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Research Article

Study of the Clinical Profile, Management and Follow Up of Patients with Longitudinally Extensive Transverse Myelitis in a Tertiary Care Centre in India

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Abstract

Objective: To evaluate the clinical profile, response to treatment of different etiologies and prognosis of patients of LETM in Indian population.

Patients and Method: A hospital based prospective study was conducted in Department of Neurology, IHBAS, New Delhi from January 2018 to June 2019.

Total of 40 patients of LETM were stidied in detail and followed up for 6 months.

Result: In our series, NMO was the most common diagnosis constituting 20% of patients. Other common diagnosis were Tubercular Myelitis (17.5%), ATM (Post viral)(17.5%). Most common symptoms were sensory abnormalities followed by bladder/bowel involvement and parapresis. Maximun patients had partial recovery at 6 months (47.5%).

Conclusion: LETM is a heterogeneous diaorder with multiple etiologies. NMO is most common etiology but doesn't constitute majority of patients. So LETM patients should be extensively evaluated to find the correct diagnosis as prognosis depends on that.

Keywords: Transverse Myelitis; LETM; Neuromyelitis Optica; Paraparesis

Introduction

Longitudinally extensive transverse myelitis (LETM) is characterized by contiguous inflammatory lesion of spinal cord extending to three or more vertebral segments. NMO is invariably the most common cause of LETM. Other causes of LETM are infective, neoplastic, autoimmune and connective tissue disorders. All other causes should be ruled out before diagnosis of NMO with appropriate investigations, as early diagnosis and management is essential for optimal outcome [1]. The syndrome can be roughly divided into two groups based on whether the syndrome is complete or partial. However, the clinical and radiologic findings do not always co-associate [2,3]. NMO is characterized by unilateral or bilateral optic neuritis and spinal cord involvement. In patients with NMO, spinal lesions are typically longitudinal and centrally located, usually extending over several vertebral levels. LETM is not only a characteristic feature of NMO, but also part of the diagnostic criteria for this disease [4]. Recently in 2015, a new diagnostic criteria for NMO spectrum disorder was introduced (IPND NMOSD DIAGNOSTIC CRITERIA) which divides the disease into AQP4 positive and AQP4 negative cases and includes wide spectrum of presentation of the disease. Autoimmune inflammatory conditions other than NMO—such as multiple sclerosis (MS), acute disseminated encephalomy-

elitis (ADEM), systemic lupus erythematosus (SLE), sarcoidosis, or Sjögren syndrome —can also present as (or with) LETM. The etiologies of LETM are broad ranging from metabolic cause to demyelinating disorders. Tuberculosis can be one of the important cause of LETM especially in developing countries like India.

Differential diagnosis of LETM

Neuromyelitis optica

Most patients who present with LETM are diagnosed with NMO on the basis of revised criteria[4] that require the presence of optic neuritis and myelitis (not necessarily simultaneously) and two of three supporting criteria: LETM; brain MRI findings that do not meet the criteria for the diagnosis of MS; and the presence of antibodies against aquaporin-4 (known as NMO-IgG). Recently in 2015, a new diagnostic criteria for NMO spectrum disorder was introduced (IPND NMOSD DIAGNOSTIC CRITERIA) which divides the disease into AQP4 positive and AQP4 negative cases and includes wide spectrum of presentation of the disease. The diagnostic work-up for patients with suspected NMO includes a search for NMO-IgG antibodies, which are highly specific for this disease [5].

Analysis of CSF samples from patients with NMO typically reveals low to moderate pleocytosis consisting of granulocytes, lymphocytes and monocytes. Oligoclonal bands are found in about one-third of patients [6]. Brain MRI in patients with NMO can show normal brain morphology, but up to 60% of patients with this disease present with brain lesions. Most of these lesions are nonspecific (for example, non enhancing deep white matter lesions that are not related to the ventricles) and are not typical of those found in patients with MS. However, some brain lesions in patients with NMO can exhibit the characteristics of MS lesions, or present as an atypical, large, confluent lesion in the hemispheres, diencephalon or brainstem [7,8]. Spinal lesions in patients with NMO often involve the center of the cord and, although rare, patchy gadolinium enhancement and cavitations can sometimes be seen [9,10].

Multisystem autoimmune inflammatory diseases

LETM can also occur in patients with multisystem autoimmune inflammatory diseases, such SLE, sarcoidosis, Sjögren syndrome, or vasculitis. An association between myasthenia gravis and NMO has also been reported [11]. NMO-IgG-negative LETM can be the initial presentation of a patient with a systemic inflammatory disease. Thus, serological tests to detect antinuclear antibodies—such as antibodies to extractable nuclear antigens, double stranded DNA and soluble IL-2 receptor, rheumatoid factor, perinuclear anti neutrophil cytoplasmic antibodies, and antiphospholipid antibodies—are needed to establish the diagnosis.

Multiple sclerosis

Acute inflammatory myelitis is common in patients with MS; these spinal cord lesions typically extend over one or two vertebrae and are often localized to the lateral or dorsal part of the spinal cord. In the acute phase of disease, the lesions demonstrate patchy, nodular or ring-shaped enhancement on MRI. LETM extending over more than three vertebrae in patients with MS is unusual and rare, but has been reported [12,13].

Acute disseminated encephalomyelitis

ADEM is a monophasic demyelinating disease with pleiotropic clinical manifestations that typically affects children and young adults. Patients with ADEM can also present with LETM [14]. Diagnostic work-up of these individuals includes CSF analysis (which typically shows a mild to moderate pleocytosis and no oligoclonal bands), and cranial MRI, which can sometimes show large lesions in the white and gray matter.

Infectious causes of LETM-like symptoms

Infectious and parainfectious myelopathies (caused by viral, bacterial or parasitic agents) can present as longitudinal spinal cord lesions.[15] CSF analysis is the most important tool for the diagnosis of infectious myelopathy. Infectious agents that are particularly liable to be involved in causing spinal cord lesions are the herpesviruses (herpes simplex, varicella zoster, Epstein–Barr virus and cytomegalovirus [16]), HIV, HTLV-1 [17,18], *Borrelia burgdorferi* [19] *Treponema pallidum* [20,21], *Mycobacterium* spp. and schistosomiasis [22].

Neoplastic disorders

Beside the spinal manifestation of a B-cell lymphoma intramedullary spinal cord tumors, such as ependymomas or spinal astrocytomas—the most frequent intramedullary tumors in adults—must be considered. Intramedullary lymphomas, hemangioblastomas, dermoid tumors, and metastases are rare causes of LETM. Paraneoplastic manifestations should also be considered in patients with LETM [23], particularly those who have spinal lesions associated with antibodies to collapsin response mediator protein 5 (CRMP5, also termed CV2) [24,25]. Antibodies to amphiphysin or glutamic acid decarboxylase have also been found in patients with an underlying paraneoplastic disorder, and should be considered when looking for a para neoplastic cause of LETM [26-28].

Vascular causes of LETM-like symptoms

Acute spinal cord infarction can mimic myelitis [29] the ischemic area can extend over several vertebral segments and mimic LETM.

Traumatic causes of LETM-like symptoms

Spinal lesions that arise after trauma are, in most cases, due to compression of the spinal cord after vertebral fractures. Traumatic LETM is indicated by medullary edema with signs of hemorrhage and paraspinal signal abnormalities.

Nutritional causes of LETM-like symptoms

Patients with vitamin B12 deficiency can develop widespread spinal lesions that predominantly affect the dorsal and lateral parts of the spinal cord [30], which leads to subacute combined degeneration with swelling of the cord in the acute phase, usually without gadolinium enhancement.

Copper deficiency is also a rare differential diagnosis of LETM.

Aim

To study the clinical profile, management and follow up of patients with Longitudinally Extensive Transverse Myelitis.

Objectives

- To study clinical profile of LETM.
- To study the response of treatment of different etiologies of LETM
- To study follow up and prognosis of patients of LETM.

Materials and Methods

This is a hospital based prospective study conducted in the Department of Neurology, IHBAS for a period of 1.5 years (January 2018 to june 2019). All the patients who presented with clinical diagnosis and radiological evidence of LETM were admitted for assessment and were followed up for 6 months. A total of 42 patients were initially recruited but later 2 patients were excluded as they found to be cases of compressive myelopathy, leaving behind 40 patients in the study. The inclusion and exclusion criteria for the study participants are given below.

Inclusion criteria

- Acute, subacute or chronic paraplegia or quadriplegia.
- MRI evidence of myelitis involving three or more segments of spinal cord.

Exclusion criteria

- Clinical or radiological evidence of spinal cord compression.
- MRI evidence of myelitis involving less than three segments of spinal cord.
- Patients refusing to give the consent for the study.

Diagnostic tests

On admission, the following investigations were carried out.

- **Routine blood investigations**: Complete haemogram, Blood sugar, Liver function test, Kidney function test, HIV, HBsAg, HCV, Thyroid function test, Vitamin B12 level
- **Neuroimaging**- Spinal cord MRI was done with contrast of every patient of the whole length of cord. MRI Brain with contrast was also done of every patient.
- **CSF Exmn:** Every patient except one of syringomyelia undergone lumbar puncture for CSF examinations. CSF studies included CSF cytology and biochemical analysis (sugar and protein). Detailed microbiological studies of CSF was done at Department of microbiology including bacterial and fungal cultures, viral PCR and serology.

Other special investigations in CSF was also done in selected patients. Which includes CSF OCB, TB PCR in CSF.

- **VEP:** It was done in every patient to detect optic neuritis which is a very common feature in various etiologies of LETM.
- **Anti NMO Ab in serum:** Done in all patients.
- **Nerve conduction studies:** Done in selected patients as per need.
- **Other investigation:** Autoimmune panel including- ANA, dsDNA, pANCA, cANCA Full ENA profile was also done in selected patients. Serum anti MOG ab was done in selected patients.

Questionnaire and scales used in study- (enclosed in annexures)

- EDSS (Expanded Disease Status Scale)- This scale was used to determine the overall neurological disability in all patients at the presentation and at 6 months follow up to determine the prognosis.
- MMSE (Mini Mental State Examination)- This was used in all patients to determine the cognitive state at presentation and at 6 months follow up.

Written consent

A written consent will be taken from patient or their next of kin for sample collection or radiological or electrophysiological investigations along with consent to archive specimen and for follow up of outcome.

Ethical issues

Appropriate procedures considering all aspects for obtaining consent was followed under which following issues were addressed

- Informed written consent was taken
- Management of patients got priority over the assessment for study
- Information gathered during the study was kept confidential.
- Subjects had the right to withdraw from the study at any point of time as per their will.

Ethical clearance

Ethical permission was obtained from the ethical review committee of IHBAS.

Statistical analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used.

Statistical tests were applied as follows-

- Quantitative variables were compared using NAOVA/Kruskal Wallis test (when the data sets were not normally distributed) between the three groups. Wilcoxon signed rank test was used to compare initial EDSS score with follow up EDSS score.
- Qualitative variableswere correlated using Chi-Square test.
- A p value of <0.05 was considered statistically significant.

Results

Total 40 patients fulfilling the criteria of LETM were enrolled in present number, 37.5% of included cases were male and 62.5% were female. In our study, mean age at presentation was 29.35 years with range from 15 to 70 years. The most common age group at presentation was 21- 30 years constituting 37.5% patients, followed by less than 20 year age group constituting 25% patients. 85% patients were less than 40 years in our study. Sensory symptoms were the most common symptoms observed in 97.5% patients followed by bladder and bowel involvement (87.5%) and paraparesis (85%) respectively. Visual symptoms were found in 22.5% patients in our study. Behavioural and cognitive symptoms were very rare in our study and were found in only in 5% of patients. Patients who presented with these symptoms were of ADEM and multiple sclerosis. Patients with other presenting symptoms included 1,(2.5%) patient of area prostema syndrome, 1, (2.5%) patient of Backache, 1,(2.5%) patient of Bulbar symptoms, 1,(2.5%) patient of fever, 1,(2.5%) patient of pulm T.B, 1,(2.5%) patient of posterior column signs, and 1,(2.5%) patient weight loss and Rt upper limb weakness. MRI brain was abnormal in 30% patients. 10% have MS like lesions and 20% have non specific findings. Anti AQP4 Ab positivity was found in 20.51% patients, that means all NMO patients found positive for this antibody. In VEP findings, 30.77% had prolonged P100 latencies indicating optic neuritis. In study of Joanna., *et al.* 27% had ON in AQP4. CSF findings showed mean cell count was 29.03 cells (predominantly lymphocytes), mean sugar was 64.2%, and mean protein was 68.69% in LETM patients. OCB was found in 3 patients (7.5%). The most common diagnosis in our study was NMO found in 20% patients followed by Acute Transverse Myelitis (post viral) in 17.5% and Tuberculer myelitis and tuberculoma in 17.5% patients. In 20% patients, cause remain unknown. Other diagnosis made in LETM patients were MS (10%), ADEM (5%), SACD (5%), Neuro Sjogrens (2.5%), Syringomyelia (2.5%). Rajendra., *et al*. found most common diagnosis of NMO (32.8%) followed by MS in 14.06% and post infectious myelitis in 9.37%. 14.06% remained undiagnosed.

The diagnostic criteria used for NMO was IPND Updated Diagnostic Criteria for NMOSD (2015). The diagnostic criteria used for Multiple Sclerosis was Revised McDonald Criteria (2017). The International Pediatric Multiple Sclerosis Study Group proposed diagnostic criteria was used for ADEM. SACD was diagnosed by establishing vitamin B12 deficiency through serum Vit B12, MMA and homocysteine levels. For Sjogren syndrome, American Europian Consensus Group criteria was used. Syringomyelia was diagnosed by radiological evidence. Tubercular myelitis was diagnosed through radiological and CSF evidence of tuberculosis.

IV MPS f/b oral steroid was given in 52.5%, IV MPS f/b DMD was given in 22.5%, IV MPS followed by ATT was given in 17.5%. Treatment protocol was followed as per the latest treatment guidelines of the respective disease. IV MPS was used for acute treatment of ADEM, Transverse myelitis(post viral), and LETM of unknown causes. IV MPS F/B Disease modifying drugs were used for NMOSD, MS and Neurosjogren's syndrome. IV MPS F/B ATT was used for tubercular myelitis and intramedullary tuberculoma. VITAMIN B12 supplementation was given for SACD. No treatment was given to syringomyelia and reffered to neurosurgery. This table shows overall treatment scenario of major drugs used in LETM patients. Prognosis was mainly determined according to change in EDSS score. 1(2.5%) patient died, 11(27.5%) patients had minimal improvement (change in EDSS – 0-1.5), 19(47.5%) patients had partial improvement (change in EDSS- 2-3.5), 9 (22.5%) have marked improvement (change in EDSS-4 or more).

Diagnosis

	Frequency	Percentage
Acute transverse myelitis post viral	7	17.50%
ADEM	2	5.00%
Intramedullary tuberculoma and tubercular myelitis	7	17.50%
Letm-cause unknown	8	20.00%
Multiple sclerosis	4	10.00%
Neuro sjogren's	1	2.50%
NMO	8	20.00%
SACD	2	5.00%
Syringomyelia with cerebellar herni ation	1	2.50%
Total	40	100.00%

Table a

Treatment given

	Frequency	Percentage
IV MPS	21	52.50%
IV MPS F/B disease modifying agents	9	22.50%
MCB	2	5.00%
MPS F/B ATT	7	17.50%
NO treatment given	1	2.50%
Total	40	100.00%

Table b

Prognosis

	Frequency	Percentage
Died	1	2.50%
Marked Improvement (change in EDSS - 4 OR more)	9	22.50%
Minimal Improvement (change in EDSS - 0-1.5)	11	27.50%
Partial Improvement (change in EDSS- 2-3.5)	19	47.50%
Total	40	100.00%

Table c

Comparison of different quantitative variables in groups

	Follow up			
	Marked improve-ment	Minimal improve-ment	Partial improve-ment	P value
Age				0.08 7
Sample size	9	11	19	
Mean ± Stdev	30 ± 12	35.82 ± 16.22	25.79 ± 7.62	
Median	25	32	25	
Min-Max	17-52	17-70	15-45	
Inter quartile Range	21.750 - 36.750	24 - 46	19 - 30.750	
Duration of symptoms in days				0.00 1
Sample size	9	11	19	
Mean ± Stdev	7.67 ± 5	174.18 ± 217.15	76.26 ± 90.86	
Median	6	120	23	
Min-Max	4-20	4-730	5-270	
Inter quartile Range	4.750 - 8.500	14.250 - 210	15.750 - 135	
Initial edss score				0.39 1
Sample size	9	11	19	
Mean ± Stdev	6.83 ± 1.25	6.18 ± 1.25	6.68 ± 1.03	
Median	7	6	7	
Min-Max	4.5-8	4-8	4.5-8	
Inter quartile Range	6.500 - 7.625	5.500 - 7.250	6.125 - 7.500	

No. of spinal seg. invoi.				0.67 3
Sample size	9	11	19	
Mean ± Stdev	9.67 ± 6.42	11.46 ± 8.09	12.32 ± 7.24	
Median	8	9	10	
Min-Max	5-25	3-25	4-25	
Inter quartile Range	5.750 - 11	5 - 16	6 - 17	
Cells				0.07 9
Sample size	9	10	19	
Mean ± Stdev	10.11 ± 13.69	8.1 ± 8.6	50.53 ± 75.14	
Median	5	4.5	21	
Min-Max	0-45	0-27	0-246	
Inter quartile Range	3 - 11.500	4 - 13	4.250 - 60.750	
Protein				0.57 2
Sample size	9	10	19	
Mean ± Stdev	49.89 ± 22.6	46.1 ± 14.72	67.16 ± 40.21	
Median	35	40	47	
Min-Max	32-89	33-76	24-148	
Inter quartile Range	33.500 - 70.750	38 - 52	34 - 89.250	
Sugar				0.40
Sample size	9	10	19	7
Mean ± Stdev	63.56 ± 13.29	72.2 ± 19.45	61.9 ± 22.18	
Median	58	68	67	
Min-Max	45-86	48-106	23-100	
Inter quartile Range	56 - 74.750	58 - 80	42.500 - 76.750	
Follow up edss score				<.00 01
Sample size	9	11	19	
Mean ± Stdev	2.06 ± 0.17	5.09 ± 1.43	4.24 ± 0.89	
Median	2	5	4	
Min-Max	2-2.5	3-7	2-5.5	
Inter quartile Range	2 - 2	4.500 - 6.500	4 - 5	

Table d

Comparison of etiologies in different group according to prognosis

		Follow up			Total	P value
		Marked improvement	Minimal improvement	Partial improvement		
Diagnosis	Acute transverse myelitis post viral	6 (85.71%)	0 (0.00%)	1 (14.29%)	7 (100.00%)	
	Adem	1 (50.00%)	1 (50.00%)	0 (0.00%)	2 (100.00%)	0.0008
	Letm-cause unknown	1 (14.29%)	4 (57.14%)	2 (28.57%)	7 (100.00%)	
	Multiple Sclerosis	1 (25.00%)	2 (50.00%)	1 (25.00%)	4 (100.00%)	
	Neuro sjogren's	0 (0.00%)	1 (100.00%)	0 (0.00%)	1 (100.00%)	
	NMO	0 (0.00%)	1 (12.50%)	7 (87.50%)	8 (100.00%)	
	SACD	0 (0.00%)	1 (50.00%)	1 (50.00%)	2 (100.00%)	
	Syringomyelia with cerebellar herniation	0 (0.00%)	1 (100.00%)	0 (0.00%)	1 (100.00%)	
	Tubercular myelitis	0 (0.00%)	0 (0.00%)	7 (100.00%)	7 (100.00%)	
Total		9 (23.08%)	11 (28.21%)	19 (48.72%)	39 (100.00%)	

Table e

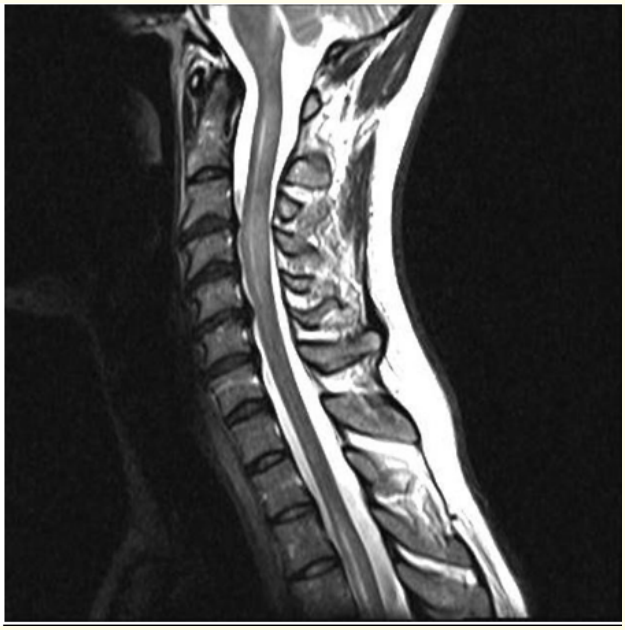

Figure 1: MRI spine in a patient of NMO showing involvement of more than 3 segments centrally with mild cord edema.

Discussion

The present study was an observational and prospective study, studying clinical profile, management and follow up of LETM patients. An effort was made to record complete information of these patients including the clinical and functional outcome. This study was conducted at the Department of Neurology, Institute of Human Behaviour and Allied Sciences (IHBAS), Dilshad Garden, New Delhi. The study evaluated the clinical profile, the response to the treatment given and the follow up of the patient of LETM. The clinical presentation was predominated with sensory symptoms, other common symptoms observed were bladder and bowel involvement and paraparesis. Our findings were similar to the study conducted by Rajendra., *et al.* [31]. In study of Rajendra., *et al.* [31], visual symptoms were present in 35.93% of patients. Most of these patients were of demyelinating illness most commonly NMO followed by MS and ADEM. Behavioural and cognitive symptoms were rarely found in our study. Maximum number of patients had duration of symptoms between 7 days and 30 days. In our study, the mean EDSS score initially was 6.6 and median EDSS score was 7 at presentation with EDSS range from (4 -8). The mean number of spinal cord segment involved was 11.35 with minimum 3 and maximum 25 in our study, as compared to study of Maria., *et al.* [32], which had median length involvement of 5 with range (3-19). In our study, all NMO patients were found positive for AQP4 antibody. The most common diagnosis in our study was NMO found in 20% patients followed by Acute Transverse Myelitis (post viral), Tubercular myelitis and tuberculoma. In 20% patients, cause remains unknown. Other diagnosis made in LETM patients were MS, ADEM, SACD, neurosjogrens, syringomyelia. Rajendra., *et al.* found most common diagnosis of NMO followed by MS and post infectious myelitis. The mean EDSS score at presentation was 6.6 with SD +-1.14 and median 7 which improved to 4.12 with SD +-1.74. and median 4 (p value < 0.0001). In our study, the minimal improvement group, mean value of spinal segment was 11.46, in partial improvement group, mean value is 12.32 and in marked improvement group is 9.67. Thus highest number of spinal segment was present in partial improvement group (p value- 0.673). Thus no. of spinal segment does not correlate with prognosis. In our study, in marked improvement group, the most common etiology was ATM (post viral), followed by ADEM. In partial improvement group, the most common diagnosis was tubercular myelitis in which 100% had partial improvement followed by NMO.

Conclusion

It may be concluded from the present study that Neuromyelitis optica was the most common diagnosis in our study constituting 20% of patients. LETM may have varied etiologies other than NMO as evident in our study as 80% had non NMO disease. After NMO, Tubercular Myelitis and ATM (Post viral) are also very common causes of LETM, both constituting 17.5% of patients. A major portion of LETM patients remained undiagnosed as in our study 20% patients have unknown causes. LETM can affect all ages and both sexes as in our study, age range is 15-70 years but it has a clear preponderance towards young females. Mean age was 29.35 years and 62.5% patients were females. The most common symptoms at presentation was sensory symptoms followed by bladder/bowel involvement and paraparesis. Maximum patients present with severe disability as mean EDSS at presentation was 6.6, median EDSS 7 in our study. The mean segment of spinal cord involved was 11.35 with range 3-25 and length of spinal cord involvement did not correlate with prognosis. Contrast enhancement in cord was found in 37.5% and 30% had abnormal MRI brain findings. Maxi-

mum patients had partial recovery at 6 months as follow up mean EDSS was 4.2, median 4. And 50% patients had change in EDSS between 2-3.5. The etiologies which have maximal improvement at 6 months(change in EDSS- 4 or more) were ATM(post viral) and ADEM. Most NMO and tubercular myelitis patients had partial recovery. (change in EDSS- 2-3.5).

Conflict of Interest

None.

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