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The Relationship Between Race and HIV-Distal Sensory Polyneuropathy in a Large Cohort of US Women

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Abstract

Introduction—HIV-distal sensory polyneuropathy (HIV-DSPN) is a common complication of HIV infection, yet race as a potential risk factor is not known.

Methods—Between April and October 2009, as part of the NIH Women's Interagency HIV Study (WIHS), 1414 women, 973 of whom were HIV-infected, were clinically evaluated for peripheral neuropathy. Utilizing available clinical, laboratory, and sociodemographic variables, we conducted a cross-sectional analysis of factors associated with HIV-DSPN. Multivariable logistic regression was used to examine factors independently associated with HIV-DSPN.

Results—36% of HIV-infected women met our definition of HIV-DSPN. 41.3% of African Americans, 34.8% of Whites and 24.7% of Hispanics had DSPN. Age, Hepatitis C-co-infection, and diabetes were each significantly associated with HIV-DSPN. After controlling for age, diabetes, Hepatitis C co-infection, alcohol use, current dideoxy-nucleoside reverse transcriptase inhibitor use, current CD4 count, and plasma HIV viral load, HIV-DSPN was significantly associated with ethnicity; the odds ratio was 1.67 (p=0.001) in African-Americans compared to other racial groups.

Conclusion—The prevalence of HIV-DSPN in women was lower than reported in prior studies. The likelihood of HIV-DSPN was higher in African-Americans compared to other racial groups. HIV-DSPN was more common in those co-infected with Hepatitis C, older individuals, and

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Conflict of Interest

The authors declare that they have no conflict of interest.

diabetics. Further prospective studies are needed to explore the relationship between gender, race, and HIV-DSPN, and the mechanistic basis for racial differences.

Keywords

HIV-associated sensory polyneuropathy; African-Americans; race; women; gender; diabetes; Hepatitis C

Introduction

HIV-distal sensory polyneuropathy (HIV-DSPN) is the most common neurological disorder associated with HIV infection, affecting as many as 50% of HIV-infected patients [1]. It is caused either by HIV infection or the result of neurotoxic antiretrovirals (ARVs), particularly the dideoxy-nucleoside reverse transcriptase inhibitors (d-NRTIs), although the precise mechanism is still unknown [2]. While early studies identified low CD4 count and high viral load as correlates of HIV-DPSN [3], later studies have not confirmed this association [4,5]. Diabetes and age are the other factors most strongly correlated with HIV-DSPN [6,7].

Race effect has rarely been studied in HIV-DSPN, with minority groups under-enrolled in HIV-DSPN studies [4]. Thus, the association between race and development of neuropathy is unclear, although a recent study did report differences geographically, possibly due to race [8]. Prior studies have been limited by small sample sizes, the presence of confounders, and by the under-representation of specific patient racial groups. Gender effects have rarely been studied in HIV-DPSN, and the few existing studies are contradictory regarding male sex as a risk factor [4,9]. In these studies, female participation rarely approached 40% of all subjects, and most had less than 25% women.

Because the incidence of HIV in the United States is rising both in women and in minority populations [10], it is imperative to understand neurologic complications that differentially affect these vulnerable populations. In this cross-sectional analysis, we investigated the prevalence of and factors associated with HIV-DSPN in a large, predominantly minority cohort of US women. We sought to determine whether there was increased vulnerability for certain races after controlling for other factors known to be associated with HIV-DSPN, including CD4 count, diabetes and age [11].

Methods

Study Design

The NIH-funded Women's Interagency HIV Study (WIHS), established in 1993, is an ongoing prospective study of HIV in women in the United States [12]. In 1994–1995, six consortia sites located in the Bronx and Brooklyn boroughs of New York City, San Francisco and Los Angeles California, Chicago, and Washington DC enrolled 2,054 HIV-infected and 569 HIV-uninfected demographically matched women. In 2001–2002, an additional 737 HIV-infected and 406 HIV-uninfected women were enrolled. Participants are evaluated every six months with an extensive interview that includes history of interval illnesses, current medications and medication adherence, and alcohol use, as well as a physical exam and blood and gynecological specimen collection. A baseline clinical neuropathy evaluation was added in 2007, with follow-up assessments conducted semiannually. Detailed WIHS study methods are described in previous publications [12,13].

The Institutional Review Board at each site approved all research, and each study participant gave written informed consent. All subjects were given the option of testing in Spanish or English, for the questionnaire and the physical examination.

Neuropathy Assessments and Definition

Examiners at each site were instructed by one neurologist, responsible for site quality assurance, in eliciting ankle reflexes and vibratory sensation. The neurologist demonstrated reflex and vibratory exam on three HIV patients. To be certified, the site examiners, ranging from one-four people, were required to agree with the neurologist in 80% of their testing of ten HIV patients.

Ankle reflexes included absent (0), hypoactive (1), or normal/increased (2). If subjects had absent or hypoactive reflexes in either ankle, a Jendrassik maneuver, in which the subject locked her hands and pulled tightly, was performed, and elicitation of ankle reflexes was repeated and scored similarly. In this analysis, values of 0 and 1 in both ankles were classified as diminished reflexes. Vibratory sensation was measured by striking and applying a 128Hz tuning fork against the distal interphalangeal joints of both great toes. Feeling the vibration for ≥10 seconds was normal, 6–9 seconds was mildly impaired, <6 seconds was moderately impaired, and absent sensation was the worst. In our analysis, values of ≤10 in both great toes were defined as abnormal. A confirmed HIV+ participant was classified as having HIV-DSPN (or "HIV-DSPN+") if at least one of the following clinical signs was present bilaterally and symmetrically: diminished vibratory sense in the great toes or absent/diminished ankle reflexes.

Neuropathy Study Participants

Data were analyzed from HIV-infected and HIV-uninfected women who had a neuropathy assessment during the period April 2009-October 2009, the most recent period available. Approximately 1,939 women were still living and active in the study. There were 1,414 (73%) who had neuropathy data available for analysis of risk factors. Retention of HIV-infected women has been quite high; 83% of the 1994–1995 enrollees and 86% among the 2000–01 enrollees, with attrition due to death (n=480) or disenrollment and loss to follow-up (n=889) [14].

Race

Subjects were classified as Hispanic or Non-Hispanic based on their self-categorization. Those in the Non-Hispanic groups were divided further into African-American, White, Asian, Native-American, or Other. The Asian and Native-American subjects were then placed in the Other group due to their small number.

Other covariates

At entry into the study, participants provided specimens for Hepatitis C antibodies and if positive, for RNA viral load measurement. Hepatitis C co-infection was defined as the presence both of positive antibodies and measurable viral load. Plasma HIV viral load and CD4 count were collected each visit (including the most recent visit, during which the neuropathy data of interest was collected), and Plasma HIV-1 RNA quantification was performed using the isothermal nucleic acid sequence–based amplification method in laboratories certified by the National Institutes of Health Virology Quality Assurance program, with a lower limit of detection set at 80 copies per milliliter. Information on demographics, height (in centimeters), most recent ARV use, and diabetes status was also evaluated each visit. Subjects were classified as diabetic if they had a fasting glucose >126 mg/dL, a self-report of diabetes, or used diabetic medications. Use of didanosine, stavudine,

or zalcitabine since the last study visit was categorized as recent d-NRTI, use for study purposes. Alcohol intake was based on the average number of drinks consumed per week during the 6 month period prior to the study visit. For our analysis, alcohol use was dichotomized into <3 and ≥3 drinks per week.

Statistical Analysis

Comparisons of characteristics of HIV-DSPN+ (subjects infected with HIV who had signs of neuropathy) and HIV-DSPN- (subjects infected with HIV who lacked signs of neuropathy) participants were made by chi-square testing of diabetic status, current use of d-NRTI drugs, and Hepatitis C co-infection. Age, height, and continuous markers of HIV disease status, including current CD4 count and plasma HIV viral load, were analyzed via ANOVA. Logistic regression was utilized to assess the independent association of variables on HIV-DSPN status. For race, African-Americans were compared to the other racial groups, including Whites, Hispanics, and Others. Factors that were significant in univariate analysis at the 0.05 level and/or were clinically relevant (CD4 count, viral load) were included in a multivariable-adjusted model. We ran a multivariable model with both CD4 count nadir and duration of HIV infection, but this model lacked significant predictor variables due to the large amount of missing values; these two variables were excluded from the final multivariable model.

Statistical analyses were undertaken with SPSS version 17.0 (Chicago, Illinois).

Results

Study Population

The overall study population included 1939 subjects, 1369 of whom were HIV-infected and 570 were uninfected.

Of the 1939 subjects, 10.8% were White, 56.9% were African-American, 28.9% were Hispanic, and 3.4% were Other. Of these 1939 subjects, 1414 were evaluated for neuropathy, of whom 63 had unknown HIV status. Of the remaining 1351 subjects, 973 were HIV-infected and 378 were uninfected.

Within the 973 HIV-infected subjects, the frequency of HIV-DSPN was 36.4%. In the 378 uninfected subjects, the frequency of neuropathy was only 19%. The HIV-infected subjects were 20.4% Hispanic, 64.3% African-American, 9% White, and 5.1% Other. 17.3 % of the infected subjects were infected with Hepatitis C, 20.5% had diabetes, and 17.4% had heavy alcohol use. The mean age was 42 years, with a standard deviation of 9.9.

Correlates of HIV distal sensory polyneuropathy

Within the 973 HIV-infected subjects tested for neuropathy, there was no significant difference between the HIV-DSPN+ (n=354) and HIV-DSPN− (n=619) groups as to alcohol use, height, CD4 count, viral load, and age. Both groups had similar percentages of white and Asian participants, although the HIV-DSPN+ group had a smaller percentage of Hispanics (20.6 versus 31.2, $p<0.001$) and greater percentage of African-Americans (66.7 versus 52.5, $p<0.001$). Diabetics comprised 26.3% of HIV-DSPN+ group and 16% of HIV-DSPN− group ($p<0.001$). Co-infectivity with Hepatitis C was found in 39.3% of HIV-DSPN + participants and 21.6% of HIV-DSPN− participants ($p<0.001$). The high CD4 counts and low viral loads in both groups, as well as the mean duration of HIV infection and use of d-NRTI drugs, are shown in Table 1.

In univariate analyses confined to HIV-infected subjects, age, diabetes, co-infection with Hepatitis C, and African-American race demonstrated significant positive associations with HIV-DSPN ($p<0.001$) and were subsequently included in multivariable analysis. Height was not significantly associated with HIV-DSPN. Although recent use of d-NRTI drugs, alcohol use, viral load, and CD4 count were not significantly associated with HIV-DSPN in univariate analysis, they were included in the multivariable model due to their clinical importance.

After multivariable adjustment, diabetes was associated with a 1.45 times increased odds of HIV-DSPN (95% CI 1.02–2.08) (Table 2), and co-infection with Hepatitis C was associated with a 1.44 times increased odds of HIV-DSPN (95% CI 1.02–2.02) (Table 2). HIV-DSPN odds were 30% higher with increasing age (OR for each five-year increase in age=1.30, 95% CI 1.20–1.40). African Americans participants were approximately 66% more likely than non-African American participants to have HIV-DSPN. The use of d-NRTI drugs, CD4 count, and viral load were not significantly associated with HIV-DSPN after multivariable adjustment. (Table 2)

Discussion

In this study, the first involving only women, we found that age, diabetes, and chronic co-infection with Hepatitis C were significantly associated with HIV-DSPN, confirming findings from other studies [7]. As described in a recent study [15], African-American race was associated with significantly higher rates of HIV-DSPN compared to other racial groups. CD4 count, HIV viral load, and the use of d-NRTI drugs were not significantly associated with HIV-DSPN, as in previous studies [1]. This may be due to the low percentages of subjects using d-NRTI drugs and the relatively high median CD4 count of 523 cells/mm^3. Furthermore, increasing height was not associated with HIV-DSPN, as in previous studies [8,16], but these studies had larger mean heights with both sexes represented. In this study of women, the mean height was smaller, only 159 centimeters, and HIV-DSPN might rely on a “threshold affect”, or affecting subjects above a certain height.

We found a frequency of HIV-DSPN of 36%, lower than previous studies, most of which contained male subjects. In the one prior study with a majority of female subjects, the prevalence of HIV-DSPN was 57%, and the median age of these women was 35, younger than in our study [16]. The presence of an entirely black-African cohort may explain this cited study’s increased prevalence of HIV-DSPN, as compared to our own study. From our data, it appears that although our participants share similar risk factors for HIV-DSPN as in other studies, our study’s women are less affected by HIV-DSPN. The lower prevalence of neuropathy in our study’s HIV-infected women was not due to the lack of known risk factors for neuropathy; 28% of these women possessed chronic co-infection with hepatitis C, 19.4% had diabetes, and 9% drank 3 or more times/week. Furthermore, one would have expected higher rates of HIV-DPSN because of the study’s expansive definition of neuropathy: one (or more) clinical signs, not two signs, as in other studies.

Reliance on one or more clinical signs, instead of symptoms, to define HIV-DSPN is not a limitation in our study, since these are performed by specially trained personnel. This definition has been used in many prior HIV neuropathy studies [15,17], including the recent CHARTER study [1, 7, 18] and has been validated against the gold standards of epidermal nerve fiber density and quantitative threshold sensory testing [19].

Compared to others women, African American women were more likely to have HIV-DSPN even after multivariable adjustment. Although it is possible that African-Americans might suffer more from risk factors for neuropathy, such as Hepatitis C co-infection, the

multivariable model controlled for these factors, and the increased odds for HIV neuropathy in African American women still persists. There may be other, as yet, uncharacterized confounders more common in African Americans that predispose them to neuropathy. This possibility is suggested by the results of a recent study, Evans *et al*, in which African-American race was positively associated with HIV-DSPN [15].

Study biases could have contributed to the higher incidence of HIV-DSPN in African-American subjects. There could be selection bias, with more African-American women possessing signs and symptoms of neuropathy enrolling in our cohort; they might have done so because of over-representation of African-Americans in study neighborhoods. A significant study limitation was the lack of data on *cumulative* antiretroviral exposure, especially of the d-NRTI drugs. Neuropathy was only evaluated recently in this cohort, much later than initial enrollment, so the cross-sectional and retrospective nature of the study prevents evaluation of causation.

Still, any limitations are counterbalanced by study strengths, including a large and diverse cohort of HIV-positive patients recruited at numerous institutions across the United States. In fact, this study has the highest minority representation of any HIV neuropathy study and includes only women, the first study to do so. This study used only *specially trained* personnel to assess HIV-DSPN, via accepted standardized methods. These evaluators obtained information on possible confounding factors, including co-infection with Hepatitis C and diabetes, which were then entered into a multivariable model for HIV-DSPN. Most importantly, the strong positive association between African American subjects and HIV-DSPN persisted even after multivariable modeling accounting for other risk factors.

In summary, this study demonstrated a lower percentage of HIV-DSPN in a cohort of HIV-infected women, compared to existing HIV-DSPN studies [6]. Factors positively associated with HIV-DSPN included diabetes, co-infection with Hepatitis C, and age, as in previous studies [6], while d-NRTI drug use, CD4 count, alcohol use, and HIV viral load were not associated with HIV-DSPN. Most intriguingly, African American women were at greater risk of developing HIV-DSPN, compared to non-African Americans. Further study is warranted to confirm and establish the basis for these racial differences.

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Table 1

Demographics in HIV-infected patients with and without distal sensory peripheral neuropathy (HIV-DSPN)

Chi Square/ANOVA Testing			
	No HIV-DSPN (n=619)	**HIV-DSPN (n=354)**	**P-value**
Alcohol use, N (%)	60 (9.7)	27 (7.6)	0.27
Age, mean (SD)	43 (8.3)	48 (8.3)	0.21
Height, mean (SD) cm	159 (15.9)	161 (16.5)	0.06
Hepatitis C, N (%)	134 (21.6)	139 (39.3)	**<0.001**
Diabetes , N (%)	96 (16)	93 (26.3)	**<0.001**
African American, N (%)	317 (51.2)	223 (63)	**<0.001**
White, N (%)	60 (9.7)	32 (9.0)	0.72
Hispanic, N (%)	193 (31.2)	73 (20.6)	**<0.001**
Other, N (%)	18 (2.9)	10 (2.8)	0.93
Current CD4, median (IQR), cells/mm^3	510 (324–692)	474 (304–700)	0.24
CD4 nadir, median (IQR), cells/mm^3	228 (113–347)	200 (97–298)	0.55
Viral Load, median (IQR), $\log_{10}$ cp/mL	1.68 (1.68–3.14)	1.68 (1.68–2.8)	0.37
Years HIV infection, mean (SD)	9.6 (4.6)	10 (4.5)	0.69
D-Drugs use since last visit, N (%)	39 (6.3)	21 (5.9)	0.79

Table 2

Risk Factors for HIV-DSPN

	Multivariable Analysis	
	Odds Ratio (95%CI)	**P-value**
Age ◆	**1.30 (1.20–1.40)**	**<0.001**
Diabetes	**1.45 (1.02–2.08)**	**0.04**
Alcohol use	0.82 (0.49–1.4)	0.48
Hepatitis C	**1.45 (1.03–2.05)**	**0.03**
CD4 count *	1.0 (1.0–1.0)	0.96
Viral load ◇	0.97 (0.83–1.1)	0.62
D-NRTI	1.19 (0.65–2.17)	0.57
African Americans	**1.67 (1.22–2.27)**	**0.001**

◆ per 5 years

* cells/mm^3

◇ log_{10} copies/mL