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Effects of Nadir CD4 Count and Duration of HIV Infection on Brain Volumes in the HAART Era

Ronald A. Cohen[1], **Jaroslaw Harezlak**[2], **Giovanni Schifitto**[3], **George Hana**[1], **Uraina Clark**[1], **Assawin Gongvatana**[1], **Robert Paul**[4], **Michael Taylor**[5], **Paul Thompson**[6], **Jeffery Algers**[6], **Mark Brown**[7], **Jianhui Zhong**[3], **Thomas Campbell**[7], **Elyse Singer**[6], **Deborah McMahon**[8], **Yuen Tso**[9], **Constantin T Yiannoutsos**[2], **Bradford Navia**[10], and **the HIV Neuroimaging Consortium**

[1]Brown University School of Medicine, Providence, RI, USA

[2]University of Indiana University School of Medicine, Indianapolis, IN, USA

[3]Rochester School of Medicine, Rochester, NY, USA

[4]Robert P, University of, University of Missouri, St. Louis, MO, USA

[5]University of California-San Diego, La Jolla, CA, USA

[6]University of California, Los Angeles, Westwood, CA, USA

[7]University of Colorado: Denver, Aurora, CO, USA

[8]University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

[9]Stanford University School of Medicine, Palo Alto, CA, USA

[10]Tufts University School of Medicine, Boston, MA, USA

Abstract

Background—Cerebral atrophy is a well described, but poorly understood complication of HIV infection. Despite reduced prevalence of HIV-associated dementia in the HAART era, HIV continues to affect the brains of patients with chronic infection. In this study we examine patterns of brain volume loss in HIV infected patients on HAART, and demographic and clinical factors contributing to it. We hypothesized that nadir CD4+ lymphocyte count, duration of HIV infection and age would be associated with reduced cortical volumes.

Methods—Volumes of cortical and subcortical regions in 69 HIV-infected neuroasymptomatic (NA) individuals and 13 with at least mild AIDS dementia complex (ADC) were measured using voxel-based morphometry. Demographic and clinical factors (age, plasma HIV RNA level, current and nadir CD4 count, duration of infection, CNS penetration of antiretroviral regimen) along with their interactions were entered into a regression model selection algorithm to determine the final models that best described regional brain volumes.

Results—Relative to NA, individuals with ADC exhibited decreased total gray matter and parietal cortex volumes and increased total ventricular volumes. Final regression models showed overall cerebral volume, including gray and white matter volume and volumes of the parietal, temporal, and frontal lobes and the hippocampus, were most strongly associated with disease

Address Correspondence: Ronald A. Cohen, PhD, ABPP, ABCN, Neuropsychology, The Miriam Hospital, Alpert School of Medicine, Brown University, Coro Bldg., 3-West, One Hoppin St., Providence, RI 02903, USA rcohen@lifespan.org or Bradford Navia, MD, PhD, Tufts University School of Medicine, Boston, MA, USA bngene@aol.com.

history factors (nadir CD4 and duration of infection). In contrast, basal ganglia volumes were related most strongly to current disease factors, most notably plasma HIV RNA.

Conclusions—These findings indicate that individuals with a history of chronic HIV infection with previous episodes of severely impaired immune function, as reflected by reduced nadir CD4 + lymphocyte count, may be at greatest risk for cerebral atrophy. The pattern of HIV-associated brain loss may be changing from a subcortical to a cortical disease among patients who are largely asymptomatic on HAART.

The advent of highly active antiretroviral therapy (HAART) has dramatically increased survival rate among HIV infected patients (Carpenter *et al*, 2000). Yet, the possibility of developing cognitive dysfunction remains a significant concern, particularly in the context of chronic infection and aging (Sacktor *et al*, 2002). Evidence from clinical and neuropathological studies suggests that HIV continues to have detrimental effects on the brain, even when plasma viral load has been reduced to undetectable levels (Masliah *et al*, 2000; McArthur, 2004; Sacktor *et al*, 2002). Furthermore, recent data suggest that treated patients develop cognitive impairment in setting of HAART, raising concern that CNS complications continue to occur in these patients (Brew, 2004; Dore *et al*, 1999; Thurnher *et al*, 2000; Valcour and Sacktor, 2002; Valcour *et al*, 2004).

Brain atrophy is a well described yet poorly understood complication of HIV infection. Marked structural brain abnormalities were observed in the early years of the HIV epidemic. Studies conducted in the pre-HAART era provided evidence of volumetric brain abnormalities in people with HIV (Aylward *et al*, 1995; Aylward *et al*, 1993; Heindel *et al*, 1994; Jernigan *et al*, 1993). Recent studies continue to show basal ganglia abnormalities among people with HIV compared to healthy controls (Gongvatana *et al*, 2009). However, relatively few brain volumetric studies have been conducted in the setting of HAART, and these are associated with chronic HIV infection. There is some evidence that reduced subcortical volumes and metabolite abnormalities can be found in HIV-infected patients on HAART and are associated with impaired neurocognitive function (Patel *et al*, 2003; Patel *et al*, 2002; Paul *et al*, 2002; Paul *et al*, 2008; Paul *et al*, 2007). Prior to the era of HAART, patients with HIV-associated dementia exhibited cortical atrophy (Heindel *et al*, 1994; Jernigan *et al*, 1993). Several recent findings continue to suggest that cortical atrophy still continues to occur in the HAART era(Thompson *et al*, 2005). Furthermore, structural brain damage incurred as a result of severe immunological compromise at some point in the distant past may increase the vulnerability to neurodegeneration (Brew *et al*, 2008; Valcour *et al*, 2004), and result in cortical changes analogous to premature aging. However, a full understanding of the evolution of CNS injury in cortical and subcortical brain regions in the context of chronic treatment is still lacking.

As an initial effort to examine this issue, volumetric measurements on brain images were obtained from a patient pool of HIV-infected patients followed in a large longitudinal multi-center study designed to assess structural and metabolic effects of HIV infection. We examined the relationship between specific demographic and clinical factors associated with HIV, and brain volume across specific brain regions. We hypothesized that disease history, including duration of infection and CD4 nadir would be associated with reductions in brain volume independent of current viral and immunological status.

METHODS

Clinical Sample

Eighty-two HIV-infected patients enrolled in a longitudinal MRI study of HIV were assessed as part of their baseline examinations. The sample had a larger proportion of men

(84%) than women. Patients came from HIV clinics at three sites (University of Rochester, University of Colorado and Stanford University) and consisted of the first set of individuals for whom brain morphometry data were available. Table 1 summarizes the demographic and clinical characteristics of the sample.

This clinical cohort consisted of individuals who were middle-aged (mean=48.6, SD=7.6 years) and relatively well educated (mean=13.6, SD=2.1 years). Most had been infected for over 10 years (66%) and had a CD4 nadir <50 cells/mL (59%). A majority (80%) of participants were HAART-treated at the time of the study. Accordingly, we observed more intact current CD4 levels (mean=359.3 cells/mL, SD=181.1), and only a small proportion (16%) of participants with detectable plasma viral load.

Thirteen participants (16%) currently exhibited at least mild level of AIDS dementia complex (ADC), according to the Memorial Sloan-Kettering staging system (ADC stage ≥ 1) (Marder *et al*, 2003), while the remaining 69 individuals were neuroasymptomatic (NA).

CNS penetration of each participant's antiretroviral treatment regimen was quantified by assigning a value of 0, 0.5, or 1 to each drug based on published data on CSF concentrations and chemical properties (Letendre *et al*, 2008). The ranks for all drugs in a regimen were summed to yield a CNS penetration effectiveness (CPE) score.

MRI Data Acquisition and Processing

High-resolution whole brain structural images were acquired using a T1-weighted MPRAGE sequence with the following parameters: TE = 3.57 ms, TR = 2730 ms, flip angle = 7°, FOV = 256 × 256 mm, 1 × 1 × 1 mm resolution.

Brain volumes were measured with the Individual Brain Atlases using Statistical Parametric Mapping (IBASPM, (Alemán-Gómez Y., 2006)) toolbox for the Statistical Parametric Mapping 5 (SPM5; Wellcome Department of Imaging Science; www.fil.ion.ucl.ac.uk/spm/) software package running under Matlab. Image processing involved segmentation of individual brain volumes into grey matter, white matter, and CSF compartments, yielding estimated volumes of each compartment along with the total intracranial volume. Segmented brain volumes were normalized via nonlinear registration to the MNI152 template, and grey matter voxels were labeled according to a predefined anatomical atlas (Tzourio-Mazoyer *et al*, 2002). Labeled brain volumes were then inverse-transformed into their native spaces, yielding estimated volumes of specific brain regions according to the atlas labels.

Statistical Analysis

Our goals in the statistical modeling were threefold. First, we tested for a possible difference in brain volumes by ADC stage using ANOVA. Second, we wanted to determine if the disease-specific factors and their interactions (plasma RNA, nadir CD4 count, current CD4 count, duration of HIV infection) and ADC stage were differentially associated with brain volumes using linear regression. Third, we tested if the addition of CPE score to the model selection algorithm accounted for a significant amount of additional variance. Analyses were performed on white matter, ventricular, cortical lobular volumes adjusted for total intracranial volume. All linear regression models were adjusted for sex and ethnicity to account for possible volume differences due to these demographic covariates. All statistical analyses were done using R-2.7.2 (R Core Development System: http://www.r-project.org).

Three separate groups of analyses were performed: 1) gray matter, white matter, and total ventricular volume; 2) frontal, parietal, and temporal lobes; and 3) caudate, putamen, thalamus and hippocampus. Modeling was performed using both main factors and the two-way interactions of disease-specific factors and age.

Final linear regression models for both main effects and the interaction models were selected by minimizing Akaike Information Criterion (AIC) (Akaike, 1974; Burnham, 2002), which balances the model fit and its complexity. Increasing the number of parameters in the models improves their fit to the data, but at a cost of increased complexity. AIC balances the goodness of fit and the number of included covariates by penalizing the number of parameters in the model. The best model is the one with the lowest AIC. This method is more robust than the traditional stepwise selection procedures and produces parsimonious models balancing the goodness of fit and model complexity. The interaction models were compared with the main effects models, and selected only if their fit was better than the main effects models. To ameliorate the selection of models that might contain non-significant variables, we used a bootstrap procedure on the results of the initial fit, and only chose the variables for the final models that were selected in more than 70% of the bootstrapped samples.

RESULTS

Candidate predictors included age in years, duration of HIV infection in years, binary ADC stage variable (0 for ADC < 1, 1 for ADC ≥ 1), binary nadir CD4 variable (0 for ≤ 50, 1 for > 50), binary current CD4 variable (0 for ≤ 400, 1 for > 400), binary plasma HIV RNA variable (0 for detectable, 1 for undetectable level), and binary CPE score (0 for ≤ 1.5, 1 for CPE >1.5).

No significant differences were found on any demographic or clinical factors between the ADC groups ($p > .05$).

Brain Volumes as a Function of ADC Stage

In general, decreased cortical and subcortical volumes were observed in subjects with ADC when compared to NA subjects but these reached significance only for the total gray matter volume ($p = 0.02$), and parietal cortex volume ($p = 0.04$). An increase in total ventricular volume ($p = 0.036$) was also associated with ADC stage (Table 2).

Global Brain Volumes

Variables corresponding to HIV history and current status as well as their interactions were examined for possible associations with different patterns of volume loss in HIV. The clinical, demographic, and HIV disease variables which were associated with each of the global brain volume indices are presented in Table 3. Decreased gray matter volume correlated with lower current CD4 count and a longer duration of HIV infection (adj. $R^2 = 0.267$, $p<0.0001$).

An increase in total ventricular volume was associated with lower nadir CD4 count, undetectable plasma viral RNA, and their interaction, as well as a longer duration of HIV infection, cognitive impairment, and their interaction (adj. $R^2 = 0.191$, $p=0.002$). In particular, patients with low nadir CD4 count and detectable plasma RNA levels had the largest ventricular volume on average amongst the four groups defined by these two variables. With respect to the interaction between ADC stage and duration of infection, cognitively impaired (ADC ≥ 1) subjects with only a short duration of HIV infection and non-impaired subjects with a long duration of HIV infection had larger ventricular volumes when compared to impaired subjects with long duration of HIV infection and non-impaired subjects with short duration of HIV infection ($p < .05$). A decrease in white matter volume (adj. $R^2 = 0.060$, $p=0.05$) was associated only with low nadir CD4 count. There were no additional effects of CPE score in any of the models.

Cortical Area

Several factors contributed to frontal lobe volume, including (adj. $R^2 = 0.233$, p=0.002) nadir CD4 count, current CD4 count, detectable plasma RNA level duration of HIV infection. (Table 4). In addition the following 4 interactions were found: nadir count with plasma RNA level, plasma RNA with current CD4 count, and duration of HIV infection, and nadir CD4 count with duration of HIV infection. Subjects who were infected for a short time (less than 5 years), had a high nadir CD4 count, detectable plasma RNA and low current CD4 count had the largest predicted frontal lobe volume whereas subjects who were infected for a long time (20 or more years), with a low nadir CD4 count, detectable plasma RNA and a high current CD4 count had the smallest predicted frontal lobe volume. In contrast a decrease in temporal lobe volume was associated only with a lower nadir CD4 count (adj. $R^2 = 0.133$, p=0.003), while cognitive impairment and a longer duration of HIV infection contributed to a reduction in parietal lobe volume (adj. $R^2 = 0.150$, p=0.002). CPE was not predictive of any lobe volumes.

Subcortical structures and the hippocampus

Volume of the thalamus (adj. $R^2 = 0.210$, p=0.001) was associated with nadir CD4 count, undetectable plasma RNA level, and their interaction, as well as with age. Younger subjects with lower nadir CD4 count had the smallest volumes (Table 5).

In the basal ganglia, a smaller caudate was associated with plasma viral RNA and cognitive impairment (adj. $R^2 = 0.074$, p=0.042) whereas plasma RNA and a lower current CD4 count were the main factor associated with a decrease in putamen volume (adj. $R^2 = 0.078$, p=0.035). Reduced volume of the hippocampus associated only with a lower nadir CD4 count (adj. $R^2 = 0.081$, p=0.023). There was no statistically significant association found between subcortical volumes and CPE score.

Summary

Across all final models for the brain volumes of interest, low nadir CD4 count and plasma RNA level were associated with volume (6 of 10 regions of interest (ROIs), followed by ADC stage (5 of 10 ROIs), and duration of HIV and age (3 of 10 ROIs).

DISCUSSION

Cerebral atrophy is a common finding in HIV-infected subjects with cognitive impairment that had been described before the widespread use of HAART (Heindel *et al*, 1994). Whether volume loss can persist or occur in the setting of HAART and what factors could contribute to this process have remained unresolved issues. Findings from this study are therefore noteworthy as they suggest a loss of brain volume in the cortical and subcortical regions in the setting of stable treatment and chronic disease, even among neuroasymptomatic subjects. Further, these results showed differences in regional susceptibility to volume loss in response to host and viral factors as well as their interactions, and together provide a framework to further understand structural change in the HIV infected brain in the setting of chronic disease and HAART.

Significant associations were found between clinical indices of disease severity and duration, and a number of different cortical and subcortical brain areas. In particular, two clinical indices reflecting the patients' HIV disease history (duration of HIV infection and nadir CD4+ lymphocytes) were significantly associated with the three global volumetric indices, as well as cortical volumes, suggesting that patients with a history of advanced immune suppression and untreated chronic disease are at greatest risk for these structural changes. Thus chronic HIV infection was the sole variable associated with reduced total

gray matter volume while lower nadir CD4 was associated with reduced white matter volume. The potential significance of these findings is augmented by the fact that age was not associated with cortical volume loss, as might have been expected. In fact, age did not interact with duration of infection, and the correlation between these two indices was weak. The results suggest that the duration of a patient's infection may influence certain brain volumes, independent of other clinical factors, such as cognitive status, viral load, and immunological status.

Similarly nadir CD4 was a significant factor in half the models examined primarily in the cortical regions and the hippocampus, suggesting that a history of advanced immune-suppression may exert a negative effect on brain structure. The reason for this association may be related to the fact that severe immune suppression is generally coupled with greater HIV replication which in turn is strongly associated with HIV infection of the brain. This suggests that early CNS injury may be in part irreversible. The association between history of immune suppression and brain volume has not been previously described in HIV infection and provides further rationale for initiating antiretroviral treatment early in the course of infection.

It is noteworthy that cognitive impairment was associated with reduced volumes in the caudate and parietal lobe, and an increase in the ventricular volume. Abnormalities involving the basal ganglia have been previously reported in HIV-associated cognitive impairment (Ances *et al*, 2006; Paul *et al*, 2008; Paul *et al*, 2007). However, findings in the parietal lobe and ventricular system often associated with Alzheimer's disease suggest that HIV brain disease may be evolving to affect these structures in the setting of chronic infection. Prior FMRI studies of attention in HIV have also indicated parietal dysfunction (Chang *et al*, 2004).

It should be noted that these findings are based on cross-sectional analysis of baseline data. Also, while we had extensive historical information regarding each participant's treatment history, the exact therapeutic regime that each person had been treated with at all points in the past were dependent in part on the recollection of participants. Because we could not verify the historical record of all past medications for each participant, a decision was made not to include this measure in the analyses. Validation of these results will depend on longitudinal studies tracking the effects on brain volume and cognitive functioning relative to possible risk factors (e.g. nadir CD4, duration of infection) identified in this analysis, as well as duration of HAART. Studies of this type may also help to further disentangle the relationship between duration of infection and aging. Furthermore, evidence of an increase in memory and other cognitive impairments associated with degradation of posterior cortical association areas would provide powerful evidence that patients with chronic HIV infection who have sustained severe immunological compromise may be vulnerable to neurocognitive decline and brain changes years later.

The results of the current study indicate that relationships exist between HIV history and current status and the volume of brain regions examined at a single point in time. These observations have potential clinical significance because they reinforce the possibility that HIV-infected patients in the HAART era are vulnerable to brain disturbances, and that specific brain regions remain susceptible to injury and volume loss despite effective treatment. Typically, gross morphometric changes are thought to occur as a late manifestation of neurodegenerative diseases. Yet, in the current study, relationships between HIV factors and brain volumes were observed among patients irrespective of ADC stage. For the most part, patients in this cohort were asymptomatic and well controlled on HAART without current severe immunological compromise. Many of the observed effects relative to

cortical structures appear related to past history of the illness, raising concern that the early and chronic effects of this infection may have an increasing toll on brain structure over time.

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Table 1

Demographic and clinical characteristics of participants in the AIDS dementia complex (ADC) groups (continuous variables reported as mean±SD, and categorical variables as percentages)

	ADC stage		Total
	0 & 0.5	≥1	
N	69	13	82
Gender (% male)	84	85	84
Age (years)	45.5±8.2	49.9±9.5	48.6±7.5
Ethnicity (% Caucasian)	72	62	71%
Education level (% high school or less)	65	77	67
% IV drug use	20	46	24
Duration of infection (years)	12.2±6.1	14.3±7.0	12.5±6.2
CD4 count (log_{10}cells/ml)	2.54±0.24	2.43±0.40	2.52±0.27
Nadir CD4 (log_{10}cells/ml)	1.53±0.51	1.42±0.40	1.51±0.50
% undetectable Plasma RNA viral load	84	85	84
% known on ART at baseline (uninterrupted)	84	62	80
CPE score	1.86±1.00	1.50±0.71	1.81±0.96

Note: The two ADC groups did not significantly differ on any demographic or clinical variables.

Table 2

Brain volumes (mm^3) in HIV-infected patients as a function of ADC stage expressed as mean (SD).

	ADC 0	ADC 0.5	ADC ≥1	Total
Global				
White Matter	464.37 (43.89)	452.54 (41.74)	464.44 (71.26)	460.2 (48.11)
Gray Matter*	716.68 (70.03)	676.60 (61.90)**	675.05 (71.46)	695.9 (69.70)
Ventricles	436.66 (81.55)	446.02 (70.36)	493.00 (79.35)**	448.9 (78.97)
Cortical				
Frontal	138.92 (19.52)	132.22 (16.43)	129.66 (14.16)	135.08 (17.93)
Parietal	60.55 (6.82)	59.30 (8.67)	56.71 (6.74)	59.50 (7.54)
Temporal	118.24 (12.97)	113.99 (12.18)	113.54 (10.20)	115.99 (12.35)
Subcortical				
Caudate	6.44 (1.15)	5.99 (0.96)	5.70 (1.01)**	6.16 (1.09)
Hippocampus	7.16 (1.04)	7.06 (0.78)	6.75 (0.94)	7.06 (0.94)
Putamen	7.56 (1.46)	6.87 (1.09)**	6.85 (0.89)	7.20 (1.29)
Thalamus	7.70 (1.22)	7.34 (1.05)	7.20 (0.88)	7.50 (1.12)

Note:

* indicates significant group differences F-test (2,79) at 0.05 significance level. Standard deviations are presented following the means for each measure.

** indicates significant difference between the given group in the table and the “ADC 0” group at 0.05 significance level.

Table 3

Significant clinical predictors of global brain volumes.

	Variable	Coefficient	p	Adjusted R^2	Model p
White Matter				0.0605	0.0490
	Nadir CD4	0.0111	0.0290		
Gray Matter				0.267	<0.0001
	Current CD4	23.16	0.0930		
	Duration of infection	−2.68	0.0280		
Ventricles				0.1911	0.0023
	Nadir CD4	−0.0617	0.0110		
	Plasma RNA	−0.0382	0.0160		
	ADC stage	0.0799	0.0056		
	Duration of infection	0.0023	0.0064		
	Nadir CD4 x	0.0556	0.0323		
	Plasma RNA				
	ADC stage x	−0.0045	0.0166		
	Duration of infection				

Note: Factor1 × Factor2 denotes the interaction of the factors.

Table 4

Significant clinical predictors of cortical volumes.

	Variable	Coefficient	p	Adjusted R^2	Model p
Frontal lobe				0.2330	0.0017
	Nadir CD4	0.0256	0.0006		
	Plasma RNA	−0.0175	0.0669		
	Current CD4	−0.0190	0.0022		
	Duration of infection	−0.0015	0.0153		
	Plasma RNA x Current CD4	0.0209	0.0019		
	Nadir CD4 x Plasma RNA	0.0128	0.0392		
	Nadir CD4 x Duration of infection	−0.0008	0.0263		
	Plasma RNA x Duration of infection	0.0015	0.0166		
Temporal lobe				0.1334	0.0026
	Nadir CD4	0.0038	0.0027		
Parietal lobe				0.1497	0.0023
	ADC stage	−0.0026	0.0778		
	Duration of infection	−0.0002	0.0835		

Note: Factor1 × Factor2 denotes the interaction of the factors.

Table 5

Significant clinical and demographic predictors of subcortical and hippocampal volumes.

	Variable	Coefficient	p	Adjusted R^2	Model p
Caudate				0.0737	0.0418
	Plasma RNA	0.8146	0.0126		
	ADC stage	−0.5520	0.0876		
Putamen				0.0785	0.0353
	Plasma RNA	−0.6050	0.1169		
	Current CD4	0.5602	0.0502		
Hippocampus				0.0806	0.0228
	Nadir CD4	0.3851	0.0655		
Thalamus				0.2074	0.0006
	Age	0.0373	0.0144		
	Nadir CD4	1.9749	0.0014		
	Plasma RNA	1.1569	0.0045		
	Nadir CD4 x Plasma RNA	−2.1699	0.0013		

Note: Factor1 × Factor2 denotes the interaction of the factors.