs due to non-COVID etiologies. Comprehensive multidisciplinary rehabilitation is of paramount importance for patients with AIM. Based on our review, similar clinical findings and rehabilitation needs are present in the COVID-associated AIM population. These issues usually include management of spasticity, pain, paraesthesia, fatigue, motor deficits, bowel bladder, and sexual dysfunctions.[46] Previous data suggest that irrespective of the etiological factors, the chances of recurrences (neurological deficits) after AIM are very high (17.5%–61%).[46] Therefore, it is essential to monitor neurological status, inflammatory, and infective markers regularly, especially if it is diagnosed as a postinfective complication of COVID-19.

LIMITATIONS

This review has several limitations. First of all, this review included only case reports. Therefore, unintentional biases are inherent in the selection and interpretation of case series. Second, there was no uniformity in reporting the clinical features of motor weakness, bowel bladder dysfunction, and functional outcomes. Third, this series could not document the severity of sensory, motor, and functional deficits after AIM as there was no standardized data. Based on motor recovery of bilateral lower limbs, the neurological outcome was assessed. No standardized functional assessment scale was used. Finally, there was no definite duration of the follow-up period or outcome assessment. The outcome assessment period varied between 6 days to 2 mos. Besides these, the majority of the included patients were assessed before initiating comprehensive neurorehabilitation. Although few cases reported that their cases received physical and occupational therapy management, details of rehabilitation management during the hospital stay and at follow-up visits were not available. Thus, details on the need for rehabilitation strategies, length of stay in rehabilitation hospitals, discharge facilities, and postinjury complications could not be discussed.

Moreover, one of the essential aspects of outcomes of COVID-19–associated AIM is the quality of life and mental health, and there were no data on these issues. Despite these shortcomings, the present organized review will act as a preliminary guide for clinicians while dealing with suspected cases of SARS-CoV-2 infection–associated AIM. In addition, these data can increase international curiosity as it can be compared with previously published results in the pre–COVID-19 era.

CONCLUSIONS

The SARS-CoV-2 virus has the potential to affect the central nervous system and can cause AIM. However, COVID-associated AIM may or may not be associated with a brain lesion. Like other myelopathies, reported cases of COVID-related AIM include sensory motor and bowel bladder dysfunctions. Acute inflammatory myelopathy associated with COVID-19 infection can range from involving a short segment to an extensive demyelinating spinal cord lesion. Lymphocytic pleocytosis

and increased protein are the commonly found abnormal parameters in CSF analysis. Early treatment with IV MPS has shown improved outcomes in patients with AIM.

This study is only a preliminary review of AIM, which can be stated as an additional cause of functional loss after COVID-19 infection. We have identified the need for further research on the outcome and success of rehabilitation in these patients on detailed analysis. Further studies with a large population having received comprehensive, holistic rehabilitation, and long-term follow-up are required to determine the exact prognosis of patients with AIM associated with COVID-19 infection.

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