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Demyelinating Inflammatory Disorders of the Central Nervous System in the Era of COVID-19: Cases with Mild Infectious Symptoms

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Highlights

- **A wide variety of autoimmune demyelinating disorders of the CNS may occur in COVID-19.**
- **NMOSD; constitutes a rare part of the neurological findings of Covid-19 patients.**
- **Cases of asymptomatic onset parainfectious NMOSD in COVID-19 infection are rare.**

The main clinical manifestation of human coronaviruses is respiratory involvement, and the leading cause of death is acute respiratory failure. However, there have been reports of extra respiratory manifestations, such as neurological findings (1). Autoimmune demyelinating disorders of the peripheral and central nervous system (CNS) are also often encountered during the course of the coronavirus disease-2019 (COVID-19) or following COVID-19 vaccination (2). The underlying mechanisms of neurologic complications in patients with COVID-19 are diverse and multifactorial. Acute neurologic complications frequently arise from systemic response to the infection or immune dysfunction. SARS-CoV-2 may gain access into the CNS by crossing the blood-brain barrier or through olfactory transmucosal invasion and subsequently cause acute or delayed CNS demyelination or axonal damage (3-4). CNS problems emerge in a spectrum ranging from more frequent manifestations such as ageusia, anosmia and encephalopathy to neuropathy, stroke and autoimmune demyelinating disorders (5). Some COVID-19 patients, especially those suffering from a severe disease, are highly likely to have CNS manifestations during or after (i.e. post-COVID-19 neurological manifestations) the acute infection period (6). A wide range of autoimmune demyelinating disorders of the CNS including neuromyelitis optica spectrum disorder (NMOSD), multiple sclerosis, acute demyelinating encephalomyelitis, isolated optic neuritis, transverse myelitis and myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) may occur in COVID-19 patients (7). Occasionally, demyelinating disorders may emerge in patients with very mild respiratory or systemic COVID-19 symptoms or even before polymerase chain reaction (PCR) positivity ensues.

An exemplary case is a previously healthy 36-year-old man, who referred to the emergency room of our hospital on March 2020 with complaints of headache and dizziness for two days. He had no fever, hyposmia or hypogeusia. His neurological and systemic examinations and cranial MRI were normal**.** A nasopharyngeal swab test done for detection of the SARS-CoV-2 genome by real-time PCR during the pandemic era was found positive. COVID-19 vaccines were not available on March 2020.

On the fifth day of admission, he developed fever, malaise and cough. COVID-19 pneumonia was suspected due to the finding of the frosted glass appearance in spiral chest computed tomography (CT) imaging. On the same day, he also experienced sudden weakness and paresthesia of the lower limbs together with urinary and stool incontinence. Neurological examination showed mild paraparesis (4/5 on Medical Research Council scale), normal muscle strength in upper limbs, normal deep tendon and absent plantar reflexes. The position and light touch sensations were impaired in both lower limbs, he had a T10 sensory level and the abdominal cutaneous reflex was absent. The patient was alert, well-oriented, had a normal level of consciousness, obeyed simple verbal commands and nuchal rigidity, Kernig or Brudzinski signs could not be elicited. The spinal MRI showed a 10-12 mm-diameter T2 hyperintense lesion in the dorsocentral area of the cervical spinal cord extending three contiguous vertebral segments (C5-7) with slight expansion and another 5-6 mm-diameter T2 hyperintense lesion in the ventrocentral region of the dorsal spinal cord (T9-12). T1-weighted images with

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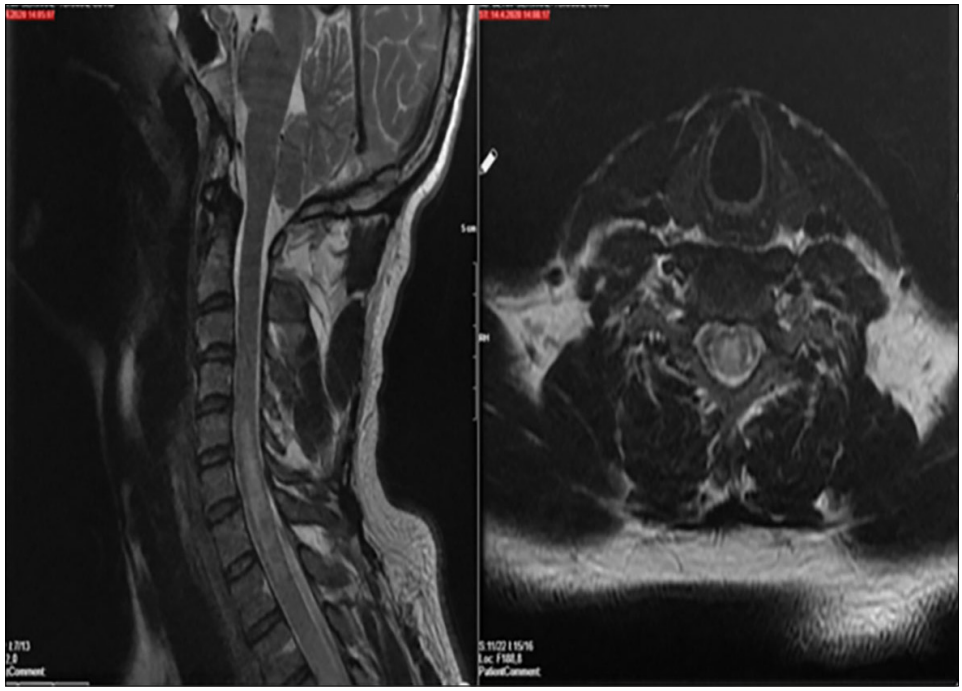


Figure 1. A T2-weighted sagittal spinal cord MRI section shows hyperintensity and slight edema at the level of C5-7 (left panel) and a T2-weighted axial spinal cord section shows hyperintensity at the T10 level (right panel).

contrast failed to show enhancement in the meninges, parenchyma and these two spinal cord lesions (Figure 1). The spinal tap showed cloudy and pale-yellow cerebrospinal fluid (CSF), 130 cells/µl (60% lymphocyte, 40% neutrophil), increased protein (57 mg/dl) and normal glucose (65 mg/dl) levels. No oligoclonal bands were found in the CSF and no microorganism was detected by Gram staining of CSF. A polymerase chain reaction (PCR) panel of CSF for SARS-CoV-2, herpes simplex 1 and 2, Haemophilus influenzae, Mycobacterium tuberculosis and Listeria monocytogenes, as well as CSF, blood and urine cultures were negative. Serological assays for anti-nuclear antibody, anti-phospholipid antibodies, well-characterized autoimmune encephalitis, aquaporin-4 (Aqp-4) and MOG antibodies were negative. Transverse myelitis was suspected leading to the commencement of pulse steroid therapy for 7 days.

On the eight day of admission, nausea, vomiting and chlorpromazine-resistant persistent hiccups started indicating the area postrema syndrome. The muscle strength was 4/5 in both upper limbs and 3/5 in both lower limbs. Cranial MRI revealed non-enhancing T2 lesions in the left cerebellar hemisphere and medulla (Figure 2). Due to ascending and progressive nature of neurological findings, neurophysiological examination was also conducted to eliminate autoimmune inflammatory neuropathies. Motor and sensory nerve conduction studies, F responses and needle electromyography findings were normal. A second attempt for Aqp-4 and MOG antibody detection failed to identify these antibodies in serum and CSF. The patient was diagnosed with seronegative NMOSD, on the basis of the presence of two core clinical characteristics of acute myelitis with longitudinally extensive transverse myelitis (LETM) and area postrema syndrome, dissemination in space (spinal cord, brainstem and cerebellum) and neuroimaging features associated with the core clinical findings (spinal cord and medulla lesions on MRI) (8). Intravenous immunoglobulin 0.4 gr/kg/day was given for 5 consecutive days in total.

The patient gave poor response to first-line immunosuppressant treatments, which ameliorated motor symptoms of the upper limb only, and he denied second-line treatments such as cyclophosphamide. Respiratory findings regressed in 2 weeks under anti-viral treatment. Oxygen saturation was always normal and intubation or intensive care was not required. In his follow-up examination on September 2022, the patient had normal motor strength in upper limbs, whereas both lower limbs were plegic (3/5). He had loss of sensation at the level of T10 and was mobilized with a wheelchair.



Figure 2. An axial T2-weighted MRI section shows two punctate lesions in the left cerebellar hemisphere and medulla (red arrows).

Apart from developing a rare COVID-19 related neurological manifestation, notable features of our patient were the onset of NMOSD during the asymptomatic period of COVID-19, highly elevated cell count in the CSF, absence of well-characterized NMOSD antibodies and resistance to first-line immunosuppressant treatments.

To the best of our knowledge, only a 3-year-old girl and another 35-year-old and 6-month post-partum woman have presented with LETM secondary to asymptomatic COVID-19 (9,10). Transverse myelitis is rare in itself, with a reported incidence ranging from one to eight cases

per million per year (11). There have only been a handful of reported transverse myelitis cases following COVID-19 infection, with outcomes ranging from fatal to a full recovery (12,13). Although the response to immunosuppression is often favorable in COVID-19 patients with autoimmune demyelinating disorders, some treatment resistant patients such as ours have also been reported (7, 14, 15).

Several recent studies have evaluated the possible mechanisms of COVID-19-associated demyelination, which are direct viral invasion, cytokine storm and autoimmune response (15). In this context, the highly elevated number of lymphocytes and neutrophils in the CSF of our patient may be indicative of enhanced inflammation in the intrathecal compartment and putatively an autoimmune reaction against the CNS. Viral infections are well known to induce an inflammatory response against the CNS, to activate myelin-specific T cells and by this way to accelerate the development of early or delayed virus-induced demyelination (16).

NMOSD constitutes a minor fraction of spinal cord disorders occurring in COVID-19 patients. In a recent review, only 2 of 31 COVID-19 patients with spinal cord involvement fulfilled the criteria for Aqp-4 antibody positive NMOSD as opposed to 23/31 patients showing acute transverse myelitis. Our patient differs from several previously reported NMOSD patients in that they exhibited Aqp-4 antibodies and severe COVID pneumonia (15). Whether herein presented seronegative NMOSD manifests via different virus-induced pathophysiological mechanisms need to be further investigated.

In a study by Espindola et al., CSF of COVID-19 patients with inflammatory neurological diseases was characterized by pleocytosis predominantly constituted by mononuclear cells. Also similar to our case, most of these patients lacked SARS-CoV-2 RNA in CSF and intrathecal IgG synthesis. Meningoencephalitis and meningitis may occur in COVID-19 patients and account for the highest cell counts ranging from 8 to 396 cells/mm^3 (17). Although we also considered these diagnostic options due to the high CSF cell count, we ruled them out due to absence of meningeal irritation signs, normal consciousness, cognition and lack of meningeal contrast enhancement.

In brief, we herein have described a rare case of para-infectious NMOSD initiating during the asymptomatic stage of the COVID-19 infection. At first hospital admission, the patient did not present any COVID-19 infection symptoms or frequently encountered neurological symptoms such as hyposmia and hypogeusia. Through the presentation of this patient, we would like to emphasize that, in para-infectious NMOSD, neurological signs may precede the onset of infectious symptoms, Aqp-4 and MOG antibodies may be absent and treatment response may be particularly unfavorable.

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