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# Distal Sensory Neuropathy and Pain in HIV-1 Patients: Retrospective Study

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## Abstract

HIV-1 associated neuropathy remains an issue that interferes with patient's quality of life. Distal Sensory Peripheral Neuropathy (DSPN) is the common neuropathy associated with HIV-1 infection. We studied the role of HIV-1 in developing DSPN in 157 HIV-positive patients. Our results pointed to the potential role of HIV-1 in the etiology of DSPN and pain syndrome.

**Keywords:** HIV-1; Sensory Neuropathy; Pain

## Introduction

It is well recognized that patients infected with HIV-1 suffer from different forms of pain in addition to other neurological symptoms [1]. In addition, peripheral neuropathy is the most frequent neurological complication in HIV-1 infected individuals. Unfortunately, these symptoms persist even with the use of the combination of antiretroviral therapy (cART) [2]. Among neuropathies, distal sensory peripheral neuropathy (DSPN) is the most common neuropathy associated with HIV-1 infection [3]. DSPN frequently manifests as a sensory neuropathy, and associated pain syndrome has been acknowledged. Several factors have been implicated in development of HIV-associated neuropathy including the cART [4]. In addition, the pain can also arise directly because of bone disease such as osteopenia/osteoporosis that could be associated with HIV-1 infection [5]. Interestingly, an HIV-1 patient might not be aware that some nerves are damaged because of the infection. In this regard, a study published in 2009 demonstrated that a significant number of these patients suffered from a mild pain [6]. Further, it has been suggested that HIV-1 associated neuropathy can be the side effect of medications used by HIV-1 patients. As a result, these medications damage the nerves especially the mitochondria and cause certain type of pain [6,7]. Therefore, it was suggested that clinicians should consider and weigh the risks and benefits of each drug before initiating any HIV-related neuropathy treatment [8]. Furthermore, it has been shown that an increase in pain especially DSPN was observed in HIV-infected patients who used or using drugs of abuse [9]. However, the exact mechanisms leading to this pain remain to be identified. In this retrospective study, we examined the incidence of DSPN and its relationship with pain syndrome in 157 HIV-positive patients that were seen at Temple University Medical Center neurology clinic between 2007 and 2012. Our data corroborate with the published data and confirmed our hypothesis regarding the potential role of HIV-1 infection in the etiology of DSPN and pain syndrome, and further emphasize the necessity of research to identify the mechanisms involved.

## Methods

### Patients

157 patients older than 18 years of age infected with HIV-1, who visited the neurology clinic (mainly as outpatients) over five year period between 2007 and 2012.

## Inclusions criteria

Inclusion criteria were: I. HIV-positive patients seen in Neurology clinic. II. Sensory symptoms for at least 3 months including numbness, tingling (pins and needles sensation) and pain. III. EMG/NCS (Electromyogram / Nerve Conduction Studies) positive findings for any sensory neuropathy (DSPN, mononeuritis, autonomic neuropathies and radiculopathy). IV. Documentation regarding presence or absence of sensory symptoms and pain.

## Exclusion criteria

Exclusion criteria were: I. Acute pain of somatic origin; II. Sensory symptoms started before diagnosis of HIV-1 infection; III. No documentations regarding their sensory symptoms. All patients had a complete neurological examination.

## Disclosure

Identities of the patients were not revealed as well as all personal information.

## Results

We were able to identify 157 patients infected with HIV-1 who were seen in our clinic as out or inpatients between the periods extending from January 1st 2007 through December 2012.

First, we sought to examine the percentage of HIV-1 infected patients that developed neuropathy. As shown in Figure 1A, HIV-1-infected patients were divided into two groups. 117 patients (G1) out of 157 patients with diagnosis of HIV-1 infection did not show symptoms of distal sensory neuropathy. However, distal sensory neuropathy was prevalent in 40 (25.4%) patients (G2) of the 157 sampled patients infected with HIV-1.

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Received May 07, 2014; Accepted July 07, 2015; Published July 18, 2015

**Citation:** Rezaei BA, Mukerjee R, Groomes C, Sethi V, Chabrashvili T, et al. (2015) Distal Sensory Neuropathy and Pain in HIV-1 Patients: Retrospective Study. J AIDS Clin Res 6: 485. doi:10.4172/2155-6113.1000485

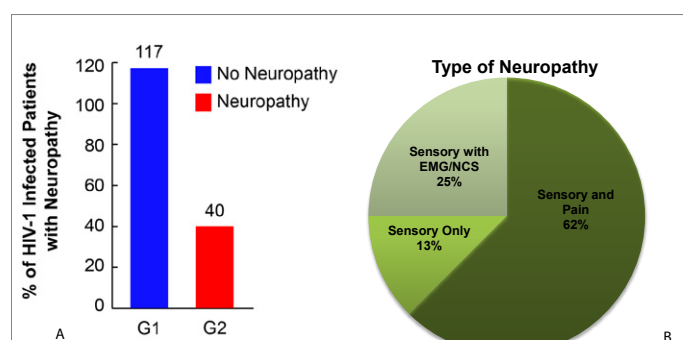
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To further evaluate the relationship between the pain and sensory neuropathy associated with HIV-1 infection, we then examined the presence of pain that patients from G2 experienced. As shown in Figure 1B, 25 out of 40 patients (a [62.5%]) suffered from distal sensory neuropathy associated with pain, while 10 patients (b [25%]) had non-painful distal sensory neuropathy confirmed by EMG/NCS, and 5 patients (c [12.5%]) had clinically documented sensory symptoms without any pain or EMG/NCS finding.

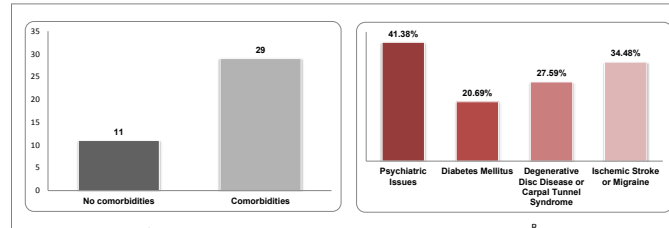
Next, we sought to examine the percentage of comorbidities in patients with sensory neuropathy. As shown in Figure 2A, no signs of comorbidities were found in 11 (27.5%) of these patients (G2). However, the remaining 29 (72.5%) patients suffered from one or more type of comorbidities (Figure 2A).

Finally, we evaluated the type of comorbidities existing in the 29 patients. As shown in Figure 2B, all the comorbidities among these 29 patients could be categorized in four different subgroups: 12 patients with psychiatric problems (depression, anxiety), 6 patients suffered from diabetes, 8 patients had degenerative disc disease or carpal tunnel syndrome and 10 patients had prior history of ischemic stroke or Migraine. Note that the some patients were diagnosed with more than one symptom, which explains the number obtained. This observation corroborate with previous studies where neurological complications have been determined as an important cause of morbidity in the HIV/AIDS population [10].

Nevertheless, to determine the percentage of patients suffering



**Figure 1:** . Percentage of HIV-1 infected patients suffering from distal sensory neuropathy. **A.** 157 HIV-1 infected patients were admitted in our clinic between 2007 and 2012. The patients were divided into two groups. Only 40 patients (25.5%) (G2) suffered from DSPN. **B.** Patients from G2 were divided into three subgroups a- sensory neuropathy associated with pain (62.5%); b- sensory neuropathy without neuropathic pain; and c- 12.5% of patients had sensory symptoms without any pain or EMG/NCS findings. The results are statistically significant using Student's t test ( $p < 0.05$  compared with the Mock control group [one-way analysis of variance and ANOVA Test]).



**Figure 2:** Percentage of patients with Comorbidities. **A.** Histogram displays the percentage of HIV-1 infected patients selected from G2 and show signs of comorbidities (29 out of 40 patients). **B.** Types of comorbidity observed in 29 patients. Note that some patients were diagnosed with more than one type of comorbidity.

from neuropathy independently of neurological complications and diabetes, we excluded those suffering from ischemic stroke, Migraine, degenerative disc disease or carpal tunnel (18 patients) and/or from diabetes (6 patients). As a result, only 12 patients (52%) with psychiatric problems will remain when compared to patients with no comorbidities (48%).

## Discussion

HIV-1 associated neuropathy is among the most frequent neurological complications associated with HIV-1 infection. This phenomenon remains prevalent even in the presence of cART. In this study, we examined the files of 157 HIV-infected patients evaluated in our clinic between 2007 and 2012 and suffering from pain by focusing only on sensory neuropathy. Our data confirmed our hypothesis that DSPN is associated with HIV-1 infection. We also examined the pain and the percentage of comorbidities involved. This demographic review of HIV-1 sensory neuropathy and pain corroborate with the national data (%) and can possibly contribute to the decision making for future treatment.

Although comorbidities were inseparable part of causing sensory neuropathy in HIV patients but our results underlined the importance of HIV as an independent risk factor for distal sensory polyneuropathy and showed specifically neuropathic pain in about third of our patient population without any comorbidities. Our study is not without precedent, in this regard, it has been shown that Neurological complications, particularly central nervous diseases, are an important cause of morbidity in the HIV/AIDS population [10,11]. In both published studies, percentage of patients infected with HIV-1 and suffering from stroke that led to neuropathy was almost similar to our numbers. Thus, we concluded that ischemic stroke is an important cause of neuropathy depending on the anatomical area affected.

Given the nature of our study design, inevitably there were some limitations including poor documentations, selection bias and individual variability. Hence, dedicated randomized trials to investigate sensory neuropathy and specifically pain in HIV patients are warranted.

Overall, HIV- associated neuropathy can be divided and classified into several categories based on their pathology (axonal or demyelinating), time of appearance during HIV-infection and whether they are associated with opportunistic infection such as CMV [12]. Previous data suggests that DSPN is prevalent in 9% to 63% of the HIV population [13-18]. Some of the factors used to explain this broad spectrum of variability include differences i) in the degree of immunosuppression, ii) in the definition of neuropathy and iii) in the exposure to neurotoxins such as antivirals [19-21]. For fact, data from an earlier study suggests that viral suppression of HIV-1 through immune restoration may decrease the risk of developing DSPN [14]. Another study showed that pain was one of the most common initial symptom of neuropathy associated with HIV-1, with pain in the soles being the most common location [16]. In another study, it was shown that the risk of general neuropathy was associated with exposure to neurotoxins such as nucleoside analogs. Therefore, Clinicians should consider and weigh the risks and benefits of each drug before initiating any HIV-related neuropathy treatment [8].

Unfortunately, the pathogenesis of DSPN is incompletely understood and thought to be multifactorial. Its pattern of distal length dependent neuropathy, known as “dying back” neuropathy, is not unique and often indistinguishable from other toxic neuropathies [21]. Furthermore, it is not understood how the virus mediates inflammation

and neuronal damage. Almost all the recovered virus from peripheral nerves was found inside macrophages and monocytes [21-25]. Two mechanisms of HIV-1 mediated neuronal injury are proposed and involved apoptosis [26] however, it is also entirely possible this neuronal injury is the result of collateral damage by the immune system, upon activation by the viral antigens.

In addition to the debate about mechanism, in the HIV-1 population there are several other risk factors for neuropathy that may serve as confounders. Namely, these are psychiatric illnesses, diabetes mellitus, degenerative disc disease, carpal tunnel syndrome, ischemic stroke, and migraines. In our study, we looked at the role that HIV-1 may play as an independent risk factor in developing distal sensory polyneuropathy. Taken together, existing observations demonstrated the need of a mechanistic study to identify the cellular and molecular mechanisms involved in the development of HIV-associated neuropathy. We believe that validating these results using animal model and developing new treatment for HIV-1 induced sensory neuropathy and pain could overturn this major complication and health care problem in our society.

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