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A CLINICAL PROFILE OF LONGITUDINALLY EXTENSIVE TRANSVERSE MYELITIS IN A TERTIARY CARE CENTRE

Neurology

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ABSTRACT

Purpose : Transverse myelitis is an inflammatory disorder with acute or subacute spinal cord dysfunction, characterized by motor, sensory, bladder and bowel involvement1 . Longitudinal extensive transverse myelopathy (LETM) is a spinal cord lesion involving three or more vertebral segments2.Most common etiology is Neuromyelitis optica (NMO), followed by infective, neoplastic, autoimmune diseases and connective tissue disorders, neoplasms and spinal cord trauma.3 This study assess the demographic, clinical, radiological and immunological characteristics and compares the aquaporin-4 positive versus negative in relation to clinical and radiological features. **Method** :This is a hospital based prospective case study that includes forty two patients presented to Neurology Department in tertiary care hospital, Hyderabad between October 2019 to November 202. The patients were studied for demographic profile, clinical presentation, blood serology,CSF studies and neuroimaging as per standard protocol. Patients with chronic progressive disease not fulfilling LETM criteria were excluded. **Results** : Mean age of onset was 36.5 ± 12.9 years. Most common complaints were sensory, followed by bowel/bladder involvement, motor weakness. Most common etiology was NMOSD (55%) Seropositive 57%, seronegative 43%. Non-NMOSD group comprised of Idiopathic (24 %), ADEM (7%), SACD (7%) and MS (5 %) and systemic autoimmune disorders (2%). Spinal cord MR imaging in NMOSD showed cervical spine involvement in 21.7 % patients, cervico-dorsal spine in 43.4%,dorsal spine involvement 17.3%. Radiologically Central full thickness pattern involving >1/2 transverse segment of cord was seen with NMOSD & ADEM. Marginal & posterior in MS. Posterior/ posterolateral in SACD. 8 had positive ANA of which 75% in NMOSD group. In our NMOSD cohort, certain clinico-radiological features were predicitve of seropositivity: female predominance; paroxysmal tonic spasms; unexplained recurrent hiccups, nausea or vomiting (Area postrema syndrome); relapsing course predominantly cervico-dorsal cord involvement , bright spotty lesions and T1 hypointense lesions on spinal MRI. **Conclusion:** In this study, NMOSD was the commonest cause of LETM. Female sex, paroxysmal tonic spasms, cervico-dorsal cord involvement, bright spotty lesions on MRI are features favoring seropositive NMOSD. Even topographical analysis, extent of lesions on MRI and contrast pattern may also give clues to the differential diagnosis. On axial topography, bright spotty lesions favour seropositive NMOSD, postero lateral pattern suggest SACD whereas posterior & marginal pattern suggests MS.

KEYWORDS

LETM, NMO, NMOSD, MS.

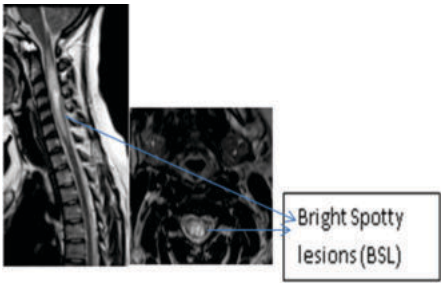
INTRODUCTION :

Transverse myelitis is an inflammatory disorder with acute or subacute spinal cord dysfunction. Clinically, it is characterized by motor, sensory, bladder and bowel involvement[1]. ***Longitudinally extensive transverse myelitis (LETM)*** is defined as intramedullary hyperintense T2-weighted signal abnormality that spans three or more vertebral segments.[4] If the lesion extends over ten or more vertebral segments then it is known as ***ultra-LETM(uLETM)***[5].Patients with LETM have varied clinical presentations. They can present with paraparesis or quadriparesis, sensory symptoms, gait abnormalities, bladder and bowel complaints and/or sexual dysfunction. In patients presenting with LETM the most common etiology and most common differential diagnosis to be considered is NMO. In patients with NMO, LETM is not only a characteristic feature but also it is a part of the diagnostic criteria.[6] Demyelinating causes of LETM include neuromyelitis optica spectrum disorders (NMOSD), acute disseminated encephalomyelitis (ADEM), Multiple sclerosis(MS) and Myelin oligodendrocyte glycoprotein(MOG). NMOSD is an inflammatory demyelinating disorder presents with optic neuritis & longitudinally extensive transverse myelitis (in some patients with involvement of the brain stem, diencephalon, or cerebral hemispheres) plus presence of anti-aquaporin-4 antibody in serum or fulfilling additional supportive criteria in seronegative patients[7]. Forty percent of patients presenting with LETM have positive aquaporin 4 antibodies in serum and the rate of relapse is higher in those individuals.[8] Female: male ratio was found to be 4:1 in epidemiological studies, and a median age at onset of around 37 years, and approximately 20% of these cases are associated with autoimmune diseases. More than 80 % of these NMO cases were found to have a relapsing and remitting clinical course. [9,10,11.] Clinical presentation depends on the involvement of the regions of the central nervous system (CNS) where AQP4 is expressed abundantly which include spinal cord (longitudinally extensive transverse myelitis), optic nerve (optic neuritis), dorsal medulla (area postrema syndrome), brainstem (acute brainstem syndromes), and thalamus/hypothalamus (acute diencephalic syndromes eg symptomatic narcolepsy). Attacks are more severe and may reach nadir in less than a week. Involvement of longitudinally extensive transverse myelitis (LETM) is the most specific presentation of NMOSD and this presentation is uncommon in MS. Inflammatory changes in LETM affects the central gray matter, involving over three or more contiguous vertebral bodies. Depending on the spinal cord involvement, patients with LETM presents with para- or tetraplegia. In NMOSD involvement of Optic neuritis (ON) also extends longitudinally and has a predilection for optic chiasm or posterior optic nerve segments. Painful visual loss with poor recovery (<6/60) and involvement of both eyes simultaneously are clues to the diagnosis. Patients with involvement of area postrema syndrome (APS) presents with intractable nausea, vomiting and/or hiccups which is due to the inflammation in the rhomboid fossa of the 4th ventricle where emetic reflex centre is located.[12] These patients initially are suspected as gastroenteritis or cyclical vomiting syndrome. Approximately 12 % of NMOSD patients will present initially as APS.[13]

NMOSD may involve more than half of the cord area and eventually may cavitate, which distinguishes from the plaques seen in multiple sclerosis. Cervical spinal cord region is the most commonly involved followed by cervico-thoracic, and it is followed by involvement of the thoracic cord. Involvement of spinal cord with its extension into the medullary region has been demonstrated to have very high prediction towards NMO spectrum disorders.[14] MRI spinal cord in NMO, demonstrates T2 signal abnormalities in intramedullary region and often T1 hypointense signal changes with a central pattern, but these signal abnormalities are not necessarily restricted to grey matter.[15] lesions may also show patchy contrast enhancement. In acute lesions there is smooth diffuse expansion and may show enhancement of lesions post gadolinium. Persistence of the hypointense signal change in T1 weighted image suggest axonal loss; so presence of T1 hypointense signal changes along with spinal cord atrophy are markers of the old lesions, and for acute spinal relapses the imaging marker is the enhancement of the lesion post gadolinium contrast.

BSL on sagittal & axial view of MRI as seen in our case of NMOSD.
Involvement of the Optic nerve may be unilateral or bilateral; On MRI swollen optic nerves have high signal intensity on T2 weighted image. However it is important to note that involvement of brain in NMO have

a predilection for those areas of brain which has high expression of aquaporin 4. Brain MRI reveals signal changes in areas with high aquaporin 4 expression which includes hypothalamus, around the third ventricle, periventricular regions, and periaqueductal grey matter.[16] NMO diagnosis is made with sensitivity & specificity of 99% and 90% respectively, by the presence of combination of optic neuritis, acute myelitis (with typical MR appearance), brain MRI lesions which do not meet MS diagnostic criteria, and presence of NMO IgG seropositivity. [17]



In NMOSD patients with seronegative for AQP4-Abs, approximately 40 % of patients may have MOG-Abs.[18] so in patients with suspecting NMOSD it is therefore reasonable to test for both AQP4-Abs and also for MOG-Abs. The most common clinical presentation of MOG-Ab-associated disease is acute disseminated encephalomyelitis (ADEM) in children who are under 7 years of age, and it may present with involvement of optic nerves in the form of optic neuritis in older children and adults.[19,20] In contrast to involvement of posterior segment of optic nerve involvement in the NMOSD ,inflammation of the anterior segments of the optic nerve is more common in patients with MOG-Abs.[21]

It is noteworthy that other conditions like systemic lupus erythematosus (SLE), sarcoidosis, or Sjögren syndrome —can also present as (or with) LETM. This highlights the importance of need for thorough evaluation and workup of patients presenting with LETM to differentiate those with NMO and those with NMO-spectrum disorders from individuals with autoimmune and inflammatory conditions.

Apart from autoimmune and inflammatory conditions, patients with an infectious, neoplastic or vascular disease, nutritional deficiencies, or traumatic injury, can also have the picture of longitudinally extensive lesion in the spinal cord[3]. So, all the above mentioned conditions should be considered in the differential diagnosis of patients presenting with LETM. In India the most common cause of acute myelitis is idiopathic. In 10–20% of NMO patients, autoimmune diseases such as thyroiditis, systemic lupus erythematosus, or Sjögren's syndrome was found.[22] Distinguishing inflammatory and non-inflammatory etiologies of LETM is important because treatment and risk of a recurrence varies. There may be varied profiles with respect to etiology, clinical presentation and radiology of LETM in our country when compared with developed world.[23] The present study aimed to highlight clinical presentation and radiological profiles of patients with LETM in tertiary centre.

AIM AND OBJECTIVES

To assess the demographic, clinical, radiological and immunological characteristics of patients with LETM and to compare between aquaporin-4 positive versus negative patients in relation to clinical and radiological features.

Methodology:

A prospective cohort Study conducted at Neurology department in a tertiary care hospital, Hyderabad during October 2019 to November 2021.

Patients evaluated by Department of neurology with clinical features of Acute/ subacute transverse myelitis (4-6 weeks) who are satisfying radiological criteria of LETM were included. Patients with chronic progressive etiologies like compressive, toxin induced causes, vasculitis, infection and malignancies, and patients not fulfilling LETM criteria were excluded. All 42 patients were studied for their demographic profile, clinical presentation, routine blood investigation followed by detail study with visual evoked potential, cerebrospinal fluid examination, serum/CSF NMO antibody, autoimmune workup with ANA antibody and when required with ANA blot by immunofluorescence, MRI brain, spine and optic nerve imaging with contrast study and other relevant investigations.

We divided our LETM cohort into NMOSD and non-NMOSD subgroups. NMOSD cohort had patients with Aquaporin-4 Ab positive and Aquaporin-4 Ab negative patients. Non-NMOSD cohort comprised of various etiologies: Multiple sclerosis, ADEM, Autoimmune, Nutritional (SACD) & Idiopathic. ON was diagnosed based on the presence of at least two of the following criteria: reduced visual acuity, afferent pupillary defect, color vision loss, visual field abnormality, and/or pain on eye movement. Visual evoked potentials were performed when ON was suspected.

As per treatment protocol all the patients diagnosed with NMOSD received five days course of injection methylprednisolone 1 gm/ day, followed by assessment of improvement.

Statistical Methods

- Statistical analyses were performed using Microsoft Excel 2019 (Ver. 16.42). Data was checked for normality.
- A p-value of 0.05 or less was considered statistically significant.

RESULTS:

Mean age of onset was 36.5 ± 12.9 years. Age distribution shown in Table 1. Female: male ratio was 1.2:1. Most common clinical presentations were sensory symptom (37/42, 88%), bowel/bladder involvement(33/42, 78.5%), paraparesis (28/42, 66.6%) and Quadriparesis (14/42 patients; 33.3%) depicted in figure 1.Most common etiology was neuromyelitis optica spectrum disorder (NMOSD) (55%).Non-NMOSD group comprised of Idiopathic (24 %), ADEM (7%), SACD (7%) multiple sclerosis (5 %) and systemic autoimmune disorders (2%) shown in Table 2 . Out of 42 LETM patients, 23 patients had NMOSD. In this NMOSD cohort, Seropositive patients were 57% and seronegative were 43%. In NMOSD cohort, spinal cord MR imaging showed cervical spine involvement in 21.7 % patients, cervico-dorsal in 43.4% dorsal spine in 17.3% Shown in table 3. Radiological topographical pattern was generally different with various etiologies. Central full thickness pattern involving >1/2 transverse segment of cord seen with NMOSD & ADEM group. Presence of Bright spotty lesions on MRI were seen significantly in NMOSD group (88%) (P Value= 0.02) .BSL had higher significance for seropositive NMO patients than seronegative NMO group (P Value=0.02).Marginal & posterior pattern was significantly seen with MS. Posterior/ posterolateral pattern, in SACD Shown in table 4.In our LETM cohort, CSF pleocytosis was common with NMOSD group whereas CSF OCB (75%) was significantly more common with MS. NMOSD group had association with other autoimmune disorders like hypothyroidism, hyperthyroidism, diabetes mellitus. Total 8 patients had positive ANA antibody. 75% of patients with positive ANA status in NMOSD group shown in table 5 .Certain clinico-radiological features were suggestive of seropositivity: female predominance; paroxysmal tonic spasm; unexplained recurrent hiccups, nausea or vomiting (Area postrema syndrome); relapsing course; predominantly cervico-dorsal cord involvement , bright spotty lesions and T1 hypointense lesions on spinal MRI shown in table 6. All patients of MS had clinical or subclinical optic nerve involvement.

Table 1. Mean Age of Onset & Gender distribution

Gender	Mean Age of Presentation (years)	Age Range (years)	Total
Male	35.05	(18-65)	19
Female	37.45	(16-72)	23
Overall	36.34	(16-72)	42

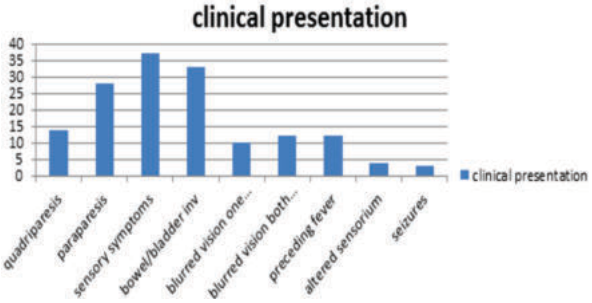


Figure:1 Overall Clinical Features of LETM cohort based on History & records

Table 2: Etiology of LETM cohort

Total	NMOSD		Non NMOSD Spectrum Disorders					
	NMO Ab +VE	NMO Ab-VE	ADEM	MS	Auto-immune	Idiopathic	SACD	Total
NO	13	10	3	2	1	10	3	42
%	31	24	7	5	2	24	7	100

Table:3 Radiological categorization of LETM Etiologies:

Total			
	NMOSD	Non Nmosd Spectrum Disorders	Total
Cervico Dorsal	10	10	20
Cervical	5	2	7
Dorsal	4	7	11
Ultra Letm	6	8	14
Contrast Enhancement	12	9	21
Cord Expansion	16	8	24
T1 Hypointensity	16	4	20

Table : 4 Pattern of Radiological involvement (Axial T2W image)

Pattern of Axial Involvement	NMOSD		Non NMOSD Spectrum Disorders					
	NMO Ab +VE	NMO Ab-VE	ADEM	MS	Auto-immune	IDIOPATHIC	SACD	Total
Central (full thickness) >1/2 segment	11	8	2	-	-	4	-	25
Central (partial thickness) <1/2 segment	2	2	1	1	1	3	-	10
Bright Spotty lesions (BSL)	7	1	-	-	1	-	-	9
Posterior /posterolateral	-	-	-	1	-	1	3	5
Marginal	-	-	-	1	-	-	-	1
Anterior	-	-	-	-	-	-	-	0
Necrotic/cavitary lesions	1	-	-	-	-	2	-	3

Table :5 Presence of ANA antibody

Ana Anti body	NMOSD		Non NMOSD Spectrum Disorders					
	NMO Ab +VE	NMO Ab-VE	ADEM	MS	Autoimmune	Idiopathic	SACD	Total
NO	4	2	1	0	1	0	0	8
%	50%	25%	12.5%	0	12.5%	0	0	100%

Table :6 Comparison of Seropositive & Seronegative patients in NMOSD cohort

Parameters	Seropositive (N=13)	Seronegative (n=10)	P value
Mean age of onset	38	32.5	0.43
Age range	16-72	16-58	-
Male: Female ratio	2:11	7:3	-
% of Female	84.6%	30%	0.007
ON at onset	3	2	0.55
Bil ON at onset	3	3	0.67
Hiccups/N/ V	2	1	0.77
Pleocytosis CSF(%)	4	5	0.94
Cervicodorsal spine(%)	7	3	0.25
Cervical spine(%)	3	2	0.85
≥10 segments	1	5	0.02
T1 hypointense lesions on MRI Spine	11	5	0.02
Bright Spotty lesions on MRI spine	7	1	0.02
Normal first brain MRI	7	5	0.85

DISSCUSSION:

Overall mean age of presentation of LETM patients was 36.5 ± 12.9 years. Age is earlier in our study as compared to Asian study from China by Zhang et al[24] but was comparable with other study by Contentti et al.[25] In NMOSD cohort, mean age at disease onset was 37.6 years (range 16 to 72 years), which was comparable to previous studies from various parts of the world. Out of total 42 patients of LETM, 23 (55%) were females and 19 (45%) were males. Female: male ratio was 1.2:1 suggestive of female preponderance which was corresponding with other studies by Zhang et al 6& contentti et al[25]. In present study, most common presenting symptoms were sensory complaints(88%); followed by bowel/bladder involvement(78.5%), motor weakness {paraparesis(66.6%) & quadriparesis(33.3%)}.Other studies have also reported sensory symptoms as the most common presenting symptoms, bowel /bladder involvement followed by motor weakness. These findings were in concordance with the studies by Jain et al[8] & Contentti et al7. Our LETM cohort patients were categorized into NMOSD (55%) and non-NMOSD (45%) categories. NMOSD group had seropositive [AQP-4 (+)] and seronegative [AQP(-)] subgroups . Out of NMOSD group Seropositive patients were 57% and seronegative patients were 43%.Non-NMOSD is a heterogenous group. Non-NMOSD group comprised of patients having varied etiology including Idiopathic(24 %), ADEM(7%) , nutritional: SACD (7%) and multiple sclerosis (5 %). This findings in present study is in concordance with the previous Indian study of Jain et al[26] .While MS classically presents as short segment myelitis, some patients of MS do present as LETM. We also found 2 (5%) patients of LETM having MS etiology. In the conventional form of MS reported from the West, 3-12.5% of patients were found to have LETM[27]. In our NMOSD cohort, spinal cord MR imaging showed cervical spine involvement in 21.7 % patients, cervico-dorsal spine in 43.4% patients whereas dorsal spine involvement in 17.3%. Yeliz et al[28] found involvement of cervicodorsal cord in 65% patients, dorsal in 55% & cervical in 52% of NMOSD patients. Present study showed reduced percentage, this may be due to less sample size in the present study. BSL (Bright spotty lesions) on MRI spine were found in 34.7% patients of our NMOSD cohort. Significantly higher number of patients in seropositive group had BSL as compared to seronegative group (P value=0.02). In various studies, BSLs were more frequently found in patients with NMOSD (54%) than in those with MS (3%).[10] In our study, cord expansion and central lesions were more frequently seen in NMOSD than in MS which was comparable to one study by Yonezu et al.[29] In our LETM cohort total 8 patients had positive ANA antibody status. We had 75% of patients with positive ANA status in NMOSD group(50% seropositive and 25% seronegative). In a study by Kanikannan et al[30], 35% of seropositive and 6.4% seronegative group had presence of ANA antibody. Present study showed significant gender difference between seropositive and seronegative group (p value=0.007). Female predominance was seen more in seropositive group, whereas a greater number of males were seen in seronegative group, which was statistically significant, this finding is in concordance with the study done by Kim et al[31]. .In the present study we found, paroxysmal tonic spasm, area postrema syndrome, T1 hypointensity and Bright spotty lesions on MRI spine (P value=0.02), along with cervicodorsal cord involvement were more commonly associated with seropositivity. Our findings of AQP-4(+) and AQP-4(-) were further supported by another study of Kanikannan et al[30].

CONCLUSION:

In our prospective study, we aimed to focus on clinical and radiological spectrum of **"Long segment Extensive transverse myelitis" (LETM)** patients. LETM is a radiological diagnosis. There are various clinical presentations and different etiologies. In this study, NMOSD was the commonest cause.

Female sex, paroxysmal tonic spasms, cervico-dorsal cord involvement, bright spotty lesions on MRI are features favoring seropositive NMOSD. Though uncommon, some MS patients may have LETM presentation. In a proportion of cases, we could not find out the exact etiology (Idiopathic) despite all available investigations. Also, it is important to test all seronegative NMOSD patients for myelin oligodendrocyte glycoprotein (MOG) antibody.

LETM represents a spinal cord syndrome; but detailed clinical and radiological evaluation of other parts of CNS may help identify the etiological process. Even topographical analysis, extent of lesions on MRI and contrast pattern may also give clues to the differential diagnosis. On axial topography, bright spotty lesions favour seropositive NMOSD, postero lateral pattern suggest SACD whereas posterior & marginal pattern suggests MS.

Ultra LETM (u-LETM) is a common entity; for which NMOSD still remains the commonest etiology. However, other etiologies like idiopathic & ADEM are also important causes of u-LETM.

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