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White Matter Lesions on Brain MRI Scan and 5-Year Cognitive Decline: The Honolulu-Asia Aging Study

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Abstract

Objectives—The relationship between cognitive decline and white matter lesions (WMLs) on brain MRI remains controversial, with different findings among ethnic groups. We studied WMLs and five-year cognitive decline in elderly Japanese-American men.

Design—Longitudinal cohort study.

Setting—Population-based study in Honolulu, Hawaii.

Participants—Japanese-American men ages 74–95 years from the Honolulu-Asia Aging Study (HAAS), who were free of prevalent dementia, underwent a protocol brain MRI scan at the fifth HAAS examination (1994–96) and returned for cognitive testing 5 years later, n=267.

Measurements—WMLs were dichotomized as present (grade 3–9, 38.2%) and absent (grade 1–2, 61.8%). Cognitive function was measured by the Cognitive Abilities Screening Instrument (CASI) and 5-year cognitive decline was defined as a drop in CASI score of >=12 points (1 SD).

Results—Men with white matter lesions on MRI at baseline were significantly more likely to experience cognitive decline at 5 years compared to those without (22.4% versus 34.4%, p=0.03). Using multiple logistic regression, adjusting for age, education, apoE4 allele, large or small infarcts on MRI, baseline CASI score and hypertension, those with WMLs were significantly more likely to develop 5-year cognitive decline (OR=2.00; 95% CI=1.10 to 3.65, p=0.02). This

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Author Contributions

Study concept and design: MI, LW, KM
Acquisition of subjects and data: LW, HP, GWR, KM
Analysis and interpretation of the data: MI, LW, CB, RC, HP, LL, RDA, GWR, KM
Preparation of manuscript: MI, KM
Critical review of manuscript: LW, CB, RC, HP, LL, RDA, GWR

association was stronger in men who were cognitively intact and free of ApoE4 genotype and clinical stroke at baseline.

Conclusion—Presence of white matter lesions on MRI was significantly associated with higher odds of five-year cognitive decline among older Japanese-American men. Presence of white matter lesions may help identify people at risk for developing dementia, who may benefit from early intervention.

Keywords

White matter lesions; Brain MRI; Cognitive decline; Aged; Japanese-American men

OBJECTIVE

White matter lesions (WMLs) are high intensity lesions on both proton density and T2 weighted MRI scans and areas of lucency on head CT scans. Pathophysiological origins of WMLs are diverse, with multiple cerebrovascular[1–2] and neuropathological factors[3] contributing. The frequency of WMLs reportedly increases with age,[4] presence of cardiovascular risk factors including hypertension, and transient ischemic attacks[5–6] or cerebrovascular accidents.[7] Previously, WMLs have been reported to be a risk factor for poor outcomes in the elderly, including functional decline[8] and death.[9–10] However, the clinical association of these lesions and cognitive decline remains controversial, since WMLs are observed in both demented and non-demented elderly individuals. There is considerable evidence from cross-sectional studies for the association between WMLs and cognitive impairment in elderly individuals.[5, 11–13] Some longitudinal studies have shown that severity of WMLs correlates inversely with cognitive test performance in older adults; however, others have not found this association. For example, Kuller and colleagues found no association between WMLs and 3-year cognitive decline in the Cardiovascular Health Study (CHS) cohort.[14] However, the Rotterdam Scan Study found that severity of periventricular but not subcortical WMLs was associated with steeper decline in cognitive function over 5 years in non-demented elderly participants in the Netherlands.[15] Most of these previous studies on WMLs have been in White and African American populations, and there have been no previous longitudinal population-based studies in Asians.

METHODS

Study Design and Population

The Honolulu Heart Program (HHP) began in 1965 as a population-based cohort study of cardiovascular diseases.[16] The cohort consisted of 8,006 Japanese-American men living on the island of Oahu, Hawaii, with ages ranging from 45 to 68 years at baseline (born 1900–1919). The Honolulu-Asia Aging Study (HAAS) began with the fourth HHP examination (1991–1993), to study cognitive function, disability and other diseases of aging.[17] A total of 3,734 men ages 71–93 years were examined, representing 80% of survivors of the original HHP cohort. The study was approved by the Institutional Review Board of Kuakini Medical Center, Honolulu, Hawaii. All subjects were informed about the study objectives and gave written informed consent.

Brain MRI scans were completed at the fifth examination cycle (1994–1996) on a sub-set of the cohort. Originally, a total of 845 men were invited for the procedure. The sub-sample included a 10% random sample (n=226) and a randomly selected over-sample (n=619) of those with prevalent dementia, poor CASI (defined as score <74),[18] Apolipoprotein E4(ApoE4) genotype, and prevalent clinical stroke.[19] MRI scans were acquired on 599 participants (70.9% of those invited), after discounting for deaths, refusals and technical difficulties with the scans. Of these, 576 scans (ages 74–95) were successfully scored at the central reading center at Johns Hopkins University.[20] Those with successful scans (n=576), compared with those who could not undergo the MRI in the total sample selected for MRI (n=269), were significantly younger, more educated, and were less likely to be demented or cognitively impaired; however, there were no significant differences in ApoE4 positivity or prevalent clinical stroke.[20] In this analysis, we used MRI scan data on 267 subjects who returned for cognitive testing at exam 7 (5 years later), and who did not have prevalent dementia at baseline.

Predictor Variable: White Matter Lesions on MRI Scan

MRI scans were acquired at the Kuakini Medical Center in Honolulu, Hawaii, with a GE Signa Advantage 1.5 T machine. The scan protocol, which took approximately 20–30 minutes to acquire, consisted of four sequences: sagittal 5 mm slices, a 3-D oblique spoiled-gradient recalled-echo sequence (SPGR) with 124 slices of 1.6 mm, axial proton density-weighted fast spin-echo sequence, and axial fast spin-echo sequence (T2-weighted, 3 mm sections).[20] Semi-quantitative readings of atrophy, white matter lesions, and infarct-like lesions were performed at Johns Hopkins University, following the Cardiovascular Health Study (CHS) protocol.[21] The White Matter Lesion (WML) load was assessed as the total extent of periventricular and subcortical white matter signal abnormality on spin density weighted axial images, and ranged from no changes (grade 0) to almost all white matter involved (grade 9). Small infarct lesions were defined by size (<3 mm), shape (round), and location (subcortical). The large infarcts were distinguished from small infarct lesions by size (larger than 3 mm) and shape (not round).

We classified the MRI parameters as categorical variables (high and low categories). We dichotomized WMLs as present (grade 3–9, 38.2% of sample, grade 3 19.1%, grade 4 8.2%, grade 5 6.4%, grade 6 3.0%, grade 7 1.5%, and grade 8–9 0%) and absent (grade 1–2, 61.8% of sample, grade 1 40.5%, and grade 2 21.4%), as previously defined by the CHS.[14] Small and large infarcts were dichotomized as present (1 or more infarcts) or absent, respectively.

Outcome Variable: Five-Year Cognitive Decline

Participants were screened for cognitive function at baseline (Exam 5, 1994–96: N=452) and at 5-year follow-up (Exam 7, 1999–2000: N=267) with the 100-point Cognitive Abilities Screening Instrument (CASI).[18] The CASI is a comprehensive measure of global intellectual function, developed for use in cross-cultural and cross-national studies. It is a combination of the Hasegawa Dementia Screening Scale, the Folstein Mini-Mental State Examination, and the Modified Mini-Mental State (3-MS) test. It measures 9 cognitive domains and scores range from 0 to 100 (higher scores represent better cognitive function than lower scores). We defined 5-year cognitive decline as a drop in CASI score of >= 12 points (1 standard

deviation of change). A total of 27 % (72/267) of participants had 5-year cognitive decline using this definition.

Co-Variates

Baseline covariates were selected because of their potential relationships with WMLs or cognitive decline. These included cardiovascular disease (CVD) risk factors and other known factors that may influence cognitive function. Seated blood pressure (BP) was measured at exam 5 with a mercury sphygmomanometer and appropriately sized cuff, and a mean of two measures was used. The presence of hypertension (HTN) was defined as systolic BP >=140 or diastolic BP >=90 or use of antihypertensive medications. We did not adjust in multivariate models for certain CVD risk factors that were not significantly associated with WMLs in bivariate analyses. These included: baseline body mass index (BMI) (weight in kg/height in m^2) at exam 5, prevalent diabetes mellitus (using modified ADA criteria) at exam 4, pack years of smoking at exam 4, total cholesterol level at exam 4, and physical activity index at exam 5. The physical activity index (PAI) is an activity measure that was designed to evaluate an individual's general history of usual activity by providing a rough estimate of overall daily energy expenditure[22] and was reported to be associated significantly with levels of other physical activity measures in a previous study.[23] We also did not adjust in multivariate models for the presence of depressive symptoms (the presence of depressive symptoms was defined as CES-D 11 score > 9), which was not significantly different in the groups with or without WMLs. Covariate information about diabetes, cholesterol, smoking and the presence of depressive symptoms was not available at exam 5 and therefore data from exam 4 (3 years previous) were used.

Other covariates included age at exam 5 in years, and the number of years of formal education by self-report. ApoE4 genotype was dichotomized into carriers (either homozygotes or heterozygotes) and non-carriers of the ApoE4 allele. The presence of large and small infarcts on MRI was assessed by the CHS protocol, as described above. We also adjusted for baseline CASI score at exam 5 for this analysis and for time of follow-up between exam 5 and exam 7.

Statistical Methods

We analyzed MRI scan data on 267 subjects who returned for cognitive testing at exam 7 (5 years later), and who did not have prevalent dementia at baseline. We divided the cohort into two groups based on WMLs, present and absent. Mean age-adjusted baseline characteristics, including demographic factors, ApoE4 genotype, cardiovascular risk factors, and small and large infarcts on MRI scan were compared between the two WML groups using General Linear Models (GLM). Mean age-adjusted CASI scores at Exam 5 and Exam 7, 5-year drop in CASI score, and percent with 5-year cognitive decline were also compared between the two WML groups using GLM.

Multiple logistic regression analyses were performed to assess the association between presence of WMLs and 5-year cognitive decline, adjusting for baseline age, education, apoE4 allele, presence of large and small infarcts on MRI scan, hypertension, time of follow-up between exam 5 and exam 7, and baseline CASI score at Exam 5. Multiple

logistic regression models were repeated, excluding those with low CASI score (< 74), history of clinical stroke at baseline and positive ApoE4 genotype. All analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina). A value of $p < 0.05$ was considered statistically significant.

RESULTS

We graded participants with WMLs by CHS grade. Men were dichotomized into two groups: those with WMLs absent (defined as grade 1–2, n=165/267; 61.8%) and those with WMLs present (defined as grade 3–9, n=102/267; 38.2%). Mean baseline characteristics of subjects by white matter lesion group are summarized in Table 1. Men with presence of WMLs were significantly older than those without WMLs. After adjusting for age, those with presence of WMLs had higher prevalence of small infarcts on MRI and hypertension at baseline. There were no significant differences in education, ApoE4 genotype, prevalence of large infarcts on MRI, prevalent diabetes, smoking pack-years, physical activity index, BMI, serum cholesterol level, the presence of depressive symptoms or alcohol consumption by presence or absence of WMLs.

Table 2 shows mean age-adjusted cognitive function characteristics by WML groups. Men with presence of WMLs had significantly lower CASI scores at baseline (exam 5, 1994–96) and five-year follow-up (exam 7, 1999–2000). They also had significantly higher rates of 5-year cognitive decline.

Table 3 shows logistic regression analyses, with presence of 5-year cognitive decline as the outcome variable. After adjusting for age, education, ApoE4 genotype, large or small infarcts on MRI, hypertension, baseline CASI score and time of follow-up between exam 5 and exam 7, those with WMLs were twice as likely to have 5-year cognitive decline (OR=1.97; 95% CI=1.08–3.61, p=0.03). We repeated multiple logistic regression analyses after excluding men with cognitive impairment, prevalent clinical stroke at baseline or ApoE4 genotype positive. The relationship between WMLs and 5-year cognitive decline grew stronger in this subgroup (OR=4.13; 95% CI=1.22–14.0, p=0.02).

CONCLUSION

We found that presence of WMLs on MRI was significantly associated with 5-year cognitive decline among older Japanese-American men without dementia in a large longitudinal population-based study. In addition, when we excluded those with cognitive impairment, history of clinical stroke at baseline or ApoE4 genotype positive, this association grew stronger. Our results suggest that presence of WMLs on brain MRI scan may be useful as a potential predictor of future cognitive decline and dementia. To our knowledge, this is the first large population-based study of the relationship between WMLs and cognitive decline in an Asian population. To date, there have been many cross-sectional studies that have found significant relationships between WMLs and cognitive function in demented and non-demented elderly subjects.[5, 11–12, 24] The CHS study performed MRI scans in 3301 community-dwelling people aged 65 years or older without clinical history of stroke or transient ischemic attack, and found that performance on cognitive tests declined with

increasing grade of WMLs, particularly in men.[5] In the Rotterdam Study, both periventricular and subcortical WMLs were associated with poorer performance on all neuropsychological measures, particularly those involving speed of cognitive processes.[11] In the Austrian Stroke Prevention Study, WMLs were associated with poorer cognitive performance among 150 elderly non-demented volunteers.[12]

However, longitudinal studies have showed conflicting results. For example, Hunt and colleagues found no association between WMLs and cognitive function and 5-year cognitive decline in non-demented Hispanic and Non-Hispanic elderly populations in the longitudinal Aging Process Study at the University of New Mexico.[4] Kuller and colleagues found no association between WMLs and 3-year cognitive decline in white and black elderly individuals from the Cardiovascular Health Study.[14] de Groot and colleagues reported that only periventricular cerebral WMLs but not subcortical WMLs were related to cognitive decline over a mean follow-up period of 7.3 years in the Rotterdam Study, which included a Dutch non-demented elderly population .[25] However, in the National Heart, Lung, and Blood Institute Twin Study by Swan and colleagues, there was a relationship between total WMLs and decline of neurobehavioral functioning over 10 years of follow-up in elderly white subjects.[26] Garde and colleagues had longitudinal data on cognitive change over 30 years in a population in Denmark, and found an association between cognitive decline and WML severity in both periventricular and subcortical regions on MRIs performed at age 80 years.[27] A recent study by Tracy and colleagues showed a strong association between total WML burden and cognitive decline over a 5-year period in elderly Caucasian and non-Caucasian subjects in the ABC study at Johns Hopkins University. They also observed a strong overlap between total and periventricular WML volumes in this study.[28]

In our study, we used semi-quantitative readings of WMLs and infarct-like lesions following the Cardiovascular Health Study (CHS) protocol.[21] Our results were different from those of the CHS study, which may be partly due to differences in the length of follow-up (3 years in CHS and 5 years in HAAS) and differences in definitions of cognitive decline (CHS - decrease of five points or more in the 3MSE; HAAS - decrease of 12 points or more in CASI).[14] It is possible that 3 years may not be sufficient time to see the cognitive changes related to WMLs. Also, our populations were different, since we only studied elderly Japanese-American men, compared to elderly white and black populations in the CHS. Unlike some studies, we did not differentiate between the location of WMLs. However, the ABC study found a strong overlap between total and periventricular WML volumes.[28]

Our study has many strengths. This is the first longitudinal population-based study on this subject in an older Asian population. The cohort has been followed since 1965, with high response rates and detailed information available about many clinical characteristics. We had a long follow-up period for cognitive decline (5 years) and the numbers were relatively large for an MRI study. Limitations of our study include limited generalizability, since only Japanese-American men were studied. The participants receiving the MRI were a small portion of the original cohort, and power to detect relationships was limited. Our population had higher ApoE genotype positivity compared to those shown in other community samples. [14,15] Although there could be potential residual bias from ApoE4 genotype positivity, by over-sampling of subjects with an ApoE4 allele who are at higher risk of

cognitive impairment, we did not find a significant interaction with ApoE4 positivity in our analyses. However, we adjusted for ApoE4 genotype positivity in logistic regression analyses. We also repeated logistic regression model where we removed all elements for which there was oversampling (prevalent dementia or cognitive impairment, ApoE4 positivity, or prevalent clinical stroke). The results did not change. Also, brain MRI examinations were done at a single point in time and there may be possible misclassification of WMLs. However, these readings were performed using a highly standardized MRI reading system previously used for a number of large national studies[6] and inter-reader reliability is close to 100 % within 1 grade difference.[29] The HAAS population was older and we could not eliminate the survivor effect since we were only able to study those who survived to participate in exam 7. However, since presence of WMLs was associated with higher mortality (48.2% versus 32.7%), we lost more participants among those with WMLs. This may weaken the significance of our results, but should not give us false positive results.

The mechanisms underlying this relationship between WMLs and cognitive decline in non-demented elderly populations remain unclear. Faith and colleagues reported the influence of WMLs on specific cognitive domains, particularly those that are reliant on processing speed and widely distributed neural networks in a quantitative review.[6] Also WMLs and infarcts were related to decline in executive function and measures of focused attention derived from the Cognitive Drug Research (CDR) system.[30] In our study, even after adjusting for large and small infarcts on MRI, WMLs were still significantly associated with 5-year cognitive decline.

In conclusion, we found that WMLs on MRI were associated with 5-year cognitive decline in non-demented elderly Japanese-American men. A possible mechanism to explain our findings is that WMLs may cause neural loss and disruption of the fibers of white matter tracts, thus slowing neural transmission. In the future, WMLs may help identify those at risk for dementia or cognitive decline, who may benefit from early interventions. Further investigations are necessary to study the relationship between WMLs and incident dementia outcomes in the HAAS, and to examine the correlation between WMLS and global functional decline.

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Sponsor's Role

The sponsors had a role in the design and methods of this study when done under contract. However, the sponsors had no role in subject recruitment, data collections, analysis, or preparation of this manuscript.

Appendix

Conflict of Interest

None of the authors report conflicts of interest with commercial enterprises.

Elements of Financial/Personal Conflicts	*Author 1 Michiko Inaba MD		Author 2 Lon White, MD		Author 3 Christina Bell MD		Author 4 Randi Chen, MS	
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		x		x		x		x
Grants/Funds		x		x		x		x
Honoraria		x		x		x		x
Speaker Forum		x		x		x		x
Consultant		x		x		x		x
Stocks		x		x		x		x
Royalties		x		x		x		x
Expert Testimony		x		x		x		x
Board Member		x		x		x		x
Patents		x		x		x		x
Personal Relationship		x		x		x		x

Conflict of Interest Disclosures:

Elements of Financial/Personal Conflicts	Author 5 Helen Petrovitch, MD		Author 6 Lenore Launer PhD		Author 7 Robert D Abbott PhD		Author 8 G. Webster Ross, MD	
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		x		x		x		x
Grants/Funds		x		x		x		x
Honoraria		x		x		x		x
Speaker Forum		x		x		x		x
Consultant		x		x		x		x
Stocks		x		x		x		x
Royalties		x		x		x		x
Expert Testimony		x		x		x		x
Board Member		x		x		x		x
Patents		x		x		x		x

Elements of Financial/Personal Conflicts	Author 5 Helen Petrovitch, MD		Author 6 Lenore Launer PhD		Author 7 Robert D Abbott PhD		Author 8 G. Webster Ross, MD	
	Yes	No	Yes	No	Yes	No	Yes	No
Personal Relationship		x		x		x		x
Elements of Financial/Personal Conflicts	**Author 9 Kamal Masaki, MD**							
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		x						
Grants/Funds		x						
Honoraria		x						
Speaker Forum		x						
Consultant		x						
Stocks		x						
Royalties		x						
Expert Testimony		x						
Board Member		x						
Patents		x						
Personal Relationship		x						

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Table 1

Mean Baseline Characteristics by White Matter Lesion groups (Exam 5, 1994–96).

Baseline Characteristics	White Matter Lesions		P Value
	Absent (WML grade 1–2)	Present (WML grade 3–9)	
Age (years)	79.7 ± 4.1	81.5 ± 5.2	**0.01**
Education (years) *	10.7 ± 2.9	10.3 ± 3.2	0.31
ApoE4 genotype (%) *	42.5 ± 49.9	34.6 ± 48.9	0.21
Large Infarct on MRI (%) *	36.3 ± 48.9	45.1 ± 46.9	0.16
Small Infarct on MRI (%) *	15.3 ± 47.7	33.1 ± 50.3	**0.01**
Hypertension (%) *	67.3 ± 36.1	80.4 ± 47.2	**0.02**
Diabetes Mellitus (%) *	25.2 ± 37.2	29.8 ± 36.3	0.43
Smoking (pack years) *	24.8 ± 3.2	24.3 ± 2.9	0.92
Physical Activity Index *	29.3 ± 47.1	29.2 ± 39.9	0.70
Body Mass Index (kg/m^2) *	23.5 ± 34.6	24.0 ± 30.2	0.15
Serum Cholesterol (mg/dl) *	194.0 ± 3.2	194.1 ± 3.1	0.99
Depressed (%) *	8.9 ± 28.5	4.2 ± 20.3	0.17
Alcohol intake (oz/month) *	14.6 ± 26.5	18.8 ± 44.9	0.36

* Age adjusted.

Abbreviations: WML=white matter lesions; MRI=magnetic resonance imaging.

Table 2

Mean Age-Adjusted Cognitive Function Characteristics by White Matter Lesion groups.

Cognitive Function Characteristics	White Matter Lesions		P Value
	Absent (WML grade 1–2)	Present (WML grade 3–9)	
Baseline CASI score (exam 5, 1994–96)	80.8 ± 9.0	77.6 ± 11.6	**0.02**
Five-Year follow-up CASI score (exam 7, 1999–2000)	73.2 ± 18.1	68.1 ± 19.6	**0.04**
Five-Year Cognitive Decline (%)	22.4 ± 41.3	34.4 ± 47.9	**0.03**

Abbreviations: WML=white matter lesions; CASI=cognitive abilities screening instrument.

Table 3

Multiple Logistic Regression Models for white matter lesions, with presence of 5-Year Cognitive Decline as the Outcome Variable. Those with prevalent dementia at baseline were excluded.

Models	Odds Ratios (95% CI)	P value
Model 1 unadjusted	1.95 (1.13–3.38)	**0.02**
Model 2	1.91 (1.06–3.44)	**0.03**
Model 3	1.97 (1.08–3.61)	**0.03**
Subgroup analysis: Excluding subjects with cognitive impairment (CASI < 74) or prevalent clinical stroke at baseline		
Model 1 unadjusted	2.10 (1.05–4.19)	**0.04**
Model 2	2.33 (1.08–5.00)	**0.03**
Model 3	2.47 (1.10–5.55)	**0.03**
Subgroup analysis: Excluding subjects with cognitive impairment (CASI < 74) or prevalent clinical stroke at baseline or ApoE genotype positive *		
Model 1 unadjusted	2.71 (1.07–6.89)	**0.04**
Model 2	3.90 (1.26–12.10)	**0.02**
Model 3	4.13 (1.22–14.00)	**0.02**

Model #1 unadjusted.

Model #2 adjusted for age, education, ApoE4 genotype, large or small infarcts on MRI, and baseline CASI.

Model #3 adjusted for age, education, ApoE4 genotype, large or small infarcts on MRI, baseline CASI, baseline hypertension, time of follow-up.

* Subgroup analyses excluding men with ApoE4 genotype were not adjusted for ApoE4.

Abbreviations: CASI=cognitive abilities screening instrument.