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Cortical Atrophy and White Matter Hyperintensities in HIV: The Hawaii Aging with HIV Cohort Study

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Abstract

Background—As many HIV seropositive individuals are now living longer after infection due to highly active antiretroviral therapy, aging related manifestations of cerebral small vessel ischemic vascular disease, such as brain white matter hyperintensities, are becoming increasingly important in this population.

Goals—This study is designed to determine the relationship between white matter hyperintensities and cortical volumes in HIV seropositive individuals.

Materials and Methods—Voxel-based-morphometry was used to compare cortical volumes between 62 HIV seropositive individuals participating in the Hawaii Aging with HIV cohort study, 30 with moderate white matter hyperintensities and 32 with minimal or no white matter hyperintensities.

Results—Presence of moderate white matter hyperintensities was associated with decreased cortical volumes in the frontal lobes bilaterally.

Conclusion—These findings suggest that age related white matter hyperintensities are associated with reduced frontal gray matter volumes in HIV seropositive individuals, supporting the hypothesis that the frontal lobes may have greater susceptibility to the effects of small vessel ischemic vascular disease.

Keywords

Leukoaraiosis; Ischemic vascular disease; Aging; HIV infection

Introduction

Human immunodeficiency virus (HIV) infection in older patients (age > 50 years) is becoming increasingly common in developed countries as HIV seropositive individuals live longer because of potent antiretroviral treatment (1). Simultaneously, the development and expression

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of aging related brain changes among HIV-infected patients is evolving. Typical aging related brain changes are now commonly observed in older patients with HIV infection, including those due to cerebral manifestations of small vessel ischemic vascular disease such as white matter hyperintensities (WMHs) (2-4).

White matter hyperintensities are considered to result from disruption of small penetrating arteries in the brain and are commonly observed in otherwise normal elderly individuals (5). The effects of small vessel ischemic vascular disease are not uniformly distributed throughout the brain and the frontal lobes may be particularly vulnerable. For example, previous studies of normal elderly populations demonstrate that presence of WMHs is associated both structurally with frontal lobe atrophy (5,-8) and functionally with worse performance on neuropsychological tests of frontal lobe functions (6,9-12). 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 (5,13). These results further support the increased vulnerability of the frontal lobes to small vessel ischemic vascular disease.

The objective of this study is to determine the relationship between brain gray matter volumes and white matter hyperintensities in patients with HIV infection. We hypothesized that presence of moderately severe white matter hyperintensities in HIV seropositive individuals would be associated with reduced gray matter volumes, particularly in the frontal lobes. The results of this study support the hypothesis that the frontal lobes are particularly vulnerable to the effects of small vessel ischemic vascular disease.

Materials and Methods

Study Population

The Hawaii Aging with HIV Cohort (HAHC) is a community-based study of aging in HIV seropositive individuals. Details of enrollment and clinical characterization are published elsewhere (14). Briefly, participants were enrolled if HIV seropositive and either age greater than 50 years (older group) or between 20-39 years (younger group), and major exclusion criteria are not present. Primary exclusion criteria include head injury, learning disability, major neurological or psychiatric disease, or brain opportunistic disease. Baseline and annual evaluations include a neurological examination, medical intake with demographic data, risk behavior inventory, HIV-1 laboratory parameters (viral load, CD4 count, and lowest ever CD4 count), medication histories, and co-morbid illnesses. Cohort participants were followed over a 5 year period from 2001 to 2006. This study included a total of 62 HAHCS participants who underwent magnetic resonance imaging (MRI) of the brain as part of their participation in the HAHCS. Institutional review board approval to conduct the study was obtained at the University of Hawaii.

Assessment of White Matter Hyperintensities

MRI examinations were performed in a GE Sigma 1.5-Tesla scanner. In all participants, axial T1, T2, and FLAIR weighted images were acquired, with a slice thickness of 5mm. Two neurologists (A.M. and B.N.) classified the severity and distribution of white matter hyperintensities according to the Rotterdam Scan Study (RSS) scale (15,16). 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 subcortical white matter lesions were present or 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 (16). 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 according to the Rotterdam Scan Study (RSS) scale (16).

Voxel-Based-Morphometry (VBM)

All MRI images were processed using Statistical Parametric Mapping (SPM2) (17). MRI images were processed based on an optimized VBM protocol (18). 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. All gray matter volumes were then smoothed with a 12 mm full width at half-maximum three dimensional Gaussian smoothing filter.

Statistical Analysis

Demographic factors, vascular risk factors, and HIV infection-related factors were compared between HIV seropositive individuals with moderate and minimal degrees of 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 Voxel-Based-Morphometry between the groups of individuals with moderate and minimal WMHs. A non-adjusted p-value for statistical significance of 0.05 was used.

Results

A total of 62 HIV seropositive individuals were included in the study, 30 with moderate WMHs and 32 with minimal WMHs. 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, vascular risk factors, or HIV infection-related factors.

The relationship between white matter hyperintensities and brain cortical volumes was evaluated using VBM. Figures 1 illustrates specific pixels representing areas of decreased cortical volume in HIV seropositive patients with moderate compared to minimal WMHs ($p < 0.01$). These pixels correspond to regions within the frontal lobes bilaterally.

Discussion

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 increase due to increased longevity with highly active anti-retroviral therapy (HAART). This investigation into the relationship between cortical atrophy and WMHs in HIV seropositive individuals found areas of significantly reduced cortical volume 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 (5-8), 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.

In the general population WMHs are regarded as one of several manifestations of small vessel ischemic vascular disease of the brain (2-4,25). Several population based studies have

demonstrated that these lesions occur frequently among older individuals and are associated with vascular risk factors (2-4,25,26). 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 (26,30-33), further indicating the clinical relevance of these lesions.

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 (6,19,20). WMHs have been associated with several markers of brain atrophy including: larger ventricular volumes (6), reduced whole brain volumes (6) and reduced cortical blood volumes (21). Additionally, the affect 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 (5,13,21).

Despite all that is known, the underlying etiology of gray matter atrophy associated with presence of WMH's 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 (5). Another possibility is axonal denervation causing neuronal loss in the gray matter as a result of axonal damage in the white matter (5). Finally, it has been suggested that WMH's do not directly cause cortical gray matter loss, but are 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 (5). 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 (5), punctate subcortical lesions with tissue hypoperfusion due to thickened arteriolar walls (5), and large patchy lesions with more extensive tissue ischemia (23). An additional possibility is that primary cortical apoptosis, which is known to occur in HIV-associated dementia, may contribute to brain atrophy as well (24).

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 (22,27-29). 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. WMHs have been reported to be associated with some cognitive measures, including worse performance on tests of psychomotor speed and verbal memory (34). Additionally, decreased white matter volume in HIV seropositive individuals has been associated with dementia (35). However, in other studies, no relationship was identified between presence of WMHs and cognitive performance (36-38). Additionally, there is evidence that development of dementia in HIV infection may be associated with atrophy of other brain regions such as the basal ganglia and hippocampus (39). However, further support for the role of white matter damage in development of cognitive impairment and dementia in HIV infection has been recently demonstrated using magnetic resonance spectroscopy (40-44). 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.

This study is limited by several factors including: the use of a visual rating of WMHs, the lack of pathological examination of the brains, the lack of MRI scans on HIV-seronegative controls for comparison, and confounding differences in mean ages between the study groups. Because

HIV infection may also cause the appearance of white matter hyperintensities, the lack of information from pathological examination of the participants' brains prevents definitive determination of the etiology of the white matter lesions identified in this study. However, the finding of associated frontal lobe atrophy in this study strengthens the hypothesis that small vessel ischemic vascular disease contributes to development of white matter hyperintensities in aging HIV seropositive individuals. Additionally, previous studies have demonstrated that treatment of HIV infection with HAART and the resulting clinical improvement, as measured by increased CD4 cell count and decreased viral load, are associated with regression of HIV induced white matter abnormalities on MRI (45). This would be consistent with a decreased contribution of HIV induced white matter abnormalities to the white matter hyperintensities identified in this study, since all participants included in this study were receiving HAART and no differences in mean CD4 cell count or mean viral load existed between participants with and without white matter hyperintensities. 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 effect 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 (46), 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 extended associations between WMHs and gray matter atrophy to individuals living with HIV infection (5,13,21), and confirmed that as reported in the general population this association appears to preferentially affect frontal lobe regions.

As HIV seropositive individuals are more commonly reaching older and elderly ages, 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, as well as neuropsychological testing to determine if the identified structural changes effect cognitive performance. These findings may also be useful to clinicians caring for aging HIV seropositive individuals.

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Figure 1. Statistical map (with t-scores linked to shading scale) derived from normalized brain gray matter volumes. Orthogonal views of statistical maps of normalized brain gray matter volume data indicating bilateral regions of decreased gray matter volume in the frontal lobes of HIV seropositive patients with moderate white matter hyperintensities compared to those with minimal white matter hyperintensities.

Table 1

Comparison of Demographic Characteristics, Vascular Risk Factors, and HIV Infection Related Factors

	Moderate WMH	Minimal WMH	Significance
Volume of subcortical WMH (cm ³)	5.88 (6.81)*	0.00 (0.00)	p < 0.001
Periventricular WMH severity	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.