Determinants of White Matter Hyperintensity Burden Differ at the Extremes of Ages of Ischemic Stroke Onset

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Background: Age is a well-known risk factor for both stroke and increased burden of white matter hyperintensity (WMH), as detected on magnetic resonance imaging (MRI) scans. However, in patients diagnosed with ischemic stroke (IS), WMH volume (WMHv) varies significantly across age groups. We sought to examine the determinants of WMH burden across the ages of stroke onset with the goal to uncover potential age-specific stroke prevention targets. *Methods:* Adult subjects from an ongoing hospital-based cohort study of IS patients with admission brain MRI were categorized as having early (<55 years), late (>75 years), or average (55-75 years) age of stroke onset. WMHv was measured using a previously validated, MRI-based semi-automated method and normalized for linear regression analyses. *Results:* Of 1008 IS subjects, 249 had early-onset stroke (24.7%), and 311 had late-onset stroke (30.9%). In multivariable analysis of WMHv using backward stepwise selection, only age ($\beta = .02$, $P = .018$), hypertension ($\beta = .24$, $P = .049$), and history of tobacco use ($\beta = .38$, $P = .001$) were independently associated with WMHv in patients with early-onset stroke, whereas male sex ($\beta = -.30$, $P = .007$), hyperlipidemia ($\beta = -.27$, $P = .015$), and current alcohol use ($\beta = .23$, $P = .034$) were independently associated with WMHv in patients with late-onset stroke. *Conclusions:* History of tobacco use is a strong independent predictor of WMH burden in patients with early-onset stroke, whereas age is no longer associated with WMHv in IS patients older than 75 years of age. These findings suggest that the major risk factors to target for stroke prevention differ across age groups and may be modifiable. **Key Words:** Leukoaraiosis—white matter disease—risk factor—acute cerebral infarction—CT and MRI—risk factors for stroke.

Age is a well-known risk factor for stroke[1,2] and white matter hyperintensity (WMH),[3,4] a radiographic marker of cerebral ischemia detected on T2 fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI), which is strongly linked to risk of stroke and unfavorable poststroke outcomes.[5-8] The etiology of WMH remains poorly understood[9,10]; however, heterogeneity of WMH is currently supported by epidemiologic and genetic data.[11,12]

Whereas age is known to contribute to WMH burden, and in turn, WMH burden has been linked to

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risk of stroke across different patient populations,[13,14] it remains unknown whether the determinants of WMH severity differ across the age spectrum. Incidence of stroke varies across age groups, as do vascular risk factors that contribute to stroke onset.[15,16] We hypothesized that variation in WMH burden may be explained in part by differential effect of vascular risk factors across age groups. Identifying these risk factors may inform future targeted, age-specific stroke prevention strategies. We tested this hypothesis in a single-center prospective cohort study, to ascertain whether the determinants of WMH volume (WMHv) measured on brain MRI differ between patients with early, late, or average age of stroke onset.

Subjects and Methods

Patient Selection and Definitions

Study subjects were recruited as part of an ongoing hospital-based study of patients with ischemic stroke (IS).[17] Consecutive patients aged 18 years of age or older admitted to the Massachusetts General Hospital Stroke Unit, including those admitted directly to the emergency department or transferred to the emergency department from a referring hospital, between July 2000 and December 2013 were considered for enrollment. Patients underwent clinical evaluation by a neurologist and diagnostic imaging on admission and were diagnosed with IS defined as either clinical stroke syndrome associated with radiographically proven infarct or a fixed neurologic deficit persisting for more than 24 hours that was consistent with a vascular event but without evidence of demyelination or nonvascular disease. Consenting patients with axial T2-FLAIR sequences of quality suitable for quantification on cranial MRIs were included in this analysis. The institutional review board approved all aspects of this study, and informed consent was provided by all subjects or their medical proxy.

Baseline characteristics were ascertained via direct patient and/or proxy interview and medical chart review. Risk factors were coded as follows: arterial hypertension (HTN) was defined as follows: (1) at least 2 raised blood pressure measurements of either more than 140 mm Hg systolic or more than 90 mm Hg diastolic recorded on different days before stroke onset, (2) physician diagnosis, or (3) use of antihypertensive medication; type II diabetes mellitus was defined as follows: (1) physician diagnosis, (2) elevated nonfasting blood glucose more than 200 mg/dL, or (3) use of hypoglycemic medication; hyperlipidemia (HL) was defined as follows: (1) previous serum cholesterol more than 200 mg/dL, (2) serum triglyceride concentration more than 150 mg/dL, (3) physician diagnosis, or (4) use of medication to control HL; atrial fibrillation (AF) was defined as follows: (1) documented history or (2) diagnosis during hospitalization; coronary artery disease (CAD) was defined as documented history of angina pectoris or myocardial infarction; current alcohol use was defined as any level of current alcohol intake; history of tobacco use was defined as current or past tobacco use; prior transient ischemic attack (TIA) was defined as history of TIA; and prior IS was defined as history of IS. Race was coded according to the National Institutes of Health categories as one of the following: (1) white, (2) black, (3) Asian, (4) Pacific Islander, (5) Native American, (6) multiple races, or (7) other.

Neuroimaging Analysis

Magnetic resonance images were acquired on 1.5-T Signa scanners (GE Medical Systems, Milwaukee, WI) and converted from Digital Imaging and Communications in Medicine format to Analyze format using MRIcro software (www.mricro.com) for computer-assisted determination of WMHv. Using a previously published semi-automated method[18] with high inter-rater reliability, WMH maps were created using axial T2-FLAIR sequences aligned with corresponding diffusion-weighted imaging sequences for exclusion of acute ischemia, edema, and chronic territorial infarcts. Total WMHv was calculated by doubling the WMHv in the hemisphere unaffected by the acute stroke and then adjusted for head size according to a previously published method.[18-20]

Age Stratification and Statistical Analysis

Given that the interquartile range of 1008 consenting IS subjects was 55.2-77.3 years, we defined patients with early-onset stroke (PEOS) as those less than 55 years of age, patients with late-onset stroke (PLOS) as those greater than 75 years of age, and patients with average age of stroke onset (PAASO) as those who experienced stroke between 55 and 75 years of age. These age strata have also been previously used as clinically meaningful definitions.[21,22]

After adjusting for head size, WMHv was natural log transformed to normalize the distribution for linear regression analysis and used as the dependent variable in single variable linear regression with each established stroke and WMH risk factor.[1,23] Multivariable linear regression was performed using backward stepwise selection of independent variables to optimize fit. All statistical analyses were performed using R version 3.0.2 (R Foundation for Statistical Computing) and significance was set at 2-sided P less than .05.