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Older individuals with HIV infection have greater memory deficits than younger individuals

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Abstract

Objectives—The prevalence of HIV-associated neurocognitive disorder (HAND) remains persistently high in the era of combination anti-retroviral therapy (cART). We aimed to characterize the pattern of neurocognitive dysfunction in older subjects with HAND, in particular amnestic versus non-amnestic impairment.

Methods—106 subjects from the Johns Hopkins University NIMH Clinical Outcomes cohort underwent standardized neuropsychological (NP) testing between November 2006 and June 2010. We examined performance in seven cognitive domains (memory, attention, speed of processing, visuospatial, language, motor and executive). Older subjects were defined as age > 50 years at the time of NP testing. Subjects were diagnosed with HAND according to established criteria, and dichotomized into amnestic cognitive impairment or non-amnestic cognitive impairment, with deficit defined as z-scores < −1.5 for the verbal and non-verbal memory domains.

Results—There were 32 older subjects with a mean age (SD) of 54.2 (2.8) years, and 74 younger subjects, 43.7 (4.3) years. Older age was associated with a 4.8 fold higher odds of memory deficits, adjusted for potential confounders (p=0.035) identified *a priori*. With age modeled as a continuous covariate, every 1-year increase in age was associated with a 1.11 fold higher odds of memory deficit (p=0.05).

Conclusion—There was a higher proportion of amnestic cognitive impairment among older subjects than younger subjects with HIV infection. Neurodegenerative processes other than those directly due to HIV may be increasingly important as individuals with chronic HIV infection and HAND survive into older age.

Search terms

HIV infection; cognitive impairment; memory impairment

Introduction

Despite successful immune reconstitution and powerful therapuetic effect of combination anti-retroviral therapy (cART) both systemically and in the CNS, the overall prevalence of HIV-associated neurocognitive disorder (HAND) persists, albeit with significant reductions in the severe form HIV-associated dementia.[1] Improved survival with cART has substantially increased the number of older individuals living with HIV infection. According to the Center of Disease Control and Prevention (CDC), in 2005, individuals older than 50

years old accounted for 24% of those living with HIV infection, an increase from just 17% in 2001. Older adults (>50 years old) account for 15% of new HIV/AIDS diagnoses.[2]

In high-income countries, older individuals with HIV infection, even if optimally treated with cART, may develop neurological dysfunction. There are 2 potentially overlapping neuropathogenic explanations: (i) the synergism/combination effects of chronic HIV infection and co-morbidities resulting in worsening cognitive deficits effects greater than the sum-total of individual factor, or the 'accelerated aging' or (ii) 'accelerated neurodegenerative processes' whereby there is speeding up of the aging processes in the presence of chronic HIV infection, with early onset premature manifestations of cognitive deficits. Both co-morbidities including cardiovascular risk factors (e.g. metabolic syndrome, hypertension, smoking, hyperlipidemia), atherosclerosis as measured by carotid intimal thickening,[3] and putative accelerated neurodegenerative processes e.g. abnormal β/A4 amyloid plaques have been reported to contribute to the pathogenesis of cognitive impairment.[3, 4] APOE ε4, an established risk factor for late-onset Alzheimer's disease (AD), was increased in older individuals with HAND, when compared to younger individuals.[4,5]

There is only sparse clinical data on the pattern of neurocognitive deficits between the younger and older individuals with HAND. The pattern of neurocognitive impairment in the pre-cART era was consistent with a subcortical dementia characterized by psychomotor slowing presenting as a combination of altered motor function (e.g. slowed movement, altered gait), behavior (apathy, irritability, emotional lability) and cognition (e.g. attention, concentration, memory, speed of processing, language)[5]. While one study in the early post-cART era found no difference in the pattern of cognitive impairment when compared with pre-cART era,[6] Cysique *et al* found improvement in immediate attention, verbal fluency, visuoconstruction deficits but a decline in complex attention and learning efficiency comparing post-cART to pre-cART cohorts.[7]

Sacktor *et al* compared neuropsychological test profiles between younger (<50 years) and older (> 50 years) individuals with HIV infection (with and without cognitive impairment) and reported that age was associated with worse performance in memory, executive functioning and motor performance in all subjects with and without cognitive impairment, and age was associated with worse performance only in executive functioning among subjects with dementia. The study concluded that the neuropsychological profile of older individuals with HAD was different from that seen in AD.[8] The comparison between older and younger subjects was adjusted for education only, and no multivariate regression models were performed.

The hallmark of AD and its precursor mild cognitive impairment (MCI), especially the amnestic subtype (aMCI) is memory deficits. Older age is the most significant risk factor for aMCI and AD. We hypothesized that older individuals with HAND will have more memory deficits than younger individuals due to the combined effect of co-morbidities and chronic HIV infection, as well as accelerated neurodegeneration, on a brain with limited reserve because of the chronic effects of HIV infection.

Methods

The Johns Hopkins University Institutional Review Board approval was obtained for the study. Written informed consent was obtained from every participant.

The Johns Hopkins University NIMH Center Clinical Outcome cohort is an on-going prospective clinical outcomes study based in Baltimore, to evaluate biologically valid outcome measures for epidemiological research and clinical trials in HIV-associated

cognitive disorders. Exclusion criteria included (i) major active psychiatric illness including schizophrenia, bipolar disorder or major depression, (ii) major systemic illness including active central nervous system infections, major stroke or other CNS pathologies for example multiple sclerosis, and (iii) history of severe head trauma. The primary language was English for all participants. Subjects were recruited via referral from HIV clinics, HIV community organizations and advertisements in local newspapers. Subjects were followed every 12 months with neuropsychological testing.

Subjects enrolled between November 2006 and June 2010 were analyzed for this study. Cross-sectional analysis was performed based on neuropsychological findings results from their last visits. Subjects were dichotomized to younger (<=50 years), and older (>50 years) age-category. Patient demographics were obtained, and all subjects underwent a clinical evaluation that included a medical interview and neurological examination. Patient history and medical records were reviewed to determine duration of HIV infection, CD4 nadir and current counts, current HIV RNA levels in plasma and CSF, co-morbidities including substance abuse, hepatitis C, depression, as well as cART use. All subjects underwent neuropsychological testing. The neuropsychological test battery included: i) Verbal memory: Rey auditory verbal learning test, RAVLT (immediate recall, recognition, delayed recall)[9]; ii) Visual memory: Rey-Osterreith Complex Figure (delayed),[10] Symbol Digit: iii) Language: F, A, S verbal fluency test; iv) Information processing and psychomotor speed assessment: California Computerized Assessment Package, Digit Symbol Modalities test; v) Executive functioning: Trail-making test B,[11] vi) Motor: Grooved pegboard, timed gait; and vii) Visuoconstruction: Rey-Osterrrieth Complex Figure (copy).[10]

Neuropsychological testing was administered by site staff that received standardized training from an experienced neuropsychologist.

The normative data used to define neuropsychological test abnormalities in HIV+ individuals with < 12 years of education were from the AIDS Linked to the Intravenous Experience study (ALIVE) cohort which included predominantly African-American HIV+ and HIV- intravenous drug users with a similar demographic background to our study subjects.[12] For Frascati classification of HAND, cognitive impairment was defined by <−1.0 SD on z score. Cognitive domain composite scores were calculated by averaging z-scores of each of the components of the neuropsychological testing. Standard Frascati classification was used. Subjects were accordingly categorized into normal, asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia.

For memory deficits, the cut-off of impairment used was <−1.5 SD, consistent with the literature in MCI and AD. Memory deficit was defined by <−1.5 SD if either one or more of 4 tests: RAVLT (immediate recall, recognition, delayed recall) or Rey Complex Figure (delayed)[10] was abnormal.

Statistical methods

Statistical analysis was completed on STATA version 11 (StataCorp, College Station, Texas, USA). Baseline demographics and clinical characteristics between the younger and older subjects were compared using t-test (continuous variables) or chi2 test (non-continuous variables). The association of age with memory deficit was evaluated using logistic regression model for age category (older vs. younger); as well as age as age modeled as a continuous covariate. Multivariate regression was fitted for potential confounders indentified *a priori*. The confounders fitted in the multivariate model included gender, race/ethnicity, education, duration of HIV infection, nadir and current CD4 nadir counts, current HIV RNA levels in plasma and CSF, hepatitis C, depression and current cART use. All statistical tests were performed at the two-tailed 5% level of significance. P values of <=0.05

was considered significant. Ninety-five percent confidence interval was constructed for estimation of effects (regression coefficients).

Results

The results are presented as mean (SD). There were a total of 106 subjects, 74 younger subjects with a mean age of 43.7 (4.3) years, and 32 older subjects with a mean age of 54.2 (2.8) years. This cohort was comprised predominantly of African-American males, with a large majority reporting a history of substance abuse. The demographics and clinical characteristics are presented in Table 1. Apart from the mean age difference between the 2 dichotomized groups, log plasma HIV RNA levels was significantly higher in the younger group when compared with the older group. The duration of HIV infection trended longer in the older group, 15.1 (4.6) years, compared to 12.3 (5.8) years in the younger group, consistent with a lower nadir CD4 counts in the older group (a surrogate for duration of HIV infection), but the differences were not statistically significant.

The overall rate of HAND was 84.9% (90/106 subjects) in this cohort. Thirteen (17.6%) younger subjects and 3 (9.4%) older subjects who had normal neurocognitive performance were excluded in subsequent analyses. There were 25 (33.8%) younger subjects with memory impairment, compared to 16 (50%) older subjects, p=NS. By the Frascati HAND classification, the proportion of subjects demonstrating memory deficit in each stage trended higher in the older group, although not statistically significant. Across both groups, memory impairment was most prominent in HAD. Almost 2/3 of older individuals labeled ANI demonstrated memory deficits, compared to only about 1/3 of younger individuals with ANI, although this did not achieve statistical significance.(Table 2)

The component of memory deficits by neuropsychological testing showed an overall trend of worse performance across all memory testing in older subjects, reported as mean z score (95% confidence interval). Rey auditory verbal learning test (RAVLT) –delayed recognition was the most affected with an average z score of −2.5SD (−3.67, −1.25) in older subjects; compared to younger subjects of −1.1 (−1.7, −0.6). Delayed recall in RAVLT was significantly lower in older subjects −0.3 (−0.7, 0.1) compared to younger subjects 0.3 (0.1, 0.5), but did not meet the definition of impairment of mean z score <−1.5SD.

In a multivariate regression model analysis, older age (>50 years) was associated with a 4.8 fold higher odds of memory deficits, adjusted for race/ethnicity, gender, years of education, nadir and current CD4 counts, log plasma HIV RNA levels, duration of HIV infection, depression, anti-retroviral therapy and chronic hepatitis C. Nadir CD4 count was not associated with increased odds of memory deficit. Modeling age as a continuous covariate, every 1-year increase in age was associated with 1.1 fold increase odds of memory deficit (p=0.037). When substance abuse (as a binary covariate) was added to the above model, the association of older age to memory deficit was attenuated to 4.13 fold higher odds (p=0.052); but was not a significant confounder. Adjusting for substance abuse may not yield a better estimate of the true association of age on memory deficit in this cohort with HAND, as dichotomizing a history of substance abuse as present/absent underestimates the complexity of substance abuse (types, duration, quantity) as a covariate.

Discussion

Our study demonstrated that (i) older subjects with HIV infection was associated with greater memory impairment, (ii) older subjects with HIV infection demonstrated memory impairment comparable to deficits reported in the literature of older individuals without HIV infection, albeit at an earlier age of onset in the former group. (iii)the pattern of memory

deficits mimics that of MCI/AD spectrum. Verbal memory was more affected, with relative sparing of the visual memory. There was a marked deficit observed in delayed recognition on RAVLT testing with older age. Our clinical findings supported other molecular and histopathological[4, 13] studies that suggested an overlap and convergence between HAND and aMCI/AD in aging in older subjects with HIV infection. This is the first study to demonstrate significantly higher odds of memory deficits in older subjects with HAND.

Our findings contrasted with an earlier study which showed no increase in memory deficit in older subjects with HAD.[8] This difference may be due in part to the inclusion of all subjects with HAND in our analysis, regardless of phenotypic severity, and the substantially larger proportion of memory impairment in milder forms of HAND among older subjects as observed in our study. About 2/3 of older subjects with ANI, and about 1/3 with MND had memory impairment. The trend of a high proportion of memory impairment in ANI among older subjects may suggest substantial roles of accelerated neurodegeneration and an Alzheimer's-like pathology resulting in cortical-pattern deficits, over the effects of HIV infection and HIV-associated neuroinflammation. The majority of older subjects in this study were 'survivors' of the initial AIDS epidemic in the 1980s, either as long term non-progressors or as those who had a slower progression of their HIV infection. Only a small proportion of older subjects had a short duration of chronic HIV infection, first diagnosed in older age. An analysis of older individuals, with comparable duration of infection to younger individuals may tease out the effects of age and aging on neurocognitive impairment. It is possible that older subjects with shorter duration of chronic HIV infection, diagnosed in the post-cART era and optimally treated, may present with a more 'cortical' pattern of neurocognitive impairment, suggesting the predominant pathology of neurodegeneration from AD-like pathology. Elucidating underlying mechanisms of neuropathology is important because of the therapeutic implications.

In the general population of adults outside the context of HIV infection, the estimated prevalence of MCI was 19.2% for ages 65–74 years, 27.6% for ages 75–84 years, and 38% for ages 85 years and older, among community dwelling African American residents,[14] while another study estimated 10% in those ages 70–79, and 25% in those ages 80–89 years.[15] The annual progression of MCI to dementia has been quoted to be around 12–14% per year, or 56% conversion to dementia, and 46% to AD over 4 years.[16] This contrasts with normal older adults who have an annual dementia rate of 1–2% per year. The progression and clinical trajectories of HAND are variable. A recent study from the 6 university-affiliated CHARTER cohort demonstrated that 22.7% of subjects declined, 61% remained neurocognitively stable, and 16.5% improved among 437 subjects followed up over 18–42 months.[17] Individuals with ANI and MND were more likely to experience neurocognitive decline compared with neurocognitively normal HIV+ subjects.[18] The study identified low CD4 count, severe co-morbidities and absence of cART to be associated with a decline in neurocognition. Memory impairment was not evaluated as an independent predictor of neurocognitive decline.

In our multivariate regression model, there was a strong association between older (>50 years) subjects with HAND and a memory deficit, adjusted for potential confounders. Classic predictors of HAND including low education levels, low CD4 count, high HIV RNA levels, and hepatitis C were not associated with increased odds of memory deficits in our model. These covariates were associated with a subcortical pattern of impairment in HAND, and the lack of its association to memory impairment lent support to the hypothesis of a greater significance of age-associated causes of memory impairment, than direct effects of HIV infection. A lower nadir CD4 count, a surrogate for the duration of HIV infection, trended towards increased odds of memory impairment, but this was only of borderline significance.

Age was the only covariate with a significant association with memory deficits. While aging and MCI in people without HIV infection commonly occurs around age 70+, this process may be accelerated in people with HIV from a vulnerable brain. There are two potential explanations: (i) accelerated aging or neurodegeneration, independent from the sequelae of HIV infection alone, accounting for memory deficits, or possibly (ii) synergistic/combination effects of HIV infection, neuroinflammation and other co-morbidities, leading to memory deficits in older subjects, suggesting heightened susceptibility of HIV patients to Alzheimer-like neurodegenerative processes with aging.

While this is a small pilot study with limitations as discussed below, our findings appeared to accord well with other studies demonstrating an overlap and convergence between AD and HAND. Enhanced amyloid-β (Aβ) generation and reduced A clearance in cART treated HAD suggested potential convergence of pathogenic pathways between HAND and Alzheimer's diseases.[6] Proteomic analyses of HIV patients with and without dementia demonstrated an >90% overlap in candidate proteins common to both HAD and Alzheimer's disease.[7]

The rate of HAND in our study was 84.9%, which was much higher that reported in the literature of 15–50%. We postulated that the high rates of substance abuse in our cohort may have contributed to the high rates of HAND.

There were several limitations of this study. The mean age of our older subjects was younger in comparison to studies of aging in MCI/AD outside the context of HIV; although it was consistent with other HAND studies reflecting the epidemiology of individuals with HIV infection. This was a cross-sectional study, thus no causal relationship could be established. The sample size was relatively small. A control cohort with older individuals without HIV infection was not available in this pilot study design, and this may be addressed in future studies. We also recognize that we combined working memory, learning, and recall into a single "memory deficit" composite. Additional studies are needed to delineate the specific components of learning and memory which are affected in older HIV+ individuals with HAND. In addition, data on vascular cofactors including hypertension, diabetes, hypercholesterolemia, smoking status were not available in this study, and may be addressed in future studies.

For future research, we propose to better characterize the phenotype and pattern of cognitive domain deficits to investigate the presence of a mild cognitive impairment phenotype in an aging HIV cohort. This will help us to (i) better understand the evolution of HAND with aging, and (ii) study the impact of accelerated aging and neurodegeneration especially of the most common pathology, an Alzheimer-like pathology.

In conclusion, there were greater memory deficits observed in older age in individuals with HAND, suggesting possible synergistic/combination effects of HIV infection, neuroinflammation, co-morbidities and accelerated neurodegeneration. Only older age was associated with increased memory deficit in our study. The implication of memory deficits, in particular verbal memory was significant as these findings may help to better assist providers in the management of older individuals with cognitive impairment. The trajectory and progression of ANI and MND need to be further investigated with longitudinal studies.

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Table 1

Demographics and clinical characteristics of participants enrolled in the Clinical Outcome cohort between November 2006 and June 2010

	Younger subjects (n=74) Age<= 50 years	**Older subjects (n=32) Age >50 years**	***p* value**
Age, mean (SD) years	43.7 (4.3)	54.2(2.8)	***<0.0001***
Male, n (%)	50 (67.6)	23 (71.9)	0.660
African American, n (%)	68 (91.9)	29 (90.6)	0.830
Education, mean (SD) years	12.7 (2.2)	13.0 (2.2)	0.569
Duration HIV diagnosis, mean (SD) years	12.3 (5.8)	15.1 (4.6)	0.052
CD4 nadir, cells/mm^3	114.9 (96.9)	79.3 (105.1)	0.112
CD4 current, cells/mm^3	385.5 (201.2)	350.2 (208.7)	0.414
HIV RNA, lg copies/μL	1.47 (1.86)	0.63 (1.49)	***0.029***
CSF HIV RNA, log copies/μL	1.02 (1.56)	0.58 (1.14)	0.259
Beck Depression Inventory	10.5 (9.4)	8.60 (10.0)	0.376
Substance abuse, n (%)	62 (83.8)	24 (77.4)	0.440
Co-morbidities: n (%)			0.826
1. Incidental	24 (32.4)	10 (31.3)	
2. Contributing	49 (66.2)	21 (65.6)	
3. Confounding	1 (1.4)	1 (3.1)	

Table 2

Proportion with memory impairment by Frascati classification

Frascati	Younger, n(%)	Amnestic, n(%)	Older, n(%)	Amnestic, n(%)	*p* value
ANI	25(41.0)	8(32.0)	9(31.0)	6(66.7)	0.070
MND	13(21.3)	3(23.1)	10(34.5)	3(30.0)	0.708
HAD	23(37.7)	13(56.5)	10(34.5)	7(70.0)	0.446
	61	*21*, *p*=0.09	29	16, *p*=0.14	

ANI = asymptomatic neurocognitive impairment

MND = mild neurocognitive disorder

HAD=HIV associated dementia

Table 3

Memory deficits by Neuropsychological testing

Memory domain z scores mean (95% C.I.)	Younger subjects (<=50 years)	Older subjects (> 50 years)	*p* value
RAVLT- immediate recall	0.06 (−0.19, 0.30)	−0.36 (−0.88, 0.16)	0.100
RAVLT-delayed recall	0.31 (0.10, 0.52)	−0.29 (−0.70, 0.12)	***0.005***
RAVLT-delayed recognition	−1.09 (−1.57, −0.62)	−2.46 (−3.66, −1.25)	***0.012***
RCF delayed recognition	−0.28 (−0.55, −0.01)	−0.45 (−0.74, −0.06)	0.814

RAVLT = Rey auditory verbal learning test

RCF = Rey-Osterrrieth Complex Figure

Table 4

Adjusted associations of memory deficits to various covariates

Memory deficit	OR	95% C.I.	*p* value
Age > 50 years	4.75	1.17, 19.26	***0.029***
African American	0.96	0.12, 8.59	0.997
Male	0.88	0.22, 3.45	0.855
Education (years)	1.02	0.73, 1.42	0.927
Nadir CD4 count/10	1.07	1.00, 1.14	0.052
Current CD4 count/10	0.996	0.993, 1.03	0.805
log plasma viral load	1.01	0.65, 1.56	0.958
HIV infection (years)	1.04	0.94, 1.16	0.440
Depression	1.52	0.47, 4.89	0.484
Anti-retroviral therapy	3.17	0.18, 55.01	0.428
Chronic hepatitis C	0.96	0.47, 1.94	0.904

OR = odds ratio

C.I. = confidence interval