Original Article

Clinical Features, Gender Differences, Disease Course, and Outcome in Neuromyelitis Optica Spectrum Disorder

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Abstract

Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is an astrocytopathy with a predilection for the optic nerve, spinal cord, and brainstem. In this ambispective study, we evaluate clinical characteristics, responses to therapy, and disability outcomes in patients with NMOSD. **Methods:** Patients diagnosed as NMOSD and following up for at least 1 year at a tertiary care center in India were recruited. Patient data were collected ambispectively from January 2012 until December 2018. **Results:** A total of 106 patients (29M/77F) with NMOSD were evaluated. The mean age of onset was 29 (±11.6) years. About 77 patients (72.64%) were positive for the AQP4 antibody. Age of onset was higher for those presenting with an opticospinal syndrome (34.2 years) as compared to either isolated longitudinally extensive transverse myelitis (LETM) (30 years) or optic neuritis (ON) (25.3 years). The most common syndrome at onset was LETM in 57 patients (53.77%) followed by ON in 31 patients (29.24%). Azathioprine was the most common immunotherapy (83.96%) prescribed followed by rituximab (7.54%) and mycophenolate mofetil (1.88%). There was a significant decrease in the number of relapses post-azathioprine ($P < 0.001$). Out of 67 patients with ON, 21 (31.34%) had complete recovery while 17 (25.37%) patients had a severe deficit at a 3-month follow-up. Out of 92 patients with a motor deficit, 49 (53.26%) patients had a partial motor deficit at a 6-month follow-up. The severe visual deficit at baseline and female gender predicted poor visual and motor recovery, respectively. **Conclusion:** This is the largest descriptive study on patients with NMOSD from India. Relapse rates were similar irrespective of the clinical presentation, age, gender, and disease course. Treatment with immunosuppressive treatment significantly affected the disease course.

Keywords: Consensus criteria, neuromyelitis optica, neuromyelitis optica spectrum disorders

Introduction

Neuromyelitis optica (NMO) is an astrocytopathy with a predilection for the optic nerve and spinal cord and was previously considered to be a variant of multiple sclerosis (MS). It was diagnosed based on Wingerchuk criteria (1996) until the discovery of aquaporin-4 antibodies (AQP-4 IgG) in 2006, which led to a revision of the diagnostic criteria in 2006.[1] In 2007, disorders with limited forms of disease or clinical features outside the optic nerve and spinal cord but with positive AQP-4 antibody were labeled as NMOSD (NMO spectrum disorder).[2] In 2015, International Consensus unified NMO and NMOSD as NMOSD based on the presence or absence of the AQP4 antibody and on the assumption that the limited forms will eventually convert to a typical NMO.[3] There are limited studies from India on the phenotypic spectrum of these disorders, their response to therapy, relapse rates, and outcomes.

In this ambispective study, we evaluate and compare clinical characteristics, imaging features, response to therapy, and disability outcomes in patients with NMOSD.

Methods

All patients suspected to have NMOSD as per Consensus criteria (2015)[4] and following up for at least 1 year in the Neurology Department of the All India Institute of Medical Sciences, New Delhi, India were retrospectively collected between January 2012 until June 2015 and prospectively from July 2015 until December 2018. Patients excluded were those with disorders other than NMOSD and tested positive for other antibodies for systemic lupus erythematosus (SLE), Sjogren, sarcoidosis, or other autoimmune disorders and/or who had imaging features suggestive of disorder other than NMOSD. This study was approved by the institutional ethics committee and all patients provided informed consent for the present study.

Details of patient demographics and disease profile were collected including age, age at onset, gender, ethnicity, time from onset to relapse, time and number of attacks until the diagnosis of NMO was made, associated autoimmune disease,

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Submitted: 21-Apr-2020 **Revised:** 03-May-2020 **Accepted:** 24-Aug-2020
Published: 06-Jan-2020

DOI: 10.4103/aian.AIAN_334_20

antibody status, cerebrospinal fluid (CSF) cell count with protein and sugar, visual evoked potentials, magnetic resonance imaging (MRI) findings (site and extent of involvement of spinal cord, normal, or abnormal brain imaging), treatment of acute attacks and extent of its recovery, relapse type and frequency, relapse rates pre- and post-immune modulation and extent of its recovery. Each relapse was documented based on clinical worsening as well as imaging, wherever available. Visual relapses were classified into the following three categories: severe attack defined as visual acuity (VA) 6/60 or worse in the affected eye, moderate attack defined as VA between 6/18 and 6/60, and mild attack defined as VA between 6/12 and 6/18. Visual recovery was assessed on follow-up at 3 months and patients were categorized to have a complete recovery if VA was less than 6/12, mild deficit if VA was between 6/12 and 6/18, moderate deficit if VA was between 6/18 and 6/60, severe deficit if VA was 6/60 or worse in the affected eye. Motor relapse was classified as severe if patients were unable to ambulate even by assistance/walking aid and partially if they could do so. Motor recovery was assessed on follow-up at 6 months and categorized into complete recovery if the patient was able to ambulate independently and partial recovery if the patient needed any assistance/walking aid for ambulation. Change of grade in motor recovery was defined as the change in ambulatory status from either partial to complete or from severe deficit to partial recovery.

All statistical analyses were conducted using Stata (version 14.2). The $\chi 2$-test was used for binary and categorical data. One-way ANOVA, student's *t*-test, and Mann-Whitney U tests were used for continuous variables.

Results

Demographic data

A total of 106 patients with NMOSD were included. The mean age of onset was 29 years (±11.09 years). The majority of the patients were females (72.64%). Seven patients had a concomitant autoimmune disease (three with rheumatoid arthritis [RA], three with Sjogren's disease, and one with sarcoidosis). Nearly 70 patients (66.04%) were positive for the AQP-4 antibody. [Table 1]

Disease presentation and course

Majority of the patients (n = 78) (73.58%) presented with either optic neuritis (ON) (27.36%) or longitudinally extensive transverse myelitis (LETM) (41.51%) or isolated brainstem syndrome (13.21%). Either in isolation or combination with others, 57.55% presented with LETM, 33.97% with ON, and 26.42% with brainstem syndrome [Table 1]. The mean age of onset of patients presenting with ON was significantly younger than those presenting with LETM (25.31 ± 7.43 years versus 30 ± 11.17 years; P = 0.03). [Table 1 & Figure S1]. On average, the diagnosis of NMO was made after two attacks. Within subgroups, the average number of attacks for making the diagnosis was higher for patients presenting with ON (n = 3) as compared to LETM (n = 2), LETM and ON (n = 1), and brainstem (n = 2). Time until the diagnosis of NMO was made was 31.8 months for ON, 23.21 months for LETM, and 21.07 months for brainstem syndrome in isolation or combination. A total of 88 patients had at least one relapse (83.01%). The mean interval between onset of disease and the first relapse was 19.33 months.

Table 1: Baseline characteristics of the patients.

Total number (n)	106
Sex (female: male)	77/29
Age at onset (years): mean (SD)	32.77 years (±11.37 years)
Optic neuritis	25.31 years (±7.43)
LETM	30 (±11.17)
LETM and ON	34.20 (±14.95)
Brainstem	24.71 (±39.58)
Brainstem and LETM	39.58 (±12.22)
Brainstem and ON	14.50 (±0.70)
Coexisting autoimmune diseases, n (%)	7 (6.6%)
Time to first relapse, months: mean (95% CI)	42.5 (32.5-52.4)
Type of attack: at onset, n (%)	
Optic neuritis	29 (27.36)
LETM	44 (41.51)
LETM and ON	5 (4.72)
Brainstem	14 (13.21)
Brainstem and LETM	12 (11.32)
Brainstem and ON	2 (1.89)
Mean time until diagnosis (range)	42.5 months (0-264)
Median no. of attacks until diagnosis made	2

ON: optic neuritis; LETM: longitudinally extensive transverse myelitis

Gender differences

On comparison of males and females (29 versus 77), females were more likely to be seropositive as compared to males (P < 0.01). There were no statistically significant differences between males and females for the age of onset, age of presentation, and a median number of attacks until diagnosis. However, females were diagnosed after a duration of almost two times after the disease onset as compared to males (mean age 27.23 months versus 48.24 months, mean difference 21.01 months, P = 0.06) despite having similar age of onset [Table 2].

Relapse rates

Overall, 25% of cases relapsed within 4.1 months, 50% relapsed within 17.3 months, and 75% relapsed within 42.6 months [Figure 1]. For specific syndromes of ON, LETM, brainstem, and mixed features, the time at which 25%, 50%, and 75% patients relapsed was 6.1,18.3, and 28.4 months for ON; 4.1, 17.1, and 41.6 months for LETM; 3.03, 4.06, and 19.4 months for brainstem and 10.1, 21.3, and 48.7 months for those with mixed features [Figure 2].

Depending on the clinical syndrome at the onset, 14/29 patients who presented with ON at the disease onset had their first relapse as ON and 21/44 patients who presented with LETM

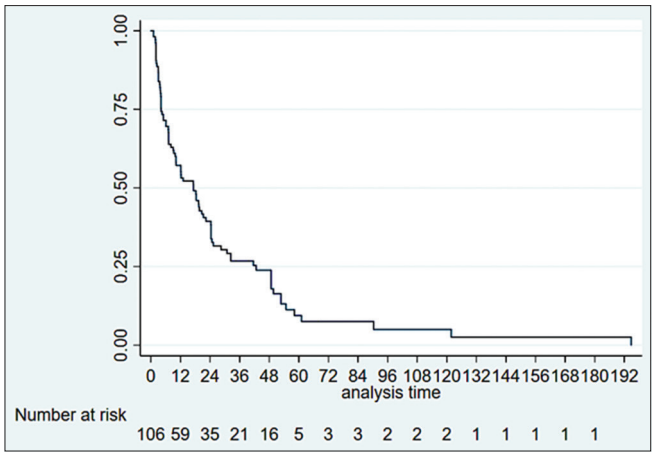

Figure 1: Kaplan-Meier analysis showing the number at risk for relapse with time in the overall population

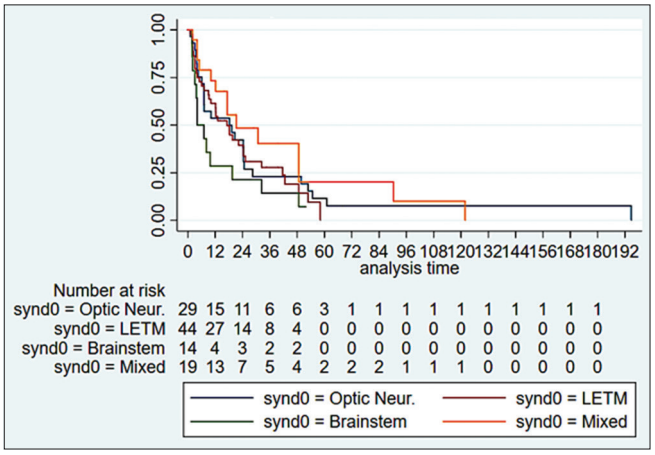

Figure 2: Kaplan-Meier analysis showing the number at risk for relapse with time as per syndrome at onset

Table 2: Gender differences at baseline in the present cohort

	Males (n = 29)	Females (n = 77)	P
Age	34.44 (±10.52)	32.14 (±11.68)	0.17
AQP4 positive	15 (51.72)	55 (71.43)	<0.01
Age of onset	31.79 (10.98)	27.96 (11.02)	<0.01
Syndrome at onset			
Optic neuritis	8 (27.59)	21 (27.27)	
LETM	15 (51.72)	29 (37.66)	
ON+LETM	0 (0)	5 (6.49)	
Brainstem	1 (3.45)	13 (16.88)	
LETM + Brainstem	5 (17.24)	7 (9.09)	
ON + Brainstem	0 (0)	2 (2.60)	0.170
Onset to diagnosis	27.23 (±32.81)	48.24 (±56.16)	0.96
Proportion of patients with any relapse.	23 (79.31)	65 (84.42)	0.38

AQP4: acquaporin 4; ON: optic neuritis; LETM: longitudinally extensive transverse myelitis

at onset had their first relapse as LETM while 4/14 patients who presented with a brainstem syndrome at onset relapsed with another brainstem syndrome. [Figure S2]

Imaging features

All patients underwent spinal cord imaging which showed LETM in cervical region in 17.5% (n = 17), cervico-dorsal region 34.02% (n = 33), dorsal cord 22.64% (n = 22), holocord involvement in 4.12% (n = 4) and was normal in 20.61% (n = 20). Brain imaging was not done in eight patients. Area postrema involvement in isolation or combination was seen in 11 (12.35%) patients, all of whom presented with vomiting. Periaqueductal grey matter was involved in 12 (13.48%) and was normal in three patients. Optic nerve enhancement was seen in 18 (20.22%) patients.

Treatment effects

The total number of acute relapses were 315, of which 233 relapses were treated with injectable or oral steroids, 28 with steroids with plasmapheresis, two with steroids and IVIG while 52 relapses were untreated. Out of the total 106 patients, eleven patients did not receive any long-term immunosuppression and were continued on low dose steroids. Among the remaining 95 patients, 88 patients received azathioprine (AZA), four received mycophenolate mofetil (MMF), out of which two were given MMF de novo while the remaining two received it as a change of therapy from the previous treatment with AZA (AZA was stopped as these patients continued to relapse on a full dose of AZA). Among the 88 patients (83.01%) who received AZA during their clinical course, AZA was stopped in 13 patients (12.26%) due to adverse effects. Eight patients received rituximab (four de novo, three after the failure of AZA, and one after the failure of methotrexate). Four patients also received methotrexate (three as an add on therapy as two had concomitant RA, and one patient had Sjogren's disease while one was started on methotrexate due to financial constraints after developing cytopenia secondary to AZA). One patient received cyclophosphamide.

The mean number of relapses per patient before starting immunosuppression with AZA was 2.85 (95% CI 2.45–3.24) and was reduced to 0.24 (95% CI 0.10–0.39) (P < 0.001). Around 58 out of 80 patients had no relapses after starting AZA over 2.5 years. The mean number of relapses per patient pre- and post-MMF and rituximab were 4 and 0.75 and 2.8 and 0, respectively, and were statistically significant. To compare the average number of relapses per patient per month, the number of relapses of each patient was divided by the number of months of follow up for that patient, separately for AZA free and AZA usage periods. These two incidences were compared pre-usage vs post usage, pair wise, for all the patients with follow up in the two periods and were statistically significant in favor of AZA (0.26 (95% CI 0.19–0.33) relapses per month pre-AZA versus 0.01 (95% CI 0.001–0.021) post AZA use; mean difference 0.25, 95% CI 0.18–0.32; P < 0.001 [Figure 3]. We also found a significant decrease in the number of relapses in a given patient after starting AZA. For instance, out of 23 patients who had at

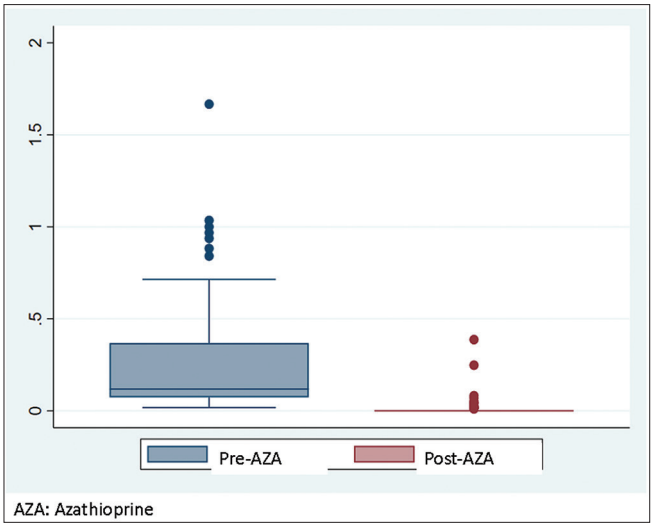

Figure 3: Relapse rates pre and post Azathioprine use in entire cohort

least three relapses before starting AZA, 20 patients did not have any relapse after initiation of AZA, two patients had one relapse, and one patient had one relapse after starting AZA.

Notably, four patients received therapy of MS, before the revision of the diagnosis. Among these, three patients were treated with interferons for a variable duration (4 months to 4 years) but continued to relapse. One patient subsequently received one dose of natalizumab as she continued to relapse on interferon. One patient received dimethyl fumarate for 3 months. All these patients did not respond to MS therapy and were subsequently diagnosed to have NMO and switched to appropriate immunosuppressive treatment.

Treatment-related adverse events were seen in 24 patients (22.6%). Six patients developed steroid-induced adverse effects (four developed cushingoid features, one patient each developed steroid-induced diabetes and osteoporotic fracture of the femur). Transient drug-induced cytopenia was seen in ten patients (eight patients on AZA and two patients on rituximab) while transaminitis was seen in three patients on AZA. Four patients developed tuberculosis (TB) on follow-up, out of which two were on steroids alone, one on AZA, and one patient on maintenance rituximab. All patients have discontinued treatment and were treated successfully with antitubercular therapy. One patient was found to be hepatitis B surface antigen (HBsAg) positive and is on antiviral therapy along with AZA and is doing well. One patient was diagnosed to have chronic myeloid leukemia (CML) and was started on imatinib and is doing well on AZA. None of the patients developed serious adverse effects.

Outcome assessment

Disability

Visual disability

About 67 (63.2%) patients had ON during their clinical course. Out of these 67 patients, 21 (31.34%) patients had a complete recovery, 21 (31.34%) patients were left with the mild deficit, 8 (23.52%) had moderate deficit while 17 (25.37%) patients were left with the severe deficit at 3-month follow-up.

In comparison with the visual deficit at baseline , all patients with a mild deficit ($n = 7$) at baseline had a complete recovery. Among 29 patients with moderate deficit 11 patients had complete recovery (37.93%), 16 patients were left with a mild deficit (55.17%) while two patients continued to have a moderate deficit (6.89%). Among 31 patients with a severe deficit at baseline, three patients had complete recovery (9.67%), five were left with a mild deficit (16.12%), six patients had moderate deficit (19.35%), and 17 patients persisted to have severe deficit (54.83%). [Table S1]

Presence of visual deficit at follow-up was not related to age of onset ($P < 0.01$), gender ($P = 0.103$), syndrome at disease onset ($P = 0.193$), or type of treatment ($P = 0.588$) [Table S2]. Improvement in vision was defined as a change in disability by more than or equal to one grade as compared to baseline deficit. As per this definition, 48 patients (71.64%) had improvement in vision and 19 patients (28.36%) did not have any improvement in vision at a 3-month follow-up. There was no association with age of onset ($P = 0.14$), sex ($P = 0.321$), or type of treatment ($P = 0.34$). However, loss of improvement had a significant association with the visual deficit at baseline ($P < 0.01$) [Table 3]

Motor deficit

A total of 92 patients had motor deficits during their clinical course. About 43 (46.74%) patients had complete recovery while 49 (53.26%) patients were left with the partial motor deficit at a 6-month follow-up. In comparison with the motor deficit at baseline , 31/37 patients (83.78%) with the partial deficit at baseline had complete recovery while 6 (16.21%) continued to have a partial deficit. None of the patients with a severe deficit ($n = 46$) at baseline had a complete recovery, while 36/46 (78.26%) had partial recovery and 10/46 (21.73%) continued to have a severe deficit [Table S3]. Patients with the residual deficit at follow-up had older age of disease onset (not statistically significant, $P = 0.984$), they were more likely to have LETM at disease onset (not statistically significant, $P = 0.221$) and were more likely to be females (statistically significant in females ($P = 0.02$). There was no difference in motor outcome depending on the type of treatment ($P = 0.09$) [Table S4]

Improvement in motor function was defined as a change in disability when compared to the baseline deficit as outlined in the methods section. As per this definition, 76 patients (82.61%) had improved and 16 patients (17.39%) did not have any improvement in motor disability at a 6-month follow-up. There was no association with age of onset ($P = 0.73$), sex ($P = 0.307$), or type of treatment ($P = 0.174$). In comparison with the motor deficit at baseline, 31 among 37 patients (83.78%) with the partial deficit at baseline had improvement. Among 55 patients with a severe deficit, 45 patients had improvement (81.81%) while ten patients did not show any improvement (18.18%). [Table 4]

Table 3: Predictors of no visual improvement (n = 19)

		OR(95%CI)	P
Age at onset (years)	24.47	0.96 (0.91-1.02)	0.27
Gender (Male/Female)	2/17 (10.53/89.47)	2.23 (0.44-11.23)	0.30
Severe deficit at baseline	17/19	NA	<0.01
Any treatment	17 (89.47)	0.36 (0.04-2.83)	0.34

Table 4: Predictors of no motor improvement (n = 16)

		OR (95%CI)	P
Age at onset	31.18	1.01 (0.96-1.06)	0.53
Gender	6/10 (37.50/62.50)	0.55 (0.17-1.73)	0.319
Any treatment	16 (100)	--	0.17
Severe motor deficit at baseline	16 (100)	1.14 (0.37-3.48)	0.80

Discussion

NMO is an immune-mediated disorder often associated with the presence of AQP-4 antibodies in the serum. The prevalence of the disease varies from 0.3–4.4 per 100,000 in Caucasians to up to 7.7 per 100,000 in Asians.[5] There are a limited number of clinical studies in NMO which describe annualized relapse rates, visual and motor outcomes, predictors of disability, and response to treatment.[6] In this study, we have tried to assess the demographic features, gender differences, treatment responses, and disability outcomes.

The mean age of disease onset is younger as compared to previous studies.[6-11] All our patients were Asian in origin which could explain the younger age of onset as reported in previous studies. Besides, our study also included seronegative patients which may have been omitted in studies published before the introduction of the International Panel for Neuromyelitis Optica Diagnosis (IPND) criteria.[9,12] In-line with previous studies, we found that patients with ON had a younger age of onset as compared to others.[9] The actual reason is not known and it may be explained by age-dependent differences in anatomical susceptibility or probably by the difference in the accessibility of the AQP 4 antibody. The fact that a similar phenomenon is seen in patients with multiple sclerosis suggests that optic nerve is probably more vulnerable to inflammation at a younger age.[13] The classic presentation of simultaneous ON with transverse myelitis as presenting syndrome was rare (4.7%), however, unlike other cohorts, most of our patients with the opticospinal presentation were seropositive (80%).[7,9,10,14,15,18] This suggests that the classic "Devic's syndrome" is not a common presentation of NMOSD. The presence of coexisting autoimmune disorders was less frequently seen in our study when compared to the published data. However, these were commoner among seropositive patients, as reported by previous studies as well.[12,16]

Median time and several attacks until the diagnosis of NMO made was higher in patients presenting with ON than LETM (median attacks three versus two, median time 23 versus 32 months, respectively). Patients with AQP-4-mediated monophasic or recurrent ON are under-recognized and may not be screened for AQP4 antibodies or may not consult neurology services as compared to those presenting with other syndromes.

We found the average time to relapse was relatively long (42.6 months) and was different in various syndromes with nine patients relapsing after 8 years. Amongst various syndromes, the maximum interval was seen in patients who presented with ON with ten patients experiencing a relapse after more than 5 years. This implies that patients and clinicians should remain alert about the possibility of relapse even years after disease onset.

We did not find any differences between males and females in terms of disease presentation, clinical course, and outcome, unlike other published studies which showed poor outcome and higher morbidity in males as compared to females.[9,17] However, we found that females were diagnosed twice as later as compared to males, which may be related to sociocultural factors.

Morbidity in our cohort was significant. After a median follow-up of 12 months, one-fourth of the patients were left with severe visual disability and motor deficit. Only one patient died of severe sepsis. Within our cohort, the presence of severe visual deficit at baseline and older age of onset was a predictor of poor outcome in patients with ON and the male gender was a predictor of poor motor outcome. Unlike other studies, age at onset did not predict disability in either group.[9,15] This indicates that there may be a lower capacity for recovery of the optic nerve in older individuals which can explain poor visual outcomes. However, it is unclear why males have a poorer motor outcome. Also, we have mainly considered motor outcome as an inability to walk or wheelchair dependence. However, there may be patients with disabling sensory impairment or ataxia despite having a normal motor function.

Patients who were not initiated on immune suppression had a median relapse at 35 months and 50% experienced a relapse within 1 year of disease onset; higher than that reported in previous studies.[9,11] This high risk of relapse supports the use of early immune suppression in NMOSD patients to prevent future relapses.[19,20] There was a significant reduction in relapse rates after the initiation of immune suppressive therapy. AZA was the most frequently prescribed medication as the first-line therapy and the majority of the patients did well and remained relapse-free on AZA. Rituximab as first-line therapy was given in only four patients due to an aggressive disease course and the presence of significant deficit at presentation. There has been emerging evidence on the use of rituximab as first-line therapy in NMO,[21,22] but considering the risk of infections and cost, especially in a developing world, we prefer to keep it as a reserve for patients with a more aggressive disease. We, however, do not have enough patients in other treatment groups to make any comparisons, which itself would have a bias considering the observational and ambispective design of this study.

We did not observe significant discontinuation rates after starting AZA in our cohort as compared to other studies.[23] It was well-tolerated with only 8% of patients developing transient cytopenia and/or transaminitis. Only one patient developed reactivation of tuberculosis which recovered after 6 months of therapy and the patient was restarted on AZA and is doing well. Only one patient in our study developed chronic myeloid leukemia in contrast to 4–5% of patients developing malignancy in other published studies.[24,25]

The study has limitations. As part of the study, data were collected retrospectively, it may have introduced recall bias. However, it is unlikely that relapses would be missed because of the nature of the illness. Since patients were predominantly treated with AZA, it may raise a concern of treatment bias. However, AZA is commonly prescribed as a disease-modifying therapy for NMOSD around the world. The study intends to describe the response to treatment in this cohort and did not aim specifically to compare different treatment regimens. The follow-up period is small for some patients. This is an observational data with its inherent limitations and more randomized controlled trials are needed to assess treatment effect in these patients. Lastly, due to a small number of subjects in subgroups we were unable to perform regression analysis.

Conclusion

The present study gives a comprehensive review of the clinical pattern, disease course, imaging and laboratory features, visual and motor outcomes, and effect of long-term immune suppression, which expands our knowledge about the diagnostic and prognostic impact of this disease.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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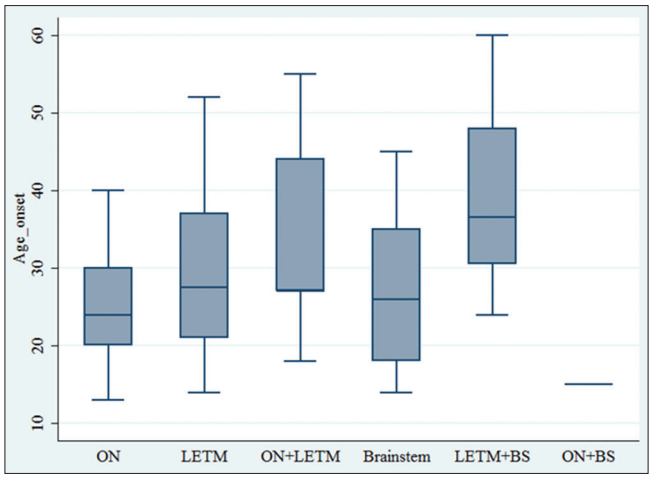

Figure S1: Box plot showing the age of onset as per syndrome of presentation ON: optic neuritis, LETM: Longitudinally extensive transverse myelitis, BS: Brainstem

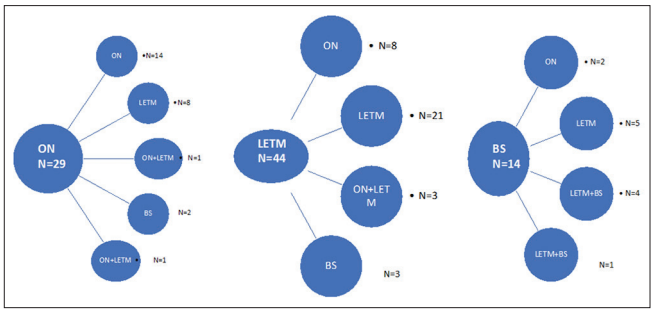

Figure S2: Relapse syndromes as per syndrome of onset. ON: optic neuritis, LETM: Longitudinally extensive transverse myelitis, BS: Brainstem

Table S1: Relationship of visual deficit at the onset to the visual deficit at 3 months after onset

Visual deficit at baseline	Visual recovery at follow-up (n = 67)				Total
	Complete	Mild	Moderate	Severe	
Mild	7	0	0	0	7
Moderate	11	16	2	0	29
Severe	3	5	6	17	31
Total	21	21	8	17	67

Table S2: Predictors of visual disability at follow-up (n = 67)

Predictor	Visual disability		
	No	Yes	*P*
Age of onset (95%CI)	27.92 (24.8-31.03)	25 (20.33-27.74)	<0.01
Gender	10/32 (23.80/76.19)	2/23 (8/92)	0.10
Syndrome at onset (%)			
Optic neuritis	15 (35.71)	14 (56)	0.193
LETM	14 (33.33)	6 (24)	
ON+LETM	2 (4.76)	3 (12)	
Brainstem	4 (9.52)	1 (4)	
LETM + Brainstem	6 (14.29)	0 (0)	
ON + Brainstem	1 (2)	1 (4)	
Any treatment			
Yes	2 (50)	23 (36.51)	0.588
No	2 (50)	40 (63.49)	
On Azathioprine			
Before visual relapse	8	1	0.188
After visual relapse	30	20	
No AZA	4	4	

Table S3: Relationship of motor deficit at the onset to the motor deficit at 6 months after onset

Motor deficit at baseline	Motor recovery at follow-up (n = 83)			Total
	Complete	Partial	Severe	
Partial	31	6	0	37
Severe	0	36	10	46
Total	31	42	10	83

Table S4: Predictors of motor disability at follow-up (n = 92)

Predictor	No	Yes	
Age of onset (95%CI)	26.88 (24.15-29.61)	25 (28.27-35.64)	0.98
Gender	7/36 (16.28/83.72)	18/31 (36.73/63.27)	0.02
Syndrome at onset (%)			
Optic neuritis	12 (27.91)	8 (16.33)	0.22
LETM	19 (44.19)	25 (51.02)	
ON+LETM	1 (2.33)	4 (8.16)	
Brainstem	7 (16.28)	3 (6.12)	
LETM + Brainstem	4 (9.30)	8 (16.33)	
ON + Brainstem	0(0)	1(2.04)	
Any treatment			
Yes	2 (4.08)	47 (95.91)	0.09
No	2 (4.65)	37 (95.35)	
On Azathioprine			
Before motor relapse	7	10	0.86
After motor relapse	28	31	
No AZA	8	8	