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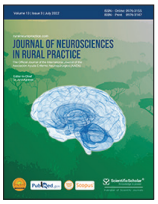

Original Article

Clinical and radiological spectrum of acquired inflammatory demyelinating diseases of the central nervous system in a tertiary care center

Yellaturi Sivaroja[1], P. R. Sowmini[1], K. Muralidharan[1], P. G. Pavan Kumar Reddy[1], K. Mugundhan[1]

[1]Department of Neurology, Government Stanley Medical College Hospital, Chennai, Tamil Nadu, India.

ABSTRACT

Objectives: Demyelinating diseases of central nervous system (CNS) are a broad spectrum of conditions with autoimmune process against myelin. In a resource limited country like India, it is imperative to perform proper clinical evaluation, neuroimaging to differentiate among various categories of CNS demyelinating diseases to decide regarding further workup and treatment. The objective of our study was to determine clinical presentation, imaging findings, serology results, diagnosis, and treatment outcome of primary demyelinating disorders of CNS.

Materials and Methods: In this prospective study, a total of 44 patients were enrolled over a period of 1 year. After proper evaluation, patients were categorized into different groups applying newer diagnostic criteria. Patients were treated with steroids, appropriate immunomodulatory therapy, and outcomes were analyzed.

Results: The majority of cases were of neuromyelitis optica spectrum disorder (NMOSD) (45.5%) with an overall female-to-male ratio of 3.4:1 and mean age of presentation was 30.5 ± 11.15. Myelitis (52.3%) followed by optic neuritis (45.5%) was the most common initial presentation. The most common site of involvement on magnetic resonance imaging was the spinal cord (particularly the cervicodorsal cord). The majority showed good response to therapy (77.27%) and two patients did not survive.

Conclusion: Higher disability observed among seropositive NMOSD patients warrants aggressive treatment during the first attack itself. It is important to suspect myelin oligodendrocyte glycoprotein antibody disease in patients with preceding viral infection. A good outcome in the majority is likely due to the availability of serological assays and aggressive immunomodulatory therapy.

Keywords: Neuromyelitis optica, Multiple sclerosis, Myelin oligodendrocyte glycoprotein

INTRODUCTION

Central demyelinating diseases are a group of heterogeneous conditions with autoimmune mechanism directed against central nervous system (CNS) myelin. The spectrum of primary inflammatory demyelinating disorders is broad including multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), idiopathic optic neuritis (ON), acute disseminated encephalomyelitis (ADEM), myelin oligodendrocyte glycoprotein antibody disease (MOGAD), and clinically isolated syndrome (CIS). There has been an increase in the overall prevalence of demyelinating disorders in the past decade. Available data suggest a rise in the prevalence of MS to 2.8 million in 2020 from 2.3 million in 2013 worldwide.[1] The non-white population has a higher prevalence of NMOSD compared to the white population.[2] With the advent of reliable antibody assays like anti-aquaporin-4, the diagnosis of primary CNS demyelinating diseases has improved. Another significant development is the availability of live cell based assays for anti-MOG antibodies detection in the past decade enabling the reclassification of patients with myelitis and ON who were previously labeled as seronegative NMOSD.[3] In India, the availability of magnetic resonance imaging (MRI) has become widespread in the past decade which has led to better diagnosis and management. However, there is still a dearth of data regarding primary CNS demyelinating disorders in India compared to its western counterparts. In particular, there are only a few studies that comprehensively include all the categories of primary CNS demyelinating disorders put together, as the majority of currently available studies have

***Corresponding author:** Yellaturi Sivaroja, Department of Neurology, Government Stanley Medical College Hospital, Chennai, Tamil Nadu, India. rojayellaturi@gmail.com

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taken individual diagnostic category into consideration. It is important to understand the clinical spectrum and differentiate among various categories of CNS demyelinating diseases as their treatments can be different. In a resource limited country like ours, it is imperative to perform a proper clinical evaluation and neuroimaging to make decisions regarding further serological workup. Furthermore, in the seronegative cases, careful history, examination, and imaging guide the diagnosis, management, prognostication, and long-term immunomodulatory treatment strategies. The objective of this study was to determine the clinical presentation, cerebrospinal fluid (CSF) analysis findings, imaging findings, serology results, diagnosis, and treatment outcome of primary inflammatory demyelinating disorders of the CNS.

MATERIALS AND METHODS

Study design and participants

This prospective study was conducted at the Department of Neurology, Government Stanley Medical College Hospital, a tertiary care hospital in Chennai, Tamil Nadu. During the one year study period, a total of 44 patients with primary inflammatory demyelinating diseases of CNS with ages more than 13 years were enrolled in the study. Written informed consent was obtained from all the participants. These included both new-onset cases and recurrences. Patients with secondary causes such as infectious diseases, granulomatous diseases, other systemic autoimmune conditions, inherited myelin disorders, hypoxic, toxic, and metabolic disorders were excluded from the study. This study design was approved by the Institutional Ethics Committee.

Method

Every patient was subjected to a detailed history taking, neurological and ophthalmological examination. In addition to routine blood investigations, other required investigations such as enzyme-linked immunosorbent assay for human immunodeficiency virus; hepatitis B antigen and hepatitis C virus antibody; venereal disease research laboratory test for syphilis; autoimmune/vasculitis workup; CSF analysis for cell count, cytology, and oligoclonal bands; serum anti-aquaporin 4 and anti-MOG antibody; visually-evoked response evaluation; and MRI of brain including optic nerves and spine (with and without contrast) were performed. MS patients were diagnosed using revised 2017 McDonald diagnostic criteria and NMOSD cases by International Consensus Diagnostic Criteria for NMOSDs. To avoid bias, all the patients fulfilling the appropriate diagnostic criteria during the study period without having secondary causes were included in the study but the sampling is not random. Patients were subsequently categorized into the following diagnostic groups after evaluating and applying appropriate diagnostic criteria:

1. ADEM
2. MS
3. NMOSD
4. MOGAD
5. Recurrent seronegative ON
6. CIS

All the patients were treated acutely with intravenous methylprednisolone 1 g for five days and followed up with tapering doses of oral steroids. Based on the severity of initial presentation, patients with NMOSD were started either on mycophenolate mofetil 1–2 g/day in two divided doses or rituximab at a dose of 375 mg/m^2 weekly for 4 weeks or 2 infusions of 1 g 2 weeks apart for maintenance therapy. None of the patients either new or recurrent were started on azathioprine. Patients who were already on azathioprine from elsewhere and presented to us with recurrence were made to discontinue azathioprine and started on an alternate regimen. The majority of patients with relapsing remitting type of MS were started on interferon beta 1a intramuscularly at a dose of 30 μg weekly and remaining MS patients on either azathioprine or mycophenolate mofetil. The majority of patients, who had recurrences while on azathioprine, were changed either to mycophenolate mofetil or rituximab. Medical research council grading of power was recorded on admission. Modified Rankin scale and visual acuity measurements were used to determine the outcome at discharge.

Statistical analysis

Data was entered into a Microsoft Excel sheet and analyzed using statistical software Statistical Package for the Social Sciences v 16. Qualitative variables were presented with their frequency distribution. Quantitative variables were summarized in their mean ± standard deviation (SD) or median and interquartile range. The association between qualitative variables was evaluated with the χ^2 test (Chi-square) or Fisher's exact test. The quantitative variables were analyzed using the Student's *t*-test (in comparisons of one variable with two categories) and/or the analysis of variance. $P < 0.05$ was considered to be statistically significant.

RESULTS

Demographic data

A total of 44 patients with primary CNS demyelinating disease were included in our study. The majority of cases were of NMOSD ($n = 20$, 45.5%) [Table 1] with a total female-to-male ratio of 3.4:1, and the mean age of presentation was 30.5 ± 11.15 (mean ± SD) [Table 1].

Table 1: Distribution based on etiology, sex, and age.

	Group												Total *n*=44	
	A (NMOSD) *n*=20		B (MS) *n*=10		C (MOGAD) *n*=7		D (ADEM) *n*=3		E (Seronegative ON) *n*=2		F (CIS) *n*=2			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Sex														
Female	16	80	10	100	3	42.9	1	33.3	2	100	2	100	34	77.3
Male	4	20	-	-	4	57.1	2	66.7	-	-	-	-	10	22.7
Mean age±SD	30.90±11.74		32±11.30		29±10.34		22.33±9.07		27.50±6.36		29.50±21.92		30.5±11.15	
Total percentage	45.5		22.7		15.9		6.8		4.5		4.5		100	

NMOSD: Neuromyelitis optica spectrum disorder, MS: Multiple sclerosis, MOGAD: Myelin oligodendrocyte glycoprotein antibody disease, ADEM: Acute disseminated encephalomyelitis, ON: Optic neuritis, CIS: Clinically isolated syndrome

Clinical presentation

Among the 44 patients, the current presentation was a recurrence in 16 (36.4%) patients, who in the past had one or more demyelinating episodes. The 11 out of these 16 patients developed recurrence while being on maintenance therapy, with 10 patients on azathioprine and one patient on rituximab. Majority of patients presented with myelitis (*n* = 23, 52.3%) as the initial manifestation, followed by ON (*n* = 20, 45.5%), whereas both ON and myelitis together in 9 (20.5%) patients [Table 2]. Overall, 16 (47.1%) out of 34 female and 4 (40%) out of ten male patients presented with ON. Myelitis was initial presentation in 15 (44.1%) out of 34 female and 8 (80%) out of ten male patients.

Laboratory investigations

CSF analysis showed elevated protein in 27 (61.3%) patients. Out of the ten MS criteria fulfilled patients, 4 (40%) showed CSF oligoclonal body positivity. Serum anti-aquaporin 4 antibody testing was positive in 15 (75%) out of 20 NMOSD patients and total seven patients came positive for serum anti MOG antibody. Visually-evoked potential (VEP) abnormality was detected in 24 (54.5%) patients out of which only 20 patients presented clinically with ON and the remaining four patients had asymptomatic VEP changes.

Radiological findings

The most common site of involvement on the MRI is the spinal cord in 29 (65.9%) patients followed by cerebral white matter in 20 (45.5%) patients [Table 3]. In the NMOSD group, cord involvement is the most common finding in 18 (90%) out of 20 patients. The most common radiological finding in the MS group is cerebral white matter lesions seen in 9 (90%) out of ten patients.

Patient outcome

Among the 44 patients, 34 (77.27%) showed good response to therapy, 6 (13.6%) showed moderate response, 2 (4.54%) showed poor response, and 2 (4.54%) did not survive. In the NMOSD group, 15 (75%) out of 20 showed good improvement, 4 (20%) showed moderate improvement, and 1 (5%) patient did not survive. In the MS group, 7 (70%) out of 10 showed good improvement with treatment, 2 (20%) showed moderate improvement, and 1 (10%) showed poor response.

DISCUSSION

In this study, we profiled patients with primary CNS demyelinating disease presenting to our tertiary care hospital into different diagnostic categories. NMOSD (*n* = 20) was found to be the most common group constituting about 45.5% followed by MS (*n* = 10) accounting for 22.7% of the cases. Manisha *et al*. in a single-center Indian study similarly reported preponderance of NMOSD over MS.[4] This is also similar to data from other Asian counterparts, which showed a higher prevalence of NMOSD compared to the western population.[2]

Overall, the mean age of presentation in our study was 30.5 ± 11.15, which is similar to results from other Indian and western population studies.[4-6] Among all the groups, patients with ADEM showed a younger age of onset (22.33 ± 9.07), which might be due to the usual common occurrence of ADEM in children and younger adults compared to older adults.[7] In our study, the NMOSD group showed younger (30.90 ± 11.74) mean age of onset compared to patients with MS (32 ± 11.30). A similar trend was seen in an Indian study by Manisha *et al*. and another multicenter cross-sectional South American study.[4,6] However, Indian studies by Nayak *et al*. and Pandit and Kundapur showed a higher age of onset in the NMOSD group compared to MS.[5,8] Likewise, other major hospital-based studies from Asia and worldwide

Table 2: Distribution based on clinical parameters.

Clinical parameter	Group												Total *n*=44	
	A (NMOSD) *n*=20		B (MS) *n*=10		C (MOGAD) *n*=7		D (ADEM) *n*=3		E (Seronegative ON) *n*=2		F (CIS) *n*=2			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Recurrent demyelination	6	30	8	80	-	-	-	-	2	100	-	-	16	36.4
First episode	14	70	2	20	7	100	3	100	-	-	2	100	28	63.6
History of preceding infection	3	15	1	10	5	71.4	2	66.6	-	-	-	-	11	25
Optic neuritis	11	55	4	40	2	28.6	1	33.3	2	100	-	-	20	45.5
Myelitis	16	80	-	-	5	71.4	2	66.7	-		-	-	23	52.3
Optic neuritis+myelitis (in same patient)	7	35	-	-	1	14.3	1	33.3	-	-	-	-	9	20.5
Weakness (other than myelitis)	-	-	3	30	-	-	-	-	-	-	-	-	3	6.81
Sensory disturbance (other than myelitis)	1	5	3	30	-	-	-	-	-	-	-	-	4	9.09
Cranial nerve involvement (other than optic nerve)	1*	5	-	-	-	-	-	-	-	-	1*	50	2	4.54
Ataxia	2	10	3	30	-	-	-	-	-	-	1	50	6	13.6
Area postrema syndrome	3	15	-	-	-	-	-	-	-	-	-	-	3	6.81
Altered sensorium	1	5	-	-	1	14.3	2	66.7	-	-	-	-	4	9.1
Mortality	1	5	-	-	-	-	1	33.3	-	-	-	-	2	4.54

*Trigeminal nerve involvement, NMOSD: Neuromyelitis optica spectrum disorder, MS: Multiple sclerosis, MOGAD: Myelin oligodendrocyte glycoprotein antibody disease, ADEM: Acute disseminated encephalomyelitis, ON: Optic neuritis, CIS: Clinically isolated syndrome

Table 3: Distribution based on site of lesion on MRI.

Site of lesion on MRI	Group												Total *n*=44	
	A (NMOSD) *n*=20		B (MS) *n*=10		C (MOGAD) *n*=7		D (ADEM) *n*=3		E (Seronegative ON) *n*=2		F (CIS) *n*=2			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Spinal cord (anywhere in the cord)	18	80	3	30	6	85.7	2	66.7	-	-	-	-	29	65.9
Cervical cord	8	40	3	30	2	28.6	-	-	-	-	-	-	13	29.5
Cervicodorsal cord	7	35	-	-	2	28.6	1	33.3	-	-	-	-	10	22.7
Dorsal cord	2	10	-	-	1	14.3	-	-	-	-	-	-	3	6.8
Whole cord	1	5	-	-	1	14.3	1	33.3	-	-	-	-	3	6.8
Cerebral white matter	5	25	9	90	1	14.3	3	100	2	100	-	-	20	45.5
Brainstem	7	35	4	40	1	14.3	-	-	-	-	2	100	14	31.8
Cerebellum	3	15	3	30	-	-	-	-	-	-	2	100	8	18.2
Optic nerve	3	15	2	20	-	-	1	33.3	1	50	-	-	7	15.9

NMOSD: Neuromyelitis optica spectrum disorder, MS: Multiple sclerosis, MOGAD: Myelin oligodendrocyte glycoprotein antibody disease, ADEM: Acute disseminated encephalomyelitis, ON: Optic neuritis, CIS: Clinically isolated syndrome, MRI: Magnetic resonance imaging

prevalence studies also showed younger clinical disease onset in MS compared to NMOSD in contrast to our study.[9-11]

Overall, female preponderance (n = 34, 77.3%) observed in our study is a usual finding for the primary CNS demyelinating disorders. The female preponderance in immune-mediated CNS inflammatory diseases is likely due to a complex interplay of factors like genetic, epigenetic effects, hormonal, and indirect modulation of microbiome.[12] The female-to-male ratio in the NMOSD patient group was 4:1 which was in acceptance with the results from other Indian studies.[13,14] All the ten MS patients in our study cohort were female (100%) which was very high compared to gender ratios seen in other MS epidemiology studies from India.[15,16] Unlike other categories, there is a slight male preponderance (57%) in the MOGAD group. Data from multicenter studies by Jarius *et al*. and Ramanathan *et al*. showed slight female preponderance in MOGAD patients.[17,18] However, the appropriate conclusion could not be drawn regarding the male majority in our

MOGAD group, keeping in mind the small number (n = 7) of patients in this group.

In our study, an infectious prodrome was reported in 11 (25%) patients. Compared to other categories, a significant proportion of patients with MOGAD (n = 5, 71.4%) had a preceding infection. Several other studies also showed a similar higher occurrence of infection preceding the demyelinating episode in MOGAD patients ranging from 30–70% compared to 15–30% in NMOSD patients.[19-21] The underlying mechanism is the infectious prodrome leading to the stimulation of autoimmune pathology by molecular mimicry, bystander activation, and epitope spreading.[22] In MOGAD, there is also an additional activation of Toll-like receptor by viruses, converting the MOG-specific B-cells into plasmablasts that secrete MOG antibodies.[23]

Overall, the most common presentation was myelitis (52.3%) followed by ON (45.5%) similar to results from other studies.[4,5] In both males and females, the most common presentations were ON and myelitis. Many of the patients were polysymptomatic especially ON and myelitis together seen in 9 (20.5%). Among the nine patients with such opticospinal syndrome, the majority (n = 7) belonged to the NMOSD group.

In the NMOSD group, myelitis was seen in 16 (80%) patients, ON in 11 (55%) patients, and both together in 7 (35%) patients. These results were very much similar to another Indian hospital-based cohort.[24] One of the NMOSD patients, who presented with altered sensorium, was a known Aquaporin 4 positive NMOSD patient with three relapses in the past, and she was on rituximab therapy. She had a history of gradually worsening cognitive disturbances over a period of two years, and this patient ultimately did not survive after being bedridden for two months. Her MRI brain showed progressive (compared to previous images) cortical and subcortical atrophy of the cerebral cortex predominantly involving temporal lobes. She was extensively evaluated for other treatable causes of dementia including screening for malignancies, autoimmune encephalitis profile, CNS, and systemic infections which all came out negative. Cognitive impairment in NMOSD is not as well described as in MS. The unique dynamics shown by AQP4-IgG may cause significant diffuse cortical neuronal loss resulting in neurodegeneration independent of clinical attacks.[25] Disruption of glutamate and water homeostasis lead to excitotoxicity with subsequent release of several neurotoxic factors triggering neurodegeneration. According to a meta-analysis done by Meng *et al*., NMOSD patients performed significantly poorly on various cognitive tests.[26]

Out of the 20 patients who met the criteria for NMOSD, 15 (75%) patients showed aquaporin 4 seropositivity only 5 (25%) were double seronegative. This detection rate was higher compared to other Indian studies probably due to the increased awareness and widespread availability of aquaporin 4 and MOG antibody assays.[27] Comparatively, aquaporin 4 positive patients showed higher female preponderance and more disability than seronegative patients, which is in acceptance with observations from studies by Pandit *et al*. and Kunadison *et al*.[28,29]

Most of the MS patients (80%) were of relapsing remitting MS type similar to other Indian studies.[30] None of the MS patients had features of myelitis at present, although they showed evidence of spinal cord involvement on imaging. In the MS group, 90% of the patients showed cerebral white matter lesions, and in a few of these patients, coexistent MS typical spinal cord lesions helped in differentiating from other radiological mimics of MS-like stroke.[31] The majority of NMOSD patients have been suspected to show longitudinally extensive spinal cord involvement on MRI, particularly cervicodorsal cord with rostral extension into the medulla. In three cases, this rostral extension characteristic of NMOSD was helpful in differentiating from other causes of longitudinally extensive myelitis.[32] The majority (85.7%) of patients with MOGAD showed spinal cord involvement on MRI but unlike the previous studies which showed prominent thoracolumbar and conus medullaris involvement; our patients showed predominant cervicodorsal cord involvement.[33,34]

Limitation

The results cannot be generalized with this study being a hospital-based study with a small sample size. The number of patients in each group is unequal, which precludes a more robust statistical analysis.

CONCLUSION

In this article, we have given an overview on CNS inflammatory demyelinating diseases in Southern India, particularly for MS and NMOSD. The NMOSDs are a common cause of demyelinating illnesses in this region like other Asian counterparts but with a younger age of onset compared to MS, unlike other previous studies. Seropositive NMOSD patients showed higher disability compared to aquaporin-negative patients warranting the need to treat these patients with a more aggressive approach even during the first attack. A higher proportion of MOGAD patients having preceding viral infection helps in identifying such patients to undergo MOG antibody testing. Most of the patients in our cohort showed good outcome, and this is likely due to the ready availability of serological assays and also the treatment with aggressive immunomodulation from the beginning. Further studies with long-term follow-up would help contrast and compare outcomes.

Ethical approval

The research/study approved by the Institutional Review Board at GOVERNMENT STANLEY MEDICAL COLLEGE AND HOSPITAL, number EC/NEW/INST/2020/461, dated 27-10-2021.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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