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

A Narrative Review

Apurba Barman, MD, Jagannatha Sahoo, DNB, Amrutha Viswanath, MBBS, Sankha Subhra Roy, MBBS, Raktim Swarnakar, MD, and Souvik Bhattacharjee, MBBS

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 intravenous methylprednisolone and the anterior funiculus of the spinal cord at one or more levels.4 Longitudinally extensive transverse myelitis results in diffuse demyelination of the cerebral white matter along with the involvement of the spinal cord.1 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.3,6 Radiologically, AIM is characterized by enhancement of the lesions (demyelinating) after contrast (gadolinium) administration.5,9

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, 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.6,7 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 “Demyelinating 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, SR) 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 AIM11–41) were included in this review. Among them (N = 33), 26 patients (24 case reports)11–33,38,40,41 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 patients15,29 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.
Of the 33 patients with AIM, 82% (n = 27) 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 to 3 wks. Six patients 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 (17%) were CSF SARS-CoV-2 RT-PCR positive.

Demyelinating change in “thoracic region only” was seen in nine patients. Simultaneous and/or overlapping involvement of both regions, “cervical and thoracic,” were seen in 15 patients. 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%) and short-segment spinal demyelinating lesions (lesions extending <3 vertebral segments) were seen in 7 patients (21%). Extent (exact length) of spinal (cervical) segment involvement (demyelination) was not reported in one patient. Among the patients with LETM lesions (n = 25), demyelinating lesions in the entire spinal cord (upper cervical to conus) were seen in three patients.

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). 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%). One had hemiplegia, 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) to 7 days. Sensory deficits (abnormal sensation) were reported in 21 patients. Definite clear sensory level (sensory loss below particular level) was reported in 66.7% of the patients whereas altered sensations (in form of tingling, numbness, and/or paraesthesia but without sensory level) were reported in 33.3% of the patients. Six patients reported low back pain. Bowel bladder dysfunctions were reported in 23 patients. Common bladder dysfunctions were urinary retention, urinary overflow incontinence, and urinary urgency (Table 1).

Laboratory Findings (AIM Without Any Brain Lesion)

On CSF analysis, pleocytosis was seen in 13 patients, and elevated protein was seen in 21 patients.
TABLE 1. Clinical features, laboratory, and radiological findings of the patients with AIM after COVID-19 infection

| SL No. | Study | Age, Yr/ Sex | Comorbidities | Latency Period (Time Since SARS-CoV-2 Infection) | Clinical Features | Laboratory Findings | Autoimmune Profiling and Viral Markers | CSF Analysis |
|--------|-------|--------------|---------------|-----------------------------------------------|------------------|---------------------|-----------------------------------------|-------------|
| 1      | Manz et al.11 | 60/M | HTN, fatty liver, ureterolithiasis | 8 d | Sensory: hypoesthesia below T9 level | Lymphocytic pleocytosis (27 μl), elevated protein levels (1177 mg/l) OCB: (−Ve) SARS-CoV-2 PCR: (−Ve) |
|        |       |   |   | Motor: spastic paraparesis, unable to walk, Babinski sign (B/L) (+Ve) (Evolution of weakness: NR) | Motor: slight spastic paraparesis, able to walk | | anti-AQP4 (−Ve), anti-MOG (−Ve), ANA (−Ve), antineuronal Ab (−Ve) Viral markers: HHV-6, EBV, Hep E, HSV, VZV: (−Ve) |
|        |       |   |   | Bladder/bowel: bladder dysfunction | Bladder: normal bladder function | | | |
| 2      | Baghbanian and Namazi12 | 53/F | T2DM, HTN, IHD | 2 wks | Sensory: sensory level at T10 and low back pain | | Lymphocytic pleocytosis, IgG index (higher normal limits = 0.71) OCB: (−Ve) SARS-CoV-2 PCR: (−Ve) |
|        |       |   |   | Motor: flaccid paraparesis (power: right lower limb: 3/5 and left lower limb: 0/5), lower limb areflexia (Evolution of weakness: 2 d) | Motor: paresis recovered to a certain degree | | anti-NMO (−Ve), anti-MOG (−Ve) |
|        |       |   |   | Bladder/bowel: urinary incontinence | Bladder/bowel: NR | | |
| 3      | Chakraborty et al.13 | 59/F | Obesity | NR | Sensory: decreased sensation below T10 level | | Lymphocytic pleocytosis, increased protein level (71.4 mg/dl) |
|        |       |   |   | 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 | | | |
| 4      | Sarma and Bilella14 | 28/F | Hypothyroidism | 1 wk | Sensory: decreased sensation below T5 | Lymphocytic pleocytosis, increased protein OCB: (−Ve) Antibody (SARS-CoV-2): (−Ve) |
|        |       |   |   | Motor: WNL | | | anti-MOG: (−Ve), ANA: (−Ve) |
|        |       |   |   | Bladder/bowel: urinary retention | Bladder/bowel: WNL | | |
| 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 | | Pleocytosis, increased protein level, IgG index (higher normal limits = 0.7) OCB: (−Ve) |
|        |       |   |   | Motor: power: 4/5 power in B/L upper limb and 3/5 in B/L lower limbs | Motor: paraplegia (no improvement) | | anti-MOG: (−Ve) |
|        |       |   |   | Bladder/bowel: urinary retention and constipation | Bladder/bowel: neurogenic bladder and bowel | | |

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| Abnormal Radiological Findings | Radiological Findings | Treatment Outcome |
|--------------------------------|----------------------|-------------------|
| Lesion at Spinal Cord | Lesion at Brain | LETM Short | Focal Region/Area Involvement | Demyelinating Pattern | 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 |

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| SL No. | Study | Age, Yr/ Sex | Comorbidities | Latency Period (Time Since SARS-CoV-2 Infection) | Clinical Features | Laboratory Findings |
|--------|--------|--------------|---------------|-----------------------------------------------|------------------|---------------------|
| 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 | Autoimmune profile: anti-AQ4: (−Ve), anti-MOG: (−Ve), RF: (−Ve) Viral markers: HSV, HIV, EBV, CMV, etc.: (−Ve) CSF Analysis: 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: bladder incontinence | Death | Autoimmune profile: ANCA (−Ve), ANA (−Ve) TB PCR (−Ve) Viral markers: (−Ve) SARS-CoV-2 RT-PCR (CSF): (+Ve) |
| 8      | Sotoca and Rodríguez-Álvarez18 | 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-AQ4P: (−Ve), antineuronal surface antibody: (−Ve) Lymphocytic pleocytosis, increased protein IgG index: WNL OCB: (−Ve) Culture (bacteria/ virus): (−Ve) Elevate protein |
| 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) |
| 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-AQ4P (−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-AQ4P (−Ve), ANA (−Ve), ANCA (−Ve), ACE (−Ve), antiphospholipid (−Ve) Lymphocytic pleocytosis OCB: (−Ve) |
| Lesion at Spinal Cord | Lesion at Brain | Spinal Involvement | Region/ Area Involvement | Demyelinating Pattern | Clinical Diagnosis | Treatment Received | Motor Recovery |
|----------------------|----------------|-------------------|--------------------------|-----------------------|-------------------|-------------------|---------------|
| C1-T6                | NAD            | + -               | + -                      | + -                   | LETM              | IV-MPS, PLEX, 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 |

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| SL No. | Study | Age, Yr/ Sex | Comorbidities | Latency Period (Time Since SARS-CoV-2 Infection) | Clinical Features | Laboratory Findings | Autoimmune Profiling and Viral Markers | CSF Analysis |
|--------|-------|--------------|---------------|-----------------------------------------------|------------------|---------------------|----------------------------------------|-------------|
| 12     | AlKetbi et al.22 | 32/M | Nil | 2 d | Sensory: normal | Autoimmune profile: ANCA: (+Ve), RF: (−Ve), antiphospholipid: (−Ve) | NR |
|        |       |              |               | 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 | Lymphocytic pleocytosis, increased protein, IgG index: elevated OCB: (−Ve) | |
| 13     | Hazrati et al.23 | 63/M T2DM, CRF, IHD | 4 d | Sensory: decreased sensation below T8, lower thoracic pain | Autoimmune profile: anti-MOG (−Ve), anti-AQP4 (−Ve), anti-NMO: (−Ve), ANA: (−Ve), antiphospholipid (−Ve), antilipoprotein (−Ve), anti-centromere: (−Ve), anti-Scl70: (−Ve), anti-dsDNA: (−Ve), anti-SS-A/SS-B: (−Ve), antinucleosome: (−Ve) | SARS-CoV-2 RT-PCR: (+Ve) |
|        |       |              |               | Motor: flaccid paraparesis, power: 1/5 in B/L LL, areflexia in lower limbs (Evolution of weakness: NR) | Bladder/bowel: urinary retention and constipation | | |
| 14     | Masuccio et al.24 | 70/F Obesity, HTN | 15 d | Sensory: decreased sensation in LL | Autoimmune profile: anti-GD1β IgM: (+Ve) | Normal protein OCB: (+Ve) |
|        |       |              |               | Motor: flaccid paralysis | | |
|        |       |              |               | (power: upper limb: 3/5, lower limb: 0/5) (Evolution of weakness: 5 d) | Motor: power lower limbs, improved to 1/5 (details: NR) | Viral markers: antibody (EBV, CMV, HSV, HZV, HIV, etc.): (−Ve) | |
| 15     | Khedr et al.25 | 60/F Hypothyroidism | 10 d | Sensory: loss of sensation below T4, girdle-like pain | Autoimmune profile: NR | NR |
|        |       |              |               | Motor: complete flaccid lower limb paralysis, areflexia (Evolution of weakness: 2 d) | Motor: complete flaccid lower limb paralysis, areflexia (Evolution of weakness: 2 d) | | |
| Lesion at Spinal Cord | Lesion at Brain | Spinal Involvement | Region/Area Involvement | Demyelinating Pattern | 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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| SL No. | Study | Age, Yr | Sex | Comorbidities | Latency Period (Time Since SARS-CoV-2 Infection) | Clinical Features | Laboratory Findings |
|--------|-------|---------|-----|---------------|-----------------------------------------------|------------------|---------------------|
| 16     | Khedr et al. | 21/F | Nil | 10 d | Sensory: loss of sensory below C4 | Sensory: no improvement (details: NR) | Autoimmune profile: | Neutrophilic pleocytosis, increased protein |
|        |       |        |     |     | Motor: flaccid quadriplegia, more weakness in B/L lower limbs, areflexia (Evolution of weakness: few hours) | Motor: power in the upper limb: mild improvement, the lower limb: no improvement | NR | |
|        |       |        |     |     | Bladder/bowel: urinary retention and fecal incontinence | Bladder/bowel: no improvement (details: NR) | | |
| 17     | Advani et al. | 47/M | NR | 10 d | Sensory: loss of sensation below T10, dull pain in the abdomen | Sensory: no improvement (details: NR) | Autoimmune profile: | |
|        |       |        |     |     | Motor: flaccid paraplegia (power bilateral lower limbs: 0/5, areflexia) (Evolution of weakness: abrupt onset) | Motor: no improvement (details: NR) | anti-AQP4: (−Ve); ANCA (−Ve); antcardiolipin: (−Ve), lupus anticoagulant, protein S, C (−Ve); anti-β-2 glycoprotein: (−Ve) | Culture (viral/ bacteria): (−Ve) |
|        |       |        |     |     | Bladder/bowel: urinary retention | Bladder/bowel: no improvement (details: NR) | | Viral markers: EBV, HSV, VZ: (−Ve) |
| 18     | Advani et al. | 67/F | NR | NR | Sensory: no sensory loss, only paraesthesia at the chest. | Sensory: complete recovery | Autoimmune profile: | No cell, normal protein IgG index: high OCB: +Ve |
|        |       |        |     |     | Motor: spastic paraparesis, weakness of the bilateral lower limbs with power: 4−/ 5, hyperreflexia | Motor: muscle power improved to 4+/5, fully ambulatory | anti-AQP4: (−Ve); ANCA (−Ve); antcardiolipin: (−Ve), lupus anticoagulant, protein S, C negative; anti-β-2 glycoprotein: (−Ve) | Culture (viral/ bacteria): (−Ve) |
|        |       |        |     |     | Duration of evolution of weakness: NR | Duration of evolution of weakness: NR | | Viral markers: EBV, HSV, VZ, etc.: (−Ve) |
| 19     | Fumery et al. | 38/F | NR | 2 wks | Sensory: hypoesthesia below T4 level | Sensory: status improved (details: NR) | Autoimmune profile: | Lymphocytic pleocytosis, elevated protein |
|        |       |        |     |     | Motor: motor paraparesis (power: 4-5), hyperreflexia | Motor: status improved (details: NR) | anti-AQP4: (−Ve), MOG: (−Ve) | OCB: (−Ve) |
|        |       |        |     |     | Duration of evolution of weakness: NR | Duration of evolution of weakness: NR | | Viral markers: HTLV-1, West Nile, CMV, EBV, EBV, HIV: (−Ve) |
|        |       |        |     |     | Bladder/bowel: urinary retention | Bladder/bowel: status improved (details: NR) | SARS-CoV-2 RT-PCR: (−Ve) | |
| Lesion at Spinal Cord | Lesion at Brain | LETM Short | Focal Swelling | 1 2 3 | Continuous Region/Area Involvement | Demyelinating Pattern | 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 |

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| SL No. | Study | Age, Yr/ Sex | Comorbidities | Latency Period (Time Since SARS-CoV-2 Infection) | Clinical Features | Laboratory Findings |
|--------|-------|--------------|---------------|-----------------------------------------------|-------------------|-------------------|
|        |       |              |               |                                               |                   |                   |
|        |       |              |               |                                               |                   |                   |
| 20     | Güler et al.28 | 14/F | NR | Sensory: neuropathic pain (details: NR) | Motor: improved, started to walk unsupported (details: 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) |
|        |       |              |               |                                               |                   |                   |
|        |       |              |               |                                               |                   |                   |
| 21     | Gracia et al.29 | 72/M | HTN | Sensory: dysesthesia, sensory loss below T9 | Sensory: status (details: NR) | Autoimmune profiling: anti-MOG (−Ve), anti-AQP4. (−Ve), anti-MOG (−Ve), ANA (−Ve), ANCA (−Ve), antiphospholipid (−Ve), anticardiolipin (−Ve), C3 and C4 (−Ve) |
|        |       |              |               |                                               |                   |                   |
|        |       |              |               |                                               |                   |                   |
| 22     | Saberi et al.30 | 60/M | DM, hyperlipidemia, HTN | Sensory: status (details: NR) | Sensory: status (details: NR) | Autoimmune profile: anti-NMO: (−Ve) |
|        |       |              |               |                                               |                   |                   |
| 23     | Domingues et al.31 | 42/M | Similar H/O neurological episode 3 yrs before. Recovered completely without evaluation and treatment. | Sensory: normal (full recovery) | Sensory: normal (full recovery) | Autoimmune profile: ANA (−Ve), anti-SSA (−Ve), anti-SSB (−Ve) |

**TABLE 1. (Continued)**
| Abnormal Radiological Findings | Radiological Findings | Treatment | Outcome |
|-------------------------------|-----------------------|-----------|---------|
| Lesion at Spinal Cord | Spinal Involvement | Region/Area Involvement | Demyelinating Pattern | 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) | At the Time of Diagnosis | At the Time of Hospital Discharge | Clinical Features | Laboratory Findings |
|--------|-------|--------------|---------------|-----------------------------------------------|--------------------------|-------------------------------|------------------|----------------------|
| 24     | Nemtan et al. | 27/M | HIV infection for the past 1 yr, on ART | Sensory: paraesthesia, numbness B/L, lower limbs and right arm, sensory loss below C6 | Sensory: details NR | Motor: power B/L lower limbs 1–2/5 | Sensory: paraesthesia, numbness B/L, lower limbs and right arm, sensory loss below C6 | Autoimmune profiling: ANA: (~Ve), ANCA: (~Ve), anti-AQP4: (~Ve), anti-MOG: (~Ve) |
|        |       |              |               | Motor: power B/L lower limbs significant improvement (details: NR) | Motor: power B/L lower limbs significant improvement (details: NR) | Bladder/bowel: sphincter disturbance less severe (details: NR) | Motor: power B/L lower limbs significant improvement (details: NR) | Viral markers: HSV-1, HSV-2, HSV-6, CMV, EBV, Borrelia burgdorferi, etc.: (~Ve) |
|        |       |              |               | Duration of evolution of weakness: 15 hrs | Duration of evolution of weakness: 15 hrs | | Duration of evolution of weakness: 15 hrs | SARS-CoV-2 RT-PCR: (~Ve) |
|        |       |              |               | Bladder/bowel: urinary retention, constipation | Bladder/bowel: urinary retention, constipation | | Bladder/bowel: urinary retention, constipation | CSF Analysis |
| 25     | Batum et al. | 50/F | Nil | Sensory: sensory loss below T4, numbness, paraesthesia | Sensory: improvement (details: NR) | Motor: weakness bilateral lower limbs, areflexia (Evolution of weakness: 1 d) | Sensory: sensory loss below T4, numbness, paraesthesia | Autoimmune profile: RF (~Ve), ANA (~Ve), ANCA (~Ve), anti-SMA (~Ve), anti-Ro (~Ve), anti-ds DNA (~Ve), antimRNA (~Ve), antihistone (~Ve), anti-AQP4 (~Ve), anti-MOG (~Ve) |
|        |       |              |               | Motor: no improvement (details: NR) | Motor: no improvement (details: NR) | | Motor: no improvement (details: NR) | Microprotein 159 mg/dl, OCB: (~Ve) |
| 26     | Maideniuc and Memon41 | 61/F | HTN, hyperlipidemia, hypothyroidism | Sensory: sensory loss below C3 tingling | Sensory: NR | Motor: weakness in all 4 limbs, unable to walk, DTR increased, Babinski positive (Evolution of weakness: 3 d) | Sensory: sensory loss below C3 tingling | Autoimmune profile: ANA (~Ve), C-ANCA (~Ve), P-ANCA (~Ve), anti-ds DNA (~Ve), anti-AQP4 (~Ve), anti-MOG (~Ve) |
|        |       |              |               | Motor: started walking with walker | Motor: started walking with walker | | Motor: started walking with walker | Normal cells, elevated protein, IgG index: WNL |
|        |       |              |               | Bladder/bowel: urinary retention, constipation | Bladder/bowel: urinary retention, constipation | | Bladder/bowel: urinary retention, constipation | OCB: (~Ve) |
| 27     | Zoghi et al. | 21/M | NA | Sensory: paraesthesia, loss of sensation T8 | Sensation: details: NR | Motor: tetraparesis (power: upper limb 4+/5, lower limb 2/5) (Evolution of weakness: 24 hrs) | Sensory: paraesthesia, loss of sensation T8 | Autoimmune profile: anti-NMDAR (~Ve), anti-AQP4 (~Ve), anti-MOG (~Ve), ACE (~Ve), antiphospholipid (~Ve), ANA (~Ve), HLA B5, B51 (~Ve) |
|        |       |              |               | Motor: tetraparesis (power: upper limb WNL, lower limb 3+/5) | Motor: tetraparesis (power: upper limb WNL, lower limb 3+/5) | | Motor: tetraparesis (power: upper limb WNL, lower limb 3+/5) | Lymphocytic pleocytosis, elevated protein, IgG index: raised |
|        |       |              |               | Bladder/bowel: urinary retention, incontinence | Bladder/bowel: urinary retention, incontinence | | Bladder/bowel: urinary retention, incontinence | OCB: (~Ve) |
|        |       |              |               | | | | | SARS-CoV-2 RT-PCR: (~Ve) |
| 28     | Novi et al.33 | 64/M | HTN, vitiligo, and monoclonal gammopathy of undetermined significance | Sensory: sensory loss below the right abdomen, visual impairment | Sensory: significant improvement in visual acuity | Motor: WNL | Sensory: sensory loss below the right abdomen, visual impairment | Autoimmune profile: anti-AQP4: (~Ve), anti-MOG: (~Ve) |
|        |       |              |               | Motor: WNL | Motor: WNL | | Motor: WNL | Lymphocytic pleocytosis, hyperproteinorrachia |

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| Abnormal Radiological Findings | Radiological Findings | Treatment | Outcome |
|-------------------------------|------------------------|-----------|---------|
| Lesion at Spinal Cord | Lesion at Brain | LETM Short | Swelling Focal | Region/Area Involvement | Demyelinating Pattern | 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) | + (P Virventricular white matter) | − | + | − | − | − | + | ADEM | IV-MPS, IVIG | Motor recovery: motor deficits were absent Categorization: not done |

(Continued on next page)
| SL No. | Study | Age, Yr/ Sex | Comorbidities | Latency Period (Time Since SARS-CoV-2 Infection) | Clinical Features | Laboratory Findings |
|--------|-------|--------------|---------------|-----------------------------------------------|-------------------|----------------------|
| 29     | Utukuri et al. 34 | 44/M          | NA            | NR                                            | Sensory: numbness B/L lower limbs | Autoimmune profile: anticardiolipin IgM: mildly elevated, ACE: WNL |
|        |       |               |               |                                               | Motor: B/L lower limb weakness, inability to walk | Lymphocytic pleocytosis, elevated protein |
|        |       |               |               |                                               | Duration of evolution of weakness: 2 d | IgG index: normal |
|        |       |               |               |                                               | Bowel/bladder: urinary retention | OCB: −Ve |
|        |       |               |               |                                               | Bladder/bowel: NR | SARS-CoV-2 RT-PCR: (+Ve) |
|        |       |               |               |                                               |                  | Culture (bacteria/virus): (−Ve) |
| 30     | Othooglu et al. 35 | 48/M          | NR            | NR                                            | Sensory: anosmia, pain (myalgia) | NR |
|        |       |               |               |                                               | Motor: WNL | Cells: absent (no cells detected), elevated protein |
|        |       |               |               |                                               | Duration of evolution of weakness: NA | Culture (bacteria/virus): (−Ve) |
|        |       |               |               |                                               | Bowel/bladder: WNL | SARS-CoV-2 RT-PCR: (+Ve) |
|        |       |               |               |                                               |              | (−Ve) |
| 31     | Wong et al. 36 | 40/M          | HTN, glaucoma  | 2 wks                                         | Cranial nerves: diplopia, oscillopsia, nystagmus, B/L facial weakness | Autoimmune profile: anti-MOG: NR, anti-AQ4: NR |
|        |       |               |               |                                               | Cerebellar sign: ataxia | Normal protein |
|        |       |               |               |                                               | Sensory: no deficit | Culture (bacteria): (−Ve) |
|        |       |               |               |                                               | Motor: WNL | |
|        |       |               |               |                                               | Duration of evolution of weakness: 24 hrs | |
|        |       |               |               |                                               | Bladder/bowel: no dysfunction | |
| 32     | Zanin et al. 37 | 54/F          | Past H/O surgery for anterior communicating artery | NR                | Sensory: no deficit | NR |
|        |       |               |               |                                               | Motor: WNL | |
|        |       |               |               |                                               | Bladder/bowel: no dysfunction | NAD |
| Abnormal Radiological Findings | Radiological Findings | Treatment Outcome |
|-------------------------------|-----------------------|-------------------|
| Cervical and thoracic spinal cord | + (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 Aminocillin, 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)
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.24,26,33 Oligoclonal bands (OCBs) were identified in three patients.24,26,33,28 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 cm. (12.74) yrs. Clinical features of these patients are summarized in Table 1. 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 patients11,13–23,25,26,28–30,38,40,41 were treated with intravenous (IV) methylprednisolone (MPS), 39%2,14–16,18,24–26,30,38,40,41 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” improvement11,18–20,22,23,26–28,38,41 and 18.2% (n = 2) had “marginal to slight” improvement12,24 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 patient14 (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), three13,24,29 reported motor deficits in the lower limb, and two did not report any motor deficits. Among the three patients with motor deficits, one death13 was reported and one showed “marginal to slight” improvement in the lower limb.24 One patient29 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 patients12–37,39 (male/female: 5/2) with a mean age of 46.6 (12.74) yrs. Clinical features of these patients are summarized in Table 1.
**Clinical Features (AIM With a Brain Lesion)**

Of 7 patients, 42.8% had lower limb weakness and 85.7% had sensory symptoms. Bowel bladder dysfunction was seen in 42.8% of the patients. Visual impairment was seen in two patients. One patient reported episodes of seizure.

**Laboratory Findings (AIM With a Brain Lesion)**

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

**Radiological Findings (AIM With a Brain Lesion)**

Among the patients with “AIM with a brain lesion,” LETM was seen in four patients and short-segment demyelinating lesion was found in two patients. Extent (exact length) of the demyelinating lesion (in cervical region) was not reported in one patient.

**Treatment Outcome (AIM With a Brain Lesion)**

Five patients were treated with MPS, One with PLEX and two with IV immunoglobulin treatment. Three patients 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 (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) receptors present in the cell surface or through the mechanism of cytokine storm or post-infectious inflammatory or immune-mediated mechanism.

A significant number of cases (86.4%) 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. Cytokine storm is the proinflammatory state characterized by increased release of interleukin 1, interleukin 6, and tumor necrosis factor α. 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.\textsuperscript{42–44} Late and insufficient release of the interferons (interferon $\alpha$ and interferon $\beta$) in COVID-19 infection further facilitates the spread of the virus in the human body.\textsuperscript{40,43}

Acute inflammatory myelopathies usually, at their peak, cause paraplegia (50%), bladder dysfunction (100%), and sensory deficits (80%–94%).\textsuperscript{45} In this review, we also observed similar findings. Besides this, we also found six patients,\textsuperscript{12,14,17,23,25,26} with low back pain, two with visual problems,\textsuperscript{33,36} and one patient\textsuperscript{47} 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.\textsuperscript{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).\textsuperscript{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,\textsuperscript{5} made by many of the included studies,\textsuperscript{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\textsuperscript{14,43}, and four patients with short-segment demyelination at the spinal cord,\textsuperscript{31,33,35,36} which had not presented with the typical acute symptom onset of motor weakness.

Cree\textsuperscript{5} 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\textsuperscript{11,18,19,24,26,27,29,33,38,41} during the peak of the attack; among them, eight patients (80.0%)\textsuperscript{11,18,19,24,26,27,33,38,41} 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.\textsuperscript{46} Of all medications, IV-MPS is used most frequently in these cases, especially immediately after diagnosis.\textsuperscript{5,8,46} 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\textsuperscript{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\textsuperscript{5,8,52,53} 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.\textsuperscript{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%).\textsuperscript{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.\textsuperscript{46} Previous data suggest that irrespective of the etiological factors, the chances of recurrences (neurological deficits) after AIM are very high (17.5%–61%).\textsuperscript{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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