Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2014;37:244–250
DOI: 10.1159/000358117

Received: July 18, 2013
Accepted: December 17, 2013
Published online: March 25, 2014

Extreme Deep White Matter Hyperintensity Volumes Are Associated with African American Race

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Key Words
White matter disease · Women and minorities · Coronary artery disease · Imaging · Risk factors

Abstract
Background: African Americans (AAs) have a higher prevalence of extreme ischemic white matter hyperintensities (WMHs) on magnetic resonance imaging (MRI) than do European Americans (EAs) based on the Cardiovascular Health Study (CHS) score. Ischemic white matter disease, limited to the deep white matter, may be biologically distinct from disease in other regions and may reflect a previously observed trend toward an increased risk of subcortical lacunar infarcts in AAs. We hypothesized that extreme deep WMH volume (DWMV) or periventricular volume (PV) may also have a higher prevalence in AAs. Thus, we studied extreme CHS scores and extreme DWMV and PV in a healthy population enriched for cardiovascular disease risk factors. ***Methods:*** We imaged the brains of 593 subjects who were first-degree relatives of probands with early onset coronary disease prior to 60 years of age. WMHs were manually delineated on 3-tesla cranial MRI by a trained radiology reader; the location and volume of lesions were characterized using automated software. DWMV and PV were measured directly with automated software, and the CHS score was determined by a neuroradiologist. Volumes were characterized as being in the upper 25% versus lower 75% of total lesion volume. Volumes in the upper versus the remaining quartiles were examined for AA versus EA race using multiple logistic regression (generalized estimating equations adjusted for family relatedness) and adjusted for major vascular disease risk factors including age ≥55 years versus <55, sex, current smoking, obesity, hypertension, diabetes and low-density lipoprotein >160 mg/dl. ***Results:*** Participants were 58% women and 37% AAs, with a mean age of 51.5 ± 11.0 years (range, 29–74 years). AAs had significantly higher odds of having extreme DWMVs (odds ratio, OR, 1.8; 95% confidence interval, CI, 1.2–2.9; p = 0.0076) independently of age, sex, hypertension and all other risk factors. AAs also had significantly higher odds of having extreme CHS scores ≥3 (OR, 1.3; 95% CI, 1.1–3.6; p = 0.025). Extreme PV was not significantly associated with AA race (OR, 1.3; 95% CI, 0.81–2.1; p = 0.26). ***Con-***

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clusions: AAs from families with early-onset cardiovascular disease are more likely to have extreme DWMVs (a subclinical form of cerebrovascular disease) and an extreme CHS score, but not extreme PV, independently of age and other cardiovascular disease risk factors. These findings suggest that this AA population is at an increased risk for DWMV and may be at an increased risk for future subcortical stroke. Longitudinal studies are required to see if DWMV is predictive of symptomatic subcortical strokes in this population.

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Introduction

Over 790,000 strokes occur annually in the USA, making stroke the fourth leading cause of death and the leading cause of disability in people over the age of 65 [1]. African Americans (AAs) have a higher risk of stroke and subcortical lacunes as well as attendant morbidity and mortality than do European Americans (EAs) [2, 3]. Ischemic white matter hyperintensities (WMHs) are thought to represent ischemic small vessel disease of the brain and have been associated with stroke and dementia [4, 5]. The Cardiovascular Health Study (CHS) score is an ordinal measure of WMH that ranges from 0 to 9 [6]. It is based on visual comparison of participant magnetic resonance (MR) images to standardized 'scoring' MR images and represents a qualitative assessment of WMH burden, including periventricular volume (PV) and deep WMH volume (DWMV), as well as ventricular size and atrophy. The Atherosclerosis Risk in Communities (ARIC) study reported that the prevalence of high CHS scores (≥3) is greater in AAs than in EAs [6, 7]. In general, the difference between a CHS of 2 and a CHS of 3 involves a higher burden of subcortical lesion, or DWMV [6]. PV represents the most critical portion of WMH volume measured by the CHS and is more predominant in elderly people than in younger individuals [8–10].

In population-based studies, AAs have been found to have a higher prevalence of subcortical small vessel disease in the form of silent lacunar strokes [8, 11]. Deep white matter lesions are anatomically specific to the subcortical region of the brain and are thought to have a different pathology and attendant risk factors than WMHs in other regions [4, 12–14]. It is unknown whether the prevalence of extreme DWMV is greater in AAs than in EAs or if other unique epidemiological characteristics are associated with DWMV. Because of the previously identified association between AA race and subcortical stroke, we hypothesized that subcortically located extreme DWMV, rather than extreme PV, may be increased in AAs.

To this end we studied the prevalence of severe WMH disease as represented by a CHS score of 3 or greater, as well as extreme DWMV and PV in the upper quartile of the range, in an asymptomatic population of AAs and EAs enriched for vascular risk to determine if extreme WMH was associated with AA race and other risk factors. We applied updated 3.0-tesla magnetic resonance imaging (MRI) volumetrics, which directly quantify and localize DWMV and PV, and compared the data to ordinal CHS scores. Our goal was to determine whether different regions, representing the components of the CHS score, would have different associations with previously identified risk factors, including race [15].

Methods

Sample and Recruitment

Participants were recruited from the ongoing prospective study called Genetic Study of Atherosclerosis Risk (GeneSTAR), which was designed to characterize genetic and biological factors associated with incident cardiovascular and cerebrovascular disease in families of patients with early-onset coronary artery disease (CAD). This study was approved by the Johns Hopkins Medicine Institutional Review Board. All participants gave their informed consent. Early-onset CAD was used as a marker for increased familial risk of vascular disease. Probands under the age of 60 (39.5% AA and 33.6% female) were identified at the time of hospitalization for an early-onset CAD event, including acute myocardial infarction or acute coronary syndromes with angiographic evidence of a flow-limiting stenosis of >50% diameter in at least 1 coronary artery. Apparently healthy, asymptomatic siblings and their offspring, and the offspring of the probands, were eligible for this study if they were 29–75 years of age and had no history of CAD, stroke or transient ischemic attacks. Siblings and offspring were excluded if they had: a history of chronic corticosteroid use; life-threatening diseases such as active AIDS, renal failure or cancer; neurological diseases that would preclude accurate MRI interpretation, or implanted metals that precluded MRI testing.

Participant Screening

Subjects underwent comprehensive screening for risk factors. Medical history, current medication use and physical condition were assessed by physical examination and standard methods. Participants self-identified their racial group and were screened for traditional Framingham stroke risk factors, including hypertension, diabetes, smoking and obesity [16]. Participants with atrial fibrillation or symptomatic heart disease were excluded. Anthropometric measures, including height in inches and weight in pounds, were determined with a fixed stadiometer and a balance scale while the participant was wearing light clothing and no shoes. The body mass index was calculated as weight in kilograms divided by height in meters squared. Obesity was defined as a body mass index ≥30, in accordance with the national obesity guidelines [17].

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Current cigarette smoking was assessed by self-report of any smoking within the past month and/or 2 expired carbon monoxide levels of ≥8 ppm. Blood pressure was measured 3 times over the course of the day according to American Heart Association guidelines. The average was used to characterize resting blood pressure. Hypertension was defined as an average blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic and/or use of an antihypertensive drug. After participants had fasted for 9–12 h overnight, blood was taken for measurement of lipids and glucose. Type 2 diabetes was defined as a physician-diagnosed history, a fasting glucose ≥126 mg/dl and/or use of hypoglycemic antidiabetic medications. Total cholesterol, high-density lipoprotein cholesterol and triglyceride levels were measured according to US Centers for Disease Control standardized methods [18], and low-density lipoprotein cholesterol was estimated by using the Friedewald formula [19]. For persons with triglyceride levels >400 mg/dl, ultracentrifugation methods were used. Hypercholesterolemia was defined as a low-density lipoprotein cholesterol ≥160 mg/dl.

Magnetic Resonance Imaging

All participants underwent magnetic resonance scanning according to a standard protocol on a Philips 3.0-tesla scanner. The series included the following imaging sequences: (1) axial T1-weighted MPRAGE (magnetization prepared rapid gradient echo): TR (repetition time) 10 ms; TE (time to echo) 6 ms; TI (inversion time) voxel size $0.75 \times 0.75 \times 1.0$ mm^3; contiguous slices, with field of view imaging (FOV) 240 mm; matrix $256 \times 256 \times 160$ mm; (2) axial turbo spin echo FLAIR (fluid attenuation inversion recovery): TR 11,000 ms; TI 2,800 ms; TE 68 ms; voxel size $0.47 \times 0.47 \times 3.0$ mm^3; contiguous slices, FOV 240 mm; matrix 256×256 mm. All images were reviewed for clinical pathology, checked, stored first on the in-house reading system and then transferred to an offsite permanent storage facility. Confirmatory clinical reading was completed by a trained neuroradiologist (D.Y.) using the methods of the CHS to define CHS scores on an ordinal scale ranging from 0 to 9 [6]. We considered a CHS score of >3 as extreme (provide REF or alternative explanation, e.g. top 15%). Image processing and volumetric analysis were completed by biomedical engineers and their technical staff.

Volumetric Assessment

MPRAGE images were skull-stripped and coregistered to FLAIR images. Spatial normalization of the coregistered MPRAGE and FLAIR images into MNI space was performed via affine transformation. A trained rater manually delineated WMHs on the normalized MPRAGE and FLAIR images using Medical Image Processing, Analysis and Visualization software [20]. We segmented the brain in native MPRAGE space using an automated probabilistic methodology that utilizes a topology-preserving algorithm; the resulting tissue mask was mapped to MNI space [21]. We measured total brain intracranial, cortical gray matter, and white matter volumes in native MPRAGE space, and WMH volumes in MNI space. Total brain volume, in cubic millimeters, was identified as the sum of white matter, WMH and gray matter volume from the vertex of the brain to the foramen magnum. Intracranial volume was defined in cubic millimeters as the sum of all dura mater, soft tissue, and sulcal and ventricular cerebrospinal fluid volumes, inferior to bone, from the vertex to the foramen magnum [22].

Spatial characterization of WMHs was carried out with in-house software designed to determine their location in relation to the ventricles and the deep white matter region in 3-dimensional space. We determined connected components of WMHs with digital 26 connectivity (by measuring all 26 adjacent voxels). We defined periventricular lesions as those that were contiguous with a lesion voxel that was within 4 mm of the ventricle and defined deep white matter lesions as those that were not contiguous.

Statistical Analysis

Extreme DWMV and extreme PV were defined as total DWMV or total PV greater than the 75th percentile. Extreme CHS scores were defined as a CHS score of 3 or greater. Demographic and vascular risk factor distributions were tabulated by the presence or absence of extreme CHS score, DWMV and/or PV. To test differences by group, we used t tests for normally distributed variables, Wilcoxon rank sum tests for nonnormally distributed continuous variables and χ^2 statistics for categorical variables. The concordance between the dichotomous variables CHS score, extreme DWMV and extreme PV was estimated by using tetrachoric correlation. We used generalized estimating equation regression analyses to correct for intrafamilial correlations and to model being in the highest quartile of DWMV, or PV, or having CHS score ≥3, after adjusting for traditional vascular risk factors, including age, race, sex, hypertension, diabetes, current smoking and obesity.

Results

Study Sample

The study population consisted of 593 apparently healthy individuals identified from 324 families of probands with early-onset CAD (1 proband per family). On average, the study population consisted of 1.8 ± 1.2 relatives per family (range, 1–8). Siblings of probands comprised 53.1% of the group, and offspring of siblings and probands comprised 46.9%. Sample characteristics stratified by race are shown in table 1. Most participants had some white matter disease; 89.9% had deep white matter disease, 73.7% had periventricular disease and 14.3% had a CHS score of 3 or greater.

Association of Extreme DWMV, PV and CHS Score with Race, Controlling for Other Risk Factors

Results of multivariate regression analyses (generalized estimating equations) to predict extreme CHS score, extreme DWMV and extreme PV are shown in table 2, respectively. Many of the variables were correlated with one another – DWMV upper quartile and CHS ≥3: tetrachoric correlation = –0.3338, p = 0.0868; PV upper quartile and CHS ≥3: tetrachoric correlation = 0.8564, p = 0.0325; DWMV upper quartile and PV upper quartile: tetrachoric correlation = –0.7485, p = 0.0592.

Variables independently associated with higher odds of extreme CHS score (table 2) included AA race, older

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Table 1. Demographic characteristics and risk factors of participants by race

Characteristic	AA (n = 220)	EA (n = 373)	p
Age, years	52±11	52±10	0.098
Total cholesterol, mg/dl	192±43	195±39	0.38
HDL cholesterol, mg/dl	58±16	57±17	0.36
LDL cholesterol, mg/dl	115±39	114±37	0.69
Diabetes	21	9	<0.0001
Female sex	64	55	0.0398
Smoking currently	24	13	0.001
Hypertension	59	35	<0.0001
Obesity (BMI ≥30)	58	39	<0.0001
Hypercholesterolemia (LDL ≥160 mg/dl)	11	10	0.58
PV upper quartile	29	23	0.087
Total lesion volume upper quartile	31	22	0.013
DWMV upper quartile	33	21	0.001

Values are means ± SD or percentages. BMI = Body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

age, current smoking and nonobesity. Variables independently associated with higher odds of extreme DWMV included AA race, older age, female sex and nonobesity (table 2). AA race was significantly associated with higher odds of extreme DWMV (OR, 1.8; 95% CI, 1.2–2.9; p = 0.0076), independently of all other risk factors, including hypertension (table 2). When race-specific upper quartiles were used for race-stratified analysis, older age and female sex were associated with higher odds of extreme DWMV in AAs (p < 0.0001 and p = 0.0021, respectively; table 3), whereas older age and thinner body habitus were associated with higher odds of extreme DWMV in EAs (p < 0.0001 and p = 0.026, respectively; table 3).

Age was the only variable independently associated with higher odds of extreme PV. AA race was not associated with higher odds of extreme PV (OR, 1.3; 95% CI, 0.81–2.1; p = 0.26), independently of all other risk factors, including hypertension (table 2).

Discussion

Our results show that the prevalence of extreme DWMV is higher in AA than in EA family members of individuals with premature CAD. This association of AA race with extreme DWMV was independent of age, hypertension and other known cardiovascular disease

Table 2. Fully adjusted logistic regression model predicting CHS ≥3, extreme DWMV and PV

Characteristic	OR	95% CI	p value
CHS ≥3 (n = 593)			
AA	1.9	1.08–3.5	0.025
Female sex	1.07	0.63–1.8	0.79
Diabetic	0.73	0.34–1.5	0.42
Smoking currently	2.1	0.10–4.2	0.036
Hypertension	1.7	0.99–2.9	0.055
Obesity	0.56	0.32–0.98	0.042
Age (estimate)	0.14	0.11–0.18	<0.0001
Extreme DWMV (n = 593)[1]			
AA	1.8	1.2–2.9	0.0076
Female sex	1.6	1.1–2.4	0.021
Diabetic	0.69	0.37–1.3	0.22
Smoking currently	1.3	0.77–2.3	0.29
Hypertension	1.23	0.77–2.0	0.39
Obesity	0.58	0.37–0.91	0.18
Age (estimate)	0.082	0.06–0.1	<0.0001
PV (n = 593)[1]			
AA	1.3	0.82–2.1	0.26
Female sex	0.91	0.60–1.4	0.66
Diabetic	1.3	0.70–12.3	0.41
Smoking currently	1.73	0.95–3.1	0.068
Hypertension	0.98	0.62–1.6	0.94
Obesity	0.69	0.44–1.07	0.10
Age (estimate)	0.11	0.084–0.13	<0.0001

CI = Confidence interval; OR = odds ratio.
[1] Lesion volume in the upper quartile, with age as a continuous variable.

Table 3. Fully adjusted logistic regression model predicting extreme DWMV in AAs and EAs

Characteristic	OR	95% CI	p value
In AAs (n = 220)			
Female sex	2.7	1.4–5.3	0.0021
Diabetic	0.54	0.26–1.14	0.11
Smoking currently	1.7	0.76–3.8	0.20
Hypertension	1.3	0.59–2.7	0.56
Obesity	0.64	0.33–1.23	0.18
Age (estimate)	0.084	0.048–0.12	<0.0001
In EAs (n = 373)			
Female sex	1.1	0.67–1.9	0.68
Diabetic	1.1	0.43–2.7	0.87
Smoking currently	1.1	0.48–2.5	0.83
Hypertension	1.2	0.65–2.2	0.55
Obesity	0.47	0.24–0.91	0.026
Age (estimate)	0.082	0.054–0.11	<0.0001

CI = Confidence interval; OR = odds ratio. Lesion volumes as found in the upper quartile, with age as a continuous variable.

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risk factors. This study confirms the observations of the previous ARIC study, which found an association between AA race and extreme CHS score [7]. Additionally, it builds on the results of the ARIC study by using modern, validated, direct measurements of DWMV with automated white matter segmentation. These methods allow for the attribution of lesions to a brain region and analysis of associations between different risk factors and regions.

AA race has been associated with an increased prevalence of many vascular disease phenotypes, including symptomatic and asymptomatic subcortical lacunar stroke and vascular disease in other organ systems, such as the coronary arteries and peripheral vasculature [23–29]. Furthermore, racial differences in white matter disease burden have been reported to be related to smoking and increased rates and severity of hypertension [7, 30]. Although other studies have emphasized smoking as a risk factor, in our study, smoking was not associated with extreme DWMV in the stratified or combined analysis. Likewise, hypertension did not appear to drive the association between DWMV and AA race. Our analysis of DWMV predictors controlled for the diagnosis of hypertension as well as age. However, we cannot exclude the possibility that genetic differences that affect hypertension, such as angiotensin-converting enzyme polymorphisms, might be more prevalent in this AA population [9]. Additionally, it is possible that an unidentified inheritable trait may be associated with the AA population in this study of related individuals.

Many of our observed associations and correlations support the idea that extreme DWMV is an independent lesion type that conveys risks that differ from those of PV and CHS score. Extreme PV and extreme CHS score shared similar associations, including age, smoking and decreased obesity. It is important to note that hypertension in AAs may represent an undertreated disease with an earlier age of onset as compared to EAs which could have contributed to the increased predominance of extreme DWMV in this group. We were unable to designate the age of onset and control for this factor in our analysis. The correlation between CHS score and PV was stronger than the correlation between CHS score and DWMV. Extreme DWMV was associated with AA race, as was extreme CHS score. However, in our stratified analysis, DWMV was independently associated with female sex but lacked associations with smoking, hypertension and obesity, which were associated with extreme CHS score, despite the fact that the CHS scale emphasized periventricular confluence. In the higher grades of CHS score (>6), involvement of the centrum semiovale is emphasized. These observations would support those of Fazekas et al. [31], who reported different pathological substrates in the periventricular and DWMV regions. In particular we did include the PV caps into the PV calculation. Lesions in this region are reported to be nonischemic in nature. Thus, the lower PV relative to DWMV may reflect a proclivity for ischemic lesions and higher extreme DWMV as compared to PV.

Small vessel vascular disease in the subcortical region has been reported to be more prevalent in the AA population than in either the EA or Hispanic population [23–29]. The DWMV and periventricular lesions lie in the subcortical and periventricular regions, respectively. These regions have very different small vessels, with long cortically based small vessels serving the periventricular region and shorter small vessel perforators serving the subcortical DWMV. In past studies, different locations of WMH have been associated with different risk factors and clinical outcomes [32, 33]. Investigators who have analyzed the pathological nature of deep white matter lesions have reported that risk factors such as endothelial activation and inflammation are more prominent in the short subcortical vessels of the deep white matter than in the long periventricular vessels [4, 12, 32, 34]. Our observations may result from enrichment of these risk factors in our study population [35].

Our findings have similarities to those of the ARIC study of severe CHS scores [7]. In both studies, extreme CHS score was associated with AA race, as well as age, hypertension and smoking. The association of extreme CHS with smoking and hypertension appeared to be stronger in AAs than in EAs in both studies. However, our population differed from that in the ARIC study. Our population was by definition asymptomatic, whereas the ARIC group included both symptomatic and asymptomatic individuals. All of our participants were relatives of a proband, whereas for the most part, ARIC participants were unrelated. The average age in our population was lower – 52, as compared to 62 in the ARIC cohort – and unlike the ARIC population, our population was notably enriched with vascular risk factors [6, 35]. Interestingly, however, the percentage of participants with extreme CHS scores was very similar in the two studies: 14.7% in our population and 12.5% in the ARIC study [36]. Our study is unusual in that obesity appeared to be associated with a reduced risk of WMH of all types by all measures. Although this finding has been reported in other studies, such as the Woman's

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Health Initiative MRI Study [37], in the preponderance of the literature, an increased body mass index is strongly associated with an increased risk of WMH and WMH progression [5, 16, 18, 19, 24, 38, 39]. As shown in other studies, age was the predominant characteristic associated with WMHs of all types [40].

Other unique aspects of our study include the use of an MRI scanner with a 3.0-tesla field strength. This MRI scanner has a greater sensitivity for the detection of WMHs than does the 1.5-tesla scanner and provides better assessment of lesion volume through improved signal-to-noise ratios [13, 15]. In general, prevalence and volume measured for deep white matter lesions and periventricular lesions were significantly higher than those obtained with similar 1.5-tesla methodologies [10]. We also used advanced programming that has been extensively validated to separate, localize and measure WMH volumes. This program has also been extensively validated in other white matter diseases such as multiple sclerosis [20].

Conclusion

AA race is an independent risk factor for extreme DWMV and extreme CHS scores in a population enriched for vascular risk factors. In contrast, PV is not associated with AA race. Extreme DWMV had unique epidemiological associations, suggesting that it represents a unique lesion type that differs from PV lesions. The association between extreme DWMV, which is a subclinical form of ischemic stroke, and AA race suggests that this population may have an increased risk of future subcortical stroke. This risk must be verified in future longitudinal studies.

Acknowledgments

Research reported in this publication was supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health under Award No. R01NS062059. Claire F. Levine, MS, ELS, contributed to the editing of this manuscript.

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