

Review Article

Investigating Spine and Spinal Cord Complications of COVID-19



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ABSTRACT

Background and Aim: SARS-CoV-2 can present with pulmonary, renal, gastrointestinal, hematological, and neurological manifestations. Neurological manifestations may occur after or before COVID-19 symptoms and signs. Spine and spinal cord complications are documented as neurological complications of COVID-19. Spinal cord pathology following COVID-19 showed inflammatory myelopathy and suspected cord ischemia. The most frequent presentation of COVID-19 myelitis is non-enhancing central expansile cord T2 signal changes, but it can present with lateral and dorsal column-specific disease and in some cases with negative magnetic resonance imaging (MRI). There is no known documented mechanism for spinal cord involvement in COVID-19 infection, but it seems as a post-infectious immunological and post-inflammatory disorder and reaction. Viral infection of SARS-CoV-2 can cause demyelination of the brain and spinal cord and also can exacerbate the known primary demyelinating disorders.

Methods and Materials/Patients: This is a narrative study about the spinal cord complications of COVID-19. To provide up-to-date information, we precisely reviewed COVID-19 articles on spine and spinal cord complications. Based on the keywords COVID-19, SARS-CoV-2, spine, and spinal cord, all the related articles were taken from Google Scholar, PubMed, and Medline and were precisely studied.

Results: There are reported cases of COVID-19 spine and spinal cord involvement. There is no documented mechanism for these involvements but the possible mechanisms are direct invasion, cytokine storm, coagulopathy, and an autoimmune response. The routine therapy of such complications is the treatment of these complications with other primary causes with a poor and unsatisfactory response of myelopathy to treatment; however, early diagnosis and vigilance of such involvement improve outcome.

Conclusion: COVID-19 can cause spine and spinal cord complications in some patients without a known incidence rate of such complications. The pathogenesis is not completely known; therefore, more conclusive studies should be performed to improve our information on COVID-19 spinal cord and spine complications.

Keywords:

COVID-19, SARS-CoV-2, Spine, Spinal cord

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Highlights

- After the COVID-19 infection, inflammatory myelopathy and suspected cord ischemia were observed in some patients.
- The most common manifestation of COVID-19 myelitis is the non-enhancing central expansile cord T2 signal changes. It can also present with lateral and dorsal column-specific disease and in some cases with negative magnetic resonance imaging (MRI).
- Although the involvement of the spinal cord is a post-infectious immunological and post-inflammatory reaction, there is still no documented mechanism for it.
- Post-COVID-19 spinal column complications include spondylodiscitis, spinal epidural abscess, vertebral algic syndrome, and aggravation of prior spine diseases.

Plain Language Summary

The severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) can cause the viral infectious COVID-19 which impacts not only the respiratory system but also multiple body organs. Neurological manifestations are sometimes observed before or after COVID-19 symptoms and signs. The potential neurological complications of COVID-19 include spinal cord complications. Inflammatory myelopathy and suspected cord ischemia have been reported after COVID-19. Non-enhancing central expansile cord T2 signal changes are the most common presentation of COVID-19 myelitis which can also manifest with lateral and dorsal column-specific disease and in some patients with negative magnetic resonance imaging (MRI). The spinal cord involvement in COVID-19 infection is not reported extensively but it can be considered as a post-infectious immunological and post-inflammatory disorder/reaction.

1. Introduction

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ARS-CoV-2 is a viral agent causing COVID-19 which was first detected in December 2019 in Wuhan City, Hubei, China. On January 30, 2020, the [World Health Organization \(WHO\)](#) declared this disease as an outbreak and a public health emergency of international concern. COVID-19 was declared a pandemic on March 11, 2020, by [WHO](#) [1]. The outbreak stimulated new studies in many areas of research and science. Severe COVID-19 affects the pulmonary tract and can often be found in different human body compartments, including the central nervous system and peripheral nervous system [2]. There are some reports of COVID-19 associated with spine and spinal cord complications [3]. One of the complications of COVID-19 is associated with myelopathy. The clinical diagnosis of this myelopathy requires a high degree of clinical suspicion. There is no determined known mechanism for COVID-19 cord involvement. However, based on the long latency period of spinal cord damage following COVID-19 (about 7 days or more) in a significant number of cases, the suggestive cause of spinal cord damage is a post-infection immunological disorder. Spinal cord demyelination is an im-

mune-mediated neurologic complication of COVID-19 and based on the presented reports in the literature, spinal demyelinating disorders were reported in COVID-19 patients without this disorder rather than with primary demyelinating disorders. There are 2 aspects between demyelinating disorders and COVID-19. One aspect is that the brain and spinal cord demyelination can be a presentation of SARS-CoV-2 infection and the other aspect is the exacerbation of pre-existing neurological features that may occur in cases with known primary demyelinating disorders [4]. Based on the pathology reports, there is evidence of inflammatory myelopathy and suspected cord ischemia following SARS-CoV-2 infection [5]. In COVID-19, several immunological manifestations affect different organ systems, including the nervous system and immunological mechanisms play a key role in creating different clinical presentations, including neurological presentations [6-10].

2. Methods and Materials/Patients

This narrative study on spinal cord complications of COVID-19 provides up-to-date information based on the precise review of COVID-19 articles on spine and spinal cord complications. Using the keywords "COVID-19",



“SARS-CoV-2”, “spine”, and “spinal cord”, all the related articles were collected from [Google Scholar](#), [PubMed](#), and [Medline](#) and were then precisely studied.

3. Results

The major manifestations of SARS-CoV-2 viral infection are fever and respiratory symptoms. However, there are several case reports with neurological symptoms affecting the nervous system [10, 11]. The most common central nervous system complication is cerebrovascular disease [10, 11] and appears with rare involvement of the spine and spinal cord. Different COVID-19-related spine and spinal cord involvements can occur and have been reported. The exact mechanisms of these involvements are not known but possible mechanisms are direct invasion, cytokine storm, coagulopathy, and an autoimmune response [12-15].

4. Discussion

COVID-19-related myelopathy

SARS-CoV-2 can involve the spinal cord and develop acute inflammatory myelopathy. COVID-19-related myelopathy is an inflammatory myelopathy that roughly starts about one month after the COVID-19 onset in association with COVID-19 symptoms or about 10 days after COVID-19 symptoms resolution. There are infrequent reports of COVID-19-related myelopathy. However, based on some reports, it is not a rare disease and for a correct diagnosis, a high degree of clinical suspicion is needed as imaging markers may be negative. It does not have any known documented mechanism with some probable pathophysiologic mechanisms [16-18]. Acute inflammatory myelopathy is because of the following inflammatory demyelinating conditions [19]:

Acute transverse myelitis: In acute transverse myelitis, there is immune-mediated involvement of spinothalamic tracts, pyramidal tracts, posterior columns, and the anterior funiculus of the spinal cord at one or more levels [20];

Longitudinally extensive transverse myelitis: In longitudinally extensive transverse myelitis (as a type of acute transverse myelitis), there is inflammatory demyelination over 3 or more vertebral segments [21]. Longitudinally extensive transverse myelitis is associated with neuromyelitis optica and acute disseminated encephalomyelitis [21], whereas short-segment demyelinations are generally present in multiple sclerosis and clinically isolated syndromes [21];

Neuromyelitis optica: In neuromyelitis optica, there is inflammatory demyelination of the optic nerve and spinal cord [21, 22];

Acute disseminated encephalomyelitis: In acute disseminated encephalomyelitis, the brain and the spinal cord are involved [23].

To evaluate acute transverse myelitis, magnetic resonance imaging (MRI) is mandatory. MRI can show intraparenchymal cord lesions and differentiate these lesions from other cord lesions. Meanwhile, in MRI with contrast, there is a positive enhancement of lesions [24, 25]. Acute transverse myelitis and its variants have an unpredictable course and with early diagnosis, treatment, and rehabilitation have an improved functional outcome [24, 25].

There is no documented mechanism for post-COVID-19 cord involvement and the suggestive mechanisms of SARS-CoV-2-related damage of cords are through the angiotensin-converting enzyme 2 receptors at the cell surface [26-29], cytokine storm mechanism, and or post-infectious inflammatory or immune-mediated mechanism [30-32]. Because of a longer latency period (≥ 7 days), in a significant number of cases of COVID-19 infection with spinal cord damage (86.4%), the most probable mechanism is post-infectious immunological disorder [33-49]. It has been postulated that in cases with SARS-CoV-2, infection, and genetic susceptibility, the altered immune response against SARS-CoV-2 with the following imbalance between the pro-inflammatory and anti-inflammatory cytokines occurs and creates a silent demyelinating process. Cytokine storm is a pro-inflammatory state that increases the level of interleukin 1, and interleukin 6, along with tumor necrosis factor α release, and can activate the glial cells following demyelination of the cord. Cytokine storm in association with the facilitation of virus spreading in the human body in COVID-19 infection due to delayed and decreased release of interferons (interferon α and interferon β) is the probable mechanism of cord demyelination in COVID-19 [50-52]. Clinical presentations of acute transverse myelitis are paraplegia, bladder dysfunction, and sensory deficits [52]. In addition, in some patients, low back pain, visual problems, and episodes of seizure are observed [53, 54]. On the cerebrospinal fluid exam of acute transverse myelitis, there is lymphocytic pleocytosis and increased protein content; also, in some cases of acute transverse myelitis, such as multiple sclerosis and acute disseminated encephalomyelitis cerebrospinal fluid findings can be normal. Based on some observational studies in acute transverse myelitis, there is no

relationship between the level of injury (sensory and or motor level) on physical examination with the level of lesions in MRI. Accordingly, in patients with clinical suspicion of inflammatory myelopathy MRI, screening of all neuroaxis irrespective of their neurological level on clinical examination must be done [53-55]. In acute transverse myelitis, several clinical features are in favor of a good outcome, namely older age at symptom onset, hyperreflexia and Babinski sign signifying corticospinal tract involvement without anterior horn cell injury and sparing of posterior column sensation at the peak of the deficit, preceding infection, recovery in less than 7 days, age less than 10 years, and a lumbar versus thoracic or cervical level [53-55].

COVID-19 myelitis cases can clinically present the following items:

- The most common presentation is central expansile cord T2 signal hyperintensity without contrast enhancement [56-69];
- Transverse myelitis clinical symptoms with paraplegia with a normal MRI [70];
- Presentation with a more tract-specific disease as ventral horn-predominant T2 hyperintensity and acute flaccid myelitis or dorsal column-predominant T2 signal abnormality with progressive numbness in the feet and hands [53] or with lateral and dorsal column-specific disease [71, 72].

The central gray matter region is the usual region of involvement in viral myelitis and the involvement of lateral and dorsal columns is relatively atypical [73]. This later atypical involvement is more common in subacute combined degeneration. In the infectious setting of HIV infection, posterior column involvement can be seen [74] or in human T-cell lymphotropic virus type 1 posterior and lateral column involvement can occur [75]. Subacute combined degeneration in a noninfectious setting can present because of a disorder in the methylation pathway [76]. This disturbance happens because of metabolic causes, such as vitamin B12 [77] and copper deficiency, vitamin E deficiency [78, 79], and toxic causes such as excess nitrous oxide with secondary qualitative B12 deficiency [80], in addition to intrathecal methotrexate [81].

For supporting the immune system, metabolic and nutritional factors have key roles especially in the COVID-19 condition [82], with some evidence supporting the effectiveness of vitamin B12 supplementation [83].

In the biochemical process of methylation, 4 atoms (CH₃) transfer from one substance to another. One of the aspects of a good methylation state is a sound healthy immune system and it supports and strengthens the protective coating along nerves. By adding a few key nutrients, such as folate, B vitamins, and choline to the diet, DNA methylation improves. According to several studies, these vitamins and nutrients appear to play a role in DNA methylation. Following a poor methylation state, the level of homocysteine is increased and causes resultant increases in arthritis, heart disease, cancer, impaired immune function, imbalanced TH1/TH2 ratio leading to high histamine levels, and so on [84, 85]. The pathophysiology of COVID-19 has a possible correlation with the methylation process. In COVID-19 cases, the insufficiencies in the immune system that are assisted by the methylation process can be exposed and this may explain the lateral and dorsal column involvement [86]. The mutation of the MTHFR gene strongly predisposes to subacute combined degeneration and a susceptibility to a more severe COVID-19 can occur in cases with MTHFR C677T polymorphism. For these cases, vitamin supplementation is recommended [87-89].

In the treatment of acute transverse myelitis for the reduction of spinal cord damage and prevention of further damage several drugs have been tried. Intravenous therapy-methylprednisolone sodium succinate is the most frequently used drug with reports of significant motor recovery after microcurrent point stimulation therapy in many studies [90-98].

Acute transverse myelitis can cause many disabilities and among these patients, about one-third recover complete motor ability, one-third achieve a moderate degree of recovery, and one-third do not recover (severe disability) or do not survive. Persistent bladder dysfunction, bowel deficits, and sexual dysfunction may be present in patients with complete motor recovery. However, such information is about cases of non-COVID acute transverse myelitis. Prior results show a high chance of recurrence of neurological deficits after acute transverse myelitis, irrespective of etiology and regular monitoring of neurological status in association with inflammatory and infective markers, especially if it is confirmed as a postinfectious problem of COVID-19, for early detection of these recurrences is important [90-98].

Aggravation of prior spine and spinal cord diseases

Spondylotic myelopathy

Mechanical compression and resultant ischemia of the spinal cord in spondylosis induce a chronic inflammatory response and make the cord more susceptible to untoward bad effects of COVID-19. Chronic compression of the spinal cord creates some pathological changes, such as ischemia, vascular remodeling, endothelial dysfunction, and overregulation of ACE2 receptor expression (the presumed receptor for the spike [S] protein of SARS-CoV-2) [99, 100]. Following these changes, the blood-cord barrier is disrupted and vascular permeability is increased and after this inflammatory infiltration to the cord, parenchyma can increase. Therefore, during COVID-19, the anti-inflammatory response can exacerbate the local inflammation in the areas of compressive spondylotic myelopathy and aggravate myelopathy symptoms and signs.

Vertebral algic syndrome

Different areas of the human body are affected by the COVID-19-related pains, but less attention is paid to vertebral pain [99]. In COVID-19, the continuation of acute pain can occur and create chronic pain [100-103]. In acute COVID-19, the incidence of pain in the cervical region is about 46.6% and in the lumbar area, it is about 50.7% without known incidence in long COVID-19 [104-111]. In long haulers, based on the high frequency of musculoskeletal and joint pain and nervous system involvement, there is an underestimation of vertebral pain and nerve root impairment because more attention is given to the former symptoms and signs than the latter ones [112-118].

The source of generated vertebral pain in COVID-19 because of the complexity of the spine can be through the effects on the muscles, bones, joints, and neural structures (because of the neurotropic features of COVID-19). There is no known exact mechanism for spinal pain generation but direct and indirect mechanisms and autoimmune processes are proposed [119-123]. Because more attention is paid to the deterioration of function and structure of the brain than nerve root, there is a gap in nerve root functional and structural deterioration in COVID-19 [124-127]. In acute and post-COVID-19 periods, nerve root irritation and back pain are common problems. Vertebral pain is a variable and even bizarre manifestation during the course of COVID-19 and may not correlate with radiological findings. Long COVID-19 or long haulers can develop in one-third

of non-severe COVID-19 cases. Meanwhile, in 80% of recovered cases after COVID-19 at least one symptom, such as vertebral pain is present. Differentiation between post-COVID-19 low back pain cases and individuals with different origins of low back pain can be difficult because of the following two reasons: 1) most of the COVID-19 cases are asymptomatic or oligosymptomatic and novel corona-virus tests might not be performed, and 2) testing strategies vary in different countries and the test may be done too early or too late with false negative results. The frequency of cases of low back pain in COVID-19 is presumably high but has not been reported. In COVID-19, there are no specific therapeutic recommendations for low back pain, and recommendation to follow routine therapeutic guidelines in long COVID-19 cases with low back pain with reasonable results of pain relief. Accordingly, we cannot compare selected and recommended therapeutic options for post-COVID-19 low-back pain therapy. During lockdowns, there is a tendency toward sedentary life changes and this can influence the development of low back pain [128-132].

Spinal epidural abscess

COVID-19 is a primary pulmonary tract infection with some effects on various parts of the human body [133-135]. SARS-CoV-2 causes a disseminated injury to the endothelium and creates a kind of disseminated intravascular coagulation [136, 137]. In a large autopsic series, in about 87% of patients, there were different degrees of endothelial injury and arteriolar thrombosis. From a practical viewpoint in COVID-19, the following conditions can occur: disseminated micro-embolisms, bleeding tendency, disseminated vasculitis, and autoimmune aggression with decreased antibacterial defense [138, 139]. COVID-19 is an immune-compromised state with lymphopenia and is a risk factor for spinal epidural abscess. Because of this immune-compromised state and lymphopenia, the frequency of spinal epidural abscesses in COVID-19 cases is higher. However, a higher incidence of spinal epidural abscess is not reported because of under-diagnosis and following under-report of SEA in comatose or severely compromised COVID-19 cases. In addition, the focus of physicians is on other aspects of COVID-19 than a spinal epidural abscess. The spinal epidural abscess of COVID-19 patients has the following characteristics:

- More common in the cervical and thoracic regions;
- Late-onset and occurrence following resolution of COVID-19;
- Poor recovery response and outcome.

The main important factor in the outcome of spinal epidural abscess is the preoperative status and because of the unexpected rate of spinal epidural abscess in COVID-19 patients, careful neurological examination of these patients with a high suspicion of spinal epidural abscess is mandatory in early diagnosis and treatment with good favorable outcome [140-144].

Spinal aspergillosis

Spinal aspergillosis is a reported complication of HIV infection [145] with a low response to treatment protocols. Corticosteroid therapy in COVID-19 cases is a part of treatment because COVID-19 makes these cases prone to fungal infections, such as aspergillosis [146, 147]. Fungal infections in these patients occur within 2 weeks after the onset of COVID-19 presentations [148]. There is a report of spinal aspergillosis 7 months after COVID-19 infection with a positive history of dexamethasone consumption. The patient presented with low back pain and cauda equina syndrome. In MRI findings, there was a lesion on T2 weighted sequence with a focus on a hypointense signal with positive enhancement on MRI with contrast. When this case was operated on, there was an ash-grey avascular epidural mass without abscess. The pathology report was in favor of fungal infection and differential diagnosis was in favor of mucormycosis. The patient was treated with amphotericin-B with good outcomes and follow-up results [149, 150].

Spondylodiscitis

COVID-19 is a pulmonary infection with increasingly recognized extra-pulmonary manifestations. In some studies, the association of COVID-19 with spinal infections like spondylodiscitis is reported. Spondylodiscitis commonly presents with back pain and occasional fever, accordingly, in COVID-19 cases who are already suffering from these manifestations, spondylodiscitis can be easily missed. If there is suspicion of spinal involvement in COVID-19 cases detailed neurological examination is mandatory to detect these patients. In SARS-CoV-2 infection, the state of immunosuppression and endothelium make these patients prone to bacteremia, from asymptomatic bacterial colonization and spondylodiscitis [151-157].

There is a different frequency of COVID-19-associated co-infections in different studies. The main key in treatment of COVID-19-associated co-infections is the early diagnosis of co-infections and because of delay in diagnosis, delayed treatment is common which can cause serious complications. No specific clinical or radiological

characteristics recognize these co-infections; however, for the differentiation of fungal and staphylococcus aureus spondylodiscitis, the following 4 factors are predictive of fungal osteomyelitis/discitis: focal paravertebral soft tissue abnormality, partial disc involvement, back pain for 10 or more weeks, and failure of current antibiotic usage for 1 week [158-166].

As a serious effect of dysbalanced immune response with immunosuppression after COVID-19 infection, spondylodiscitis with or without spinal abscess can occur. In COVID-19 infection, a cytokine storm syndrome with a native immune suppressed state has been reported [169, 170]. Moreover, secondary haemophagocytic lymphohistiocytosis is another condition that has also been seen in viral infections [168, 169].

Candida-induced spondylodiscitis is reported in less than 5% of spondylodiscitis patients. Because of the increased number of endangered cases, the frequency of candida infection is increased [170-172]. In COVID-19 cases with intensive care, invasive fungal infections are higher [173-175]. The overall outcome in candida spondylodiscitis is favorable with a cure rate of nearly 85%. For this favorable result, early diagnosis and treatment are important [176-178]. Similar to other types of SD, medical therapy is crucial, although surgical therapy has some role in certain conditions. In patients with candida spondylodiscitis and operation with hardware implant placement, there is a risk of delayed cryptic infectious processes related to the hardware implants so long-standing follow-up is necessary for prevention. [179].

SARS-CoV-2-induced polyradiculitis

Polyradiculitis is an extrapulmonary manifestation of COVID-19. SARS-CoV-2-related Guillain-Barré syndrome more commonly occurs in male and elderly patients. The most prevalent subtype of Guillain-Barré syndrome is acute inflammatory demyelinating polyneuropathy. In most instances, infection preceded the onset of Guillain-Barré syndrome. SARS-CoV-2-related Guillain-Barré syndrome more frequently develops about 10 days after the first non-neurological symptoms. The exact mechanism of SARS-CoV-2-associated Guillain-Barré syndrome is unknown. The suggestive mechanism of SARS-CoV-2 associated Guillain-Barré syndrome is an immune-mediated mechanism, such as antibody precipitation on myelin sheaths or axons, or a mimicry between epitopes on the surface of the virus and on membranes of motor or sensory neurons that causes simultaneous attack to these neurons (such as Guillain-Barré syndrome due to *C. jejuni*), and/or COVID-19-associated cytokine storm and dysregulated immune response. SARS-

CoV-2 direct viral invasion against nerve roots cannot be a mechanism for this disease because of the absence of the virus in the cerebrospinal fluid of these cases. However, because of the viral involvement of the neurons and endothelial cells of the frontal lobe, the SARS-CoV-2 direct invasion of motor and sensory neurons can be a conceivable mechanism. Based on some suppositions, in COVID-19 patients, the brain can be a reservoir for the virus without severe clinical manifestations [180-184]. From a therapeutic viewpoint, there is a favorable response to intravenous immunoglobulin in the majority of patients. Mechanical ventilation is required in about one-third of SARS-CoV-2-associated Guillain-Barré syndrome. It is unknown whether there is any difference between the prevalence of SARS-CoV-2-associated Guillain-Barré syndrome in cases with and individuals without pre-existing peripheral nerve damage. The prevalence of Guillain-Barré syndrome of SARS-CoV-2 is lower than that of Guillain-Barré syndrome due to other triggers but the clinical presentation, course, response to treatment, and outcome are similar [183-185].

Conclusion

COVID-19 can cause spine and spinal cord complications. The real incidence and pathogenesis of these complications are not well known. More conclusive studies are obligatory to improve our information about COVID-19 spine and spinal cord complications. Further conclusive studies are needed regarding the incidence, mechanism, etiology, and treatment of COVID-19 spine and spinal cord complications.

Ethical Considerations

Compliance with ethical guidelines

No human or animal subjects participated in this study.

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Authors' contributions

Conception and design: Seyed Reza Mousavi, Owrang Eilami, Ali Kazeminezhad; Data collection: Navid Kalani, Tina Mosalanezhad; Data analysis and interpretation: Navid Kalani, Tina Mosalanezhad; Drafting the article: All authors; Critically revising the article: Majidreza Farrokhi, Tina Mosalanezhad, Owrang Eilami; Reviewing the submitted version of the manuscript: All authors; Approving the final version of the manuscript: All authors.

Conflict of interest

The authors declare that there is no conflict of interest.

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