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Association of self-reported painful symptoms with clinical and neurophysiologic signs in HIV-associated sensory neuropathy

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Abstract

Sensory neuropathy (HIV-SN) is a common cause of pain in HIV-infected people. Establishing a diagnosis of HIV-SN is important, especially when contemplating opioid use in high risk populations. However physical findings of HIV-SN may be subtle, and sensitive diagnostic tools require specialized expertise. We investigated the association between self-report of distal neuropathic pain and/or paresthesias (DNPP) and objective signs of HIV-SN. Data were obtained from the Central Nervous System HIV Antiretroviral Therapy Effects Research (CHARTER) study. Out of 237 participants, 101 (43%) reported DNPP. Signs of HIV-SN were measured by a modified Total Neuropathy Score (TNS), composed of 6 objective sensory subscores (pin sensibility, vibration sensibility, deep tendon reflexes, quantitative sensory testing for cooling and vibration, and sural sensory amplitude). Self-report of DNPP was associated with all 6 TNS items in univariate analysis

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and with 4 TNS items in multivariate analysis. The sensitivity and specificity of self-report of DNPP in detecting the presence of a sensory abnormality was 52% and 92% respectively with a PPV of 96% and a NPV of 34%. Increasing intensity of pain measured on a visual analog scale was associated with increasing severity of sensory abnormality. In summary, our results suggest that HIV-infected patients reporting symptoms consistent with HIV-SN, such as tingling, pins and needles, or aching or stabbing pain in the distal lower extremities, usually have objective evidence of HIV-SN on neurologic examination or with neurophysiologic testing. This finding holds true regardless of demographic factors, depression or substance use history.

Introduction

HIV-infected patients frequently report chronic pain to their healthcare providers. According to a recent literature review, the prevalence ranges between 28% to 97% depending on the pain assessment method and the setting of the study.[2] Many authors have decried the high prevalence of pain in HIV as demonstrative of underestimation and undertreatment.[4,8] However there are significant barriers to effective pain management in this population.[11, 12,17] A problem common to all types of chronic pain is the lack of objective measures of pain. Other factors are relatively more specific to the HIV-infected population. Psychiatric disorders, which are prevalent among HIV-infected patients, may worsen pain, limit treatment options, and interfere with the establishment of an effective therapeutic relationship between patient and healthcare provider.[7] Substance abuse disorders raise similar issues with the additional complexity of provider concern over the legal, ethical and therapeutic implications of prescribing opiates in this population. Recent guidelines on the treatment of chronic non-cancer pain advise taking such factors into account when weighing the risks and benefits of opioid therapy.[5] There are also cultural barriers to pain control which are important among HIV-infected patients because of the disproportionate number of minority patients affected. These include a historic mistrust of the medical establishment in some minority communities, as well as disparities such as the unequal prescription of analgesia to Hispanics and African-Americans as compared to white patients.[14-16]

A common cause of chronic pain among HIV-infected patients is sensory neuropathy (HIV-SN).[9,13] Typical symptoms of HIV-SN include paresthesias, neuropathic pain and numbness. These symptoms usually occur in a distal symmetric distribution. Neuropathic pain and paresthesias are often the focus of clinical care for HIV-SN, because there are currently no neuroregenerative therapies. Current guidelines for the management of chronic non-cancer pain emphasize the importance of determining the disorder underlying a painful condition, [5] but abnormalities on physical examination may be subtle in HIV-SN. There are validated objective instruments to diagnose neuropathy and measure its severity, such as the total neuropathy score (TNS).[6] However these instruments typically include detailed neurologic assessments that are not practical in most HIV primary care or pain management settings. Accordingly it would be useful to know if a simple self-report of neuropathic pain and/or paresthesias in a distal symmetric distribution is helpful in establishing the diagnosis HIV-SN.

In this study we investigated the association between the self-report of distal neuropathic pain and/or paresthesias (DNPP) and objective signs of sensory abnormality, and assessed whether this relationship is affected by demographics and other factors that commonly complicate pain management in HIV, namely substance use and other psychiatric disorders.

Methods

Data were obtained from the Central Nervous System HIV Antiretroviral Therapy Effects Research (CHARTER) study. CHARTER is a multicenter, observational study designed to

examine the neurologic effects of HIV in the era of combination antiretroviral therapy (CART). A subset of CHARTER participants comprised of all participants willing to undergo nerve conduction studies (NCS) and quantitative sensory testing (QST) were included in the present study. As per CHARTER protocol, participants were interviewed and examined by a clinician (MD, NP or RN) experienced in the care of HIV-infected individuals. The examiners were unaware of the hypothesis of this study. Neurophysiologic testing was performed by trained and centrally-certified technicians. All testing was reviewed centrally for quality control. Participants were queried on symptoms of paresthesias and neuropathic pain, specifically tingling or burning, aching, or stabbing pain in a bilateral, predominantly distal distribution (e.g. in the fingers and toes only, extending to the ankles or wrists, or extending to the knees or elbows). If they endorsed tingling in this distribution they were considered to have a positive self-report of paresthesias; if they endorsed any of the pain symptoms in this distribution they were considered to have a positive self-report of distal neuropathic pain. They were then given a visual analog scale with instructions to "Place an "X" on the line corresponding to the average intensity of your neuropathy pain over the last 12 hours", and a score on a scale of 0 (no pain) to 10 (worst pain imaginable) was determined. Objective signs of HIV-SN were quantified using the total neuropathy score (TNS). The TNS is a quantitative measure of neuropathy severity initially used in studies of toxic neuropathy, and later validated in diabetic neuropathy.[6] The TNS has since been used in the study of HIV-SN.[13] The TNS has a total of 10 items each rated on a scale of 0-4 where 0 is normal and 4 is most severe, yielding a total possible score of 0-40 where 0 is normal. The 10 items include symptoms, signs on clinical neurologic examination, and data from neurophysiologic testing including NCS and QST. Six of the 10 items are objective measures of sensory function and were included in the present study: pin sensibility, vibration sensibility, deep tendon reflexes, QST cooling, QST vibration, and sural nerve sensory evoked amplitude on NCS. These 6 items were summed to generate a modified TNS reflecting only objective sensory items. This yielded a total possible score of 0-24 where 0 is normal. Self-reported demographic data included age, gender, ethnicity and years of education. The following data pertaining to substance use and psychiatric disorders were also obtained: modules of the Composite International Diagnostic Interview (CIDI) for assessment of substance dependence/abuse and major depressive disorder (MDD) using DSM-IV criteria,[18] current use of psychiatric medications, the Beck Depression Inventory (BDI-II),[3] self-report of a history of intravenous drug use (IVDU) as an HIV-risk factor, and results of urine toxicology (testing for cocaine, opiates, methadone, amphetamines, barbiturates, benzodiazepines, and phencyclidine). Current use of psychiatric medications was defined as use of antipsychotics, antidepressants, mood stabilizers, sedatives/hypnotics, or stimulants. Opiates, anticonvulsants (carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, pregabalin, primidone, tiagabine, valproate, topiramate), duloxetine and tricyclic antidepressants were excluded because they are often used for treatment of pain or neurologic conditions rather than psychiatric disorders, and the indications for which medications were prescribed were not available.

Statistical Analyses

The following characteristics were compared between the group that reported DNPP and the group that did not: age, gender, ethnicity, years of education, past or current substance abuse or dependence (as assessed by the CIDI substance abuse module, a self-report of history of IVDU, and results of urine toxicology), psychiatric disorders (as assessed by the CIDI MDD module, the BDI-II, and use of psychiatric medications as described above). Continuous variables were compared using independent samples T-tests if their distribution was near normal, and Wilcoxon rank sum test if not. Categorical variables were compared using Chi-square analysis.

Binary logistic regression was then used to examine the association of self-reported DNPP with abnormalities in each of the 6 objective sensory TNS items. In order to adjust this analysis for potential confounds, any characteristics that were found to differ between the groups with and without DNPP were entered into the model as covariates. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of self-reported DNPP in detecting the presence of an objective sensory abnormality (defined by the presence of a non-zero score in at least 1 of the 6 items) were calculated. Finally the association of pain intensity with objective sensory abnormalities, quantified by the modified TNS described above, was examined with linear regression, co-varying any characteristics that were found to differ between the groups with and without DNPP.

Results

Cohort characteristics

One-thousand five-hundred and seventy-five participants were enrolled in the CHARTER study. Of these, 237 participants agreed to neurophysiologic testing and were included in this analysis. Forty-six had incomplete NCS or QST data and so were excluded from analyses requiring these data. The reasons for missing neurophysiologic data included the following: inability to tolerate NCS, multiple inconsistent responses on QST leading to “failure” of the test (e.g. the participant reports feeling a null stimulus), missed appointments for neurophysiologic testing and technically unacceptable data. There were demographic differences between the subgroup of 237 participants and the larger cohort. The subgroup had a higher percentage of men (82% vs. 76%; p=.03) and a lower percentage of African-Americans (35% vs. 48%; p<.001). The subgroup was similar to the larger cohort in age and prevalence of DNPP (p-values >.1). The participants with missing data did not differ in ethnicity, gender or prevalence of DNPP from those with complete data (all p-values > .10). The group with complete data was slightly older although this difference did not reach statistical significance (p = .074). The characteristics of the subgroup of 237 are summarized in table 1.

Characteristics of participants with and without self-report of distal neuropathic pain/ paresthesias

Sixty-seven participants (28%) reported symptoms of both distal neuropathic pain and paresthesias, 23 (10%) reported paresthesias only, 11 reported neuropathic pain only (5%), and 136 (57%) reported neither pain nor paresthesias. Due to the relatively small numbers of participants with only paresthesias or only pain, participants with distal neuropathic pain or paresthesias or both were considered together for all subsequent analyses (101 participants, 43% of total). Comparison of characteristics between participants with and without DNPP revealed that the group with DNPP was older (M = 47.6, SD = 7.7) than the group without (M =41.1, SD 9.2); t(235) = −5.9, p < .001. There was no difference in mean education level or difference in the distribution of gender or ethnicity between the groups (p-values > .10). A greater percentage of participants in the group with DNPP reported use of psychiatric medications (as defined above), (66% vs. 43%; $\chi^2(1) = 12.2$, p <.001) and the median BDI-II in this group was higher, (M = 11, IQR = [5,21.5] vs. M = 7.5, IQR = [2,14]; W ($n_1 = 134$, $n_2 = 101$) = 14225, p = .002). However there was no difference in the percent of participants in each group meeting CIDI diagnostic criteria for current MDD. There was a trend for a greater percentage of participants with positive urine toxicology in the group with DNPP, (24% vs. 15%; $\chi^2(1) = 3.08$, p = .079). However there was no difference between the two groups in the other substance abuse variables (all p-values > .10).

Association of self-report of distal neuropathic pain /paresthesias and objective signs of neuropathy

The sensitivity and specificity of self-report of DNPP in detecting the presence of an objective sensory abnormality, defined by an abnormality in at least 1 of the 6 TNS items, was 52% and 92% respectively with a PPV of 96% and a NPV of 34%. If the more stringent criterion of abnormality in at least 2 of the TNS items was applied, the sensitivity was 64%, specificity 87%, PPV 87% and NPV 63%. In univariate analysis, binary logistic regression revealed that self-report of DNPP was associated with each of the 6 objective sensory abnormalities measured by the TNS items (all p-values <.05). When the potentially confounding variables of age, use of psychiatric medications, BDI-II score and the presence of a positive urine toxicology were entered into the models as covariates, 4 out of the 6 TNS items remained significantly associated with self-report of DNPP (vibration sensibility, pin sensibility, deep tendon reflexes, and QST vibration). The remaining two items (sural NCS and QST cooling) were associated with DNPP at the trend level (see table 2).

Intensity of distal neuropathic pain and objective signs of neuropathy

Multiple linear regression was used to examine the association of pain intensity measured by the VAS and objective signs of sensory abnormality measured by the modified TNS. As in the analyses described above, the potentially confounding psychiatric and substance abuse variables as well as age were entered into the model as covariates. In this multivariate model, age ($\beta = .107$, $p < .001$) and increasing intensity of pain were associated with increasing severity of neuropathy ($\beta = .697$, $p < .001$).

Discussion

In this study we determined that the self-report of distal neuropathic pain/paresthesias (DNPP) was strongly associated with objective findings of HIV-SN in a diverse group of HIV-infected participants with high rates of psychiatric illness and substance abuse. Such symptoms predicted the presence of at least one objective sensory abnormality in 96% of participants and two objective sensory abnormalities in 87%. The absence of such symptoms was less predictive of the absence of objective signs of sensory neuropathy (NPV 34% using criterion of one TNS abnormality and 63% using criterion of two TNS abnormalities). This is not surprising given that HIV-SN may be asymptomatic. Increasing intensity of pain was associated with increasing severity of objective sensory abnormality. The group that reported DNPP was older than the group that did not, had a higher median BDI-II score and a higher percentage of participants using psychiatric medications (excluding agents commonly used for neurologic disorders and pain). There were no ethnic, racial or gender differences or differences in syndromic substance abuse diagnoses or historical IVDU between the two groups.

The older mean age in the group with DNPP is likely attributable to a higher prevalence of neuropathy among older patients, rather than a difference in the experience or reporting of pain/paresthesias. Older age has previously been reported to be a risk factor for HIV-SN.[9, 13] The higher BDI-II score and use of psychiatric medications in the DNPP group, are consistent with the known high co-morbidity of psychiatric disease, such as depression, with pain.[1] Importantly, even after accounting for these variables, the association of DNPP and objective sensory findings was not altered in any meaningful way.

There are several limitations in this study. Although the population sample was fairly diverse with respect to race/ethnicity, 80% of participants were male which may limit the applicability of the results to women. Participants were recruited from multiple, geographically dispersed centers, however each of these centers has recognized expertise in the neurological complications of HIV. It is possible that this could have led to oversampling of participants

with neurologic problems. This potential selection bias could have been exacerbated by the use of a subgroup (all those who participated in neurophysiologic testing) for this analysis. However the similar prevalence of DNPP in the subgroup as compared to the larger cohort is reassuring. Participants were queried about their pain in a research setting which could produce different responses than similar queries in a clinical setting. Perhaps the major limitation in this study is the unblinded nature of the neurologic examinations. Examiners were aware of whether the participant reported DNPP. This could have influenced their findings on neurologic examination, and indeed the clinical examination variables were most closely and consistently associated with DNPP. However, the neurophysiologic testing is more objective and was performed by independent examiners and also trended toward an association with DNPP. An additional limitation is the lack of specific psychiatric diagnoses other than MDD.

In summary, our results suggest that HIV-infected patients reporting symptoms consistent with HIV-SN, such as tingling, pins and needles, or aching or stabbing pain in the distal lower extremities, usually have objective evidence of HIV-SN on neurologic examination or with neurophysiologic testing. This finding holds true regardless of demographic factors, depression or substance use history. This result is important because of the particular challenges faced in the treatment of pain in this population. Many of the risk factors for aberrant prescription-drug related behaviors and the development of addiction to prescribed opiates are highly prevalent in HIV-infected populations including: family or personal history of substance abuse or addiction, psychiatric history of any kind, younger age, current status as a smoker, and history of preadolescent sexual abuse.[10] This makes the treatment of neuropathic pain in HIV particularly challenging. Establishing a diagnosis of the condition underlying pain is an important part of pain management, especially when using opioids in potentially high risk patients.[5] This may be difficult in the HIV primary care or pain management setting, where the resources to definitively confirm the diagnosis of HIV-SN may be unavailable. Our results provide evidence that in the majority of patients presenting with complaints suggestive of painful HIV-SN, a comprehensive neurologic assessment will confirm the diagnosis.

SYNOPSIS

The self-report of symptoms consistent with distal neuropathic pain predicts objective sensory abnormalities in HIV-infected individuals, regardless of demographics, substance use or depression.

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Table 1

Cohort Characteristics

Age, mean (SD)	**43.9 (9.1)**
Gender	82 % male 18% female
Ethnicity	35% African-American 14% Hispanic 49% white 3% other
Education, mean (SD)	12.8 (2.5)
Past or current substance abuse*	79%
Self-report of IVDU as HIV risk-factor	17%
Positive urine toxicology	18%
Current major depressive disorder*	12%
Beck Depression Inventory, median [IQR]	9 [3,16]
Current psychiatric medication use**	53%
Current CD4+ cells (cells/mm^3), median [IQR]	500 (321-711)
Nadir CD4+ cells (cells/mm^3), median [IQR]	200 (51-333)
Plasma HIV viral load (log_{10}(copies/ml), median [IQR]	1.76 (1.69-3.82)

* Diagnosed using the Composite International Diagnostic Interview (CIDI)

** Psychiatric medications included were antipsychotics, antidepressants (other than duloxetine and tricyclic antidepressants), mood stabilizers (other than the anticonvulsants e.g. gabapentin, lamotrigine, valproate, pregabalin) sedatives/hypnotics, or stimulants. These criteria were adopted in an effort to exclude medications that are commonly used for both psychiatric and non-psychiatric purposes.

Table 2

Association of distal neuropathic pain/paresthesias (DNPP) and objective signs of sensory neuropathy in multivariate analysis

Total Neuropathy Score (TNS) item	Odds ratio (95% CI) of TNS item being abnormal in DNPP group compared to non-DNPP group	P
Vibration Sensibility	14.9 (7.1, 31.1)	<.001
Pin Sensibility	10.9 (5.5, 21.7)	<.001
Deep Tendon Reflexes	5.5 (2.8, 10.6)	<.001
QST Vibration	3.8 (1.5, 9.8)	.006
QST Cooling	1.8 (.90, 3.4)	.099
Sural NCS	2.0 (.97, 4.0)	.060

QST = quantitative sensory testing; NCS = nerve conduction study