Determinants of White Matter Hyperintensity Volume in Patients with Acute Ischemic Stroke

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Background: White matter hyperintensity (WMH) is a common radiographic finding in the aging population and a potent risk factor for symptomatic cerebrovascular disease. It is unclear whether WMH represents a single or multiple biological processes. We sought to investigate the extent and determinants of WMH in patients with acute ischemic stroke (AIS). *Methods:* We retrospectively analyzed a prospectively enrolled hospital-based cohort of patients with AIS. WMH volume (WMHV) was measured using a previously published method with high interrater reliability based on a semiautomated image analysis program. *Results:* WMHV was measured in 523 consecutive patients with stroke (mean age 65.2 years, median WMHV 8.2 cm^3). In univariate linear regression analyses, individuals who were older, had elevated homocysteine (HCY) level or systolic blood pressure, or history of hypertension (all $P < .0001$), decreased glomerular filtration rate ($P < .0002$), atrial fibrillation ($P < .0008$), or coronary artery disease ($P < .03$) had significantly greater WMHV. After multivariable adjustment, only age ($P < .0001$) and HCY levels greater than 9 μmol/L ($P < .003$) remained independently associated with WMHV. *Conclusions:* In patients with AIS, risk factors for WMH severity do not appear to overlap with those previously reported for population-based cohorts. Only age and higher HCY levels were independently associated with more severe WMH in patients with stroke. This suggests that some of the processes underlying WMH burden accumulation in patients with stroke may differ from those in the general population and are not simply mediated by traditional vascular risk factors. **Key Words:** White matter hyperintensity—leukoaraiosis—ischemic stroke—cerebral infarct—risk factors—magnetic resonance imaging.

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Magnetic resonance imaging (MRI)-detectable white matter hyperintensity (WMH), also known as leukoaraiosis, is a common radiographic finding in elderly people.[1] Pathophysiology of WMH is poorly understood and it is unclear whether WMH represents one or multiple disease processes. Accumulating evidence suggests a final common pathway of chronic ischemic injury to the white matter,[2] as evidenced by neuropathological studies[3] and, furthermore, by strong epidemiological links between WMH and known vascular risk factors, including hypertension (HTN),[4] atherosclerosis,[5] homocysteine (HCY) levels,[6,7] and cigarette smoking.[8] Progression of WMH has similarly been associated with smoking and elevated levels of inflammatory markers, in addition to age, HTN, and pre-existing WMH volume (WMHV).[9-12]

The presence of WMH contributes to risk of future symptomatic ischemic stroke,[13] deterioration in gait,[14] and dementia[15] and correlates in a dose-related manner with the presence of cognitive dysfunction[16] and perhaps late-life depression.[17] WMH appears to determine the severity of cerebral injury in acute ischemic stroke (AIS), serving as a risk factor for the development of symptomatic hemorrhage after thrombolysis,[18] predicting infarct growth,[19] and poststroke outcomes.[19-21]

Severity of WMH has been studied in population-based cohorts, using both semiquantitative visual grading methods and semiautomated volumetric analysis.[4,7-9,22] These studies have identified advancing age, the presence of cardiovascular disease, HTN, and cigarette smoking as independent predictors of severity of WMH.[8,22,23] After adjusting for age and sex, the Framingham Stroke Risk Score, a composite measure of multiple stroke risk factors that is highly predictive of future cerebrovascular events,[24] even in healthy individuals younger than or equal to 55 years of age, strongly correlated with WMHV.[8] In addition, other population-based studies showed that HCY[7] and chronic kidney disease[25,26] were independent predictors of the WMH severity in otherwise healthy individuals.

It is unknown whether WMH in patients with stroke may represent a more homogeneous biology than WMH observed in the general population. We sought to investigate the extent and determinants of WMH in patients with AIS.

Methods

Patient Selection and Characteristics

All consecutive patients 18 years of age or older who presented to the Massachusetts General Hospital Emergency Department (ED) with AIS were considered for this study. Potential subjects were ascertained by reviewing ED admission logs and then approached prospectively for consent. Inclusion criteria were: (1) symptoms of AIS with corresponding evidence of restricted diffusion, consistent with acute infarction, on diffusion-weighted MRI completed within 12 hours of symptom onset; (2) T2 fluid-attenuated inversion recovery (FLAIR) axial sequence available within the same study and in usable format for volumetric analysis; and (3) patient or proxy consent. The current study is a retrospective analysis of the patients with AIS recruited between 2002 and 2005 as part of the ongoing prospective study conducted at a single academic center. The study protocol was approved by the local institutional review board and all subjects provided informed consent.

All patients underwent clinical evaluation by a neurologist, diagnostic neuroimaging, and laboratory testing on the ED admission. For patients who consented for participation in this study, baseline characteristics, medical history, clinical presentation, and admission laboratory and neuroimaging data were abstracted via direct patient and/or proxy interview and the medical chart review. Baseline characteristics were coded following the definitions of international guidelines[27] as follows: arterial HTN (evidence of at least two raised blood pressure measurements [systolic $>$ 140 mm Hg or diastolic $>$ 90 mm Hg] recorded on different days before stroke onset; a physician diagnosis; or use of an anti-HTN medication), diabetes mellitus (DM) (a physician diagnosis or use of DM medication), hyperlipidemia (physician diagnosis, use of medication to control it, previous serum cholesterol concentration $>$ 220 mg/dL, or serum triglyceride concentration $>$ 150 mg/dL), coronary artery disease (documented history of angina pectoris, coronary atherosclerosis, or coronary artery intervention), myocardial infarction (documented electrocardiogram and/or cardiac enzyme criteria for myocardial ischemic damage), and atrial fibrillation (AF) (documented history or diagnosis during hospitalization). First available systolic and diastolic blood pressure measurements on admission were recorded. Admission serum creatinine was abstracted from the medical chart and used to calculate glomerular filtration rate (GFR) based on the Modification of Diet in Renal Disease formula [GFR = $186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$ (mL/min/1.73 m^2)].[28] Plasma HCY levels were measured during the inpatient evaluation of patients with AIS using a standard clinical laboratory protocol (normal range 0-12 μmol/L).

Image Analysis

Clinical MRI scans were preformed on all subjects for evaluation of the acute stroke syndrome using 1.5-T whole body scanners (GE Signa, GE Medical Systems, Milwaukee, WI; or Siemens Sonata, Siemens Medical Solutions, Germany). WMH volumetric analysis was performed on the FLAIR sequence using a previously published semiautomated method.[29-31] In this method a human operator reviews each scan to exclude T2 hyperintensities not caused by WMH, including hyperintensity related to acute or chronic infarcts. The diffusion-weighted imaging and apparent diffusion coefficient sequences were simultaneously viewed, along with the