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Newly Diagnosed Tumefactive Demyelinating Lesion and Multiple Sclerosis After COVID-19 Infection

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ABSTRACT

Introduction: To describe the parainfectious or postinfectious effects of COVID-19 infection on the first demyelinating presentation of Multiple Sclerosis and tumefactive demyelinating lesion (TDL) developing with Longitudinally Extensive Transverse Myelitis (LETM).

Methods: We present six patients who presented with a first CNS demyelination event or whose demyelinating lesions had aggravated after COVID-19 infection between May and December 2020. Nasopharyngeal swab SARS-CoV-2 PCR positivity was detected in five cases and cerebrospinal fluid (CSF) PCR was positive in one. The symptoms, neurological signs, radiological and CSF findings of the cases were examined.

Results: A 24-year-old woman presented with LETM aggravated by COVID-19, accompanied by a newly developed open-ring enhanced TDL. Four patients were diagnosed with the first presentation of MS, and one presented with clinically isolated syndrome according to the McDonald 2017 criteria. The interval between SARS-CoV-2 infection and the onset of clinical symptoms ranged from 4–93 days. All of the cases present with pyramidal or brain stem findings and have high brain and/or spinal MRI load. This suggests the moderate activity of CNS demyelinating disease after COVID-19 infection.

Conclusions: Based on this case series, all these first demyelinating events suggested that COVID-19 infection might trigger or exacerbate CNS demyelinating disease. SARS-CoV-2 plays a role in the clinical onset of Multiple Sclerosis. Active delayed demyelination developed within the first three months. This can be explained by COVID-triggered neuroimmune response that had been latent, and the initiation of the active disease process began with triggering or aggravation of the lesions in MRI. Multiple Sclerosis should be maintained during the COVID-19 pandemic.

Keywords: COVID-19, longitudinally extended transverse myelitis, magnetic resonance imaging, multiple sclerosis, SARS-CoV-2, tumefactive demyelinating lesion

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INTRODUCTION

An increasing number of cases with neurological symptoms and diseases developing due to central nervous system (CNS) involvement of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) have been reported during the coronavirus disease – 2019 (COVID-19) pandemic (1,2). However, the type of the first presentation of demyelinating disease among these patients had a narrow range and has very rarely been reported. Acute disseminated encephalomyelitis (ADEM), acute transverse myelitis (ATM), and longitudinally extensive transverse myelitis (LETM) have been reported as diseases occurring after coronavirus disease (COVID-19) in a small number of case reports (3–10); however, both Multiple sclerosis (MS) and clinically isolated syndrome (CIS) have only been reported in the literature once (11).

SARS-CoV-2 has a neurotropic character. It enters the CNS via retrograde transmission through the olfactory bulb (12). SARS-CoV-2 may affect the CNS through neuronal retrograde dissemination, hematogenous dissemination, or indirect routes (13). Acute or delayed central nervous system demyelination or axonal damage after SARS-CoV-2 infection has been reported (12,14). SARS studies with SARS-CoV-1 showed that delayed self-reactive T-cell suppression occurs as a result of viral replication. This immune response may lead to neuroinflammation, demyelination and axonal damage (15,16). Neurological involvement is considered to be a neuroinvasive direct effect of the virus, postinfectious immune-mediated disease, or neurological complication of the systemic inflammatory response to COVID-19 in the CNS (1,2).

Highlights

- **The first CNS demyelinating events can occur associated with SARS-CoV-2 infection.**
- **Active delayed demyelination can be developed within the first three months after SARS-CoV-2 infection.**
- **This can be explained with the initiation of the active disease process by COVID-19.**
- **All of the cases present with pyramidal or brain stem findings that suggests the moderate activity.**
- **Newly diagnosed Multiple Sclerosis could be develop during the COVID-19 pandemic.**

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METHODS

We present six patients who developed the first CNS demyelinating event after COVID-19 infection between May and December 2020 when admitted to department of neurology. A 24-year-old woman presented with longitudinally extensive transverse myelitis aggravated by SARS-CoV-2 infection and developed a cerebral open-ring enhanced tumefactive demyelinating lesion after SARS-CoV-2 infection. Four exhibited the first presentation of clinically definite multiple sclerosis (CDMS), and one presented with clinically isolated syndrome according to the 2017 McDonald criteria (17). In addition, SARS-Cov-2 polymerase chain reaction (PCR) positivity was detected in the cerebrospinal fluid (CSF) of one of the patients diagnosed with CDMS. The informed consent were acquired from all patients. This study was approved by Gazi University School of Medicine Ethics Committee (Date: 07.06.2022, Decision no: 14).

RESULTS

Case 1

A 24-year-old woman complained of back pain and numbness in both lower extremities in June 2020. She visited a local hospital. In her neurological examination, she had sensory loss below the T8 spinal cord sensory level. Her cranial magnetic resonance imaging (MRI) was described as normal, but thoracic MRI revealed an extensive lesion in T7-T12 spinal cord segments with T2/FLAIR hyperintensity and T1 hypointensity. Patchy contrast enhancement was observed on T1 contrast images. Her CSF analysis showed 10% mononuclear cells, slightly increased protein levels (51.7 mg/dl), and normal glucose levels. The CSF *Brucella* agglutination test, *Borrelia burgdorferi* PCR, and *Mycobacterium tuberculosis* PCR tests were negative. Serum and CSF angiotensin-converting enzyme (ACE) levels were normal, and serum aquaporin-4 (AQP-4) antibody was negative. Her CSF oligoclonal band (OCB) was negative, and her immunoglobulin G (IgG) index was normal (0,52). She was diagnosed with longitudinally extensive transverse myelitis (LETM), and 1000 mg of intravenous methylprednisolone was administered daily for five consecutive days. She recovered completely. Six weeks later, she complained of numbness in the lower extremities again. She visited the same hospital, and 1000 mg/day of intravenous methylprednisolone was administered for seven consecutive days. She recovered partially.

Three weeks later, she complained of a cough. Her nasopharyngeal swab SARS-CoV-2 PCR test was positive. She did not receive any treatment for COVID-19. Simultaneously, she complained of severe weakness in both lower extremities, an inability to void, and constipation. She was admitted to our hospital. Her neurological examination revealed flaccid paraplegia with areflexia and sensory loss below the T8 spinal cord sensory level. Subsequently, urinary catheters were inserted due to bowel dysfunction. Her serum anti-Neuthrophil antibody (ANA), anti-Neuthrophil Cytoplasmic antibody (ANCA), anti double stranded DNA antibodies (anti-ds-DNA), antiphospholipid antibodies, anti-SSA/anti-SSB antibodies, anti-AQP4 antibody, and Anti-Myelin Oligodendrocyte Glycoprotein (anti-MOG) antibody were negative. Visual evoked potentials (VEP) were normal. Cranial MRI revealed a tumefactive demyelinating lesion with open-ring contrast enhancement in the deep white matter extending to the right lateral ventricle. A centrally located extensive lesion in the spinal cord extending from the T7 spinal cord level to the T12 level with peripheral contrast enhancement was observed. Short-segment demyelinating lesions were posterolaterally located at C2–3 and C3–4 in the spinal cord (Figure 1). Six sessions of plasmapheresis were performed on the patient every other day due to recurrent long extensive transverse myelitis. After plasmapheresis, she recovered partially. Based on her neurological examination, she had paraparesis

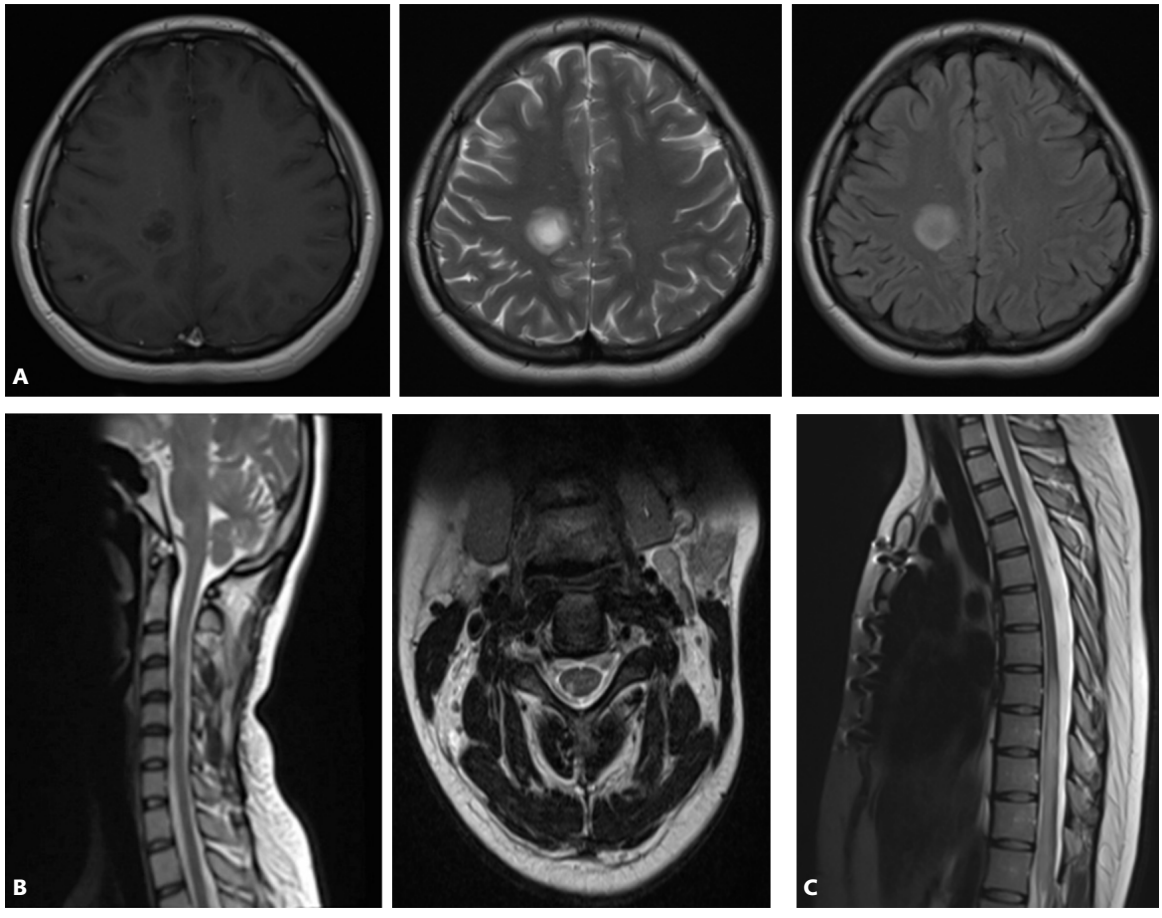


Figure 1. Tumefactive lesion open-ring contrast enhancement in the deep white matter extending to the right lateral ventricle **(a)**. Short-segment demyelinating lesions posterolaterally located at C2–3 and C3–4 **(b).** Centrally located extensive lesion at T7-T12 **(c).**

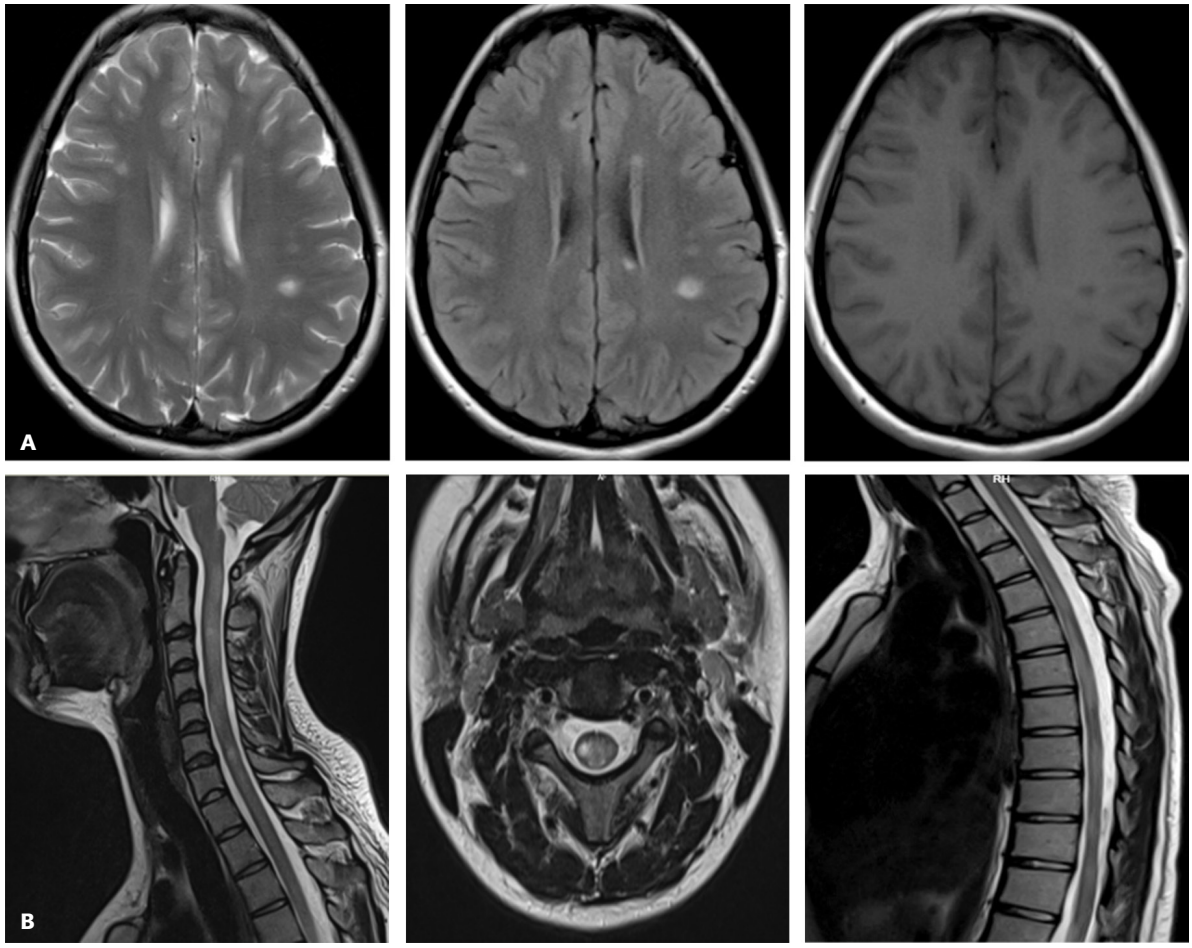


Figure 2. Multiple periventricular, subcortical and juxtacortical demyelinating plaques with T2/FLAIR hyperintensity and T1 hypointensity **(a).** Multiple, confluent, and expansile multisegmented demyelinating lesions in the cervical and upper thoracic spinal cord **(b).**

(3/5 Medical Research Council (MRC) score) and sensory loss in the lower extremities. Intravenous immunoglobulin (IvIg) was administered at a dose of 0.4 g/kg per day to the patient for five consecutive days due to the partial recovery after plasmapheresis. Four weeks later, she experienced 5-/5 weakness and spasticity in the left lower extremity, bilateral Babinski signs, and bilateral hyperactive Achilles reflexes on her neurological examination. The cervical and thoracic lesions regressed; however, all cranial demyelinating lesions had progressed, and new cranial demyelinating lesions had developed. Because of the cranial MRI progression, she took 1000 mg/day of intravenous methylprednisolone for ten consecutive days and oral corticosteroids for maintenance treatment. Her management plan was close clinical and radiological monitoring for MS or neuromyelitis optica spectrum disease (NMOSD). Three months later, there was no difference on neurological examination of the patient. She was diagnosed with seronegative NMOSD according to the clinical course and MRI follow-ups. Rituximab was started.

Case 2

A 20-year-old woman complained of tingling in both lower extremities in October 2020. After four weeks, tingling in the right hand, weakness in the left intrinsic hand muscles, and gait ataxia were added to her complaints. She had a fever (38.5°C) approximately eight weeks prior to when the first symptoms began, but she never experienced anosmia or ageusia. In her neurological examination, nystagmus of the left lateral gaze was observed. She experienced muscle weakness in the upper left extremity and both lower extremities (4/5 in MRC score). Patellar and Achilles' reflexes were hyperactive. A decrease in feeling pain and rough touch was detected in the left lower extremity. Bilateral Hoffman and Babinski signs were positive. Achilles clonus and an intentional tremor occurred on the left side. Cranial MRI revealed multiple periventricular, subcortical and juxtacortical demyelinating plaques with T2/FLAIR hyperintensity and T1 hypointensity. No signs of diffusion restriction in diffusion weighted imaging (DWI) or contrast enhancement were observed. Multiple, primarily confluent, and expansile multisegmented demyelinating lesions were detected at the cervical and upper thoracic regions with T2 hyperintensity and T1 hypointensity (Figure 2). Her nasopharyngeal swab SARS-CoV-2 PCR test was negative, and a chest computer tomography (CT) scan revealed no infiltrative changes in the lungs. Her serum anti-AQP-4 IgG antibody and anti-MOG antibody were negative. The CSF protein level was elevated (66 mg/dl), and glucose levels were within the normal range. Bacteria and leukocytes were not detected by Gram/Wright staining, and no microorganisms were detected in the CSF culture. Her meningoencephalitis rapid test panel was negative; CSF Herpes Simplex virüs-1 (HSV-I), Herpes Simplex virüs-2 (HSV-II), Ebstein-Barr virüs (EBV), Cytomegalovirus (CMV), *Brucella* agglutination, Venereal Disease Research Laboratory Test (VDRL), Rapid plasma reagin (RPR) tests, and *Mycobacterium tuberculosis* PCR tests were negative. The CSF OCB was type 2 positive, the IgG index was elevated (2,06), and her CSF SARS-CoV-2 PCR test was positive. P100 wave latency was prolonged in the left VEP system and was normal in the right VEP system. She was diagnosed with a clinically definite multiple sclerosis (CDMS) first attack according to the 2017 McDonald criteria (17) aggravated by SARS-CoV-2 infection. 1000 mg/day intravenous methylprednisolone was administered to the patient for ten consecutive days. COVID-19 treatment was not considered. She was discharged with oral methylprednisolone as maintenance therapy for three weeks. At the end of corticosteroid therapy, minimal muscle weakness in the left intrinsic hand muscles, bilateral positive Hoffman and Babinski signs, hyperactive patella and Achilles reflexes were detected as sequelae in her neurological examination. Teriflunomide was started as a maintenance therapy. No significant differences were observed in cranial and spinal cord MRI which was repeated after a month.

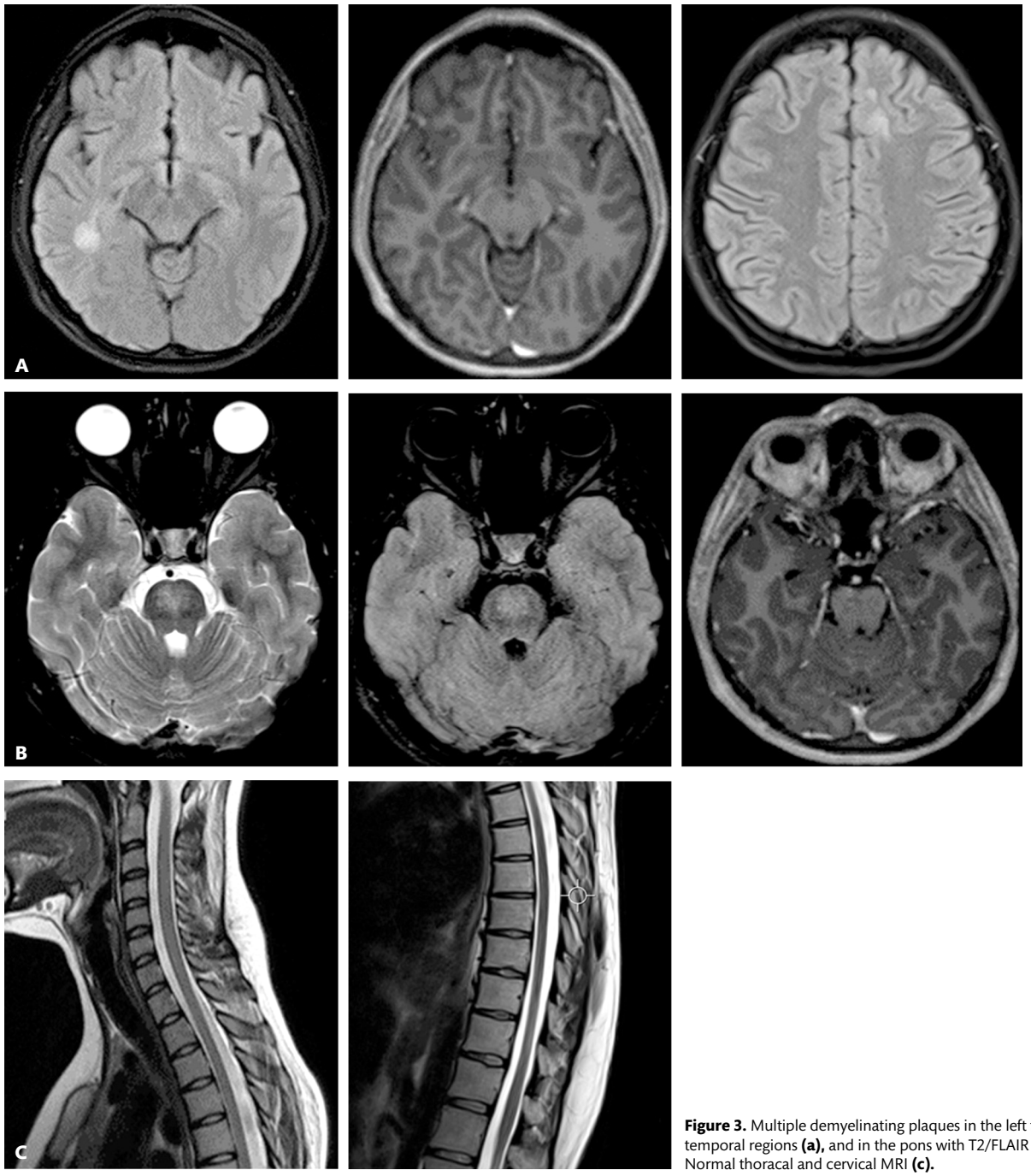


Figure 3. Multiple demyelinating plaques in the left frontal and right temporal regions **(a),** and in the pons with T2/FLAIR hyperintensity **(b).** Normal thoracal and cervical MRI **(c).**

Case 3

An 18-year-old woman was admitted with dysarthria in May 2020. She had a history of SARS-CoV-2 infection and presented with anosmia, back pain, and fatigue which occurred 93 days prior. Her nasopharyngeal swab test for SARS-CoV-2 and serum SARS-CoV-2 IgM and IgG antibodies were positive. A chest CT scan revealed no infiltrative changes in the lungs. She completely recovered from COVID-19. Only minimal dysarthria was observed in her neurological examination. Cranial MRI revealed multiple demyelinating plaques in the pons, left frontal, and right temporal regions with T2/FLAIR hyperintensity. A sign of diffusion restriction in DWI imaging and contrast enhancement on the T1 contrast series was detected in one of the pons lesions. Her cervical and thoracic spinal cord MRI results were normal (Figure 3). Her CSF glucose and protein levels were normal. Bacteria and leukocytes were not detected by Gram/Wright staining, and no microorganisms were detected in the CSF culture. Her CSF OCB was type 2 positive, and the IgG index was elevated (2.76). Serum ANA, anti-ds-DNA, anti-SSA/anti-SSB antibodies, pANCA/cANCA, serum anti-AQP4, and anti-MOG antibodies were negative. She was diagnosed with CDMS according to the 2017 McDonald criteria (17), and 1000 mg per day intravenous methylprednisolone was administered for ten consecutive days. After methylprednisolone treatment, she recovered completely. The patient started dimethyl fumarate as a maintenance therapy.

Case 4

A 39-year-old woman was admitted to the hospital for gradually increasing paraparesis that lasted two weeks in December 2020. She had a history of a cough, sore throat, and fever with nasopharyngeal swab SARS-CoV-2 PCR test positivity 5 days prior to the paraparesis. Her chest CT scan revealed no infiltrative changes in the lungs. Favipiravir treatment

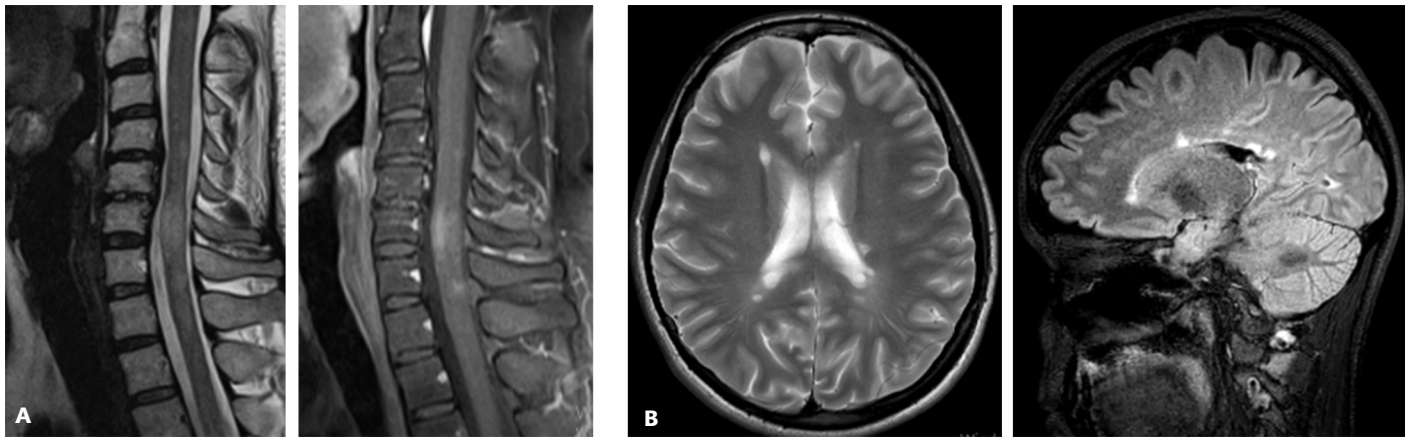


Figure 4. A short-segmented demyelinating lesion with heterogeneous contrast enhancement at C6-C7 **(a).** Multiple periventricular and juxtacortical demyelinating plaques with T2/FLAIR hyperintensity **(b).**

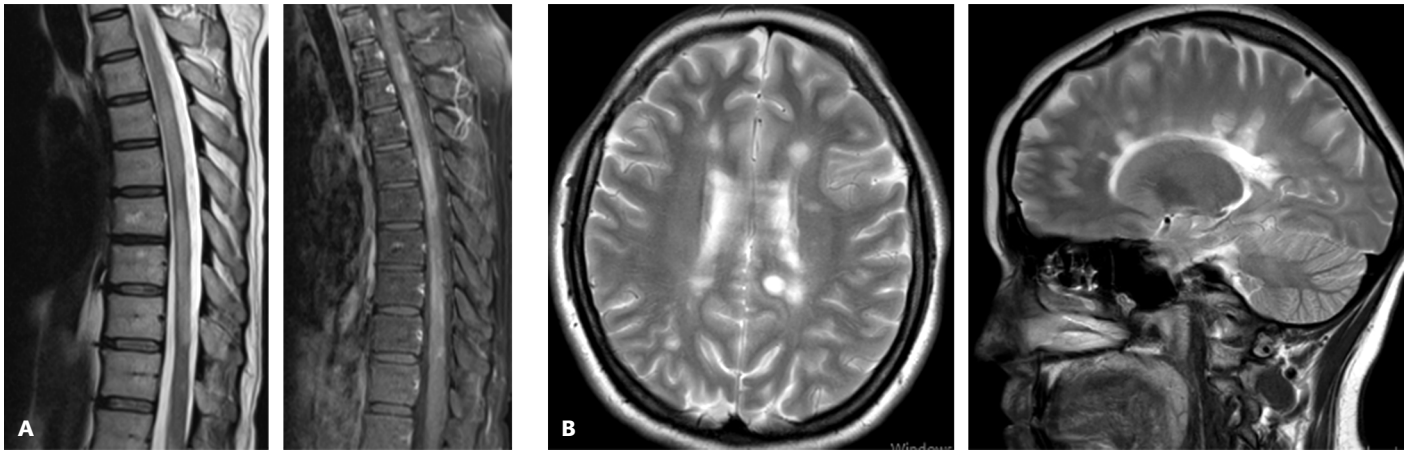


Figure 5. Multiple short-segmented demyelinating lesions at C6, T4 (with contrast enhancement), and T10 **(a).** Periventricular and juxtacortical demyelinating plaques with T2/FLAIR hyperintensity **(b).**

was administered to the patient. She completely recovered from COVID-19 within ten days. She had no history of illness. Her neurological examination revealed paraparesis (3/5 bilaterally) with deep tendon reflex hyperactivity in both lower extremities. A decrease in feeling pain and rough touch below the T1 spinal cord sensory level was observed. Cranial MRI revealed multiple periventricular and juxtacortical demyelinating plaques with T2/FLAIR hyperintensity. In cervical MRI, a short-segmented demyelinating lesion (one and a half vertebral segments in length) with heterogeneous contrast enhancement was observed at the C6-C7 spinal cord segments (Figure 4). Thoracal spinal cord MRI was normal. Her serum anti-AQP4 and anti-MOG antibodies were negative. Her CSF OCB was type 3 positive, and her IgG index was elevated (1.21). All routine blood examinations for vasculitis and infection were normal. She was diagnosed with CDMS according to the 2017 McDonald criteria (17), and 1000 mg/day intravenous methylprednisolone was administered for seven consecutive days. After methylprednisolone treatment, she recovered completely. Subcutaneous injections of 44 µg of interferon beta-1a were administered to the patient three times per week as an immunomodulatory therapy.

Case 5

A 36-year-old man was admitted to the hospital with paraparesis in November 2020. Before paraparesis, he complained of numbness in both of the lower extremities for one week. He had a history of SARS-CoV-2 infection 20 days prior to presentation and had positive nasopharyngeal swab SARS-CoV-2 PCR tests twice in the initial period of the pandemic. He was isolated at his home with mild symptoms, and favipiravir treatment was administered to the patient. His neurological examination revealed tetraparesis with 4/5 muscle strength in the upper extremities and 3/5 in the lower extremities. Deep tendon reflexes were globally hyperactive. Bilateral Babinski signs were positive. He exhibited a decreased sensation to light touch in the bilateral lower extremities. Cranial MRI revealed multiple periventricular plaques and one juxtacortical demyelinating plaque with T2/FLAIR hyperintensity and no contrast enhancement on T1 contrast series. Multiple short-segmented (one vertebral segment in length) demyelinating lesions at C6, T4, and T10 vertebral segments were observed in spinal MRI. Contrast enhancement was observed in the T4 vertebra segment lesion in the T1 contrast series (Figure 5). His serum ANA, anti-ds-DNA, anti-SSA/anti-SSB antibodies, pANCA/cANCA, antiphospholipid antibodies, serum anti-AQP4, and anti-MOG antibodies were negative. His bilateral VEP was normal. His CSF protein and glucose levels were normal. Bacteria and leukocytes were not detected by Gram/Wright staining, and no microorganisms were detected in the CSF culture. His CSF OCB was type 2 positive, and the IgG index was 0.97. He was diagnosed with CDMS according to the 2017 McDonald criteria (17), and 1000 mg/day intravenous methylprednisolone was administered for seven consecutive days. He recovered partially after methylprednisolone treatment. Upper extremity weakness and sensory complaints ceased almost completely. He had muscle weakness in both lower extremities (4/5). He was enrolled in the physical therapy and rehabilitation program. Dimethyl fumarate was administered as maintenance therapy.

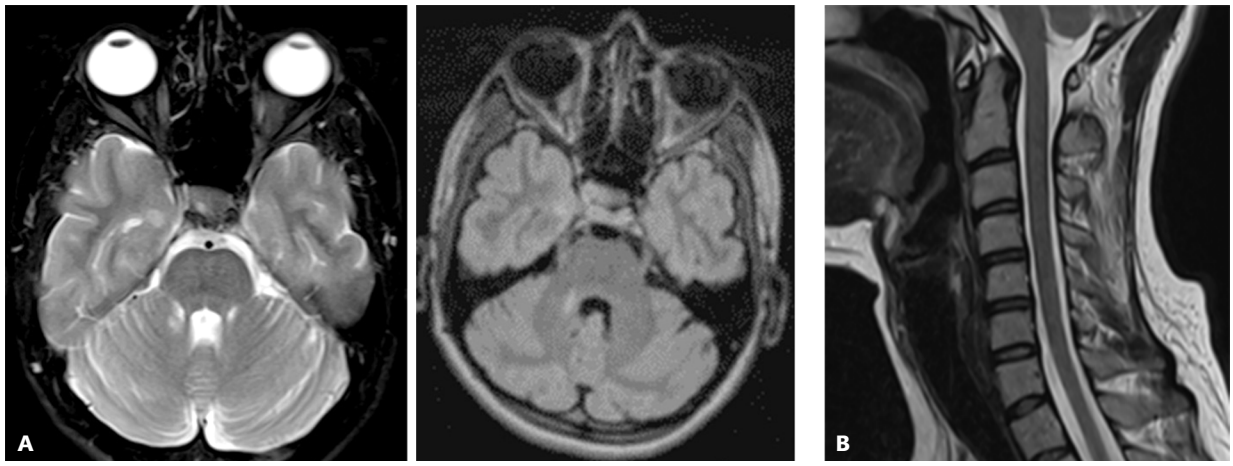


Figure 6. Demyelinating plaques in the right middle cerebellar peduncle and right temporal lobe with T2/FLAIR hyperintensity **(a).** Normal cervical MRI **(b).**

Table 1. The demographic, clinical, radiological characteristics and CSF findings of the patients

Patients	Age	Gender	Clinical Presentation	Diagnosis	SARS-Cov-2 infection interval	CSF			MRI		
						Protein	Oligoclonal band	IgG index	Cranial	Cervical	Thoracal
1	24	F	Paraparesis	LETM	5 days	51.7 mg/dl	Type 1 negative	0,52	Tumefactive demyelinating lesion and Multiple demyelinating plaques	Short-segmented demyelinating plaques at C2-C3 and C3-C4	Centrally located extensive lesion at T7-T12
2	20	F	Triparesis, Ataxia	MS	32 days	66 mg/dl	Type 2 positive	2.06	Multiple demyelinating plaques	Multi-segmented demyelinating plaques	Multi-segmented demyelinating plaques
3	18	F	Dysarthria	MS	93 days	Normal	Type 2 positive	2.76	Multiple demyelinating plaques	Normal	Normal
4	39	F	Paraparesis	MS	5 days	Normal	Type 3 positive	1,21	Multiple demyelinating plaques	Short-segmented demyelinating plaque at C6-7	Normal
5	36	M	Tetraparesis	MS	20 days	Normal	Type 2 positive	0,97	Multiple demyelinating plaques	Short-segmented demyelinating plaque at C6	Short-segmented demyelinating plaques at T4 and T10
6	29	F	Vertigo, Ataxia, Paresthesia in the right side extremities	CIS	4 days	Normal	Type 1 negative	0.49	Multiple demyelinating plaques	Normal	Normal

CIS: Clinically Isolated Syndrome; LETM: Longitudinally Extensive Transverse Myelitis; MS: Multiple Sclerosis; Normal value of IgG index is <0.6, normal value of CSF protein is <45 mg/dl; PTM: Partially Transverse Myelitis;

Case 6

A 29-year-old woman was admitted to the hospital with vertigo, ataxia, and paresthesia of the right upper and lower extremities in November 2020. She was a health care worker at a regional hospital. She had anosmia, ageusia, and fatigue history 4 days prior to presentation, with nasopharyngeal swab SARS-CoV-2 PCR test positivity. Her serum SARS-CoV-2 IgM and IgG antibodies were also positive. Her chest CT scan revealed no infiltrative changes in the lungs. Her neurological examination revealed an ataxic gait and decreased vibration sense in the lower extremities (vibration duration was 19 seconds in the upper extremities and 13 seconds in the lower extremities). Cranial MRI revealed multiple demyelinating plaques in the right middle cerebellar peduncle, right temporal lobe, and left periventricular areas with T2/FLAIR hyperintensity. One of the right middle cerebellar peduncle lesions was an active lesion showing contrast enhancement on T1 contrast series and diffusion restriction in DWI imaging (Figure 6). The cervical and thoracal spinal cord MRI were normal. Her serum ANA was low positive (<1/100), and anti-ds-DNA, anti-SSA/anti-SSB, pANCA/cANCA antibodies, serum anti-AQP4, and anti-MOG antibodies were negative. Cerebrospinal fluid protein, glucose, and cell counts were normal. Her CSF OCB was type 1 negative, and her IgG index was normal (0.49). She was diagnosed with CIS according to the 2017 McDonald criteria, and was administered 1000 mg/day intravenous methylprednisolone for seven consecutive days. After methylprednisolone treatment, she recovered completely. However, the patient did not want to use any disease-modifying therapy. Six months later, paresthesia started in the patient's left arm. A new lesion was observed on cervical spinal cord MRI. Oligoclonal band was type 2 positive in the repeated CSF. She was diagnosed with CDMS according to the 2017 McDonald criteria (17), and was administered 1000 mg/day intravenous methylprednisolone for ten days. Dimethyl fumarate was started as maintenance therapy. The demographic, clinical and radiological characteristics and CSF findings of all patients are described in Table 1.

DISCUSSION

An increasing number of case reports has described the neurological manifestations of COVID-19 in the literature. Ellul et al. reported neurological manifestations associated with COVID-19 in 901 patients; among these patients, 2 presented with encephalopathy, encephalitis, seizures, stroke, peripheral nervous system (PNS), muscle involvement, and ADEM, and myelitis occurred in one patient whose neurological symptoms started 5–9 days after COVID-19; all patients improved after treatment (1). In a review of 580 cases by Maury A et al., only 6 patients with acute transverse myelitis experienced neurological symptoms starting 2–10 days after the onset of COVID-19 with significant clinical improvement, and 13 cases of ADEM were observed in the demyelinating disease group (2). The cases we reported are characterized by LETM developing an open-ring contrast-enhancing tumefactive demyelinating lesion and patients were diagnosed with CDMS and CIS.

NMOSD is the most common cause of LETM and should be considered in the differential diagnosis of recurrent episodes of transverse myelitis involving the long segment, even in patients negative for the AQP4-IgG antibody. However, LETM can have various etiological spectra and differential diagnoses, such as multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), systemic lupus erythematosus (SLE), sarcoidosis, primary Sjögren syndrome, Behçet's disease, viral, bacterial, and parasitic infections (18). Longitudinally extensive transverse myelitis (LETM) following acute COVID-19 has been reported to be very uncommon (3,4,9). Our first patient had a longitudinally extensive thoracic lesion characterized with T1 hypointensity and T2 hyperintensity. However, she had a coexistent cerebral tumefactive demyelinating lesion and cervical short-segment posterolateral lesion, which led us to consider both NMOSD and MS. A differential diagnosis should be based on demographic, clinical, laboratory, and radiological features, as well as clinical follow-up (19). Because 10% of longitudinally extensive transverse myelitis cases could convert to MS during the follow-up period, MS should be considered in the differential diagnosis as well (20). Although our first patient presented with the clinical picture of LETM, the cranial and cervical demyelinating lesions that occurred after COVID-19 were typical for MS, and no serious clinical sequelae compatible with NMOSD occurred during follow-up. She showed some of the symptoms before SARS-CoV-2 infection. Nevertheless, her cerebral lesion was detected and her myelitis aggravated after SARS-CoV-2 infection. In this situation, we postulated that coronaviruses might cause immune responses that potentiate central nervous system demyelination.

MS is a chronic autoimmune disorder of the CNS mediated primarily by activated T cells, with a significant contribution from B cells. Peripherally, autoreactive T-cells drive immune attacks of the CNS (21). The trigger might be a virus that activates T cells or cross-reactivity between an endogenous protein (e.g., myelin basic protein) and a pathogenic exogenous protein (e.g., viral antigen) (22). Epstein-Barr virus infection may lead to the development of multiple sclerosis (23). The causal relationship with multiple sclerosis has very rarely been described for SARS-CoV-2. But intrathecal anti-Human Coronavirus (HCoV) antibody and HCoV RNA was detected in MS patient brains and CSFs (24,25). This finding supports that coronavirus triggers neuroinflammation in the central nervous system. One patient who presented with optic neuritis attributed to SARS-CoV-2 infection and diagnosed with MS has been reported. The nasopharyngeal exudate and CSF SARS-Cov-2 PCR tests were negative in this patient, but both IgM and IgG were positive, consistent with a past infection (11). Patients 3, 4, 5 and 6 were diagnosed with MS according to the McDonald 2017 criteria. All patients had a history of SARS-CoV-2 infection with symptoms (fever, sore throat, anosmia, ageusia, and fatigue) and nasopharyngeal swab SARS-CoV-2 PCR test positivity. Patient 3 had SARS-CoV-2 PCR positivity in CSF with negative nasopharyngeal swab PCR results. A potential explanation for this finding is the long interval between COVID-19 and the first presentation of symptoms, as emphasized in the case report by Domingues et al. (26). The patient had a history of fever before the first symptoms began. Patient 2 presented with a first myelitis attack after nasopharyngeal swab SARS-Cov-2 PCR test positivity with no symptoms. His SARS-Cov-2 IgM antibody test was also positive. Based on the data from our patients, SARS-CoV-2 may trigger or exacerbate CNS demyelinating disease. Moreover, tumefactive demyelinating lesions and MS can develop in the interval up to the first 3 months after COVID-19.

The effect of COVID-19 can be parainfectious or postinfectious. The interval between the onset of COVID-19 symptoms and the development of neurological symptoms ranges from 3 days to 3 weeks (1). Viral entry to the CNS could initiate the first stage of MS via innate and adaptive immune system modification (27). SARS-CoV-2 and cytokines that cross the BBB activates the glial cells and initiate inflammatory signaling cascade that could leads to MS development (28). In our cases, the interval between COVID-19 symptoms and the onset of neurological manifestations ranged from 4 to 32 days. In contrast, the interval was 93 days in only one patient, and this patient was diagnosed with CDMS according to the McDonald 2017 criteria with a newly developed clinical attack six months later and an objective radiological lesion. In this patient, COVID-19 infection triggered acute central nervous system demyelination at the beginning of the disease and active delayed demyelination developed within the first three months. In cases 2, 3, 4 and 5, new active lesions develop on the radiologically isolated syndrome (RIS) background, while new active lesions develop for the first time in cases 1 and 6. Cases 2, 3, 4, 5 can be explained by the development of an attack with systemic immune activation in radiologically isolated syndrome cases, and cases 1 and 6 by newly developing acute inflammation-related demyelination. Therefore, demyelination can be triggered by systemic immune activation after COVID-19 infection, as well as newly developing demyelinating diseases are expected (28). The final result can be determined by increasing number of cases, clinical, radiological and neuropathological studies.

In conclusion, we aim to highlight that SARS-CoV-2 infection may potentiate cerebral and spinal cord demyelination at different levels of disease. Additionally, when cerebral tumefactive demyelinating lesions and LETM lesions coexist, clinical follow-up is needed for a differential diagnosis. All these first demyelinating events suggested that SARS-CoV-2 infection might trigger CNS demyelination. Previously published cases and studies on coronavirus show that in addition to triggering central nervous system demyelination, may cause MS to occur (28). Further neuropathological investigations will provide more detailed information on this topic.

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