Original Article

Comparative Study of Spectrum of Neuromyelitis Optica and Multiple Sclerosis in Indian Population

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Abstract

Purpose: *The purpose of this study is to differentiate neuromyelitis optica and its related disorders.*

Materials and Method: *A retrospective single site study of 104 patients from July 2014 to October 2017 with optic neuritis and/or myelitis was done. After history taking and complete ocular examination, neurological examination, cerebrospinal fluid examination, magnetic resonance imaging and aquaporin 4 antibody testing, patients were categorised as neuromyelitis optica, multiple sclerosis and others.*

Results: *Neuromyelitis optica was diagnosed in 38 patients, multiple sclerosis in 48 patients and 18 were others. Female predominance (76%) was noted in neuromyelitis optica patients. Seropositivity for aquaporin 4 autoantibodies was associated with higher relapse rate. In neuromyelitis optica 55% patients responded to steroid therapy, 30% referred for plasmapheresis, and 15% patients needed imunosuppressive therapy.*

Conclusion: *Considerable overlap exists between neuromyelitis optica and multiple sclerosis, both have to be differentiated because both diseases have different treatment guidelines.*

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Keywords: *Neuromyelitis optica, Multiple sclerosis, Transverse myelitis, Cerebrospinal fluid pleocytosis, Aquaporin 4 auto antibodies*

Introduction

Neuromyelitis optica (NMO) or Devic disease is a rare, inflammatory disorder of the central nervous system. The condition was defined by Dr Eugene Devic, in 1894.[1] The definitive diagnosis of neuromyelitis optica requires the presence of optic neuritis and transverse myelitis. Limited forms of the disease associated with NMO-IgG seropositivity are termed neuromyelitis optica spectrum disorder (NMOSD). Early, accurate diagnosis of neuromyelitis optica or neuromyelitis optica spectrum disorders has major impact on patient treatment outcomes. The choice of therapy should be rationale. Several disease modifying agents used in multiple sclerosis patients should be avoided in neuromyelitis optica because of their apparent lack of efficacy or, in some cases, their potential to exacerbate the disease. Considering the importance of diagnosis of neuromyelitis optica and its treatment implications present study focuses on clinical features,blood investigations, radiological investigations and cerebrospinal fluid examination of neuromyelitis optica and various other features that differentiate it from multiple sclerosis.

Material and Methods

This study is the retrospective,single site study. Total 104 patients were enrolled in study presenting with optic neuritis and/or myelitis from July 2014 to October 2017. All the patient were informed about the design of study and informed consent was taken. Patients were categorised into various groups based on clinical and various diagnostic test. Each patient underwent detailed ophthalmic and neurological evaluation, fundus examination, magnetic resonance imaging scans, cerebrospinal fluid examination, aquaporin 4 antibody test.

Results

Patients categorised into following three groups based on clinical and various diagnostic test

Group 1- Neuromyelitis optica [38 patients]

Group 2- Multiple sclerosis [48 patients]

Group 3- Others [18 patients]

Neuromyelitis optica affects comparatively younger female population as compared to multiple sclerosis as shown in Table 1 and Graph 1 female preponderance of around 76% was found in neuromyelitis optica patients and 70% among multiple sclerosis patients as shown in Table 2 Graph 2.

Table 3 shows, visual recovery was poor in 24 patients out of 38 patients with neuromyelitis optica. Visual recovery was comparatively better in multiple sclerosis, out of 22 patients of multiple sclerosis having visual manifestations, 18 patients had good visual recovery as show in Graph 3. 9 patients having associated macular oedema in neuromyelitis optica while one patient had macular oedema in multiple sclerosis patients.

Table 4 and Graph 4 shows that statistically significant (p value ≤0.05) difference was present in overall average, between extensive longitudinal cord lesions of patients seropositive and seronegative for aquaporin 4. Relapse rate of 0.001 was also statistically significant (p value ≤0.05) difference present in overall average between patients who tested positive and negative on Aquaporin 4. Favourable response to steroids was present in 55% of patients ,30% of patients were treated by plasmapheresis,15% patients treated by immunosuppressive therapy (Table 5 and Graph 5). Patients with multiple sclerosis received steroids, relapsing forms of MS received interferon or glatiramer acetate as a first-line therapy.

Discussion

Neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorders (NMOSD) are inflammatory disorders of the central nervous system characterized by severe, immune-mediated demyelination and axonal damage predominantly targeting optic nerves and spinal cord. Traditionally considered a variant of multiple sclerosis, Now neuromyelitis optica is recognized as a distinct clinical entity based on unique immunologic features. The disease specific serum NMO-IgG antibody that selectively binds aquaporin-4 (AQP4) has led to increased understanding of a diverse spectrum of disorders.

Optic neuritis (ON) is a disorder of the optic nerve, characterised by acute inflammation and presenting with sudden onset monocular visual loss and ocular pain in young adults, more commonly in women. It is a common initial manifestation of multiple sclerosis (MS).[2] When optic neuritis occurs, brain magnetic resonance imaging (MRI) often demonstrates demyelination lesions.[3]

Multiple sclerosis (MS) is a chronic autoimmune disease characterized by inflammation, demyelination, gliosis scarring, and neuronal loss. Attacks of optic neuritis in neuromyelitis optica can be bilateral (rare in multiple sclerosis) or unilateral; myelitis can be severe and transverse (rare in multiple sclerosis) and is typically longitudinally extensive, involving three or more contiguous vertebral segments as shown in Figure 1. NMO was initially considered to be a monophasic disease but recently more than 80% of cases NMO is a relapsing disease.[4,5]

Neuromyelitis optica spectrum disorders encompasses forms of NMO that do not satisfy the 2006 criteria of neuromyelitis optica. Isolated unilateral or simultaneous bilateral or recurrent optic neuritis (ON); isolated or recurrent transverse myelitis (TM); typical neuromyelitis optica brain lesions (corpus callosum, hypothalamus, brainstem, periventricular) with or without detectable anti AQP4-IgG autoantibody and seropositive patients with NMO Ig G having myelitis associated with collagen vascular disorders and many more are also loosely termed as neuromyelitis optica spectrum disorders(NMOSD).[6]

Neuromyelitis optica has variable prevalence. It had previously been suggested that neuromyelitis optica has ethnical predilection for nonwhites.[7-12] About 15% to 57% of central demyelinating diseases in African–American, Japanese, and Indian populations were consistent with

Table 1: Age distribution of patients

	Neuromyelitis optica [%]	Multiple sclerosis [%]	Others [%]
11-30	74%	68%	46%
31-50	20%	27%	40%
51-70	6%	5%	14%

Table 2: Sex distribution of patients

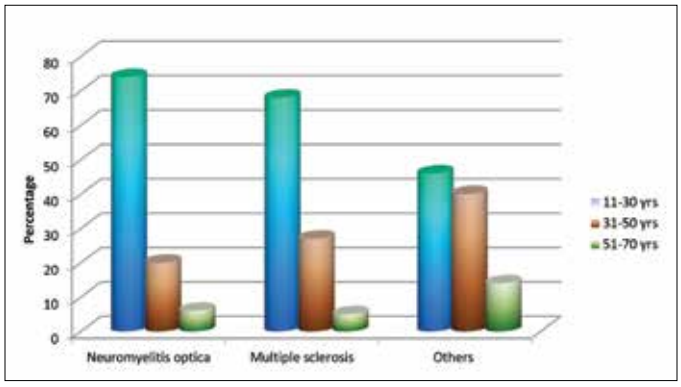
Sex of patient	Neuromyelitis optica [%]	Multiple sclerosis [%]	Others [%]
Male	24%	30%	42%
Female	76%	70%	58%

Table 4: Aquaporin 4 serology testing of NMO cases

Parameters	Seropositive for aquaporin 4	Seronegative for aquaporin 4	p value <0.05 is significant
Extensive longitudinal cord lesions	5.66 ± 4.9	1.90 ± 2.5	<0.001
Relapse rate	5.05 ± 4.4	2.0 ± 1.7	0.001

Table 5: Treatment outcome of neuromyelitis optica patients

Mode of treatment	Response to treatment (%)
Steroids	55%
Plasmapheresis	30%
Immunosuppressive therapy	15%

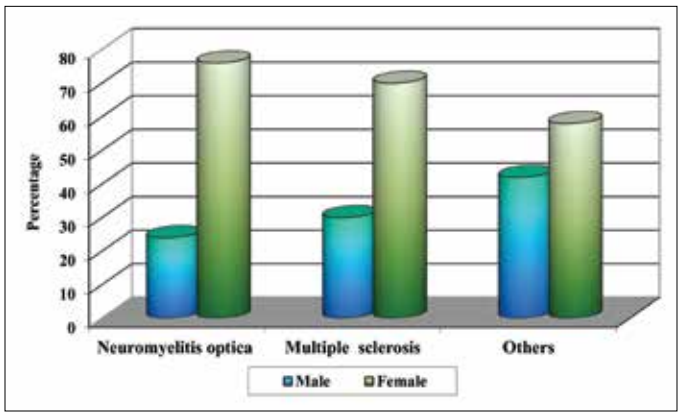


Graph 1: *Age distribution of patients*

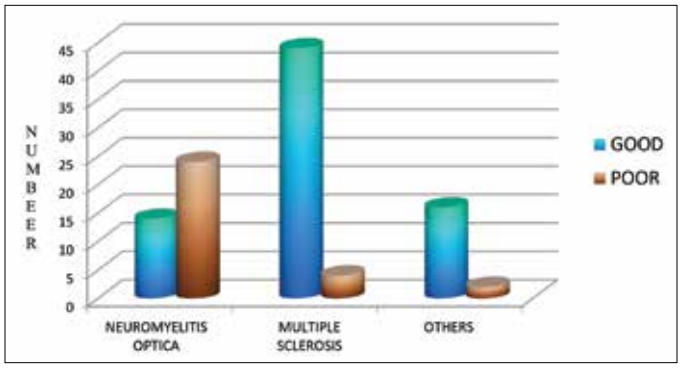
Table 3: Ocular and CNS manifestations of patients presenting with optic neuritis or myelitis or both

	Fundus Optic Neuritis			Myelitis	MRI Affecting segments		Aquaporin 4	CSF [leucocytes]			Visual outcome	
	B	U	OP		CONTIGUOUS SEGMENTS			Per cu mm		OB	GOOD	POOR
					<3	>3		<50	>50			
Neuromyelitis optica [38]	12	13	10	32	16	22	33	8	30	-	14	24
Multiple Sclerosis [48]	8	14	2	26	46	-	-	43	-	41	44	4
Others [18]	-	2	6	10	17	1	-	18	-	-	16	2

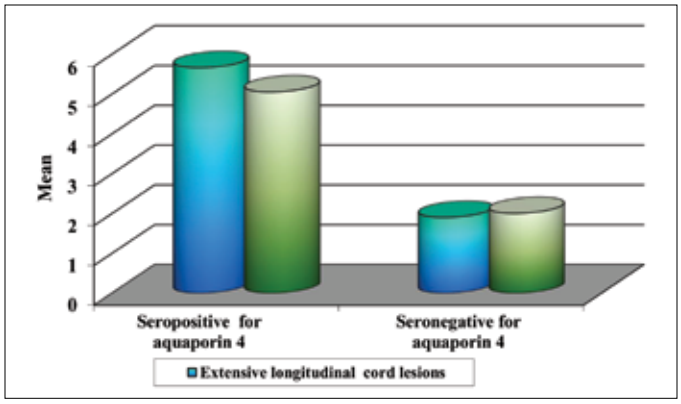
B-bilateral optic neuritis,U-unilateral optic neuritis, OP-ocular pain OB-oligoclonal bands



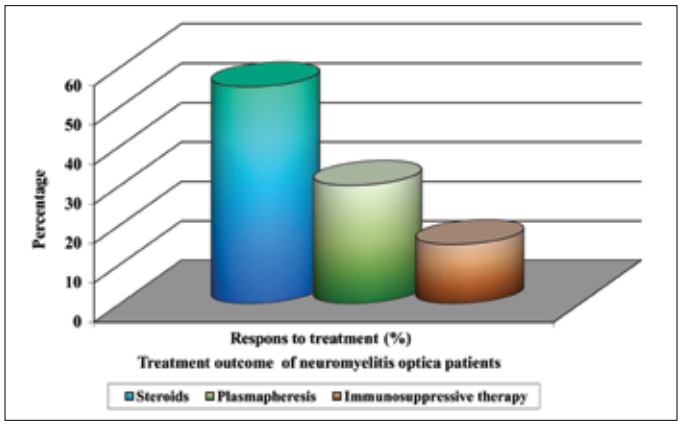
Graph 2: *Sex distribution of patients*



Graph 3: *Visual Outcome of Patients*



Graph 4: *Aquaporin 4 Serology of Neromyelitis Optica Patients*



Graph 5: *Treatment response of neuromyelitis optica patients*

neuromyelitis optica while this disease comprised less than 2% of demyelinating diseases of the CNS in Caucasians.[9-12] In Asian countries, however, neuromyelitis optica, often called optico-spinal MS (OSMS) constitutes 15–40% of all MS forms.[13]

Isolated optic neuritis (ON) is a common presenting sign in neuromyelitis optica and multiple sclerosis (MS) as shown in Figure 2. Multiple sclerosis patients recover significant visual acuity following optic neuritis, neuromyelitis optica patients often manifest severe visual loss. The mechanisms behind these distinct clinical outcomes was elucidated after the discovery of a highly specific serum immunoglobulin G autoantibody (AQP4-IgG) that targets AQP4, the major plasma membrane water channel on astrocytes, suggested AQP4 as a specific immunologic target in neuromyelitis optica optic neuritis.[13,14]

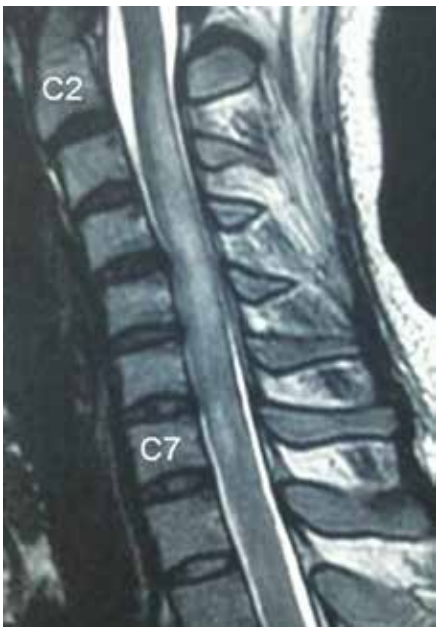


Figure 1: *MRI spine showing longitudinally extensive increased signal intensity of spinal cord from C2 to C7 on T2-weighted imaging*

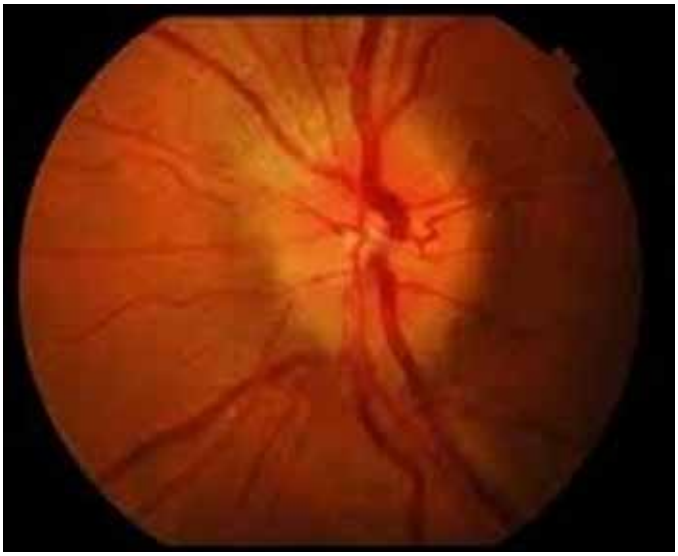


Figure 2: *Fundus photographs showing optic neuritis*

Neuromyelitis optica spectrum disorders optic neuritis and multiple sclerosis optic neuritis is different ; bilateral involvement is more common, and recurrent optic neuritis and severe residual visual dysfunction more likely in former.[15-20] Common MRI imaging features include lesions extending over one-half the length of the optic nerve, posterior nerve involvement, and chiasmal inflammation.[21,22]
Merle et al in 2008 showed that there was more substantial peripapillary retinal nerve fiber layer loss in on optical coherence tomography in neuromyelitis optica than multiple sclerosis optic neuritis.[23]
Raz et al in 2010 showed that bitemporal or homonymous visual field defect occurred in neuromyelitis optica optic neuritis due to potential to involve the optic chiasm and tracts.[24]
Fernandes et al in 2012 showed that neuromyelitis optica optic neuritis generally causes more severe visual field defects than multiple sclerosis optic neuritis. They also found that there was significant thickening of inner nuclear layer in neuromyelitis optica optic neuritis compared to multiple sclerosis.[25]
Gelfand et al in 2012 recognised microcystic changes in inner retinal layer in 25% of neuromyelitis optica patients.[26]
Relapsing–remitting form constitutes 80-90% of cases and thus more frequent than the monophasic.[5,27-28] Prognostic factors for a relapsing course are female gender, older age at onset, a benign first myelitis attack, longer interval between the first two episodes (more than six months).[29] Monophasic neuromyelitis optica has less predilection for females, has a less significant respiratory involvement and has a lower mortality rate than the relapsing form.[30] Relapsing–remitting neuromyelitis optica has been considered initially as a aggressive form of multiple sclerosis. Even though the clinical appearance of the two diseases are similar, in particular at onset when patient may have optic neuritis or myelitis, the neuroradiologic and pathological features are considerably different.[31] Furthermore, a progressive course rarely occurs in neuromyelitis optica, while it is the natural course in most multiple sclerosis patients, indicating a different pathogenic mechanism of CNS damage.[6] The presence of antibodies directed against AQP4 in sera of patients affected by neuromyelitis optica disease has greatly contributed to differentiate neuromyelitis optica from multiple sclerosis. Neuromyelitis optica is similar to multiple sclerosis in that the body's immune system attacks the myelin surrounding nerve cells. Unlike multiple sclerosis the attacks are not believed to be mediated by the immune system's Tcells, but rather by antibodies called NMO-IgG. These antibodies target the protein aquaporin 4 in the cell membrane of astrocytes which acts as a channel for the transport of water across the cell membrane.[32]
Thus, we now consider neuromyelitis optica as a syndrome with a wide spectrum of clinical manifestations, from classical defined neuromyelitis optica to isolated longitudinally extensive transverse myelitis, isolated recurrent optic neuritis, or optic neuritis and longitudinally extensive transverse myelitis associated with systemic autoimmune diseases such as Systemic Lupus Erythematosus.[6]
A revised set of diagnostic criteria for neuromyelitis optica was proposed in 2006 by Mayo clinic. These new guidelines require two absolute criteria plus at least two of three supportive criteria.[33]
In 2015 a new review was published by an international panel refining the previous clinical case definition but leaving the main criteria unmodified.[34]

Absolute criteria:
1. acute myelitis
2. optic neuritis

Supportive criteria:
1. Spinal cord MRI with continuous T2-weighted signal abnormality extending over three or more vetebral segments, indicating a relatively large lesion in the spinal cord
2. Brain MRI not meeting criteria for multiple sclerosis at disease onset
3. NMO-IgG seropositive status

Neuromyelitis optic common in Africans and Asians while multiple sclerosis is common in white races. Simultaneous or successive and severe involvement of optic nerves and spinal cord present in neuromyelitis optica while confluent involvement is absent in multiple sclerosis. Longitudinal extension involving ≥3 spinal cord segments and CSF WBCs >50 cells/mm3 is is an important feature of neuromyelitis optica while in multiple sclerosis longitudinal involvement is always <3 segments and CSF WBCs <50 cells/mm3. Oligoclonal bands in CSF seen in 85% patients of multiple sclerosis patients.
Patients who fulfill neuromyelitis optica criteria but do not have detectable AQP4-IgG pose a diagnostic challenge[35]. A major proportion of patients with neuromyelitis optica who have monophasic disease appear to be AQP4-IgG-seronegative compared to those with established relapsing disease.[36] Few patients with clinical characteristics of neuromyelitis optica and AQP4- IgG-seronegative have detectable serum myelin oligodendrocyte glycoprotein (MOG) antibodies and might have different characteristics from those with AQP4-IgG.[37,38] These findings might suggest that some AQP4-IgG seronegative patients with clinical and neuroimaging features of neuromyelitis optica spectrum disorders have a different pathogenesis. The role of MOG or other antibodies in disease pathogenesis remains to be elucidated.[36]
First line therapy of neuromyelitis optica consists of intravenous methylprednisolone 1 gm daily for 5 days followed by oral steroids. For steroid unresponsive attacks treatment given is plasma exchange. For prevention of relapses immunosuppressant medications like azathioprine, mycophenolate, and rituximab. Recent studies suggest first line monotherapy for neuromyelitis optica with azathioprine or mycophenolate or rituximab or prednisolone.
Methylprednisolone, plasmapheresis and immunosuppressants play role in management of neuromyelitis optica while management of multiple sclerosis consists of methylprednisolone and immunoglobulins. Interferon can worsen neuromyelitis optica, but

comparatively helpful in multiple sclerosis.[6]
Natalizumab it is an integrin inhibitor worsens neuromyelitis optica while it is beneficial as escalation therapy in multiple sclerosis[35] Fingolimod worsens neuromyelitis optica[39] and has beneficial role in the treatment of relapsing-remitting multiple sclerosis by its unique immunoregulatory properties.[39] Thus subtle differences exist between treatment of both disease.

Conclusion

In our study it was found that there is more significant positive relation between longitudinally extensive transverse myelitis and relapse rate with Aquaporin 4 positivity. There was female predominance in neuromyelitis optica patients. Considerable overlap exists between neuromyelitis optica and multiple sclerosis, both have to be differentiated because both diseases have different treatment guidelines.

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