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Systematic Review of Cases of Acute Myelitis in Individuals with COVID-19

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ABSTRACT

Background

An incremental number of cases of acute transverse myelitis (ATM) in individuals with ongoing or recent coronavirus disease 2019 (COVID-19) have been reported.

Methods

We performed a systematic review of cases of ATM described in the context of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection by screening both articles published and in preprint.

Results

Twenty cases were identified. There was a slight male predominance (60.0%) and the median age was 56 years. Neurological symptoms first manifested after a mean of 10.3 days from the first onset of classical, mostly respiratory symptoms of COVID-19. Overall, COVID-19 severity was relatively mild. PCR of CSF for SARS-CoV-2 was negative in all 14 cases examined. Cerebrospinal fluid findings reflected an inflammatory process in most instances (77.8%). Aquaporin-4 and myelin oligodendrocyte protein (tested in 10 and 9 cases, respectively) antibodies in serum were negative. On MRI, the spinal cord lesions spanned a mean of 9.8 vertebral segments, necrotic-hemorrhagic transformation was present in three cases and two individuals had additional acute motor axonal neuropathy. More than half of the patients received a second immunotherapy regimen. Over a limited follow-up period of several weeks, 90% of individuals recovered either partially or near fully.

Conclusion

Although causality cannot readily be inferred, it is possible that cases of ATM occur para- or post-infectiously in COVID-19. All identified reports are anecdotal and case descriptions are heterogenous. Whether the condition and the observed radiological characteristics are specific to SARS-CoV-2 infection needs to be clarified.

Keywords SARS-CoV-2; COVID-19; acute transverse myelitis; neurological complication; autoimmune; neuroinfection; immune-mediated.

INTRODUCTION

The ongoing severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic is beginning to provide further insights to infection-related neurological manifestations (1). The conditions reported in the context of the coronavirus disease 2019 (COVID-19) include but are not limited to encephalitis, myelitis, meningitis, acute disseminating encephalomyelitis (ADEM), metabolic and acute hemorrhagic necrotizing encephalopathy, cerebrovascular diseases, Guillain-Barre syndrome (GBS), cranial polyneuritis, dysautonomia, and myopathies (2). From a pathogenetic viewpoint, neurologic manifestations can fall into any of four categories—direct virus effects on the nervous system, para- or post-infectious immune-mediated diseases and neurologic conditions stemming from complications of systemic COVID-19 (3).

Reports of neurological manifestations in observational cohorts vary widely from 3.5% to 84% (4). One large prospective study of 4491 individuals with COVID-19 in New York City (USA) reported neurologic complications in 606 of them (13.5%) (4). In that study, encephalopathy, seizures, and stroke were the most common manifestations. At the same time, one of the earliest studies from Wuhan also considered mild and unspecific neurologic symptoms like anosmia, headache, and dizziness and found that 78 out of 241 individuals (36.4%) with COVID-19 were affected (5).

Neither one of the above cohort studies depicted cases of myelitis in the context of COVID-19. Yet, there is mounting—though, at this point, largely anecdotal—evidence of individuals with acute transverse myelitis (ATM) and a history of infection with SARS-CoV-2. Considering more than 50 million cases of COVID-19 have been recorded worldwide to date and that this number will only grow, even rare complications may be important to recognize, especially if they require specific management strategies. Eight cases of acute and subacute neurologic complications in the form of encephalitis, seizures, leukencephalopathy, neuropathy or myopathy due to direct viral invasion have been reported for SARS-CoV-1 and Middle Eastern Respiratory Syndrome (MERS)-CoV (6-8). Yet, no reports of ATM associated with these two beta-coronaviruses, which

caused epidemics in the recent history, are found in the literature (9). However, the total number of infected individuals for both viruses combined only totaled to approximately 11,000 individuals; the frequency may not have been sufficient to notice potentially rarer complications (3). For CoV-OC43 or CoV-229E, which belong to another subspecies of coronaviruses, cases of severe central nervous system (CNS) manifestations including encephalitis, ADEM or GBS in combination with detection of the virus by histological analysis of brain section have been reported (10, 11). There has also been a case of acute flaccid myelitis in association with respiratory CoV-OC43 and CoV-229E co-infection (12).

In order to elucidate a potential occurrence of ATM in association with SARS-CoV-2 infections, we systematically reviewed all cases reported to date.

METHODS

This systematic review was carried out in accordance with PRISMA guidelines (13). We searched Medline and two preprint servers (MedRxiv and BioRxiv) from database inception to October 20th, 2020, using the following search terms “myelitis”, “myelopathy”, “spinal cord”, “neurologic manifestations”, “neurological manifestations” as well as “neurology“ in combination with “SARS-CoV-2” and “COVID-19”. No language restrictions were applied. All types of studies were considered but only studies presenting original data were included in downstream analyses. Additionally, reference lists of included articles were also followed up to check for additional relevant studies that might have been missed.

Study bias was assessed using the Newcastle-Ottawa scale to identify possible selection bias, assessment bias, comparability issues, causality bias, and reporting bias (14).

Cases were defined as “confirmed”, “probable”, or “suspected” COVID-19 cases using the case definitions put forth by the World Health Organization (WHO) and as “confirmed”, “probable”, or “possible” SARS-CoV-2 myelitis as described previously (3). Confidence in SARS-CoV-2-associated myelopathy/myelitis was established using the four categories (“suspected myelopathy”, “myelopathy”, “possible myelitis”, and “myelitis”) suggested by Ellul et al.(3). Overall COVID-19 severity was judged using the 0 to 10 scale of the WHO outcome criteria (15). Wherever timeframes of disease course were not stated explicitly, we employed, where possible, a “best

guess" using data derived from the case descriptions. If this was not deemed possible, the cases were left out of the analyses. Accordingly, for a reference, the number of cases which were used is stated in all analyses. Averages are reported as means ± standard deviation.

RESULTS

Systematic review and bias assessment

In total, 497 records were identified on Medline, 156 records from preprint servers and 4 records from other sources, totaling to 657 records.

After the removal of 36 duplicates, titles and abstracts of 621 records were screened and 52 full-length articles were assessed for eligibility. 20 full-length articles were included in the individual level data synthesis (Figure 1). We identified two case reports (16, 17), which seemed to report the same patient. This notion was confirmed by at least one of the corresponding authors (personal correspondence). Accordingly, in the analyses, we synthesized information from both reports into one case presentation.

Bias assessment revealed low quality for almost all studies, with only one case series with moderate quality (Supplementary Table 1). Most cases being reported as single case reports, compromised quality was mainly due to selection or reporting bias.

Demographics

Over the period from January 1st, 2020, to October 20th, 2020, a total of 20 cases of ATM in the context of COVID-19 were reported in the form of case reports or case series with individual level data. The first case of acute myelitis reported in Wuhan appeared on March 16th, 2020—though currently still only available on a preprint server (18).

Cases were reported from 14 different countries, ancestries included European, Arabic, Native American, African, and East Asian. 60.0% were men (12/20). The average age was 48.1±19.2 years, with a median of 56. The comorbidities included hypertension (7/18), diabetes (4/18),

obesity (2/18), hyperlipidemia (2/18), and hypothyroidism (2/18). Among the rarer comorbidities were HIV (1/18) and glucose-6-phosphate-dehydrogenase deficiency (1/18). Six out of 18 individuals did not have comorbidities (Table 1).

Clinical presentation

In most instances, neurological symptoms consisted of the classical triad of weakness of the lower extremities, sensory deficits in the form of a sensory level, and bladder or bowel dysfunction. Details on the neurological presentation and individual findings are presented in Tables 1 and 2.

Progression from onset of neurological symptoms to maximum symptom severity was approximately 80.8 $\pm$ 66.9 hours, range 6 hours to approximately 7 days, median 48 hours (data available for 17/20 cases; Table 1). Neurological symptoms first manifested on average 10.3 $\pm$ 5.8 days after the first onset of classical, mostly respiratory symptoms of COVID-19 (range 0 to 19 days, data available for 15/20 PCR-positive cases; Table 1). The most frequently reported symptoms of the initial manifestation of SARS-CoV-2 infection included fever/subfebrile temperatures (15/18 cases), cough (7/18 cases), dyspnea (5/18), rhinorrhea (3/18), and myalgia (4/18) (also see Table 1). Only in the instance of a 3-year-old child, no symptoms of respiratory tract infection or fever were reported prior to the onset of neurological symptoms(19). COVID-19 manifestation overall was relatively mild with an average WHO score(15) of 3.2$\pm$1.7 (median 2, range 1 to 8), equivalent to respiratory symptoms that can be treated at home without need for hospitalization. Two cases with mild respiratory symptoms and sudden death from cardiac arrest were not included in the analysis due to the fact that the association between the COVID-19 and the deaths could not be established. Pneumonia was diagnosed in 68.4% of cases (13/19). Additional possibly COVID-19 related complications included cardiac arrest (2/19), hepatic inflammation and failure (1/19), and pulmonary embolism (1/19). Of note, distal axonal motor neuropathies were reported in two individuals with myelitis (2/19; 10.5%). No individual was described as having had a prior episode of TM or other autoimmune conditions of the central nervous system (CNS).

Laboratory and CSF findings

Polymerase chain reaction (PCR) from nasopharyngeal swabs was performed in all cases. It was positive at some point in the disease course in 75.0% of cases (16/20 cases). In the four cases without a positive SARS-CoV-2 PCR, anti-SARS-CoV-2 antibodies were present in serum (IgG-only in 2/4; IgG/IgM in 1/4; IgG/IgM/IgA in 1/4). At the time of onset of neurological symptoms, 8/16 cases were PCR-positive. Of the 8/16 negative cases, two turned positive two or three days later, the others remained negative or where not tested again but had had a positive SARS-CoV-2 PCR prior to the onset of neurological symptoms. Chest X-rays (8/18 cases) or CTs (10/18 cases) were performed in 90.0% of individuals (18/20 cases). In five cases, these were within normal limits (5/18 cases; 27.8%). 13 of 18 showed patchy infiltrations, which were unilateral in 3/13 cases and bilateral in 7/13 cases. Data regarding the extend of infiltrations was lacking in 3/13 cases. Blood laboratory findings were reported in 15/20 cases although the extend of what was reported was very heterogeneous (Supplementary Table 2). In the majority of cases (13/15 cases), laboratory changes showed a mild, often times incomplete systemic inflammatory syndrome with slightly elevated white blood cell counts (5/14 cases), erythrocyte sedimentation rates (1/5 cases), and C-reactive protein (8/13 cases) as well as lymphocytopenia (3/11 cases). In five out of 15 cases, additional changes often seen in the context of SARS-CoV-2 infection, such as elevated d-dimer levels or liver enzymes, were also observed. In half of the cases, serological work-up for autoimmune diseases was performed. Where tested, anti-AQP4 (10/20 cases) and anti-MOG (9/20 cases) antibodies were not present and panels for systemic autoimmune diseases (9/20 cases) or anti-neuronal antibodies (3/20) returned negative results. In one individual who also had axonal motor neuropathy, anti-GD1b IgM ganglioside antibodies were detected (20).

Cerebrospinal fluid (CSF) findings were heterogeneous but reflected some form of inflammatory process in most cases (14/18 cases): lymphocytic pleocytosis with elevated protein was seen in 6/18 cases, isolated lymphocytic pleocytosis was present in 3/18 cases and isolated protein elevation was found in 5/18 cases. CSF glucose levels were available in 11 of 18 cases and were within normal limits in nine and increased in two individuals with diabetes. If evaluated, CSF-specific oligoclonal bands were not detected (8/18) and IgG Index was unremarkable or at the

upper limit of normal (5/18) (Table 2). In all 14 cases examined, no SARS-CoV-2 RNA was detected by real-time PCR in the CSF. In two of three cases, CSF was positive for anti-SARS-CoV-2 IgG (21), in one case, it was negative(22). No other viral or bacterial infections were detected in the CSF or serum of those 19 individuals for whom it was reported (Tables 2 and 3 for details). Based on the WHO definitions for describing associations between SARS-CoV-2 and myelitis/myelopathy, the association was "confirmed" in two cases based on the presence of anti-SARS-CoV-2 IgG in CSF. In 40% of cases, it was "probable" (8/20 cases) with neither viral RNA or SARS-CoV-2 antibodies found in CSF but clear evidence of SARS-CoV-2 infection and no evidence of alternate causes for TM. In the remaining 50%, association was "possible" (10/20 cases) due to incomplete exclusion of potential alternate causes of TM (Tables 1 to 3).

Neuroradiological imaging

19 out of 20 cases had an MRI of the spinal cord, two of these (10%) were unrevealing and two showed degenerative changes, in one instance with concomitant T2 hyperintensities of the cauda. In the remaining 78.9% (15/19), classical T2 hyperintensities of the spinal cord were observed. At the time of first spinal cord imaging, lesions in nine individuals were described as non-enhancing while in three individuals they were enhancing. In the remaining cases, it is unclear whether MRIs were performed with contrast (Table 2). In three instances, there was also evidence of hemorrhagic transformation and necrosis of the spinal cord lesion (19, 23, 24). Transverse localization was central, frequently with extension throughout most of the transverse diameter, in 7/11 cases. The thoracic subsegment of the spinal cord was affected most frequently (93.3%; 14/15 cases), followed by the cervical subsegment (53.3%; 8/15) (Table 2). Interestingly, in most cases, lesions were longitudinally extensive extending over an average of 9.8 ± 8.3 vertebral body segments (median 6; range 2 to 24) (Table 2). In 93.3% of individuals with a clear lesion on spinal cord imaging, the lesion extended over three or more spinal cord segments, fulfilling the criteria for longitudinally extensive transverse myelitis (LETM). In five out of 15 individuals with a spinal cord lesion, the lesion spanned more than half the spinal cord. Whenever performed (16/20 cases), brain MRI showed no additional supratentorial inflammatory lesions (Table 2). In several instances, T2 hyperintensities were described as

"patchy" (3/15) or with "patchy enhancement" (2/15), while they were continuous in the other cases (10/15).

Applying the diagnostic levels set forth by Ellul et al. specifically for myelopathy /myelitis in the context of infections with SARS-CoV-2 (3), 16/20 cases were classified as having "myelitis", three as having "possible myelitis" and one as having "myelopathy" only, due to the lack of both CSF analysis and imaging studies (Table 1).

Treatment and outcome

The majority of cases (90.0%, 18/20 cases) received some form of immune therapy. Eight of 18 cases, received either intravenous methylprednisolone (MP, seven cases) or plasma exchange (one case) alone. However, in 10 of 18 cases, more than one immune therapy was administered. Eight individuals were treated with a combination of two different immune therapies—in most instances, intravenous methylprednisolone followed by plasma exchange—, in one case a combination of three and in another of four different immune therapies was necessary (Table 3). Additional antivirals or antibiotics were administered in five cases each (Table 3). While antibiotic regimes varied, acyclovir was the most commonly used antiviral (4/5 cases). Only one of the reported individuals received an antiviral combination specifically geared at SARS-CoV-2 (ritonavir/lopinavir). Other SARS-CoV-2-specific therapies such as remdesivir, convalescent plasma, or monoclonal antibodies were not administered to any of the individuals.

Follow-up was mostly limited to several weeks of in-hospital treatment. Over this limited time period, 90.0% of individuals recovered either partially (15/20 cases) or near fully (3/20 cases). Two patients died from sudden cardiac arrest on day five after onset of myelitis symptoms while undergoing treatment in the hospital. In one case, cardiac arrest occurred immediately following sudden-onset respiratory failure; in the other, no additional details are provided (Table 3).

DISCUSSION

In most of the reported cases reviewed herein, the diagnosis of myelitis in the context of SARS-CoV-2 infection was undisputed. Yet, since the majority of cases was reported as single case reports, there is likely to be reporting bias and one needs to be wary of inferring causality directly from the anecdotal data provided. Although presented as a set of cases for reasons of practicality, one needs to be wary of seeing them as a uniform cohort as they really represent single cases documented in unique individual settings. Further, interpretability is hampered by the limited number of available cases, the highly diverse patient population spanning many ages and ancestries, and the heterogeneous and, in many cases, incomplete work-up.

None of the 20 cases could be classified as confirmed SARS-CoV-2 myelitis. Most frequently, this was due to the fact that SARS-CoV-2 could not be detected by PCR in the CSF, and the work-up did not include analysis of spinal cord specimen. Of note, at least one large prospective cohort study of neurological manifestations in COVID-19 did not identify any cases of myelitis among 4491 individuals with COVID-19 (4). At the same time, even though the follow-up period was not long enough to fully exclude this possibility, none of the reported cases showed signs or laboratory or imaging findings suggestive of other underlying autoimmune diseases that could manifest with LETM such as neuromyelitis optica spectrum disorders or spinal cord manifestation of systemic autoimmune disease (25, 26). The work-up included the exclusion of viruses with neuroinvasive potential as well as other viruses known for para- or postinfectious spinal cord complications.

Another possible way to assess whether SARS-CoV-2 is actually responsible for cases of TM would be to compare the incidence of myelitis cases pre-SARS-CoV-2 pandemic to the current incidence to see if there is an overall increase in cases of TM. The incidence of TM has been reported to range somewhere between 1 and 8 cases per 1 million population per year, with rates relatively stable across ancestries (27, 28). If cases that are later diagnosed as having an underlying autoimmune disorder are included, this number increased to around 32 cases per 1 million population per year (30). Extrapolated to the 107 million reported infections to date, this would mean that between 107 and 3,317 cases of TM would be expected to occur among these individuals from causes unrelated to COVID-19. Not least due to this large number and the wide

range of TM cases that can be ascribed to causes other than potentially COVID-19, it will be very important to continue to survey the situation of myelitis in COVID-19 by both systematically including neurological manifestations as outcomes in large COVID-19 cohort studies and by collecting myelitis cases in the context of COVID-19 in Neuro-COVID-19 registries (29).
A number of demographic characteristics reinforce the notion that the cases depicted herein, for the most part, truly represent myelitis caused by SARS-CoV-2 infection. First, affected individuals were of all different ages and ancestries, and had a slight predominance for males. Male predominance and a median age of 56 are not in line with TM as the first manifestation of autoimmune disorders of the CNS, where patients are predominantly female and much younger. Observational cohorts of ATM of any cause show a bimodal age distribution with peaks between 10 and 20 years of age and 30 and 40 years of age with the mean age of onset between 35 and 40 (30). Sex and age distributions of the cases herein are, on the other hand, in line with more complicated presentations of COVID-19 and the finding that neurological symptoms in COVID-19 have been reported to occur more frequently in men and older individuals (5). As opposed to other neurological manifestations in the context of SARS-CoV-2 infection, overall, individuals with myelitis did not seem to have very severe respiratory COVID-19.

Several possible mechanisms exist by which SARS-CoV-2 could lead to spinal cord manifestations. Coronaviruses have been shown to be both neuroinvasive and neurovirulent and can lead to demyelination and as well as an inflammatory response (31). One possible mechanism for myelitis in the context of SARS-CoV-2 infection is the direct invasion of and replication in spinal cord neurons by the virus itself (32). The presence of angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2`s primary entry receptor, on membranes of spinal cord neurons further renders this possible (33). The fact that no viral RNA was detected in the CSF of the cases reviewed herein or in the vast majority of other individuals with neurological manifestations of COVID-19 depicted in the literature (4, 21, 34) and that SARS-CoV-2 RNA has only very rarely been detected in the CSF or in CNS tissue, argues against this as the primary mechanism (35-37). Yet, the presence of very low viral copies in general or following degradation, as well as the examination of CSF specimen outside the peak of viral copy numbers in CSF, are potential explanations for the rare detection of SARS-CoV-2 in CSF, cannot be excluded (2). A second possibility is indirect injury due to severe

systemic disease or cytokine storm syndrome (23, 38). In the described cases, however, COVID-19 severity was rather mild making this possibility less likely. A third possible way by which TM in the context of COVID-19 could arise is in the form of para- or postinfectious disease. The latency of on average 11 days from the onset of the first COVID-19 symptoms to the first signs of myelitis would speak to a para- or post-infectious mechanism. In the literature, there is no clear definition as to when para-infectious disease ends and when post-infectious disease starts. The latency in the cases described here is a little bit shorter than what is commonly seen in, for example, GBS (median 23 days) (39). Also, at least 52.9% of cases were PCR-positive for SARS-CoV-2 on nasopharyngeal swab at the time of presentation of myelitis symptoms. Accordingly, should SARS-CoV-2 infection be the driver of myelitis in these cases, the most likely mechanism would be immune-mediated or autoimmune with no clear distinction between para- and post-infectious processes possible at present.

Under the conjecture of a para-infectious mechanism of myelitis in the context of SARS-CoV-2 infection, the question of the most appropriate therapeutic strategy imposes itself. High-dose intravenous MP alone was administered in 36.8% of individuals. 57.8% received more than one immune therapy—in most instances, high-dose MP followed by plasma exchange. This argues for treatment failure with steroids in the majority of the patients. To our knowledge, there are no evidence-based treatment guidelines available for parainfectious ATM. If a para- or postinfectious pathogenesis is corroborated, intravenous immunoglobulins (IVIG) may be another treatment option.

The large majority of cases assessed in this review had a myelopathy fulfilling LETM criteria. While LETM is often times perceived as characteristic of NMOSD, there are many potential causes which include viral infections. Some viruses have a greater tendency to cause LETM than others. LETM is more frequently observed with flaviviruses and enteroviruses. Herpes simplex virus type 2, varicella zoster virus, Epstein-Barr virus, or cytomegalovirus tend to cause ATM of shorter longitudinal extension (40, 41). SARS-CoV-2 should probably be added to that list. This is relevant not least because LETM has been associated with poorer outcome compared to short segment ATM (30).

Hemorrhagic transformation and necrosis are only rarely seen in LETM (23). Interestingly and in line with what has been described for ADEM cases in the context of SARS-CoV-2 infection, which also seem to show hemorrhagic transformations relatively frequently (34, 42), this was also observed in three out of 16 of this case series.

Another interesting finding emerging from this systematic review is the co-occurrence of TM with the GBS variant acute motor axonal neuropathy (AMAN). In two individuals, AMAN was reported in addition to TM. GBS—of the AMAN and more frequently the acute inflammatory demyelinating (AIDP) variant—has been described in individuals with COVID-19 (43, 44). Critical illness neuropathy seems unlikely as an alternate diagnosis because both patients were not severely ill from COVID-19 (WHO score of 2 = very mild symptoms) and the CSF findings were in line with immune-mediated neuropathy (Table 2). Although the number of undiscovered cases may be much higher, less than 30 cases of GBS/ATM overlap syndromes are found in the literature, the majority having occurred after viral infections (45). Accordingly, the fact that two of the depicted cases showed this overlap syndrome merits attention, arguing for the need to screen individuals with ATM or GBS in the context of COVID-19 for the other disease as well. This could have important treatment implications as first-line treatments for GBS (IVIG or plasma exchange) differ from those usually used in ATM (intravenous methylprednisolone) and IVIG may be more effective in individuals with combined demyelinating disorders of the central and peripheral nervous systems (46).

TM has also occurred in at least one participant in a trial for a SARS-CoV-2 vaccine developed by AstraZeneca and the University of Oxford (47). Although causality cannot be readily inferred, TM is known as a potential complication of several different vaccines and causality has shown for the oral polio vaccine and ATM (47, 48). Accordingly, with a significant portion of the world`s population going to receive a SARS-CoV-2 vaccine, post-vaccination ATM will be something to watch as vaccine trials are intensifying and vaccination efforts are starting to get underway (47).

Current estimates of neurological manifestations in COVID-19 of 7.8 to 13.5% seem high and are most likely subject to significant reporting and selection bias (4, 21). True numbers for

neurological sequelae may be closer to the 0.09% and 0.36% estimated for SARS-CoV-1 and MERS-CoV (3). Nonetheless, even if the true rate of neurological manifestations in COVID-19 remains to be established and reports of myelitis are anecdotal, at the current scale of this global pandemic, they merit further scrutiny in a timely fashion.

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Ethical approval

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Conflict of interests statement

Authors have no conflict to declare.

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TABLES

Table 1: Demographics and clinical presentation

Reference	Demographics			Diagnosis	Neurological presentation	Neurologic findings	Time to NLO max	COVID-19 presenting symptoms	COVID-19 non-NLO symptoms	Comorbidities	Latency to NLO (d)	WHO confidence	Myelitis diagnosis category	WHO severity
	Sex	Age	Origin											
Abdelhady (40)	M	52	Qatar	TM	bilateral lower limb weakness, lower abdominal pain, urinary retention, fever	flaccid paraparesis lower limbs, urinary retention	4d	fever	P, cardiac arrest	DM II	0	possible	myelitis (1)	2 or 10
AlKetbi (49)	M	32	UAE (Asian)	LETM	bliateral lower limb weakness, difficulty sitting up, difficulty on urination	paraparalysis upper (3-4/5) and lower (0/5) limbs, truncal weakness, urinary retention	8h	fever, flu-like symptoms	PE	none	2	probable	myelitis (1)	3
Baghbanian (50)	F	53	Iran	LETM	bilateral lower limb weakness, lower back pain, transient urinary incontinence	asym hypotonic paraparesis lower limbs, areflexia, up-going plantars, sensory level Th11/Th12	48h to 96h	NA	none	DM, HTN, IHD	14	probable	myelitis (1)	4 to 5
Chakraborty(51)	F	59	India	TM	progressive bilateral lower limb weakness, urinary retention, constipation	flaccid paraplegia (0/5) and areflexia lower limbs, no plantar responses, sensory level Th10, urinary retention, constipation	4d	fever	RF, cardiac arrest	none	4	possible	myelitis (1)	5 or 10
Chow (52)	M	60	Australia	LETM	bilateral lower limb weakness, urinary retention, constipation	global weakness, increased muscle tone, hyperreflexia, reduced proprioception lower limbs, paraesthesia to umbilicus	48h	fever, cough, dysgeusia, anosmia	P	HTN, HLP	16	probable	myelitis (1)	2

Durrani (53)	M	24	USA	TM	bilateral lower limb weakness, urinary incontinence	flaccid paraplegia and areflexia lower limbs, urinary incontinence	few d	fever, chills, vomiting, tachypnea	P	none	~14	probable	myelitis (1)	4 to 5
Giorgianni (54)	F	22	Italy	flaccid tetraparesis	flaccid tetraparesis, fecal and urinary incontinence, fluctuating dysaesthesias	acute flaccid tetraparesis, hyperreflexia, hypo-/dysaesthesias lower limbs, fecal/urinary incontinence	<15d	fever, dyspnea	P, RF	DM I, keto-acidotic coma	5 to 20	possible	possible myelitis (2)	8
Kaur (19)	F	3	USA (Navajo)	LETM	progressive weakness and decreased sensation of all limbs	flaccid tetraparesis, neurogenic respiratory failure, generalized areflexia, no response to pain below neck	12h	asymptomatic	none	none	14 to 21	probable	myelitis (1)	1
Lisnic (55)	M	27	Moldova	LETM	bilateral lower limbs paralysis, numbness lower limbs and right arm, bladder/bowl dysfunction	spastic tetraparesis lower>upper extremities, sensory level Th7	15h	subfebrile	P	HIV on antivirals	asymp	possible	myelitis (1)	1 to 2
Maideniuc (16)* Valiuddin (17)*	F	61	USA	TM+AMAN	weakness all limbs, loss of ability to walk, numbness from chest down, urinary retention	spastic weakness limbs, hyperreflexia/up-going plantars lower limbs, sensory level C3⇢areflexive tetraparalysis	36h	rhinorrhoea, chills	P, AMAN	HTN, HLP, HT, post-solid tumor	5	possible	myelitis (1)	2
Masuccio (20)	F	70	Italy	TM+AMAN	progressive weakness of all limbs, inability to walk, ascending paraesthesias	hyperreflexia, up-going plantars, tetraparesis upper (3/5) and lower (0/5) limbs, urinary retention, perineal areflexia	5 to 10d	fever, myalgia, anosmia	P, AMAN	HTN, obesity	15	possible	myelitis (1)	2
Munz (22)	M	60	Germany	TM	bilateral lower limb weakness, bladder dysfunction	moderate spastic paraparesis lower limbs, hypaesthesia below Th9, hyperreflexia, up-going plantars	48h	respiratory symptoms	P	HTN, urolithiasis	~13	probable	myelitis (1)	4
Paterson (42)	M	48	UK	LETM	unsteady gait, umbness hands & feet, band of itching sensation at level of umbilicus	weakness of hip flexion, hyperreflexia, extensor plantars, vibration/pinprick to Th10,	NA	fever, cough, dyspnea	P	HTN, DM	19	possible	myelitis (1)	4

						sensory ataxia								
Rifino (21)	M	66	Italy	TM	unsteady gait, numbness of lower limbs	spastic paraparesis (4/5) lower limbs, reduced sensation to touch, acroparaesthesia, hyperreflexia with bilat distal clonus	NA	fever, anosmia, ageusia	P	NA	24	confirmed	possible myelitis (2)	2
Rifino (21)	M	62	Italy	TM	lower limb weakness, back pain radiating to lower limbs, sensory changes, constipation	paraparesis (4/5) lower limbs, sensory level Th11	NA	NA	NA	none	NA	confirmed	possible myelitis (2)	NA
Sarma (56)	F	28	Denmark	LETM	lower back pain, bilateral symmetric numbness of all limbs and chest & tip of tongue, urinary retention, nausea/vomitting	sensory level Th5, paraparesis upper limbs (4/5), wide-based gait, Lhermitte`s sign positive, urinary retention	8d	fever, productive cough, lower back pain, myalgias, rhinorrhoea	none	HT	8	possible	myelitis (1)	2
Sotoca (23)	F	69	Spain	acute necrotizing TM	cervical pain, tetraparesis, numbness both hands, incontinence	right facial and left hand hypoaesthesia, interosseus weakness left hand, general hyperreflexia	7d	fever, dry cough	none	none	8	probable	myelitis (1)	2 to 3
Wong (24)	M	40	UK (African)	rhombencephalomyelitis	unsteady gait, limb ataxia, altered sensation right arm, hiccups, diplopia, oscillopsia	bilatl facial weakness, tongue weakness, upbeat nystagmus, limb ataxia greater on right and lower limbs	24h	fever, dyspnea, cough, diarrhoea	P, hepatitis, rhombencephalitis	HTN, glaucoma	13	possible	myelitis (1)	4 to 5
Zachariadis (57)	M	60	Switzer-land	TM	lower limb weakness, par- and hypoaesthesias of both feet progressing to abdominal area	moderate proximal paraparesis lower limbs, pyramidal signs, sensory level Th10→paraplegia, sphincter dysfunction	7d	headache, rhinorrhea, myalgia, subfebrile	P	obesity, smoking, alcohol abuse	12	probable	myelitis (1)	2
Zhao (18)	M	66	China	TM	bilateral lower>upper limb weakness, reduced sensation lower limbs, urinary/bowl incontinence	tetraparesis (3/5 arms, 0/5 legs), hyporeflexia lower limbs, sensory level at Th10	4-8h	fever, fatigue, cough, dyspnea	P	NA	8	possible	myelopathy (3)	5

M=male; F=female; UAE=United Arab Emirates; USA=United States of America; UK=United Kingdom; TM=transverse myelitis; LETM=longitudinally extensive transverse myelitis; NA=not available; temp=temperature; DM=diabetes mellitus; HTN=hypertension; IHD= ischemic heart disease; HLP=hyperlipidemia; HIV=human immunodeficiency virus; HT=hypothyroidism; asymp=asymptomatic; NLO=neurologic; P=pneumonia; PE=pulmonary embolism; RF=respiratory failure; AMAN=acute motor axonal neuropathy; asym=asymmetrical; bilat=bilateral; *same case reported in two publications

Table 2: Neuroimaging and CSF findings

Reference	MRI-spinal cord					MRI-brain	CSF					ENG/EMG
	T2 hyperintensity	enhance-ment	spinal cord subsegment	lesion length (vertebral segments)	pattern		lymphocytes	protein	glucose	pathogens	other	
Abdelhady (40)	+	-	thoracic	6	continuous	WNL	+	+	NA	cultures negative, SARS-CoV-2 PCR negative	none	NA
AlKetbi (49)	+	-	cervical, thoracic, lumbar	23	patchy	NA	NA	NA	NA	NA	NA	NA
Baghbanian (50)	+	NA	thoracic	3	continuous	WNL	+ (13/µl)	WNL	WNL	PCR for HSV, CMV and SARS-CoV-2 negative	no CSF-specific OCBs, IgG index upper limit of normal, MOG/AQP4 Abs neg	NA
Chakraborty (51)	+	NA	thoracic	2	continuous	NA	WNL	+ (71.4 mg/dL)	WNL	Ziehl-Neelsen- and gram-stain negative, SARS-CoV-2 PCR negative	none	NA
Chow (52)	+	NA	thoracic	4	continuous	WNL	WNL	+ (79 mg/dL)	WNL	cultures negative, SARS-CoV-2 PCR negative	MOG/AQP4 Abs neg	NA

Durrani (53)	+	NA	thoracic	6	continuous	NA	+	WNL	WNL	NA	no CSF-specific OCBs, IgG index normal, AQP4 Abs neg	NA
Giorgianni (54)	WNL	NA	NA	NA	NA	tiny subacute frontal hemorrhage	WNL	WNL	+	SARS-CoV-2/VZV/HSV PCR, Borrelia Abs, microbial culture, and Tbc negative	none	NA
Kaur (19)	+/+, necrosis, hemorrhages	-/+	medulla, cervical, thoracic	13	continuous	WNL	+ (42/μl), 96% neutrophilic)	+ (58 mg/dL (15 to 45 mg/dL))	NA	SARS-CoV-2, viral, and microbacterial panels negative	incl MOG/AQP4 Abs negative; hemorrhagic (282/mm3)	NA
Lisnic (55)	+	-	cervical, thoracic	9	continuous	WNL	WNL	WNL	WNL	SARS-CoV-2, viral, and bacterial tests negative	no CSF-specific OCBs, MOG/AQP4 Abs neg	NA
Maideniuc (16)* Valiuddin (17)*	+	+	medulla, cervical, thoracic, lumbar	24	continuous	WNL	d10: WNL d21: WNL	d10: + (87 mg/dL) d21: + (153 mg/dL)	WNL	d10: SARS-CoV-2 negative, other viral pathogenes not done, VDRL/culture neg	no CSF-specific OCBs, IgG index normal, ganglioside Abs not tested, MOG/AQP4/anti-neuronal Abs neg; d10: hemorrhagic (312/ul)	ENG/EMG: acute motor axonal neuropathy
Masuccio (20)	+	-	cervical, thoracic	3	continuous	WNL	WNL	WNL	NA	viral and bacterial work-up negative	anti-GD1b-IgM pos, no CSF-specific OCBs, viral/bacterial work-up neg in serum	ENG/EMG: acute motor axonal neuropathy
Munz (22)	+	-	thoracic	3 plus 2	patchy	WNL	d1: + (16/μl) d6: + (27/μl)	d1: + (79 mg/dL) d6: + (118 mg/dL)	NA	HSV, VZV, HHV-6, EBV, HEV, SARS-CoV-2 neg, anti-SARS-CoV-2 IgG neg	no CSF-specific OCBs, MOG/AQP4/anti-neuronal Abs neg	NA
Paterson (42)	+	-	thoracic, lumbar	> 4	patchy	WNL	+ (10/μl)	+ (70mg/dL)	+	culture and viral PCRs negative	no CSF-specific OCBs	ENG/EMG: WNL
Rifino (21)	+, diffuse degeneration	-	NA	NA	NA	WNL	WNL	+	NA	PCR for bacteria/neurotropic viruses/SARS-CoV-2 neg, anti-SARS-CoV-2 IgG pos	none	ENG/EMG: reduction of maximal voluntary activity; SEP/MEP lower limbs: bilat medullar conduction block
Rifino (21)	diffuse degeneration	-	NA	NA	NA	WNL	WNL	+	NA	PCR for bacteria/neurotropic viruses/SARS-CoV-2 neg,	none	ENG/EMG: reduction of maximal voluntary activity; SEP/MEP lower limbs: bilat medullar conduction block

										anti-SARS-CoV-2 IgG pos		
Sarma (56)	+	+	medulla, cervical, thoracic, lumbar	24	continuous	NA	+ (125/µl)	(+)	WNL	gram-stain and cultures unremarkable	Abs neg	NA
Sotoca (23)	+, necrosis, hemorrhages	+	medulla, cervical, thoracic	13	continuous	WNL	+ (75/µl)	+ (283 mg/dL)	WNL	bacterial culture, viral multi-PCR neg	no CSF-specific OCBs, IgG index normal, MOG/AQP4/anti-neuronal Abs neg	NA
Wong (24)	+, hemorrhages	NA	rhomencephalic, medulla, cervical	NA	continuous	T2 hyperintensity right inf cerebellar peduncle, microhemorrhages	WNL	WNL	NA	bacterial culture neg	MOG/AQP4 Abs neg	NA
Zachariadis (57)	WNL	NA	NA	NA	NA	WNL	d1: + (16/µl) d6: + (36/µl)	d1: + (57.3 mg/dL) d6: + (60.0 mg/dL)	WNL	negative for bacteria and viruses including SARS-CoV-2	MOG/AQP4/anti-neuronal/anti-ganglioside neg	NA
Zhao (18)	NA	NA	no MRI	no MRI	no MRI	lacunar infarctions, atrophy	NA	NA	NA	NA	NA	NA

NA=not available; MRI=magnetic resonance imaging; WNL=within normal limits; CSF=cerebrospinal fluid; OCB=oligoclonal bands; AQP4=aquaporin 4; Ab=antibody; MOG=myelin oligodendrocyte glycoprotein; neg=negative; pos=positive; d=day; *same case reported in two publications

Table 3: SARS-CoV-2 diagnostics, treatment, and outcome

Reference	SARS-CoV-2 diagnostics	SARS-CoV-2 at NLO onset	Chest imaging	Blood laboratory findings	Additional pathogens tested (all negative)	Additional antibodies	Treatment of myelitis	Recovery
Abdelhady (40)	NPS PCR pos	positive	Chest-X-ray: bilat scattered infiltrations	NA	HSV, HBV, HCV, Tbc	ANA/ANCA neg	ACV, iv MP	death
AlKetbi (49)	NPS PCR pos	positive	Chest-CT: no consolidations/pleural effusions, PE	CRP +, Hb - , D-dimer +, CK +	AdV, HSV, EBV, CMV, HIV, IAV/IBV, PIV 1-4, RSV, EV, RV, C. pneumoniae, B. pertussis, M. pneumoniae, B. burgdorferii	AID panel neg	iv MP, ACV, LMWH	partial
Baghbanian (50)	NPS PCR pos	not done	Chest-CT: patchy ground-glass consolidation right lung	WNL	HSV, CMV	NA	PEX	partial
Chakraborty (51)	d1: NPS PCR neg d2: NPS PCR pos	d1: negative d2: positive	Chest-X-ray: WNL	WNL	HIV, HBV, HCV	NA	iv MP	death
Chow (52)	NPS PCR pos; SARS-CoV-2 IgG/IgM/IgA sero-pos	negative	Chest-CT: bilat peripheral ground-glass opacities and consolidation	ESR +, CRP (+), D-dimers +, lympho -	EBV, CMV, HIV, HBV, HCV, M. pneumoniae	AID panel neg	iv MP	full

Durrani (53)	NPS PCR pos	d1: negative d4: positive	Chest-CT: multifocal pneumonia	NA	HIV, L. pneumophila, blood and respiratory cultures	AID panel neg	iv MP	partial to full
Giorgianni (54)	NPS and BAL PCR pos	NA	Chest-CT: extensive bilat ground-glass opacities	WBC +, CRP +, D-Dimers +, LDH +, ASAT +, glucose ++, pH +	HIV, VZV, HSV, M. pneumoniae, L. pneumophila, C. pneumoniae, B. burgdorferii, M. tuberculosis, CSF bacterial culture	NA	antiviral, immunemodulatory for repiratory/metabolic syndromes	partial
Kaur (19)	NPS PCR pos	positive	Chest-X-ray: WNL	NA	VZV, HSV, EV, HIV, EBV, CMV, IAV/IBV, T. pallidum, M. tuberculosis, M. pneumoniae	AID panel neg	iv MP and IVIG⇢PEX⇢rituximab	partial
Lisnic (55)	d1: NPS PCR neg d19: NPS PCR pos	positive	Chest-CT: slight patchy ground-glass opacities basal on the left (d19)	WBC + , ESR +, HIV <40 copies, CD4 340/ul	HSV 1/2/6, CMV, EBV, HIV, HBV, HCV, B. burdorferi, T. pallidum, T. gondi, C. trachomatis, M. pneumoniae, U. urolyticum	AID panel neg	iv MP⇢PEX	partial
Maideniuc (16)* Valiuddin (17)*	NPS PCR pos	positive	NA	ANA 1:80; WBC (+); CRP (+)	infectious pathogens in serum	AID panel neg	iv MP⇢PEX	partial
Masuccio (20)	NPS PCR neg; SARS-CoV-2 IgG sero-pos	negative	Chest-CT: interstitial pneumonia with ground-class opacities	CRP +, lympho -	EBV, CMV, HSV, VZV, HIV, B. burdorferi, C. pneumoniae, M. pneumoniae	NA	PEX, IVIG	partial
Munz (22)	NPS PCR pos	negative	Chest-X-ray: bilat mild ground-glass opacities	CRP (+)	HSV, VZV, HHV-6, EBV, HEV	NA	MP, ceftriaxone, ACV	partial
Paterson (42)	NPS PCR pos	NA	Chest-X-ray: patchy infiltrates	ferritin (+)	viral PCRs, blood/urine/CSF cultures, HTLV-1/2, syphilis neg	NA	iv MP, antibiotics for secondary bacterial pneumonia	partial
Rifino (21)	NPS PCR neg; SARS-CoV-2 IgG sero-pos	negative	Chest-CT: small ground-glass opacities	NA	bacteria, common neurotropic viruses	NA	iv MP⇢PEX	partial
Rifino (21)	NPS PCR neg; SARS-CoV-2 IgG sero-pos	negative	Chest-X-ray: WNL	NA	bacteria, common neurotropic viruses	NA	iv MP⇢IVIG⇢PEX	partial
Sarma (56)	NPS PCR pos	NA	NA	NA	NA	NA	iv MP⇢PEX	near full

Sotoca (23)	NPS PCR pos	positive	Chest-X-ray: WNL	WNL	panviral PCR, CSF culture	AID panel neg	iv MP⇢2nd iv MP⇢PEX	partial
Wong (24)	NPS PCR pos	positive	Chest-X-xay: right lower zone consolidation	CRP (+), GGT (+), ALAT (+)	HAV, HBV, HCV, HIV 1/2, syphilis	NA	amoxicillin, paracetamol, gabapentin	partial
Zachariadis (57)	NPS PCR neg; SARS-CoV-2 IgG/IgM sero-pos	negative	Chest-CT: bilat ground-glass opacities; PET-CT: non-revealing	WBC (+), CRP (+)	broad serology panel	AID panel neg	IVIG⇢iv MP	partial
Zhao (18)	NPS PCR pos	positive	Chest-CT: bilat patchy infiltrations	WBC +, lympho/eosino - , CRP++, Hb - , ALAT/ASAT (+), CK +, iron -	EBV, IAV/IBV, AdV, EV, PIV, CMV, RSV, M. pneumoniae, C. pneumoniae, Tbc	NA	dexamethason, IVIG, ganciclovir, lopinavir/ritonavir, moxifloxacin	partial

NA=not available; NPS=nasopharyngeal swab; pos=positive; d=day; BAL=brochioalveolar lavage; pos=positive; sero-pos=sero-positive; neg=negative; bilat=bilateral; PE=pulmonary embolism; AID=autoimmune disease; WNL=within normal limits; + = above normal limits; ++=greatly above normal limits; - = below normal limits; (+)=upper limit of normal or slightly above normal; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; Hb=hemoglobin; CK=creatinine kinase; WBC=white blood cell count; LDH=lactate dehydrogenase; ASAT=aspartate transaminase; ANA=antinuclear antibodies; ANCA=antineutrophil cytoplasmic antibodies; lympho=lymphocytes; eosino=eosinophils; GGT=gamma-glutamyltransferase; ALAT=alanine transaminase; HSV=herpes simplex virus; HBV=hepatitis B virus; HCV=hepatitis C virus; Tbc=tuberculosis; AdV=adenovirus; EBV=Epstein-Barr virus; CMV=cytomegalovirus; IAV/IBV=influenza virus A/B; PIV=parainfluenza virus 1-4; RSV=respiratory syncytical virus; RV=rhinovirus; EV=enterovirus; VZV=varicella zoster virus; HHV=human hepatitis virus; HEV=hepatitis E virus; iv=intravenous; MP=methylprednisolone; PEX=plasma exchange; ACV=acyclovir; LMWH=low molecular weight hemoglobin; IVIG=intravenous immunoglobins;
*same case reported in two publications

FIGURES

Figure 1. Record selection in accordance with PRISMA guidelines