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Retrospective Observational Study of Series of Longitudinal Extensive Transverse Myelitis

Research Article

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Abstract

Introduction: Longitudinally extensive transverse myelitis (LETM) is characterized by a contiguous inflammatory lesion of the spinal cord involving more than 3 segments. It is most commonly associated with various acquired demyelinating diseases of the Central Nervous system. Clinical and Radiological differentiation can help in diagnosis and predicting disease prognosis.

Materials and Methods: We did a Retrospective observational study to evaluate the Clinical and Radiological Characteristics of LETM cases and also tried to evaluate the outcome.

Results: We observed All patients were presented with spastic Paraparesis or Quadriparesis depending on spinal cord level with predominant 13 (81.25%) patients with early bladder involvement & 2 patients (12%) presented with Brainstem Syndromes. Majority of which were found to be serum NMO positive (60%) rest 40% equally distributed among Seronegative NMOSD, MOG and Idiopathic LETM. We found Predominately Thoracic cord (31%)& lower cervical cord and thoracic cord (31%) involvement on MRI Spine with Characteristic Central Bright spotty lesion involving More than > 50 % of Areaon Axial T2 Weighted scan in Seropositive NMOSD.2 patients (12 %) with NMOSD Showed Characteristic Brainstem involvement of MRI. We also spotted outpatients who didn't respond to Conventional immunotherapy 62% of them responded to Rituximabat a Mean follow of 18 months.

Conclusion: Longitudinally extensive transverse myelitis (LETM) has Characteristic Clinical & Radiological Presentations that need to be addressed. We observed better results with Rituximab to non-responders to conventional immunotherapy.

Keywords: Longitudinally extensive transverse myelitis (LETM); Neuromyelitis Optica (NMO); NMO spectrum disorder (NMOSD); Myelin Oligodendrocyte Glycoprotein Antibody (MOG)

Introduction

Longitudinally extensive transverse myelitis (LETM) is a neurological condition characterized by a contiguous inflammatory lesion of the spinal cord involving more than 3 segments [1]. it is most commonly associated with the acquired demyelinating disease of central nervous system diseases such as Neuromyelitis Optica (NMO), NMO spectrum disorder (NMOSD), Myelin Oligodendrocyte Glycoprotein Antibody (MOG) [2]. Here we tried to study the clinical and radiological profile of LETM patients presenting to our tertiary institute and clinical outcome with various immunosuppressive therapy including rituximab.

Methodology

Here we collected details of 16 cases presented to our institution over one year. Patients with long-segment myelitis of more than three vertebral Segments involved on magnetic resonance imaging (MRI) were included in the study.

All patients underwent detailed clinical neurological examination, routine blood tests, serum autoimmune antibody (ANA), ANA blot test, thyroid profile, and vitamin B12, Routine cerebrospinal

fluid (CSF) analysis, Serum Aquaporin-4 antibodies (NMO-IgG) and Myelin Oligodendrocyte Glycoprotein Antibody (MOG), CSF analysis including cell count with differential, protein, glucose, the Venereal Disease Research Laboratory (VDRL) test, immunoglobulin G (IgG) index, and cytology. oligoclonal band (OCB).

All patient who has suspected demyelinating aetiology underwent MRI brain with whole spinal cord screening with optic nerve study as per demyelinating protocol.

Cases were included as per the Transverse Myelitis Consortium Working Group. Proposed diagnostic criteria and nosology of acute transverse myelitis Diagnosis of NMO / NMOSD was done as per International consensus diagnostic criteria for neuromyelitisoptica spectrum disorders [3,4].

Diagnosis of associated Optic Neuritis was done by Clinical Presentation of visual Diminution and Ophthalmic evaluation as per needed. Every Patient was evaluated by bedside evaluation, Fundus copy and MRI Orbit plain and with Gadolinium contrast and Visual Evoked potentials.

We analysed the clinical profiles of patients in real-world settings. 16 patient data we could compile with completeness in terms of follow-up over the mean period of 18 months. We analysed the data to determine factors significantly affecting the outcome in terms of improved The Modified Rankin Scale (mRS) from 0 to 3. Simple basic analysis was done using the excel function to describe our findings. Categorical variables were compared using Fisher's exact test. All *p*-values were two-tailed, with values of < 0.05 considered significant.

Results

Clinical characteristics

In our sample, there was a high preponderance of female subjects 11 (68.75%) compared to male subjects 5 (31.25%). The mean age of our patients was 31.00 years and the median also shows almost the same value. To evaluate the groups, we divided all the subjects into three categories based on age 15 years to 30 Years, 30-45 years and those above 45. Roughly equal representation was seen in 15 to 30 years 8 subjects (50%) and 30 to 45 years 7 (43.75%) with one patient in group >45 years.

In our series of 14 patients (87.50 %) subjects were newly diagnosed and 2 patients (12.50%) were presented with relapse from previously attained functional level.

Patents were presented clinically as spastic quadriparesis or paraparesis with sensory Involvement as per Level of spinal Cord involvement. 13 (81.25%) patients were presented with bladder involvement and the remaining 3 (18.75%) subjects had no bladder complaints at presentation. More females 10 (62.25%) compared to males 3 (18.75%), in our opinion, this preponderance is due to the over-representation of female subjects.

In this series of subjects, we could see the optic neuritis in 3 (18.75%) subject's rest of 81.25% of subjects did not have any complaints related to optic neuritis.

2 patients (12 %) presented with Brainstem Syndromes accompanied by LETM.1 patient presented with diplopia, and bulbar dysfunctions and another patient presented with Area postrema syndrome in form of vomiting, Nausea and intractable hiccups.

Serological examination

AQP4 antibodies were determined using a cell-based assay on an AQP4-transfected cell line from a commercial BIOCHIP kit and MOG antibody immunoglobulin G (IgG) is detected in serum, using a cell-based assay (fluorescence-activated cell sorting)

Majority of which were found to be serum NMO positive (60%) rest 40% equally distributed among Sero negative NMOSD,MOG and Idiopathic as 13.33% in each category.

MRI scanning

Brain and spinal cord MRI scans were carried out for all patients using a GE 1.5 T MR scanner.

We found all patients were having 4 or more than 4 spinal cord level involvement on T2 weighted images. Interestingly 2 patients were With Holocord involvement as in Figure 1.

The average numbers of Segments involved in all patients were 7.

The most common presentation was equally distributed in the Thoracic cord involvement 5 patient (31%) and 5 patients (31%) with lower cervical cord and thoracic cord involvement. 3 patients(18%) were presented with upper cervical cord involvement and 2 patients (12%) with Holocord involvement as mentioned earlier and 1 (6%) patient with Lumbosacral cord involvement.

We Found that out of 9 Seropositive NMOSD (60%), 4 patients had Involvement of Lower Cervical cord with Thoracic cord involvement, 2 patients had Holocord involvement, 2 patients had Thoracic cord and 1 patient had upper Cervical Cord Involvement .6 Patient had Characteristic Central Bright spotty lesion involving More than > 50 % of Area on Axial T2 Weighted scan (Figure 2).

3 patients showed Predominately Grey Matter T2 weighted Hyperintense signal on axial images as shown in Figure 3.

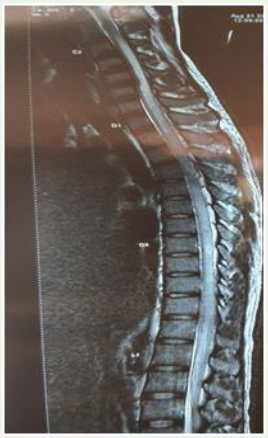

Figure 1: Sagittal T2-weighted image shows LETM extending contiguous spinal cord lesions extending ≥ 17 vertebral segments.

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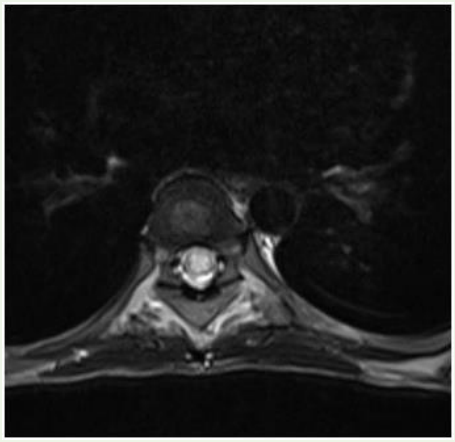

Figure 2: Axial T2-weighted image shows a bright spotty lesion.

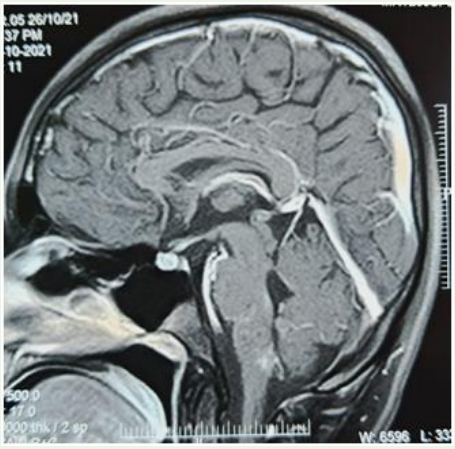

Figure 3: Axial T2-weighted image shows characteristic involvement of the central grey matter.

Amongst 2 (13%) Patients of NMOSD with Sero negative Status, 1 Patient had Lower Cervico thoracic with Thoracic Cord Myelomalacia and another patient with Upper cervical cord involvement.

Amongst 2 MOG (13%) patients 1 patient has Lumbo sacral Cord involvement and one patient with Thoracic Cord involvement.

2 Patients (13%) with Idiopathic Long Segment Transverse Myelitis patient had Predominant Thoracic cord involvement.

On Brain MRI imaging, 2 patients showed Significant Findings. 1 Patient with Seropositive NMO showed T2 weighted hyper intensity in Lateral Pons Figure 4.

1 patient who was Seronegative NMOSD had T 2 weighted hyper intensity in Area postrema and periependymal region as shown in Figure 5a & b.

Clinical Outcome

We documented the treatment Received by Every patient. All patients had Received 1 gm/day of Intravenous Methylprednisolone for 5 days as initial Immunosuppressive therapy.

3 patients Showed Improvement after initial Immunosuppressive therapy and were maintained on Oral Prednisolone at a dose of 1mg / Kg with a Second Immunosuppressant Oral Azathioprine at a dose of 1- 3 mg/kg. These patients showed significant modified Rankin scale (mRS) improvement at a mean follow-up of 2 months only.

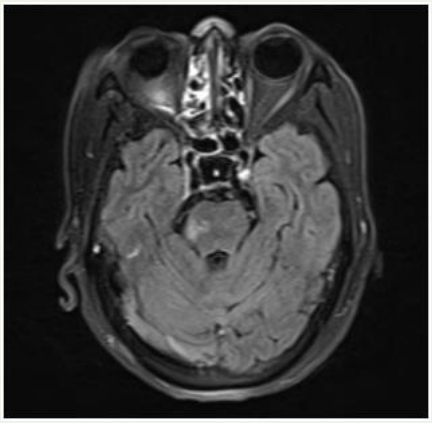

Figure 4: T1 Flair image shows lateral pontine hyper intensity.

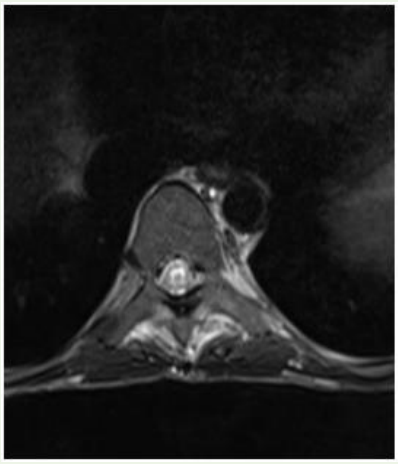

Figure 5A: T2-weighted image shows characteristic involvement of the area postrema area.

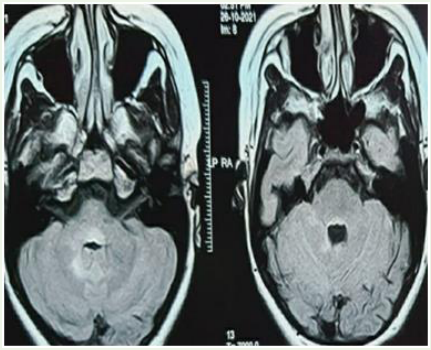

Figure 5B: Axial FLAIR images show hyper intense lesions compromising the periependymal surfaces of and fourth ventricle.

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Amongst these 3 (19%) well responders, 2 patients were MOG positive and one patient with NMO positive. All these patients were presented within 7 days of onset.

13 patients who didn't respond to initial Immunosuppression therapy underwent 5 cycles of plasmapheresis. Those who did not respond to conventional therapy including plasmapheresis were given Rituximab at 2 gm iV loading as 1 gm iv 15 days apart and maintenance dose at 6 monthly intervals. These Patients were followed for a mean period of 18 months and Evaluated for outcome in terms of Improvement in modified Rankin scale (mRS) from 0 to 3.

We found that 8 (62%) patients who received Rituximab showed an Improved mRS scale at a Mean follow of 18 months. 2 patients developed minimal and treatable complications in Form of Flare-up of Herpes simplex and Urinary tract infection post-Rituximab. No other significant complication was observed. Out of 8, 6 patients were seropositive NMO and 2 were seronegative NMOSD.

As compared to conventional immunotherapy, Rituximab was more effective in achieving improvement, at last, follow up with a P-value of 0.02 (P-value<0.05 significant)

We observed 5 patients who did not improve with any immunosuppressive therapy including Rituximab. The majority of these patients were Idiopathic 3 (60%) and 2 patients (40%) were seropositive NMO.

Discussion

Long Segment transverse myelitis (LETM) is a rare entity. It is characterized by a contiguous inflammatory lesion of the spinal cord involving more than 3 segments. Contemplating differential diagnosis it is very important to identify clinical radiological features remarking causative factors. In this study, we try to evaluate the Clinical and radiological characteristics of LETM and Its response to Conventional immunotherapy and special consideration to Rituximab.

In our series of cases, the range of age of patients was 17 to 53 years with mean and median ages of 31.06 and 31.0 respectively. Most patients as equal as 15 subjects fall into two categories of age 15 to 30 years 8 (50%) and 30 to 45 years 7 (43.75%) subjects, only 1 (6.25%) subject was of the age of 70 years. This finding correlates with the findings of other studies where most subjects fall between the age group of 20-40 years (5). In our series, we found a 2.5:1 ratio of female subjects compared to males.

In our series, most of the chunk is formed by Seropositive NMOSD (60%) rest 40% equally distributed among Seronegative NMOSD,MOG and Idiopathic as 13.33% in each category. It is coherent with many series of LETM including 33 subjectsseries from another part of India as well [6].

Patients with NMOSD presented With MRI spine changes of Central Bright spotty lesion involving more than > 50 % of Area on Axial T2 Weighted scan has been described as a characteristic MRI finding in NMOSD with Predominately Grey matter T2 weighted Hyper intense signal on the axial scan [7,8].

We observed Patients with NMOSD had prominent involvement of Lower cervical and thoracic cord and Holocord involvement with an Average number of Segments involved were 7 these findings overlap with findings mentioned by Sven Jarius et al [9].

A patient with MOG was presented with Characteristics MRI features of Involvement of the Lumbosacral Cord segment as described in the literature [10].

2 Patients with NMOSD Each from the seropositive and sero negative group showing typical brainstem involvement defines the core feature of NMOSD [11].

While observing the response to immunotherapy we found a better response to conventional immunotherapy was found in MOG-positive myelitis. This echoes from finding of Dubey et al (10).

In Non-responders conventional immunotherapy including Plasmaphareis, Rituximab was more effective in achieving improvement; at last, follow up with statically significance, especially those presenting early in course of the disease. This finding supplements the role of Rituximab in preventing permanent Disability and relapses as described by previous studies in the Indian population [12].

Rituximab which is a monoclonal antibody against CD20 Epitope all B cells and depletes CD 20 +B and thus suppressing production and antibodies including AQP4 [13,14].

In our studies, Rituximab was well tolerated without any significant adverse effects.

Conclusion

Longitudinally extensive transverse myelitis (LETM) poses a challenge needing clinical and radiological experience. Patients with LETM present clinically with spastic Paraparesis or Quadriparesis with early Bladder involvement. The majority of patients were NMOSD with Predominately Thoracic cord & lower cervical cord and thoracic cord involvement on MRI Spine with Characteristic Central Bright spotty lesion involving More than > 50 % of Areaon Axial T2 Weighted scan. We observed better results with Rituximab to non-responders to conventional immunotherapy, particularly in early disease presentation.

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