Original Article

DOI: 10.7860/JCDR/2014/8143.4531

HIV Associated Sensory Neuropathy

Neurology Section

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ABSTRACT

Background: In the era of highly active antiretroviral therapy (HAART), sensory neuropathies have increased in prevalence. We have documented the frequency and profile of the two most common forms of sensory neuropathies associated with Human Immunodeficiency Virus (HIV) infection and looked into clinico-electrophysiological correlates to differentiate the two entities.

Methods: The study population comprised of all consecutive patients detected to be HIV positive and attending the Neurology outpatient department (from March 2011 to March 2012) who were aged ≥ 18 years and were able to give informed consent. The data were collected from the patient records (including CD4 counts and treatment details) and questionnaire based interview with each patient. All patients underwent detailed clinical examination and nerve conduction studies (NCSs).

Results: Among the total study population of 50 patients, there were 31 men and 19 women. Thirty two patients were in age range of 21 - 40 years and rest were above 40 years. 25 were on antiretroviral therapy (18 on regimen containing zidovudine; seven on regimen containing stavudine). The mean duration of antiretroviral therapy was 16.6±8.4 months. Low CD4 counts (<200) were noted in 24 patients (13 of these were on antiretroviral therapy). Clinically, the patients were classified as asymptomatic (n=34) and symptomatic (n=16). Among the symptomatic patients, nine were on antiretroviral therapy since less than one year (seven of these were on regimen containing stavudine). Ten patients aged more than 40-years had symptomatic neuropathy. No significant correlation was found between low CD4 counts and symptomatic neuropathy (p=0.21). Impaired vibration (100%) and absent ankle jerks (75%) were commoner than reduced pin sensitivity (46.6%). Twenty two patients had abnormal NCS results (18 of these were on antiretroviral therapy). Axonal distal symmetrical sensory neuropathy was the commonest pattern noted in 14 patients who were receiving antiretroviral therapy. Subclinical involvement as evidenced by NCSs was noted in 5 asymptomatic patients who were all on antiretroviral therapy.

Conclusion: Symptomatic neuropathy was seen predominantly in HIV patients who were on antiretroviral therapy. All patients receiving stavudine containing regimen had severe symptomatic neuropathy within 1 year. There was an increase in the likelihood of symptomatic neuropathy among patients aged > 40 years. Subclinical neuropathy was common in those on antiretroviral therapy. Axonal neuropathy was the commonest pattern noted in patients who were receiving antiretroviral therapy and demyelinating neuropathy in patients not on antiretroviral therapy. Surprisingly no significant correlation was found between low CD4 counts and symptomatic neuropathy.

Keywords: Anti-retroviral therapy, Antiretroviral toxic neuropathies, Distal sensory peripheral neuropathies, HIV associated sensory neuropathy, Human immune deficiency Virus, Peripheral neuropathy, Stavudine

INTRODUCTION

Human Immunodeficiency Virus - associated sensory neuropathies (HIV-SN) include the distal sensory peripheral neuropathies (DSP) due to HIV and antiretroviral toxic neuropathies (ATN). Apart from the temporal relationship between the antiretroviral nucleoside reverse transcriptase inhibitors (NRTI) drug exposure and symptom onset, ATN is clinically and electrophysiologically indistinguishable from DSP. Symptom onset is variable, with some data suggesting that ATN is more likely to be sudden in onset and rapidly progressive and DSP is more insidious. DSP is uncommon in the early stages of HIV infection. DSP was noted in 30% of hospitalized patients with advanced HIV disease before the Highly active antiretroviral therapy (HAART) era [1-3]. In addition, the prevalence of DSP continues to rise as patients with HIV infection are living longer [4]. DSP occurring in HIV patients, may result as a consequence of immunological dysregulation [5]. Incidence rates correlated with lower CD4 counts and high viral loads. ATN is associated with exposure to Stavudine, Didanosine or Zalcitabine dideoxynucleoside reverse transcriptase inhibitors (dNRTIs). Controversy exists over the relative importance of ATN in HIV-SN. Non-NRTI risk factors described for HIV-SN include prior neuropathy, older age, poor nutrition and advanced HIV disease. A case definition of DSP for clinical research has been proposed [6]. The optimal diagnostic methods for HIV-SN have not yet been defined. Nerve conduction study (NCS) may demonstrate an axonal neuropathy but can be normal with clinically apparent HIV-SN.

It is of immense clinical importance to document the incidence and profile of HIV-SN in patients with and without ART. We have attempted to study the clinical and electrophysiological parameters in a cohort of HIV patients in order to document the frequency and profile of the sensory neuropathies associated with HIV infection and tried to look into, if any, clinico-electrophysiological correlates to differentiate the two entities of HIV-SN. We conducted the present study in our hospital with rapidly growing diagnostic and treatment services for HIV patients aiming to determine the frequency and profile of Peripheral Neuropathies in HIV infected patients with or without ART. We also review briefly the literature regarding HIV-SNs.

MATERIALS AND METHODS

This was a hospital based observational cohort study conducted in the Neurology outpatient department in co-ordination with the ART unit located in a tertiary care general hospital in a resource poor setting, during the time period between March 2011 and March 2012. The study was approved by the Institutional ethical committee.

Parameters		Patients on ART (n=25)	Patients not on ART (n=25)
Mean age		41.56±11.02 years	37.08±12.38 years
M:F		16:9	15:10
Duration of HIV detection	< 1 year	11 (3*)	21 (1*)
	1-2 years	4 (2*)	2 (1*)
	> 2 years	10 (8*)	2 (1*)
CD4 Counts	< 100	4	5
	101-200	9	6
	201-350	7	7
	> 351	5	7
Co-existent TB infection		12 (7*)	9 (2*)
Neuropathic symptoms		13	3
Reduced pin sensitivity		4	3
Reduced vibration		13	3
Absent ankle jerks		9	3
Duration of ART	< 1 year	15 (9*)	
	1-2 years	6 (2*)	
	> 2 years	4 (2*)	

[Table/Fig-1]: The demographic and clinical details of patients
(*) indicates number of patients with presence of symptomatic neuropathy

We studied the consecutive patients detected to be HIV positive and attending the Neurology outpatient department (from March 2011 to March 2012) who were aged ≥ 18 years and were able to give informed consent.

We excluded the patients with severe dementia, uncontrolled major psychiatric disorders and/ or any active opportunistic infections of the Central Nervous System (CNS). We screened the patients for any other major risk factors for sensory neuropathy other than HIV or ART (Diabetes Mellitus, alcoholism, Vitamin B12 deficiency and other causes as clinically required).

The socio-demographic details namely—age, sex, mode of transmission of disease, duration of HIV Infection (from the time of detection of HIV positivity), whether on ART, history of Tuberculosis and ATT were collected by questionnaire based interview from each patient. Few data were collected from the patient records namely – CD4 counts and nature of the ART regimen. All patients underwent detailed clinical examination and NCSs.

Normative Data

We obtained the NCS normative data of our electrophysiology laboratory by performing and analysing the NCS including the common peroneal and sural nerves in 25 healthy subjects (15 men and 10 women).

STATISTICAL ANALYSIS

SPSSv10 was used for statistical analysis. The results of our study were depicted using the descriptive statistics and correlations were done using paired t-test. The level of significance was set at $p < 0.05$.

Clinical Definition

The participants were categorized into three groups: neuropathy free (asymptomatic and no neuropathy signs – either clinical or electrophysiological), presymptomatic (neuropathic signs present; no symptoms), symptomatic (both symptoms and signs present). Subjects reporting isolated symptoms without signs of neuropathy were excluded from the analysis.

RESULTS

Of the cohort of 50 patients enrolled in this study, 25 were on ART and 25 were not on ART. The demographic and the clinical details of the two groups are listed in [Table/Fig-1].

According to the aforementioned clinical definition we have used, none of the patients were presymptomatic. Sixteen patients were symptomatic and 34 were neuropathy free. Of them 13 (81%) were on ART and three (19%) were not on ART.

The mean duration of HIV patients who were on ART and those not on ART were 2.22±2.14years and 1.04±2.36 respectively (p=0.15). The mean duration of sensory symptoms were 0.8±1.37 years and 1.2±2.2 months in patients who were on ART and not on ART respectively (p=0.23).

Vibration sensitivity was reduced in all of these 16 symptomatic patients. Pin sensitivity was reduced in seven (46.6%) and ankle jerks were reduced in 12 out of 16 (75%) HIV patients who had neuropathic symptoms. No significant correlation was found between low CD4 counts and symptomatic neuropathy (p=0.21).

Twenty one out of the 50 patients with HIV infection had tuberculosis in the past or were diagnosed presently as tuberculosis. Five had extrapulmonary tuberculosis and 16 had pulmonary tuberculosis. Among 21 of these patients with tuberculosis and on ATT, 12 (57%) were in HIV patients on ART and nine (43%) were in HIV patients not on ART. Seven out of 12 patients with tuberculosis (58%) and on ART had neuropathic symptoms as against only two patients with tuberculosis not on ART.

Among the 25 patients with HIV who were on ART, none had discontinued the medications. The mean duration of ART was 16.6 ± 8.4 months. Eighteen were on Zidovudine combination therapy (Zidovudine + Lamuvudine + Nevirapine in 12 and Zidovudine + Lamuvudine + Efavirenz in six). Of them six (33%) had neuropathic symptoms. Seven were on Stavudine combination therapy (Stavudine + Lamivudine + Nevirapine in three and Stavudine + Lamuvudine + Efavirenz in four). All seven (100%) of them had neuropathic symptoms.

All patients underwent bilateral upper and lower limb NCSs. Upper limb nerve conduction parameters were within normal limits in all patients. Sural nerve sensory action potential (SNAP) amplitudes were reduced in 22 out of 50 (44%) patients with HIV. Among them, 18 (81%) were on ART and four (19%) were not on ART. Out of the 18 patients on ART with reduced sural SNAP amplitudes, 13 had symptomatic neuropathy. Among the four patients not on ART who had reduced sural SNAP amplitude, two had sensory symptoms. Twenty one out of 50 (42%) HIV patients had abnormal NCSs. Among 18 HIV patients who had abnormal NCSs on ART, 14 (77.8%) had distal sensory neuropathy of axonal type, four (22.2 %) had mixed type of neuropathy. Among the four HIV patients not on ART who had abnormal NCSs, three (75%) had distal sensory demyelinating type of neuropathy.

DISCUSSION

With the effectiveness of ART and the consequent decline in the incidence rates of CNS opportunistic infections and HIV dementia, HIV-SN have become the most common neurological disorders in AIDS [2-4]. There is an immense need for better understanding of the pathogenesis of HIV-SN, identify risk factors, develop effective preventative strategies, and improve symptom control among existing sufferers.

Despite the association between HIV-SN and advanced HIV disease in patients not receiving ART, the introduction of effective HIV treatment has not been associated with the predicted fall in HIV-SN prevalence [2-5]. Indeed, where data are available regarding ART (NRTI, in particular), HIV-SN prevalence has been on the rise, probably due to ATN [3-5].

Either as the result of immunological dysregulation produced by HIV infection, opportunistic infections or the neurotoxic ART, involvement of the PNS may occur at different stages of the disease with distinctive clinical, electrophysiological and neuropathological findings [5].

The profound neurotoxicity of stavudine was highlighted in a study of postexposure prophylaxis where healthy men not infected with HIV were offered 28 days of ART as prophylaxis following a possible HIV exposure. 6% of them developed symptoms consistent with neuropathy within 28 days of starting stavudine-containing prophylaxis [7]. In our study, all seven HIV patients who were on stavudine containing regimen had symptomatic neuropathy.

One recent study has suggested that the use of dNRTI may be protective against HIV-SN after a year of use. This paradox might be explained by the observation that individuals susceptible to ATN will often become symptomatic within a few months of dNRTI exposure [8]. Thus, ATN-susceptible individuals may be switched to alternative antiretroviral drugs when they develop neuropathy symptoms, leaving only those who are at intrinsically low risk for ATN on dNRTI therapy after a year. In ATN, the standard time to resolution of neuropathy after discontinuation of the neurotoxin is at least eight weeks. Many patients improve within one to three weeks following discontinuation of NRTIs, but resolution of DSP may also take considerably longer [7,8].

The mean duration of ART in our patients was 16.6±8.4 months. Nine of these 13 were on ART since less than one year (7 of these were on regimen containing stavudine). Eight patients on ART out of the 10 detected to be HIV positive for more than two years were symptomatic. Hence, it can be inferred that the earlier neuropathy (within one year), is seen in patients on ART (NRTI), which has also been seen in earlier studies.

Increasing age is associated with HIV-SN risk in many published cohorts, both before and after the introduction of ART and is attributed to the vulnerability of the aging peripheral nervous system in most types of polyneuropathies [9]. In our study, there was an increase in the likelihood of symptomatic neuropathy among patients aged > 40 years.

There was no significant correlation of CD4 count with neuropathic symptoms between the groups. The mean CD4 was 125 cells/cumm and no correlation was found in patients with clinical evidence of peripheral neuropathy. Similar findings were noted by Barohn et al., [7].

Seven of the 12 HIV patients on ART group receiving ATT had neuropathic symptoms and two of the nine HIV patients not on ART group but on ATT had peripheral neuropathy symptoms. Hence, patients who had received both groups of drugs had increased incidence of peripheral neuropathy symptoms, probably because of the combined toxicity of both the drugs.

HIV-SN is a typical small-fibre sensory neuropathy and is primarily a clinical diagnosis. In a patient with HIV infection, a diagnosis of HIV-SN is supported by symptoms and signs that are largely symmetrical and distal in nature, and by the absence of significant motor involvement. In a study by Evans et al., [10] absent tendon reflexes and pin sensitivity was 85% sensitive and 80% specific. In our study, impaired vibration (100%) and absent ankle jerks (75%) were common than reduced pin sensitivity (46.6%).

Importantly, normal NCSs do not necessarily exclude the diagnosis of HIV-SN, as they primarily detect the function of large-diameter afferent nerve fibers. Such testing is most often indicated when atypical features (such as motor involvement) necessitate the exclusion of alternative diagnoses. In our study, axonal distal symmetrical sensory neuropathy was the commonest pattern noted in patients who were receiving ART and demyelinating type in HIV patients who were not on ART. HIV neuropathy preferably affects the myelinated fibres and ART the unmyelinated fibres [10-12]. In our study, subclinical involvement was noted even in five asymptomatic patients (all were on ART) as evidenced by abnormal NCSs. In a study by Germia et al., [13] 33.33% asymptomatic patients with HIV had subclinical neuropathy more in lower limbs as detected by NCS. In another study of 20 asymtomatic HIV seropositive patients. Kakkad [14] concluded the presence of subclinical peripheral neuropathy of axonal variety in peroneal and sural nerves by NCSs. Use of diagnostic tests to investigate primary sensory neuron morphology or function (such as quantification of epidermal nerve fiber density, thermal threshold testing) may be helpful, but such testing is not always available outside specialist centers.

When HIV-SN develops in a patient naive to ART, symptomatic improvement may be observed with commencement of (non-neurotoxic) ART to control HIV replication. In early clinical trials, immediate cessation of dNRTI therapy on development of neuropathic symptoms was associated with symptomatic improvement in 2/3rd of cases [2-5, 8].

In HIV-infected individuals on long-term ART, ATN has been observed to occur as long as one year after commencement of therapy including a dNRTI. In this clinical situation, the temporal association between dNRTI exposure and the onset of neuropathy symptoms is typically the sole feature that suggests a diagnosis of ATN rather than DSP. Importantly, an initial worsening of symptoms, or “coasting,” commonly occurs prior to any improvement and may continue for months. Some improvement in neuropathic symptoms may then be seen up to a year after discontinuation of the causative agent. Beyond this time, further improvement is unlikely [2-5,8,10].

CONCLUSION

Our study reiterates that symptomatic neuropathy is seen predominantly more in HIV patients who were on ART (especially, early in stavudine containing regimen), in patients who were on both ART and ATT and more likely among patients aged > 40 years. Subclinical neuropathy is common in those not on ART and hence we suggest NCS in all HIV patients. Axonal neuropathy was the commonest pattern noted in patients who were receiving ART and demyelinating neuropathy in patients not on ART.

The limitations of the present study are that this was a small hospital based observational study and quantitative sensory testing for detection of heat, cold, pain and vibration sensitivity were not done. Further studies with epidermal nerve fiber density may help in early detection of the subclinical neuropathy.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Nov 22, 2013**
Date of Peer Review: **Mar 03, 2014**
Date of Acceptance: **Apr 14, 2014**
Date of Publishing: **Jul 20, 2014**