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Cytokine profile and case series of tract-specific myelitis following SARS-CoV-2 infection

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Keywords
COVID-19; Myelitis; Transverse Myelitis; Cytokines; Autoimmune Diseases; Central Nervous System

Abstract

Background: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a potential trigger for central nervous system (CNS) autoimmune disorders. The most common type of spinal cord pathology following novel coronavirus infection is immune-mediated/autoimmune transverse myelitis (TM); however, there are also rare forms of spinal cord pathology – tract-specific myelitis – previously considered as non-autoimmune-originated.

Methods: The current study includes case series of 5 patients with a rare type of myelitis with predominant involvement of the dorsal and lateral columns following coronavirus disease 2019 (COVID-19). We aimed to analyze cytokines parameters in cerebrospinal fluid (CSF) of affected patients. In order to support the autoimmune origin of the disease, CSF cytokine profiles were compared to patients with TM following COVID-19 (n = 12). Scale variables were compared between two independent groups using t-test or Wilcoxon-Mann-Whitney test depending on the distribution.

Results: In contrast to patients with TM, patients with tract-specific myelitis demonstrated higher levels of a proliferation-inducing ligand (APRIL), B cell activating factor (BAFF), interleukin (IL)-11, and thymic stromal lymphopoietin (TSLP). The BAFF/APRIL system is renowned for its involvement in the genesis and advancement of autoimmune disorders, and its pronounced increase in this case supports the autoimmune origin of the disease.

Conclusion: The heightened activation of BAFF and APRIL cytokines, which promote B-cell maturation, suggests an autoimmune origin of tract-specific myelitis, thereby informing prognosis and treatment strategies for affected patients.

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Introduction

Since the first case of neurological complication associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was described at the beginning of the pandemic, scientists have increasingly reported acute or long-term neurological disorders occurring simultaneously or after coronavirus disease 2019 (COVID-19). These neurological complications include a wide range of clinical manifestations, ranging from mild symptoms such as loss of smell and taste, headache, and fatigue to more severe conditions including viral encephalitis, stroke, and various immune-mediated and autoimmune diseases [autoimmune encephalitis, myelitis, optic neuritis (ON), Guillain-Barre syndrome (GBS), etc.].[1-5]

According to a retrospective cohort study that included 3814479 participants, since 2020, the development of autoimmune diseases was observed more often in patients who had COVID-19 than in people who did not.[6] Connective tissue disorders (CTDs) as well as type 1 diabetes mellitus (DM), Graves' disease, and multiple sclerosis (MS) are among the most frequently reported autoimmune pathologies following COVID-19.[7,8]

The pathways of viral-induced autoimmune and immune-mediated diseases development are diverse. They could be associated with the mechanisms of molecular mimicry, neuroinflammation with the following destruction of nerve cells, and cross-reactivity due to accessibility of cryptic epitopes of autoantigens. Moreover, SARS-CoV-2 is a powerful trigger for activating the synthesis of proinflammatory cytokines and other soluble inflammatory mediators, majorly interleukin (IL)-1β, IL-6, interferon gamma-induced protein 10 (IP-10), tumor necrosis factor (TNF), interferon (IFN)-γ, macrophage inflammatory protein (MIP)-1α and 1β, and vascular endothelial growth factor (VEGF) which interferes with both innate and acquired immunological responses in humans, causing self-antigen intolerance.[7] In addition, several studies have shown the activation of the B cell and an increased level of cytokines B cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) in serum, in particular in multisystem inflammatory syndrome in children associated with COVID-19,[9] as well as in patients with severe COVID-19.[10]

Spinal cord lesions account for approximately 2.7% of neurological complications of the novel coronavirus infection.[11] Among various spinal cord lesions, the most common are para- or post-infectious transverse myelitis (TM). Rarely, lesions could be associated also with direct virus effects (acute TM, polio-like myelitis) or effects stemming from systemic complications of COVID-19 (hypoxic myelopathy, subacute combined degeneration, and vascular pathology with the formation of spinal cord infarction).[12,13] The clinical picture of post-infectious acute TM associated with COVID-19 does not significantly differ from myelitis developing after other viral diseases (caused by varicella-zoster, herpes simplex, Epstein-Barr, etc.). Patients respond well to immunosuppressive therapy and make almost complete recovery.

In 2021, Huang et al. have first described 5 cases of COVID-19-associated myelitis with tract-specific involvement of the dorsal and lateral columns.[4] In the Research Center of Neurology, Moscow, Russia, we have also observed 5 similar patients. Clinically, this illness is marked by the subacute development of muscle weakness, paresthesias, and sensitive ataxia; eventually, genitourinary dysfunction and spasticity also emerge. Comparable radiological and clinical images were seen in subacute combined degeneration, which was predominantly linked to vitamin B12 insufficiency. In rare instances, vitamin E, folic acid, or copper deficiencies were also implicated. Nonetheless, the blood serum concentrations of copper, group B, and group E vitamins in observed patients remained within the reference ranges. Patients with tract-specific myelitis following COVID-19 exhibited a gradual exacerbation of symptoms, an inadequate response to treatment [B vitamins, glucocorticoids, plasma exchange (PLEX)], and the emergence of significant neurological deficits. The etiology of this disorder remains unidentified; however, the disruption of the methylation cycle, namely the transfer of the methyl group from methyltetrahydrofolate to myelin proteins by the SARS-CoV-2 virus, has been suggested as a potential explanation.[4]

In our prior investigation, we have conducted a comparative analysis of the cerebrospinal fluid (CSF) cytokine profiles from individuals who developed myelitis following COVID-19 infection, and a cohort of patients with MS. Our study revealed that individuals with myelitis following COVID-19 had lower levels of IL-10, IFN-α2, IFN-β, thymic stromal lymphopoietin (TSLP), and higher levels of BAFF and IL-19 compared to

participants with MS. Out of the eight described patients with myelitis, two had tract-specific spinal cord damage. These two patients had the highest levels of BAFF and APRIL among the group, that led us to suspect that an autoimmune process with the predominant B cell activation could be the primary cause of this pathology.[14] Establishing the autoimmune origin in these patients is crucial for formulating their treatment strategies.

In this paper, we present five cases of tract-specific myelitis following novel coronavirus infection. We also provide data on CSF cytokine profiles of these patients and compare it with CSF of patients with TM following SARS-CoV-2 in order to support the hypothesis of predominating autoimmune pathogenesis of this disease.

Materials and Methods

Patients study: CSF findings of patients with predominant involvement of lateral and posterior columns (n = 5) were analyzed and compared to the group of TM (n = 12) following COVID-19.

The inclusion requirements for both groups encompassed a definitive diagnosis of myelitis supported by clinical and radiographic evidence, as well as confirmation of coronavirus infection through polymerase chain reaction (PCR)/antibodies (Abs) testing within a maximum of 3 months prior to the onset of myelitis symptoms. The study excluded individuals with a past medical history of chronic autoimmune or immune-mediated central nervous system (CNS) diseases such as MS, neuromyelitis optica spectrum disorders (NMOSD), and autoimmune encephalitis. Additionally, individuals with spinal cord injury caused by non-inflammatory conditions such as compression myelopathy, ischemic spinal cord injury, and subacute combined degeneration of the spinal cord due to vitamin B12 deficiency were also excluded.

The group of patients with TM included 12 individuals (8 women), and the mean age at diagnosis was 46.80 ± 1.46 years (range: 24-66 years). Out of the 12 patients, 7 had partial TM, 2 patients had multifocal spinal cord lesions, and 3 had longitudinal extensive TM. The symptoms of myelitis typically appeared 3.50 ± 0.35 weeks following the infection.

The group of patients with tract-specific myelitis included 5 patients (2 women), and the mean age at diagnosis was 38.80 ± 1.27 years (range: 24-55 years). Detailed clinical, radiological, and CSF investigation data are presented in the table 1.

Laboratory study: Cytokine profiles were analyzed in patients' CSF using 37-PLEX Bio-Plex Pro Human Cytokine Inflammation Panel (Bio-Rad, USA). The panel included the following biomarkers: APRIL, BAFF, soluble CD30 (sCD30), sCD163, chitinase-3-like 1 (CHI3L1), gp130, IFN-α2, IFN-β, IFN-γ, IL-2, soluble form of the IL-6 receptor (sIL-6Rα), IL-8, IL-10, IL-11, IL-12 (p40), IL-12 (p70), IL-19, IL-20, IL-22, IL-26, IL-27 (p28), IL-28A, IL-29, IL-32, IL-34, IL-35, LIGHT (TNF superfamily member 14), matrix metalloproteinase (MMP)-1, MMP-2, MMP-3, osteocalcin, osteopontin, pentraxin-3 (PTX-3), soluble TNF receptor 1 (sTNF-R1), soluble TNF receptor 2 (sTNF-R2), TSLP, and TNF-like weak inducer of apoptosis (TWEAK).

Statistical analysis was performed using SPSS software (version 26, IBM Corporation, Armonk, NY, USA). Scale variables were described as median, 25 and 75 percentiles. After normality testing with the Shapiro-Wilk method, scale variables were compared between two independent groups. Variables with normal distribution were compared using t-test. Variables with non-normal distribution were compared using the Wilcoxon-Mann-Whitney test. The level of significance was set at $P < 0.05$.

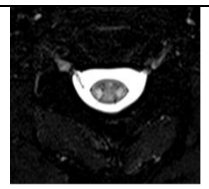
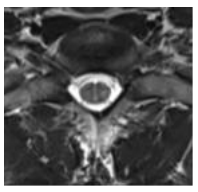
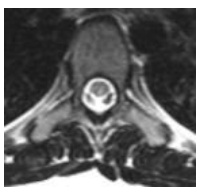
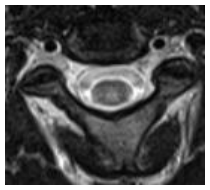
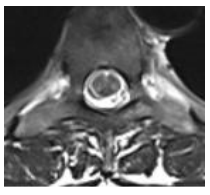
Results

CSF cytokine profile investigation: Compared to patients with TM, patients with tract-specific myelitis had significantly higher levels of APRIL, BAFF, IL-11, and TSLP (Table 2). No significant difference was found for other cytokines, including sCD30, sCD163, CHI3L1, gp130, IFN-α2, IFN-β, IFN-γ, IL-2, sIL-6Rα, IL-8, IL-10, IL-12 (p40), IL-12 (p70), IL-19, IL-20, IL-22, IL-26, IL-27 (p28), IL-28A, IL-29, IL-32, IL-34, IL-35, LIGHT, MMP-1, MMP-2, MMP-3, osteocalcin, osteopontin, PTX-3, sTNF-R1, sTNF-R2, and TWEAK.

Case series of tract-specific myelitis

Case 1: A 37-year-old man was diagnosed with the novel coronavirus infection in June 2021. Two weeks after the recovery, the patient first noted a feeling of unbearable cold in his legs. A few days later, he experienced urinary incontinence. He underwent a magnetic resonance imaging (MRI), but the results were reported as normal. In the beginning of August 2021, over the course of a week, numbness in the feet began to spread to the level of the ribs, and weakness in the legs appeared and steadily progressed. In September 2021, he was referred to the hospital.

Table 1. Clinical characteristics of 5 patients with tract-specific myelitis following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection

Sex	Age (year)	Time from infection to symptoms onset	Symptoms	MRI	CSF analysis cytosis protein, OCB	Treatment	Response	1-year follow-up	2-year follow-up
Man	37	2 weeks	Lower paraparesis up to 1/5 MRC, core muscles weakness, reduced vibration and proprioception in a length-dependent pattern from the Th5-6 level, bladder dysfunction		10 cells/mm^3, 0.36 g/l, type 1	PLEX, IVMP, vitamin B	None, sent for rehabilitation	Lower limbs weakness of 3/5 MRC, ambulating with cane, bladder and bowel symptoms being diminished	Walking independently, although not for extended distances
Woman	25	3 weeks	Lower paraparesis of 2/5 MRC, length-dependent hypoesthesia from Th6, urinary urgency, difficulty with voiding, bowel constipation		10 cells/mm^3, 0.213 g/l, type 1	PLEX, IVMP, vitamin B	None, sent for rehabilitation	Lower limbs weakness of 3/5 MRC, ambulating with cane, bladder and bowel symptoms being at previous severity degree	Numbness throughout her body, stiffness in her legs, urge incontinence, and persistence of episodes of retention
Woman	52	3 weeks	Lower paraparesis up to 3.5/5 MRC on the left, 4.5 MRC on the right, reduced vibration and proprioception below the knees, detrusor-sphincter dyssynergia		7 cells/mm^3, 0.5 g/l, type 1	IVMP, vitamin B	Partial recovery	Complete recovery	-
Man	23	During the infection	Tetraparesis (up to 4/5 in upper limbs, 3/5 in lower limbs), descending dysesthesia from the level of the knees, loss of joint position, vibration below knees, sensory ataxia		5 cells/mm^3, 0.574 g/l, type 1	PLEX, IVMP	Partial improvement, sent for rehabilitation	One-sided support walking	Walking independently, although not for extended distances
Man	55	2 weeks	Lower limbs weakness of 1.5 MRC, weakness of the abdominal and back muscles, upper limbs weakness of 4.5 MRC, urinary retention (continuous catheterization), hypoesthesia below the Th7 level		5 cells/mm^3, 0.33 g/l, type 1	PLEX, IVMP, vitamin B	None, sent for rehabilitation	Lower limbs weakness of 3.5 MRC, weakness of the abdominal and back muscles, sitting in wheelchair, and standing up for seconds, continuous catheterization being used	Moving with one-sided support for short distances, the suprapubic catheter being removed

MRC: Medical Research Council; MRI: Magnetic resonance imaging; PLEX: Plasma exchange; IVMP: Intravenous methylprednisolone; CSF: Cerebrospinal fluid; OCB: Oligoclonal band

Table 2. Cytokine profiles of study participants (descriptive statistics)

Cytokine	TM (n = 12) [median (Q1-Q3)]	Tract-specific myelitis (n = 5) [median (Q1-Q3)]	P
APRIL	94804.24 (75116.69-108235.68)	120096.50 (116750.80-167774.27)	0.019
BAFF	5537.53 (4860.18-6550.66)	7918.30 (6710.36-9971.34)	0.011
IL-11	2.54 (0.81-3.34)	4.86 (4.56-5.37)	0.009
TSLP	3.26 (0.22-3.89)	5.32 (3.84-6.75)	0.035

TM: Transverse myelitis; APRIL: A proliferation-inducing ligand; BAFF: B cell activating factor; IL-11: Interleukin-11; TSLP: Thymic stromal lymphopoietin

Neurological assessment showed lower-limb paraparesis [3/5 Medical Research Council (MRC)], muscle hypotonia, hyperreflexia, reduced vibration and proprioception in a length-dependent pattern from the Th5-6 level, hyperesthesia of the legs and feet, sensory ataxia, Lhermitte's symptom, and hyperactive bladder dysfunction.

Neuroimaging (MRI): T2 and T2 fluid-attenuated inversion recovery (FLAIR) hyperintensities were observed in the lateral and dorsal columns throughout the entire length of the spinal cord; no brain pathology was detected (Figure 1, A-C).

Considering the alterations observed on spinal MRI, a differential diagnosis between deficiency (subacute combined degeneration), autoimmune [aquaporin-4 (AQP4)-associated diseases, myelin oligodendrocyte glycoprotein (MOG)-associated diseases, etc.], CDDs, and viral disorders was carried out.

Laboratory findings: Levels of vitamins B1, B6, B12, as well as copper, zinc, methylmalonic acid (MMA), and vitamin E were normal. CSF analysis demonstrated cytosis – 10 cells/mm^3. Oligoclonal bands (OCBs) were negative. Further laboratory studies were unremarkable, including various antiviral, anti-AQP4, anti-MOG Abs, Abs associated with CTDs, and antineuronal Abs.

Patient was treated with PLEX, methylprednisolone (in total 5 g), followed by oral prednisolone 72 mg/day for a month with the following gradual dose decrease. Despite normal levels of B vitamins, additional intramuscular administration of B1, B6, and B12 was carried out. He developed a severe paraparesis while receiving medical care, necessitating continuous bilateral support for walking. Over the course of a month, the patient's condition gradually deteriorated: weakness in the core muscles prevented him from sitting without assistance or turning over in bed, and his lower paraparesis progressed to plegia. Pelvic disturbances progressed to complete urinary and fecal incontinence. Methylprednisolone (in total 5 g) was repeated but yielded no discernible impact. He was referred for rehabilitation where 2 months later, he began to move within the room with bilateral support and 4 months later with the cane.

Case 2: A 25-year-old woman noted shortness of breath in October 2020 and due to respiratory failure, she was admitted to the infectious department where coronavirus infection was confirmed and antiviral therapy was initiated. Three weeks after the discharge, she noticed weakness in arms and legs that gradually increased over a week, followed by an acute urinary retention. Neurological symptoms emerged in conjunction with periods of elevated body temperature reaching 38 ^{o}C.

The patient's medical history comprised recurrent herpes infections.

Neurological assessment showed lower limbs weakness (2/5 MRC), hyperreflexia, length-dependent hypoesthesia from Th6, bladder dysfunction requiring continuous catheterization, and constipation. She used a wheelchair for mobility.

Neuroimaging (MRI): Intramedullary T2WI hyperintense lesions in the posterior columns of the cervical and thoracic regions were detected; no evidence of focal or diffuse changes in the brain was observed (Figure 1, 2A-B).

Diagnosis of tract-specific myelitis was established. To clarify the genesis of the disease, the following examinations were carried out.

Laboratory findings: CSF analysis was notable for slight cytosis – 10 cells/mm^3. OCBs were negative. Additional laboratory investigations yielded no notable findings, including anti-AQP4, anti-MOG Abs, and Abs associated with CTDs. Levels of vitamins were normal.

Pending CSF cultures results, therapy with acyclovir, ceftriaxone, and dexamethasone was initiated. After receiving negative CSF PCR results [herpes simplex virus (HSV), SARS-CoV-2], she was treated with PLEX and methylprednisolone (in total 6 g). She was discharged home on oral prednisolone for 2 months. In 2 months, she was able to stand up from a wheelchair for seconds.

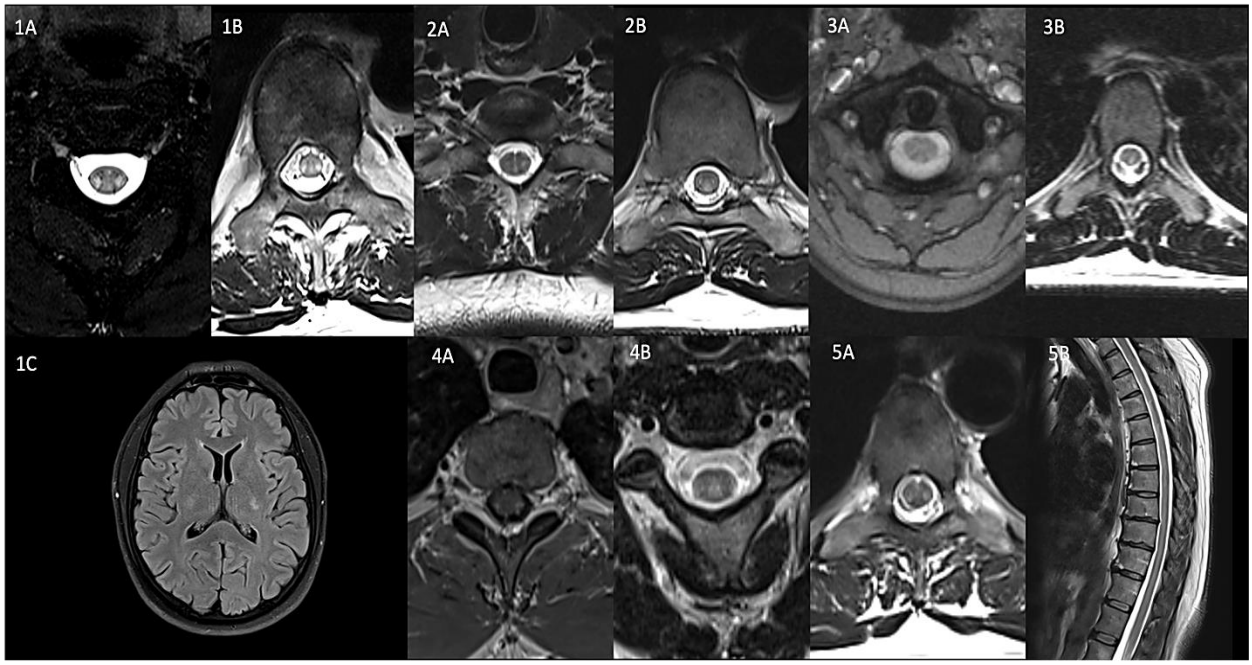


Figure 1. Magnetic resonance imaging (MRI) of patients with tract-specific myelitis following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection

In all patients, axial T2WI MRI has detected symmetrical intramedullary extended zones located in the lateral and posterior columns of the spinal cord at the cervical and thoracic levels. Most patients also had symmetrical cerebral T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities of the corticospinal tracts. Patient 1: 1A) Axial T2WI of the cervical spine at the C2 level; 1B) Thoracic spine at the Th3 level; 1C) Sagittal brain T2-FLAIR WI showing symmetrical hyperintensities of the corticospinal tracts from medulla oblongata to the semioval centers. Patient 2: 2A) Axial T2WI of the cervical spine at the C7 level; 2B) Thoracic spine at the Th7 level. Patient 3: 3A) Axial T2WI of the cervical spine at the C2 level; 3B) Thoracic spine at the Th4 level. Patient 4: 4A) Axial T1-Gd of the thoracic spine at the Th3 level showing contrast accumulation in the zones located in the lateral and posterior columns of the spinal cord; 4B) Axial T2WI of the cervical spine at the C2 level. Patient 5: 5A) Axial T2WI of the thoracic spine at the Th3 level; 5B) Sagittal T2WI indicating diffuse hyperintensity throughout the entire length of the spinal cord

At one-year follow-up, she walked with one-sided support; bladder and bowel impairments remained. By December 2022, she achieved the ability to walk without assistance, but she still had numbness throughout her body and stiffness in her legs. The catheter was successfully withdrawn, but urge incontinence and episodes of retention persisted.

Case 3: A 52-year-old woman suffered from an acute respiratory viral infection in January 2022. Subsequent SARS-CoV-2 Ab test proved novel coronavirus infection. Shortly after her recuperation, she noticed periodic shooting pain along the spine while tilting her head forward. Within a month, she also noted walking instability and gait disturbances. She conducted an MRI, but the results were reported as normal. By the end of April 2022, her state had significantly deteriorated due to increased instability, stiffness, and heaviness in her legs, necessitating one-sided support for long-distance walking; she also noted frequent urination.

Neurological examination revealed lower paraparesis (3.5/5 MRC on the left, 4/5 MRC on the right), diffusely brisk reflexes, increased muscle tone, bilateral Babinski sign, reduced vibration and proprioception below the knees, pronounced sensory ataxia, and detrusor-sphincter dyssynergia (DSD).

Neuroimaging (MRI): Scattered T2-hyperintense regions located in the posterior columns of the cervical and thoracic areas were observed on spinal MRI; brain MRI revealed symmetrical hyperintensities of the corticospinal tracts (Figure 1, 3A-B).

Subsequent analyses to exclude deficiency, autoimmune, and viral causes of the pathology were performed.

Laboratory findings: CSF analysis showed slightly elevated protein (0.5 g/l). OCBs were negative. Further workup, including antiviral and antineuronal Abs, anti-MOG and anti-AQP-4 Abs, CTD Abs, antineuronal Abs, and vitamins, was unrevealing.

The patient received methylprednisolone treatment (total dose of 5 g), followed by intramuscular injections of B vitamins. Throughout the treatment course, there was a noticeable walking improvement. She achieved complete recovery within one year. Repeated MRI (May 2024) showed almost complete disappearance of hyperintense zones in the lateral and posterior columns.

Case 4: A 23-year-old asymptomatic man received a positive PCR SARS-CoV-2 result in February 2021. A few days later, he first noted the clumsiness and numbness in his hands, and a week later in his feet. It was followed by acute back pain, sudden loss of coordination, and a feeling of banding in his chest.

Examination findings were notable for flaccid tetraparesis (4/5 MRC in upper limbs, 3/5 in lower limbs), hyporeflexia, descending dysesthesia from the level of the knees, loss of joint position, vibration below knees, and sensory ataxia.

Neuroimaging (MRI): No changes in brain and spinal cord were detected.

Nerve conduction study (NCS) showed reduced motor nerve conduction velocity and motor evoked amplitudes, as well as sensory axonal damage in legs. CSF analysis showed elevated protein (0.574 g/l) with normal cell count. Based on clinical picture, negative MRI, and electrophysiological findings, GBS was suspected. Patient was treated with PLEX which resulted in a subsequent improvement in sensory and motor function; however, relative limitation of the walking distance remained.

In August 2021, he got COVID-19 for second time. Two weeks later, he experienced a recurrence of weakness in legs, walking instability, and feet numbness that steadily progressed within a week causing patient to use a wheelchair.

MRI was repeated and revealed symmetrical damage of posterior and lateral columns at the cervical and thoracic levels (Figure 1, 4A-B). CSF analysis was unremarkable. Serum analysis markers for CTDs and autoimmune processes were negative. Level of B vitamins was within normal limits.

NCS: Signs of a generalized, symmetrical neural level of damage of a primary axonal nature, more pronounced in the lower extremities, were recorded: in the arms – with the involvement of axons of only sensory nerve fibers, in the legs – with the involvement of axons of sensory and motor nerve fibers. The conductive function of all long nerves of the limbs in the distal sections was not impaired. There was no compliance with clinical, neurophysiological, and supportive diagnostic criteria for chronic inflammatory demyelinating polyneuropathy (CIDP) European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) 2021.

Diagnosis of myelitis was established. Patient was treated with PLEX followed by methylprednisolone (in total 7 g) with a partial improvement. He was reoriented for rehabilitation and by May 2022, he started to use a cane for walking, and by May 2023, he was able to walk without assistance, although not for extended distances.

Case 5: A 55-year-old man had COVID-19 in March 2022. In the early April 2022, he experienced a sensation of numbness in his feet that progressively extended over the course of a week reaching the level of ribs. Later he noted gradual ascending weakness in the legs accompanied by a steady decline in walking ability. In May 2022, he experienced acute urinary retention requiring catheterization and cystostomy afterwards. An MRI was conducted, which revealed no abnormal findings. The patient was monitored and diagnosed with myelopathy of uncertain origin. In June 2022, he started to use a wheelchair.

Neurological assessment showed tetraparesis: mild in arms and severe in legs (proximally – up to 2/5 MRC, distally – plegia), hyperreflexia of the arms, hyporeflexia of the legs, increased muscle tone in legs, bilateral Babinski sign, feet clonus, reduced vibration and proprioception below the Th5, and urinary retention.

Neuroimaging (MRI): T2 and FLAIR hyperintense signal from the lateral and dorsal column throughout the entire length of the spinal cord; brain MRI revealed symmetrical hyperintensities of the corticospinal tracts from medulla oblongata to the semioval centers (Figure 1, 5A-B).

Laboratory investigations to ascertain the etiology of the condition (deficiency, autoimmune, viral) were obtained.

Laboratory findings: Levels of vitamins B1, B6, B12, copper, zinc, MMA, and vitamin E were within normal limits. CSF analysis was normal. Further laboratory studies were unremarkable.

Therapy with methylprednisolone (in total 6 g) and B vitamins was carried out without significant changes. By mid-summer, he was bedridden due to core muscle weakness; arm strength continued to deteriorate. During second hospitalization in August 2022, he was treated with PLEX followed

by methylprednisolone (in total 5 g) that effectively halted the progression of the disease. The patient was referred for rehabilitation center. By December 2023, the lower limbs strength increased up to 3/5 MRC; he was sitting in wheelchair and could stand up for seconds. By May 2024, he moved with a cane for short distances, and the suprapubic catheter was finally removed.

Timelines summarizing key events (COVID-19 infection, symptom onset, treatment, and recovery) for each patient are presented in the supplementary materials.

Discussion

Myelopathy affecting the lateral and posterior columns typically arises in subacute combined degeneration, which is primarily linked to a vitamin B12 deficiency. In rare cases, it may also be associated with deficiencies in vitamin E, folate, or copper, as well as with paraneoplastic syndrome. Additionally, there have been rare instances of myelopathy occurring in the presence of viral infections such as human T-cell lymphotropic virus type 1 (HTLV-I) and human immunodeficiency virus (HIV).

In this article, five patients with the development of tract-specific lesions after COVID-19 infection were described. In all our patients, other causes of myelopathy, including vitamin and mineral deficiencies and infectious and autoimmune (MOG, AQP4) pathologies, have been excluded. In one patient, initial symptoms of myelopathy were noted during the infection, while the others experienced them several weeks later. The escalation of clinical symptoms was noted over a span ranging from a few days to several months. Interestingly, neuroimaging in most cases lagged behind the clinical presentation, revealing lesions only 1-2 months after the onset of severe symptoms. Comparable findings were described in the article, where the diagnosis of myelitis was established clinically and confirmed radiologically later.[15]

The therapeutic intervention (PLEX or/and methylprednisolone) typically resulted in a mild to moderate response, effectively halting the advancement of the disease. The primary approach for restoring lost functions was rehabilitation. Regarding presented patients, in two-year follow-up, almost all of them could ambulate independently.

The etiology of this illness remains elusive. Huang et al. proposed that the SARS-CoV-2 virus affected the methylation cycle, as evidenced by the similarities between this disease and subacute combined spinal cord degeneration.[4] Our investigation demonstrated a significant elevation in APRIL and BAFF cytokines among these patients, in comparison to patients with TM following COVID-19. BAFF, which stands for B lymphocyte activating factor of the TNF family, and its homologue APRIL, have a significant impact on the development of autoimmunity. These proteins are responsible for promoting the survival and selection of B cells. An increased level of these cytokines has been observed in various autoimmune diseases, such as systemic lupus erythematosus (SLE), primary Sjögren's syndrome (pSS), and rheumatoid arthritis (RA), as well as in MS during the relapse.[16] It is well known that APRIL/BAFF antagonist is widely used in the management of SLE. Consequently, the utilization of these compounds for the treatment of COVID-associated tract-specific myelitis may prove advantageous.

The retrospective nature of the analysis and the limited number of participants are the primary limitations of this study. Furthermore, the diagnosis was consistently established by eliminating other potential causes of tract-specific myelitis (deficiencies, viral, and autoimmune diseases). Therefore, potential confounders (e.g., undetected vitamin deficiencies) could be possibly overseen.

Further studies with a larger cohort and longer follow-up are needed to confirm the role of BAFF/APRIL and justify the possible use of target therapy such as BAFF-neutralizing therapies in these patients.

Conclusion

Myelopathy with lateral and posterior column involvement due to coronavirus infection is a rare but potentially disabling condition. The spinal cord is impacted throughout its entire length, resulting in the development of severe motor, sensory, and bowel/bladder dysfunction. In the 5 described patients, the immunosuppressive treatment rarely resulted in an improvement in symptoms, and in the majority of cases, it only halted the progression. Nevertheless, all of our patients recovered over time, despite the severity of their condition and the extent of the MRI lesion. Although etiology of this illness remains elusive, the examination of cytokines in these patients and the observed increase in APRIL and BAFF cytokines in comparison with TM group indicate that individuals with tract-specific myelitis have a

robust immune response, specifically the activation of B-cells, suggesting its autoimmune origin. Additional research including a larger cohort and extended follow-up is necessary to validate the significance of BAFF/APRIL and to substantiate the potential application of targeted medicines, such as BAFF-neutralizing treatments, in these individuals.

Conflict of Interests

The authors declare no conflict of interest in this study.

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References

1. Nabizadeh F, Balabandian M, Sodeifian F, Rezaei N, Rostami MR, Naser Moghadasi A. Autoimmune encephalitis associated with COVID-19: A systematic review. Mult Scler Relat Disord 2022; 62: 103795.
2. Zhou S, Jones-Lopez EC, Soneji DJ, Azevedo CJ, Patel VR. Myelin Oligodendrocyte Glycoprotein Antibody-Associated Optic Neuritis and Myelitis in COVID-19. J Neuroophthalmol 2020; 40(3): 398-402.
3. Akhmedzhanova LT, Voskresenskaia ON, Isaikin AI, Ermilova EV, Nasonova TI, Chernousov PA, et al. [Acute disseminated encephalomyelitis and myelitis associated with new coronavirus infection COVID-19. Case report]. Ter Arkh 2021; 93(11): 1375-80.
4. Huang HY, Shah LM, McNally JS, Sant T, Hutchins TA, Goldstein ED, et al. COVID-19-Associated Myelitis Involving the Dorsal and Lateral White Matter Tracts: A Case Series and Review of the Literature. AJNR Am J Neuroradiol 2021; 42(10): 1912-7.
5. Batum M, Kisabay Ak A, Mavioğlu H. Covid-19 infection-induced neuromyelitis optica: a case report. Int J Neurosci 2022; 132(10): 999-1004.
6. Chang R, Yen-Ting Chen T, Wang SI, Hung YM, Chen HY, Wei CJ. Risk of autoimmune diseases in patients with COVID-19: A retrospective cohort study. EClinicalMedicine 2023; 56: 101783.
7. Peng K, Li X, Yang D, Chan SCW, Zhou J, Wan EYF, et al. Risk of autoimmune diseases following COVID-19 and the potential protective effect from vaccination: a population-based cohort study. EClinicalMedicine 2023; 63: 102154.
8. Tesch F, Ehm F, Vivirito A, Wende D, Batram M, Loser F, et al. Incident autoimmune diseases in association with a SARS-CoV-2 infection: A matched cohort study. Clin Rheumatol 2023; 42(10): 2905-14.
9. Klocperk A, Bloomfield M, Parackova Z, Aillot L, Fremuth J, Sasek L, et al. B cell phenotype and serum levels of interferons, BAFF, and APRIL in multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C). Mol Cell Pediatr 2023; 10(1): 15.
10. Farris AD, Guthridge JM. Overlapping B cell pathways in severe COVID-19 and lupus. Nat Immunol 2020; 21(12): 1478-80.
11. Chou SH, Beghi E, Helbok R, Moro E, Sampson J, Altamirano V, et al. Global Incidence of Neurological Manifestations Among Patients Hospitalized With COVID-19-A Report for the GCS-NeuroCOVID Consortium and the ENERGY Consortium. JAMA Netw Open 2021; 4(5): e2112131.
12. Garg RK, Paliwal VK, Gupta A. Spinal cord involvement in COVID-19: A review. J Spinal Cord Med 2023; 46(3): 390-404.
13. Sampogna G, Tessitore N, Bianconi T, Leo A, Zarbo M, Montanari E, et al. Spinal cord dysfunction after COVID-19 infection. Spinal Cord Ser Cases 2020; 6(1): 92.
14. Kozlova A, Dzharullaeva A, Tukhvatulin A, Zakroyshchikova I, Simaniv T, Askarova L, et al. Myelitis associated with COVID-19: clinical, radiological, and laboratory characteristics. Exploration of Immunology 2024; 4(1): 115-28.
15. Alimohammadi A, Herrington R, Chen T. Corticospinal and Dorsal Column Tractopathy in the Setting of Preceding COVID-19 Infection. Can J Neurol Sci 2024: 1-2.
16. Zhang Y, Tian J, Xiao F, Zheng L, Zhu X, Wu L, et al. B cell-activating factor and its targeted therapy in autoimmune diseases. Cytokine Growth Factor Rev 2022; 64: 57-70.