Brain White Matter Hyperintensities, HIV Disease, Cognition and Diabetes

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Background

Since the onset of combination antiretroviral therapy (cART) use, the incidence of HIV-associated dementia and of HIV encephalitis have fallen dramatically. The present study investigates the extent of white matter hyperintensities (WMHs) among individuals with HIV disease, and factors that predict their presence and their impact on psychomotor speed.

Materials & Methods

322 men participating in the Multicenter AIDS Cohort Study (MACS) (185 HIV-infected, age: 57.5+6.0) underwent MRI scans of the brain. T1-weighted MP-RAGE and T2-weighted Fluid Attenuated Inversion Recovery (FLAIR) images were obtained and processed using an automated method for identifying and measuring WMHs. An automated pipeline was used to segment WMHs on the T2w FLAIR images. First, individual cerebral and cerebellar white matter masks were created in the T2w FLAIR image space using SPM12. Second, seeds of WMHs were identified and an automated clustering method was used to cluster WMHs within the cerebral white matter masks on the T2w FLAIR images. The automated segmentation method ranks the identified WMH seeds based on their intensities, iteratively updates the seeds, creates and combines white matter clusters into the final WMH segmentation on the Z-transformed FLAIR image.

WMH burden was expressed as the $\log_{10}$ transformed percentage of total white matter that was abnormal.

Results

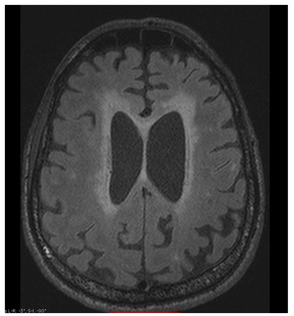
TABLE 1: Characteristics of Study Sample

	HIV Uninfected	HIV Infected	Statistic[1]
N =	137	185	
Age[2]	59.0 (6.95)	56.4 (4.97)	.49
Education[2]	16.6 (2.45)	16.8 (9.0)	-.03
CES-D[2]	8.91 (11.1)	9.76 (10.4)	-.08
Caucasian[3]	83.2 (114)	70.8 (131)	2.10 (1.2 – 3.6)*
Cohort[3]	19.0 (26)	33.0 (61)	2.04 (1.18 – 3.5)*
Diabetes[3]	13.9 (19)	14.6 (27)	1.06 (.56 – 2.0)
Hypertension[3]	45.3 (62)	44.3 (82)	.96 (.62 – 1.5)
eGFR[2]	82.2 (15.6)	84.4 (17.6)	-.13
HbA1c[2]	5.81 (1.2)	5.73 (.98)	.08

1) Cohen's d or Odds Ratio (± 95% Confidence Interval)
2) Mean (± S.D.)
3) Percent (Number) condition present
*p<.05
Abbreviations: CES-D-Center for Epidemiological Studies Depression; eGFR- estimated glomerular filtration rate; HbA1c- hemoglobin A1c.

TABLE 2[1]: Unadjusted Correlations Between WMH volume[2] and Covariates

Age	.19*
Education	-.001
Race[3]	.12*
Recruitment Cohort	.05
CES-D score	-.05
HIV Infected	-.02
Diabetes	.12*
Years Diabetic	.13[4]
HbA1C	.03
Hypertension	-.02
Years Hypertension	-.06[5]
eGFR	-.13*
Carotid IMT	
Coronary Artery Calcium	.12*



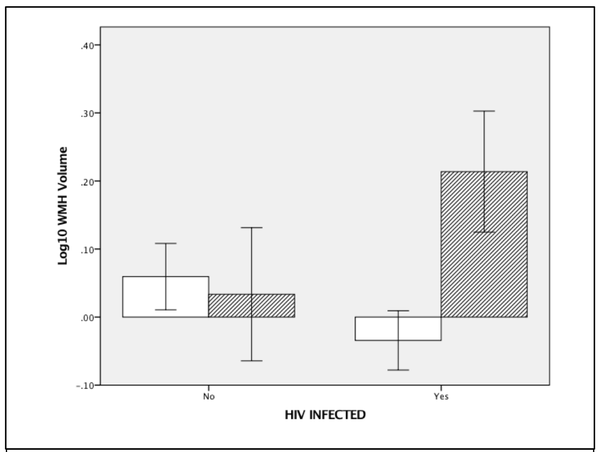
The results of the analysis of WMH volume adjusting for critical covariates are shown in Table 3. In the first model we entered eGFR, coronary calcium (CAC), and carotid artery IMT, and none of these were statistically significant. However, when we added diabetes to the model, eGFR and CAC were now statistically reliable (Model Two). In Model Three we added variables related to age, race, education, and cohort, and the impact of race and age on prediction attenuated the impact of the other variables. HIV disease did not contribute significantly to predicting the volume of WMHs.

TABLE 3: Adjusted Models to Predict WMH Volume (Standardized Regression Coefficients) (n=322)

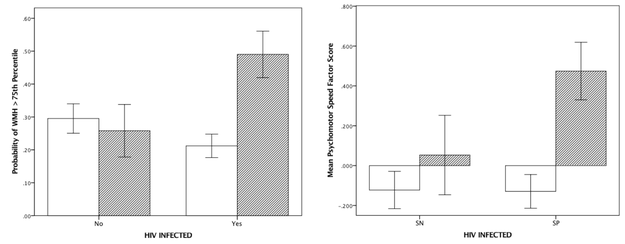
	Model 1	Model 2	Model 3	Model 4
eGFR	-.11	-.11*	-.10	-.10
CAC	.11	.12*	.07	.07
Cartoid IMT	.06	.04	.01	.001
Diabetes		.12*	.07	.07
Hypertension		-.03	-.04	-.04
Cohort			.02	.02
Education			.004	.004
Race			.14*	.14*
Age			.17*	.17*
HIV Infected				-.01

TABLE 5: Predictors of Psychomotor Speed (n=82)

	Model 1	Model 2	Model 3
Diabetes	.07	.03	.02
HbA1c	.17*	.07	.08
Cartoid IMT	.18*	.07	.07
WMH	.17*	.10	.10
Recruitment Cohort		.28*	.27*
Race		.21*	.21*
CES-D		.13*	.13*
Age		.29*	.29*
HIV Infection			.04



Log_{10} WMH volumes among seronegative (left) and seropositive (right) men as a function of the presence of diabetes (hashed columns).



Probability of abnormal WMH volume (left-hand figure) as a function of serostatus and diabetes. Mean psychomotor speed (right-hand figure) as a function of serostatus and WMH abnormality.

Conclusions

There are four principal findings from this study. First, there is no association between the volume of WMHs and HIV serostatus in this group of gay and bisexual men either in unadjusted or adjusted analyses. Second, there is a significant association between WMH volume, diabetes, kidney function, and coronary artery calcium deposition, but only until age and race are accounted for. Third, there is a significant interaction between HIV serostatus and diabetes such that those individuals who are both diabetic and HIV-infected have significantly greater volumes of WMHs than nondiabetics and individuals without HIV disease. Finally, WMH volume, but not HIV infection, was a significant predictor of psychomotor speed.

The HIV-by-Diabetes interaction might help explain apparent HIV-related cognitive impairment (esp. psychomotor slowing), while in fact poorer performance among infected individuals may be due to the greater extent of WMHs, and not to their HIV infection. From the perspective of treating physicians the greater volume of WMHs among the HIV-infected individuals suggests that physicians should screen for and aggressively treat diabetes and pre-diabetes among their patients with HIV disease.

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