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Higher frequency of dementia in older HIV-1 individuals:

The Hawaii Aging with HIV-1 Cohort

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Abstract

Background—Antiretroviral therapy has improved survival for HIV-1-infected individuals. The neuroepidemiologic implications of HIV-1 in an aging population are not well known, particularly the prevalence of HIV-associated dementia (HAD).

Methods—The authors report a baseline cross-sectional analysis of 202 HIV-1-seropositive individuals enrolled into one of two groups of the Hawaii Aging with HIV Cohort: older (50 or more years old, n = 106) and younger (20 to 39 years old, n = 96). Neuropsychological, neurologic, medical, and laboratory data were obtained at enrollment. Participant cognitive status was classified (research case definitions) using American Academy of Neurology (1991) criteria in a consensus conference of physicians and neuropsychologists.

Results—HAD was more frequent in older (25.2%) compared to younger (13.7%) individuals ($p = 0.041$) corresponding to an OR of 2.13 (95% CI: 1.02 to 4.44) for the older compared to the younger group. After adjusting for education, race, substance dependence, antiretroviral medication status, viral load, CD4 lymphocyte count, and Beck Depression Inventory score, the odds of having HAD among individuals in the older group was 3.26 (1.32 to 8.07) times that of the younger group.

Conclusions—Older age is associated with increased HAD in this HIV-1 cohort. Underlying mechanisms are unclear but do not appear related to duration of HIV-1 infection.

As of December 2001, 90,513 cases of AIDS were reported in individuals 50 or more years of age to the Centers for Disease Control and Prevention in the United States, representing a cumulative frequency of 11%.[1] Since the introduction of highly active anti-retroviral therapy (HAART) in 1996, the number of deaths among persons with AIDS has declined sharply and continued to decline through 2001. While advances in HIV-1/AIDS treatment within the United States have had a remarkable impact on opportunistic diseases and mortality, the impact on dementia is mixed. Excluding patients with a diagnosis of AIDS due to a low CD4 lymphocyte count, HIV-associated dementia (HAD) accounted for 3% of all initial AIDS-defining events prior to widespread use of HAART.[2] An estimated 15% of such patients would eventually develop HAD.[3] Reports published after HAART indicate a decreased incidence of HAD, however prevalence appears to be rising and the prevalence of HIV-1-encephalitis identified postmortem has not changed.[4,5] Rates of mild cognitive/motor disorder (MC/MD) among adults with symptomatic HIV-1 disease may now exceed 30%.[6] Notably, these reports have

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not included concentrated numbers of older individuals where a higher prevalence of neurodegenerative diseases might be expected.

While dementia is associated with advanced HIV-1 infection, it is not firmly established that frequency increases with age. In contrast, advanced age is a known risk factor for dementia among individuals not infected with HIV-1, for example, Alzheimer disease (AD), cognitive impairment due to vascular disease, and the dementia associated with Parkinson disease.[7–9] Age-associated increases in medical comorbidities are reported in HIV patients, as are increased cognitive symptoms.[10,11] Epidemiologic data from both Europe and the United States suggest an increased HAD prevalence associated with the extremes of age.[12,13] Prior to the widespread use of HAART, trends for age-associated neuropsychological abnormalities were identified in specific cognitive domains, particularly for timed measures.[14]

In 2001, the University of Hawaii in collaboration with The Johns Hopkins University began enrollment of an older HIV-1-seropositive cohort with a younger seropositive comparative group to identify the frequency and characteristics of cognitive dysfunction associated with aging. We now report enrollment data captured during the first 24 months of this longitudinal study.

Methods

Recruitment of the cohort

The Hawaii Aging with HIV Cohort Study is a longitudinal prospective examination of older (50 or more years old) compared to younger (20 to 39 years old) HIV-1-seropositive individuals. All participants were living in Hawaii at the time of enrollment. Major exclusion criteria included the following: 1) diagnosed major psychiatric disorder including bipolar illness, schizophrenia, or active major depression, 2) head injury with loss of consciousness greater than 1 hour, 3) opportunistic brain infection, 4) learning disability, and 5) major neurologic disease such as multiple sclerosis, major stroke, or current delirium. Individuals who reported transient ischemic attacks or stroke syndromes with near total resolution of their symptoms were allowed to enroll but excluded from this analysis (one younger and three older participants). All individuals identified English as their principal language of communication. Broad community-based recruitment techniques were implemented, including recruitment from AIDS service organizations, advertisement in local newspapers, referrals from community physician clinics, and participation in local HIV/AIDS events. Participants were recruited from all major islands of Hawaii.

Evaluations

Participant evaluations included the macro-neurologic examination as used in the Adult AIDS Clinical Trials Group, a medical history questionnaire, a medication/adherence history, a Diagnostic and Statistical Manual of Mental Disorders (DSM)–IV-based substance abuse/dependence inventory, immunologic and virologic laboratory tests, and neurocognitive testing. The macro-neurologic examination is commonly used in HIV-1-related trials and includes the United PD Rating Scale to examine for extrapyramidal signs.[15,16]

The 80-minute neuropsychological battery was designed to assess multiple cognitive domains most affected by HIV-1 and included the following: Choice and Sequential Reaction Time (CalCap), Rey Auditory Verbal Learning Test (RAVLT), Rey-Osterreith Complex Figure (RCF) Copy and Recall, Trail Making Tests A and B, WAIS-R Digit Symbol, Grooved Pegboard, Timed Gait, Odd Man Out, FAS, Animal Naming, Boston Naming Test (BNT), and WAIS-R Digit Span (Forward and Backward). Depressive symptomatology was assessed using the Beck Depression Inventory (BDI). This neuropsychological battery was adapted from that

used in the NorthEast AIDS Dementia Cohort (NEAD).[17] All of the tests used in the NEAD are included with additional tests added to address working memory, auditory span of attention, verbal fluency, and executive functions.

Normative neuropsychological data were acquired from the Multicenter AIDS Cohort Study (MACS) consisting of 733 seronegative subjects with similar risk profiles to our cohort.[18] This normative set has poor representation of individuals over 54 years old or individuals with less than a high school education; consequently, for individuals over 54, alternative published normative data were used.[19–22] Normative data for the RCF were taken from alternative published norms for individuals over 59 and the main MACS normative set for individuals under 60.[23] Normative data for the CalCap and Odd Man Out have not been reported for individuals over 54 years old; thus utility of these scores was minimized among this age group. For individuals with less than a high school education (six younger and three older participants), the AIDS Link to IV Experience (ALIVE) study (n = 150) served as the main source for normative data with supplementation from the above normative values given the differing risk profiles of participants in this dataset.[24]

All test results were transformed to whole number z-scores using appropriate normative sets. A sum score of the following tests was used to categorize degree of neuropsychological impairment: RAVLT trial 5, delayed recall, and delayed recognition; RCF immediate recall and copy; Odd Man Out; FAS; Digit Symbol; CalCap choice and sequential reaction times; and Grooved Pegboard dominant and non-dominant hands. Individual z-scores that exceeded 0 were entered as 0. Other administered tests not used in this summary score served as supplemental data.

An algorithm supported objective interpretation of the overall cognitive impairment severity; however, final classification was not strictly dependent upon the algorithm. This algorithm is used in the NEAD cohort and is described elsewhere.[25] Briefly, the summary score, reflecting degree of neuropsychological impairment, is combined with information from both the neurologic examination and functional assessment to obtain a disease stage of normal, equivocal, mild, moderate, or severe disease. While this algorithm complements the Memorial Sloan Kettering Scale (MSK), the NEAD-based algorithm places greater emphasis on neuropsychological and neurologic findings, thus maximizing consistency across sites.[26]

Definition of covariates

Plasma viral loads were assessed using Amplicor HIV-1 Monitor Ultrasensitive Assay (Roche Molecular System, Branchburg, NJ) and CD4 lymphocyte counts were obtained in real-time by standard technique from a local CAP certified reference laboratory. Current substance dependence was defined as meeting DSM-IV criteria based on a structured interview by trained personnel. For logistic regression models, we defined race as Caucasian, Asian-Pacific Islander, or other; treatment with HAART as taking medications that included at least three antiretroviral medications; viral load as detectable or not detectable; and low CD4 lymphocyte count as a count of less than 200 cells/dL. Reporting of nadir CD4 lymphocyte count, date of first HIV-1 positive test, and risk for HIV-1 were obtained by a structured interview with each participant. Duration of HIV-1 infection was defined as elapsed time since first HIV-1 positive test. Greater than 85% of participants were able to report dates of first HIV test and CD4 nadir.

Consensus diagnosis

Individual cases were presented to a consensus conference involving two neurologists, two neuropsychologists, and a geriatrician in collaboration with Johns Hopkins University. Using American Academy of Neurology (AAN) 1991 criteria, a diagnosis of HAD or MCMD was determined.[27] In general, a diagnosis of HAD required the following: 1) an abnormality in at

least two cognitive domains including: attention/concentration, speed of information processing, abstraction/reasoning, visuospatial skills, memory/learning, or speech/language; and 2) either an abnormality in motor function or decline in motivation/emotional control. For a diagnosis of MCMD, requirements included the following: 1) at least two of the following symptoms: impaired attention/concentration, mental slowing, impaired memory, slowed movements, incoordination, or personality change; and 2) a cognitive or motor abnormality on examination or testing. Individuals diagnosed with dementia received brain MRI unless contraindicated or refused (80% compliant) and serologic tests for B12 deficiency, syphilis, cryptococcal infection, and thyroid dysfunction. Diagnostic modifiers ("possible" and "probable") were applied to indicate presence or absence of other existing factors that could contribute to the research diagnosis, in accordance with AAN 1991 criteria and after all testing was completed to rule out those etiologies that could confidently be excluded. Individuals with neuropsychological testing abnormalities beyond acceptable variance from normal as determined by the research neuropsychologists yet insufficient to meet MCMD or HAD criteria were categorized as NP abnormal.

In some cases, marked abnormality on neuropsychological and neurologic examination sufficient to meet HAD criteria existed, but solid evidence for decline in work, instrumental activities of daily living (IADLs), or activities of daily living (ADLs) was lacking. All such participants met NEAD stage 1 or greater due to the degree of neuropsychological and neurologic abnormality.[25] For the purpose of this analysis, these individuals were included in the dementia category; however, a separate analysis excluding these participants is also reported.

Data management and statistical analysis

All participants signed institutional review board–approved informed consent forms prior to participation. Separate technicians entered data in duplicate. Baseline data were analyzed using χ^2 tests and Student *t*-tests for categorical and continuous variables (or non parametric Fisher exact tests and Wilcoxon tests). Multivariate logistic regression models were used to estimate odds ratios using S PLUS v6.1 statistical package (Insightful Corporation, Seattle, WA).

Results

Demographics

Evaluation of basic demographic variables revealed several expected differences between older and younger patients. The age distributions in each group were skewed toward the fifth decade of life, as anticipated given a higher prevalence of HIV-1 in the mid-40s in Hawaii. The median age was 54.8 years in the older and 36.7 years in the younger group (table). The older group consisted primarily of Caucasian men who were born or raised on the mainland United States and have lived in Hawaii for a mean of 19.7 years. Most of these individuals also completed high school on the mainland. Seventy-four percent endorsed homosexual contact as the only risk for HIV-1 infection. This group was generally well educated, similar to that seen in the Multicenter AIDS Cohort Study where normative neuropsychological data for this report were obtained.[18,28]

In contrast, the younger group exhibited greater diversity, as is noted nationally for younger subsets.[1] A greater percentage of women and non-Caucasian populations were represented and a greater distribution of risk factors. Compared to the older group, this group had a lower mean level of education, although the majority (68%) was either still attending college or had attended some college. A shorter self-reported duration of HIV-1 infection and duration since CD4 nadir was observed in the younger group.

Diagnosis of dementia by AAN 1991 criteria

The frequency of research case diagnoses differed between the older and younger groups (figure). This was most notable for the diagnosis of dementia, where 25.2% of older compared to 13.7% of younger individuals met diagnostic criteria ($p = 0.041$). Significant differences were also noted in MCMD diagnoses with 44.7% of older and 26.3% of younger participants meeting these criteria ($p = 0.007$). Important comorbidities were present in 70% of HAD and MCMD cases requiring a "possible" modifier. HAD without contributing factors (probable cases) occurred in 8.7% of older and 3.2% of younger participants ($p = 0.14$). Cases of HAD with endorsed decline in work, ADLs, or IADLs occurred in 9.5% of younger and 14.6% of older participants in the cohort ($p = 0.273$).

The odds of meeting HAD criteria among individuals in the older group were 2.13 (95% CI: 1.02 to 4.44) times that of the younger group. After adjusting for differences in education, race, current substance dependence, HAART status, viral load, low CD4 count, and BDI, the older group remained 3.26 (1.32 to 8.07) times more likely to meet HAD criteria. Adding duration of HIV-1 infection to the model had little effect on this relationship (OR: 2.84 [1.12 to 7.24]). This analysis was repeated for both self-reported CD4 lymphocyte nadir count and duration since CD4 nadir occurred. Each had negligible affect on the OR. Among individuals with HAD, only 1/13 (7.7%) of younger compared to 10/26 (38.5%) of older individuals were classified as moderate or greater in severity using the NEAD-based staging ($p = 0.063$).[25]

Risk factors for dementia among older participants

In a multivariate model including the above covariates and adding age, meeting HAD criteria was significantly associated with a low CD4 lymphocyte count (OR: 7.13 [1.80 to 28.23]) and BDI score (OR: 1.07 [1.01 to 1.15]) among older participants. Age was not associated with HAD within the older group ($p = 0.439$); however, 85% of older individuals were less than 60 years old. Other assessed factors, including CD4 nadir, duration of HIV-1 infection, and duration of time since CD4 nadir occurred, did not show significant associations with HAD among older participants.

Discussion

The Hawaii Aging with HIV Cohort was designed to capture a representative set of individuals in Hawaii living with HIV-1. The demographic constitution of the cohort closely matches that reported by the Hawaii State Department of Health regarding sex, ethnicity, risk profile, and distribution by island, suggesting a modest degree of representative recruitment.[29] In this cohort, older age is associated with an increased risk of HAD after adjusting for other important differences between groups. A trend for greater severity of HAD is also observed. While based on a relatively small number of participants with HAD, these findings add strength to the previous assertions by confirming epidemiologic observations in a structured research protocol designed to test cognition across age groups.

The overall rate of MCMD in this cohort is 36%, somewhat higher than rates described in other seropositive populations in the post-HAART era.[6] In our cohort, this higher frequency may represent not only the changing epidemiology of HIV-1-related cognitive impairment but also an added contribution associated with aging. Given the high degree of reliance on neuropsychological testing abnormalities in our research case definition and only one time point of testing, it is also possible that this rate overestimates true MCMD in the cohort. Longitudinal data are being acquired. Older individuals are also less likely to have normal neurocognitive test findings, although many participants in both groups had only mild abnormalities on neuropsychological testing, insufficient to meet MCMD criteria. These mild abnormalities may represent subtle neurocognitive impairment associated with HIV-1 or

limitations in the normative data. Our analysis was not designed to characterize subtle neuropsychological findings; however, we are currently acquiring additional data from seronegative controls to address this issue.

The high frequency of comorbid illness among seropositive participants is exemplified by the rates of "possible" compared to "probable" modifiers to our research diagnoses. Coexisting factors were expected and have been described in other HIV-1 cohorts.[6,11] In our study, commonly identified examples of such confounders included the following: motor or sensory findings on examination that could have affected testing (14.3% of possible cases), high degree of depressive symptoms or situational stressors (45.5% of possible cases), and past or present substance abuse (66.2% of possible cases). More than one confounder was identified in 44.2% of possible cases. While our protocol required both the presence of such cofactors and some suggestion that it could have affected testing, it is possible that this categorization was overly conservative, thus overestimating the contribution of these factors. The frequency of such factors supports a multifaceted etiology to cognitive impairment among most HIV-1 patients and limits our ability to isolate pure age or HIV-1 effects.

The etiology of the observed increase in HAD associated with older age is not clear. Important factors not identified could be critical. While speculative, mechanisms common to other degenerative diseases, such as AD, could contribute to a greater degree of cognitive impairment.[30] In addition, characteristics of seropositive patients who survive into advanced age (not age itself) may be important mediators. For example, factors associated with HIV-1 infection prior to HAART, such as prolonged or greater past immunosuppression, could be vital. In such cases, HAD may have been present prior to immune reconstitution and could contribute to increased prevalence (rather than incidence) of HAD.

Comorbid illness could also appreciably modulate frequency of HAD in older patients where coexisting diseases are more prevalent.[31] These factors could explain the unexpected lack of correlation between duration of HIV-1 and HAD among older participants. Historical data in our study are limited by a potential recall bias and diagnostic lag bias among older seropositive participants.[32] Taken together, these hypotheses can be understood using a cerebral reserve model of HAD in older individuals.[33] In this model, multiple factors such as increased prevalence of comorbid illness among older patients, presenile presentation of CNS degenerative disorders, and differential responses among older and younger patients to the chronicity of immune activation and duration of infection prior to HAART each may contribute to an increased risk of neurologic pathology, decreased cerebral reserve, and increased risk for clinical neurocognitive impairment among older seropositive patients.

Several limitations to this work need to be considered. The AAN HAD criteria were developed before the widespread use of HAART and before aging became an emergent issue in HIV-1 care. It is possible that the characteristics of cognitive impairment in the post-HAART era and particularly among older adults differ, potentially decreasing both sensitivity and specificity of these criteria. Some HAD participants had marked neurologic and neuropsychological testing abnormalities sufficient to meet HAD diagnostic criteria yet lacked confirmation of cognition-related functional decline in work, IADLs, or ADLs. However, important limitations in assessing functional change impair our ability to objectively capture these data, particularly among patients who are retired or otherwise no longer working. In fact, most of such individuals within our cohort were no longer working (82%), typically due to other HIV-1-related concerns, and 63% reported receiving disability coverage. Many individuals had changed their work status before HAART-associated immune reconstitution and had not been re-challenged with a similar work experience, limiting their ability to assess work capabilities. In some cases, individuals endorsed functional impairment but indicated a noncognitive etiology. Consequently, a change in ADLs and IADLs due to noncognitive aspects of HIV may confound

our ability to identify changes associated with cognition. Further, many participants were unwilling or unable to provide appropriate proxy contacts for reporting of function due to confidentiality issues. This limits our ability to identify objective changes in ADLs and IADLs. Longitudinal follow-up of these individuals will further clarify our findings.

The normative data used in this study are from several sources to maximize goodness of fit to our cohort. All normative data were acquired on the mainland United States rather than in Hawaii, increasing the risk of a possible ethnicity/acculturation bias. Adjusting for ethnicity did not significantly affect our statistical results; however, limitations exist in using this approach. Self-identified ethnicity may not fully capture variation among normative data across populations and across age groups, although addition of education should decrease this potential risk. An interaction between age and race may further confound our findings whereby normative data are more appropriate for younger compared to older non-Caucasian populations (cohort affect). Further research into culture and ethnicity appropriate normative data is needed. We are currently capturing matched data in seronegative populations in Hawaii to address a need for local normative data and more appropriate data for our older HIV subset. As the HIV population in the United States ages, it may be important to expand current normative datasets for neuropsychological measures commonly used in HIV populations to include a greater representation of older age groups.

Future analyses will address other covariates when a larger sample of participants has been enrolled. Medication use, for example, will be further evaluated to assess HAART class affects. Evaluation of coexisting medical conditions would be useful, particularly age-associated and antiretroviral medication-associated cerebrovascular risk factors. Ischemic disease may be particularly concerning due to attenuated protective astrocytic activation in response to ischemic injury in older compared to younger human brains.[34]

As we enter the third decade of HIV-1 treatment in the United States, encountering patients with advanced age and HIV-1 will become increasingly common. These data suggest increased frequency of cognitive dysfunction among older seropositive patients. Based on our current knowledge of HAD, this may have implications for mortality, morbidity, and functional life expectancy. Future research should investigate the underlying etiologies and search for modifiable risk factors to decrease morbidity in this unique and emerging population.

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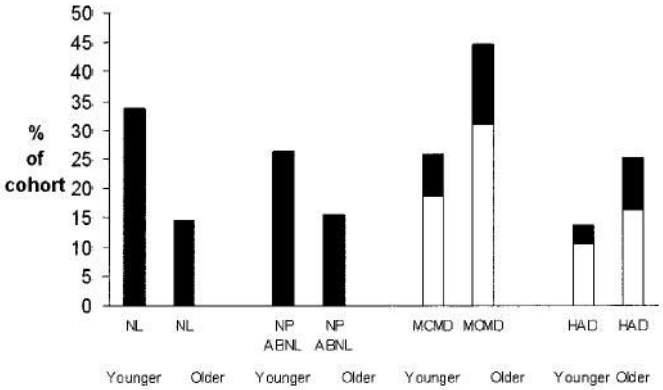

Figure.

Frequency of NP abnormalities (NP Abnl), mild cognitive motor disorder (MCMD), and HIV-1-associated dementia (HAD) in older compared with younger seropositive subjects. (black square) = Probable cases; (white square) = possible cases.

Table

Baseline demographics

Characteristics	Younger group	Older group	*p* Value
Sample size, n	95	103	
Mean age, y, mean ± SD	34.9 ± 4.74	55.4 ± 4.85	
No. (%) male	70 (74)	94 (91)	<0.01
Years living in Hawaii, mean ± SD	16.7 ± 2.6	19.7 ± 16.1	0.36
Education, n (%)			<0.01
HS or less	32 (34)	17 (17)	
Some college	49 (47)	32 (31)	
College or greater	16 (17)	54 (52)	
Risk category			<0.01
MSM only	51 (54)	76 (74)	
IVDU only	0	1 (1)	
Heterosexual only	28 (29)	10 (10)	
More than one	10 (11)	15 (15)	
Ethnicity			<0.01
White	37 (39)	71 (69)	
Asian Pacific Islander	39 (41)	23 (22)	
Hispanic	9 (9)	4 (4)	
Other	10 (11)	5 (5)	
Medical parameters			
Current CD4 count	430 ± 237	473 ± 269	0.51
Nadir CD4 count	253 ± 227	196 ± 155	0.22
Years since CD4 nadir	3.0 ± 3.1	5.1 ± 3.1	<0.01
Years since 1st HIV-1-1 test	7.6 ± 5.5	11.9 ± 5.0	<0.01
Detectable viral load	57 (60)	54 (52)	0.32
Log viral load	3.2 ± 1.5	2.7 ± 1.2	<0.01
Currently on ART	64 (67)	80 (78)	0.2
Current substance dependence	10 (11)	8 (8)	0.63
BDI score	8.7 ± 7.0	9.1 ± 7.7	0.93

HS = high school; MSM = men who have sex with men; IVDU = IV drug use; ART = antiretroviral therapy; BDI = Beck Depression Inventory.