Aquaporinopathy- A study of clinical, laboratory, MRI and outcome profile

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Abstract:
Neuromyelitis optica (NMO) (also known as Devics disease) is an idiopathic, severe, demyelinating disease of the central nervous system that preferentially affects the optic nerve and spinal cord. The presence of highly specific serum autoantibody marker (NMO IgG) further differentiates NMO from multiple sclerosis and has helped to define a neuromyelitis optica spectrum of disorders. Clinical studies in India have consistently reported high incidence of optic nerve and spinal cord involvement in patients diagnosed to have multiple sclerosis (MS). Though speculated, it is not clear whether the NMO spectrums of disorders are responsible for this site specificity. We retrospectively studied 7 patients with NMO-IgG positivity with complete work up. We compared our data with the most recent studies on NMO and with the criteria proposed by Wingerchuck et al. Neurology 66(2006) 1485. Seven patients (6 women and one man, with a mean age of 26.28 years) were included in the study. We found good clinical outcome in patients with NMO spectrum disorders. There is a good response to immunosuppressive therapy to our patients. Furthermore, all NMO patients should be investigated for vasculitis, even those with no history of systemic disease.

Keyword : Neuromyelitis optica, multiple sclerosis, aquaporinopathy, optic neuritis

INTRODUCTION:
Optico-spinal phenotype of multiple sclerosis (MS) dominates demyelinating disorders in Asia, among Japanese as well as Indian patients, with Asian MS becoming synonymous with the Japanese optico-spinal MS. It has been suggested that neuromyelitis optica (NMO) is a disease entity distinct from MS.
This is said to be supported by high prevalence of anti-AQP4 antibody (NMO-IgG) found among NMO patients. It has also been reported that optico-spinal MS among Japanese has high positivity of NMO-IgG, thus it may be the same disease as NMO reported in the West. The common occurrence of spinal cord and optic nerve involvement in Indian patients with MS has been consistently reported in several hospital based studies since the 1950’s. It has been speculated that this may be due to over representation of NMO and its variants among the Indian patients with demyelinating disorders. As NMO-IgG is 91% specific and 100% sensitive in NMO, a reliable tool to distinguish NMO spectrum of disorders from other demyelinating illnesses. NMO-IgG seropositivity rates are approximately 50% in patients with recurrent longitudinally extensive transverse myelitis (LETM) and about 25% in patients with simultaneous or recurrent optic neuritis and negative brain MRI. Patients presenting with a first-ever LETM event and who are found to be NMO-IgG seropositive have a 56% risk of LETM recurrence or optic neuritis (conversion to NMO). We therefore undertook this study to determine the clinical spectrum, laboratory, and MRI outcome profile of aquaporin antibody positive patients.

**METHOD:**

We retrospectively studied 7 patients with NMO-IgG seropositivity. We only included, in this study, patients with a complete workup including brain and spinal cord MRI, CSF analysis, visual evoked potentials (VEPs) and screening for systemic disease (SLE, Sjogren’s syndrome or antiphospholipid syndrome). A total of 7 patients (1 male and 6 female) were enrolled in this study. Clinical and demographic details and results of investigations were collected and compiled in all patients. Sera were collected for NMO-IgG estimation during the acute phase of illness. Criteria for diagnosis of NMO (Revised diagnostic criteria by Wingerchuck et al. 2006)

Two absolute Criteria

(1) Optic Neuritis
(2) Myelitis At least two of the three supportive criteria

(1) Presence of contiguous spinal cord MRI lesion extending over three or more vertebral segments
(2) MRI criteria not satisfying the revised McDonald diagnostic criteria for MS and (3) NMO-IgG in serum

NMO Spectrum Disorders

Neuromyelitis optica (2006 definition)

Limited forms of NMO

- “Idiopathic” single or recurrent events of longitudinally extensive myelitis (3 vertebral segment spinal cord MRI lesion)
- Bilateral simultaneous or recurrent optic neuritis
- Asian optic-spinal MS
- Optic neuritis or longitudinally extensive myelitis associated with systemic autoimmune disease
- Optic neuritis or myelitis associated with “specific” NMO brain lesions (hypothalamic, periventricular, brainstem)

Long cord lesion was defined as spinal MRI lesions extending more than three vertebral segments. All patients had a brain and spinal cord MRI on 1.5-T machine. All patients had a control MRI during the follow-up to look for signs of spinal cord atrophy.
Lesion length, cord swelling-gadolium enhancement and atrophy were recorded for spinal cord lesions. In addition to the standard haematological investigation, all patients underwent an autoantibody investigation, consisting of screening for antinuclear antibody, rheumatoid factor, anti-DNA and ANCA antibodies, thyroid hormone, thyroglobulin antibodies and anticardiolipin antibodies.

**OBSERVATION**

Clinical findings are reported in Table 1. Six patients were women and the mean age at onset was 26.28 years (range: 11–41). The presenting symptom was isolated cord involvement (LETM) in three cases, optic neuropathy in one case and three had myelopathy and optic neuritis (ON). Symptoms indicating motor involvement included paraparesis in 2 patients and quadriparesis in 2 patients. All the patients with myelopathy were having significant bowel and bladder disability. There was no history of antecedent fever, loose motion, respiratory tract infection or any vaccination. One patient had Lhermitte’s symptom and another patient had Uhthoff’s phenomena. One had presented with recurrent optic neuropathy. A relapsing–remitting pattern was observed in all the patients. At onset, ON was bilateral in all patients and followed a relapsing–remitting pattern of optic nerve involvement. All optic neuritis patients had abnormal VEPs with increased latencies.

**Abbreviations**---Cyclo- Inj Cyclophosphamide, Steroid- Inj Methylprednisolone, Myco- Tab. Mycophenolate, Aza- Tab Azathioprine, EDSS- Expanded disability status scale, OCB- oligoclonal band, VEP- visual evoked potential

| F 41 | 0 | 3.5 | 6 | 28 | 0 | Neg | normal | present | absent | Cyclo-steroid |
| F 11 | 3 | 2.5 | 6 | 30 | 1 | Neg | normal | present | absent | Myco+steroid |
| F 30 | 1 | 3 | 3 | 85 | 4 | Neg | normal | present | present | Myco+steroid |
| F 20 | 2 | 4.5 | 4 | 3 | 40 | 4 | Neg | normal | present | present | Myco+steroid |
| F 31 | 3 | 4 | 2 | 3 | 70 | 4 | Neg | normal | present | present | Myco+steroid |
| F 34 | 5 | ON | 2 | 2 | 35 | 35 | Neg | normal | absent | absent | Aza+Steroid |
| M 37 | 2 | 4.5 | 2 | 3 | 85 | 40 | Neg | normal | absent | absent | Aza+Steroid |

**CSF, brain and spinal cord MRI and laboratory results**

CSF was normal in five cases. Pleocytosis was observed in 2 cases with a mean cell count of 37.5/cumm (range: 35–40) and with a lymphocyte predominance. Protein level was increased (85 mg/dl) in the CSF of two patients. OCBs were not found in all the cases. In four cases, brain MRI was abnormal and the lesions were most commonly in the corpus callosum, deep white matter, and periventricular and brain stem lesions. Spinal cord MRI was abnormal in
with long cord lesion mostly in cervico-dorsal cord. With follow up the cord region which was swollen initially, were found to be having significant atrophy. In two cases, we observed gadolinium enhancement. None of the patients fulfilled the criteria for MS. A systemic disease was suspected in two of our patients as ANA positivity, but they did not fulfill the diagnostic criteria of SLE. One patient had laboratory supported hypothyroidism without any clinical signs.

**DISCUSSION:**
The clinical and radiological profile of our patients was largely similar to reports from other parts of Asia. Three of our patients met the criteria of NMO as revised diagnostic criteria by Wingerchuk et al (2006) and other were neuromyelitis spectrum. The female predominance of our study is corroborated by other studies. The average age of presentation was younger than other series but NMO also occurs in children and elderly people. Another atypical feature seen in our patients was the good clinical outcome for patients with recurrent long cord lesion in spite of long duration of illness. These patients with good outcome have clinical features consistent with NMO spectrum disorders. There were similar reports of favorable outcome from other centers in India. Pradhan et al described 6 patients (3 male and 3 female) with clinical and radiological features consistent with relapsing NMO who recovered well after recurrent attacks of visual loss and myelitis, remaining ambulant 2-10 years after onset of disease. Three of our patients with NMO and 1 with recurrent TM had large brain lesions during the course of the illness. This is not unusual as large lesions.
and even tumefactive lesions have been described occasionally in patients with NMO. The specificity of NMO-IgG has expanded the clinical spectrum of NMO. It allowed confirmation that brain lesions may occur in NMO, occasionally in a rather specific pattern that includes the hypothalamus and regions adjacent to the third and fourth ventricles.

CONCLUSION:
In this small case series, the varied presentation of Aquaporinopathy was demonstrated. Neuromyelitis optica and its spectrum by a combination of clinical, neuroimaging, serological, and pathological characteristics can be distinguished from multiple sclerosis, which has considerable implications for clinical practice and is important for prognostication. The presence of NMO-IgG in the pathogenesis of neuromyelitis optica has not yet been proved and could be a surrogate marker. But it has definite implications for prognostication and long term immunotherapy.

REFERENCES: