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A descriptive study of clinical and radiological profile of longitudinal extensive myelitis in a tertiary hospital in Rajasthan, India

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ABSTRACT

Objectives: To explore the aetiological, clinical and radiological profiles of patients with LETM presenting to this tertiary care hospital in North India.

Patients and methods: All eligible LETM patients presenting to our hospital between April 2015 and Jan 2016 were prospectively studied. A total of 37 patients were included and after thorough history, examination, relevant laboratory and radiological investigation, were profiled according to the various aetiologies of LETM.

Results: Our study included 37 patients (62% males and 38% females). Most patients were young (21–30 years). Main aetiologies of LETMp were NMO (8), inflammatory (9), idiopathic (6), NMOSD (4), Vitamin B_{12} deficiency (4) and others (6). Most patients (62%) had acute onset of symptoms except NMOSD and B_{12} deficient patients who presented subacutely too. NMO group was most disabled (poor Rankin and MRC assessments) at presentation; prognostically no (87%) or minimal improvement (13%) at discharge was seen in this group compared to other aetiologies. Forty point five percent patients had thoracic sensory complaints. CSF (pleocytosis 62%) and raised protein (81%) and brain abnormalities on MRI were seen in 11% patients. Bladder and optic nerve involvement (75.7% and 35% patients respectively). Seventy five percent NMO and 67% probable inflammatory aetiology patients also had B_{12} deficiency.

Conclusion: This study concludes that LETMp has varied aetiologies with NMO having more disability and poorer outcomes. Thoracic cord segment is most commonly involved. Vitamin B_{12} deficiency may predispose patients to inflammatory LETM including NMO syndromes.

1. Introduction

Longitudinal extensive transverse myelitis (LETM) is defined as an inflammatory spinal cord lesion extending over three or more spinal segments [1]. However, varied disorders cause long segment cord lesions resembling LETM. Consequently longitudinal extensive transverse myelopathy (LETMp) includes LETM and similar non inflammatory myelopathies too. A number of conditions may be associated with LETMp; although neuromyelitis optica (NMO) is the most frequent, followed by infective, neoplastic, autoimmune diseases and connective tissue disorders. The onset may be sudden (progressing rapidly in hours to days), subacute (e.g. B_{12} associated LETMp) or chronic. The signs and symptoms of LETMp include disturbances in the sensory and motor pathways and the autonomic nervous system at and below the level of the lesion [2]. Radiological findings show MRI spinal cord lesion extending over three or more contiguous segments; focal spinal cord atrophy is seen in chronic cases. MRI brain may have normal findings or only nonspecific white matter lesions, or specifically in cases of NMO-LETM may include dorsal medulla/area postrema lesions, periependymal brainstem lesions &/or lesions extending over half of optic nerve length or involving optic chiasma [3]. Although NMO is thought to be the commonest cause of LETMp [4,5], with commoner incidence and prevalence of infections in India, it is possible that aetiological, clinical and radiological profiles of LETMp patients in this country may differ from that of the developed world (from where most of the LETM literature originates). There is a paucity of literature on LETM from North India; consequently, this study is aimed to explore the aetiological, clinical and radiological profiles of patients with LETMp presenting to this tertiary care hospital in North India.

2. Patients and methods

This prospective study was conducted at Department of Neurology, Santokba Durlabhji Memorial Hospital cum medical research institute, a tertiary care hospital in Jaipur, Rajasthan. A total of 37 patients presented to our hospital with LETMp during the study period (May

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2016 - May 2017) and were included in the study. LETMp was defined as transverse myelitis longer than three vertebral segments or with hyperintense spinal cord lesion extending over three or more vertebral levels on sagittal T2 weighted spinal MRI. NMO and NMOSD patients were diagnosed according to the NMOSD diagnostic criterion 2015 [3]. Following parameters were noted – Clinical (history, examination), Total and Differential cell count, Eythrocyte sedimentation rate, Vitamin B_{12} levels, Thyroid stimulating hormone (TSH), Hepatitis B and C serology, HIV serology, vasculitis workup (ANA, Anti Ro and La antibodies, Anti Sm, ds DNA, Anti SS-A, Anti SS B, Anti JO antibodies), workup for infective aetiology, CSF analysis (cytology, biochemistry, viral serology and oligoclonal bands), serum copper level, serum Angiotensin Converting Enzyme (ACE) levels, Brucella serology (if suggested by history and symptoms) and Visual Evoked Potential (VEP) studies. AQP4 autoantibody (also known as NMO-IgG antibody) was done using Immunofluorescence (IFA) method which has sensitivity of 86% and specificity of 91% [6]. Medical research council (MRC) grading of power on admission and Modified Rankin Scale (MRS) at the time of admission (RP) and discharge (RD) were noted. Motor weakness was scored according to MRC grading as score 1 (MRC grade 0–1), score 2 (MRC grade 2–3) and score 3 (MRC grade 4–5). All patients were subjected to MRI spinal cord (relevant segment/s) with/out brain with routine MR sequences such as sagittal T1-weighted (T1W) sequence, sagittal and axial T2W sequences. Outcome was determined by length of hospital stay and condition at discharge as evaluated by the difference between the Rankin scale at presentation (RP) and at discharge (RD) rating RP – RD. Aetiologies of LETM were defined and classified as follows:

Group A - NMO: LETM patients with NMO antibody (AQP-4 IgG) positive fulfilling NMOSD diagnostic criteria 2015 [3].

Group B - NMOSD: LETM patients negative for NMO antibody but fulfilling other criterion for NMOSD according to the NMOSD diagnostic criteria 2015 [3].

Group C - Probable Inflammatory(PI): LETM patients who did not fulfil the NMOSD diagnostic criteria 2015 [3] and had a temporal, radiological and CSF profile consistent with inflammatory aetiology. Patients with autoimmune antibodies suggesting definite inflammatory aetiology were also included in this group.

Group D - Idiopathic/undetermined: LETMp patients in whom no other cause could be found.

Group E - Vitamin B_{12} deficient SACD: LETMp patients with vitamin B_{12} deficiency and clinical profile consistent with combined degeneration.

Group F - Other/miscellaneous: LETMp patients presenting with heterogenous aetiologies (Tables 1–15).

3. Results

Eight patients were NMO positive (Group A); 4 were NMOSD (Group B); 9 were Probable inflammatory (Group C); 6 were Idiopathic/undetermined (Group D); 4 were Vitamin B_{12} deficient SACD (Group E) and 6 were in Group F (other/ miscellaneous) which included 1 patient with Dural Arterio Venous fistula (AVF), 1 patient with Arterio-Venous malformations (AVM), 1 patient with Brucella, 1 patient having HIV and 2 patients had TB with Hepatitis C. One patient had Brucella antibodies and 2 were positive for ANA (1 each in Group A - NMO and C - PI) while 2 patients had Anti Ro and La antibodies (1 each in Group A - NMO and C - PI). VZV serology was positive in 3 patients – 2 in Group A (NMO) and 1 in Group F (Other/miscellaneous).

Table 1
Aetiologies of LETMp.

Group	N (%)	Aetiology
A	8 (21.62%)	NMO
B	4 (10.8%)	NMOSD
C	9 (24.32)	Probable Inflammatory
D	6 (16.21)	Idiopathic/undetermined
E	4 (10.81)	Vitamin B_{12} deficient SACD
F	6 (16.21)	Others/miscellaneous

Group F (Other/miscellaneous) was excluded from statistical analysis because of varied aetiologies and heterogenous group. Thus, treating it as a single group for statistical comparison in most situations is not scientifically valid.

Age range of the patients was from 13 to 73 years with bimodal peaks of presentation between the ages of 21–30 years (32.4%) and 41–50 years (27%). Majority of the patients in Group A (NMO) and B (NMOSD) had a comparatively younger age of presentation (< 40 years) in comparison to the patients in group E (vitamin B_{12} deficient SACD) and F (Other/miscellaneous) in which most of the patients presented at a later age.

Sixty-two point two percent patients were males and 37.8% were females. Seven out of the 8 patients (87.5%) in Group A (NMO) were females; Group B (NMOSD) had equal number of males and females whereas males were more in Group C - PI (66.7%), D – Idiopatic/undetermined (83.3%), E – vitamin B_{12} deficient SACD (75%) and F – Other/miscellaneous (100%). Male : Female ratio in different groups were 1:7 in Group A (NMO), 1:1 in Group B (NMOSD), 2:1 in Group C (PI), 5:1 in Group D (Idiopathic/undetermined) and 3:1 in Group E (vitamin B_{12} deficient SACD).

Sixty-two point two percent patients had acute onset of illness and 37.8% had subacute onset. Majority of patients in Group A - NMO (87.5%), C - PI (66.67%), D – Idiopathic/undetermined (100%) and F – Other/miscellaneous (66.67%) had acute onset of symptoms whereas all the patients in Group B (NMOSD) and E (vitamin B_{12} deficient SACD) presented subacutely. These five groups were highly significantly ($P < 0.001$) different in their onset of symptoms.

Twenty two (59.46%) patients had asymmetric symptoms and included majority of the patients in Group A (NMO), Group C (PI) and Group D (Idiopathic/undetermined) while 15 (40.54%) patients came with symmetrical symptoms which included all the patients Group B (NMOSD) and 50% of the patients in Group E (vitamin B_{12} deficient SACD) and F (Other/miscellaneous). These five groups were highly significantly ($P < 0.001$) different in their onset of symptoms.

Twenty eight patients presented with sensory symptoms out of which 12 (32.43%) had symptoms limited to cervical distribution while 15 (40%) were in thoracic and 1 patient had symptoms involving both cervical and thoracic level. All the 8 patients in Group A (NMO) and 2 patients (50%) in Group B (NMOSD) had cervical sensory level while in other groups majority of patients (44.44% in Group C - PI, 66.67% in Group D – Idiopathic/undetermined, 75% in Group E – vitamin B_{12} deficient SACD and 66.67% in Group F – Other/miscellaneous) had thoracic sensory level. On examination the most common sensory level seen was T4; seen in 45.95% of the patients followed by T10 level which was localized in 21.62% patients. These five groups were highly significantly ($p = 0.003$) different in their manifestations of clinical sensory symptoms.

Bladder involvement was seen in 75.68% of the patients. Majority of patients in Group A - NMO (87.5%), C - PI (88.89%), E – vitamin B_{12} deficient SACD (75%) and F – Other/miscellaneous (83.33%) had bladder complaints on presentation.

Thirty two patients in this study had paraparesis out of which 24 patients (75%) had weakness of grade 3 i.e. MRC power grade of 4–5 while 8 patients (25%) had grade 2 weakness i.e. MRC power grade of 2–3. Majority of the patients in Group A (NMO) had grade 2 weakness i.e. they had poorer MRC power grading in comparison to other groups where most of the patients had better power at presentation. Five patients presented with asymmetrical quadriparesis and all of them were in Group A out of which 3 patients had grade 1 weakness i.e. MRC power grade of 0–1 and 2 patients had grade 2 weakness i.e. MRC power grade of 2–3.

Majority of the patients in NMO group had poor Rankin score at

Table 2
Distribution according to groups and age.

Age (yrs)	Group												Total	
	A(NMO)		B (NMOSD)		C (PI)		D (Idiopathic/ undetermined)		E (Vitamin B_{12} deficiency SACD)		F (Others/ miscellaneous)			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
≤20	0	0.00	0	0.00	1	11.11	1	16.67	0	0.00	0	0.00	2	5.41
21-30	4	50.00	2	50.00	2	22.22	2	33.33	1	25.00	1	16.67	12	32.43
31-40	2	25.00	0	0.00	2	22.22	1	16.67	0	0.00	1	16.67	6	16.22
41-50	1	12.50	2	50.00	2	22.22	1	16.67	3	75.00	1	16.67	10	27.03
51-60	1	12.50	0	0.00	0	0.00	1	16.67	0	0.00	2	33.33	4	10.81
> 60	0	0.00	0	0.00	2	22.22	0	0.00	0	0.00	1	16.67	3	8.11

presentation (mean score of 4) as compared to the patients in other groups where most of the patients presented with better score. It was also noticed that majority of the patients in NMO group had poor recovery on discharge (mean recovery of 0.13 rankin score) as compared to the patients in other groups where better recovery was observed.

Vitamin B_{12} deficiency was seen in 20 (54.05%) patients. 75% of the patients in Group A (NMO), all the 4 patients in Group B (NMOSD) and 66.67% patients in Group C (PI) were deficient in Vitamin B_{12}. These groups were significantly different ($p = 0.003$) with regard to vitamin B_{12} deficiency. These data clearly show vitamin B_{12} deficiency to be ubiquitous in inflammatory (NMO, NMOSD, PI) and vitamin B_{12} deficient SACD group.

In this study 1 patient was positive for HIV serology, 1 had Hepatitis C and 1 had Brucella antibodies. 2 patients had Tuberculosis, 2 were positive for ANA (1 each in Group A - NMO and C - PI) while 2 patients had Anti Ro and La antibodies (1 each in Group A - NMO and C - PI). VZV serology was positive in 3 patients – 2 in Group A (NMO) and 1 in Group F (Other/miscellaneous).

Ocular symptoms were present in 14 patients (37.84%). Bilateral ocular involvement was seen in only one patient who was in Group A (NMO) while unilateral eye involvement was found in 13 patients (35.14%). None of the patients had any previous history of optic neuritis.

CSF pleocytosis was observed in 24 (64.86%) of the patients. Majority of patients in Group A – NMO (87.5%), B - NMOSD (75%) and F – Other/miscellaneous (66.67%) and all the patients in Group C (PI) had increased cells in CSF. CSF protein was increased in 62.16% patients. Fifty percent patients in Group A (NMO), D (Idiopathic/undetermined) and F (other/miscellaneous) and all patients in Group B (NMOSD) and C (PI) had raised protein in CSF. Four patients (10.81%) had low CSF sugar and all were in Group F (Other/miscellaneous).

The total number of spinal segment involvement ranged from 4 – 29 segments. Mean number of segment involvement in Groups A (NMO), B (NMOSD), C (PI), D (Idiopahtic/undetermined), E (vitamin B_{12} deficient SACD) and F (Other/miscellaneous) were 15.75, 11.25, 12.11, 11.5, 8.75 and 15.17 respectively.

In this study number of spinal segment involvement ranged from 4 – 29 segments. Mean number of segment involvement in Groups A (NMO), B (NMOSD), C (PI), D (Idiopahtic/undetermined), E (vitamin B_{12} deficient SACD) and F (Other/miscellaneous) were 15.75, 11.25, 12.11, 11.5, 8.75 and 15.17 respectively. No significant association could be found between the mean number of spinal segment involved across the different aetiologies of LETM ($p = 0.49$).

Six patients had typical cord hyperintensities of NMO (i.e. central hyperintensity involving more than 50% of the cord) – 5 patients (62.5%) in Group A (NMO) and 1 patient (25%) in Group B (NMOSD). Six patients had atypical spinal cord hyperintensities (i.e. lesion involving both central and peripheral cord or lesions with flow void or feeding arteries) which included 3 patients (37.5%) in Group A (NMO) and 3 patients (75%) in Group B(NMOSD).

Brain MRI was normal in 59.46% patients. Typical brain lesions (i.e. lesions located within the periventricular regions of third and fourth ventricle, midbrain and cerebellum) were seen in only 4 patients and all were in Group A (NMO). Atypical lesions included non specific white matter hyperintensities, chronic lacunar infarcts and multiple tuberculomas (1 patient).

Total duration of stay of patients in hospital ranged from 3 – 10 days. Mean stay of patients in different groups were 5.63 days in Group A (NMO), 5.75 days in Group B (NMO), 5.78 days in Group C (PI), 6.5 days in Group D (Idiopathic/undetermined), 5.75 days in Group E (vitamin B_{12} deficient SACD) and 7 days in Group F (Other/miscellaneous).

3.1. Summary of patients's characteristics in different groups

Group A patients (NMO) had a mean age of presentation of 34.13 years; majority were < 40 years of age. Male : Female ratio was 1:7 with 87% patients in this group being females. Acute onset of illness was seen in 87.5% patients and asymmetric symptoms observed in 62.5% patients. All had cervical sensory symptoms, bladder involvement in 87.5% and 66.67% patients presented with grade 2 (MRC grade 3 to 3) paraparesis. 5 patients had quadriparesis (MRC grade 0–1). 5 patients (62.5%) had ocular involvement: 1 had bilateral while 4 patients had involvement of only one eye. Majority of patients in Group A presented with a poor Rankin score of either 4 (50%) or 5 (37.5%) and 87.5% patients did not show any improvement in their Rankin score at the time discharge. 75% patients also had Vitamin B_{12} deficiency and on CSF examination pleocytosis in 87.5% and increased protein level in 50% patients was observed. On MRI imaging mean cord length involvement was 15.75 segments along with typical cord lesion of NMO in 62.5% patients. Typical NMO lesions were seen in 50% patients on brain MRI.

Table 3
Distribution according to groups and sex.

Sex	Group												Total	
	A(NMO)		B (NMOSD)		C (PI)		D (Idiopathic/ undetermined)		E (Vitamin B_{12} deficiency SACD)		F(Others/ miscellaneous)			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Male	1	12.50	2	50.00	6	66.67	5	83.33	3	75.00	6	100.0	23	62.16
Female	7	87.50	2	50.00	3	33.33	1	16.67	1	25.00	0	0.00	14	37.84

Table 4
Distribution according to groups and onset.

Onset	Group												Total	
	A (NMO)		B (NMOSD)		C (PI)		D (Idiopathic/ undetermined)		E (Vitamin B_{12} deficiency SACD)		F (Others/ miscellaneous)			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Acute	7	87.50	0	0.00	6	66.67	6	100.0	0	0.00	4	66.67	23	62.16
Subacute	1	12.50	4	100.0	3	33.33	0	0.00	4	100.0	2	33.33	14	37.84
Total	8	100.0	4	100.0	9	100.0	6	100.0	4	100.0	6	100.0	37	100.0

Chi-square = 18.882 with 4 ° of freedom; P < 0.001.

In Group B (NMOSD) mean age of presentation was 34.75 years. Male : Female ratio was 1:1. All the 4 patients had subacute onset of illness with symmetric symptoms. 50% presented with sensory symptoms involving the cervical region, bladder involvement in 50% and all the patients presented with grade 3 (MRC grade 4–5) paraparesis. All patients had uniocular involvement and a Rankin score of 2 on presentation. 50% patients did not show any improvement in their Rankin score at the time discharge and the remaining 50% had an improvement of one point on Rankin score. Vitamin B_{12} deficiency was seen in all the patients and on CSF examination pleocytosis observed in 75% patients and all the patients had increased protein level. On MRI imaging mean cord length involvement was 11.25 segments along with typical cord lesion in only 25% patients. Typical NMO lesions were not seen in any patient on brain MRI.

In Group C (PI) mean age of presentation of the patients was 41.67 years with a Male : Female ratio of 2:1. 66.67% patients had acute onset of illness while subacute onset witnessed in 33.33% and majority (77.78%) presenting with symmetric symptoms. Sensory symptoms involving the thoracic region was seen in 44.44% and bladder involvement in 88.89% patients. Most of the patients (77.78%) presented with grade 3 (MRC grade 4–5) paraparesis. Uniocular involvement seen in 44.44% patients and 55.56% did not have any ocular symptoms. Majority presented with a Rankin score of ≤ 3 on presentation and 66.67% patients had improvement in their score on discharge. Vitamin B_{12} deficiency was seen in 66.67% of the patients and on CSF examination all the 9 patients had pleocytosis and increased protein level. On MRI imaging mean cord length involvement was of 7.15 segments.

Group D patients (Idiopathic/undetermined) had a mean age of presentation of 33.17 years with a Male : Female ratio of 5:1and 83.33% patients in this group were males. All the patients had acute onset of illness and asymmetric symptoms were seen in 83.33% patients. Most of the patients (66.67%) presented with sensory symptoms relating to thoracic region and 50% patients had bladder involvement. 66.67% patients had grade 3 (MRC grade 4–5) paraparesis while 33.33% patients presented with grade 2 (MRC grade 2–3) paraparesis. None of the patients had ocular involvement. Majority of patients 66.67% had a Rankin score of ≤ 2 at presentation and 33.33% had a score of 4. Improvement in Rankin score of 1 point was seen in 66.67% patients while 33.33% had no improvement. On CSF examination pleocytosis was observed in only 1 patient and 50% patients had abnormal protein level. On MRI imaging mean cord length involvement was of 11.5 segments.

In Group E (Vitamin B_{12} deficient SACD) mean age of presentation was 39.75 years with a Male : Female ratio of 3:1. All the 4 patients had subacute onset of illness with symmetric symptoms in 50%. 75% presented with sensory symptoms involving the thoracic region, bladder involvement in 75% and all the patients presented with grade 3 (MRC grade 4–5) paraparesis. On examination all had a localization of Thoracic vertebrae level and only 25% patients had ocular involvement. All the patients presented with a Rankin score of 2 and 50% had an improvement of 1 point on Rankin scale while 50% did not show any improvement. All the patients had normal CSF examination. On MRI imaging mean cord length involvement was of 8.75 segments. Mean length of stay was 5.75 days and all patients received Vitamin B_{12} replacement along with steroids.

Group F patients (Other/miscellaneous) had a mean age of presentation of 46.83 years and all the patients were males. 66.67% patients had acute onset of illness and 33.33% had subacute onset. Asymmetric symptoms were seen in 50% patients and most of the patients (66.67%) presented with sensory symptoms relating to thoracic region. Bladder was involved in 83.33% patients and none had ocular involvement. 66.67% patients had grade 3 (MRC grade 4–5) paraparesis while 33.33% patients presented with grade 2 (MRC grade 2–3) paraparesis. Majority of patients 66.66% had a Rankin score of ≤ 2 at presentation and 33.33% had a score of 4. Improvement in Rankin score of 1 point was seen in 83.33% patients while 16.67% had no improvement. On CSF examination pleocytosis was observed in 66.67% patients, abnormal protein level seen in 50% and low sugar in 66.67% patients. On MRI imaging mean cord length involvement was of 15.17 segments.

4. Discussion

This study profiles LETMp in patients referred consecutively to our hospital and classifies aetiologies of LETMp. There were no studies available in Indian literature except Jain et al[7] (published in 2016) looking at the profile of LETM. Similarly there are very few studies in the world literature (Cobo calvo et al [8], Apostolos et al [9], Sepulveda et al [10], Contentti et al [11]). NMO antibody was positive in 21.62% patients; Pokalkar et al [12] and Jain et al [7] also showed that NMO antibody was present in 28% and 20.3% of their patients respectively. Other aetiologies in this study included Probable Inflammatory (PI) in

Table 5
Weakness distribution according to groups.

Symmetry	Group												Total	
	A (NMO)		B (NMOSD)		C (PI)		D (Idiopathic/ undetermined)		E (Vitamin B_{12} deficiency SACD)		F (Others/ miscellaneous)			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Asymmetrical	5	62.50	0	0.00	7	77.78	5	83.33	2	50.00	3	50.00	22	59.46
Symmetrical	3	37.50	4	100.0	2	22.22	1	16.67	2	50.00	3	50.00	15	40.54

Chi-square = 18.882 with 4 ° of freedom; P < 0.001.

Table 6
Distribution according to groups and clinical sensory symptoms.

Clinical Sensory symptoms	Group												Total	
	A (NMO)		B (NMOSD)		C (PI)		D (Idiopathic/ undetermined)		E (Vitamin B_{12} deficiency SACD)		F(Others/ miscellaneous)			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Cervical	8	100	2	50	1	11.11	0	0.00	1	25.00	0	0.00	12	32.43
Cervical + Thoracic	0	0.00	0	0.00	0	0.00	1	16.67	0	0.00	0	0.00	1	2.70
Thoracic	0	0.00	0.0	0.00	4	44.44	4	66.67	3	75.00	4	66.67	15	40.54

chi-square = 30.255 with 12 ° of freedom; P = 0.003.

24.3% patients, Other/miscellaneous 16.2%, NMOSD 11% and Vitamin B_{12} deficient SACD in 11% patients. Two patients (5.4%) had autoimmune aetiology as they were positive for Anti Ro and La antibodies while in the study done by Pokalkar et al [12] 2.3% patients had these antibodies and Jain et al[7] observed that 5% of their LETM patients had SLE. Five point four percent patients in our study presented with Tuberculosis which was also reported by Jain et al [7] where 6.2% patients in their series also had Tuberculosis.

In our study of 37 patients, 23(62.2%) were males and 14(37.8%) were females which is similar to the study by Jain et al [7] where 75% were males and 25% of their patients were females. However studies done in western literature showed a female preponderance as observed by studies done by Cobo calvo et al [8], Zhang et al [13], Apostolos et al [9], Sepulveda et al[10] and Contentti et al [11] where 62.5%, 75%, 70%, 70% and 74% of their patients were females. This difference in the sex preponderance among the Indian and western literature may be due to geographic variations, racial differences and/or access to medical services. Most of the NMO patients were females (87.5%) which is in accordance to the study by Kitley et al [14] where 86% of the NMO patients were females. Asgari et al [15] observed that 73.8% of their NMO patients were females.

In our study LETM affected individuals of all ages, ranging from 13 to 73 years but studies done by Apostolos et al [9] and Sepulveda et al [10] showed age range of 11–72 years and 20-77yrs respectively in their study. Jain et al [7] in their study showed that 59.37% patients presented < 30 yrs while 41% of the patients presented in the age group > 30 years. Majority of the patients in NMO and NMOSD group had a comparatively younger age of presentation (< 40 years) in comparison to the patients in Vitamin B_{12} deficient SACD group and in Other/miscellaneous group in which most of the patients presented at a later age.

LETM may present with acute, subacute or chronic onset. In our study 62.16% presented with acute onset of symptoms, 37.84% presented subacutely and none presented with chronic onset. Study done by Jain et al [7] showed acute onset in 67%, subacute in 19% and chronic onset in 14% of the patients. Majority of patients in NMO group (87.5%), Probable inflammatory (66.67%), Idiopathic/undetermined (100%) and Other/miscellaneous (66.67%) had acute onset of symptoms whereas all the patients in NMOSD group and vitamin B_{12} deficient SACD presented subacutely. These five groups were highly significantly (P < 0.001) different in their onset of symptoms.

In our study all the patients presented with weakness and involvement of the corticospinal tract. Similar finding was also seen in a study done by Sepulveda et al [10] where corticospinal tract was affected in all their patients. In our study 59.46% patients presented with asymmetric symptoms while 15 (40.54%) patients came with symmetrical symptoms. Sepulveda et al [10] observed that 35% patients in their study had asymmetric symptoms on presentation. Sixty two point five percent patients in NMO, 77.78% patients in Probable Inflammatory and 83.33% patients in Idiopathic/undetermined group had asymmetric presentation of complaints. All patients in NMOSD group and 50% of the patients in vitamin B_{12} deficient SACD and Other/miscellaneous groups had symmetric symptoms.

In our study a defined clinical sensory level was present in 28 (75.67%) patients which is similar to the finding observed by Sepulveda et al [10] where 78% patients presented with a sensory level. Out of the 37 patients in this study, 12 (32.43%) had symptoms limited to cervical distribution while 15 (40%) were in thoracic and only one patient had symptoms involving both cervical and thoracic level. In a study done by Jain et al [12] they observed that 25% patients had cervical and 70% patients had thoracic involvement on presentation. In another study by Contentti et al [11] 74% patients had a thoracic level while 14.81% had a cervical level.

In our study bladder was involved in 75.68% patients which is similar to the observations made by Cobo calvo et al [8], Sepulveda et al [10] and Jain et al[7] and where bladder involvement was seen in 71%, 69% and 67% patients respectively. Majority of patients in NMO (87.5%), NMOSD (88.89%), vitamin B_{12} deficient SACD (75%) and other/miscellaneous (3.33%) groups had bladder complaints on presentation.

In our study 32 (86.49%) patients presented with paraparesis. Majority of the patients in Group A (NMO) had grade 2 paraparesis i.e. they had poorer MRC power grading in comparison to other groups where most of the patients had better power at presentation. Five patients (13.5%) presented with asymmetric quadriparesis and all of them were in NMO group. In a study done by Jain et al [7] 38% patients of LETM presented with quadriparesis.

Ocular symptoms were present in 37.84% of the patients. Similar finding was seen in studies done by Pokalkar et al [12] and Jain et al [7] where ocular involvement was present in 28% and 36% patients

Table 7
Distribution according to groups and bladder involvement.

Symmetry	Group												Total	
	A (NMO)		B (NMOSD)		C (PI)		D (Idiopathic/ undetermined)		E (Vitamin B_{12} deficiency SACD)		F (Others/ miscellaneous)			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Present	7	87.5	2	50.0	8	88.89	3	50.00	3	75.00	5	83.33	28	75.68
Absent	1	12.5	2	50.0	1	11.11	3	50.00	1	25.00	1	16.67	9	24.32
Total	8	100	4	100	9	100.0	6	100.0	4	100.0	6	100.0	37	100.0

Table 8
Distribution according to groups and weakness.

Paraparesis maximum Deficit (MRC)	Group												Total	
	A (NMO)		B (NMOSD)		C (PI)		D (Idiopathic/ undetermined)		E (Vitamin B_{12} deficiency SACD)		F(Others/ miscellaneous)			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
2	2	66.67	0	0.00	2	22.22	2	33.33	0	0.00	2	33.33	8	25
3	1	33.33	4	100.0	7	77.78	4	66.67	4	100.0	4	66.67	24	75
Quadriparesis maximum Deficit (MRC)														
1	3	60	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	3	60
2	2	40	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	2	40

respectively. Bilateral ocular involvement was seen in only one patient who was in NMO group while unilateral eye involvement was found in 13 patients (35.14%).

Most of patient in this study presented with Rankin score of 2 (32.43%) followed by 29.73% patients who had a score of 4 on presentation. Thirty eight percent of the patients in this study were bed bound at the time of presentation which is almost similar to the finding of Sepulveda et al [10] where they observed that about 48% patients were bed bound at the time of admission. Majority of patients in NMO group presented with poor Rankin score of either 4 (50%) or 5 (37.5%) while most of the patients in other groups had better Rankin score on presentation. In NMO group 87.5% patients and 50% patients in NMOSD and vitamin B_{12} deficient SACD groups each showed no improvement at discharge on their Rankin score as compared to Probable inflammatory, Idiopathic/undetermined and Other/ miscellaneous groups, where majority of the patients showed improvement at the time of discharge. These five groups were significantly different ($p < 0.002$) in their Rankin score at presentation and at discharge.

Vitamin B_{12} deficiency was seen in 20 (54.05%) patients in this study. In NMO (75%), NMOSD (100%) and 66.67% patients in Probable inflammatory groups were deficient in vitamin B_{12}. The low B_{12} levels and clinical profile of LETMp matching combined degeneration were found only in 4/37(10.8%). The incidence of vitamin B_{12} and folate deficiencies in Indian population has been found to be ranging from 33 to 76%. [16,17]In our hospital the incidence of low B_{12} levels found in patients who have been investigated for B_{12} levels for various clinical reasons is 39.3%. In stark contrast the prevalence of vitamin B12 deficiency in the United Kingdom and United States is around 6% in people aged less than 60 years, and closer to 20% in those aged more than 60 years. [18] This difference could possibly be due to consumption of a vegetarian diet, higher incidence of infections such as H.Pylori (leading to atrophic gastritis) or due to absence of food fortification with vitamin B_{12} in our country. Thus this study has found that vitamin B_{12} deficiency in LETM patients is far more common than the total incidence of low B_{12} levels according our hospital based data, hence it may be inferred that Vitamin B_{12} deficiency may be a contributing triggering factor in inflammatory aetiologies of LETM. Vitamin B_{12} deficiency leads to reduced S-adenosyl methionine (SAM) or elevated methylmalonic acid (MMA) levels. SAM deficiency results in abnormal methylated phospholipids such as phosphatidylcholine, and is linked to central myelin defects and abnormal neuronal conduction, which may account for the myelopathy. Elevated MMA results in abnormal odd chain and branched chain fatty acids with subsequent abnormal myelination, possibly leading to defective nerve transmission. Recently it was observed that in human and rodent serum and CSF, concomitantly with a vitamin B-12 decrease, Epidermal Growth Factor (neurotrophic) levels are decreased, while at the same time, TNF-alpha (neurotoxic) increases in step with homocysteine levels. These observations provide evidence that the clinical and histological changes of vitamin B_{12} deficiency may result from up-regulation of neurotoxic cytokines and down-regulation of neurotrophic factors. [19]

In our study CSF pleocytosis was seen in 64.86% patients while in the studies by Cobo calvo et al [8], Spulveda et al [10] and Jain et al [7] pleocytosis was seen in 31%, 45% and 48.3% patients respectively. Sixty two point two percent patients in this study had increased protein level (> 60 mg/dl) in CSF but in the study done by Cobo calvo et al [8] increased protein in CSF were seen in 53.1% patients. This variation in CSF abnormalities among different studies could be because of the

Table 9
Distribution according to groups and Rankin score at presentation, discharge and. RP−RD.

Rankin Scale	Group	N	Mean	SD	Median	Min.	Max.	'p' Value*	'p' < 0.05 from**
At Presentation	**A**	8	4.00	1.31	4	1	5	NA	NA
	B	4	2.00	0.00	2	2	2		
	C	9	2.56	1.33	3	1	4		
	D	6	2.17	1.47	1.5	1	4		
	E	4	2.00	0.00	2	2	2		
	F	6	2.33	1.37	2	1	4		
On Discharge	**A**	8	3.88	1.25	4	1	5	0.002	BCD
	B	4	1.50	0.58	1.5	1	2		A
	C	9	1.56	1.42	1	0	3		A
	D	6	1.50	1.38	1.5	0	3		A
	E	4	1.50	0.58	1.5	1	2		A
	F	6	1.50	1.22	1	0	3		
RP-RD	**A**	8	0.13	0.35	0	0	1	0.196	NA
	B	4	0.50	0.58	0.5	0	1		
	C	9	0.78	0.67	1	0	2		
	D	6	0.67	0.52	1	0	1		
	E	4	0.50	0.58	0.5	0	1		
	F	6	0.83	0.41	1	0	1		

* ANOVA - Analysis of Variance**Tukey HSD.

Table 10
Distribution according to groups and Vitamin B_{12} deficiency.

Vit B12	Group									
	A (NMO)		B (NMOSD)		C (PI)		D (Idiopathic/ undetermined)		E (Vitamin B_{12} deficiency SACD)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Low	6	75.00	4	100.0	6	66.67	0	0.00	4	100.0
Normal	2	25.00	0	0.00	3	33.33	6	100.0	0	0.00

Chi-square = 15.711 with 4 ° of freedom; P = 0.003.

Table 11
Distribution according to groups and positive serology.

Positive serology for	Group												Total	
	A (NMO)		B (NMOSD)		C (PI)		D (Idiopathic/ undetermined)		E (Vitamin B_{12} deficiency SACD)		F (Others/ miscellaneous)			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
HIV	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	16.67	1	2.70
Anti HCV	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	16.67	1	2.70
Brucella	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	16.67	1	2.70
Tuberculosis	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	2	33.33	2	5.41
ANA (IFA)	1	12.5	0	0.00	1	11.11	0	0.00	0	0.00	0	0.00	2	5.41
Ro & La antibodies	1	12.5	0	0.00	1	11.11	0	0.00	0	0.00	0	0.00	2	5.41
VZV	2	25.0	0	0.00	0	0.00	0	0.00	0	0.00	1	16.67	3	8.11

Table 12
Distribution according to groups and unilateral / bilateral optic involvement clinically and subsequently confirmed by VEP study.

Unilateral/ Bilateral	Group												Total	
	A (NMO)		B (NMOSD)		C (PI)		D (Idiopathic/ undetermined)		E (Vitamin B_{12} deficiency SACD)		F (Others/ miscellaneous)			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Bilateral	1	12.50	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	2.70
Unilateral	4	50.00	4	100	4	44.44	0	0.00	1	25.00	0	0.00	13	35.14
Absent	3	37.50	0	0.00	5	55.56	6	100.0	3	75.00	6	100.0	23	62.16

Table 13
Distribution according to groups and CSF abnormality.

CSF	Group												Total	
	A (NMO)		B (NMOSD)		C (PI)		D (Idiopathic/ undetermined)		E (Vitamin B_{12} deficiency SACD)		F (Others/ miscellaneous)			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Abnormal Cells	7	87.50	3	75.00	9	100.0	1	16.6	0	0.0	4	66.67	24	64.86
Abnormal Protein	4	50.00	4	100.0	9	100.0	3	50.0	0	0.0	3	50.00	23	62.16

*Chi-square test.

Table 14
Distribution according to groups and number of spinal segments involved.

Group	N	Mean	SD	Median	Minimum	Maximum	'p' Value*
A (NMO)	8	15.75	7.94	16	5	29	0.492
B (NMOSD)	4	11.25	4.03	10	8	17	
C (PI)	9	12.11	7.15	9	5	27	
D (Idiopathic/ undetermined)	6	11.50	5.54	11	4	19	
E (Vitamin B_{12} deficiency SACD)	4	8.75	5.50	6	6	17	
F (Others/ miscellaneous)	6	15.17	8.75	15.5	4	29	

* ANOVA - Analysis of Variance.

different cut off values for normal CSF taken in each study. Majority of patients in NMO (87.5%), NMOSD (75%) and other/miscellaneous (66.67%) group and all the patients in PI group had increased cells in CSF. Fifty percent patients in NMO, Idiopathic/undetermined and other/miscellaneous groups each and all patients in NMOSD and PI group had raised protein in CSF. These five groups were significantly different ($p < 0.001$ for CSF pleocytosis, $p = 0.003$ for abnormal protein level) in their CSF.

Table 15
Distribution according to groups and cord hyperintensities.

Cord hyperintensities	Group			
	A (NMO)		B (NMOSD)	
	No.	%	No.	%
Typical	5	62.5	1	25.0
Atypical	3	37.5	3	75.0
Total	8	100	4	100

In our study the number of spinal segment involvement ranged from 4 to 29. Fifty four percent of the patients in our study had > 10 segments of spinal cord involvement on MRI which is similar to the study done by Pokalkar et al [12] where 50% of their patients had involvement of > 10 segments of the cord. The most common site of cord involvement on MRI of spinal cord was thoracic, seen in 86% patients and similar observation was also made by Cobo calvo et al [8] wherein 78% patients had thoracic cord involvement. We also noted that B_{12} deficient SACD patients tend to have fewer number of spinal segment involvement as compared to other groups, the difference though not reaching statistical significance.

In our study brain MRI was normal in 59.46% of the patients which is in accordance to the study done by Contentti et al [11] where 59% patients had normal brain MRI and similar finding was also reported by Jain et al [7] in which 66% had normal MRI. NMO specific brain lesions were seen in 10.58% patients (all were in NMO group) but in the studies done by Contentti et al[11] and Pokalkar et al [12] they observed that MRI lesions specific for NMO was present in 3.8% and 2.3% of the patients respectively.

Our study was done in a tertiary hospital in north-western region of India hence all the patients included, belonged to a similar ethnicity. There are certain ethnic differences between northern and southern/eastern region of our country but no study, as yet, has highlighted the differences in presentation of LETM among various ethnic groups in India. Although there have been few studies [20–22]from south India on CNS demyelinating disorders but these studies used a different diagnostic criteria for NMOSD and moreover none of these studies explored the entire spectrum of LETMp as done in our study.

This study is first of it's kind from Rajasthan which is truly inclusive of all LETMp patients and there are very few such previous studies both in the western and Indian literature. Commonest cause of LETMp remains inflammatory (NMO, NMOSD, PI), however, low vitamin B_{12} levels far exceeds the expected background rates suggesting additional aetiological role in LETMp regardless of primary aetiology.

5. Conclusion

LETM is a subset of LETMp, an inflammatory myelitis with NMO and NMOSD being the commonest underlying aetiologies. There are very few studies globally (especially Indian literature, an isolated study (Jain et al[7] in 2016)) addressing LETMp from a broad clinical perspective. Our study reports a broad spectrum of aetiologies underlying LETMp syndrome. Vitamin B_{12} deficient subacute combined degeneration (SACD) is a reversible cause of LETMp. The prevalence of Vitamin B_{12} deficiency in this population was 54% of which only 11% account for SACD LETMp syndrome. The remaining 43% of patients with low Vitamin B_{12} had other primary causes mainly inflammatory, including (NMO) accounting for their clinical and radiological syndrome. This leads to the conclusion that low Vitamin B_{12} predisposes patients to LETM. This study dictates an urgent need to study a possible link between low Vitamin B_{12} and inflammatory LETM, including NMO positive LETM so that B_{12} replacement could be done at the earliest, possibly with immunomodulation.

A major limitation of this study is its cross–sectional nature. Further studies with longer term follow ups would help compare and contrast outcomes with a dominant western literature studying a vastly divergent population.

References

[1] D.M. Wingerchuk, V.A. Lennon, S.J. Pittock, C.F. Luchinetti, B.G. Weinshenker, Revised diagnostic criterion for Neuromyelitis Optica, Neurology. 66 (2006) 1485–1489.
[2] R.C. Dale, A. Vincet, Inflammatory and autoimmune disorders of nervous system in children, J. Child Neurol. 26 (6) (2010) 96–106.
[3] Barnella B. Wingerchuk, J.L. Benetton, P. Cabre, W. Carrole, T. Chitinis, et al., International consensus on diagnostic criterion for NMOSD, Neurology. 85 (2015) 1–13.
[4] Corrinna Trebst, P. Raab, E.V. Voss, P. Rommer, M.A. Mughheisib, U.K. Zettl, et al., Longitudinal extensive myelitis- it's not all neuromyelitis optica, Nat. Rev. Neurol. 7 (2011) 688–698.
[5] J.L. Kitley, M.I. Liete, J.S. George, J.A. Palace, The differential diagnosis of LETM, Mult. Scler. 18 (3) (2012) 271–285.
[6] P.J. Waters, Serologic diagnosis of NMO: a multicentre comparison of AQP-4 assays, Neurology. 78 (February (9)) (2012) 665–671.
[7] R.S. Jain, S. Kumar, T. Mathur, S. Tejwani, Longitudinal extensive transeverse myelitis: a Retrospective analysis of 64 patients at a tertiary care centre of North West India, Clin. Neurol. Neurosurg. 148 (September) (2016) 5–12.
[8] Cobo Calvo Alvaro, Agusti Alentorn, Martinez Mane, Laura Bau, Elisabet Matas, Jordi Bruna, et al., Etiological spectrum and prognosis of longitudinal extensive transeverse myelopathies, Eur. Neurol. 72 (2014) 86–94.
[9] Paulo Marchiori Apostolos-Pereira, Alessandra Dellavance, Leandro Lucato, Frederico Jorge, Renata Simm, et al., Differential diagnosis of longitudinally extensive transverse myelitis, Neurology. 80 (February (7)) (2013) 109.
[10] M. Sepulveda, Y. Blanco, A. Rovira, J. Rio, M. Mendibe, S. Llufriu, et al., Analysis of prognostic factors associated with longitudinally extensive transverse myelitis, Mult. Scler. 19 (2013) 742–748.
[11] E.C. Contentti, J. Hryb, F. Leguizamon, J.L. Di Pace, J. Celso, E. Knorre, et al., Differential diagnosis and prognosis for longitudinally extensive myelitis in Buenos Aires, Neurologia. 32 (June (2)) (2015) 99–105.
[12] D. Pokalkar, V. Narisetty, M. Chekuri, S. Poosarla, S. Sripuram, S.K. Kamera, Clinical profile of longitudinal extensive transeverse myelitis in Indian population: a Prospective study from a tertiary teaching hospital of South India, Neurology. 82 (10) (2014) 153.
[13] W.H. Zhang, Y.J. Jiao, J.S. Jiao, Z.J. Liu, R.B. Wang, Clinical features of ultra-longitudinally extensive transverse myelitis, Zhonghua Yi Xue Za Zhi 91 (35) (2011) 2464–2467.
[14] J. Kitley, M. Leite, W. Kuker, G. Quaghebeur, J. George, P. Waters, et al., Longitudinally extensive transverse myelitis with and without aquaporin 4 antibodies, JAMA Neurol. 70 (2013) 1375–1381.
[15] N. Asgari, S.T. Lillevang, H.P. Skejoe, M. Falah, E. Stenager, K.O. Kyvik, A population based study of neuromyelitis optica in Caucasians, Neurology. 76 (May (18)) (2011) 1589–1595.
[16] K.M. Sanket, C.A. Swati, A study of prevalence of serum Vitamin B_{12} and folic acid deficiency in Western Maharashtra, J. Family Med. Prim. Care 4 (March (1)) (2015) 64–68.
[17] Kaushik Sen, Pradyot Sinhamahaptra, Joseph Lalmachhuana, Subhabrata Ray, A study of clinical profile of vitamin B_{12} deficiency with special reference to dermatological manifestations in a tertiary care hospital in sub –Himalayan Bengal, Indian J. Dermatol. 60 (4) (2015) 419.
[18] Alesia Hunt, Dominic Harrington, Susan Robinson, Vitamin B12 deficiency : clinical review, BMJ 349 (2014) g5226.
[19] K. Leishear, L. Ferrucci, F. Lauretani, R.M. Boudreau, S.A. Studenski, C. Rosano, et al., Vitamin B12 and homocysteine levels and 6-year change in peripheral nerve function and neurological signs, J. Gerontol. A Biol. Sci. Med. Sci. 67 (May (5)) (2012) 537–543.
[20] Lekha Pandit and, Rashmi Kundapur, Prevalence and patterns of demyelinating central nervous system disorders in urban Mangalore, South India, Mult. Scler. 20 (October (12)) (2014) 1651–1653.
[21] Kavita Sohan Barhate, Malti Ganeshan, Bhim Sen Singhal, A clinical and radiological profile of neuromyelitis optica and spectrum disorders in an Indian cohort, Ann. Indian Acad. Neurol. 17 (2014) 77–81.
[22] Sujit Abajirao, Alok Mandliya Jagtap, C. Sarada, M.D. Nair, Neuromyelitis optica and neuromyelitis optica spectrum disorder:natural history and long-term outcome, an Indian experience, J. Neurosci. Rural Pract. 6 (3) (2015) 331–335.