Neuromyelitis optic spectrum disorder following COVID-19 (ChAdOx1-S) vaccine

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Abstract:
Neuromyelitis optic spectrum disorder is an autoimmune demyelinating astrocytopathy of the central nervous system. It has emerged as a distinct clinical entity following the discovery of pathogenic antibody named AQP4-IgG against aquaporin-4 water channels in astrocytes. The clinical spectrum includes optic neuritis, acute myelitis, acute brainstem syndrome, area postrema syndrome, acute diencephalic syndrome and symptomatic cerebral syndrome.

This case describes a young male patient who presented with subacute onset painful visual impairment of left eye along with bilateral lower limb weakness and numbness in the background of recent vaccination for COVID-19 infection. Examination revealed bilateral papillitis and bilateral flaccid paraparesis with a sensory level at T4 level. Investigations revealed a longitudinally extensive myelitis spanning the entire length of the spinal cord, bilateral optic neuritis, positive serum AQP4-IgG antibodies with negative infective screening and autoimmune profile. Central nervous system demyelination has been observed with all types of COVID-19 vaccines.

Key words: Neuromyelitis Optica spectrum disorder, vector COVID-19 vaccine, post-vaccination demyelinating disorders

Introduction:
Neuromyelitis Optica spectrum disorder (NMOSD) is an autoimmune demyelinating disorder of the central nervous system which was initially thought to be similar and related to multiple sclerosis. The first case of NMOSD was reported in 1894 by Eugene Devic and then was known as Devic's Disease. But later on, NMOSD evolved as a separate distinct clinical entity with the discovery of disease-specific auto antibody for aquaporin-4 water channels (AQP4-IgG) in the astrocytes of central nervous system.

Core clinical presentations of NMOSD include optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, acute diencephalic syndrome and symptomatic cerebral syndrome.

NMOSD is commonly seen at the age of 35-45 years with a predilection to Asian, African and Hispanic ethnicities. The global prevalence is reported to be 0.5-10 per 100,000. There is an interplay between genetic susceptibility and environmental triggers in the pathogenesis of NMOSD. Different types of viral infections and vaccinations have been linked as triggering factors for central nervous system demyelination syndromes. The most commonly reported vaccines in this regard were influenza, human papilloma virus (HPV), hepatitis A or B, rabies, measles, and rubella.

Corona virus disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as a global pandemic in 2020. In turn, this led to discovery of several novel types of vaccines against SARS-CoV-2 infection. However, there were reported cases with adverse neurological outcomes including central nervous system demyelination syndromes that appeared in temporal relationship with the COVID-19 vaccination.

This case describes a young male patient presenting with longitudinally extensive transverse myelitis and bilateral optic neuritis following vaccination with a viral vector vaccine for COVID-19 infection.

Case report:
A 23-years-old previously healthy man presented with bilateral lower limb numbness and weakness for one week duration and visual impairment of left eye for 3 days duration. He claimed a gradual onset symmetrical bilateral weakness and numbness of lower limbs with no upper limb involvement. He had experienced difficulty in walking. Numbness was present up to the level of nipples. He also had urinary retention. There was no preceding fever or history of spinal trauma. This was followed by visual impairment of left eye with blurring of vision and pain on eye movements. There was no diplopia, dysphagia or dysarthria. There was no associated headache, seizures or altered behavior. He denied recent history of symptomatic COVID-19
infection, photosensitive skin rashes, oral ulcers, alopecia thromboembolic episodes, sicca symptoms, loss of appetite or weight, past or contact history of tuberculosis.

He had received the first dose of viral vector vaccine ChAdOx1-S (AstraZeneca) for covid-19 10 days prior to the appearance of his symptoms. He denied unsafe sexual behaviors or substance abuse.

He was conscious and rational with a GCS of 15. General examination was unremarkable. His visual acuity was 6/12 in the right eye and 6/60 in left with relative afferent pupillary defect. Visual field examination by confrontation was normal. Fundoscopic examination showed bilateral blurred disc margins with preserved retinal venous pulsations. Rest of the cranial nerve examination and cerebellar functions were normal. Limb examination revealed bilateral symmetrical flaccid paresis of lower limbs with a muscle power of 4/5 both proximally and distally. He had diminished deep tendon reflexes, bilateral extensor plantar response and a sensory level at T4 level. Sacral sensation, joint position sensation and vibratory sensation were impaired. There was a palpable bladder. Upper limb examination was normal. Cardiovascular, respiratory, and abdominal system examination were unremarkable.

His full blood count, serum electrolytes, serum calcium level, renal and liver function tests were unremarkable. Coagulation profile was within the normal range. C reactive protein was < 6mg/dl and erythrocyte sedimentation rate was 30mm/1st hour. Serology for viral screening with Ebstein Barr, cytomegalovirus, human immune deficiency virus and polymerase chain reaction (PCR) for human herpes simplex virus and Covid 19 RT-PCR were negative. Serology for syphilis and mycoplasma were negative. Serum covid 19 IgG antibodies were positive with a titer more than 10U/ml (negative if < 1 U/ml).

Cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis with 12 mononuclear cells/mm³. There was mildly elevated CSF protein level of 0.6 mg/dl with normal sugar levels (62mg/dl). CSF pyogenic culture showed no growth and TB gene Xpert was negative. Oligoclonal bands were not detected in cerebrospinal fluid. CSF for covid-19 antibodies were positive with a titer 4.2 U/ml. Auto antibody profile was positive for serum AQP4-IgG antibodies but negative for anti-nuclear antibodies (ANA) and anti MOG antibodies.
Case reports

With his clinical presentation and investigations, vaccine related CNS demyelination following COVID-19 vaccine resulting in NMSOD was considered as the probable diagnosis. He was managed with intravenous methylprednisolone 1g daily pulse therapy for 5 days followed by oral prednisolone 1mg/kg/day. Later Azathioprine 50mg bd was added as a steroid sparing agent while slowly tapering off prednisolone. He showed a remarkable response to steroid pulse therapy where blurring of vision and pain in his left eye resolved and he regained a left side visual acuity of 6/9. Limb weakness improved by the end of one week of therapy where he regained normal power in bilateral lower limbs.

Discussion:

NMO is a demyelinating astrocytopathy involving the central nervous system that shares similar presentations with other demyelinating syndromes like multiple sclerosis, acute demyelinating encephalomyelitis (ADEM) and MOG antibody associated disorders. NMO evolved as a separate distinct clinical entity with the discovery of disease specific auto antibody for aquaporin-4 water channels (AQP4-IgG) in the astrocytes of central nervous system. These aquaporin-4 water channels are present on astrocytic foot processes which are abundantly expressed in the optic nerves, brainstem, and spinal cord. The resultant autoimmune damage and demyelination of above areas of central nervous system give rise to a variety of clinical presentations in NMO comprising optic neuritis, acute longitudinally extensive transverse myelitis, area postrema syndrome, acute brainstem syndrome, acute diencephalic clinical syndrome and symptomatic cerebral syndrome. AQP4-IgG is positive in 80% of patients with NMO and the rest (AQP4-IgG negative NMO) often become positive for myelin oligodendrocyte glycoprotein (MOG) antibodies. They are categorized as MOG antibody associated disorders (MOGAD).

NMO related optic neuritis presents with subacute onset visual loss accompanied by pain and discomfort with eye movements. Simultaneous involvement of bilateral optic nerves, altitudinal field defects, scotomas, more severe form of optic neuritis that poorly responds to treatment should raise the suspicion for an NMO than multiple sclerosis. MRI features of extensive and more posterior involvement of optic nerves and the involvement of the optic chiasm are highly suggestive of an NMO. NMO is associated with a longitudinally extensive acute myelitis that spans more than three vertebral segments on MRI. Acute cord swelling usually results in a complete cord syndrome in contrast to MS where short-segment myelitis with a more dorsolateral cord involvement is seen. Sometimes cord involvement can be quite extensive, involving the whole length of the spinal cord. Extension of high cervical lesions up to the level of brainstem has been reported and highly suggestive of NMO.

This patient presented with simultaneous bilateral optic neuritis which was severe on the left eye. There was a LETM involving the entire spinal cord from cervical to lumbosacral segments. Both of these findings made MS unlikely to be the diagnosis for his presentation. In addition, he had no oligoclonal bands in CSF and positive serum aquaporin-4 antibody confirmed the diagnosis of NMO.

Myelin oligodendrocyte glycoprotein antibody associated disease (MOG AD) was unlikely in this patient as this disorder has more predilection to involve optic nerves than spinal cord. In MOGAD spinal cord involvement mainly occurs in the sacral segments different to what was observed in this patient.

In the background of a recent vaccination for COVID-19, ADEM was also considered a differential diagnosis. However, ADEM is unlikely in the absence of encephalopathy. Also, presence of initial spinal lesions without supratentorial lesions is rare in ADEM.
The International Panel for Neuromyelitis Optica Diagnosis (IPND) (14) and this patient had fulfilled criteria that is required for the diagnosis of NMOSD. In addition, possible infective, connective tissue related etiologies were excluded.

There was a temporal relationship between covid-19 vaccination and the current presentation of this patient. He had received the first dose of ChAdOx1-S Oxford-AstraZeneca, a viral vector vaccine 10 days prior to the onset of symptoms. He had negative RT-PCR for SARS-CoV-2 virus and had mounted an antibody response for the vaccine with a serum anti covid antibody titer > 10U/ml (negative if < 1 U/ml). Also, his CSF covid-19 antibodies were positive. However, the reference range was not validated to be used in the CSF and the significance of that result was not known.

CNS demyelination has been reported following all types of covid-19 vaccines in the literature including Bell's palsy, Guillain–Barre syndrome, transverse myelitis and the first manifestation of MS or MS relapse (15). Most were reported following mRNA-based vaccines followed by viral vector vaccines and inactivated vaccines (15). Most presentation were within the first 1–2 weeks following vaccination.

The exact pathogenesis of demyelination following COVID-19 vaccines is not known. However, it is postulated that an interplay between vaccine-related factors and the susceptibility of the individual could play a role. Molecular mimicry with cross-reactivity between viral antigens or adjuvants used in the covid 19 vaccines and the aquaporin-4 channels in astrocytes is one such theory behind the pathogenesis of vaccine induced demyelination (16).

Conclusion:
NMOSD is a rare CNS demyelinating disorder that has a significant morbidity and at times mortality. Bilateral optic neuritis and longitudinally extensive transverse myelitis are salient clinical features of NMOSD. Viral infections and vaccination could act as triggers for the development of this disorder. Prompt recognition, accurate diagnosis followed by early treatment with immunosuppressant agents can result in better outcomes.

References: