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Age differences in periventricular and deep white matter lesions

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ABSTRACT

Deep white matter hyperintensity (DWMH) and periventricular (PV) white matter lesion volumes are associated with age and subsequent stroke. We studied age differences in these volumes accounting for collinearity and risk factors. Subjects were 563 healthy family members of early-onset coronary artery disease patients. Using 3T magnetic resonance imaging, lesions were classified as DWMH or PV. Age association with lesion classification was analyzed using random effects Tobit regression, adjusting for intracranial volume (ICV) and risk factors. Subjects were 60% women, 36% African-American, mean age 51 ± 11 years. In multivariable analysis adjusted for PV and ICV, DWMH was associated with age ($p < 0.001$) and female sex ($p = 0.003$). PV, adjusted for DWMH and ICV, was age associated ($p < 0.001$). For each age decade, DWMH showed 0.07 log units/decade greater volume (95% CI = 0.04–0.11); PV was 0.18 log units/decade greater (95% CI = 0.14–0.23); slope differences ($p < 0.001$). In people with a family history of coronary artery disease, PV and DWMH are independently and differentially associated with age controlling for traditional risk factors.

1. Introduction

White matter hyperintensities (WMHs) on cranial magnetic resonance imaging (MRI) are thought to represent lesions caused largely by ischemic small vessel disease in the brain, although other pathophysiologic possibilities exist. WMH lesions increase in volume and number with age and are associated with an increased risk for subsequent stroke and dementia (Vermeer et al., 2003; Young et al., 2008). Two lesion subtypes have been proposed based on their proximity to the ventricles (1) periventricular (PV) lesions, which are contiguous with the ventricles and (2) deep WMH (DWMH) lesions, which are distinct and separate from the ventricles. (Enzinger et al., 2006; Fazekas et al., 1993; Rostrup et al., 2012; Spilt et al., 2006) Extreme DWMH lesion volumes have been associated with African-American race and in women in the oldest age ranges. (Nyquist et al., 2014; van den Heuvel et al., 2004) Additionally, hypertension causing aortic pulse wave variability and pulse wave encephalopathy may affect PV and DWMH lesions differently (Henry-Feugeas and Koskas, 2012; Inatomi et al., 2008; Ishimitsu et al., 2008). Both types are strongly associated with age (The LADIS Study Group et al., 2011). These lesion classifications have been supported by previous pathologic and radiologic studies. Specifically, DWMHs have been associated with endothelial activation and different magnetization transfer and diffusion tensor imaging characteristics (Enzinger et al., 2006; Fernando et al., 2006; Jack et al., 2001; Rostrup et al., 2012; Spilt et al., 2006; Young et al., 2008). Nonetheless, physiologic differences and the robustness of these categorizations remain uncertain. Cross-sectional studies have shown the 2 subtypes to be highly collinear, with similar progression patterns in lesion size and total WMHs burden (DeCarli et al., 2005; Sachdev and Wen, 2005).

Distinctions in the total burden of PV and DWMH lesions across different age groups may help to establish a physiologic substrate

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for each lesion type. We hypothesized that DWMH volume and PV volume would demonstrate different patterns of association with age even when accounting for the correlation between the 2 types of lesions, intracranial volume (ICV) and risk factors.

We have reported a markedly higher prevalence of vascular disease risk factors in healthy family members of patients with early-onset coronary artery disease (CAD) (Becker et al., 1998; Nyquist et al., 2009). This population is enriched for vascular disease of all types and may represent a group at increased risk for ischemic white matter disease at younger ages. To date, almost all studies of PV and DWMH have been carried out in older populations or in the context of dementia or other neurologic disease where WML volumes of both subtypes are so great that discrimination is not possible. We thus examined distinct DWMH and PV lesion volumes in relation to age and risk factors in a cross-sectional study of generally middle-aged healthy asymptomatic subjects at an increased risk of vascular disease to determine the extent to which the different regions represent possible distinct and different pathophysiologic subprocesses.

2. Methods

2.1. Sample and recruitment

Using a cross-sectional study design, subjects were randomly selected from among 2573 participants in a long-term prospective study of predictors of incident cardiovascular and cerebrovascular disease in families of index patients with documented early-onset CAD (The GeneSTAR Study: Genetic Study of Atherosclerosis Risk) (Vaidya et al., 2007). The study sample consisted of 563 healthy asymptomatic individuals from 315 families with an early-onset CAD index case (1 per family); on average, 1.8 $\pm$ 1.2 relatives per family (range, 1–8). Early-onset CAD, defined as any acute coronary syndrome before the age of 60 years, was used as a marker for increased risk of vascular disease in healthy relatives. CAD index patients and study subjects were 36% African American. Index cases were 33.6% female. The original index cases, not included in this MRI study, were identified during hospitalization for an acute myocardial infarction or an acute coronary syndrome with angiographic evidence of a flow-limiting stenosis of $>$50% diameter in at least 1 coronary artery. Apparently, healthy asymptomatic siblings, their offspring, and the offspring of the index cases were eligible for this MRI study if they were 30–75 years of age and had no known history of CAD, stroke, or transient ischemic attacks, no history of atrial fibrillation, heart disease of any kind, life-threatening diseases such as active AIDS, renal failure, or cancer; no neurologic diseases that would preclude accurate MRI interpretation; and no implanted metals that were contraindications to performing cranial MRI.

2.2. Participant screening

Subjects underwent a physical examination, medical history, and comprehensive screening for traditional Framingham stroke and cardiovascular risk factors, including blood hypertension, total cholesterol, diabetes, obesity, and smoking (Wang et al., 2003). We measured height (in inches) and weight (in pounds) in light clothing with no shoes. Body mass index was calculated as weight in kilograms/(height in meters)^2. Obesity was defined as a body mass index $\geq$30 kg/m^2 in accordance with national guidelines (Expert-Panel, 1998). Current cigarette smoking was assessed by self-report of any smoking within the past month and/or 2 expired carbon monoxide levels of $\geq$8 ppm. Blood pressure was measured at 3 standard times over the course of an 8-hour day. The average systolic and diastolic blood pressures were each recorded and used to characterize blood pressure. Hypertension was defined as an average blood pressure $\geq$140 mm Hg systolic or $\geq$90 mm Hg diastolic, and/or use of any antihypertensive medication. After subjects had fasted for 9–12 hours overnight, blood was taken for measurement of total cholesterol and glucose levels. Type 2 diabetes was defined as a fasting glucose level $\geq$126 mg/dL ($\geq$7 mmol/L), and/or use of antidiabetic medications. Total cholesterol was measured according to the United States Centers for Disease Control standardized methods (Myers et al., 2000).

2.3. Magnetic resonance imaging

All subjects underwent MRI with a Philips 3T scanner according to a standard protocol. The series included the following imaging sequences: (1) axial T1-weighted MPRAGE (magnetization prepared rapid gradient echo): repetition time = 10 ms, time to echo = 6 ms, inversion time = 983 ms, voxel size = 0.75 $\times$ 0.75 $\times$ 1.0 mm^3, contiguous slices, with field of view imaging = 240 mm, matrix 256 $\times$ 256 $\times$ 160 mm and (2) axial turbo spin echo fluid attenuated inversion recovery (FLAIR): repetition time = 11000 ms, inversion time = 2800 ms, time to echo = 68 ms, voxel size = 0.47 $\times$ 0.47 $\times$ 3.0 mm^3, contiguous slices, field of view imaging = 240 mm, matrix 256 $\times$ 256 mm. All images were reviewed by a study neuroradiologist for clinical pathology, and confirmed by a clinical neuroradiologist, and then stored on the in-house reading system for processing. Final image processing and volumetric analyses were completed by study biomedical engineers, neuroradiologists, radiologists, and their technical staff.

2.4. Volumetric assessment

MPRAGE images were skull-stripped and co-registered to FLAIR images. Spatial normalization of the co-registered MPRAGE and FLAIR images into Montreal Neurologic Institute (MNI) space was performed via affine transformation. A trained neuroimaging rater manually delineated the WMHs on the normalized FLAIR images (with reference to the MPRAGE images for verification of pathology) using Medical Image Processing, Analysis, and Visualization (MIPAV) software (Bazin et al., 2007). We segmented the brain in native MPRAGE space using an automated probabilistic methodology that uses a topology-preserving algorithm and mapped the resulting tissue mask to MNI space (Shiee et al., 2010). We measured total brain, intracranial, cortical gray matter and white matter volumes in native MPRAGE space, and WMH volumes in MNI space (taking into account the transformation of volume between the 2 spaces). Total brain volume (in cubic millimeters) was identified as the sum of white matter, WMHs, 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 meningeal material, soft tissue, and sulcal and ventricular cerebrospinal volumes inferior to bone from the vertex to the foramen magnum (Carass et al., 2011).

We characterized the WMHs spatially using in-house software designed by biomedical engineers to determine location in relation to the ventricles and subcortical region (also called the deep white matter region) in 3-dimensional space. Connected components of WMHs were determined by using digital 26-connectivity.

Periventricular lesions were defined as contiguous with a lesion voxel that was within 4 mm of a ventricle. DWMH lesions were those that were not contiguous with the ventricles (for reference, total WMH was the sum of the DWMH and PV lesion volumes in cubic millimeters). Fig. 1A and B respectively represent concentrated PV lesions and DWMH lesions.

Although certain approaches for separating WMH voxels into PV and DWMH are based on thresholding the distances from the ventricle, meaning that part of a contiguous lesion might be classified as both PV and DWMH (DeCarli et al., 2005; Sachdev et al.,