Case Report

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# Bilateral optic neuritis and encephalopathy as the atypical presentations of multiple sclerosis following severe acute respiratory syndrome coronavirus 2 infection

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**Abstract:**

Numerous evidence suggests coronavirus disease 2019 (COVID-19) potentially triggers demyelinating diseases, inclusive of multiple sclerosis (MS), and acute disseminated encephalomyelitis (ADEM), and various mechanisms have been proposed. We report a 42-year-old male presented with bilateral optic neuritis and encephalopathy, 2 weeks following COVID-19 infection. He denied any history or family history of neurological and ocular diseases. Severe bilateral visual impairment (only light perception) and pain with eye movement were reported. Fundoscopy revealed bilateral optic disc swelling. Magnetic resonance imaging showed tortuous bilateral optic nerves with optic nerve and nerve sheath enhancement. Multiple hyperintense nodules in bilateral cerebral white matter were noted on fluid-attenuated inversion recovery T2-weighted imaging without diffusion restriction or gadolinium contrast enhancement. Hypointense nodules in cerebral white matter were also noted on T1-weighted imaging, which implied some old lesions. Dissemination in space and time and cerebrospinal fluid-specific oligoclonal bands confirmed the diagnosis of MS. Both serum aquaporin-4 and myelin oligodendrocyte glycoprotein antibodies were negative. He received pulse steroid therapy for 5 days, followed by slowly tapering oral prednisolone. His vision, ocular motion pain, and encephalopathy improved gradually. However, the visual outcome was still poor (bilateral 20/400), and optic atrophy was noticed during 1-year follow-up. To our knowledge, this is the first case of MS following severe acute respiratory syndrome coronavirus 2 infection presented with bilateral optic neuritis and encephalopathy. Since these manifestations are exceedingly rare in MS, we suspect acute immune reactions induced by COVID-19 could bring about the atypical ADEM-like presentations of MS.

**Keywords:**

Coronavirus disease 2019, encephalopathy, multiple sclerosis, optic neuritis

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## Introduction

Growing evidence suggests severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could potentially trigger demyelinating diseases, including multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), myelin oligodendrocyte glycoprotein (MOG) MOG-associated disease (MOGAD), and neuromyelitis optica spectrum disorder (NMOSD).[1] Few cases of MS associated with SARS-CoV-2 presented with optic neuritis have been reported, all of which were unilateral.[2-4] Bilateral optic neuritis linked to coronavirus disease 2019 (COVID-19) has also been documented in prior literature,[5,6] with a majority of cases diagnosed with demyelinating diseases such as MOGAD or



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ADEM[7] but not MS. Most of these individuals exhibited positive responses to intravenous corticosteroid treatment.[5,8] Herein, we reported a case of bilateral optic neuritis and encephalopathy after SARS-CoV-2 infection with poor visual recovery despite timely treatment. Further investigations confirmed the diagnosis of MS.

## Case Report

A 42-year-old male presented with bilateral blindness 2 weeks after SARS-CoV-2 infection. The patient's past medical history was unremarkable, and he had received the first dose of the Moderna COVID-19 vaccine (Spikevax™) about 1 month before this presentation without any adverse effects. He denied any family history of neurological or ocular diseases. Seventeen days before this presentation, he developed a fever, sore throat, and cough. Polymerase chain reaction (PCR) testing of nasopharyngeal swabs confirmed SARS-CoV-2 infection. The patient only received medication for symptom control. No specific antiviral agents were given. During home quarantine, excessive sleepiness and blunted responsiveness were noted. The day after completing quarantine, he was trapped on his way to work due to acute onset blindness. On arrival at our hospital, he was alert but disoriented to time. His response was slow but still could follow two-step orders, such as stretching out his right index finger to touch his right ear. The examination of visual acuity showed no light perception in the right eye and only light perception in the left eye. Pupil sizes were symmetrical (5 mm). No light reflexes were detected in both eyes. Extraocular movement was intact, but pain with eye movement was reported. Other physical and neurological examinations were unremarkable. Fundoscopy revealed bilateral optic disc swelling [Figure 1]. Brain magnetic resonance imaging (MRI) showed tortuous bilateral optic nerves with optic nerve and nerve sheath enhancement [Figure 2a]. Swollen optic nerves with hyperintense signals on fat-suppressed T2-weighted and short-tau inversion recovery images were noticed [Figure 2b and c]. Multiple hyperintense nodules in bilateral cerebral white matter were noted on fluid-attenuated inversion recovery, T2-weighted imaging without diffusion restriction, or gadolinium contrast enhancement [Figure 3a]. Hypointense nodules in cerebral white matter were also noted on T1-weighted imaging, which implied some old lesions [Figure 3b].

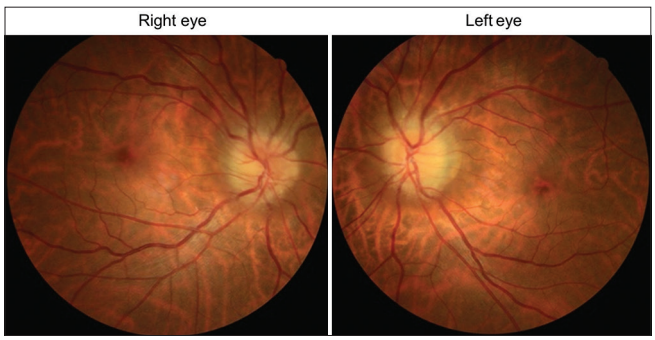


**Figure 1:** Color fundus photography showed bilateral optic disc edema

Workup of endocrine, autoimmune, and infection profiles, including COVID-19 PCR testing, was normal. The opening pressure of the lumbar puncture was 17 cm $H_2O$, which was within normal limits. Cerebrospinal fluid (CSF) study revealed elevated protein levels (53.5 mg/dL), high immunoglobulin G index (0.77), and lymphocytosis. CSF glucose level was normal, and the FilmArray Meningitis/Encephalitis PCR Panels were all negative. Visual-evoked potential was absent with flash goggle, and electroencephalography revealed mild-to-moderate regional cortical dysfunction in bilateral frontal-temporal areas. Both serum aquaporin-4 and MOG antibody were negative. Notably, the oligoclonal band (OCB) was detected in the CSF.

He was treated with 0.5 g intravenous methylprednisolone daily for 5 days, followed by slowly tapering oral prednisolone. A reduced steroid dosage was administered due to the patient's lower body mass index (16.47). The vision, ocular motion pain, and encephalopathy improved gradually. His visual acuity was bilateral 20/400 6 months later, and optic atrophy was noticed [Figure 4a]. His vision was stationary 1 year after the disease onset. Follow-up brain MRI 3 months and 6 months after this attack showed a decreased number and hyperintensity of bilateral cerebral white matter lesions on T2WI without new lesions noted. However, marked optic nerve atrophy was found on MRI [Figure 4b]. The timeline of our patient's clinical course is displayed in Figure 5.

## Discussion

Our patient meets 2017 revised McDonald criteria for MS[9] of one clinical attack, dissemination in two or more central nervous system (CNS) regions, dissemination in time by MRI findings, and the presence of OCB in CSF. To our knowledge, this is the first case of MS following SARS-CoV-2 infection presented with bilateral optic neuritis and encephalopathy. During the follow-up period of more than 1 year, no new symptomatic attacks or new MRI lesions were noted in this patient.

The pathogenesis of MS is the interplay between genetic and environmental factors. Viral infection is an important trigger, inclusive of Epstein–Barr Virus, human herpesvirus 6, measles virus, and coronavirus. There are several proposed mechanisms regarding SARS-CoV2 in the pathogenesis of MS. First is the neurotropism of

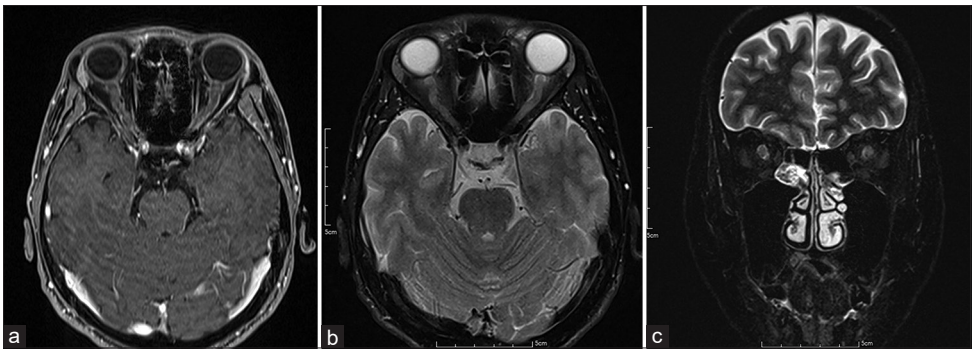


**Figure 2:** Magnetic resonance imaging (MRI) showed bilateral optic neuritis. (a) Brain MRI (fat-suppressed contrast-enhanced T1 weighted) revealed bilateral tortuous optic nerve with optic nerve and nerve sheath enhancement. (b) Brain MRI (fat-suppressed T2-weighted) showed swollen optic nerves with hyperintense signals. (c) Brain MRI (short-tau inversion recovery) demonstrated enlarged optic nerves with high-intensity signals

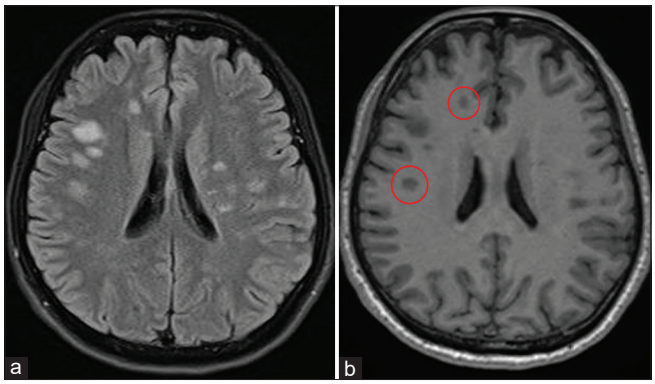


**Figure 3:** Magnetic resonance imaging (MRI) showed the evidences of multiple sclerosis. (a) Brain MRI (fluid-attenuated inversion recovery T2-weighted) showed multiple hyperintense nodules in bilateral cerebral white matter. (b) Brain MRI (T1 weighted) showed some hypointense nodules (red circles) in the cerebral white matter

coronavirus. Previous studies revealed the existence of coronavirus or its RNA in the CNS of MS patients. SARS-CoV-2 enters into host cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor. ACE2 is abundantly expressed in neurons, astrocytes, and oligodendrocytes in CNS. Second, SARS-CoV2 triggered cytokine storm. Dysregulations of pro-inflammatory cytokines are observed in COVID-19 patients, inclusive of interleukin 1 (IL-1), IL-6, and interferon γ. The IL-6- and T-helper cell 17-mediated inflammatory responses are crucial in the development of MS.[10] Ultimately, molecular mimicry between viral and human proteins may also play some roles. Sequences shared between myelin proteins and coronavirus have been identified.[11] Coronavirus-myelin cross-reactive T-cells were also discovered in MS patients. These evidence highlights the importance of viral infection, coronavirus in particular, in the pathogenesis of MS.

Our patient exhibited bilateral optic neuritis and encephalopathy, both of which are rare presentations of MS. Moreover, the visual outcome of optic neuritis in this patient was relatively poor despite receiving pulse steroid treatment immediately. These atypical presentations implicate the need for differential diagnosis with ADEM, MOGAD, and NMOSD. ADEM typically affects pediatric groups, requires encephalopathy for diagnosis, and remains a diagnosis of exclusion.[12] The results of MRI usually show diffuse large (>1–2 cm) and poorly demarcated lesions involving cerebral white matter. OCB is uncommon but can be present. Cases of COVID-19-associated ADEM had been reported with the predominance of adults, and the preceding systemic infection was often severe.[13] Compared to MS, NMOSD occurs even more frequently in females, tends to induce bilateral optic neuritis, and the visual prognosis is relatively poor. On MRI, optic neuritis in NMOSD usually involves the posterior optic nerve. Chiasm and optical tract could also be affected. In patients with MOGAD, the gender ratio is more balanced. The patients also frequently have bilateral optic neuritis, with a higher percentage of disc edema. In cases of MOGAD-related optic neuritis, MRI scans typically reveal involvement in the anterior segment of the optic nerve, often accompanied by perineural enhancement. MOGAD and NMOSD are both more inclined than MS to exhibit longitudinal lesions that extend over 50% of the length of the optic nerve.[14,15] Our patient fulfills the 2017 revised McDonald criteria and presented with T1 hypointense lesions (black holes), which is still pertinent to making the diagnosis of MS. We suspect the immune reaction induced by COVID-19 infection could bring about the ADEM-like presentations in this patient.

The influence of vaccination exposure on this patient should also be contemplated. Numerous cases of optic neuritis occurring after COVID-19 vaccination have been reported. A proportion of patients with postvaccination optic neuritis were MOG seropositive.[16] In addition, multiple cases of MS diagnosed after COVID-19 mRNA vaccine were also documented.[17] The reported cases of optic neuritis and MS mostly happened within 2 weeks after vaccination, but there were also instances occurring several months later.[17-19] From a chronological perspective, the association with

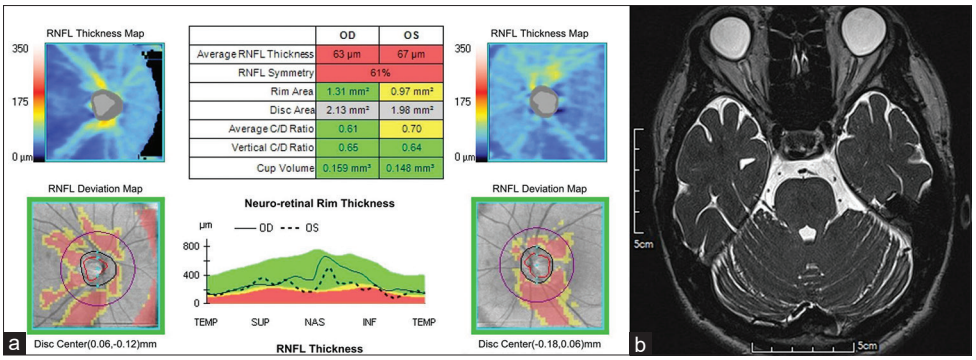


**Figure 4:** Optical coherence tomography (OCT) and magnetic resonance imaging (MRI) showed bilateral optic nerve atrophy after the episode of optic neuritis. (a) Spectral-domain OCT 6 months later showed reduced retinal nerve fiber layer thickness and thin neuroretinal rim in the both eyes, which indicated bilateral optic nerve atrophy. (b) Brain MRI (T2-weighted, sampling perfection with application optimized contrast using different flip angle evolution) revealed atrophic change of both optic nerves 3 months later

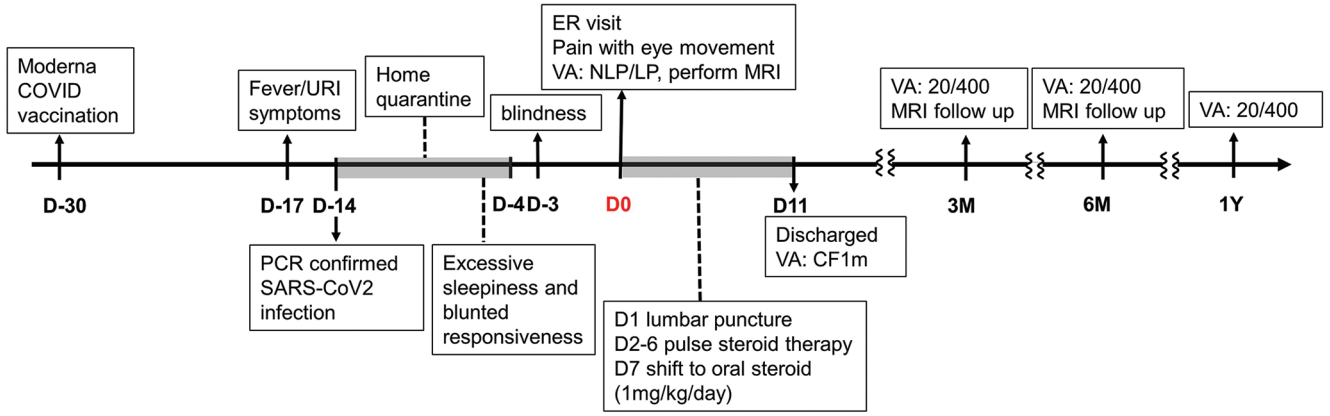


**Figure 5:** Timeline of the patient's clinical course. (D: Day, M: Month, Y: Year, COVID: Coronavirus disease, URI: Upper respiratory tract infection, PCR polymerase chain reaction, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, ER: Emergency room/department, VA: Visual acuity, LP/NLP: Light perception/no light perception, MRI: Magnetic resonance imaging, CF 1 m: Counting finger at 1 m)

COVID-19 infection may be more significant than vaccination in our case. Nevertheless, the influence of vaccination cannot be completely excluded. A case with a tentative diagnosis of MS after COVID-19 mRNA vaccination presented with bilateral optic neuritis, hypophysitis (central diabetes insipidus), and symptoms of spinal cord involvement (gait disturbance, hyperesthesia, hemiplegia, and urinary retention) was reported, indicating possible extensive CNS involvement in COVID-19 vaccine-associated MS.[20]

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

## Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.


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Nil.


## Conflicts of interest

Dr. Chao-Wen Lin, an editorial board member at *Taiwan Journal of Ophthalmology*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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