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PROJECT REPORT

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Programme: DM Neurology
Month & year of: November 2003
Submission
CERTIFICATE

I, Dr. Parameswaran K hereby declare that I have actually carried out the project, under report.

Place: Trivandrum  
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DR PARAMESWARAN K

Forwarded, he has carried out the project under report.

Signature

Head of the Department
PROJECT REPORT

Title

Mononeuritis multiplex- A clinical, electrophysiological, pathological, etiological factors and outcome measures study.

Name : DR Parameswaran K
Programme : DM Neurology
Month & year of submission : November 2003
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I wish to express my heartfelt gratitude towards my teacher, Dr C Sarada, Additional professor of Neurology, who has been my thesis guide. Madam helped me a lot from the very beginning and without her help I might not be able to complete this study.

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I wish to express my heartfelt gratitude towards Dr Asha Kishore, Additional professor of Neurology who helped me to prepare this topic for presentation at NSI- National conference which was held in December 2002 at Cochin and the paper was well recognized and accepted.
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INTRODUCTION

Mononeuritis multiplex (MM) is a common neurological entity. MM is often associated with various systemic illnesses like diabetes mellitus, leprosy, and collagen vascular diseases. Among them vasculitic neuropathy is commonest (L. Davis et al Brain 1996). Vasculitic neuropathy commonly occurs in association with various systemic vasculitis – frequently PAN (poly arteritis nodosa) group. Isolated peripheral nervous system vasculitic neuropathy (IPNSV) without any manifestations of systemic vasculitis was made first by PJ Dyck et al in 1987. They are characterized by lack of serological markers, fever, weight loss and having a rather indolent course of illness.

MM, as a whole are usually sensory motor (SM) involvement which are painful at onset. There are some pure sensory MM neuropathies like Wartenberg migratory sensory neuropathy, which carry very good prognosis and pure motor neuropathy like multifocal neuropathy with conduction block, lead neuropathy etc. Even though majority of MM consisted of a group of predominantly axonopathic neuropathy, there are some rare specific demyelinating conditions like MADSAM (Lewis Sumner syndrome or multifocal acquired demyelinating sensory and motor neuropathy), multifocal motor neuropathy with conduction block and hereditary neuropathy with liability to pressure palsy (HLPP).

There is only limited data available regarding the clinical & electrophysiological profile of MM in Indian literature. Even though there are various reports available in literature about individual MM subgroup in details, there are no reports available about MM as a whole, stating its prevalence; it’s subgroup prevalence or mode of presentation.

This is the first study in India to our knowledge to address the above problems and systematically studied the various factors like electrophysiology, pathology, and electrophysiological - pathological correlation and outcome measure of various subgroup cases. We report the clinical, electrophysiological, etiological, pathological features of 32 patients with MM and the response to treatment in these cases.
Review of literature

Causes of MM

Axonal
1) Vasculitis - PAN
   Churg Strauss angitis
   Connective Tissue disease (RA, SLE, MCTD, SS)
   Wegener's granulomatosis
   Hypersensitivity vasculitis
   Giant cell arteritis
   Behcet disease
   IPNSV

2) DM

3) Inflammatory leprosy, sarcoidosis, Lyme, HIV, CMV, Hepatitis B

4) Infiltrative lymphoma, amyloidosis

Demyelinating

   Lewis Sumner syndrome
   MMNC
   HLPP

There are various literatures available on individual neuritis.

J. M. K. Murthy et al described the clinical, electrophysiological and pathological features of 16 patients with vasculitic neuropathy. Vasculitic neuropathy accounted for 5.3% of biopsy proven cases of various neuropathies. They included 7 cases for systemic vasculitic neuropathy (SVN) and 9 cases of nonsystemic vasculitic neuropathy (NSVN), Mononeuritis multiplex, both clinically and electrophysiologically was seen in neuropathy in 11 (69.7%) patients. Three patients had sensory neuropathy. All the patients had a necrotizing vasculitis on nerve biopsy.
Axonal degeneration was seen in teased fibers in all the patients. Fifteen patients were treated with steroids and one patient with cyclophosphamide. Seven patients with NSVN recovered completely. Two patients with SVN were left with asymptomatic foot drop and one patient with NSVN developed bilateral mild claw hands and there were no deaths.

Peter James Dyck et al reported 65 patients with necrotizing vasculitis, 45 had systemic and 20 had nonsystemic vasculitic neuropathy. The clinical and pathological features are those of an ischemic neuropathy caused by necrotizing vasculitis of small arterioles. These 20 patients had neuropathic symptoms for a median time of 11.5 years (range 1.35 yrs.). The clinical pattern of neuropathy was that of multiple mononeuropathy in 13, asymmetric neuropathy in 4, and distal neuropathy in 3, and sensory poly neuropathy in 1. As compared with initial evaluation, 8 became worse, 5 were better, 4 were approximately the same, and 3 died from unrelated causes. Prednisone was thought to prevent the development of new lesions in some cases. By contrast of the 41 patients with systemic necrotizing vasculitis whose outcome was poor, 12 were dead (median time, 1.5 years, range 3 months – 8 years) and 29 were alive (median time, 6 years, range 6 months – 22 yrs.) This was the first report of ‘isolated peripheral nervous system vasculitis (IPNSV)’.

S. H. B. Hawke et al reported clinical electrophysiological and pathological features and prognosis of 34 patients with peripheral neuropathy caused by necrotizing vasculitis. The causes included polyarteritis nodosa, Churg – Strauss variant, rheumatoid arthritis, undifferentiated connective tissue disease, Wagener’s granulomatosis, primary Sjogren’s disease and chronic lymphocytic leukemia with cryoglobulinaemia; 2 patients had no evidence of systemic vasculitis. Mononeuropathy multiplex was the most common clinical manifestation followed by asymmetrical polyneuropathy and distal symmetrical polyneuropathy. Pain was a frequent symptom. Nerve conduction studies were abnormal in all cases, and in 3 patients there were conduction block & severe slowing of motor conduction. Necrotizing vasculitis was present in sural nerve biopsies of most cases, and severe active axonal degeneration was a dominant feature. All patients were treated with prednisone alone or in
combination with other immunosuppressive agents, or with plasma pheresis. Long-term follow-up studies demonstrated that although the peripheral neuropathy usually improved and caused only mild to moderate functional disability, the long-term prognosis of the systemic disease was poor with a 5-year survival of only 37%.

L. Davies, J.M. Spies et al reported clinical electrophysiological and pathological features and prognosis of 25 patients with vasculitis selectively affecting the peripheral nervous system (IPNSV) were evaluated. Although most patients had a history of Mononeuritis multiplex or asymmetrical neuropathy, 6 out of 25 had a symmetrical neuropathy, both clinically and on neurophysiologic testing, by the time of presentation. There were no signs of accompanying systemic vasculitis in any of the patients and serological abnormalities were limited to an elevated erythrocyte sedimentation rate (ESR) in nine out of 21 patients and low titer anti-nuclear antibodies in four out of 20 patients. Most patients had narcotizing vasculitis on nerve biopsy. The meantime from symptom onset to diagnosis was 46 weeks. All patients were treated with corticosteroids and most with additional immunosuppressive therapy. In contrast to vasculitic neuropathy associated with systematic vasculitis the prognosis was good with 24 out of 25 survivals at a mean of 176 weeks follow-up having mean improvements of 1.4 units on a six point disability scale.

Peripheral neuropathy is a common feature in both systemic and non-systemic vasculitis as the vasculitic process involves vessels of the size of 50-300μm (Sundaram and Murthy 1995). Vasculitic neuropathies, both systemic and non-systemic, constituted 5.33 to 40.1 percent of biopsy proven cases of various types of neuropathies in different series (Kissel et al 1985, Hawke et al 1991).

The commonest pattern of nerve involvement is patients with vasculitic neuropathy is MM, which can be at times confluent, or partially confluent. Burning dysesthetic pain in the distribution of involved nerves occurs in 70-80 per cent of patients. Associated features suggest systemic nature of the disease in patients with systemic vasculitic neuropathy.

The electrophysiological studies in vasculitic neuropathies demonstrate the extent and distribution of involvement of peripheral nervous system and will often identify the focal nature of the neuropathy which some times may not be clinically evident (Bouche et al 1986). In patients with nonsystemic vasculitic neuropathy severity of electrophysiological abnormalities do not predict poor prognosis. Patients with minute or absent distal compound muscle action potentials surprisingly show good recovery (Davies et al 1996).

Nerve biopsy is critical in the diagnosis of vasculitic neuropathy. Vasculitic process predominantly affects arterioles of diameter 50-300μ as seen in the study (Dyck et al 1987). Widespread occlusion of epineurial arterioles causes, multifocal, Ischemic - a central fascicular or sectorial degeneration of nerve fibers.(Dyck et al.,1972,1984). There are no characteristic histological features in the affected vessels that distinguish different clinical diseases (Hawake et al 1991). The frequency of the presence of vasculitic changes in sural nerve biopsies of patients with suspected vasculitic neuropathy is variable (Dyck et al 1987, Parry et al 1981). For this reason some authors suggested that biopsies should only be done if the sural sensory nerve sensory action potential is abnormal (Wees et al 1981)

Pathological changes commonly result from the deposition of immune complexes in blood vessel walls. This evidence has been reinforced by the finding of immuno-globulin and complement deposited in blood vessel walls in neuropathies associated with systemic vasculitis (Kissel et al., 1989; Hawke et al., 1991)
Different Necrotizing Arteritis and Multisystem Disorders causing MM

(Geradr Said: Ann neurology 1988;23;461)

Series with total 68 patients

Connective tissue disorders (CTD) (55 patients)
- Rheumatoid arthritis (25)
- Classic polyarteritis nodosa (19)
- Overlapping CTD (3)
- Sjogren’s syndrome (2)
- Systemic lupus erythematosus (1)
- Poly myositis (1)
- Systemic sclerosis (1)

Necrotizing arteritis and non connective tissue disorders (13 patients):
- Asthma (6)
- HIV infection (3)
- Mastocytosis (1)
- Sarcoidosis and rheumatoid arthritis (1)
- Chronic lymphocytic leukemia and rheumatoid arthritis (1)
- Giant cell arteritis (1)
Features of IPNSV

1. Only peripheral nerves were affected, even after many years of follow up.
2. Joints, visceral organs, and skin remained unaffected;
3. There were no or only mild, constitutional symptoms or serological abnormalities (non-significant low titer)
4. The disease was indolent and protracted over years and appeared not to be life-threatening;
5. The severity of nerve symptoms and deficits varied considerably
6. An underlying indolent narcotizing vasculitis of small epineurial arterioles

The disease process appeared to affect smaller epineurial arterioles in NSVN than in SVN and the process tends not to be as severe. Do patients with NSVN have a tissue-specific vasculitic disorder affecting nerve? or do they simply represent early, mild or unusual manifestations of systemic narcotizing vasculitis? Judging by severity of nerve involvement and comparison with systemic disease, selective involving of nerve is not explained by lack of severity. Mendell et al postulated that IPNSV, rather than being an organ-specific vasculitis, is a mild form of systemic vasculitis where nerves are most affected because their long course makes them especially vulnerable to small areas of ischemia.

The clinical picture in patients with IPNSV is dominated by their neuropathy and even if there is sub-clinical involvement of other tissues this does not appear to have either symptomatic or prognostic relevance. If the initial sections in a nerve biopsy from such a case with suspected vasculitis were not diagnostic, it is often helpful to cut further sections from the biopsy tissue as the process is often patchy and deeper blocks may well be diagnostic.

The prognosis in NSVN (IPNSV) is different from that in SVN, another reason for separation of the disorders. Systemic vasculitis with an associated neuropathy is a devastating illness with a 5-year survival of 37% (Hawake et al 1991, Davies et al 1996). The vast majority of patients with non-systemic vasculitic neuropathy survive and, with treatment show improvement in their disability (Dyck et al a987, Davies et al 1996). This difference is not due to duration of follow-up because patients
with NSVN were followed for longer times than were those with SVN. Another possible reason for separating the disorders is that in NSVN the process appeared to affect smaller arterioles and to be more indolent. The difference in natural history has implications for therapy. Less therapy-related side effects and risks are justified in NSVN than SVN. This reflects the finding in studies of generalized vasculitis with peripheral nerve involvement that the poor prognosis is in these conditions was not generally attributable to the nerve involvement per se with most deaths being due to failure of other organ systems.

**Why some particular nerves and nerve-areas are selectively affected in vasculitic neuropathy?**

It depends on many factors. Vasculitis produces sectorial involvement and ischemia to the nerve. So the maximum affection will be on those nerve area sites where the

1. Nerves are metabolically active
2. Nerves are thick so that cross sectional area of nerves are large
3. By the same time there is some particular ‘watershed’ area in the nerves like lower part of sciatic nerve and at the level of its division to 2 branches. Here the ratio between “nerve cross sectional area / perfusion “ will be maximum, so most of the Ischemic etiology preferentially affect these area
4. The same rule apply in upper limb nerves also.

**How vasculitic neuropathy show marked recovery?**

One of the interesting characteristics of IPNSV is the marked recovery in function seen in individual nerves that appear devastated at the height of the illness. This is somewhat surprising in a condition where the presumptive pathology for nerve injury is axonal degeneration due to Ischemic infarction. *Some of this recovery may be due to Ischemic injury that has stopped short of nerve fiber infarction. The occasional occurrence of distinct conduction block in some patients with vasculitis suggests that nerve ischemia from vasculitis can produce demyelination or functional disruption of conduction without necessarily resulting in axonal infarction* (Ropert
and Metral, 1990). There are clinical and experimental models that provide support for this concept of "sub-infarctive ischaemic damage" (Nukada and Dyck, 1987; Nukada, 1990; Homberg et al., 1992). Even in patients where peripheral nerves have been severely damaged by vasculitis, as evidenced by complete clinical paralysis and absent distal compound muscle action potentials accompanied by profuse denervation potentials, the degree of long-term recovery can be surprisingly good. *This may be because the underlying anatomy of the nerve sheath is preserved, permitting axonal regrowth down the original pathways. The relative resistance of fibroblasts to ischemia probably contributes to this.*

David Walk, MD et al report a case of progressive mononeuropathy multiplex in a patient with lymphoma in hematological remission. At the time of presentation there was no evidence of meningeal or central nervous system metastasis. At autopsy, extensive infiltration of tumor cells was found in both femoral nerves. They concluded that multifocal malignant lymphoid infiltration of peripheral nerves can occur during hematological remission or in the absence of any evidence of systemic lymphoma.

Churg Strauss angitis (allergic angitis and granulomatosis) was described in 1951. It is an uncommon disease, mean age of this is 41 yrs, male to female ratio is 1.3:1. This involve small, medium-sized arteries, capillaries, venules and veins. Characteristic histology is allergic angitis and granulomatosis reaction in the tissue and vessel wall, usually associated with infiltration with eosinophils. CSA presents with fever, asthma, weight loss, pulmonary infiltrates, and peripheral nervous system involvement. The characteristics laboratory findings are eosinophilia (usually above 1000cell/cmm). Prognosis of this rare disease is poor with 5 yr survival rate is less than 25%.

Sarcoidosis is a multisystem chronic disorder of unknown cause characterized by accumulation of T lymphocytes, mononuclear phagocytes, noncaseating epitheloid granuloma. Neurological involvement (Neurosarcoidosis) occur in 5%. Recurrent seventh cranial nerve involvement, recurrent optic nerve eighth
CN and other CN involvement, chronic meningitis, hypothalamo-pituitary affection, peripheral nerve involvement including MM are the common manifestations.

Henoch Schonlein purpura (anaphylactoid purpura) is a distinct systemic vasculitis characterized by palpable purpura, arthralgia, GIT signs; glomerulonephritis. It is a disease of children (4-7yrs). Various systemic manifestations can occur in HSP due to systemic vasculitis. Prognosis of HSP is excellent.

Temporal arteritis (TA) or giant cell arteritis is inflammation of medium and large sized arteries. It commonly involve temporal arteries, and so it is called as TA. It occurs almost exclusively in individual above 55yrs. It is more common in females. Patients often have associated other features of systemic vasculitis. The disease is characterized by fever, weight loss, anemia, high ESR, polymyalgia syndrome, recent onset headache, thickened nodular TA, scalp tenderness, jaw claudication. Main neurological manifestations include AION, other various involvements due to vasculitis. Vasculitic neuropathy involves secondary to systemic vasculitis.

**Aims and objectives**

To study the clinical, electrophysiological, etiological and pathological profile of Mononeuritis multiplex in our locality who were admitted at Neurology department SCTIMST, Trivandrum and the response to treatment in these cases.
Material and Methods

Records of 32 consecutive cases of MM which were diagnosed in the department of Neurology, SCTIMST (a tertiary care referral centre) between the period of January 1995 to December 2001 were retrospetively analyzed using a structured proforma. Clinical, electrophysiological data, features of preexisting diseases like collagen vascular disease, diabetes mellitus, and malignancy were recorded from case records. The type of collagen vascular diseases is classified wherever possible according to standard criteria. Patients with vasculitic neuropathy without systemic features or any laboratory indicators of collagen vascular diseases were grouped into non systemic vasculitic neuropathy or isolated vasculitis of peripheral nervous system (PJ Dyck et al 1987) according to criteria stated earlier. Pathologic study was done at department of pathology NIHANS Bangalore, many of the slides are reviewed by the author with the help from department of pathology NIHANS and some classical pathognomonic pathology slides got photographed for illustration.

Electrophysiological data were analyzed and the neuropathy was classified as axonal or demyelinating according to criteria. The pattern of neuropathy was classified as MM or confluent form of MM mimicking peripheral neuropathy. The clinical outcome of the patients will be measured.

Follow up details are carefully recorded at 3 months, 6 months and 1yr follow up periods. The treatment and duration of treatment and side effects of treatment if any, developed are also recorded wherever possible. The outcome are measured as good, moderate and poor.

(Good - $\geq 3$ MRC grade power improvements $\geq 60\%$ sensory
Moderate - 2 - 3 MRC grade power improvements $30 - 60\%$ sensory
Poor < 2 MRC grade power improvements $< 30\%$ sensory)
**Inclusion criteria**

1) Patients with involvement of noncontiguous two or more peripheral nerve areas.
2) Between January 1995 and December 2001
3) Minimum follow-up for 3 months.
4) Electro physiology and nerve biopsy done.

**Exclusion criteria**

1) Diagnosis of carpal tunnel syndrome
2) Neuropathy following a trauma.
3) Brachial plexus pathology.

**Definitions**

*Mononeuritis multiplex* – involvement of two or more peripheral nerve in more than two non-contiguous areas clinically or electro physiologically.

*Painful at onset* – sensation of pain or burning at the site of pathology, which may precedes or concurrently with disease onset.

*Nerve area involvement* – delineated by either clinically or electro physiologically

*Diabetes mellitus control status* – HbA1c – (< 9 – mild, 10 - 11 – moderate, > 12 poorly controlled )

**Pathology**

Methods used of pathological study

Nerve biopsied are sural nerve ( where all biopsied nerve area were Electro physiologically showing abnormal sensory studies.)

2 cm long unteased nerve section sent in 3% gluteraldehyde and studied

a) H &E stain

b) Bodian silver staining for axonal study

c) K Pal for myelin

d) Lepromin staining for lepra bacilla
Necrotizing vasculitis – by criteria by S. H. B. Hawke

1) Definite (D) if there was either a) vessel wall necrosis and an inflammatory reaction, or b) evidence of healing;
2) Probable (P) if an inflammatory reaction was seen in or around a vessel with a diameter greater than 30μm;
3) Absent (A) if none of the above, or only nonspecific such as intimal proliferation, were present.

IPNSV – by criteria

Hansen’s disease – characteristic pathology of HD

Diabetic neuropathy – hyaline arterial sclerosis, sectorial involvement of axonal involvement.

Lymphoma – infiltration of lymphomatous cells in endoneurium and perineurium

Sarcoidosis – by noncaseating granuloma and Asteroid bodies

Skin biopsy

Hansen’s disease – by characteristic pathology in HD.

Henoch Schonlein purpura – skin biopsy shows leukocytoclastic vasculitis.

Vasculitis and other serology work up includes

- a) ANA
- b) Anti ds DNA (if needed)
- c) APLA
- d) HBs Ag
- e) CRP
- f) RA factor
- g) VDRL
- h) HIV
- i) ANCA (if indicated)
Results

Total number of cases – 32 (male -17, female -15)
Age – 10- 79 (mean age 49.8)
Duration of hospital stay for proper diagnosis and institution of proper treatment- 3-15 days (mean hospital stay 9.29 days)
Peripheral neuropathy which are painful at onset – 22 (68.7%)
Initial manifestation of symptoms
  a) Sensory - 20 (62.55)
  b) Motor – 9 (28%)
  c) Sensory motor – 3 (9%)

Peripheral nerve enlargement – 20 (62%)
Hypo pigmented patches – 5(15%)
Cutaneous markers of vasculitis – 9 (28%)
Optic neuropathy 2 (Churg Strauss angitis, temporal arteritis)
Systemic effects of vasculitis
  a) Bronchial asthma , ILD- 2
  b) Abdominal colic - 1

Upper limb and lower limb together -24
Lower limb alone - 7 (22%)
Upper limb alone - 1
Sensory motor involvement – 28 (88%)
Pure motor involvement - 2
Pure sensory involvement – 4 (12%)
Electrophysiological findings

Axonopathic involvements - 32 (100%)
Conduction block – nil
Sensory motor 28
Pure motor 2
Pure sensory 3

Electromyogram

Done in 16 cases
Normal – 2
Neurogenic changes – 14

Laboratory findings

ESR 2-140 (mean ESR -43)
Absolute eosinophilic count – elevated in 2
( elevated upto 35000/cmm - 30000/cmm
both cases are Churg Strauss syndrome)
Vasculitic work up – positive in 6
Hypercalcemia - 1 (sarcoidosis)
Uncontrolled hyperglycemia – 3

Pure sensory nerve distribution

Total – 4
Hanson’s disease – 2
Sarcoidosis –1
WSMN -1

Pure motor involvement

Total – 2
IPNSV- 1
Systemic vasculitis – 1
Additional findings

2 cases with TA – optic nerve involvement
1 case with DM – 3\textsuperscript{rd} CN
1 case with DM – hypothyroidism
1 with neurosarcoidosis – bilateral 7\textsuperscript{th} and 6\textsuperscript{th} CN

Lower limb nerve alone affected

total - 7
IPNSV- 4 (CPN & TN )
SV – 1
Diabetes mellitus – 1
HD- 1

Upper limb alone – 1 (IPNSV )

Pattern of Nerve involvement in different conditions

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Ulnar</th>
<th>Radial</th>
<th>CPN</th>
<th>Tibial</th>
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<td>5/11(45%)</td>
<td>4/11(36%)</td>
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<td>10/11(90%)</td>
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<td>7/7(100%)</td>
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<td>HD</td>
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<td>6/8(75%)</td>
<td>1/8(11%)</td>
<td>7/8(90%)</td>
<td>6/8(75%)</td>
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<td>1/3(33%)</td>
<td>0</td>
<td>3/3(100)</td>
<td>2/3(66)</td>
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<td>1/1</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1</td>
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<tr>
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<td>0</td>
<td>1/1</td>
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<td>WSMN</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1</td>
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</table>
**Pathological study**

**Skin biopsy**
- Done in 11
- Hansen's disease – 7
- Malignancy (Lymphomatous) deposit -1
- Henoech Schonlein purpura –1
- Non specific -2

**Temporal artery biopsy** – 1(temporal arteritis).

**Nerve biopsy**
- Vasculitis – 17
- Hansen’s disease – 8
- Diabetes mellitus – 2
- Sarcoidosis – 1
- Non Hodgkin’s lymphoma – 1
- Non specific – 2
- Axonal involvement – 32

**Vasculitis group** - Nerve biopsy; H&E stain showed panarterits and fibrinoid necrosis & axonal loss. Special stain for axon shows axonal drop out and myelin stain showes secondary myelin changes.

**Hansen disease** showed variable involvement of fascicles, thin relatively preserved fascicle and markedly thickened fascicle with inflammation, Hansen's neuritis shows end neural granuloma and sometimes with gaint cells.
Photo graphs of Nerve biopsy (sural nerve) of patients with MM due to diabetes mellitus, vasculitis, and Hansen's diseases in the study series

Picture 1 – diabetic neuropathy with hyaline arteriosclerosis, large fiber loss, Schwann cell prominence
Picture 2, Vasculitic neuropathy; PAN – panarteritis with fibrinoid necrosis of vessel wall

Picture 3, Vasculitic neuropathy; acute axonal breakdown, linear rows of granular material within the axolemma – Maisson’s trichrome staining
Picture 4, active myeline breakdown and thinly myelinated Large fibre in Vasculitic neuropathy - K Pal staining

Picture 5, Hansen’s neuritis with variable involvement of fascicle
2 large nerve fascicle with endoneural granuloma low magnification pictures
Picture 6 - Hansen’s neuritis, thin relatively preserved fascicle and markedly thickened fascicle with inflammation.

Picture 7, Hansen’s neuritis, epithelial cell granuloma in endoneurium. Giant cell within granuloma.
Picture 8 Hansen’s neuritis with endoneural granuloma

Picture 10 Vasculitic neuropathy – acute axonal degeneration
**Disease wise data**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age</th>
<th>M/F</th>
<th>Painful</th>
<th>ESR</th>
<th>S/SM</th>
<th>other</th>
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<td>80%</td>
<td>48</td>
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<td>85%</td>
<td>62</td>
<td>1/6</td>
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<td>75%</td>
<td>19</td>
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<td>1- 3 CN</td>
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<td>100%</td>
<td>30</td>
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<tr>
<td>Sarcoidosis</td>
<td>52</td>
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<td>100%</td>
<td>60</td>
<td>0/1</td>
<td>7, 6 CN</td>
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3 CN – oculomotor nerve palsy, 7,6 CN – cranial nerve palsy.

**Final Diagnosis**

Vasculitis

- Isolated Peripheral Nervous System Vasculitis (NSV) 11
- Churg Strauss Angitis 2
- Rheumatoid Arthritis 2
- Temporal Arteritis 1
- Poly Arteritis Nodosa 1
- Henoch Schonlein Purpura 1
- Hansen’s disease 8
- Diabetes mellitus 3
- Non Hodgkin’s Lymphoma 1
- Sarcoidosis 1
- Wartenberg sensory migratory neuropathy 1
Treatment

Vasculitis group

Steroid alone  12
Steroid + Cyclophosphamide –  3
Steroid + Cyclophosphamide + Azoran  1
Steroid + azoran  1

Sarcoidosis – steroid
Hansen’s disease – anti HD treatment
NHL - Chemo therapy
DM - strict control of DM
WSMN + 1 NSV – No specific therapy taken

Outcome

<table>
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<th>Diagnosis</th>
<th>Good</th>
<th>Moderate</th>
<th>Poor</th>
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<td>5/11 (45%)</td>
<td>4/11(36%)</td>
<td>2/11(18%)</td>
</tr>
<tr>
<td>SV</td>
<td>4/7(57%)</td>
<td>3/7(43%)</td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>6/8(75%)</td>
<td>2/8(25%)</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>1/3(33%)</td>
<td>1/3 (33%)</td>
<td>1/3 (33%)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
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<tr>
<td>NHL</td>
<td>1/1</td>
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<td>WSMN</td>
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** 1 CSA, NHL died on course due to unassociated causes.
Discussion

In our study the majority of MM are constituted by vasculitis and HD. Among vasculitis IPNSV constituted the majority. The mean age group of IPNSV is slightly older than SV (53 vs 45). In IPNSV the male/female ration is nearly equal, but in SV majority of affected individuals are female. Mean ESR is also slightly lower in IPNSV in our series. These findings are agreeing with those were previously described by several other authors. Other symptomatologies including sensory motor distribution, painful at onset etc were similar in both the groups. In both groups the distribution of affection of nerves are also comparable, eventhogh isolated lower limb nerve involvement was seen more with IPNSV. There is no satisfactory explanation for this, and this was not observed in any other previous studies also. It may be because the disease severity in IPNSV as such is less severe than SV and so in IPNSV the pathology may be target ( nerve ) specific and so the maximum involvement may be targeted to the most bulkier nerves at the watershed areas in lowerlimbs.

The SV group needed most aggressive treatment in view of their systemic symptoms with various immunosuppressants (steroid, cyclophosphamide, AZA or in combination). All IPNSV group was treated with steroid alone (except in two cases, where one was switched over to AZA in view of intolerable side effects of steroids and other recovered without any specific therapy). 9/11 patients (80%) showed moderate to good improvement in IPNSV, 2/11 showed no signs of improvements. Among SV group 75% showed good and remaining showed moderate improvement on follow up. These observations was in contrast to the observations made by others previously. But as a whole SV group showed bad prognosis in our series also, one patient with SV (Churg Strauss angitis) died on follow up due to unrelated causes.

Our series showed 8 cases of MM due to HD. They are predominantly SM in distribution and all of them were male. Their mean age was 48 yrs, mean ESR was 35 and all were painless at onset. All were treated with intense anti-HD treatment and all showed marked response to therapy. These observations are well agreeing with previous observations.
There are 3 patients with MM due to uncontrolled DM; we could not find any other etiological factors in those patients. Moreover the biopsy picture was suggestive of diabetic neuropathy. Mean age was 60 yrs, all having poorly controlled glycemic status, all are men and among them two were painful at onset. The mean ESR was low (19). one patient had associated painful papillary sparing 3 rd CN involvement also. All were treated with good glycemic control and multivitamin supplementation. 2/3 showed moderate improvement.

The Churg Strauss angitis (CSA) patients presented with recent onset allergy, bronchial asthma and rapidly worsening devastating MM. Both patients had very high absolute eosinophil counts (AEC-upto 36000cells/cmm). Available previous reports about CSA reports elevation upto a maximum of 1000-2000 cells/cmm only. CSA group carry very bad prognosis, one patient died on follow up due to systemic complications

Sometime the MM is associated with polyneuritis cranialis. In this study four cases of MM are associated with polyneuritis cranialis (two case of temporal arteritis with optic neuritis, one case of diabetic neuropathy with 3rd cranial nerve, and other of neurosarcoidosis with bilateral 7th & 6th cranial nerves). TA is usually presented with optic nerve involvement by AION by the involvement of posterior ciliary arteries. By specific institution of therapy the symptoms improved in our two cases of diagnosed TA. They are enjoying almost near total recovery, one case completed follow up of 6 yrs and she is asymptomatic on alternate day dosage of very low dosage (5 mg) steroid. Diabetes can present with papillary sparing oculomotor nerve involvement as in our case. The prognosis of this entity is guarded and needed good and strict control of diabetes state. In our case patient had partial recovery of cranial nerve function only.

The electrophysiology proved to be axonopathic in involvement in all, these finding were very well correlating with our subsequent biopsy reports. So there were strong EP-pathology correlations in all these cases. All previous studies are also in agreement of an axonopathic involvement in EP in majority of MM. Secondly there were no correlation between clinical outcome and electrophysiological severity. Some
inelicitable nerves showed very good recovery on follow up. These are also in agreement with previous observations. There was no predominating demyelinating electrophysiological finding or conduction block in this study.

Most of the MM are sensory motor (SM) in distribution, but 2 were pure sensory both by clinically and electro physiologically. Both these cases are Hansen's disease by pathology. Rest of the HD presentations is SM in distribution. Two cases were pure motor in distribution both by clinically and electro physiologically and are of vasculitic etiology (1-IPNSV, 1-SV).

One 27 yr old young lady has migrating pure sensory migrating neuropathies involving common peroneal nerves, ulnar nerves, medial nerves. Electro physiologically was mainly mixed type of involvement. All other etiological work up were negative. Her symptoms were migrating from one sensory nerve area to other and spontaneously resolved completely without any residue. Watenberg in 1958 described "migrant sensory neuritis" consisting of recurrent, intermittent, remittent Mononeuritis multiplex with sensory involvement only. It is often painful and "nerve stretch test" will be positive. Average duration of nerve involvement will be 2-4 weeks and mean age will be 35 years. The classical pathology will be "perineuritis and endoneurial edema" but nerve biopsy was inconclusive in our case. They usually recover spontaneously without any immunosuppressant. Our patient also recovered completely without any sequelae and without any specific therapy.

One elderly lady presented with MM involving the bilateral CPNs and ulnar nerve on one side. She was previously diagnosed to have non Hodgkin's lymphoma. When she presented with neurological manifestations (MM), there were no evidence of systemic lymphoma by repeated blood and bone marrow examination. She had lymphoma (NHL) which was in hematological remission. Neuropathy in NHL can present as symmetric or asymmetric neuropathy. Symmetric peripheral neuropathy are usually due to side effect of chemotherapy, secondary to cachexia and subsequent nutritional etiology, or due to paraneoplastic involvement. Asymmetric neuropathies are due to "intraneuronal Lymphomatous infiltrates". Intraneuronal Lymphomatous infiltrates" tends to occur in 3 particular situations;
1) Wide spread metastasis of lymphoma to neuraxis
2) Lymphomatous infiltrations of nerves can occur as the sole site of involvement in neuraxis with no prior history of systemic involvement.
3) As a neuropathy in "systemic lymphoma in hematological remission".

Our patient presented with the third situation. The mechanism by which this develops is not clear. But Krendel et al proposed that during the systemic lymphomatous stage, lymphoma cells get sequestrated in neuraxis. ‘Blood – Nerve barrier’ created by capillary tight junction may reduce the penetration of chemotherapeutic agent into endoneurium, allowing the tumor cells to survive inside the nerve very safely. Once the chemotherapeutic agents are over, the sequestrated cells will manifest as MM at a later time when patient is in hematological or systemic remission. By appropriate reinstitution of therapy for relapse of the malignancy, the neuropathy can be treated successfully and carry better prognosis as in our case, where the MM was treated successfully by chemotherapy alone. But 18 months later, when her neuropathy got improved, the patient died on follow up secondary to a serious systemic relapse.

One child aged 10 yrs presented with features suggestive of HSP and MM. HSP etiology was proved by leukocytoclastic vasculitis in skin biopsy and the nerve biopsy was conclusive of a Vasculitic pathology. The neurological manifestation of HSP are rare, while other organ involvement are more common. But in this case other systemic involvement other than GIT was less and renal system was unaffected. She had a very good systemic and neurological outcome.
How to differentiate between symmetrical peripheral neuropathy and
Confluent form of Mononeuritis multiplex – which became confluent

This differentiation is at times very difficult.

Pointers for a confluent MM other than DSPN are

1) Historically if there is a definite asymmetric onset between nerve areas by more than 4 weeks
2) Clinical examination suggestive of significant differential involvement between limbs or different nerve areas.
3) Differential involvement in one limb – plantar flexion is more involved than DF
4) EP – clear asymmetry between the limbs or nerve areas.

Which nerve to be biopsied for nerve biopsy

It is preferable to take biopsy from an accessible superficial sensory nerve which is involved either clinically or electro physiologically.

Conclusion

- Our experience in a tertiary level referral centre reveals that MM caused by the vasculitis (SV + IPNSV) constituted the majority.
- Hence the major pathology is axonopathic (1 – demyelinating)
- Rare causes like CSA, sarcoidosis, HSP etc should be investigated for in MM.
  a. Bronchial asthma, markedly raised ESR → CSA
  b. ON + MM → temporal arteritis
  c. 3 rd Cranial neuropathy + MM → DM
  d. 7th Cranial neuropathy + MM → sarcoidosis
  e. purpura → HSP
- Investigations like hematology, serology and biopsy clinch the diagnosis in most of them.
- Majority of cases improved well with steroids with or without other immunosuppressant and carry good prognosis.
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