SMALL VESSEL VASCULAR DISEASE IN HIV INFECTION

A THESIS SUBMITTED TO THE GRADUATE DIVISION OF THE UNIVERSITY OF HAWAI'I IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

IN

BIOMEDICAL SCIENCES

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By

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We certify that we have read this thesis and that, in our opinion, it is satisfactory in scope and quality as a thesis for the degree of Master of Science in Biomedical Sciences.

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ACKNOWLEDGEMENTS

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Abstract

**Background:** This study is designed to determine the relationship between age and occurrence of cerebral manifestations of small vessel ischemic vascular disease in HIV seropositive individuals. **Methods:** Periventricular leukoaraiosis severity and white matter lesion volume were determined by magnetic resonance imaging (MRI) of the brain on 57 HIV seropositive individuals. **Results:** Cerebral small vessel ischemic vascular disease manifestations correlated with age and systolic blood pressure, but not with HIV infection-related parameters. **Conclusion:** These findings suggest that, in the era of highly active antiretroviral therapy, leukoaraiosis severity and white matter lesion volume may be more indicative of small vessel ischemic vascular disease than HIV-related CNS pathology; and support the need for aggressive treatment of vascular risk factors in HIV seropositive individuals.
# TABLE OF CONTENTS

Acknowledgements......................................................................................iii
Abstract........................................................................................................iv
List of Tables...................................................................................................vi
List of Figures..................................................................................................vii
Chapter 1: Introduction..................................................................................1
Chapter 2: Methods.......................................................................................3
  Study Population..........................................................................................3
  Assessment of Luekoaraiosis Severity and White Matter Lesion Volume...3
  Statistical Analysis......................................................................................4
Chapter 3: Results.........................................................................................5
Chapter 4: Conclusion....................................................................................9
References......................................................................................................13
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Comparison of Demographic Characteristics and Risk Factors</td>
<td>6</td>
</tr>
</tbody>
</table>

vi
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Regression of Periventricular Leukoaraiosis Severity and Age</td>
<td>7</td>
</tr>
<tr>
<td>2.</td>
<td>Regression of White Matter Lesion Volume and Age</td>
<td>8</td>
</tr>
<tr>
<td>3.</td>
<td>Regression of White Matter Lesion Volume and Blood Pressure</td>
<td>8</td>
</tr>
</tbody>
</table>
1. Introduction

Widespread availability of highly active antiretroviral therapy (HAART) changed the epidemiology of human immunodeficiency virus, type 1 (HIV) infection in developed countries [1]. HIV seropositive individuals are now living longer after infection, and consequently the prevalence of older HIV seropositive individuals is dramatically increasing [1]. However, increased longevity, resulting in chronic exposure to HIV infection and therapeutic medications, may exacerbate cerebral damage due to the small vessel ischemic vascular disease that normally occurs with aging.

Cerebral manifestations of small vessel ischemic vascular disease include lacunar strokes, punctate white matter hyperintensities (WMH), and periventricular leukoaraiosis, all of which result from disruption of small penetrating arteries in the brain as a typical consequence of the aging process [2-4]. Previous studies in seronegative elderly populations suggest that cumulative damage resulting from small vessel ischemic vascular disease is associated primarily with advancing age, and that these lesions may have sizable effects on cognitive performance [5-7]. Small vessel ischemic vascular lesions are also likely associated with advancing age in HIV seropositive individuals, possibly contributing to impairment of cognitive performance in this population as well.

The objective of this study is to determine the relationships between cerebral small vessel vascular disease manifestations on brain magnetic resonance imaging (MRI) and age, vascular risk factors, and HIV infection related parameters, in HIV seropositive individuals. We hypothesized that both age and vascular risk factors, but not HIV
infection-related parameters, would affect severity of leukoaraiosis and volume of white matter lesions in HIV seropositive individuals. The results of this study support the need for aggressive evaluation and treatment of vascular risk factors in aging HIV seropositive individuals.
2. Methods

**Study Population:** The Hawai‘i 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 [8]. Briefly, participants are enrolled if age is 50+ (older group) or between 20-39 years old (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. To date, 305 participants have entered the study. 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, 57 underwent MRI of the brain; and the current report is drawn from these 57 participants. Participants were eligible for brain MRI if they met HAD criteria, based on AAN 1991 criteria, or if they had a CD4 total lymphocyte count of 200cells/dL or less.

**Assessment of Leukoaraiosis Severity and Volume of White Matter Lesions:** The 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 classified the severity and distribution of periventricular leukoaraiosis, and volume of punctate white matter lesions (lacunar stroke and punctate white matter
hyperintensities) evident on MRI according to the Rotterdam Scan Study (RSS) scale [9]. In this scale, the severity of periventricular leukoaraiosis 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 leukoaraiosis is then calculated by summing the scores from all three regions. Volume of punctate white matter lesions were calculated by assuming all 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 patient’s clinical care.

**Statistical Analysis:** Continuous demographic factors, vascular risk factors, and HIV infection-related factors were compared between older and younger HIV seropositive individuals using two-tailed t-tests, and frequency of occurrence of categorical variables were compared between groups using chi-square analysis. Factors significantly associated with presence of either periventricular leukoaraiosis or punctate white matter lesions were entered into linear regression models, using leukoaraiosis severity and white matter lesion volume as dependent variables in separate models.
3. Results

Compared to the younger subjects, the older subjects had greater mean years of education (14.35, S.D. = 2.62; 13.13, S.D. = 1.69; p = 0.036), greater mean years since diagnosis (11.67, S.D. = 5.50; 8.51, S.D. = 4.64; p = 0.023), greater mean systolic blood pressure measured in mm Hg (131.59, S.D. = 18.10; 120.57, S.D. = 11.13; p = 0.006), and trended towards having a greater mean pack-year smoking history as well (16.36, S.D. = 15.50; 10.11, S.D. = 7.79; p = 0.056). Other demographic variables, vascular risk factors, and HIV infection-related factors did not differ between the subjects when divided by age group. Compared to the younger subjects, the older subjects demonstrated greater mean total severity of leukoaraiosis (2.41, S.D. = 1.40; 1.61, S.D. = 1.12; p = 0.025), and mean total volume of white matter lesions (measured as cubic centimeters; 3.72, S.D. = 6.62; 0.00, S.D. = 0.00; p < 0.01).

Presence of white matter lesions was associated with greater mean age in years (55.16, S.D. = 5.93; 43.42, S.D. = 9.07; p < 0.001; See Table 1) and greater mean systolic blood pressure in mm Hg (134.12, S.D. = 19.01; 124.18, S.D. = 14.54; p = 0.036; See Table 1). No differences were detected for other demographic variables, vascular risk factors, or HIV infection-related factors. Trends towards significance were detected for presence of white matter lesions to be associated with not being on HAART (p = 0.064; See Table 1), and for greater mean years of education (p = 0.057; See Table 1).
Table 1. Comparison of Demographic Characteristics and Risk Factors

<table>
<thead>
<tr>
<th></th>
<th>Periventricular Leukoaraiosis</th>
<th>Punctate White Matter Lesions</th>
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<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Number</td>
<td>48</td>
<td>9</td>
</tr>
<tr>
<td>Age*</td>
<td>47.54 (9.59)</td>
<td>43.64 (11.08)</td>
</tr>
<tr>
<td>Years of education</td>
<td>14.62 (2.43)</td>
<td>13.56 (1.94)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>127.54 (17.19)</td>
<td>125.00 (12.61)</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>79.60 (8.36)</td>
<td>79.78 (9.28)</td>
</tr>
<tr>
<td>Serum glucose</td>
<td>99.38 (27.95)</td>
<td>96.89 (16.00)</td>
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<tr>
<td>Serum cholesterol</td>
<td>183.91 (51.88)</td>
<td>165.11 (31.17)</td>
</tr>
<tr>
<td>Smoking (Pack Years)</td>
<td>14.17 (13.80)</td>
<td>11.56 (9.29)</td>
</tr>
<tr>
<td>Viral load</td>
<td>133.39 (316.30)</td>
<td>266.50 (596.63)</td>
</tr>
<tr>
<td>CD4 count at examination</td>
<td>327.96 (277.55)</td>
<td>313.89 (206.23)</td>
</tr>
<tr>
<td>CD4 nadir</td>
<td>131.11 (151.59)</td>
<td>144.22 (155.89)</td>
</tr>
<tr>
<td>Reported years since HIV</td>
<td>10.49 (5.12)</td>
<td>9.93 (6.85)</td>
</tr>
<tr>
<td>diagnosis</td>
<td>41/7</td>
<td>8/1</td>
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<tr>
<td>Gender (male/female)**</td>
<td>44/3</td>
<td>9/0</td>
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<tr>
<td>Reported diagnosis of diabetes</td>
<td>13/35</td>
<td>4/5</td>
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<td>On HAART / not on HAART</td>
<td>24/19</td>
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n/a = not-applicable.
HAART = highly active antiretroviral 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.
We then evaluated the relationship between white matter lesion volume and severity of leukoaraiosis in a linear regression model identifying a direct correlation between these measures of cerebral small vessel ischemic disease (regression coefficient $= 2.07$, $r = 0.436$, $p = 0.0098$). In separate linear regression models including age, education, systolic blood pressure, HAART status, only age (regression coefficient $= 0.34$, S.D. $= 0.19$; $r$-square $= 0.13$; $p < 0.01$; See Figure 1) met statistical significance for correlation to leukoaraiosis severity.

Figure 1. Regression of Periventricular Leukoaraiosis Severity and Age.

![Graph showing regression of leukoaraiosis severity and age.](image)

In similar models using white matter lesion volume as the dependent variable, both age (regression coefficient $= 0.13$, S.D. $= 0.0072$; $r$-square $= 0.062$; $p = 0.039$; See Figure 2) and systolic blood pressure (regression coefficient $= 0.12$, S.D. $= 0.0041$; $r$-square $= 0.19$; $p < 0.001$; See Figure 3) met statistical significance.
Figure 2. Regression of White Matter Lesion Volume and Age.

Figure 3. Regression of White Matter Lesion Volume and Blood Pressure.
4. Conclusion

As the mean age of HIV seropositive individuals continues to rise due to effective therapy, age-related cerebral manifestations of small vessel ischemic vascular disease are likely to become more apparent. This investigation into the occurrence of periventricular leukoaraiosis and punctate white matter lesions in older and younger HIV seropositive individuals found a significantly increased burden of cerebral small vessel ischemic vascular disease manifestations among older individuals, and direct correlation of these lesions with age and systolic blood pressure. Given the devastating effects of cerebral small vessel ischemic vascular lesions in the general population [5-7], these findings emphasize the need to aggressively evaluate and treat aging HIV seropositive patients for preventable or modifiable vascular risk factors.

The epidemiology of HIV infection in developed countries has been changing dramatically since the widespread availability of HAART, which has lead to long-term survival for many individuals. As the population of HIV seropositive individuals lives longer through use of HAART, the increased duration of survival shifts the age-distribution towards older ages [1]. Previous studies suggest that most older HIV seropositive individuals developed infection prior to age 50, and with HAART are now living to older ages with HIV as a chronic disease [1]. This is particularly evident in Hawai‘i, where nearly 20% of AIDS cases reported to the State Department of Health in 2001 were in individuals over the age of 50 [10]. Similar trends have also been reported in Florida and California, with both states reporting higher percentages of AIDS among older individuals, compared to the National average of 15% [11,12]. As the
demographics of HIV age-related prevalence continue to shift towards older ages, resulting in longer duration of chronic treatment, the importance of potential interactions with other diseases common among the elderly is increased.

Punctate white matter lesions, including lacunar infarcts, and leukoaraiosis are considered manifestations of small vessel ischemic vascular disease of the brain [2-4,13]. These vascular lesions occur commonly among older individuals, and are typically related to presence of vascular risk factors, such as hypertension and diabetes [2-4,13,14]. Furthermore, presence of these vascular lesions is associated with cognitive decline and development of dementia. For example, when compared to elderly individuals without lacunar infarcts, those with lacunar infarcts score lower on cognitive tests, and have approximately twice the risk of developing future dementia [6,7]. Additionally, lacunar infarction in certain “strategic locations” alone, such as the basal ganglia, may result in profound cognitive deficits and even dementia [5]. Multiple studies also demonstrate that presence of leukoaraiosis is independently related to cognitive impairment and decline in the elderly [15-17], and when present in patients with lacunar strokes, leukoaraiosis indicates increased severity of small vessel ischemic vascular disease and exacerbates adverse effects of these lesions on cognitive performance [18]. In elderly individuals, cerebral manifestations of small vessel ischemic vascular disease are also important components of vascular dementia [14,19-22].

In this study, age was determined to be a strong predictor of both white matter lesion volume and leukoaraiosis severity. Additionally, neither of these lesions
correlated with HIV-specific parameters, suggesting that in our cohort, white matter lesions as well as periventricular leukoaraiosis may be more indicative of small vessel vascular disease than HIV-related CNS pathology. Given the known relationship between cerebral small vessel vascular disease manifestations and cognitive decline in the seronegative population, it is likely these lesions will similarly affect cognitive performance in aging HIV seropositive individuals as well.

However, the relationship between white matter hyperintensities (WMH) and cognitive performance in HIV infection is somewhat controversial. An association between presence of WMH and worse performance on tests of psychomotor speed and verbal memory has been reported [23]. Additionally, presence of dementia in HIV is associated with decreased white matter volume [24]. However, other studies have reported no relationship between WMH and cognitive performance in HIV infection [25-27]. This discrepancy has been partially resolved with the advent of newer neuroimaging techniques which allow improved detection of white matter injury [28,29], and provide further support for a relationship between white matter damage and severity of cognitive impairment in HIV seropositive individuals [30-34]. Additionally, the results of this study suggest white matter lesions are likely to be even more common in HIV seropositive individuals (leukoaraiosis was present in 84% of the subjects, and punctate white matter lesions in 30%) than as reported in the general population (up to 20% of elderly individuals) [6], suggesting these lesions may play an even greater role in cognitive impairment among aging HIV seropositive individuals than in the general population.
This study is limited by the lack of pathological corroboration of the imaging findings, without which enlarged perivascular spaces may be mistaken for lacunar infarcts [35]. However, this type of error would be expected to be randomly distributed among all patients and not associated with one group or another. Further investigations into the rate of development of these lesions in HIV seropositive individuals, and the contribution of cerebral small vessel vascular disease manifestations to cognitive impairment and decline in elderly HIV seropositive individuals is warranted.

With an increasing percentage of HIV seropositive individuals living to older ages, combined with the high rate of occurrence of small vessel vascular disease lesions in this population and the known cognitive effects of these lesions in the general population, the importance of small vessel vascular lesions as an etiology of cognitive impairment in HIV infection is likely to increase in the coming years. The results of this study suggest the need for aggressive evaluation and treatment of vascular risk factors in HIV seropositive individuals.
References


Petition for Admission to a Doctorate in Same Discipline

**Part I.** To be completed by the student

<table>
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<tr>
<th>Name</th>
<th>McMarthen, Aaron</th>
<th>UH ID No.</th>
<th>1466975</th>
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<tr>
<td>Mailing Address</td>
<td>2333 Kapiolani Blvd. #3106</td>
<td>Honolulu</td>
<td>HI 96826</td>
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<td>Date of Graduation</td>
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- Are you currently pursuing a doctorate in another discipline? [ ] Yes [X] No
- Do you already hold a doctorate? [X] Yes [ ] No

I certify that I have read and understand the policies and instructions for this form.

Signature of Student: ____________________________ Date: 4/5/07

**Part II.** To be completed by the graduate chair

- [X] Approved, for Summer 2007
- [ ] Not Approved

If the student is an international student, indicate whether the student will be receiving a 0.50 FTE graduate assistantship:

- [ ] Yes [X] No

I certify that this petition is in compliance with the policies and instructions for this form.

Signature of Graduate Chair: ____________________________ Date: 4/5/07

**GRADUATE DIVISION ACTION**

- [ ] Approved [ ] Not Approved By ____________________________ Date ____________________________

Remarks

C: Graduate Program

2540 Maile Way, Spalding Hall 352, Honolulu, Hawaii 96822
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Master's Plan A – Student Progress Form III

Part I. To be completed by the student

Name: Aaron McMurtry
UH ID No.: 16669751

Graduate Program: Biomedical Science
Degree Objective: MS

Date of Final Exam / Thesis Defense: 04/04/07

I certify that I have read and understand the policies and instructions for this form.

Signature of Student: ____________________________ Date: 04/04/2007

Obtain signatures from the thesis committee:

We certify that we have read and understand the policies and instructions for this form.

<table>
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<th>Signature</th>
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Part II. To be completed by the graduate chair

☑ Approved
☐ Not Approved

Signature of Graduate Chair: ____________________________ Date: 04/04/07

GRADUATE DIVISION ACTION

☐ Approved ☐ Not Approved  By ____________________________ Date ____________

Remarks

C: Graduate Program / Student