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Case Study

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UNMASKING THE MASQUERADER – NEUROMYELITIS OPTICA : A CASE REPORT

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ABSTRACT

Background: Neuromyelitis optica (NMO) is an inflammatory and auto-immune demyelinating disease which dwindles the quality of life. The disease course is waxing and waning with spectrum of manifestations. Diagnosing the case based on presentation, clinical history and appropriate investigations at the earliest is of extreme importance as prompt intervention and maintenance of remission is pivotal in determining the quality of life. Hence we intended to present one such case of typical NMO. **Case Report:** We illustrate the case of a 35-year-old female patient enduring frequent bouts of vision abnormalities and progressive muscle weakness over a decade. The patient was diagnosed as multiple sclerosis and was on chronic steroid therapy but futile. While detailed examination, clinical acumen and investigations helped this young lady in ascertaining the cause of her woe as NMO and culminated in apt and successful treatment. **Conclusion**: Intensive research, awareness and education of primary care physicians armed with comprehensive knowledge alongside timely diagnosis, recognition of complications and prompt referral to higher centres will advance the patient to obtain timely intervention ensuing in averting predictable complications and leading a life of contentment.

KEYWORDS: Neuromyelitis optica, Neuromyelitis optica spectrum disorder, autoimmune, demyelinating, NMO, NMOSD.

INTRODUCTION

Neuromyelitis optica (NMO) formerly appreciated as Devic's disease is a severe inflammatory demyelinating disorder that causes recurrent attacks of optic neuritis and transverse myelitis. NMO is actually a translation of the French term 'neuro-myélite optique aiguë', utilized first by Eugène Devic (1858–1930) in a paper published during the event of the Congrès Français de Médecine in Lyon in 1894. Devic proposed the term to signify a novel syndrome characterized by acute myelitis and optic neuritis. Devic's student Fernand Gault (1873–1936) in his doctoral thesis 'De la neuro-myélite optique aiguë' published in the same year consisted of review of the previous medical literature and a clinicopathological analysis of Devic's case.[1]

Neuromyelitis optica spectrum disorder (NMOSD)has been introduced to include individuals with involvement of additional areas of the CNS and atypical presentations of NMO.

Prevalence of NMO is more in women when compared to men (3-9:1) with a mean age of onset around 40 years but can occur in any age. There are documented cases in 3 years old as well as 90 years old.[2]

In the past, Multiple sclerosis was relatively rare in Asia and other parts of the world where patients with recurrent optic neuritis and myelitis alone were diagnosed with 'opticospinal MS' and patients with brain manifestations with or without optic neuritis and myelitis were classified as 'conventional MS'. With the groundbreaking discovery of highly specific neuromyelitis optica immunoglobulin G i.e., AQP4-antibody in 2004 by Lennon and Wingerchuck[2], these disorders gained worldwide attention earning them a separate entity rather than remaining as a subtype of Multiple Sclerosis.

The pathogenesis of NMOSDs is believed to be development of autoimmunity against aquaporin-4 (AQP4) which is a cell membrane water channel protein expressed on the foot processes of astrocytes helping in maintaining blood–brain barrier integrity. These water channel proteins are also found in high concentrations in gray matter of spinal cord, periaqueductal and periventricular regions.[2,3]

These AQP4 antibodies, also called NMO IgG antibodies are considered to be the pathogenic marker of NMO.[4]

NMO has a relapsing and remitting course with a spectrum of clinical features

1. Optic neuritis which can be unilateral or bilateral presenting with variable degree of visual loss usually associated with painful eye movements.
2. Transverse myelitis characterised by symmetric paraparesis, quadriparesis, bladder dysfunction or sensory loss below the level of spinal cord lesion sometimes may be associated with radicular pain, Lhermitte symptoms and paroxysmal tonic spasms of trunk and limbs.
3. Area postrema syndrome – nausea and vomiting or intractable hiccups.
4. Hypothalamic dysfunction- symptomatic narcolepsy or excessive daytime sleepiness, obesity, hypotension, bradycardia and hypothermia. [5]
5. Encephalopathy, posterior reversible encephalopathy syndrome (PRES), severe diffuse cerebral edema and demyelination can lead to brain herniation and death.[5]

THE DIAGNOSTIC CRITERIA FOR NMOSD[6]
DIAGNOSTIC CRITERIA FOR NMOSD WITH AQP4-IgG
1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses
DIAGNOSTIC CRITERIA FOR NMOSD WITHOUT AQP4-IgG OR NMOSD WITH UNKNOWN AQP4-IgG STATUS
1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements: a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome. b. Dissemination in space (2 or more different core clinical characteristics) c. Fulfillment of additional MRI requirements, as applicable.
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable.
3. Exclusion of alternative diagnoses.
CORE CLINICAL CHARACTERISTICS
1. Optic neuritis 2. Acute myelitis 3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting. 4. Acute brainstem syndrome 5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions. 6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions
ADDITIONAL MRI REQUIREMENTS FOR NMOSD WITHOUT AQP4-IGG AND NMOSD WITH UNKNOWN AQP4-IGG STATUS
1. Acute optic neuritis: requires brain MRI showing a. normal findings or only nonspecific white matter lesions, OR b. optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm. 2. Acute myelitis: requires associated intramedullary MRI lesion extending over 3 contiguous segments (LETM) OR 3 or more contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis. 3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions 4. Acute brainstem syndrome: requires associated periependymal brainstem lesions

Management of acute attacks is usually by **Glucocorticoid therapy** preferably intravenous Methylprednisolone and **Adjunctive plasma therapy** is employed in cases of high severity or poor response to glucocorticoids. Agents for long term immunomodulation to prevent relapses are eculizumab, inebilizumab, satralizumab approved by USFDA, while clinicians also use Rituximab and tocilizumab alternatively. [7]

CASE

We report a 36 years old female who presented with complaints of recurrent episodes of blurring of vision and weakness of both lower limbs for the past 11 years. The patient was apparently alright prior to 2012 with no previous history of any comorbidities.

Table 1: Timeline of Significant Events.

YEAR	CLINICAL FEATURES
2012	• Blurring of vision in left eye associated with painful eye movements progressing to near complete loss of vision within a day. • Development of diminution of vision in right eye the following day progressing to a state that she could appreciate hands movements close to face. • History of fever one week back with unsteadiness on walking and giddiness. • Examination revealed nystagmus and Finger Nose Test incoordination while other systems were unremarkable. • The patient improved on pulse steroid therapy.
2013	• She developed diminution of vision in both eyes with worsening over few days. • No complaints of weakness of upper or lower limbs. • Improvement on treatment with pulse steroids
2014	• She developed numbness of both lower limbs which was insidious in onset with reduced sensation initially in the left followed by right lower limb below the groin. • Difficulty in wearing her foot wear. • Difficulty in walking with weakness of both lower limbs. • The patient received pulse steroids, gradually improved and was able to walk by her own in few months.
2015	• The patient delivered a male child, the pregnancy was uneventful. • She had no similar complaints during pregnancy or in the postpartum period.
2016	• Following 11 months of childbirth, she complained of diminution of vision in right eye progressing to no perception of light. • Vision subsequently improved on treatment with oral steroids.
2018	• She developed weakness of both lower limbs subacute in onset which progressed to almost inability to move her limbs within 5 days • Documented power of 1 in bilateral lower limbs. • She was catheterized for her urinary complaints. • Treated with pulse steroids and gradually improved.
2019	• Developed weakness of both lower limbs with paresthesias such that she had to be carried to the hospital. • The patient was bed ridden and was able to sit up only with help of support. • She improved with pulse steroid therapy.
2022	• The patient developed inability to move her limbs even in bed, unable to sit up without support • Progressive worsening of vision. • Referred to higher center.

Table 2: Current Detailed Examination.

OPHTHALMIC EXAMINATION	**Visual Acuity** Right eye: 6/60 Left eye: perception of hand movements at 1 meter. **Visual evoked potentials** Right eye: Prolonged P100 Left eye: Absent waves **Bilateral internuclear ophthalmoplegia**.
MOTOR SYSTEM	**Tone:** Bilateral lower limb hypotonia **Power**: 1/5 across all joints of right lower limb 2/5 in left lower limb. **Reflexes:** Jaw jerk exaggerated, Deep tendon reflexes- hyporeflexia. Bilateral plantar- extensor.

SENSORY SYSTEM	Graded sensory loss in bilateral lower limbs with sensory loss more in the right compared to left lower limb. Joint position impaired at great toe reduced vibration sense in both lower limbs. Cerebellar examination: Impaired finger nose test. Gait could not be assessed.

INVESTIGATIONAL PROFILE

Routine investigations: Complete hemogram, renal function parameters, liver function test, serum electrolytes, vitamin B12 levels, homocysteine levels, chest X Ray and ECG were normal.

Secondary demyelination workup: ANA profile showed positivity for antihistone antibody and **serum Aquaporin 4 antibody was strongly positive**. (2022)
The viral markers for HIV, Hepatitis B, Hepatitis C and VDRL were negative. Lumbar puncture CSF analysis were within normal limits. CSF oligoclonal bands report was negative. MRI of our patient revealed bilateral optic atrophy with hyperintensities and no enhancement, long segment hyperintensities in central part of dorsal cord with atrophy of cord. Somatosensory evoked potentials were absent in lower limbs and normal in upper limbs. BERA was normal.

DISCUSSION

NMOSD is a disorder which presents acutely and leaves considerable residual neurological sequelae in absence of treatment. NMOSD is commonly found in polyphasic form (90%) than monophasic form (10%)[6,8] where polyphasic form of presentation is seen in our patient as well. The mean age of onset is around 40 years while our patient had her first attack at the age of 25. The patient presented with bilateral lower limb weakness, urinary incontinence and visual impairment with history of similar attacks in the past which only worsened each time which is classically seen in typical NMOSD.

Immunological and autoimmune examinations in NMOSD are generally normal[5] while our patient exhibited positivity for anti histone antibody as well.

The MRI of the spinal cord in NMOSD have typical features of longitudinally extensive transverse myelitis (LETM), a lesion that extends over 3 or more segments of the adjacent spinal cord, MRI of the optic nerve can be seen as hyperintensity in optic neuritis. Brain MRI features can vary, such as normal or periependymal lesions surrounding the ventricular system, dorsal brain stem lesions bordering the fourth ventricle, periependymal lesions that surround the lateral ventricles, white matter hemispheres, lesions involving the corticospinal tract, non-specific lesions and enhancing lesions.[9,10] MRI of our patient revealed bilateral optic atrophy with hyperintensities and no enhancement, long segment hyperintensities in central part of dorsal cord with atrophy of cord.

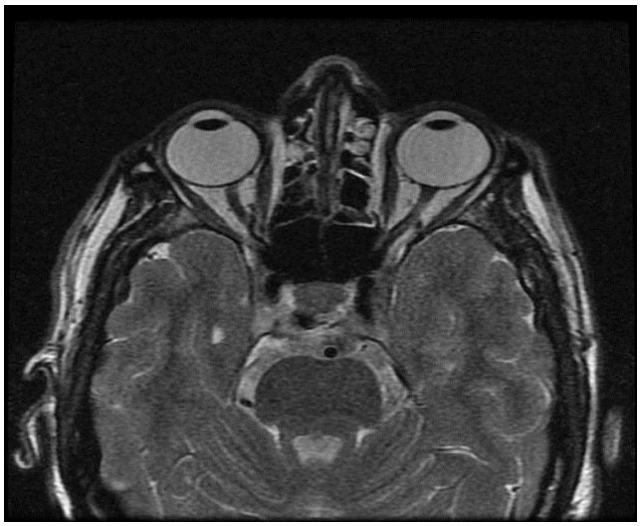

Figure 1: MRI brain with bilateral optic atrophy

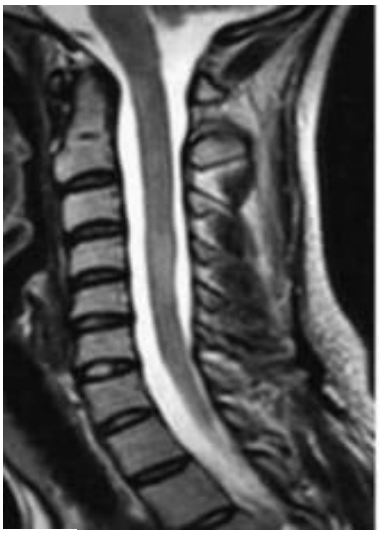

Figure 2: MRI spine with long segment hyperintensities in thoracolumbar cord

Therapy in NMOSD consists of acute exacerbation phase therapy and long-term immunomodulation care to reduce the risk of relapse. Treatment options available are oral corticosteroids, immunosuppressant therapy, therapeutic plasma exchange(TPE) and immunomodulatory therapy. Corticosteroids are the main choice in the acute phase while TPE is considered if the patient's condition does not improve or neurological symptoms worsen.

Here the patient was treated with intravenous corticosteroids and 5 cycles of large volume plasmapheresis. For immunomodulation the pateint is put on Rituximab infusions.

Long-term care is crucial such as medical rehabilitation, management of anxiety, depression, gastrointestinal disturbances and bladder problems with adequate pain relief.

There is a dearth of epidemiological data about multiple sclerosis (MS) and related demyelinating disorders in India. In a study from Southern India by Pandit L et al., NMO IgG was positive in 39% of patients where Neuromyelitis optica spectrum disorders (NMOSD) constituted 13.9% of all demyelinating disorders, with a prevalence of 2.6/100,000. Larger studies with more refined survey methodologies are required to understand the true prevalence of demyelinating disorders in India.[11]

Due to the high sensitivity and specificity of anti-aquaporin 4 antibody, several atypical presentations including brainstem syndrome, area postrema syndrome, cerebral syndrome and hypothalamic syndrome were described and reported in patients with positive aquaporin-4 antibody. Brain and brainstem lesions are often symptomatic and brain lesions are often the source of the first ever clinical presentation of NMO. With International consensus diagnostic criteria (ICDC) for NMO spectrum disorder, all the varied non optico spinal presentation of NMO spectrum disorder can be accurately diagnosed.[12]

CONCLUSION

With the advent of newer technologies and imaging modalities there is an unprecendented rise in diagnosis of NMOSDs with atypical presentations peaking interests of clinicians and researchers. Attacks of NMOSD can be very severe if not life-threatening when the lesion extends to the cervical spinal cord and brain stem as it has the potential to result in respiratory failure. NMOSDs are believed to represent a higher proportion of IDMs in the non-Caucasian population including India, despite this, there is lack of data on epidemiological, clinical, and investigational profile of NMOSDs in developing nations especially India. Thus, there is a need to determine epidemiological, clinical, investigational profile as well as response of NMOSDs to commonly used immunosuppressant drugs (azathioprine, cyclophosphamide, mycophenolate mofetil and more) in developing countries compared to expensive treatments such as pulsed intravenous (IV) immunoglobulin therapy in the West.

Conflict of interest statement: Nil.

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