CORTICAL ATROPHY AND WHITE MATTER HYPERINTENSITIES IN HIV INFECTION

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Abstract

Background: In normal elderly individuals (age greater than 65 years) presence of brain white matter hyperintensities is associated with cortical atrophy, particularly of the frontal lobes. As HIV-seropositive individuals experience increase longevity due to highly active antiretroviral therapy it is likely they will also develop typical aging related changes in brain structure such as white matter hyperintensities. The aim of this study was to determine the relationship between white matter hyperintensities and brain cortical gray matter volumes in human immunodeficiency virus, type 1 (HIV) seropositive individuals.

Methods: Voxel-based-morphometry was used to compare cortical gray matter volumes between 62 HIV seropositive participants in the Hawaii Aging with HIV cohort study, 30 with moderate brain white matter hyperintensities and 32 with minimal or no white matter hyperintensities. The Hawaii Aging with HIV Cohort study included two groups of HIV seropositive individuals, an older group comprised of individuals with age greater than 50 years old, and a younger group comprised of individuals with age from 20-39 years old.

Results: Presence of moderate brain white matter hyperintensities was associated with decreased cortical gray matter volumes in the frontal lobes bilaterally ($p < 0.05$) in HIV seropositive individuals.

Conclusions: The findings of this study suggest that presence of moderate brain white matter hyperintensities is associated with frontal lobe cortical atrophy in HIV seropositive individuals. These results are supportive of the hypothesis

that the frontal lobes have greater susceptibility to the effects of small vessel ischemic vascular disease than other brain regions.

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1. Introduction

The changing demographics of HIV-1 infection in the USA

Human immunodeficiency virus, type 1 (HIV) infection in older patients (age > 50 years) is becoming increasingly common in the United States and throughout the world (1). Widespread use of highly active antiretroviral therapy (HAART) has changed the age-related demographics of HIV infection by increasing long term survival and shifting the age distribution of HIV infection towards the elderly (Figure 1). Current estimates suggest there are between 60,000 to 90,000 older adults living with acquired immune deficiency syndrome (AIDS) in the United States and the number of older people newly infected with HIV may be increasing as well (2-4). Additionally, the rate at which new HIV infections are occurring may be increasing faster among the elderly compared to younger individuals. For example, in the 1990's the number of persons newly diagnosed with AIDS at elderly ages increased at approximately twice the rate of new AIDS cases in young people (2). Consequently, older adults now account for up to 15% of all AIDS cases, a percentage that is expected to continue to increase in the future (2).

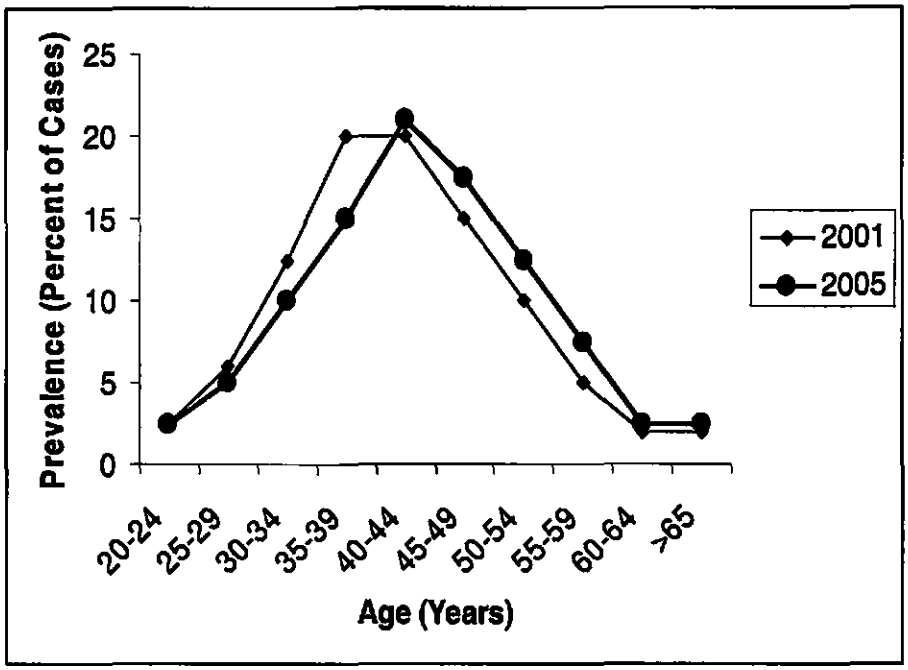

Figure 1: Age distribution of HIV prevalence in the USA in 2001 and 2005. The line with small black dots indicates HIV prevalence in the USA in 2001 by age groups, and the line with larger black dots indicates HIV prevalence in the USA in 2005 by age groups.

Definition of white matter hyperintensities and relationship to HIV-1 infection

On gross examination the brain can be divided into "gray matter" regions comprised primarily of nerve cell bodies and "white matter" regions comprised of nerve axons including the surrounding myelin sheath and glial cells that help to support the nerve cells by maintaining the extracellular environment. The "white matter" appears white on gross pathological examination of the brain due to the presence of lipid-rich myelin sheaths that surround the nerve cell axons. The

white matter does not contain nerve cell bodies or synapses. Most brain gray matter is located in the cerebral cortex, although, additional gray matter regions can also be found deeper inside the brain such as in the basal ganglia.

Occurring simultaneously with the transformation in HIV-1 infection demographics is an evolution of the understanding of development and expression of age-related brain changes among HIV-infected patients. Typical age-related brain changes are now commonly observed in older patients with HIV infection (5-7). Aging related changes in brain structure include those due to cerebral manifestations of small vessel ischemic vascular disease such as the appearance of areas of hyperintense signal on MRI in the deep white matter tracts and periventricular regions of the brain, collectively called white matter hyperintensities (WMHs) (5-7). WMHs appear as areas of increased signal intensity on magnetic resonance imaging (MRI) T2 weighted and fluid attenuated inversion recovery (FLAIR) images (8). These lesions commonly occur in the periventricular and deep white matter regions of the brain and are associated with both advancing age and vascular risk factors.

Pathogenesis of white matter hyperintensities

WMHs are hypothesized to develop from disruption of small penetrating arteries in the brain and are commonly observed in otherwise normal elderly (age > 65 years old) individuals (9). The deep cerebral white matter is more susceptible to hypoperfusion than other brain areas because these regions are supplied by small arterioles (10). Widespread stenosis of these arterioles can

result from aging related factors that contribute to tissue ischemia, such as arteriolosclerosis and amyloid angiopathy (11). Additionally, presence of WMHs is commonly associated with vascular risk factors such as hypertension and stroke, further strengthening the hypothesized vascular etiology of these lesions (11). On pathological examination, WMHs are associated with progressive loss of the myeliln sheath surrounding the nerve cell axons, and with continued disease progression axonal loss develops due to the prolonged effects of tissue ischemia (11).

Interestingly, the effects of the underlying small vessel ischemic vascular disease causing WMHs are not uniformly distributed throughout the brain and the frontal lobes may be particularly vulnerable to this type of injury. For example, previous studies of normal elderly (age > 65 years old) populations demonstrated that presence of WMHs is associated both structurally with frontal lobe atrophy (9, 12-14) and functionally with worse performance on neuropsychological tests of frontal lobe functions (12, 15-18). In individuals meeting clinical criteria for Alzheimer's disease, other studies have reported a frontal lobe predominance for location of WMHs as well as correlations between WMHs and loss of frontal lobe cortical volumes (9, 19), further supporting an increased vulnerability of the frontal lobes to the effects of small vessel ischemic vascular disease.

Relationship between white matter hyperintensities and cortical atrophy

Several theories have been proposed to explain how cortical nerve cell bodies in the gray matter of the brain can be affected by damage to axons in the white matter. These theories include Wallerian degeneration and axonal denervation. Wallerian degeneration is a well described phenomenon which occurs after an injury to a nerve cell axon such as a cut resulting in isolation of the segment distal to the injury from the nerve cell body (20). Degeneration of the distal axonal segment then occurs first because proteins and other materials formed in the cell body that are necessary for maintaining the axon are no longer able to be transported to the segment distal to the injury (20). However, after injury to the axon, the nerve cell body also undergoes a distinct set of histiologic changes which have been termed axon reaction or chromatolysis (20). These changes include: swelling of the cell body and nucleus, displacement of the nucleus from the center of the cell body, dispersion of the endoplasmic reticulum, and in some cases detachment of afferent synapses accompanied by swelling of nearby astrocytes and microglia (20). The nerve cell may also attempt to regenerate the damaged axon, (20), however, if the axon is not able to be regenerated the neuron may then undergo programmed cell death (apoptosis) (20).

Axonal denervation is a related phenomenon in which the axon is not able to be maintained by the nerve cell body rather than being triggered by a direct injury to the axon as in Wallerian degeneration (20). In axonal degeneration, the

most distal segment of the axon is affected first with the remainder of the axon degenerating in a "dying back" fashion (20). Axonal denervation is observed mostly in the peripheral nervous system but can also occur in the central nervous system as well. Degeneration of the axon and cell body occurs in an orderly process that is similar but not equivalent to apoptosis (20). In axonal denervation cell death is accompanied by swelling, myelin sheath breakdown, compartmentalization and then disorganization of the axon and sometimes the nerve cell body (20). Hypoperfusion of white matter tissue may trigger axonal denervation when the neuron cell body is unable to support the axon in an ischemic environment.

Study overview and objective

The objective of this study is to determine the relationship between brain cortical gray matter volumes and white matter hyperintensities in patients with HIV infection. The results of this study support the hypothesis that the frontal lobes are particularly vulnerable to the effects of small vessel ischemic vascular disease. We hypothesized that presence of moderately severe white matter hyperintensities in HIV seropositive individuals would be associated with reduced cortical gray matter volumes, particularly in the frontal lobes. Because presence of white matter hyperintensities is strongly associated with advancing age the potentially confounding effect of aging on cortical gray matter volumes in this study can not be excluded. Consequently further study using age-matched participants is warranted.

2. Methods

Study Population

The Hawai'i Aging with HIV Cohort (HAHC) was based out of the University of Hawaii John A. Burns School of Medicine Hawaii AIDS Clinical Research Program and focused on the study of aging in HIV seropositive individuals. Details of enrollment and clinical characterization were previously published (21). Briefly, participants were enrolled from Oct. 1, 2001 to Sept. 30, 2006 if they were ≥ 50 years old (older group) or between 20-39 years old (younger group). Primary exclusion criteria included head injury, learning disability, major neurological or psychiatric disease, or brain opportunistic disease. Baseline and annual evaluations included a neurological examination, medical intake with demographic data, risk behavior inventory, HIV-1 laboratory parameters (viral load, CD4 cell count, and lowest ever CD4 cell count), medication histories, and co-morbid illnesses. A total of 305 participants were included in the HAHC. Participants were enrolled regardless of HAART status. Individuals meeting current substance dependence criteria or with a positive urine drug screen for cocaine or methamphetamine (n = 29) were excluded from this analysis. Of the remaining 276 participants, 62 underwent MRI of the brain. Participants were eligible for brain MRI if they met HIV-associated dementia criteria based on American Academy of Neurology 1991 criteria of if they had a CD4 total lymphocyte count of 200cells/dL or less (22). This study includes only those 62 HAHC participants who underwent brain MRI because the main

outcome measures of interest for the study depended on availability of neuroimaging findings for quantification.

Assessment of White Matter Hyperintensities

MRI examinations were performed in a GE Sigma 1.5-Tesla scanner (General Electric Healthcare, Piscataway, New Jersey, United States of America). In all participants, axial T1, T2, and FLAIR weighted images were acquired, with a slice thickness of 5mm. Two neurologists classified the severity and distribution of white matter hyperintensities according to the Rotterdam Scan Study (RSS) scale (23, 24) (Figure 2). Discordant ratings were resolved by consensus. In this scale, the severity of periventricular white matter hyperintensities is rated in a semi-quantitative manner by assigning a score ranging from zero to three (0 = none present, 1 = thin rim or halo, 2 = thick rim, 3 = large confluent areas) for each of three periventricular brain regions (adjacent to the frontal horn, adjacent to the lateral wall, and adjacent to the occipital horn), for both hemispheres simultaneously. The total score for severity of periventricular white matter hyperintensities is then calculated by summing the scores from all three regions. The volume of punctate subcortical white matter hyperintensities was calculated for each participant by assuming all identified lesions to be spherical with fixed diameter, using the largest measurement for diameter within all slices in which the lesion could be seen. At the time of reviewing the MRI images, the raters were blinded to the patient's identity, demographic factors including ethnicity, sex, hypertension, diabetes, and had not

participated in the patients' clinical care. Participants were considered to have a moderate degree of WMHs if either punctate subcortical white matter lesions were present or if the severity of the periventricular white matter lesions was graded as 2 or higher in any of the three periventricular regions according to the Rotterdam Scan Study (RSS) scale (23). Subjects were considered to have a minimal degree of WMHs if no subcortical white matter lesions were present and ratings for severity of periventricular white matter lesions were 1 or less in each of the three periventricular regions (23).

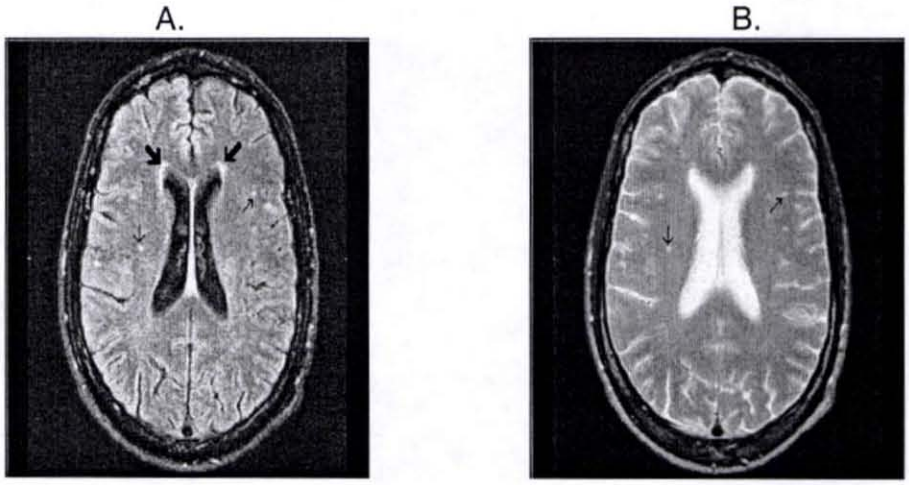

Figure 2: Brain white matter hyperintensities. Examples of T2-weighted axial brain magnetic resonance images showing periventricular white matter hyperintensities (A), and T2 FLAIR weighted axial brain magnetic resonance image showing punctate subcortical white matter hyperintensities (B). Large arrows indicate periventricular WMHs capping the anterior portion of the lateral ventricles, and the small arrows indicate punctate subcortical WMHs.

Voxel-Based-Morphometry

All MRI images were processed using the computer program Statistical Parametric Mapping (SPM2, Wellcome Department of Neuroimaging Science, University College London, London, England) (25). MRI images were processed based on an optimized VBM protocol (26). VBM is a computer based technique for comparing mean volumes of neuroanatomical structures between different groups of individuals. VBM is an example of tensor based morphometry, which is different from the other common computer based analytic method used for comparing brain volumes between subject groups, which is deformation based morphometry (27).

Deformation based morphometry is used to identify differences in the overall shape of the brain using neuroimaging volumes (27). In deformation based morphometry differences are identified by determining the amount of change needed for the brain image volume to be mapped onto a standard reference space (27). In other words, this technique compares the amount of deformation or change in location needed for each voxel to be fitted onto the corresponding location in a standardized space. In this way differences in the relative position of brain structures can be identified through the alterations needed to fit the areas onto the standardized space. Consequently, differences in the degree of deformation need to fit equivalent brain areas onto the standardized space directly indicates presence of structural differences between

the brain volumes (27). Alternatively, statistical parametric maps can be generated to determine if differences in displacements are significantly greater than would be seen by random fluctuation (27).

Tensor based morphometry is a different but related computer based analytic method that is commonly used to identify regional shape differences between groups of patients (27). In this technique, a matrix is generated for each voxel of the image. This matrix describes the relative position of the voxel to all of its neighboring voxels (27). Consequently, the values in the matrix can then be used to identify voxels that differ in their relative distances from their neighbors between individuals or between groups of individuals, indicating the existence of a difference in localized morphology or shape of the structure between the individuals or groups (27). Any differences that are identified can be expressed in terms of their relative difference from the equivalent location in the standardized space, allowing comparison between different individuals or groups of individuals (27). Voxel based morphometry is a specific application of tensor based morphometry utilizing spatially normalized brain volumes and has most commonly been applied to comparison of brain cortical gray matter volumes between groups of subjects (27).

In order to perform VBM the brain images underwent a series of processing steps. First the images were coregistered and spatially normalized using a twelve-parameter affine transformation to the standard coordinate system

of Talairach and Tournoux. Global normalization by proportional scaling was used. The normalized images were then segmented into gray matter, white matter and cerebrospinal fluid volumes (Figure 2). All gray matter volumes were then smoothed with a 12 mm full width at half-maximum three dimensional Gaussian smoothing filter. The smoothing step is used to compensate for any incorrect deformation applied to voxels during spatial normalization and also helps to make the data more normally distributed and thereby increasing the validity of the parametric statistical tests.

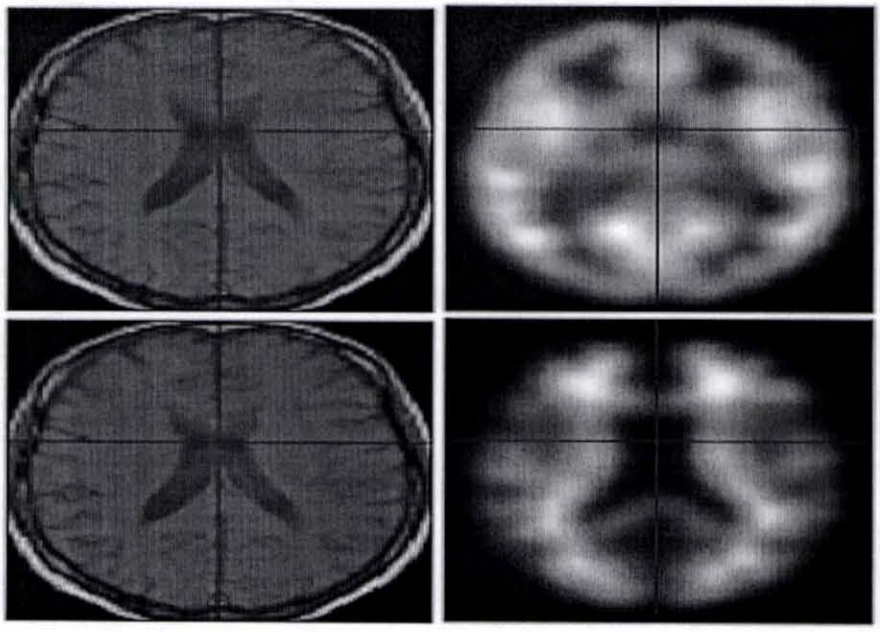

Figure 3: Tissue segmentation of brain MRI images. Segmentation of T1 weighted brain MRI images into gray matter volumes (top row) and white matter volumes (bottom row).

Statistical Analysis

Demographic factors and HIV infection-related factors were compared between HIV seropositive individuals with moderate WMHs and those with minimal WMHs using two-tailed t-tests for continuous variables and chi-square analysis for categorical variables. A generalized linear model was then used to compare the volume of gray matter on a voxel-by-voxel basis using VBM between the groups of individuals with moderate and minimal WMHs. Non-adjusted p-values for statistical significance of < 0.05 were used in the VBM comparison.

3. Results

Comparison of demographic and HIV-infection related factors

A total of 62 HIV seropositive individuals participating in the HAHC were included in the study, 30 with moderate WMHs and 32 with minimal WMHs (Figures 4 and 5). Presence of moderate WMHs was associated with greater mean age in years (54.59, S.D. = 6.38; 42.70, S.D. = 8.56; $p < 0.001$) and greater mean years of education (14.77, S.D. = 2.34; 13.13, S.D. = 1.76; $p = 0.003$) compared to those with minimal WMHs (Table 1). A trend towards greater mean systolic blood pressure in mm Hg in participants with moderate WMHs compared to those with minimal WMHs was also identified (133.07, S.D. = 16.17; 126.41, S.D. = 14.99; $p = 0.098$). No differences were detected for other demographic variables or HIV infection-related factors.

Table 1: Comparison of Demographic Characteristics, Vascular Risk Factors and HIV Infection Related Factors.

	Moderate WMH	Minimal WMH	Significance
Volume of subcortical WMHs (cm^3)	5.88 (6.81)*	0.00 (0.00)	$p < 0.001$
Mean periventricular WMH severity score	3.03 (1.03)	1.41 (1.01)	$p < 0.001$
Age (years)	54.59 (6.38)	42.70 (8.56)	$p < 0.001$
Years of formal education	14.77 (2.34)	13.13 (1.76)	$p = 0.003$
Viral Load (1000 copies/mL)	122.85 (291.91)	185.98 (441.86)	N.S.
CD4 cell count (cells per mL)	314.77 (183.67)	333.81 (304.65)	N.S.
CD4 nadir (cells per mL)	125.71 (121.07)	134.93 (148.58)	N.S.
Systolic Blood Pressure	133.07 (16.17)	126.41 (14.99)	$p = 0.098$
Smoking (pack-years)	12.50 (15.35)	13.81 (12.17)	N.S.
Gender (Men/Women)	26/4**	29/3	N.S.
On HAART (yes/no)	24/6	25/7	N.S.

WMH = White matter hyperintensity.

N.S. = non-significant ($p > 0.05$).

HAART = highly active anti-retroviral therapy.

*Continuous variables are reported as: mean (standard deviation).

**Categorical variables are reported as the number present in each category, with categories separated by a forward slash.

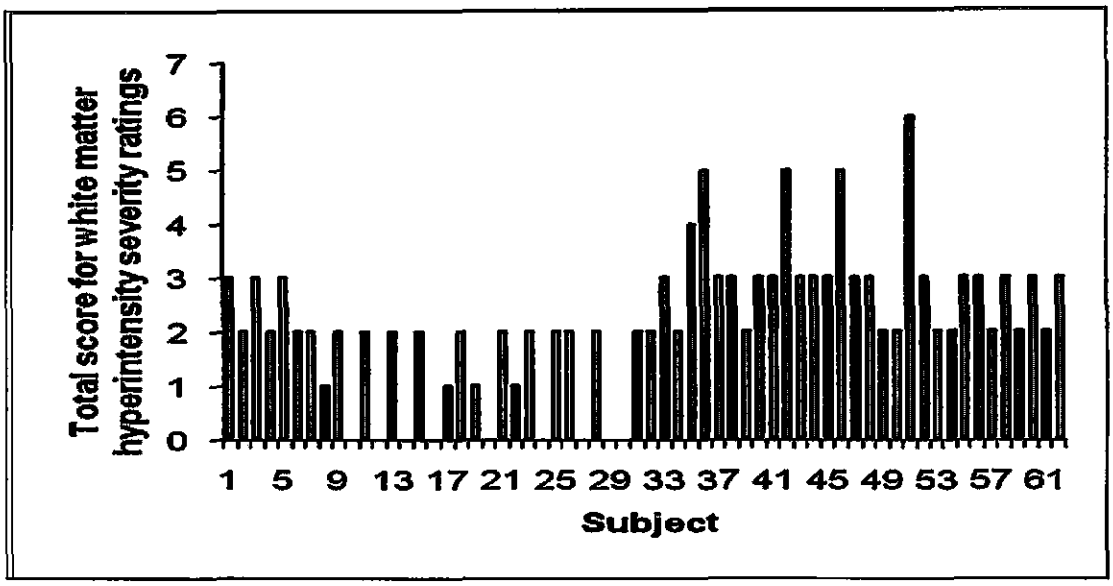

Figure 4: Plot of periventricular white matter hyperintensity severity ratings. Total score of periventricular white matter hyperintensity severity ratings are shown for all study subjects.

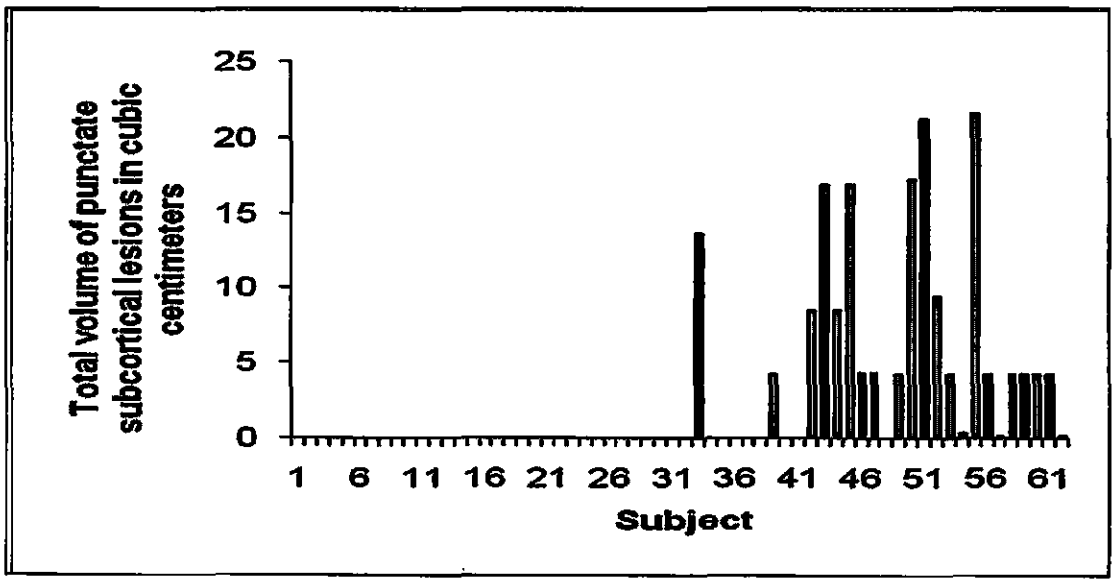

Figure 5: Plot of subcortical punctate white matter hyperintensity volumes. The volume of punctate white matter hyperintensities for each of the subjects is given in cubic centimeters.

Relationship between white matter hyperintensities and cortical gray matter volumes

The relationship between white matter hyperintensities and brain cortical gray matter volumes was then evaluated using VBM. Figure 6 illustrates specific voxels representing areas of decreased cortical volume in HIV seropositive patients with moderate compared to minimal WMHs ($p < 0.05$). These voxels are overlayed on a series of three orthogonal mask images and correspond to regions within the frontal lobes bilaterally.

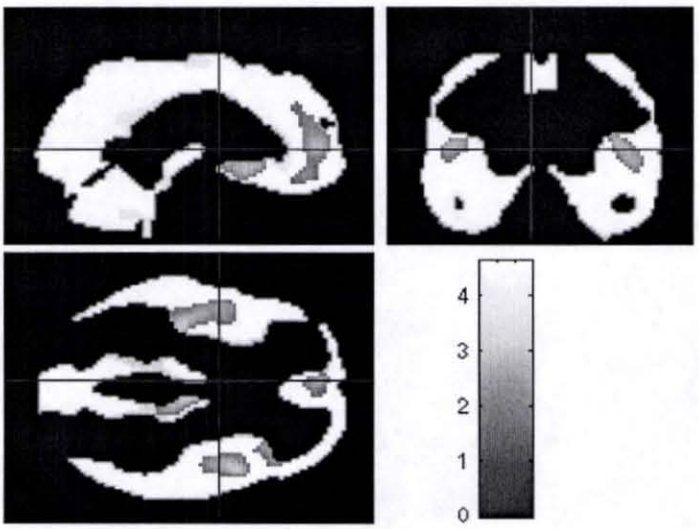

Figure 6: Statistical map of differences in cortical gray matter volumes associated with white matter hyperintensities. Orthogonal views of statistical maps (with t-scores linked to shading scale) of normalized brain gray matter volume data indicating bilateral regions of decreased gray matter volume in the frontal lobes of HIV seropositive individuals with moderate white matter hyperintensities compared to those with minimal white matter hyperintensities.

4. Conclusion

Cerebral manifestations of small vessel ischemic vascular disease such as WMHs are of increasing importance for HIV seropositive individuals as the prevalence of older and elderly patients continues to rise due to increased longevity with HAART. This investigation into the relationship between cortical atrophy and WMHs in HIV seropositive individuals found areas of significantly reduced cortical gray matter volumes in the frontal lobes of HIV seropositive individuals with moderate WMHs compared to those with minimal WMHs. Given the relationship between WMHs and frontal lobe cortical atrophy in the general population (9, 12-14), these findings extend knowledge regarding the increased vulnerability of the frontal lobes to the effects of small vessel ischemic vascular disease to HIV seropositive individuals.

The relationship between white matter hyperintensities and small vessel ischemic vascular disease

In the general population WMHs are regarded as one of several manifestations of small vessel ischemic vascular disease of the brain (5-7, 28). The other common manifestation of brain small vessel ischemic vascular disease is lacunar strokes. Lacunar strokes are complete infarcts of brain tissue that can measure up to 15 mm in diameter. These lesions are commonly seen on neuroimaging of the brain either with computer assisted tomography or magnetic resonance imaging and are also easily identified on gross examination during

autopsy. Lacunar strokes are most commonly found in the cerebral white matter as well as in subcortical structures such as the thalamus, basal ganglia and brainstem. Most lacunar strokes do not cause cognitive or other neurological symptoms and consequently are detected long after they occur as a small cystic area containing no viable brain tissue. However, even in the chronic state these lesions can be surrounded by areas of incomplete infarction, which is particularly common when they occur in the deep cerebral white matter. While lacunar infarcts are produced by focal ischemic insults of severity sufficient to result in tissue loss and a resulting small area of necrosis, WMHs are commonly considered to represent areas of incomplete infarction with selective damage to some cellular components but insufficient to result in tissue necrosis and cystic changes. Several population-based studies have demonstrated that WMHs occur frequently among older individuals and are associated with presence of vascular risk factors (5-7, 28, 29). Consequently, in normal elderly populations, presence of these lesions is often considered a reliable marker for small vessel ischemic vascular disease. Additionally, presence of these lesions is now considered an important component of commonly used clinical criteria for vascular dementia (29-33), further indicating the clinical relevance of these lesions.

White matter hyperintensities and cortical gray matter atrophy in elderly individuals

Neuroimaging studies using magnetic resonance imaging and positron emission tomography have demonstrated significant associations between presence of WMHs and measures of brain atrophy in the general population (12, 34, 35). WMHs have been associated with several markers of brain atrophy including: larger ventricular volumes (12), reduced whole brain volumes (12) and reduced cortical blood volumes (36). Additionally, the effect of presence of WMHs on cortical gray matter is not uniformly distributed and a predilection for reduction in frontal lobe gray matter volumes compared to other brain regions is now well established in normal elderly populations (9, 19, 36).

Etiology of cortical gray matter atrophy associated with white matter hyperintensities

The underlying etiology of cortical gray matter atrophy associated with presence of WMHs has not yet been established and several theories exist. First, cortical gray matter loss has been suggested to occur as a result of Wallerian degeneration after damage to axons through small vessel ischemic disease (9). Another possibility is axonal denervation causing neuronal loss in the gray matter as a result of axonal damage in the white matter (9). Finally, it has been suggested that WMH's do not directly cause cortical gray matter loss, but instead serve as a marker for the effects of reduced cerebral blood flow to the cortex due to small vessel vascular disease with resulting cortical hypoperfusion

as the direct cause of neuronal loss and cortical atrophy (9). Additionally, several types of WMHs can be distinguished that may have different underlying associated pathophysiologies: periventricular changes may be associated mainly with disruption of the subependymal lining and gliosis (9), punctate subcortical lesions with tissue hypoperfusion due to thickened arteriolar walls (9), and large patchy lesions with more extensive tissue ischemia (37).

Cognitive effects of white matter hyperintensities

Clinically, several studies have demonstrated associations between presence of these lesions and worse performance on cognitive tasks as well as an increased risk for cognitive decline and development of dementia (38-41). While the association between presence of WMHs and cognitive decline in the general population is well recognized, the relationship between WMHs and cognitive performance in individuals living with HIV infection is still somewhat controversial. Presence of WMHs is reported to be associated with impaired performance on some cognitive measures, including worse performance on tests of psychomotor speed and verbal memory (42). Additionally, decreased white matter volume in HIV seropositive individuals has been associated with presence of dementia (43). However, in other studies, no relationship was able to be identified between presence of WMHs and cognitive performance (44-46). Further support for the role of white matter damage in development of cognitive impairment and dementia in HIV infection has recently been demonstrated using magnetic resonance spectroscopy (47-51). The findings of this study add

support to the role for WMHs in development of cognitive impairment and dementia in HIV infection through the identified associations with frontal lobe atrophy.

Limitations of the study

This study is limited by several factors including: the use of a visual rating of WMHs, the lack of pathological examination of the brains, and confounding differences in mean ages between the study groups. While WMHs may be best quantified using computerized volumetric methods, several studies have used semi-quantitative visual scales as a means of providing a clinical rather than research assessment. Additionally, the use of a clinical measurement technique increases the applicability of the study results to practicing physicians who are unlikely to have access to computer based quantification methods. In our study, the group with moderate WMHs was significantly older than the group with minimal WMHs, and further study with age-matched controls would be useful to confirm that these findings are not related to an affect of the aging process. Additionally, our results may be strengthened by the use of a computer based quantitative method of measuring brain WMHs such as that used by Bartzokis et al (52) (Figure 8), as well as a more sophisticated quantification of gray matter volumes such as cortical thickness mapping. The main strength of the study is that we have validated previous studies on the association between WMHs and gray matter atrophy to individuals living with HIV

infection (9, 19, 36) and confirmed that, as reported in the general population, this association appears to preferentially affect frontal lobe regions.

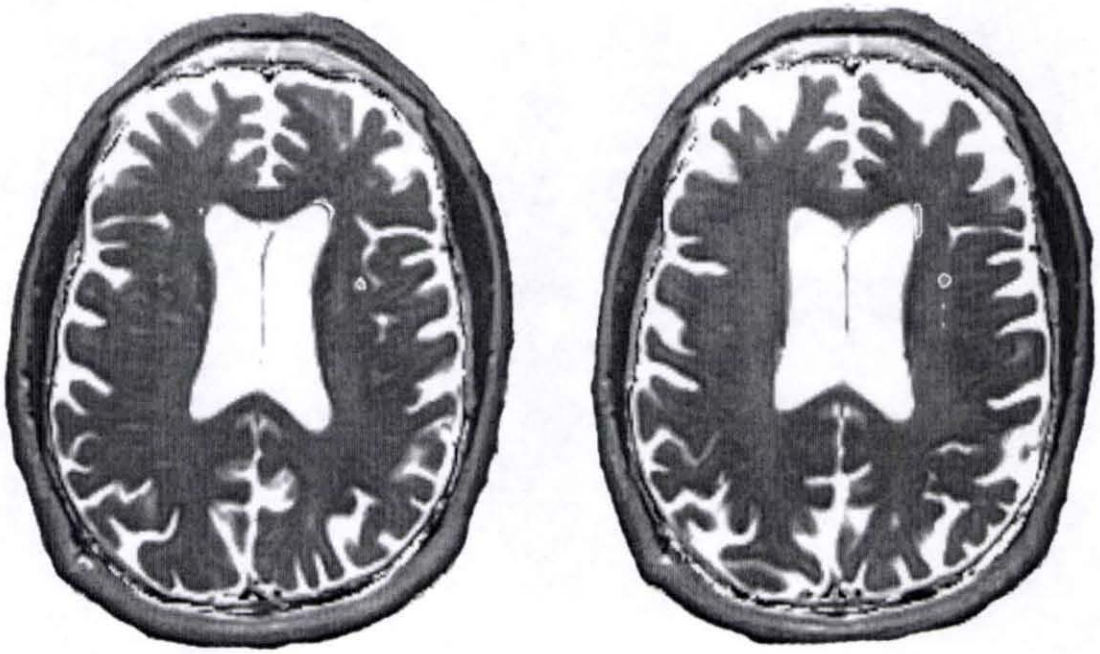

Figure 7: Computer assisted quantification of brain white matter lesions. Depiction of quantification of brain white matter hyperintensity lesion volumes. Lesions were identified and quantified using calculated T2 maps that were created from the early and late spin-echo images (TE 10 and TE 101).

Overall conclusions

As HIV seropositive individuals are aging, understanding cerebral small vessel ischemic vascular disease and its effects on brain structure and function is becoming increasingly more important in this population. The results of this study are consistent with those reported in normal elderly populations and

provide further support for increased susceptibility of the frontal lobes to the effects of small vessel ischemic vascular disease. Further investigation using techniques such as cortical thickness mapping and computerized quantification of white matter hyperintensities are indicated, especially when combined with neuropsychological testing to determine if the identified structural changes affect cognitive performance. These findings may also be useful to clinicians caring for aging HIV seropositive individuals and indicate that prevention of small vessel ischemic vascular damage to the brain is an important clinical goal.

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