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Original Research Article

Clinical profile of longitudinally extensive transverse myelitis: A study in a tertiary care hospital in Western Rajasthan

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ABSTRACT

Objective: As there are wide differentials for longitudinally extensive transverse myelitis (LETM), its aetiology should be found to optimise therapy.
Aims: Clinical profile of LETM.
Settings and Design: ambispective observational study.
Methods and Materials: 73 patients with acute to subacute myelitis involving 3 or more vertebral segments were properly investigated.
Statistical analysis used: Student t test and Mann-whitney test used, and comparison of data done using SPSS version 22.0
Result: The etiology found were in form of neuromyelitis optica spectrum disorder (NMO-SD) in 18(24.6%), para-infectious in 13(17.8%), idiopathic in 17(23.2%), infectious in 9(12.3%), and rest were acute disseminated encephalomyelitis (ADEM), subacute combined degeneration (SACD), infarct, radiation myelitis etc.
Conclusions: It is important to find etiology of LETM to optimise the therapy as the in inflammatory myelitis other than NMOSD, the line of management differs. Relapsing nature of some myelitides is an important aspect in management

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1. Introduction

Transverse Myelitis is an inflammatory disorder of spinal cord which can result from demyelination, autoimmune, connective tissue, vascular, infectious and metabolic disorders in the absence of demonstrable compression by imaging techniques. Longitudinally Extensive Transverse Myelitis (LETM) is characterized by contiguous inflammatory lesion of spinal cord extending into three or more vertebral segments as seen on MRI.[1] LETM is usually thought to be synonymous with Neuro myelitis Optica (NMO), so it's important to find underlying etiology so that therapy can be optimized. There are few Indian studies on LETM profile from with some similarities and some differences.[2–5] We conducted retrospective and prospective study find the clinical profile of the LETM.

2. Materials and Methods

It's an ambispective observation study being conducted in department of Neurology in our institute, a tertiary health care centre. Patients included in study were those who presented with acute, sub-acute or chronic neurological dysfunction consistent with myelopathy and MRI was suggestive of non-compressive myelopathy with spinal cord inflammation extending to three or more vertebral segments Cases were defined based on standard diagnostic criteria. Neuromyelitis optica spectrum

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disorder patients were defined as per Wingerchuk criteria,[6] diagnosis of Multiple sclerosis was based on 2010 revised Mc Donald Criteria.[7] Infectious myelopathy was diagnosed with positive serology, or evidence of other organ involvement with temporal relationship. Para-infectious myelitis was labelled in presence of history suggestive of preceding infection with in 1 month of onset of neurological symptoms. Paraneoplastic myelitis was diagnosed in presence of malignancy or positive paraneoplastic antibodies and excluding other causes of LETM. ADEM was diagnosed in patients who presented with encephalopathy and multifocal brain lesions along with spinal cord lesions, as per diagnostic criteria proposed by International Pediatric Multiple Sclerosis Study Group.[8] A relapse was considered when there was appearance of new symptoms or worsening of an existing symptom along with an objective documentation in the absence of fever and lasted for at least 24 hours. Acute myelopathy was considered when spinal cord dysfunction reaching nadir within 7 days of onset, sub-acute myelopathy when spinal cord dysfunction reaches nadir within 7 to 21 days[9] and chronic myelopathy when spinal cord dysfunction is insidious onset and progressing gradually over months to years.

Based on above mentioned criteria 73 patients were included in the study from September 2014 to march 2018 with the final diagnosis of LETM. Thorough history and clinical examination of all the patients was undertaken and baseline EDSS score was calculated. Investigations performed were hemogram, biochemistry (renal function tests, liver function tests, random blood sugar), HBsAg, anti HCV antibodies, HIV 1 & 2, thyroid profile, urinalysis, chest X-ray and visual evoked potential, MRI spine and brain, cerebrospinal fluid examination for total counts, differential counts, protein and sugar and oligoclonal bands and other relevant ones. Immunological tests included antibody against aquaporin 4(AQ4-IgG), antinuclear antibodies, anti dsDNA, anti-smith, anti Ro, anti La, anti-phospholipid antibody, angiotensin converting enzyme levels and anti thyroid peroxidase (TPO) antibodies. Metabolic profile included vitamin B12 and folate levels. Special investigations were performed depending on clinical setting included CSF PCR for VZV, HSV, CMV, EBV, Mycobacterium tuberculosis, Toxoplasma, ADA, VDRL, cryptococcal antigen. Investigation in suspected paraneoplastic myelitis were antibodies against Hu, Ri, Yo, Ma, collapsing response mediator protein-5(CRMP-5) & amphiphysin. In patients with suspected systemic disease or malignancy; ultrasonography abdomen and pelvis, computerized tomography scans of thorax and abdomen were also performed.

2.1. Data collection and statistical analysis

Data was collected in form of clinical, radiological and laboratory parameters in a predesigned Performa. During follow up visits observations were made in form of EDSS Score, any relapse, side effects, death and lastly ΔEDSS (difference in EDSS score at baseline and follow up) was calculated. Comparison of data was done using the Statistical Package for the Social Sciences version 22.0(SPSS). Student t test and Mann –Whitney U-test were used in this study. P value less than 0.05 was considered statistically significant.

3. Results

Out of 73 patients, 48(65.7%) were male and 25(34.2%) were female. Female predominance was seen in patients of NMO-SD, ADEM and connective tissue disease. Mean age of onset is 40.50 years and range is 15-85 years.

Mean age of onset in NMO-SD group was 32.9 years, parainfectious myelitis 38.6 years, spinal cord infarct 45 years, multiple sclerosis 34 years, idiopathic myelitis 46.5 years and ADEM was seen in relatively younger population with mean age of onset 25 years.

3.1. Clinical features

In motor manifestations paraparesis seen in 56.1%, quadriparesis 37%, triparesis in 2%, monoparesis in 3% and spasticity was present in 87% patients. Paraesthesia were present in 68%, Spinothalamic tract involvement in 84.9%, posterior column in 69%. Radiculopathy was seen in 4.10% and bladder involvement was seen in 85%. Associated features like optic neuritis/optic sequential in 3 patients i.e within 10 days and simultaneous in 6 patients out of which 2 were ADEM and rest NMOSD) and unilateral in 2 patient of NMO-SD, and MS each one each.

Neuropathy was seen in 20.5%, brainstem involvement in 21.9% and encephalopathy in 5.4 %. Optic nerve involvement was bilateral in 11 patients.

3.2. Etiological spectrum of LETM patients (n=73)

Neuromyelitis spectrum disorder - 18(24.6%)
- Parainfectious - 13(17.8%)
- Infectious - 9(12.3%)
- Tubercular 3, VZV 2, Chikungunya 1, Dengue 1, HIV 2
- Acute disseminated encephalomyelitis - 4(5.4%)
- Subacute combined degeneration - 2(2.73%)
- Multiple sclerosis - 2(2.73%)
- Spinal cord infarction - 2(2.73%)
- Hashimoto disease - 2(2.73%)
- Connective tissue disease - 1(1.36%)
- Undifferentiated CTD - 1(1.36%)
- Radiation - 2(2.73%)
- Paraneoplastic - 1(1.36%)

Undetermined etiologies - 17(23.2%)

3.3. Disease onset

40% patients had acute onset (i.e. disease progression less <7 days), 52% patients had sub-acute onset i.e. disease progressed over 7 to 21 days and 8.2% had chronic onset with disease progression over more than 21 days of onset.

Cauterization /aetiologies as per onset-

in acute, sub-acute and chronic LETM-

Acute onset <7 days -(40%)

Sub-acute onset 7-21 days -(52%)

Chronic onset >21 days- (8.2%)

Idiopathic (6)

Para infectious (7)

Neuromyelitis spectrum disorder (9)

Multiple Sclerosis (1)

Acute disseminated encephalomyelitis (1)

Infarcts (2)

Infectious (3) Neuromyelitis spectrum disorder (9)

Idiopathic (11)

Parainfectious (6)

Infectious (5)

Acute disseminated encephalomyelitis (3)

Undifferentiated connective tissue diseases (1)

Paraneoplastic (1)

Hashimoto's disease (2) Tubercular (1)

Sub-acute combined degeneration (2)

Multiple Sclerosis (1)

Radiation (2)

On MRI spine thoracic segments were most commonly involved (52%) followed by cervical cord (46%), but involvement of cervical spine was seen commonly in NMO-SD patients (n=12), para-infectious (n=7), infectious (n=5), ADEM (n=4) and Radiation myelitis (n=2). Thoracic spine involvement was seen predominantly in idiopathic myelitis (n=14) and spinal cord infarcts (n=2). Whole cord involvement was seen in 6.80% and multifocal involvement in 4.10% of total patients.

On MRI spine 3-5 segment involvement was seen in idiopathic myelitis (6 patients=), NMO –SD (3), infectious myelitis (3), ADEM (2), Radiation myelitis (2), Connective tissue disease (1), Multiple sclerosis (1) and Paraneoplastic myelitis (1). ADEM patients mainly had multifocal lesions with each focus involving 2-3 segments. Lesions more than 10 segments were found in patients with NMO-SD(10), Para-infectious(7), idiopathic (4), infectious(3) ADEM(1). Whole cord involvement was seen in NMO SD, ADEM, Infectious myelitis as well as in SACD patients. On MRI thoracic segments were most commonly involved followed by cervical.

Table 1: The number of spinal segments involved in different etiologies

Category	3-5 segments	6-10 segments	>10 spinal segments
NMOSD-	3	5	10
Idiopathic	6	7	4
Parainfectious -		6	7
ADEM	2	1	1
Radiation	2	1	1
Infectious	3	3	3
Cord infarction	2	-	-
M S	1	-	-
Paraneoplastic	1	-	-

3.4. The CSF analysis

On CSF analysis, CSF pleocytosis was seen in 9 patients of NMO-SD, 1 ADEM, 5 infectious myelitis, 6 para-infectious and 7 patients of undetermined aetiology. Infectious myelitis patients had cells in the range of 23-310 cells/μL with lymphocytic predominance, NMO-SD had cells in the range of 12-222 cells/μL with lymphocytic predominance & ADEM patient had 5-460 cells.

Protein elevation >45 mg/dl was seen in NMO-SD (number of patients = 10), Multiple sclerosis (1), ADEM (3), Infectious myelitis (6), Para-infectious myelitis (10), and connective tissue disease (1), and 15 patients of unknown etiology.

Relapsing myelitis was seen in total 15 (20.5%) patients (7 NMO-SD, 3 Idiopathic, 2 multiple sclerosis, 2 Hashimoto's disease and 1 paraneoplastic myelitis).

3.5. The AQ4 Antibody association with NMOSD and relapsing remitting course

Out of 18 patients clinically diagnosed NMOSD 8 were AQ4 Antibody positive out of which 6 patients relapsed. Among the 10 patients who were AQ4 Antibody negative only 3 patients relapsed. The difference is statistically significant ($p < 0.005$).

4. Discussion

In our ambispective study, mean age of onset of illness was 40 years and most common presentation was bladder disturbance, paraparesis followed by quadriparesis. This is much similar to earlier study from our nearby area in the same state,[3] but different from other studies from distant areas of our nation Although idiopathic transverse myelitis is a monophasic illness it is important to identify etiology and patients prone to recurrent myelitis because these patients will require long term immunosuppression. In our study there are group of patients who were clinically diagnosed as a case of NMOSD but are found to have negative AQ4 Antibody. Reason for this could be inferiority

of immunoassay methods used to detect NMO antibody. In our patients Aquaporin antibody was detected by using fluorescent immunoprecipitation assays which has low sensitivity 48%-53%.[10] A meta-analysis.[11] in which 30 studies for three different immunoassays were included and found the approximated sensitivity for the cell based assay(CBA), the tissue-based assay (TBA) and the ELISA test were 76%, 59%, and0 65% respectively. The mean specificity of the CBA was 99% TBA 98% and ELISA 97%.

NMOSD and MS are described as relapsing remitting diseases but in our study relapsing myelitis was found in myelitis associated with anti TPO Antibody, paraneoplastic myelitis and 17.6% of idiopathic myelitis. Our two female patients with recurrent myelitis were found negative for AQ4 antibody and did not fulfilled Wingerchuk criteria of NMOSD, and neither other etiology was found but was positive for Anti TPO antibody. It is still not answerable whether these patients have negative AQ4antibody because of inferior immunoassays or anti TPO antibody has any pathological role in causing demyelinating disease as there are biopsy proven reports which showed CNS demyelination as a complication of autoimmune thyroiditis.[12–14] So anti TPO antibody may be considered as an independent marker of relapsing myelitis but need further studies. As we know LETM can also occur in infectious pathologies, tuberculosis being more common in our clinical setting followed by varicella zoster virus, HIV, Dengue and chikungunya.

We described a patient who presented with both CNS and spinal tuberculomas. Spinal intramedullary tuberculomas are rarely seen at a rate of 2/1,000 cases of CNS tuberculomas.[15] The coexistence of intracranial and intramedullary tuberculoma is also extremely rare. In our patient CNS tuberculoma was coexistent with spinal tuberculoma and CSF was suggestive of tuberculosis. One patient has spinal meningitis associated with LETM and radiculopathy.

Also there are few case reports of Dengue myelitis.[16,17] One of the patients with LETM was found to have positive Dengue virus serology with positive NS1 antigen and responded well to steroids.[18]

Four patients were diagnosed to have ADEM, one patient had preceding upper respiratory tract infection, two patients had varicella zoster infection and in one patient no preceding event was found.

Among metabolic causes subacute combined degeneration was found in two patients, one patient was found to be positive for anti-parietal cell antibody and showed typical inverted V lesions in posterior cord and also hyperintense signal in lateral cord.

Two patients were diagnosed as spinal cord infarcts because of the rapidity of symptoms and MRI spine showing lesions predominantly in anterior cord. One patient was known case of hypertension and diabetes and one was newly detected case of diabetes, hence the potential risk factors for atherosclerotic vascular disease.

Radiation myelitis (delayed post radiation demyelination) was diagnosed in two patients with chronic myelitis because affected spinal cord was within the irradiated zone and latency of more than 6 months was present, one patient was case of cystic adenoid tumor of left submandibular gland and presented after 2 years of radiotherapy, he had exposure of total dose of 54 Gy, which is more than required to produce post radiation demyelination. Delayed post-radiation demyelination occurs most often 1-2 years after radiation (with exposure to a total dose over 50 Gy), although it can also occur several years after exposure.[19] Second patient was known case of carcinoma tonsil, presented after latency of 1 year post radiotherapy.

Of course largest of the other Indian studies except one[4] but still small study sample is limitation of our study. It's difficult to give any conclusion as it needs further larger studies from different places and uniformity of data analysis.

5. Conclusion

NMO is characteristically associated with LETM but still there are wide differentials for LETM. So it is important to take thorough history regarding onset, progression, associated clinical features and then imaging both spine, brain sometimes orbits and AQ4 antibody to find etiology. In areas endemic for infectious diseases like tuberculosis it is important to rule out infections. Small study sample is limitation of our study but what we have observed is that in patients of inflammatory myelitis (other than NMOSD) with severe disability combination therapy with IVMP, CP, PLEX has been found to show significant improvement in EDSS Score and Azathioprine is a good alternative in NMOSD patients who do not afford costly drugs like Rituximab etc.

6. Source of Funding

None.

7. Conflicts of Interest

There are no conflicts of interest.

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