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Original Article

Internal Medicine Section

# A Retrospective Study on the Profile and Treatment Response of Patients with Mononeuritis Multiplex and Connective Tissue Diseases

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## ABSTRACT

**Introduction:** Though Mononeuritis Multiplex (MM) can be caused by many pathological conditions, vasculitis is the most important cause.

**Aim:** To study clinical features of MM in patients with connective tissue diseases, the time of presentation of MM from disease onset, its association with disease activity, and functional outcome after treatment.

**Materials and Methods:** A retrospective study was conducted at Outpatient Department (OPD) of Madras Medical College (Government Hospital), Chennai, Tamil Nadu, India, between April 2015 to April 2017. The study included medical records of 18 patients with connective tissue disease who had attended the OPD, with sensory and motor symptoms and who were also diagnosed with MM. Paired t-test was used to find associations. Disease activity levels were determined using various measures and modified Rankin Score (mRS) was used to assess the response to treatment. Data analysis was done using Statistical Package for Social Sciences (SPSS) version 28.0.

**Results:** Of the 18 study subjects 14 (77.8%) were 18-40 years of age, and 10 (55.6%) were females. The mean duration between the time of diagnosis of connective tissue disease and the development of MM was 18.17 months. Ulnar nerve was the most common nerve involved, 11 subjects (61.1%) had ulnar nerve involvement. Axonal neuropathy was present on nerve conduction studies in 17 (94.4%) of the study subjects and sensory symptoms on history were present in 100% of the study subjects. There was a statistically significant difference (p-value <0.001) between the mRS before treatment (3.89) and after treatment (2.78) for a duration of six months.

**Conclusion:** It was seen that the disease activity indices for connective tissue diseases were quite high at the time of development of MM, and starting treatment would help improve the functional outcome as is evident by the difference in mRS.


**Keywords:** Cryoglobulinemic vasculitis, Rheumatoid arthritis, Systemic lupus erythematosus

## INTRODUCTION

Autoimmune connective tissue disorders are a heterogenous group of diseases that affect connective tissue in various organs resulting from poorly controlled autoimmune responses, complement activation, interferon dysregulation, and associated inflammation [1]. Originally, connective tissue diseases represented a group of disorders in which connective tissues, such as the joints, skin, muscle, and blood vessels, were the primary site of inflammation. Because infiltration of immune, inflammatory, and other cells may also cause inflammation and abnormal immune responses in neuron, nearly all connective tissue diseases and related disorders can be complicated by various neuropsychiatric syndromes [2].

Neurological involvement is associated with significant morbidity in patients with rheumatic diseases and may indicate heightened disease activity. The most prominent features of neurological involvement in rheumatic diseases include cerebral ischaemia, polyneuropathy, and psychiatric symptoms [3]. The American College of Rheumatology (ACR) case definitions of neuropsychiatric Systemic Lupus Erythematosus (SLE) include seven types of Peripheral Nervous System (PNS) disease: (i) peripheral neuropathy; (ii) cranial neuropathy; (iii) mononeuropathy single or multiplex; (iv) plexopathy; (v) autonomic neuropathy; (vi) acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome); and (vii) myasthenia gravis [4]. Mononeuritis Multiplex (MM) is caused by various pathological conditions, although the main cause is vasculitis [5]. The MM is a syndrome of the Peripheral Nervous System (PNS) involving progressive multifocal peripheral nerve lesions. Its distribution is typically asymmetric, and the course of the disease varies with the underlying aetiology. The MM is associated with several medical conditions, including vasculitis, immune-mediated diseases, diabetes, infections, neoplasms, infiltrative diseases, and drugs [6]. Modified Rankin Scale (mRS) has several major strengths: it covers the entire range of functional outcomes from no symptoms to death, its categories are intuitive and easily grasped by both clinicians and patients. The scale runs from 0-6, running from perfect health without symptoms to death [7].

Mononeuritis multiplex is a condition that affects the PNS. So, the symptoms are related to those of damaged peripheral nerves. It can cause, motor weakness severe pain and loss of sensation in at least two separate areas of the body [8]. In vasculitis, MM occurs due to ischemic insult to vasa nervosum leading to wallerian degeneration and there is deposition of endoneurial immune complex. A study was taken up with the prime objectives of identifying the clinical features of MM, mean duration between diagnosis of connective tissue disease and development of MM, to identify the association between MM and disease activity levels and to study the response to treatment with the help of mRS.

## MATERIALS AND METHODS

A retrospective study was done on all eligible medical records between April 2015 and April 2017, in the Rheumatology Department of Madras Medical College, (Government Hospital), Chennai, Tamil Nadu, India. Since the study was done on

secondary data (medical records), it had no ethical considerations. The retrospective observational study was done on medical records of connective tissue disease patients who had confirmed MM and had details on mRS before treatment and six months after treatment. The total eligible case records were 18 which was the final sample size.

**Inclusion criteria:** All connective tissue disease patient's records with MM and all data available were included in the study. In our institute, connective tissue disease patients with motor weakness and sensory symptoms involving contiguous nerve, nerve conduction study and sural nerve biopsy (optional) were performed to diagnose MM.

**Exclusion criteria:** Subjects with diabetes, Hansen's disease, Human Immunodeficiency Virus (HIV), malignancy, Hepatitis B, Hepatitis C, Hepatitis A, alcoholics, and those with other form of neuropathies were excluded from the study as their pre-existing conditions would have interfered with the study findings.

### Study Procedure

Nerve conduction reports were used to identify axonal neuropathy among the study participants. Sural nerve biopsy reports were used to confirm the presence of vasculitis. Different disease activity markers were used in the study, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and Systemic Lupus Collaborating Clinics (SLICC) scores were used for Systemic Lupus Erythematosus (SLE). The Birmingham Vasculitis Activity Score (BVAS) levels and Vasculitis Damage Index (VDI) levels were used to measure disease activity of Antineutrophil Cytoplasmic Antibodies (ANCA) associated vasculitis, Cryoglobulinemic vasculitis, Polyarteritis Nodosa (PAN) and Rheumatoid Arthritis. Sjogren's Syndrome Disease Activity Index (SSDAI) was used as a measure of disease activity for Sjögren's syndrome. The mRS was used to measure the patient's disabilities due to neurological deficits and the initial score (out of 6) was compared with the mRS after six months of treatment with either combinations of steroids with cyclophosphamide or steroids with rituximab to measure the efficacy of treatment and functional improvement [9-12].

## STATISTICAL ANALYSIS

Data entry was done on excel and the data was imported and analysed using Statistical Package for Social Sciences (SPSS) version 28.0. Percentages and 95% confidence intervals were calculated for descriptive data and paired t-test was used to find the association between before and after levels of the mRS. The p-value <0.05 was considered as statistically significant.

## RESULTS

Among the study participants 2 (11.1%) were below the age of 18 years and majority of the study population (77.8%) were between the ages of 18 and 40 years. Males were more (55.6%) when compared to females [Table/Fig-1]. Among the study participants, seven had SLE and four had PAN [Table/Fig-2]. Sural nerve biopsy showed probable vasculitis in 8 (44.4%) of the study subjects and vasculitis in 3 (16.7%) of the study subjects and the rest had a normal biopsy report [Table/Fig-2]. The mean duration between the time of diagnosis of connective tissue disease and the time of development was 18.17 months with a standard deviation of 14.29 months. Nerve conduction studies revealed that 17 (94.4%) of the study participants had axonal neuropathy. The most common nerve involved was the ulnar nerve (61.1%), and the least commonly involved nerve was the peroneal nerve (22.2%) [Table/Fig-3]. The symptoms based on the initial records showed that among the subjects with SLE, it was seen that five out of seven subjects (71.4%) had positive anti-ds-DNA, low complement three levels, musculoskeletal manifestations, and haematological manifestations. All 7 (100%) of the subjects with SLE had mucocutaneous manifestations, whereas lupus nephritis was present in 5 (28.6%) of the patients with SLE, and serositis was present in 1 (14.3%) of the patients with SLE. It was seen that the commonest symptom was weakness which was present in 16 (88.9%) subjects followed by tingling which was present in 13 (72.2%) subjects [Table/Fig-4]. The mean SLEDAI and SLICC scores can be seen in [Table/Fig-5]. The mean mRS before treatment was 3.89 (out of a total score of 6) and the mean mRS after initiation of treatment with steroids and

| Variable | n, % | 95% CI |
|---|---|---|
| **Age** | | |
| <18 years | 2 (11.1%) | 1.3-34.7 |
| 18-40 years | 14 (77.8%) | 52.4-93.6 |
| >40 years | 2 (11.1%) | 1.3-34.7 |
| **Gender** | | |
| Female | 8 (44.4%) | 21.5-69.2 |
| Male | 10 (55.6%) | 30.8-78.5 |

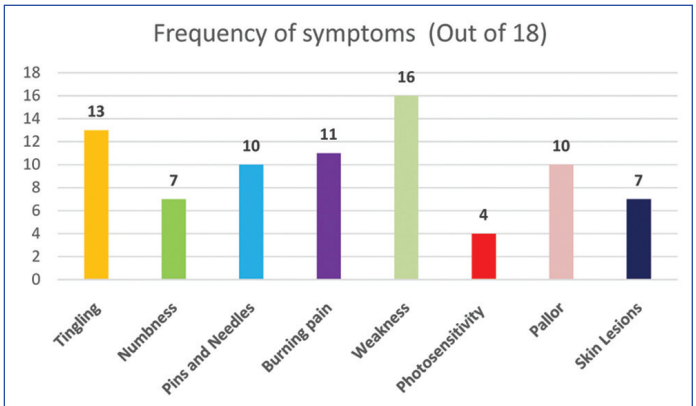
**[Table/Fig-1]:** Socio-demographic profile of the study participants (N=18).

| Disease diagnosis \ Sural nerve biopsy | Normal | Probable vasculitis | Vasculitis | Total (%) |
|---|---|---|---|---|
| ANCA-Associated Vasculitis (AAV) | 0 | 2 | 1 | 3 (16.7%) |
| Cryoglobulinemic Vasculitis (CV) | 1 | 0 | 0 | 1 (5.55%) |
| Polyarteritis Nodosa (PAN) | 2 | 1 | 1 | 4 (22.2%) |
| Rheumatoid Arthritis (RA) | 1 | 1 | 0 | 2 (11.1%) |
| Sjögren's Syndrome (SS) | 0 | 1 | 0 | 1 (5.55%) |
| Systemic Lupus Erythematosus (SLE) | 3 | 3 | 1 | 7 (38.9%) |
| Total (%) | 7 (38.9%) | 8 (44.4%) | 3 (16.7%) | 18 |

**[Table/Fig-2]:** Disease profile of the study participants and the corresponding sural nerve biopsy report.

| Clinical profile | n, % |
|---|---|
| Motor symptoms | 16 (88.9%) |
| Sensory symptoms | 18 (100%) |
| Ulnar nerve involvement | 11 (61.1%) |
| Median nerve involvement | 7 (38.9%) |
| Tibial nerve involvement | 8 (44.4%) |
| Sural nerve involvement | 6 (33.3%) |
| Peroneal nerve involvement | 4 (22.2%) |
| Axonal neuropathy (On nerve conduction studies) | 17 (94.4%) |
| Erythrocyte Sedimentation Rate (ESR) (>30 mmhr) | 16 (88.9%) |
| C-Reactive Protein (CRP) (>10 mg/L) | 9 (50%) |

**[Table/Fig-3]:** Clinical profile of the study participants (N=18).




**[Table/Fig-4]:** Symptom profile of the study participants.

cyclophosphamide or rituximab was 2.78, the paired t-test value was 6.52 and the difference was statistically significant with p-value <0.001 [Table/Fig-6].

| Name of the variable | Lower Limit (LL) | Upper Limit (UL) | Mean±Standard deviation |
|---|---|---|---|
| SLEDAI (For SLE out of 7 patients) | 21.00 | 30.00 | 24.00±3.51 |
| SLICC (For SLE out of 7 patients) | 2.00 | 3.00 | 2.43±0.54 |
| BVAS (For AAV, CV, PAN, RA out of 10 patients) | 12.00 | 28.00 | 17.20±5.51 |
| VDI (For AAV, CV, PAN, RA out of 10 patients) | 1.00 | 6.00 | 2.500±1.65 |
| SSDAI (For Sjögren's syndrome out of 1 patient) | - | - | 9.00 |

**[Table/Fig-5]:** Disease activity measure Connective tissue disease patients.
ANCA: Antineutrophil cytoplasmic antibodies; SLEDAI: Systemic lupus erythematosus disease activity index; SLICC: Systemic lupus collaborating clinics scores; SLE: Systemic lupus erythematosus; SS: Sjögren's syndrome; PAN: Polyarteritis nodosa; BVAS: Birmingham vasculitis activity score levels ; VDI: Vasculitis damage index; SSDAI: Sjogren's syndrome disease activity index; CV: Cryoglobulinemic vasculitis; PAN: Polyarteritis nodosa; RA: Rheumatoid arthritis; AAV: ANCA-associated vasculitis

| Variable | Grouping of variable | Mean | Standard Deviation | t-value (Paired t-test) | p-value |
|---|---|---|---|---|---|
| Modified rankin score | Before treatment | 3.89 | 0.66 | 6.52 | **<0.001** |
| | 6 months after treatment | 2.78 | 0.53 | | |

**[Table/Fig-6]:** Impact of treatment on Modified Rankin Score (mRS).
p-value <0.05 was considered as statistically significant

## DISCUSSION

The current study was done to study clinical features of MM in patients with connective tissue diseases, the time of presentation of MM from disease onset, its association with disease activity, and functional outcome after treatment. Because of paucity of literature from the Indian setup, comparison with Indian studies could not be done.

In the current study all 100% of the participants had mucocutaneous manifestations and high ESR was seen in 88.9% of the study population, whereas according to a study done in Barcelona Spain on SLE related vasculitis [13] and published in the year 2006, 89% had cutaneous manifestation and 60% had high ESR levels, the minor differences could be because the current study had included other forms of connective tissue diseases along with SLE. Anti-ds-DNA was positive in 95% and hypocomplementemia was present in 83% of the study population which was slightly higher than in the current study where 71.4% of the SLE patients had positive Anti-ds-DNA and 71.4% had low complement three levels and 57.1% had low complement four levels. This difference could be because of difference in population type and sample size.

A systematic review based on 53 articles with extractable data [14] done to predict damage and mortality among SLE patients using SLEDAI and SLICC found that higher mortality was seen with higher SLEDAI and SLICC scores in six studies and two studies had a statistically significant association between SLEDAI and neuropsychiatric complications. The current study revealed high disease activity in all patients with MM, the mean SLEDAI was 24.00 in the current study and in the systematic review mean scores (>15, 19.6, 23) were significantly associated with mortality by three different studies. A study done on the association between autoimmune rheumatological studies with peripheral neuropathies [15] published in 2021 concluded that 5-93% of patients with connective tissue diseases have PNS involvement, the current study showed axonal neuropathy in 94.4% of the subjects. The higher proportion could be because the current study was done on those with coexisting MM along with connective tissue diseases.

The other study also revealed that the most affected nerves are the peroneal and tibial followed by the Ulnar nerve, whereas according to the current study the most frequently involved nerve was the Ulnar nerve, and the least involved nerve was the peroneal nerve. Further research on higher sample size should be done to corroborate the findings of the current study. A study done on 18 churg strauss syndrome patients [16] where the mRS for functional outcomes were compared before and after treatment with steroids, cyclophosphamide and immunoglobulins showed a statistically significant reduction in the score after 12 months of treatment (p-value <0.04). The findings were consistent with that of the current study were the mean mRS reduced from 3.89 to 2.78 after six months of treatment and the p-value was <0.001 suggesting a significant improvement in functional outcomes with treatment. When vasculitis is pinpointed as cause of MM as in our study, there is high disease activity, patients functional improvement as assessed by mRS shows improvement in the quality of life.

### Limitation(s)

The low sample size of 18 is the limitation in the study. Higher sample size could not be achieved because of the rarity of the combination of connective tissue diseases and MM, in the absence of other factors like diabetes.

## CONCLUSION(S)

This study showed that the mean duration between diagnosis of connective tissue diseases and development of MM was around 18 months. So, it will be worthwhile to screen connective tissue patients for MM around this time. The study also reported the significant improvement in functional outcomes with treatment, which emphasises the need for initiation of early treatment.

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