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Case Report
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Case Report: Seronegative Neuromyelitis Optica in a Bangladeshi Male

Ishtiaq Ahmad[1]*, Sarwat Rahman[2] and Kenichi Sato[3]

1Neuromedicine Department, Apollo Imperial Hospital, Zakir Hossain Road, Pahartali, Chattogram, Bangladesh

2Neuro-ophthalmology Department, Bangladesh Eye Hospital, House, Satmasjid Road, Dhaka, Bangladesh

3Neurosurgery Department, Tohoku Medical and Pharmaceutical University, Hukumuro, Miyagino-Ku, Sendai, Japan

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***Corresponding author:** Ishtiaq Ahmad, Department, Apollo Imperial Hospital, Zakir Hossain Road, Pahartali, Chattogram, Bangladesh

Abstract

Introduction: Neuromyelitis Optica (NMO) is an inflammatory disorder involving central nervous system predominantly optic nerve and spinal cord is rare in Bangladesh. The diagnosis depends of the clinical presentation then confirmed by antibodies against aquaporin-4 immunoglobulin (AQP4-IgG) or myelin oligodendrocyte glycoprotein (MOG-IgG). Here we present an interesting seronegative case in a young male, first case to be reported in Bangladesh.

Case presentation: This is 21-year-old Bangladeshi male with complaint of lower extremities numbness, falls, and mild urinary retention for last 3 weeks in January 2021. On examination, motor strength 5/5 on both lower extremities, heel and toe standing normal, brisk knee jerk and ankle jerk, Babinski was up going on both sides. Sensory examination revealed diminished pinprick and vibration sensation in both lower extremities, right side was more affected. Sensory level was thoracic 8 dermatome. Romberg test was negative. Gait was normal including tandem gait. MRI spine showed long cord lesion involving thoracic segment 2 to 9 consistent with transverse myelitis. Patient has right eye blindness since 2014 related to optic neuritis. Patient was treated with intravenous Methylprednisolone (IVMP) 1000 mg daily for 5 days. His urinary symptom was resolved after IVMP. MRI brain gadolinium was noted to be normal. Cerebrospinal fluid study showed white cell count 5/mm3, lymphocytic pleocytosis, oligoclonal band negative, and normal immunoglobulin synthesis rate. Patient was found to be negative for aquaporin-4 immunoglobulin and myelin oligodendrocyte glycoprotein immunoglobulin. As the patient remained stable after IVMP treatment, currently being monitored clinically with periodic neurological examination during office visit.

Conclusion: There is no definite recommendation on disease modifying treatment for seronegative NMO. Instead of prophylactic disease modifying treatment clinical monitoring could be cost effective in a developing country like Bangladesh.

Keywords: Seronegative neuromyelitis optica; Aquaporin-4 immunoglobulin; Myelin oligodendrocyte glycoprotein immunoglobulin; Serology; NMO spectrum disorder

Abbreviations: NMO: Neuromyelitis Optica; IVMP: Intravenous Methylprednisolone; MS: Multiple Sclerosis; AQP4-IgG: Aquaporin-4 Immunoglobulin; ON: Optic Neuritis; LETM: Longitudinally Extensive Transverse Myelitis; NMOSD: NMO Spectrum Disorder; MOG-IgG: Myelin Oligodendrocyte Glycoprotein Immunoglobulin; T8: Thoracic 8; PLEX: Plasma Exchange; IVIg: Intravenous Immunoglobulin

Introduction

Neuromyelitis Optica (NMO) is an autoimmune inflammatory demyelinating disease involving central nervous system, initially it was considered as a variant of multiple sclerosis (MS). The identification of NMO-specific antibody, aquaporin-4 immunoglobulin (AQP4-IgG) helped these patients to be identified as different from MS since 2004 [1]. NMO commonly presents with optic neuritis (ON), longitudinally extensive transverse myelitis (LETM) with lesion more than 3 contiguous segment in spinal cord and seropositive AQP4-IgG. Immune-mediated disorder related to AQP4-IgG targeting water channels of astrocytes to cause demyelination. Some NMO patients with similar clinical presentation but seronegative AQP4-IgG or with limited clinical presentation was identified as NMO spectrum disorder (NMOSD). Among NMOSD, some of the patients are found to have autoantibody against myelin oligodendrocyte glycoprotein (MOG-IgG), which is a demyelinating disorder targeting

oligodendrocytes. The demyelinating disorders and MS are rare in Bangladesh. We present this unique case of NMO with negative for both AQP4-IgG and MOG-IgG. There are several reported cases of seronegative NMO, implied negative for AQP4-IgG [2-4]. There was one reported case of NMO from Bangladesh that was positive for AQP4-IgG [5]. We are reporting first seronegative NMO case in Bangladesh.

Case Report

A 21-year-old Bangladeshi male with right eye blindness since 2014 related to ON (visual field test showed severely depressed field on right eye, Figure 1; visual evoked potential showed prolong P100 wave latency on left eye and absent P100 wave on right eye, Figure 2). Currently, patient presents with lower extremities numbness and mild urinary retention for last 3 weeks. There were also several falls which were difficult to explain. On cranial nerve examination showed right afferent pupillary defect, visual acuity on right 20/200 and left 20/20, fundoscopy revealed right optic atrophy (Figure 3). Further neurological examination showed motor strength in both legs 5/5 in all muscle groups, heel and toe standing normal on both sides. Sensory examination revealed diminished pin-prick and vibration sensation in both legs, sensory level was at thoracic 8 (T8) dermatome. Romberg sign was negative, knee jerk and ankle jerk were brisk on both sides, planter was up going on both sides. MRI spine showed thoracic cord long segment lesion extending T2 to T9 segment consistent with transverse myelitis (Figure 4). He was treated with intravenous Methylprednisolone (IVMP) 1000 mg daily for 5 days. His urinary retention was resolved, but mild numbness in legs persisted. With the history of ON and now with TM, MS was one of the strong differential diagnosis. However, his MRI brain with contrast enhancement showed no feature of MS (Figure 5).

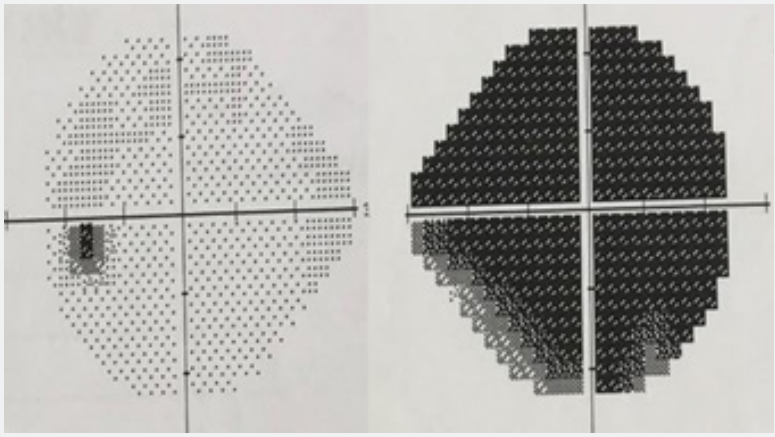

Figure 1: Visual field test, November 2014 showed severely depressed field in right eye.

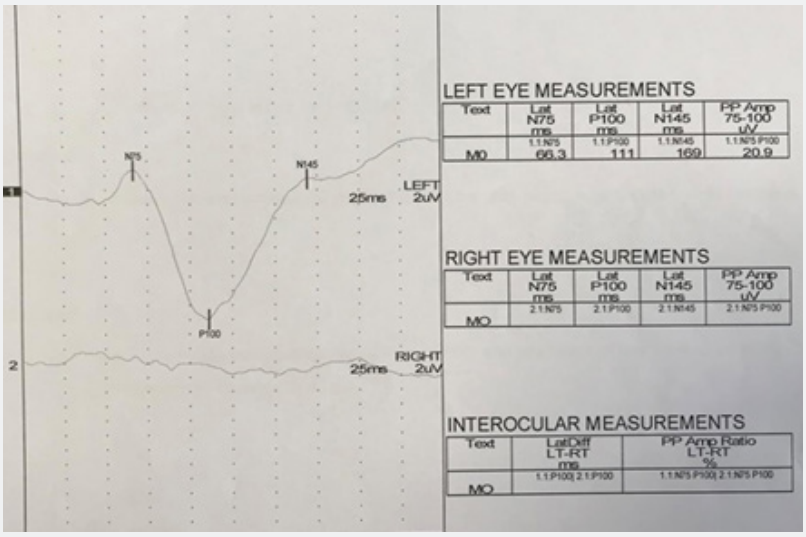

Figure 2: Visual evoked potential, November 2014 showed absence of P100 wave in right eye and prolong P100 latency in left eye.

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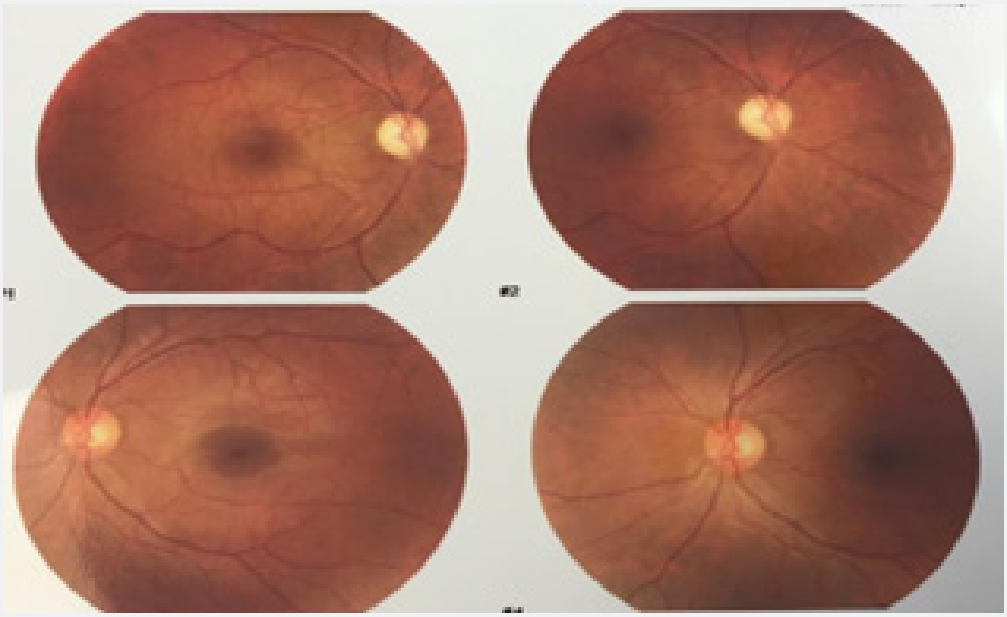

Figure 3: Fundoscopy, February 2021, right eye (top row) shows optic atrophy and left eye (bottom row) noted to be normal.

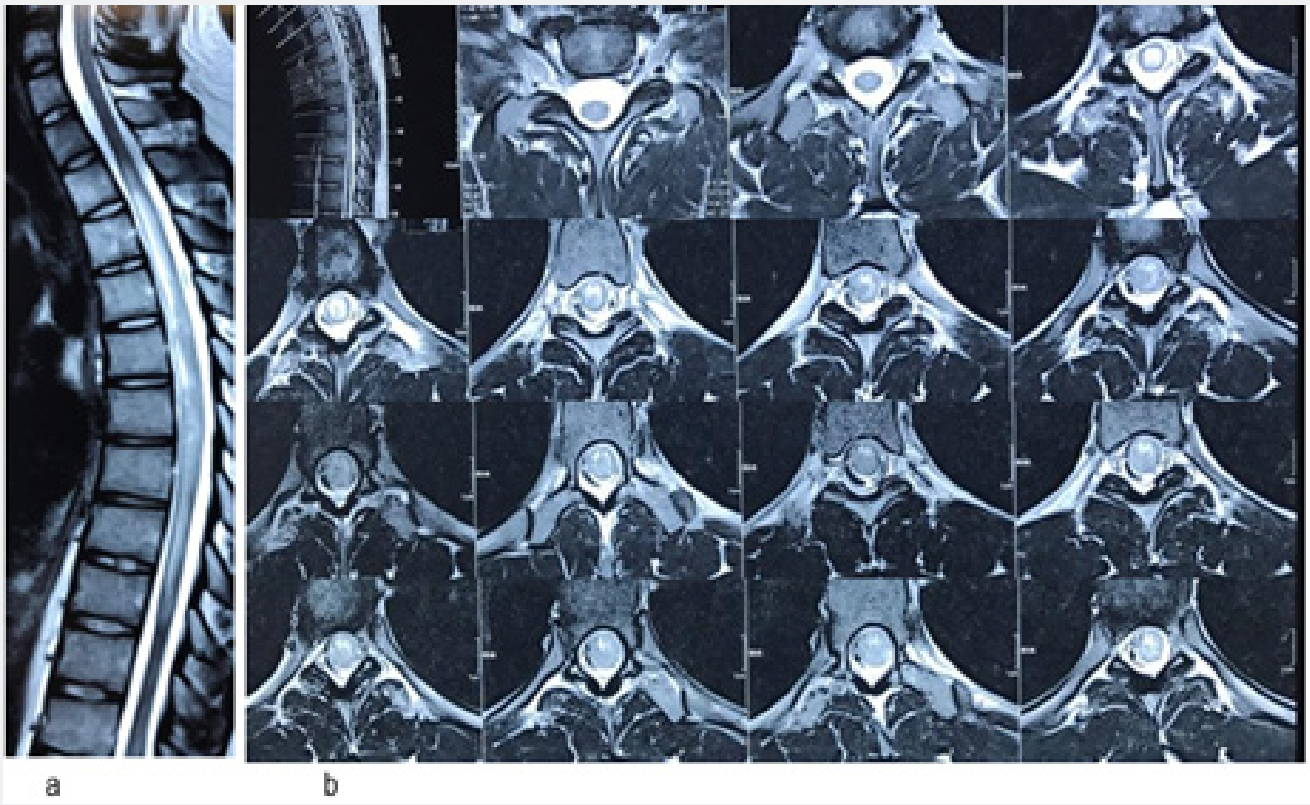

Figure 4: MRI spine, midline sagittal (a), serial axial sections showed thoracic segment 2 to 9 longitudinally extensive intramedullary lesion.

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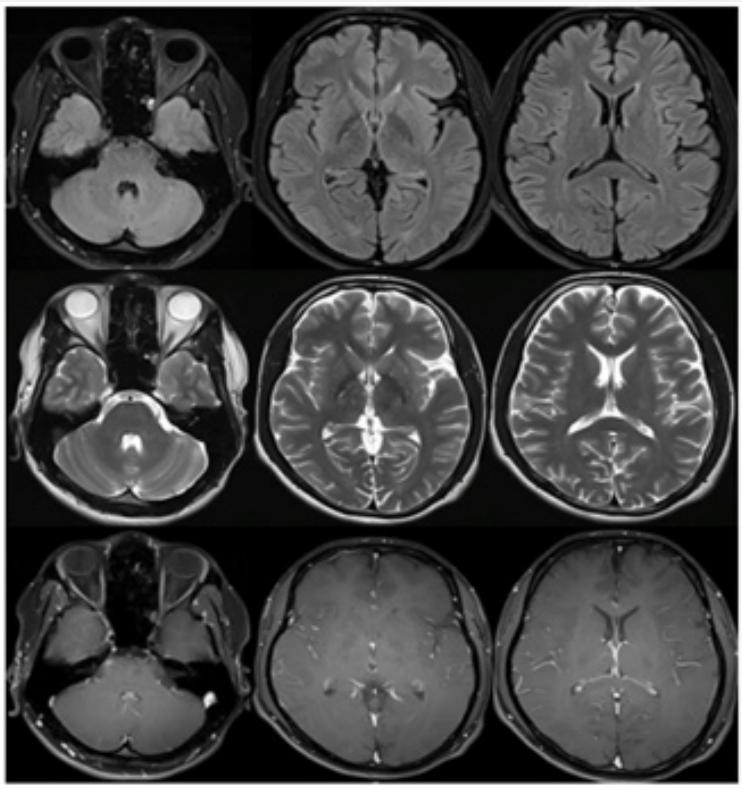

Figure 5: MRI brain axial images, FLAIR sequence (top row), T2 sequence (middle row) and T1 gadolinium enhanced (bottom row) showed no intra-parenchymal plaque and no abnormal enhancement to implicate demyelination.

Further CSF study for oligo clonal band and immunoglobulin index were also negative for MS (Table 1). With negative MRI brain for MS, current presentation with long cord segment TM and history of ON, NMO became another strong differential diagnosis. But cell base assay for serum AQP4-IgG and MOG-IgG were also negative. As the patient is milder in clinical presentation with TM and responded well with IVMP, subsequently remained stable, we are perplexed about initiating prophylactic disease modifying treatment (DMT). We are keeping in mind about using DMT which are available in Bangladesh as well as affordable if there is significant symptom progression. Preserving the function of left eye and spinal cord are the utmost priority.

Table 1: Laboratory results.

Parameter	Date	Result	Reference range
Blood studies			
Creatinine	02/4/2021	1.07 mg/dL	0.59-1.04
Sodium	02/4/2021	139mM/L	135-145
ALT	02/4/2021	26 IU/L	5-40
WBC	02/4/2021	15.9 10^9/L	4-10
Hemoglobin	02/4/2021	16.1 gm/dL	12.0-15.0
Hematocrit	02/4/2021	47.40%	36.0-46.0
ESR	02/4/2021	2 mm 1st hour	M 0-10, W 0-20
TSH	02/4/2021	0.28microIU/mL	0.3-4.2
BUN	02/4/2021	24 mg/dL	7-23
Rheumatoid factor	02/4/2021	5.29 IU/mL	<14

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Anti-nuclear antibody	02/4/2021	2.48 AU/mL	<40
Glucose, fasting	02/4/2021	5.7mM/L	3.6-5.5
HbA1c	02/4/2021	6.20%	<5.7
Total cholesterol	02/4/2021	138 mg/dL	<200
Triglyceride	02/4/2021	77 mg/dL	<150
Low density lipoprotein	02/4/2021	90 mg/dL	<100
High density lipoprotein	02/4/2021	47 mg/dL	40-60
B12	02/4/2021	547 pg/mL	180-915
NMO panel			
Anti-AQP4 IgG	02/17/2021	negative	Cell base assay, IFA
Anti-MOG IgG	02/17/2021	negative	Cell base assay, IFA
CSF studies			
Glucose-CSF	02/17/2021	59 mg/dL	40-80
Glucose-Plasma	02/17/2021	95 mg/dL	<140
Protein-CSF	02/17/2021	40 mg/dL	15-45
WBC-CSF	02/17/2021	5 cells/mm^3	<5
Lymphocytes	02/17/2021	100%	
RBC-CSF	02/17/2021	18 cell/mm^3	0
IgG serum	02/17/2021	987 mg/dL	700-1600
IgG CSF	02/17/2021	21.7 mg/L	<34.0
IgG index	02/17/2021	0.59	0.3-0.7
IgG synthesis rate	02/17/2021	-1.2	3.3 to -9.9
Oligoclonal band	02/17/2021	absent	
MTB-PCR	02/17/2021	negative	
VDRL	02/17/2021	negative	
AFB stain	02/17/2021	negative	
Gram stain	02/17/2021	negative	

Discussion

NMO and NMOSD are different from MS, but the treatment for acute attack remained similar to MS with high dose IVMP daily for 3-5 days with objective to reduce the severity of the initial deficit. If acute symptoms do not improve with steroid treatment plasma exchange (PLEX) has been noted to be effective. There are also report of benefit in small case series of NMO patients during acute attack with the use of intravenous immunoglobulin (IVIg) therapy. Preventative immunosuppressive DMT is also employed to reduce the chance future attack with corticosteroid, Azathioprine, Mycophenolate Mofetil, Methotrexate, Mitoxantrone, Rituximab, Eculizumab etc. All these effective preventative DMTs were administered in NMO patient who were seropositive. However, there is no definite recommendation for seronegative cases.

NMO and NMOSD are immunological disorders could be multifaceted, until now we can detect 2 antibodies AQP4-IgG and MOG-IgG related to these disorders. AQP4-IgG and MOG-IgG related NMOSD are similar in clinical presentation. But MOG-IgG related NMOSD has chance of good recovery after initial attack [6] and prevalent in male gender, Caucasian ethnicity, present with single or few clinical attack, bilateral or recurrent ON, LETM involving lumber segment. The impact of seronegative status in the clinical course of the patient with NMO is yet not well understood. Our case is unique as the patient is seronegative for both AQP4-IgG and MOG-IgG as well as episodes of ON and TM happened several years apart. The severity of the disease process is palpable as the patent is blind in right eye with ON. Serology was not tested in 2014 during the initial attack of ON, thus the possibility remains that he was probably seropositive at that time and later converted to seronegative status. Seroconversion after initial attack happens more often with MOG-IgG positive patients [6]. Our patient's current presentation with LETM, which involves T2-9 cord segment without significant motor deficit but with mild sensory symptoms which got better after high dose IVMP and remained stable afterwards. The seronegative status in our case may and current mild presentation with TM may reflect the prognosis for better ultimate outcome.

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The etiology of TM in our case we looked for several possibilities. TM is a focal inflammation of the spinal cord. There are two possibilities about the cause of TM in our case idiopathic TM, secondary TM, or NMO related TM. The evidence for secondary cause of TM related to connective tissue disease was negative in our case e.g. normal ESR, anti-nuclear antibody and rheumatoid factor (Table 1). As our patient has history of ON in the past which excludes the case to be identified as idiopathic TM [7]. Thus, LETM in our case was identified as related to NMO.

There are 3 reported cases of seronegative NMO, in one patient DMT was applied and got better outcome with Rituximab [4]. The reported seropositive case from Bangladesh was treated with Azathioprine and Prednisolone. The outcome of these DMTs was good in that case [5].

Conclusion

NMO is a rare disorder with various clinical presentation. Clinical research is needed for better understanding of the treatment option specially for seronegative NMO. The severity of the symptom at the initial presentation guides us about the use of DMT to prevent future relapse irrespective of seropositive or seronegative status. We planned in our patient if there is any clinical deterioration to use DMT either Mycophenolate or Prednisolone which are available in Bangladesh and affordable. Rituximab and Azathioprine are also available but not affordable by all patients in Bangladesh because of the cost. We did plan to apply at this moment a watchful clinical monitoring which may be a reasonable safe option as there is no aggravating neurological deficit to affect his activity of daily living in our case of seronegative NMO. Thus, we are learning from our case that the natural course of the disease process further to guide us about subsequent course of action on DMT.

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