DOI: *http://dx.doi.org/10.18502/cjn.v21i4.11723*

Current Journal of Neurology

Clinical Note

Curr J Neurol 2022; 21(4): 251-5

Initial clinical presentation of multiple sclerosis with concurrent COVID-19 infection: Case report and literature review

Received: 27 May 2022
Accepted: 02 Aug. 2022

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Keywords
COVID-19; Multiple Sclerosis; Diagnosis

Coronavirus disease-2019 (COVID-19) was described as the most critical health problem in the last century after the World Health Organization (WHO) notified it as a pandemic in March 2020. In addition to the respiratory system, it involves other organs including the central nervous system (CNS). Many studies have investigated its neurological symptoms indicating various neurological manifestations. This virus may engage the CNS and peripheral nervous system (PNS) directly (via the olfactory bulb) or through para-infectious, post-infectious immune-related diseases as well as systemic effects.[1] Many demyelinating diseases associated with CNS and PNS have been reported to be concurrent with COVID-19 infection such as acute disseminated encephalomyelitis (ADEM).[2]

Multiple sclerosis (MS) is a chronic immune-mediated disease of the CNS. The pathophysiological hallmarks of this disease are inflammation, demyelination, axonal loss, and neurodegeneration. The cause of MS is not fully known. However, some viruses may be involved in its pathogenesis. In this regard, the association between COVID-19 and the incidence of MS could be suggested, which might open a new area to research meticulously. This report discusses the clinical, radiological, and laboratory features as well as outcomes of MS attacks concurrent with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Moreover, the literature was searched for similar case reports of MS presented after developing COVID-19.

The present study reported a 32-year-old woman presented with a 25-day history of paraparesis and paraparestesia. In September 2021, she developed headache, anosmia, cough, and myalgia concerning COVID-19.

How to cite this article: Ebadi Z, Naser Moghadasi A. Initial clinical presentation of multiple sclerosis with concurrent COVID-19 infection: Case report and literature review. Curr J Neurol 2022; 21(4): 251-5.

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The polymerase chain reaction (PCR) test in the nasopharynx was positive. The chest computed tomography (CT) scan of the lung was normal. The course of her disease was mild with no hospitalization, and there was no need to get antiviral drugs. Three days later, upon improving her headache and myalgia, she noted new right leg numbness, which slightly worsened. After one week, she developed left leg paresthesia; these symptoms aggravated over the next two weeks, causing the patient to refer to the emergency.

She disclaimed any previous events of neurological symptoms, such as optic neuritis (ON), paresis, and ataxia. Past medical and family history were negative for any disorder. She did not use any drugs.

On admission, her anosmia had improved. Physical examinations showed mild paraparesis and an increase in deep tendon reflexes. Her magnetic resonance imaging (MRI) demonstrated white matter lesions in juxtacortical and periventricular locations without enhancement. The cervical MRI was normal (Figure 1).

Laboratory tests were normal. A lumbar puncture was done. COVID-19 PCR in the cerebrospinal fluid (CSF) was negative. 12 unique oligoclonal bands (OCBs) were found in the CSF, not present in the serum. Cell count, protein, and glucose levels in CSF were normal. Serum aquaporin-4 (AQP4) was negative. Vasculitis tests were negative. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were in the normal range.

The patient was treated with 1 g intravenous methylprednisolone (IVMP) for five days. Her symptoms resolved relatively. Following a diagnosis of MS, she underwent treatment with glatiramer acetate. On follow-up, she was stable.

Various virus groups have been suggested as triggers for MS development, including the herpes virus family. In this group, alpha [varicella-zoster virus (VZV)], beta [cytomegalovirus (CMV) and human herpesvirus 6 (HHV-6)], and gamma [Epstein–Barr virus (EBV)] are more suspected.[3,4] These viruses can activate lymphocytes and induce the release of proinflammatory cytokines that lead to neurodegeneration.[5] EBV is one of the most well-known viruses in MS development.[6] Pediatric MS population has a high prevalence of EBV serology that confirms its role in MS pathogenesis.[7] Another example, HHV-6, is a neurotropic virus.[7] Antibody titers against this virus in patients with MS were higher than in healthy people.[8]

There have been reports of demyelinating involvement in the corona family, including SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV).[9]

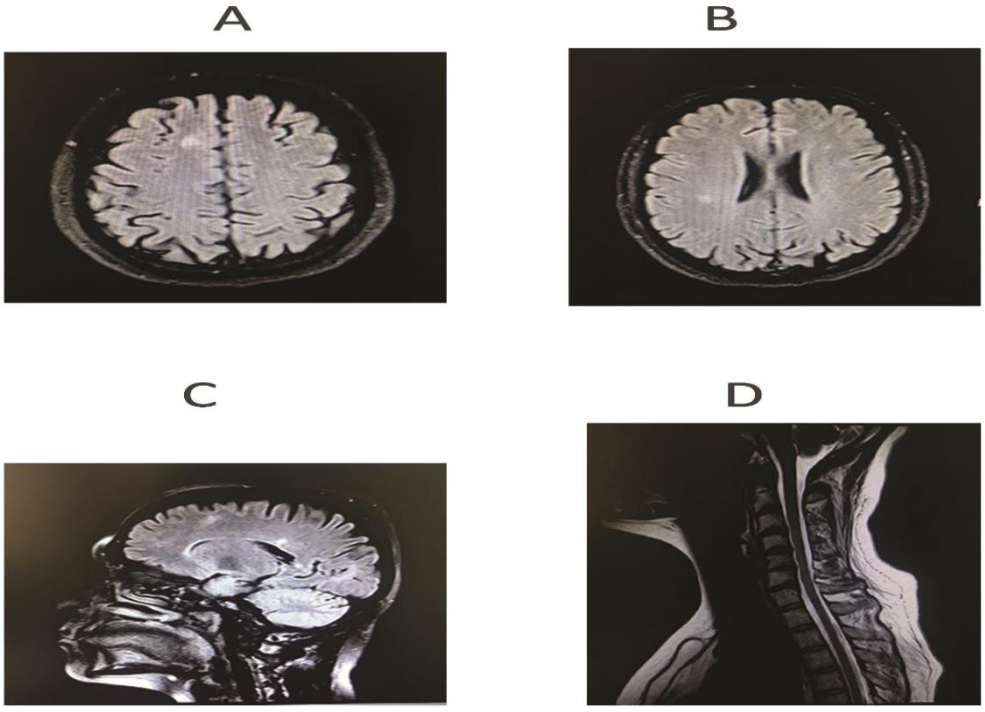

Figure 1. Brain (A-C) and cervical (D) magnetic resonance imaging (MRI) of the patient showing periventricular, juxtacortical white matter hyperintensities

COVID-19 is genetically similar to these viruses and may also have the same abilities. Several demyelinating case reports may confirm this idea.

It is understood from the literature that SARS-CoV-2 is neurotoxic and neurotropic, can induce autoimmunity, and can impress the CNS in various ways. For instance, this virus can cause inflammatory cascades and cytokines including interleukin (IL)-2, IL-6, IL-17, and tumor necrosis factor alpha (TNF-α) which disrupt the blood-brain barrier, change immunity, and interact with immune cells, microglia, and neurons. These proinflammatory cytokines have been shown in experimental autoimmune encephalomyelitis (EAE) to be effective in the pathogenesis of MS.[10] This status induces an immune response in the CNS, neuroinflammation, mitochondrial dysfunction, and amplified neurodegeneration, which are possible mechanisms of early or late demyelination and MS. Moreover, SARS-CoV-2 can spread through the olfactory nerve route and cause encephalitis, encephalopathy, and ADEM in patients with COVID-19.[11]

Based on the revised 2017 McDonald criteria, our patient met the dissemination in space and time needed to diagnose MS. Her first presentation of MS occurred at the same time when COVID-19 symptoms were manifested.

Interestingly, similar to our patient, there are five other reports of patients presenting with neurological manifestations associated with active COVID-19 infection (positive nasopharyngeal PCR and COVID-19 symptoms).[12-16] This temporal association between viral infection and the onset of demyelinating attacks is in favor of a para-infectious disorder.

Table 1 presents information on patients with suspected MS following the development of COVID-19 infection.

Palao et al. reported a patient infected by COVID-19 who developed ON 21 days later. Her MRI demonstrated demyelinating lesions in the optic nerve and the CNS. As the patient fulfilled the 2017 McDonald criteria, clinicians claimed that COVID-19 triggered MS in this patient.[17]

Zanin et al. reported a patient affected by severe COVID-19 who presented lung involvement and seizure. The patient's condition worsened, and she was intubated. Her brain MRI indicated a high load of hyperintense lesions in T2-weighted image (T2WI), without enhancement.[14]

Karsidag et al. mentioned three cases of MS following COVID-19 development whose MRI confirmed typical demyelinating lesions. Interestingly, unlike other cases and our patient, SARS-COVID-19 PCR in CSF was positive in one case. Follow-up MRI of the other two patients showed new T2 lesions, but in the first case, who was 18 years old, all lesions resolved.[12]

Another MS case concurrent with COVID-19 symptoms was described by Yavari et al., a 24-year-old woman admitted with blurred vision who complained of COVID-19 symptoms. The MRI of this patient was notable for typical MS plaques. They decided to treat the patient with a disease-modifying drug. To this end, subcutaneous interferon beta-1a was chosen.[13]

In two other case reports, after some weeks of developing COVID-19 infection, the patients complained of imbalance and ataxia with typical brain lesions for MS.[18,19]

Sarwar et al. presented a 47-year-old woman with blurry vision and numbness that had begun 21 days after developing COVID-19 infection. Her brain MRI revealed inflammatory lesions suggestive of MS.[15]

Naser Moghadasi described a 31-year-old woman who complained of blurred vision concurrent with COVID-19 symptoms and whose brain MRI was remarkable for MS.[16] Our patient had common COVID-19 symptoms and, at the same time, complained of neurological symptoms with typical MS lesions in her MRI.

The mean age of the patients in these case reports was 34.36 years. Out of the 11 patients, only two were men. The severity of COVID-19 was mild in all patients except for two cases.[14,15]

Six out of eleven patients had concurrent neurological symptoms with COVID-19**.** In other patients, the mean interval between the development of COVID-19 and the onset of neurological symptoms was 6.4 weeks. In all cases, the most common site of CNS involvement was the periventricular location. Seven out of eleven patients showed contrast enhancement. OCB was positive for six out of eight patients.

To our best knowledge, the case presented here is the sixth report in the literature that announces MS attack concurrent with COVID-19 infection. The main question is whether this virus triggers MS or exacerbates silent MS. Our information is still insufficient to confirm the causal relationship between COVID-19 and MS development. This case report suggests that the COVID-19 may induce an MS attack, even during the acute phase of the infection.

Table 1. Multiple sclerosis (MS) development in relation to **s**evere acute respiratory syndrome coronavirus 2 **(**SARS-CoV-2) infection

Case	**Palao et al.[17]**	**Karsidag et al.[12]**	**Karsidag et al.[12]**	**Karsidag et al.[12]**	**Sarwar et al.[15]**	**Yavari et al.[13]**	**Ismail et al.[18]**	**Moore et al.[19]**	**Zanin et al.[14]**	**Naser Moghadasi[16]**	**Current study**
Sex	Woman	Woman	Woman	Man	Woman	Woman	Man	Woman	Woman	Woman	Woman
Age (year)	29	18	42	32	47	29	36	28	54	31	32
Symptom	Ataxia	Jaw paresis	Paresthesia	Jaw paresthesia	ON	Diplopia	Ataxia	Ataxia	LOC	ON	Paresis
Nasopharynx COVID PCR	-	Negative	Negative	Positive	Ig M	Positive	-	Negative	Positive	Positive	Positive
First symptom after COVID-19 infection (week)	2	Concomitant	4	16	Concomitant	Concomitant	8	2	Concomitant	Concomitant	Concomitant
MRI lesion	MS		MS/ADEM	MS/ADEM	MS	MS	MS	MS	MS	MS	MS
IVMP	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Yes
DMT	-	-	-	-	-	Interferon beta-1a	Fingolimod	-	-	Glatiramer acetate	Glatiramer acetate
Recovery	Good	Excellent	Good	Good	-	Good	Good	-	Good	Good	Good
CSF COVID PCR	Negative	Negative	Negative	Positive	-	-	-	-	Negative	Negative	Negative
OCB	Positive	Negative	Negative	Positive	-	-	Positive	Positive	-	Positive	Positive
Enhancement	Positive	Positive	Positive	Positive	Positive	Positive	Negative	Positive	Positive	Positive	Positive

COVID-19: Coronavirus disease-2019; ON: Optic neuritis; LOC: Loss of consciousness; MRI: Magnetic resonance imaging; CSF: Cerebrospinal fluid; Ig M: Immunoglobulin M; PCR: Polymerase chain reaction; MS: Multiple sclerosis; ADEM: Acute disseminated encephalomyelitis; IVMP: Intravenous methylprednisolone; DMT: Disease-modifying treatment; OCB: Oligoclonal band

Following the occurrence of the COVID-19 pandemic, the incidence of inflammatory diseases has increased.

Our patient was an example of a case with an immune-mediated disease who had already developed the virus. It is essential to follow up on such cases and investigate new clinical and imaging changes.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

None.

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