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Aquaporin-4 Protein Antibody Seropositivity after Acute SARS-CoV-2 Infection

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Abstract

Background: Development of autoimmune neurological disorders after Coronavirus Disease 2019 (COVID-19) has been reported. Though many cases of multiple sclerosis developing after COVID-19 are present in current literature, Neuromyelitis Optica Spectrum Disorder (NMOSD) is much rarer sequela of the disease.

Methods: Two cases that meet the international consensus diagnostic criteria for NMOSD were encountered at a regional hospital in West Texas in the same month. Both were preceded by acute SARS-CoV-2 infection and developed newly diagnosed NMOSD with Aquaporin-4 Protein Antibody seropositivity.

Results: Case 1 was a 28-year-old Hispanic female who presented with opsoclonus and ophthalmoplegia; Case 2 was a 20-year-old African American female who presented with transverse myelitis. Both patients had no neurological co morbidities or symptoms prior to SARS-CoV-2 infection. Neither of them was vaccinated for COVID-19, and both were of non-Caucasian ethnicity. They presented with a typical features including younger onset, ocular presentation of opsoclonus, negative neuroimaging, no response to steroids, and relapse after a short interval.

Conclusion: New developments of NMOSD in previously healthy individuals can be a neurological sequela of COVID-19, especially among unvaccinated individuals. The correlation and pathophysiology of NMOSD after COVID-19 are not fully understood, but molecular mimicry of the virus and cytokine storm are postulated mechanisms. Additional observational studies are needed to further explore the correlation between acute COVID-19 infection and NMOSD.

Introduction

Neuromyelitis Optica Spectrum Disorder (NMOSD) is a rare autoimmune disorder of the central nervous system (CNS) characterized by transverse myelitis and optic neuritis. The discovery of Aquaporin-4 protein antibody (AQP-4 Ab) in 2004 has greatly advanced the diagnosis of NMOSD, and its seropositivity was found to be associated with an increased risk of recurrent attacks [1].

While neurological deficits are a common manifestation following Corona virus Disease 2019(COVID-19) [2], The development of autoimmune disease is less frequently depicted. There have been several cases reporting the development of relapsing-remitting multiple sclerosis after COVID-19 infection [3], but there is limited literature pertaining to the prevalence of NMOSD after COVID-19, and some of these cases are with seronegative AQP-4 Ab [4,5]. Here, we describe two AQP-4Ab seropositive NMOSD cases that occurred as a sequela to SARS-CoV-2 infections as well as their clinical features.

Methods/Results

Both patients met international consensus diagnostic criteria for NMOSD and had no neurological symptoms priorto being infected with SARS-CoV-2 [6].

Case 1

A 28-year-old Hispanic female with a history of systemic lupus erythematosus presented with progressive right leg paresthesia and paresis 3 weeks after a second time COVID-19 infection without prior vaccination. Paresthesia and weakness of the left leg, blurry vision and dyschromatopsia of the left eye, and bladder incontinence ensued shortly after. Physical exam revealed weakness involving four extremities, with right worse than left, diminished right patellar reflex, and a sensory level of T4 more pronounced on the right side. Fundoscopy confirmed left eye papillitis. Magnetic Resonance Imaging (MRI) was remarkable for numerous patchy enhancing lesions throughout thecervical and thoracic spinal cord (Figure 1),

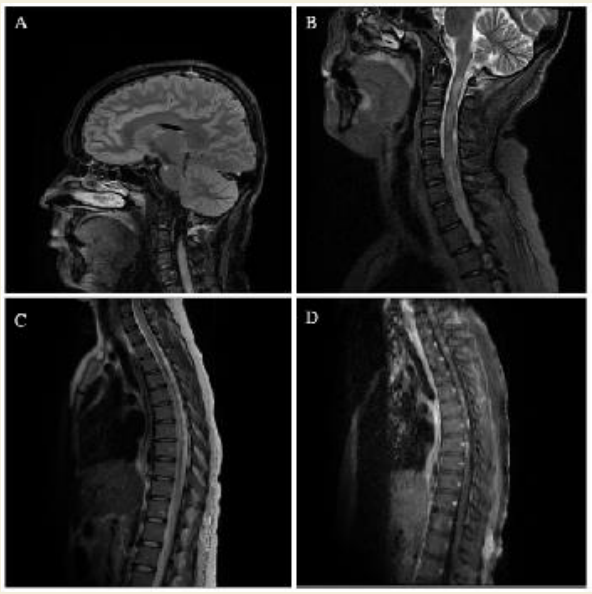

Figure 1: MRI of Patient 1 in sagittal view. (A) T2 hyper intensity in the right pons. (B) Numerous T2 hyper intensities are seen throughout the cervical and (C) Thoracic cord, (D) Some are enhancing with gadolinium.

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a sub-centimeter lesion at the right pons, and the left optic nerve with high FLAIR intensity. No pleocytosis and protein elevation was present in the cerebrospinal fluid (CSF). She received a seven day course of high dosage Solumedrol (methylprednisolone) and later received a five day course of intravenous immunoglobin (IVIG) due to a lack of improvement in symptoms from the steroids. The patient's motor strength was significantly improved after receiving IVIG. AQP-4 Ab was found to be positive in serum. Following treatment, the patient experienced her first relapse after one month and second relapse after three months.

Case 2

A 20-year-old African American female with no history of autoimmune disease or other co morbidities presented with diplopia as well as blurry vision and ptosis of the left eye. Her symptoms rapidly progressed, and right eye ptosis and weakness involving all four extremities developed within three days after admission to the hospital. The patient reported no prodromal infection besides a mild SARS-CoV-2 infection three months prior, which was associated with new-onset left retro orbital headache. Her headache persisted and became worse during her emergency room visit, and it was described as feeling like her "left eye was going to explode." Physical exam showed blurry vision of the left eye, opsoclonus with oscillopsia, bilateral ptosis, bilateral abducens nerve palsy with left globe being worse than right, left facial paresis, and generalized weakness with preserved reflexes. An extensive workup was performed. Full neuro-axis MRI with and without contrast, Magnetic Resonance Angiography (MRA) and Magnetic Resonance Venography (MRV) of the brain, full body CT, CSF studies, myasthenia gravis auto-antibodies, autoimmune and paraneoplastic antibodies, ganglioside auto-antibodies, common tumor markers, and muscle enzymes were all negative. The patient was treated with high doses of Solumedrol but was later switched to IVIG treatment due to a lack of symptom improvement. IVIG was discontinued due to dyspnea during infusion. Plasmapheresis was given and her symptoms stabilized. Serum AQP-4 Ab returned positive. One month later, she experienced an attack of complete left eye achromatopsia and describedseeing everything as yellow. She was evaluated by a neuro-ophthalmologist who agreed with the diagnosis of NMOSD and considered this could be a lesser common variant: acute brainstem syndrome. Treatment with high-dose steroids again failed to provide any improvement. A repeat full neuro-axis MRI was unremarkable. Nerve conduction studies and needle electromyography showed no signs of neuropathy and myopathy.

Discussion

The two patients described had similarities in case presentation: they both had minor COVID-19 symptoms that did not require hospitalization or supplemental oxygen and were healthy individuals who subsequently developed disabling neurological presentations after recovering from COVID-19. Additionally, they were both young females of non-Caucasian ethnicity (Hispanic and African American) and unvaccinated status. Both patients had unremarkable CSF results and a poor response to steroids.

NMOSD is known to cause recurrent attacks; however, the interval between attacks in our patients was much shorter compared to general NMOSD patients (8-12 months) [7]. Atypical features were also noted, including opsoclonus and complete unremarkable MRI in the second patient. Brainstem involvement is now more commonly discovered due to the broadened criteria of NMOSD. Brain MRI can be normal at initial presentation, and the lesions in brainstem are usually less extensive compared to spinal cord. Cases with small dot-like lesions at brainstem have been reported [8]. The atypical features of our patients and short interval to recurrent attacks suggest a low threshold for post-COVID-19AQP-4 Ab testing and NMOSD evaluation, so timely management can be pursued.

The correlation of NMOSD after acute COVID-19 infection is not fully understood. Demyelinating changes may occur due to a hyper inflammatory state with release of cytokines caused by infection, leading to glial activation, or it may occur as part of a delayed immune response [9]. Molecular mimicry of SARS-CoV2 antigens and neurological self-antigens is another potential mechanism. It was reported that both natural SARS-CoV-2 infection and SARS-CoV-2 vaccination can induce the formation of AQP-4 Ab and lead to newly diagnosed NMOSD, or it can also trigger a relapse in patients who already had an established diagnosis [5,10-13]. Of note, the post-immunization NMOSD cases are not limited to a certain type or certain company-made vaccine [10]. These literatures suggest that the shared antiviral immune response between natural infection and vaccinations may play a role in the NMOSD pathogenesis.

Conclusion

Our two cases indicate NMOSD after acute COVID-19 can have atypical presentations. AQP-4 Ab test is vital for the accurate diagnosis and timely management of the NMOSD. The correlation of NMOSD after acute COVID-19 is not fully understood. Molecular mimicry of the virus and cytokine storm are postulated mechanisms for NMOSD pathogenesis. Shared antiviral immune response between natural infection and COVID-19 vaccination may also play a role. Additional observational studies are needed to further explore the correlation between acute COVID-19 infection and NMOSD.

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