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Original Research Article

A study on peripheral neuropathy in HIV infected patients: clinicoepidemiological and electrophysiological profile

K. Gunasekaran*, S. Sivakumar

Department of Neurology, Government Mohan Kumaramangalam Medical College Hospital, Salem, Tamilnadu, India

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***Correspondence:**
Dr. K. Gunasekaran,
E-mail: drgunasekaranneuro@gmail.com

ABSTRACT

Background: Peripheral neuropathy is one among the commonest HIV-associated neurologic complications. The spectrum and the frequency of this complication are changing due to the introduction of new antiretroviral drugs, aging of the HIV-infected people, etc. Hence there is need for a better understanding of these complications and their pathogenesis. This study was done with the aim of finding out the risk factors, clinical characteristics and various types and patterns of peripheral neuropathy in HIV infected patients of our region.
Methods: This study was a cross sectional study conducted for about a period of one year. Patients attending the out patient department of anti retroviral therapy (ART) centre were taken for the study. Selected patients were analysed for the signs and symptoms of peripheral neuropathy and they underwent electrophysiological study.
Results: Prevalence of peripheral neuropathy in HIV infected patients in our study population was 43.3%. Peripheral neuropathy was seen more in patients with advanced clinical stage and increasing age. Distal symmetric polyneuropathy was the commonest type. Common pathological pattern of neuropathy was mixed (both axonal and demyelination) neuropathy.
Conclusions: As peripheral neuropathy is a common HIV-associated neurologic complication, large number of studies are needed to elucidate the mechanisms leading to peripheral neuropathy in HIV infected patients, which in turn will allow for the development of effective therapies that provide adequate symptomatic relief and halt or reverse the damage to the nerves.

Keywords: Distal symmetric polyneuropathy, Electrophysiology, HAART, HIV infection, Peripheral neuropathy

INTRODUCTION

The life expectancy of human immunodeficiency virus (HIV) infected patients is increasing nowadays as a result of highly active antiretroviral therapy (HAART).[1] Consequently, treating physicians need to deal with neurologic complications from the HIV disease, from concurrent diseases, and from drugs used to treat them. Peripheral neuropathy is one among the commonest HIV-associated neurologic complications.[2] The spectrum and the frequency of this complication are changing due to the introduction of new antiretroviral drugs, aging of the HIV-infected people, and the emergence of other long-term complications of HIV and its treatment.[3] Several forms of neuropathy may occur, depending on the level of immunosuppression and the presence of risk factors. Hence, there is a great need for a better understanding of these complications and their pathogenetic mechanisms, for the development of effective therapies that provide sufficient symptomatic relief and halt or reverse the damage to the nerves.

Aims of the study was to study the prevalence of peripheral neuropathy in HIV infected patients. Also, to find out the risk factors associated with the development of peripheral neuropathy and to study the clinical profile and various types and patterns of peripheral neuropathy in HIV infected patients.

METHODS

This study was a cross sectional study, conducted during the period of January 2009 to December 2009, for about 1 year at Department of Neurology, Tirunelveli Medical college Hospital, Tirunelveli, southern part of Tamilnadu state.

Patient selection

Patients attending the out patient department of anti-retroviral therapy (ART) Centre of our institute were taken for the study. Patients already diagnosed as HIV positive and on highly active anti-retroviral therapy (HAART) only were selected. Both male and female patients were taken. Study was done with the consent of the patients as well as with the institution's ethical committee approval.

Inclusion criteria

- Patients who were seropositive for HIV infection and registered with ART Centre.
- Patients on HAART.
- Both symptomatic and asymptomatic patients, irrespective of stage of the disease, CD4 count and duration of the HIV illness.

Exclusion criteria

- HIV seropositive patients who were not on HAART at the time of the study.
- Patients with other systemic illness like diabetes mellitus, renal disease, thyroid disease, nutritional anaemia, Hansen's disease.
- History suggestive of collagen vascular diseases, recent Chikungunya fever or any other viral illness or jaundice.
- Patients who regularly consume alcohol of > 40 units/week.

All the patients were analysed for symptoms and signs of peripheral neuropathy and biochemical investigations and complete hemogram were done to rule out other systemic illness.

Electrophysiological study

All the patients were encouraged to undergo nerve conduction study (NCS). But only in 30 patients NCS could be done. Sensory nerve conduction studies of the sural, ulnar and median nerves were performed orthodromically. For motor nerve conduction studies, supramaximal nerve stimulation was applied transcutaneously to a distal and proximal segment of the tibial, peroneal, median and ulnar nerves. F-wave latencies were obtained from the median, ulnar, peroneal and tibial motor nerves. Electrophysiological diagnosis of peripheral neuropathy was done with standard reference values.[4-6]

RESULTS

Data of total study population

Epidemiological data

Total number of patients in our study group was 60. Among them males were 33 (55%) and females were 27 (45%). Patients were in varying age groups, minimum of 21 years to maximum of 54 years. Males were aged from 28 to 54 years and females were from 21 to 52 years. Among the total number of 60 patients, 23 (38.3%) patients had symptoms of peripheral neuropathy and remaining were asymptomatic.

Clinical data

Patients were staged according to WHO staging system.[7] More number of patients were in stages III and IV (65%) compared to stages I and II (35%). (Chi-square: 18.750; df: 3, p-value <0.0001) (Figure 1).

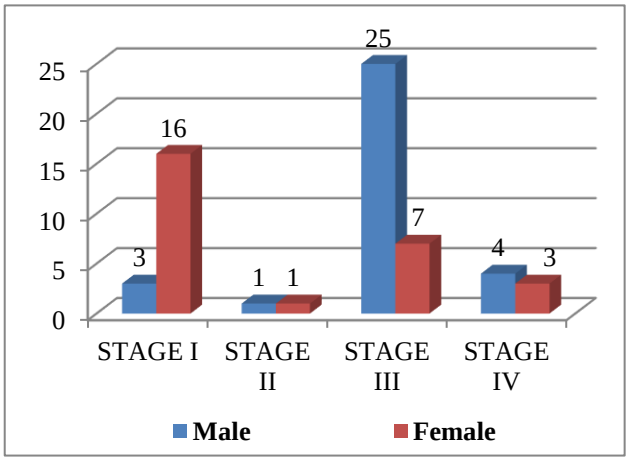

Figure 1: Clinical stage and sex distribution of study population.

The duration of HAART varied from 1-48 months with mean of 23 months. Those who were on HAART of <12 months were 20, 13-24 months were 19, in 25-36 months were 12, >37 months were 9. (Chi-square: 3.015, p-value = 0.398). CD4 count was done twice in ART clinic. One at time of diagnosis of HIV seropositivity and another one done recently, that is while undergoing this study. Patients having CD4 <200 are 31 (51.7%) >200 are 29 (48.3%). Patients were on various regimen. In the ART centre, 4 types of regimens were followed, which contain

2 NRTIs and 1 NNRTI. The following regimens are used: ZLN, ZLE, SLN, SLE. Among NRTIs lamivudine was compulsorily added and either zidovudine (if no anemia) or stavudine (if no PN) was added. Among NNRTIs either nevirapine (if no ATT or hepatotoxicity) or efavirenz (if nevirapine contraindicated) was used. Some patients who were suffering from pulmonary tuberculosis (PT) were started on ATT (anti-tuberculosis treatment) first and then after completing ATT, later started on HAART and in between also if PT was detected, HAART stopped and ATT started and HAART restarted later. Totally 23 such patients were given ATT at one point of time. Among whom one was presently on ATT at the time of our study. The following table shows the various treatment regimen patients were on (Table 1).

Table 1: Various treatment regimens of the total study population.

Regimen		Frequency	Percentage
	On ATT	1	1.7
Stavudine regimen	SLE ATT	1	1.7
	SLE SLN	4	6.7
	SLE ZLN	6	10.0
	SLN	12	20.0
	SLN SLE	1	1.7
	SLN ZLN	8	13.3
	ZLE SLN	1	1.7
	ZLN SLN	1	1.7
Non-Stavudine regimen	ZLE	1	1.7
	ZLE ATT	1	1.7
	ZLE ZLN	8	13.3
	ZLN	15	25.0
	Total	60	100.0

(Z-zidovudine, L-lamivudine, S-stavudine, N-nevirapine, E-efavirenz, ATT-Antituberculosis Treatment)

Data of peripheral neuropathy group

Among the study group of 60 patients, 26 were having evidence of peripheral neuropathy (Figure 2). Different topographical and clinical types of peripheral neuropathy were noticed (Figure 3). These patients were in different age groups as follows (Table 2).

In the total study group, 39/60 were in stages III and IV and 21/60 were in stages I and II. Among the 39 patients of stage III and IV, 19 (48.7%) had peripheral neuropathy and among the 21 patients of stage I and II, 7 had peripheral neuropathy (Table 3).

Duration of HAART

Among the 39 patients of less than 24 months duration of HAART, 18 (46.2%) suffered from peripheral neuropathy and among the 21 patients of more than 24 months duration of HAART, 8 (38.1%) suffered from peripheral neuropathy. (Chi-square: 3.825, p-value = 0.281) (Figure 4).

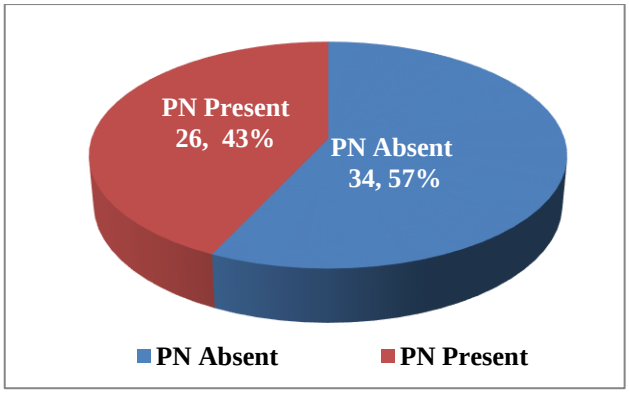

Figure 2: Peripheral neuropathy prevalence.

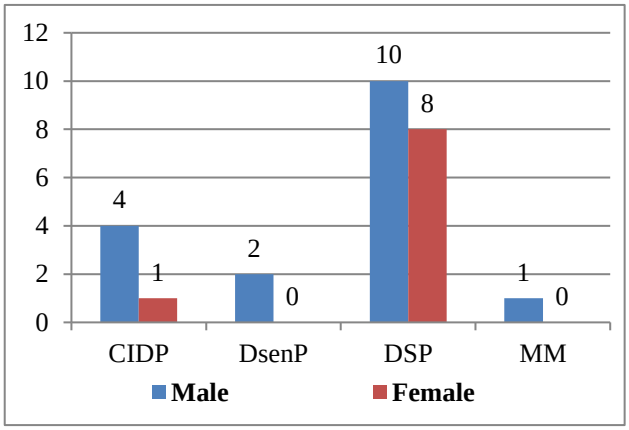

Figure 3: Sex and peripheral neuropathy types.

Table 2: Number of patients with peripheral neuropathy in various age groups.

Age group (Yrs)	Total	Peripheral Neuropathy present	peripheral neuropathy absent	% of peripheral neuropathy
21-30	13 (21.7%)	5 (19.2%)	8 (23.5%)	38.5 %
31-40	33 (55.0%)	13 (50.0%)	20 (58.8%)	39.4 %
41-50	11 (18.3%)	5 (19.2%)	6 (17.6%)	45.5 %
Above 51	3 (5.0%)	3 (11.5%)	0 (0.0%)	100 %
Total	60	26	34	

Chi-square: 4.277, p-value: 0.233

CD4 count

Those patients with peripheral neuropathy with CD4 <200 were 9 (34.6%), and >200 were 17 (65.4%). In total study group, patients with CD4 <200 were 31 (51.7%) and >200 were 29 (48.3%).

Treatment regimen

When correlating the duration of HAART with type of regimen and peripheral neuropathy, it shows the

following results: (Figure 5) (Table 4). Distribution of symptoms and signs were as mentioned (Figure 6).

Table 3: Number of patients with peripheral neuropathy in various clinical stages.

Stage	Peripheral Neuropathy – Present	Peripheral Neuropathy - Absent	Total
I	6 (23.1%)	13 (38.2%)	19 (31.7%)
II	1 (3.0%)	1 (2.9%)	2 (3.3%)
III	15 (55.7%)	17 (50.0%)	32 (53.3%)
IV	4 (15.4%)	3 (8.8%)	7 (11.7%)
Total	26	34	60

Chi-square: 1.812, p-value: 0.612.

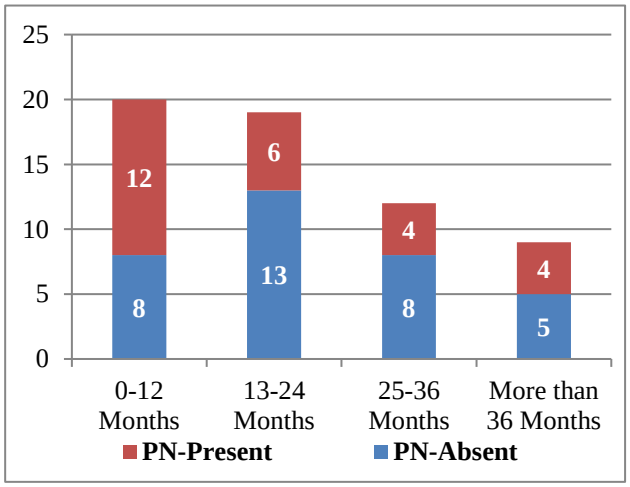

Figure 4: Duration of HAART and peripheral neuropathy.

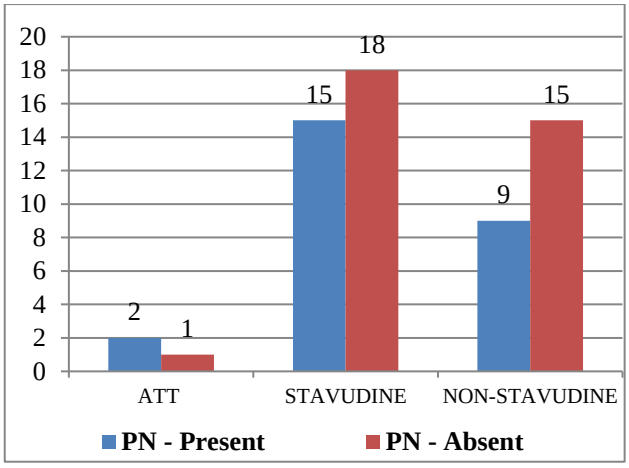

Figure 5: Regimen group and peripheral neuropathy in total study population.

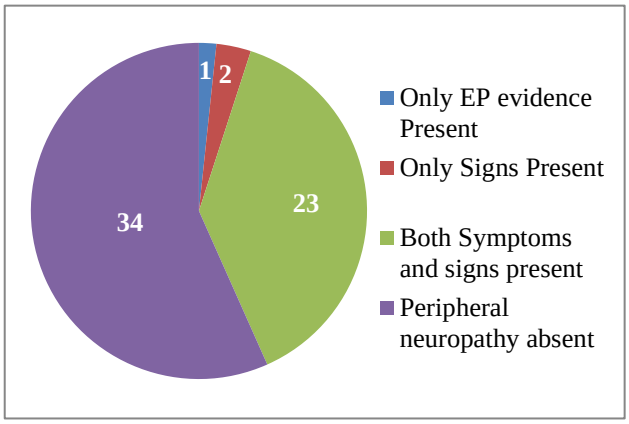

Figure 6: Distribution of symptoms and signs in total study population.

Table 4: Duration of HAART and type of regimen in relation to peripheral neuropathy.

Duration of HAART	Total no. patients	Stavudine users (A)	Peripheral neuropathy present in (A)	Non-stavudine users (B)	Peripheral neuropathy present in (B)
0-12 months	20	10	5 (50%)	10	7 (70%)
13-24 months	19	10	4 (40%)	9	2 (22.2%)
25-36 months	12	8	3 (37.5%)	4	1 (25%)
> 36 months	9	6	4 (66.7%)	3	Nil
Total	60	34	16 (47.1%)	26	10 (38.5%)

Patients, who didn't have either symptoms or signs of peripheral neuropathy, were 35. Among them 5 underwent electrophysiological analysis. One of them showed electrophysiological evidence of peripheral neuropathy. All the symptomatic patients had electrophysiological evidence of peripheral neuropathy and this is statistically significant as p-value was <0.0001.

Symptoms and signs

Symptoms were numbness (17 patients), tingling (8 patients), electric shock-like sensation (5 patients), burning pain (3 patients), pins and needles sensation (5 patients), cramps (4 patients) and weakness (2 patients). Most of the patients showed symptoms in lower limbs

(20 patients). Only in 5 patients symptoms were present in both upper and lower limbs.

Sensory signs were diminished vibration, touch, pain and temperature in that order. In 17 patients all modalities like vibration, touch, pain and temperature were lost in lower limbs. In 8 patients, only vibration impairment was seen. In 3 patients sensory signs (impairment of vibration) were present in hands. Ankle jerk was diminished in 6 patients and absent in 11 patients. 4 patients had diminished knee jerk. Weakness in ankle dorsiflexion and plantar flexion were seen in 2 patients, weakness in extension of great toe was present in 4 patients and in 7 patients toe-grip was weak. Wasting seen in intrinsic foot muscles in 3 patients. In upper limbs, signs were not seen except in patients with CIDP (Chronic Inflammatory Demyelinating Polyneuropathy) who showed both sensory and motor features. Likewise CIDP patients had both proximal and distal weakness in lower limbs.

Electrophysiology

Nerve conduction study was done totally in 30 patients. Among them, electrophysiological evidence of peripheral neuropathy was seen in 26 patients. Predominant pattern seen was mixed neuropathy (both axonal and demyelination) in 18 patients. Among the 5 patients with CIDP, 1 patient had features of both axonal and demyelination pattern and others had predominant demyelination pattern. 3 patients had only axonal pattern. Both motor and sensory neuropathy were seen in 24 patients and only sensory neuropathy was seen in 2 patients.

DISCUSSION

In this study, a survey of variables related to peripheral nerve function was done in the group of HIV-infected individuals. Also nerve conduction studies and several potential pathogenetic factors have been systematically studied. Among the 60 patients under the study, 26 patients were having peripheral neuropathy and electrophysiological study confirmed this.

Types of peripheral neuropathy

Among the 26 patients with peripheral neuropathy, distal symmetrical polyneuropathy (DSP) was the commonest (69.2%) type. Other types seen were distal symmetric polyneuropathy with only sensory findings (Distal Sensory Polyneuropathy) (7.7%), CIDP (19.2%) and Mononeuritis Multiplex (MM) (3.8%). Among the inflammatory demyelinating polyneuropathies, both AIDP (acute inflammatory demyelinating polyradiculoneuroathy) and CIDP (chronic inflammatory demyelinating polyradiculoneuropathy) can occur in HIV infected patients.[8] Acute form often presents at the time of HIV seroconversion or primary infection. But we did not encounter AIDP though we had 5 patients of CIDP. This may be because of the method of patient selection. We selected patients from out patient department of ART centre where they come for follow up and getting drugs. Other types described in text books and literature like progressive polyradiculopathy, autonomic neuropathy and mononeuropathy were not seen in our study, as noted in other Indian study.[9,10]

In our study, distal symmetric polyneuropathy was the commonest type (76.9%), an observation similar to those described in literature.[11-13] As this distal symmetric polyneuropathy can occur due to HAART as well as due to ATT, it needs prospective analysis to find out whether it was drug induced.

Age

In our study prevalence gradually increased from 38.5% to 100% as the age advanced, similar to other studies.[14] But it is not statistically significant (p- value= 0.233). An article reviewing the impact of aging in HIV infection and its neurological complications explains that aging is associated with a higher viral load and immunosenescence, with a decrease in the naive subsets of CD4 cells, decreases in T cell proliferative responses and decreased ability to respond to novel pathogens, resulting in a potential synergism between HIV infection and aging.[15]

Duration of HAART

In our study, PN was less in those patients on HAART of longer duration. HAART lessens disease progression, improves immunity, and widens the ratio of therapeutic to toxic effects of individual antiretroviral drugs, resulting in a significantly lower risk of developing peripheral neuropathy.

Treatment regimen

Among the drugs used as HAART, the ‘d’ drugs (didanosine, zalcitabine, stavudine) are prone to produce neurotoxicity. In our ART centre stavudine was used and other 2 drugs were not used. So, patients were divided into those on stavudine (stavudine group) and not on stavudine (non-stavudine group).

Peripheral neuropathy was seen in 47.1% of stavudine users and in 36% of non-stavudine users. This shows more number of peripheral neuropathy in stavudine users, an observation similar to the findings seen in other studies.[16]

Another observation was that in all the stages of the disease, peripheral neuropathy was slightly more in stavudine users. This suggests the possibility of drug toxicity of the stavudine was an added factor for the development of peripheral neuropathy in all the stages.

Interestingly in less than 12months duration of HAART, peripheral neuropathy patients on stavudine regimen were 5 and on non-stavudine regimen were 5. That is, at the time of seroconversion, peripheral neuropathy was seen equally in both stavudine and non-stavudine regimen. But when duration of HAART increased, more number of patients were seen in stavudine regimen. This indicates that peripheral neuropathy in the initial period of seroconversion might be due to the disease process itself whereas in peripheral neuropathy of later period, might have been due to drug toxicity, as it was noted mainly in stavudine users. However, this is a study of small group and this needs to be evaluated with large number of patients.

Stage of disease

Increased risk of developing peripheral neuropathy noted in advanced stages (stage III and IV), an observation similar to other studies. But it is not statistically significant in our study (p-value: 0.612).

CD4 count

There was no increased risk of developing peripheral neuropathy for those patients with less CD4 count. Peripheral neuropathy in patients with CD4 count more than 200 suggest that peripheral neuropathy may be due to drug toxicity or other underlying conditions as described in literature.[17]

Analysis of symptoms and signs

Frequent symptoms we came across were numbness, tingling, electric shock like sensation with less frequently burning pain, pins and needles. Our findings are comparable with those reported in previous studies, in which subjective pain was uncommon and usually present in more advanced stages.[18,19] These observations are similar to that reported in some other studies also. Some patients (4) had cramps in both legs, as reported in some other series, which could be due to motor neuropathy or metabolic or drug related and could not be differentiated. Electrophysiological study picked up the presence of peripheral neuropathy even in upper limbs in some patients who had signs only in lower limbs. This indicates the presence of subclinical neuropathy in asymptomatic sites.

Sensory signs seen in our study were diminished vibration, touch, pain and temperature in that order. Predominant motor sign was diminished or absent ankle jerk. Others were diminished knee jerk, weakness in ankle dorsiflexion and plantar flexion, weakness in extension of great toe, toe-grip weakness and wasting in foot intrinsic muscles. Both sensory and motor signs present in our study are similar to what described in literature.

The following table shows the statistical analysis of peripheral neuropathy with various as mentioned factors (Table 5).

Table 5: Statistical analysis of peripheral neuropathy with various factors.

Factor	peripheral neuropathy - present (N= 26)	Peripheral neuropathy - absent (N= 34)	Odds ratio	Chi- square	p-value
Age > 36 years	19 (73.1%)	15 (44.1%)	3.48	5.032	0.025
Sex -male	17 (65.4%)	16 (47.1%)	1.37	1.999	0.157
Duration ≥ 22 months	11 (42.3%)	19 (55.9%)	0.58	1.086	0.297
Symptom of PN	23 (88.5%)	0 (0.0%)	21.3	48.77	0.000
Clinical stage –III and IV	19 (73.1%)	20 (58.8%)	1.24	1.321	0.251
Cd4 count ≤ 200	12 (46.2%)	19 (55.9%)	0.67	0.558	0.455

The above analysis conclude that increasing age and advanced clinical stages are significantly associated with more prevalence of peripheral neuropathy.

Electrophysiological study

Among the 26 patients with electrophysiological evidence of peripheral neuropathy, 23 had symptoms and 2 had signs. It infers peripheral neuropathy might be seen in patient with either symptoms or signs. Hence detailed history and clinical examination for symptoms and signs of peripheral neuropathy is essential in all HIV infected patients as it can pick up patients with peripheral neuropathy earlier and so they can be treated earlier.

Among those patients who neither had symptoms nor signs of peripheral neuropathy, 5 patients accepted to undergo nerve conduction study after counseling them and 1 of these 5 patients (20%) showed electrophysiological evidence of peripheral neuropathy. This indicates subclinical neuropathy may be present in 20% of HIV infected patients. However, this is a group of

small number and it has to be evaluated with large number of patients.

Predominant pattern seen was mixed neuropathy (both axonal and demyelination), which was seen in 18 patients. But in literature predominant pattern seen is axonal.[20,21]

In 13 patients, electrophysiological evidence of peripheral neuropathy was seen in both upper limbs and lower limbs. But clinically many (20/23) had symptoms only in lower limbs. It shows subclinical peripheral neuropathy may be present in upper limbs. Following are the comparison of our study with other studies (Table 6 and 7).[22,23]

Table 6: Comparison of our study with other Indian study.

Factor	Garg J et al[20]	This study
Total no. of patients	39	60
Peripheral Neuropathy present in	20	26
Mean duration of HAART (months)	24	19
CD4 <200	17	9
>200	3	17
Symptoms seen in	20/20 (100%)	23/26 (88%)
Signs seen in	20/20 (100%)	25/26 (96%)
Electrophysiological evidence of Peripheral Neuropathy seen	4/20	26/26
Pattern of peripheral neuropathy	Distal symmetric polyneuropathy. Axonal pattern	Commonly distal symmetric polyneuropathy, others: CIDP, MM. Mixed pattern (both axonal and demyelinating)
No. of patients on HAART	17/20	26/26
Correlation between duration of HAART and peripheral neuropathy	No significant relation	less number of peripheral neuropathy patients seen in longer duration of HAART

Table 7: Comparison of our study with other international studies.

Factor	Zanetti C et al[22]	Gastaut JL et al[23]	This study
Total no. of patients	49	41	60
M:F	32:17	-	33:27
Mean age	36.8	-	35.6
Age range (years)	21-53	-	21-54
Peripheral Neuropathy seen in	34 (69.4%)	36 (88%)	26 (43.3%)
Both symptoms and signs seen in	12/34	-	23/26
Only signs seen in	22/34	-	2/26
Subclinical (no symptoms, no signs) Peripheral Neuropathy	2	17	1/26
Neurotoxic drug intake	32 (94.1%)	-	18 (69.2%)
Electrophysiological study done in	39	-	30
Peripheral Neuropathy seen in (among those underwent Electrophysiology)	13/39	-	26/30
Common type seen	Distal symmetric polyneuropathy (8/13)	Distal symmetric polyneuropathy	Distal symmetric polyneuropathy (20/26)

Some observations of our study go along with other studies.[24,25] For example the common type, distal symmetric polyneuropathy seen in other studies was also the common type in our study. Prevalence seen in our study (43.3%) was similar to other studies.[26] In our study, male sex, advanced stage of disease and increasing age were associated with more risk of developing peripheral neuropathy. But these observations were not statistically significant. Only the positive symptom by history and increasing age were significantly associated with the occurrence of peripheral neuropathy. Like other studies CD4 count doesn't correlate with prevalence of peripheral neuropathy.

CONCLUSION

Several mechanisms might have involved in the pathogenesis of HIV related peripheral neuropathy like neurotoxic effects of the virus and its gene products as well as neurotoxicity of medications used for the treatment of HIV infection. While the diagnosis of HIV related peripheral neuropathy remains largely clinical, other conditions that lead to peripheral neuropathies need to be excluded. Additional research and studies with large number of patients are needed to elucidate the mechanisms leading to peripheral neuropathy in HIV infected patients, which in turn will allow for the development of targeted treatment strategies.

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