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The Roles of Ethnicity and Antiretrovirals in HIV-associated Polyneuropathy: A Pilot Study

J. Robinson-Papp, MD,

Assistant Professor of Neurology and Pathology, Mount Sinai School of Medicine, Department of Neurology, Box 1052, One Gustave L. Levy Place, New York, NY 10029, Tel: 212-241-8390, Fax: 212-987-3301, jessica.robinson-papp@mssm.edu

A. Gonzalez-Duarte, MD,

Instituto Nacional de Ciencias Medicas y Nutricion Salvador, Zubiran

D.M. Simpson, MD,

Mount Sinai School of Medicine

M. Rivera-Mindt, PhD, and

Mount Sinai School of Medicine

S. Morgello, MD

Mount Sinai School of Medicine

for the Manhattan HIV Brain Bank

Abstract

Background—In the pre-HAART era, distal sensory polyneuropathy (DSP) was associated with markers of advanced HIV infection and the use of neurotoxic antiretrovirals (ARV). As HAART became widespread, and the AIDS epidemic shifted into minority populations, the risk factors for DSP became less clear. We explore the roles of ethnicity and ARV in the development of DSP in a HAART-era cohort.

Methods—Data from 336 HIV-positive adults were obtained from the Manhattan HIV Brain Bank. One hundred and four participants had no DSP at entry visit, at least one follow up visit, and a self-identified ethnicity of non-Hispanic white, Hispanic, or African-American.

Results—50% of participants developed DSP; of those 67% were symptomatic. Participants who developed DSP were older ($p = .02$) and had higher CD4 counts ($p = .001$). ARV-DSP was more common in Hispanics ($p = .02$), and intravenous drug users ($p = .02$). There was a trend for higher pain scores in Hispanics with symptomatic DSP ($p = .08$).

Conclusions—This study suggests that there are ethnic disparities in the clinical manifestations of HIV-related neuropathies including pain and the susceptibility to ARV-DSP. Further studies of larger cohorts are indicated to explore the etiology of these differences.

Keywords

Distal sensory polyneuropathy; Antiretrovirals; Ethnic Disparities

Introduction

Distal sensory polyneuropathy (DSP) is the most common neurological disorder associated with HIV infection. DSP may occur as a consequence of HIV infection itself, or as the result of neurotoxic antiretrovirals (ARV) such as the nucleoside reverse transcriptase inhibitors stavudine (d4T), didanosine (ddI), and zalcitabine (ddC), the so-called “d-drugs”. Early studies recognized markers of advanced HIV infection, such as low CD4+ count and high viral load, and exposure to d-drugs, as predictors of DSP.^{1, 2} However, since highly active antiretroviral therapy (HAART) use has become widespread in the developed world, these risk factors have not been consistently reproduced. Several HAART-era studies have shown no increased risk of DSP in participants receiving d-drugs.^{3, 4} In other studies demographic factors including age, male gender, and non-Hispanic white ethnicity were associated with increased risk of DSP.^{3, 5, 6}

The impact of demographic factors in the development of DSP is of particular importance in light of the steady shift of the U.S. HIV/AIDS epidemic into women and minority populations, and in the context of the global epidemic. In this study we explored the roles of d-drug exposure and ethnicity in the development of incident neuropathy in a diverse HAART-era cohort with advanced HIV infection.

Methods

Participants

Data were analyzed from 336 HIV-positive adults enrolled in the Manhattan HIV Brain Bank (MHBB; R24MH59724, U01MH083501). MHBB is a prospectively followed cohort of HIV-positive participants that is a member of the National NeuroAIDS Tissue Consortium (NNTC). The enrollment criteria for the MHBB were designed to target patients with advanced disease, and list qualifying conditions, such as hemoglobin less than 10 g/dL, CD4 count less than 50, or opportunistic infections. The full enrollment criteria for the MHBB have been described elsewhere.⁶ All participants that had a complete neurologic examination at entry, no DSP at entry, at least one follow up visit, and a self-identified ethnicity of Hispanic/Latino, non-Hispanic white, or black/African-American were included (n = 104). Patients with more than one ethnicity or Asian ethnicity were excluded because they were few in number (n=3).

Study procedures

Upon enrollment all participants provided detailed demographic data and medical history including age, sex, race/ethnicity, HIV risk factor (heterosexual sex, homosexual sex, intravenous drug use, or other), date of HIV diagnosis, past and current antiretroviral regimens (including dose, duration of treatment, and an estimate of medication compliance), and medical co-morbidities potentially relevant in the diagnosis of DSP (history of alcohol abuse within two years of the onset of DSP, renal impairment, and diabetes mellitus). Participants were asked about symptoms of neuropathy including pain, paresthesias, and numbness. The duration and location of any such symptoms, and the severity of pain and paresthesias (on a scale from 0-10 with 0 being no symptoms and 10 being the most severe) were recorded. Laboratory studies including CD4+ count, serum HIV RNA, and urine toxicology were obtained. A standardized neurological examination was performed by a neurologist experienced in the care of HIV-positive patients. A Karnofsky score was assigned.⁷ The evaluation described above was repeated at three to six month intervals. For the purposes of this study, all evaluations until the development of DSP were considered. If DSP did not develop, all available evaluations were included.

A standardized diagnostic algorithm was used for the diagnosis of DSP. Participants were required to have two of the following three signs: diminished sense of vibration at both great toes, bilateral distal decreased sensation to pin prick in both lower extremities, and ankle reflexes absent or diminished as compared to the knees. If these criteria were met, the participant was assigned a diagnosis of DSP, regardless of the presence or absence of symptoms. These criteria have been used previously in studies of HIV-associated DSP.⁴⁻⁶

To further document the severity of DSP, the results of the neurological evaluation were used in a modification of the Total Neuropathy Score (TNS), which has also been used in previous studies of HIV-associated DSP.³ This modified TNS yielded a potential score of 0-16, where zero is normal (see Appendix). This modification, which excluded symptoms and diagnostic studies, was used because symptoms were considered separately and diagnostic studies (quantitative sensory testing and nerve conduction) were not routinely performed in the entire cohort.

There is no standard definition of antiretroviral toxic neuropathy (ATN), although definitions of ATN used in prior studies all include a temporal relationship between exposure to a neurotoxic ARV and the onset of neuropathy.^{8,9} For this study, participants who received a new diagnosis of DSP while taking a d-drug, or within 6 weeks after stopping a d-drug, were diagnosed as ATN. The 6 week post-exposure interval was chosen because there may be a “coasting phenomenon,” whereby the neurotoxic effects of antiretrovirals persist after the cessation of the agent.¹⁰ If the participant did not receive d-drugs at the time of the DSP diagnosis or within the preceding 6 weeks, a diagnosis of HIV-DSP was assigned. Cumulative total d-drug exposure was calculated using the medication dosage, duration of therapy, and estimate of compliance. Neuropathy was further designated as symptomatic or asymptomatic depending on whether the participant reported bilateral distal lower extremity pain, burning, tingling, or numbness.

Statistical analysis

Chi-square, *t*-test, and ANOVA analyses were used to study the characteristics of participants who developed DSP while on study, and within this subset those who were symptomatic. Chi-square, *t*-test, and ANOVA analyses were then used to study the characteristics of a subset of participants who received d-drugs while on study, and within this group those who developed ATN. All statistical analyses were conducted using SPSS (version 14.1 for Windows; SPSS, Chicago, IL).

Results

One hundred and four participants did not have DSP at baseline and were analyzed longitudinally. As detailed in Table 1, this subgroup was heterogeneous in ethnicity, gender, and HIV risk-factors. All participants were seen at least twice. The duration of follow up ranged from 3 to 84 months (*M* = 19 months). The median duration of follow up was 12 months for both the participants who developed DSP and those who did not. Sixteen patients (15%) had at least one interval of a year or greater during which they were lost to follow up. There was no difference between the number of these patients in the group that developed DSP and those that did not χ^2 (1, *N* = 104) = 1.2, *p* = .28.

Fifty-two of the 104 participants (50%) who were neuropathy-free at baseline, developed DSP at follow up. Participants who developed DSP were older, had higher CD4 counts at baseline and higher CD4 nadir during the study. The mean age was 43 years (*SD* = 6.8) in the DSP group, compared with 40 (*SD* = 7.4) in the group without DSP, *t*(104) = -2.4, *p* = .02. The mean CD4+ count was 290 (*SD* = 300) at baseline and 169 (*SD* = 219) at “on study” nadir in the DSP group, compared with 120 (*SD* = 210) at baseline and 70 (*SD* = 164) at “on study” nadir in the

group without DSP, $t(103) = -3.3, p = .001$; $t(103) = -2.6, p = .004$). There was no difference in gender, ethnicity, HIV-risk factor, duration of HIV disease, mean log viral load, exposure to d-drugs during the study, mean cumulative dose of d-drugs, missed study visits, or prevalence of co-morbid conditions associated with neuropathy (diabetes mellitus, alcohol abuse, renal impairment) between participants that developed DSP and those that did not (Table 1). Patients with DSP had a mean modified TNS of 3.7 (range 1-10; $SD = 1.9$).

Sixty-seven percent of participants who developed DSP were symptomatic with pain, paresthesias, or numbness at the time of diagnosis. Comparisons between symptomatic and asymptomatic participants revealed no difference in gender, ethnicity, HIV risk-factor, age, CD4+ count or log viral load at the time of incident DSP, or the presence of positive urine toxicology for licit or illicit pain-modifying medication (methadone, opiate, barbiturate, cocaine, cannabis), (all p values $> .10$). Women were more likely than men to report positive symptoms (pain, paresthesias), $\chi^2 (1, N = 52) = 5.7, p = .02$. Patients with symptomatic DSP had a higher mean modified TNS compared to those with asymptomatic DSP (4.34 vs. 2.7, $p = .002$), reflecting more severe neuropathy on neurologic exam. Among participants with symptomatic DSP, there was a trend for higher mean pain scores among Hispanics than non-Hispanics, with means of 4.5 ($SD = 4.1$) and 2.2 ($SD = 3.1$) respectively, $t(32) = -1.8, p = .08$. Among the non-Hispanic participants there was no difference between African-Americans and non-Hispanic whites, with mean pain scores of 2.33 ($SD = 3.2$) and 2.13 ($SD = 3.1$) respectively. There was no difference between ethnic groups in the severity of DSP (as measured by the modified TNS), the presence of a positive urine toxicology, or co-morbidities for DSP ($p > .10$ for all variables). Higher pain scores were correlated with poorer performance status as measured by the Karnofsky score, $r(51) = -.30, p = .03$.

Antiretroviral Toxic Neuropathy (ATN)

A subset of 53 of the 104 participants who were neuropathy free at baseline (51%), were exposed to d-drugs during the study. Comparisons between participants who received d-drugs and those who did not revealed no difference in ethnicity, age, gender, HIV risk-factor, baseline CD4 count, viral load, or co-morbidities for DSP ($p > .10$ for all variables). Of the participants receiving d-drugs on study, 18 (34%) developed ATN. Comparisons between participants who developed ATN and those who did not revealed no difference in gender, age, cumulative total d-drug exposure, or hepatitis C co-infection ($p > .10$ for all variables). Participants with ATN had higher CD4 count $t(17) = -2.3, p = .03$, and lower HIV viral load than those without ATN $t(18) = 2.0, p = .05$, (Table 2). There was an association between ethnicity and the development of ATN. Of the 53 participants exposed to d-drugs, 10 (19%) were non-Hispanic white, 19 (36%) were African-American, and 24 (45%) were Hispanic. Only 2 (11%) of the 19 African-Americans exposed to d-drugs developed ARV-DSP, whereas 4 out of 10 non-Hispanic whites (40%) and 12 out of 24 Hispanics (50%) developed ATN, $\chi^2 (2, N = 53) = 7.6, p = .02$. There was no difference in the cumulative total d-drug exposure between ethnic groups.

There was also an association between HIV-risk factor and incident ATN. Participants who reported intravenous drug use (IVDU) as their risk factor developed ATN most commonly, and those with heterosexual sex as their risk factor, least commonly, $\chi^2 (3, N = 53) = 10.0, p = .02$. Of the 12 participants with both Hispanic ethnicity and IVDU risk factor, 8 (67%) developed ATN. There was also an association between HIV-risk factor and ethnicity, $\chi^2 (6, N = 104) = 19, p = .004$; a disproportionate number of African-American participants had heterosexual sex as their risk factor.

Discussion

In this study we sought to explore the roles of ethnicity and d-drug exposure in the development of distal sensory polyneuropathy (DSP) in participants with advanced HIV. The results indicate

that participants who develop DSP are older and have a higher baseline CD4+ count. There was a trend for higher numeric pain scores in Hispanics with DSP, despite equal degrees of DSP severity on physical examination, and equal usage of pain-modifying agents detectable by urine toxicology. Women were more likely than men to report positive symptoms of DSP, such as pain and paresthesias. In participants with exposure to d-drugs on study, Hispanic ethnicity and IVDU risk factor were associated with the highest rates of ATN, whereas African-American ethnicity and heterosexual sex risk factor were associated with the lowest rates of ATN, despite equal prevalence of d-drug exposure in the three ethnic/racial groups, and in the four HIV-risk factor groups.

Increased CD4+ count and older age have been reported previously as risk factors for DSP in the HAART-era.^{5,6} This is in contrast to earlier findings associating low CD4+ counts with DSP.¹ There are several possible explanations for this change. Patients with improved overall health and higher CD4+ counts live longer, and so have more time to develop DSP, which may create a survivor effect. The diagnosis of DSP may also be missed in sicker patients with more pressing medical issues, resulting in acquisition bias. A difference in painful symptoms due to DSP among Hispanics and women is a novel observation. This may be due in part to the underrepresentation of these groups in many cohorts. It is unclear if this finding represents a difference in the pathophysiology underlying DSP in different demographic groups, or in the causative mechanism, perception, treatment, or communication of painful symptoms. Experimental models have shown ethnic differences in pain perception.¹¹ Differences have also been demonstrated between ethnicities in pain severity and behavioral and emotional responses to chronic pain syndromes.¹² Polymorphisms in a number of genes are associated with differences in pain sensitivity. The genes encoding catecholamine-*O*-methyltransferase (COMT) and GTP cyclohydrolase (GCH1) are of particular interest in the context of our findings. Certain haplotypes of the COMT gene are associated with pain sensitivity¹³ and the frequency of haplotypes varies with race/ethnicity.¹⁴ GCH1 has been identified as a modulator of neuropathic pain, and a particular haplotype has been associated with reduced levels of neuropathic pain.¹⁵ The mechanism underlying differences in painful symptoms due to DSP is likely multifactorial, including genetic factors, issues of health utilization behavior (including utilization of pain medication), health literacy, and coping mechanisms. Studies to elucidate the interactions of all these factors will require large cohorts and control for a spectrum of genetic, neurobiologic, and sociocultural variables. The cause of the association between ethnicity and incident ATN is uncertain. There is evidence that d-drugs are mitochondrial toxins.¹⁶ There is significant genetic heterogeneity in mitochondrial DNA, and an increased rate of a specific mitochondrial haplotype in non-Hispanic white participants who developed neuropathy while receiving d-drugs.¹⁷ In U.S. populations, different mitochondrial haplogroups are typically seen in non-Hispanic blacks, non-Hispanic whites, and Hispanics.¹⁸⁻²⁰ Differential vulnerability of mitochondrial haplogroups to ARV toxicity is a potential explanation of the ethnic disparities we found.

The relationship of HIV risk factor to incident ATN is potentially more complicated. Some of the observed association may be due to the unequal distribution of ethnicity between risk factors, and there were too few participants in this study to determine with certainty if ethnicity and HIV-risk factor were independent predictors of ATN. However if ATN is associated with IVDU, neurotoxicity from chronic exposure to illicit "street" drugs is a potential mechanism. Mitochondrial dysfunction and neurotoxicity from injected street heroin has been demonstrated in rats.²¹ It is possible that the high rate of ATN observed in Hispanic participants with IVDU is the result of mitochondrial dysfunction due to cumulative toxicity from IVDU and ARV superimposed on a genetic predisposition.

In summary, the results of this study suggest that there are ethnic disparities in the clinical manifestations of HIV-related DSP, including pain and the susceptibility to neurotoxicity from

d-drugs. Understanding the role of ethnic disparities in the neurological complications of HIV is of particular importance in the context of the current demographics of both the U.S. and global epidemics. However, the results of this study should be interpreted with caution as they are based on a small number of participants. It is also possible that excluding patients who had DSP on study entry, introduced an acquisition bias, selecting for patients who were relatively resistant to DSP, although the high rate of incident DSP argues against this. Further studies in larger cohorts will be required to fully elucidate the role of genetics and other risk factors that may segregate with racial, ethnic, or socio-cultural variables.

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References

- Childs EA, Lyles RH, Selnes OA, et al. Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy. *Neurology* 1999;52:607–613. [PubMed: 10025796]
- Simpson DM, Tagliati M. Nucleoside analogue-associated peripheral neuropathy in human immunodeficiency virus infection. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995;9:153–161. [PubMed: 7749792]
- Simpson DM, Kitch D, Evans SR, et al. HIV neuropathy natural history cohort study: assessment measures and risk factors. *Neurology* 2006;66:1679–1687. [PubMed: 16769940]
- Schifitto G, McDermott MP, McArthur JC, et al. Markers of immune activation and viral load in HIV-associated sensory neuropathy. *Neurology* 2005;64:842–848. [PubMed: 15753420]
- Cherry CL, Skolasky RL, Lal L, et al. Antiretroviral use and other risks for HIV-associated neuropathies in an international cohort. *Neurology* 2006;66:867–873. [PubMed: 16567704]
- Morgello S, Estanislao L, Simpson D, et al. HIV-associated distal sensory polyneuropathy in the era of highly active antiretroviral therapy: The Manhattan HIV Brain Bank. *Arch Neurol* 2004;61:546–551. [PubMed: 15096404]
- Karnofsky, DA.; Burchenal, JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod, CM., editor. *Evaluation of Chemotherapeutic Agents*. Columbia Univ Press; 1949. p. 196
- Youle M, Osio M. A double blind, parallel-group, placebo-controlled, multi-centre study of acetyl L-carnitine in the symptomatic treatment of antiretroviral toxic neuropathy in patients with HIV-1 infection. *HIV Med* 2007;8:241–50. [PubMed: 17461852]
- Pettersen J, Jones G, Worthington C, et al. Sensory neuropathy in human immunodeficiency virus/acquired immunodeficiency syndrome patients: protease inhibitor-mediated neurotoxicity. *Ann Neurol* 2006;59:816–24. [PubMed: 16634006]
- Berger A, Arezzo J, Schaumburg H, et al. 2',3'-dideoxycytidine (ddC) toxic neuropathy: a study of 52 patients. *Neurology* 43:358–62. [PubMed: 8382349]
- Campbell CM, Edwards RR, Fillingim RB. Ethnic differences in responses to multiple experimental pain stimuli. *Pain* 2005;113:20–26. [PubMed: 15621360]
- Edwards RR, Moric M, Husfeldt B, Buvaendran A, Ivankovich O. Ethnic similarities and differences in the chronic pain experience: A comparison of African-American, Hispanic, and white patients. *Pain Med* 2005;6:88–98. [PubMed: 15669954]
- Diatchenko L, Slade GD, Nackley AG, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Hum Mol Genet* 2005;14(1):135–143. [PubMed: 15537663]
- McLeod HL, Fang L, Luo X, Scott EP, Evans WE. Ethnic differences in erythrocyte catechol-O-methyltransferase activity in black and white americans. *J Pharmacol Exp Ther* 1994;270(1):26–29. [PubMed: 8035323]

15. Tegeder I, Costigan M, Griffin RS, et al. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. *Nat Med* 2006;12(11):1269–1277. [PubMed: 17057711]
16. Kohler JJ, Lewis W. A brief overview of mechanisms of mitochondrial toxicity from NRTIs. *Environ Mol Mutagen* 2007;48:166–172. [PubMed: 16758472]
17. Hulgán T, Haas DW, Haines JL, et al. Mitochondrial haplogroups and peripheral neuropathy during antiretroviral therapy: An adult AIDS clinical trials group study. *AIDS* 2005;19:1341–1349. [PubMed: 16103764]
18. Allard MW, Miller K, Wilson M, Monson K, Budowle B. Characterization of the Caucasian haplogroups present in the SWGDAM forensic mtDNA dataset for 1771 human control region sequences. *J Forensic Sci* 2002;47:1215–1223. [PubMed: 12455642]
19. Allard MW, Polanskey D, Miller K, Wilson MR, Monson KL, Budowle B. Characterization of human control region sequences of the African-American SWGDAM forensic mtDNA data set. *Forensic Sci Int* 2005;148:169–179. [PubMed: 15639612]
20. Allard MW, Polanskey D, Wilson MR, Monson KL, Budowle B. Evaluation of variation in control region sequences for Hispanic individuals in the SWGDAM mtDNA data set. *J Forensic Sci* 2006;51:566–573. [PubMed: 16696703]
21. Cunha-Oliveira, Rego AC, Garrido J, Borges F, Macedo T, Oliveira CR. Street heroin induces mitochondrial dysfunction in rat cortical neurons. *J Neurochem* 2007;101:543–554. [PubMed: 17250679]

Table 1

Comparison of participants with incident neuropathy during study to those without

	No neuropathy at baseline	Incident neuropathy	No incident neuropathy	<i>p</i>
n	104	52	52	
Age, y	42 (7.2)	43 (6.8)	40 (7.4)	.02
Gender, %				.69
Male	60	61	58	
Female	40	39	42	
Ethnicity, %				.98
non-Hispanic white	21	21	21	
African-American	38	37	39	
Hispanic	41	42	40	
HIV risk factor, %				.66
Heterosexual sex	39	33	44	
Homosexual sex	24	25	23	
IVDU	36	40	31	
Other/multiple	2	2	2	
Co-morbidities, %				.11
Diabetes Mellitus	9	4	14	
Alcoholism	13	14	12	
Renal failure	5	8	2	
Time HIV-positive, y	9.8 (4.9)	9.5 (5.2)	10.1 (4.6)	.53
D-drug exposure during study, %	51	50	52	.84
Cumulative d-drug exposure during study, 133 (196) grams		156 (310)	130 (123)	.94
CD4 count at baseline, cells/mm ³	210 (280)	290 (300)	120 (210)	.001
CD4 nadir during study, cells/mm ³	119 (199)	169 (219)	70 (164)	.004
HIV-1 viral load (copies/ml)*	3.5 (1.5)	3.3 (1.5)	3.8 (1.6)	.09

Values are mean (SD), except where indicated.

* Value expressed as log base 10.

Table 2

Analyses performed on a subset of patients who received neurotoxic antiretrovirals, comparing those who developed antiretroviral toxic neuropathy (ATN) to those who did not

	ATN	No ATN	p
n	18	35	
Age, y	41.4 (6.2)	41.1 (8.3)	.91
Gender, %			.78
Male	67	63	
Female	33	37	
Ethnicity, %			.02
non-Hispanic white	22	17	
African-American	11	49	
Hispanic	67	34	
HIV risk factor, %			.02
Heterosexual sex	6	43	
Homosexual sex	28	26	
IVDU	61	31	
Other/multiple	6	0	
Co-morbidities, %			.72
Diabetes Mellitus	9	0	
Alcoholism	11	11	
Renal Failure	3	0	
Cumulative d-drug exposure during study, grams	120 (160)	200 (360)	.25
CD4 count at baseline, cells/mm ³	290 (280)	130 (210)	.02
HIV-1 viral load (copies/ml)*	3.0 (1.4)	3.8 (1.5)	.05

Values are mean (SD), except where indicated.

* Value expressed as log base 10.

Appendix

Modified Total Neuropathy Score

Parameter	0	1	2	3	4
Pin sensitivity	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Vibration sensitivity	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon Reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent