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Gender differences in HIV-related neurological progression in a cohort of injecting drug users followed for 3.5 years

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Abstract

We evaluated potential gender differences in the development of HIV related neurologic impairment, by matching 38 pairs of HIV positive male and female injecting drug users on their baseline age, education, disease stage and CD4 counts, and following them for 3.5 years. Adjusting for age, education, drug use, history of head injury and baseline CD4 count, more women had sensory abnormalities and symptoms than men at baseline, but the odds of having neurological impairment, particularly extrapyramidal signs and sensory abnormalities were increased over time in men but not in women. Men with ARC or AIDS had more neurological impairment than women in similar stages of illness. This study suggests further investigations of gender differences in HIV disease progression.

Key words: HIV, injecting drug users, neurologic impairment, gender differences.

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Introduction

We previously reported that in a population of injection drug users (IDUs) followed biannually for up to 3.5 years, neurological impairment became increasingly apparent in HIV-infected men as they became more immunosuppressed and had clinical evidence of AIDS. Overall, fewer neurological signs were seen in the women, although women had more neurological impairment at baseline (1). While this finding raised the question of whether there are gender differences in neurological progression in HIV, this issue could not be addressed using both complete cohorts (men and women) because they differed significantly at baseline. To address this issue, we examined the progression of neurological signs over 8 biannual visits in HIV-positive men and women matched on their baseline age, education, disease stage and CD4 count .

Methods

Subjects

Subjects were drawn from the IDU population previously described (2, 3). We matched each of the HIV-positive IDU women to one of our group of 85 HIV-positive IDU men based on baseline age (within 5 years), number of years of education (within 2 years), disease stage based on medical assessment, and CD4 count ($\leq$200, 200-500, $\geq$500), yielding 38 matched pairs of men and women.

Assessments

At each visit, subjects received a standardized medical examination to stage HIV severity, a neurological assessment and laboratory tests including complete blood count and lymphocyte typing.

Medical assessment

Physicians performed physical examinations targeted at HIV-related symptoms and signs. During follow up, HIV-positive subjects were characterized as physically asymptomatic, mildly symptomatic, symptomatic meeting criteria for AIDS related complex (ARC) but not AIDS, or AIDS. Mildly symptomatic subjects had signs such as lymphadenopathy, diarrhea for 2 weeks or fever for 2 weeks but they did not meet criteria for ARC. ARC subjects had signs such as oral thrush, fever or diarrhea for >30 days or oral hairy leukoplakia, but did not meet criteria for AIDS. Nomenclature and staging reflect the 1986 CDC staging system (4).

Neurological Assessment:

Neurological examinations were performed as previously described (3,5). The neurological data were summarized in two ways. First, an overall measure of neurological disability (Kurtzke) was determined for each subject, based on the Kurtzke Disability Status Scale for Multiple Sclerosis (6). A Kurtzke score of 3 or greater was indicative of a level of impairment that most neurologists would reliably detect and consider clinically meaningful. A subject with a Kurtzke score of 3 would have moderate neurological disability but remain fully ambulatory. We also used six factors which represented major neurological domains (3,7). The factors were dichotomized at a level we believed indicated clinical significance (Table 1).

Evaluation of Drug and Alcohol Use

We examined both history of drug and alcohol use prior to baseline examination and recent drug and alcohol use. Subjects were systematically interviewed at visits 1 through 7 about their drug and alcohol usage. Use of all forms of heroin, all forms of cocaine, benzodiazepines, hallucinogens and phencyclidine were queried. Because the number of years of drug or alcohol

use was highly correlated with the age of the subjects and may have been inconsistently reported, we created a variable to reflect the length of time subjects used either heroin, cocaine or alcohol, based on the age they had begun using the substances. Years of illicit drug use were dichotomized into "long" ($\geq$ 15 years) and "short" (< 15 years), and alcohol use was dichotomized into "long" ($\geq$20 years) and "short" (<20 years). If either drug use or alcohol use was considered "long", the subject was considered to have a "long" history of substance abuse. The cut points were chosen in the previous study of the original cohorts (1) to simplify analysis such that about one fourth of the subjects were older "long" term users, one fourth were younger "short" term users and half of the cohort were younger subjects with "long" use. No women over age 40 and no men over age 45 in the original cohorts had a "short" history of drug or alcohol use. The frequency of substance abuse in the 6 month interval prior to each visit was also dichotomized into "high" for weekly or daily use, "low" for less frequent use.

Statistical Analysis

Chi-square test and Fisher's exact test (8) were applied to test gender differences in the prevalence of baseline characteristics and neurological outcomes at baseline (Table 2 and 3).

A proportional hazard model (9) was used to examine the gender difference in progression to AIDS.

To examine gender differences in CD4 decline, we applied a regression model with CD4 change over 6 month intervals as the outcome, using CD4 count at the beginning of the time interval, gender, and the interaction of the two variables (CD4 and gender) as covariates.

Analyses of the longitudinal data were performed by applying generalized estimating equations (GEE) to regression analyses with repeated measures (10). This statistical method

takes into account the multiple visits per subject and the fact that the characteristics of a single individual over time are likely to be correlated with one another. The repeated measures for each subject (up to 8 per variable) are treated as a cluster. A second advantage of GEE is that it takes into account the status or changing value of each covariate and outcome at each visit.

The logistic regression analyses provide estimates of the odds of the occurrence of an outcome dependent on the values of the covariates. The outcomes included the six neurological factors and the modified Kurtzke Disability Status Score (Kurtzke), as described above.

We explored the effect of age, education, substance abuse history, recent drug and alcohol use frequencies, and history of head injury with loss of consciousness on the outcomes. We included those potential confounders which had a significant effect on the outcome in the main analyses. We examined the gender difference in developing each outcome over time, using a gender by time interaction term in the analysis.

Immune status (CD4 count) and stage of HIV infection were included as covariates in another set of analyses. CD4 count was categorized into $\leq$200 and 200-500 with CD4 $\geq$500 as a reference group. Subjects were also classified into those satisfying criteria for ARC and those with AIDS, with those who were asymptomatic or mildly symptomatic combined as the reference group. Gender difference in the association between neurologic outcome and CD4 or disease stage was examined by the appropriate interaction term.

Results

Baseline characteristics

Baseline characteristics of the matched sample are presented in Table 2. The two groups were comparable in age, years of education, ethnic representation and average CD4 counts. No

one met 1986 CDC criteria for AIDS at baseline, but 58% of the men and women met 1986 CDC criteria for ARC, indicating that this sample of IDUs was moderately ill at baseline. A higher proportion of men than women had a history of long-term drug use at baseline (p=.03). There was a borderline gender difference in the frequency of long term alcohol use (p=.06).

Baseline prevalences of neurological outcomes are presented in table 3. These were comparable in men and women except for sensory abnormalities, where women had a higher crude prevalence than men (p=.05).

Disease progression

About 80% of men and 87% of women completed at least 3 visits and about 70% of men and women completed at least 5 visits. Eighteen men and 21 women completed 3.5 years follow up. Men had an average of 5.39 visits and women had an average of 5.47 visits. Twelve out of 20 men and 9 out of 17 women who withdrew from the study subsequently died. Of those who died, 6 men and 6 women died of AIDS.

Five men and 5 women developed AIDS during the follow up period. A Cox proportional hazard model was used to examine the gender difference in progression to AIDS adjusted for baseline CD4 count. No gender difference was detected.

We modeled CD4 change over 6 month intervals as a function of CD4 at the beginning of the interval, gender and the interaction of gender and CD4 count. The CD4 change over a six month interval depended on the CD4 count at the beginning of the time interval, with higher CD4 count related to larger decline. There was no gender difference in CD4 decline.

Gender difference in HIV neurological progression

Age, education, head injury with loss of consciousness, substance use history, and recent

drug and alcohol use were considered as potential confounders. Logistic regression analyses suggested that baseline age was related to high Kurtzke score, extrapyramidal signs, frontal release signs and sensory abnormalities. The older the subject, the more likely he or she had "high" neurological outcome scores. Education was negatively related to these four outcomes. Head injury history was positively related to cranial nerve signs and recent drug use frequency was related to neurological symptoms. Subsequent analyses controlled for these confounders as appropriate.

In logistic regression analyses controlling for relevant confounders and baseline CD4 count, there were significant gender differences in the presence of sensory abnormalities and symptoms at baseline, and significant time by gender interactions for the outcomes of high Kurtzke score, extrapyramidal signs, sensory abnormalities, and symptoms. In table 4 column 1, we can see that after adjusting for relevant confounders, the odds of having sensory abnormalities or symptoms in men were significantly lower than in women at baseline (for sensory abnormalities OR=0.39, 95% CI (0.18-0.82); for symptoms OR=0.40, 95% CI (0.19-0.83)). In contrast, despite being less likely (sensory abnormality and symptoms) or equally likely (high Kurtzke score and extrapyramidal signs) to have these four outcomes at baseline, men were more likely than women to develop these neurologic outcomes over time (column 2 in Table 4). For example, relative to the previous year, the odds of having a high Kurtzke score for men was 1.86 times that for women. Figure 1 shows the pattern over time in the proportion of high Kurtzke score. The odds of the four neurologic outcomes increased each year of men (column 3 in Table 4) but no significant time trend was found for women (column 4 in Table 4). No gender difference or time trend was related to the presence of frontal release signs, alternating movements and cranial nerve

signs. The non-significant results are not included in table 4.

The association between CD4 count and neurological impairment did not differ by gender. After adjusting for the relevant confounders, both men and women with CD4 between 200 to 500 were more likely than those with high CD4(≥500) to have high Kurtzke score (OR=2.26, 95% CI (1.13-4.51)), extrapyramidal signs (OR=2.92, 95% CI (1.11-7.70)), or abnormal alternating movements (OR=2.20, 95% CI (1.36-3.53)). Similarly, both men and women with low CD4(≤200) were more likely than those with high CD4(≥500) to have high Kurtzke score (OR=3.23, 95% CI (1.49-7.01)) and extrapyramidal signs (OR=5.19, 95% CI (1.84-14.68)).

Neurological outcomes became more common in advanced stages of HIV infection, but no gender differences were seen in the relationship between HIV stage and neurologic outcomes except for high Kurtzke score. Compared to a reference group of asymptomatic and mildly symptomatic subjects combined, both men and women with AIDS were more likely to have extrapyramidal signs (OR=3.98 with 95% CI (1.17-13.53)), sensory abnormalities (OR=3.85 with 95% CI (1.65-8.99)) and symptoms (OR=10.07 with 95% CI (3.18-31.88)).

After adjusting for confounders and CD4 count, asymptomatic and mildly symptomatic women were more likely than men to have high Kurtzke score (p=.053, OR=2.87 with 95% CI (.98-8.37)). Relative to the asymptomatic and mildly symptomatic stage, men with ARC were more likely than women with ARC to have high Kurtzke score (OR=5.97, 95% CI (1.75- 20.39)). Men with ARC were more likely than the asymptomatic and mildly symptomatic men to have high Kurtzke score (OR=2.69, 95%CI(1.13-6.42)) while the same pattern was not seen in women (OR=0.45, 95%CI(0.18-1.13)). Similarly, in AIDS, relative to the asymptomatic and mildly symptomatic stage, men were more likely than women to have high Kurtzke score, OR=13.52

with 95% CI(2.82-64.73). For men with AIDS, the odds of having high Kurtzke score was much higher than the asymptomatic and mildly symptomatic men (OR=37.34, 95%CI(10.90-127.85)), while for women with AIDS the odds of having high Kurtzke score was not significantly higher than the asymptomatic and mildly symptomatic women (OR=2.76, 95%CI(0.71-10.82)).

In summary, men were more likely to have overall neurological impairment. There were gender differences in the odds of neurological impairment at different medical stages of HIV. Neurologically, men were more often impaired in the late medical stages while in early disease stages women were more frequently impaired.

Discussion

To investigate the gender differences in neurologic progression in a prospectively followed cohort of HIV-positive injecting drug users, we selected 38 men and 38 women, matched on their baseline age, education, medical stage and CD4 counts. Most of the subjects were moderately ill at baseline. The rate of loss to follow up and the average number of visits were similar in men and women. After adjusting for potential confounders, there were gender differences in the presence of neurologic impairment at baseline and during the follow up period. At baseline, women had more sensory abnormalities and symptoms than men. Over time, men were more likely to have overall neurologic impairment than women, and were more likely to develop extrapyramidal signs, sensory abnormalities and symptoms. Men were more likely to be neurologically impaired than women when they had ARC and AIDS while women were more likely to have impairment than men in the asymptomatic and mildly symptomatic stages.

By employing the 1986 classification criteria, some subjects with low CD4 count (<200) were classified as asymptomatic, mildly symptomatic or ARC. The updated 1992 CDC criteria

(11) considers those with CD4 count less than 200 to have AIDS. The three other qualifying conditions added to the 1992 AIDS definition are pulmonary tuberculosis, bacterial pneumonia recurring within a one year period and invasive cervical cancer. It is possible that subjects (potentially women) who would have qualified for AIDS using 1992 criteria were classified as asymptomatic, mildly symptomatic or ARC by 1986 criteria. We do not, however, have information on how many subjects would change stage if the 1992 criteria (other than CD4<200) were applied. Because invasive cervical cancer is rare, the other two conditions are unlikely to occur differentially with respect to gender, and the distributions of CD4 count in the three groups of staging by 1986 CDC criteria were similar in both men and women, we would argue that the gender differences in neurological impairment at the different medical stages using 1986 criteria cannot be solely explained by potential differential misclassification.

Lower CD4 was associated with neurological disability, but we did not see a gender difference in neurological impairment within CD4 categories. However, CD4 is not the only measure of HIV disease severity. Viral load, beta-2-microglobulin level, and neopterin level might possibly distinguish men and women with neurological outcomes, but were not available for our analysis.

A number of studies have reported that the progression of HIV infection in men and women is similar. Progression to CD4<200, development of AIDS defining illness and death from AIDS are similar in men and women (12, 13, 14). Although immunological parameters were found to be predictive of progression to AIDS, an AIDS defining illness was the strongest predictor of death in a retrospective review of 224 HIV-infected women (15). One large multicenter cohort study did find an increased risk of death in HIV-infected women compared to

men, (RR=1.33, 95%CI=1.1-1.9). This difference was larger when only drug users were considered (RR=1.68, 95%CI=1.2-2.4). However, no increased risk for disease progression was seen in the women (16). The authors concluded that differential access to health care, socioeconomic status and social support might be contributing to the risk of death in these women. These studies suggest that there are factors other than immune status that may be contributing to outcomes such as death. We also did not find any gender differences in the progression to AIDS adjusted for baseline CD4 count or in the rate of CD4 decline. However, to our knowledge, ours is the first study to directly comment upon differences in neurological progression between men and women.

One possible explanation for the gender difference in neurologic progression over time is gender difference in drug and alcohol use. There was more frequent use in men than women of both drugs (OR=2.03, 95% CI (1.00-4.14)) and alcohol (OR=2.36, 95% CI (1.06-5.26)) during follow up. In addition, women with low CD4($\leq$200) count were less likely to report frequent drug use in the past six months than women with higher CD4 count, while in men the odds of frequent drug use were not associated with CD4 count. It is also possible that men and women used different quantities of drugs and alcohol. In those who died after withdrawal from the study, 3 men but no women died of drug overdoses.

We used several variables to control for the possible confounding effect of drug and alcohol abuse on neurological impairment, including life time history of drug and alcohol usage, and frequency of drug and alcohol use in the past six months. Still, these variables may not fully represent the complicated characteristics of the substance abuse. Lifetime drug and alcohol use was highly correlated with baseline age. The data for frequency of recent drug and alcohol use

were incomplete at baseline and unavailable on visit 8, forcing us to reduce sample size when including these variables in the analysis. Also, information on the quantity of drug use or alcohol consumption was unavailable. Thus we may not be able to fully control for drug effects in our analysis.

In conclusion, no gender difference was seen in the relationship between neurologic outcomes and CD4 count in this IDU cohort. In contrast, using 1986 staging system, men with AIDS had more overall neurologic impairment than women. Lastly, men had more rapid progression of neurologic impairment over time than women.

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Table 1. Neurologic factors and their components

Factor	Cut point	Total Items	Items
Frontal release signs	≥3	7	Glabellar, snout, suck, grasp, palmomental reflexes,
Alternating movements	≥1	8	finger tapping, opening and closing hands, foot tapping, pronation supination
Extrapyramidal signs	≥2	13	rigidity in all limbs, bradykinesia, gait, salivation, hypomimia, speech, tremor (rest and action) posture
Sensory abnormalities	≥5	16	pain and temperature, vibration, position
Cranial nerve signs	≥2	21	all cranial nerve signs
Symptoms	≥3	11	all cognitive, motor, behavioral items

Table 2. Baseline characteristics of HIV positive IDUs

	38 Men	38 Women	
	Mean (SD)	Mean (SD)	P value
Ages (years)	38.11 (5.05)	37.78 (5.29)	0.78
Education (years)	12.24 (1.78)	12.26 (1.87)	0.96
CD4 counts	398.79 (229.45)	434.97 (313.83)	0.57
	% (n)	% (n)	
African-American	76 (28)	74 (28)	
Hispanic	14 (5)	11 (4)	
Caucasian	11 (4)	16 (6)	0.78
Asymptomatic	26 (10)	26 (10)	
Mild symptomatic	16 (6)	16 (6)	
ARC	58 (22)	58 (22)	
Drug use ≥ 15 years	82 (31)	55 (21)	0.03
Alcohol use ≥ 20 years	66 (25)	42 (16)	0.06
Long term use	87 (33)	63 (24)	0.03
Head injury (LOC)	42 (16)	29 (11)	0.34

Table 3. Prevalence of neurological outcomes at baseline in HIV positive IDUs

	38 Men	38 Women	P-values
Overall impairment (Kurtzke score≥3)	26% (10)	32% (12)	0.80
Extrapyramidal signs	16% (6)	11% (4)	0.74
Frontal release signs	13% (5)	11% (4)	0.99
Alternating movements	34% (13)	32% (12)	0.99
Cranial nerve signs	50 % (19)	39% (15)	0.49
Sensory abnormality	21% (8)	45% (17)	0.05
Symptoms	53% (20)	61% (23)	0.64

Table 4. Odds Ratios and 95% CI of developing neurological outcomes over time (per year) adjusted for drug use, education, baseline age and baseline CD4 count

Outcome	Baseline (men vs. women)	Time (year) (men vs. women)	Time (men)	Time (women)
Kurtzke score≥3	0.55 (0.23-1.30)	1.86*(1.27-2.71)	1.69*(1.28-2.21)	0.91 (.68-1.21)
Extrapyramidal signs	0.59 (0.22-1.55)	1.67*(1.11-2.50)	1.74*(1.24-2.43)	1.04 (.78-1.37)
Sensory abnormalities	0.39*(0.18-0.82)	1.62*(1.05-2.51)	1.69*(1.21-2.34)	1.04 (.77-1.39)
Symptoms	0.40*(0.19-0.83)	2.06*(1.32-3.20)	1.66*(1.17-2.36)	0.81 (.61-1.07)

* P≤0.05

Figure 1. Proportion of neurologic impairment (high Kurtzke score) in IDU men and women (modeled [lines] vs. crude [dots])

Figure 1. Proportion of neurologic impairment (high Kurtzke score) in IDU men and women (modeled [lines] vs. crude [dots])