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

Cathy R Zhang, MA, **Lisa Cloonan, BS**, **Kaitlin M Fitzpatrick, BSc**, **Allison S Kanakis, MD**, **Alison M Ayres, BA**, **Karen L Furie, MD, MPH**, **Jonathan Rosand, MD, MSc**, and **Natalia S Rost, MD, MPH, FAAN**

Stroke Service, Department of Neurology (C.R.Z., L.C., K.M.F., A.S.K., A.M.A., J.R., N.S.R.) and Center for Human Genetic Research (J.R., N.S.R.), Massachusetts General Hospital; Rhode Island Hospital (K.L.F.)

Abstract

Background and Purpose—Age is a well-known risk factor for both stroke and increased burden of white matter hyperintensity (WMH), as detected on 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 1,008 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 (β=0.02, p=0.018), hypertension (β=0.24, p=0.049), and history of tobacco use (β=0.38, p=0.001) were independently associated with WMHv in patients with early-onset stroke, whereas male sex (β=−0.30,p=0.007), hyperlipidemia (β= −0.27, p=0.015), and current alcohol use (β=0.23, p=0.034) were independently associated with WMHv in patients with late-onset stroke.

Correspondence and Reprints: Natalia S. Rost, MD, MPH, FAAN, Massachusetts General Hospital, 175 Cambridge Street, Suite 300, Boston MA 02114 USA, Tel: (617) 643-3877, Fax: (617) 643-3939, nrost@partners.org.

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Conclusions—History of tobacco use is a strong independent predictor of WMH burden in patients with early-onset stroke, while age is no longer associated with WMHv in IS patients older than 75 years. These findings suggest that the major risk factors to target for stroke prevention differ across age groups and may be modifiable.

Keywords

leukoaraiosis; white matter disease; risk factor; acute cerebral infarction[44]; CT and MRI[30]; risk factors for stroke[66]

Introduction

Age is a well-known risk factor for stroke[1,2] as well as white matter hyperintensity (WMH),[3,4] a radiographic marker of cerebral ischemia detected on T2 fluid attenuated inversion recovery (FLAIR) MRI, which is strongly linked to risk of stroke and unfavorable post-stroke 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 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 admitted to the Massachusetts General Hospital (MGH) Stroke Unit, including those admitted directly to the emergency department (ED) or transferred to the ED from a referring hospital, between July 2000 and December 2013 were considered for enrollment. Patients underwent clinical evaluation by a neurologist and diagnostic imaging upon admission, and were diagnosed with IS defined as either (1) clinical stroke syndrome associated with radiographically proven infarct, or (2) a fixed neurological deficit persisting for >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: (1) at least two raised blood pressure measurements of either >140mmHg systolic or >90mmHg diastolic recorded on different days before stroke onset, (2) physician diagnosis, or (3) use of antihypertensive medication; type II diabetes mellitus (T2DM) was defined as: (1) physician diagnosis, (2) elevated non-fasting blood glucose >200 mg/dL, or (3) use of hypoglycemic medication; hyperlipidemia (HL) was defined as: (1) previous serum cholesterol >200mg/dL, (2) serum triglyceride concentration >150mg/dL, (3) physician diagnosis, or (4) use of medication to control HL; atrial fibrillation (AF) was defined as: (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; 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

MR images were acquired on 1.5 Tesla Signa scanners (GE Medical Systems, Milwaukee, WI) and converted from Digital Imaging and Communications in Medicine (DICOM) 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 (DWI) 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 (IQR) of 1,008 consenting IS subjects was 55.2 to 77.3 years, we defined patients with early-onset stroke (PEOS) as those <55 years, patients with late-onset stroke (PLOS) >75 years, 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 two-sided $p<0.05$.

Results

The mean age of 1,008 consenting subjects with IS was 65.9 (±14.7) years of age; there were 249 (24.7%) PEOS, 448 (44.4% total) PAAOS, and 311 (30.9% total) PLOS (Table 1). Males represented 61.7% of the cohort. Median adjusted WMHv for all subjects was 6.0 cm^3 (IQR 2.7 cm^3 – 12.5 cm^3); mean normalized WMHv was 1.8 (±1.1). WMHv and prevalence of AF, CAD, and history of TIA increased with age of stroke onset. A majority of subjects had HTN, except within the PEOS population (39.4%), which also had a noticeably lower burden of HL (28.5%) than the other groups. Current alcohol use was similar across all groups, and approximately 90% of subjects were of white race.

In single-variable analysis of the overall cohort, age, sex, creatinine, HTN, AF, CAD, current alcohol use, prior IS, and non-white race were significantly associated with WMHv ($p<0.05$) (Table 2); in multivariable analysis, age, HTN, HL, current alcohol use, prior IS, and non-white race independently predicted WMH burden ($p<0.05$) (Table 3). However, the risk factors contributing to WMH severity differed significantly across the age groups in both single-variable and multivariable analyses.

At early age of stroke onset (PEOS), age, HTN, and history of tobacco use were significantly associated with WMHv ($p<0.05$), and these all remained independent predictors in multivariable analysis; notably, history of tobacco use had a strong effect size of 0.38 in the final multivariable analysis. In contrast, only sex, HL, and current alcohol use remained as independent predictors of WMH burden ($p<0.05$) among the elderly (PLOS). All risk factors except sex, T2DM, AF, CAD, and history of tobacco use were significant predictors of WMHv in PAASO.

Discussion

In this analysis, we report that the determinants of WMH burden differ with age of stroke onset. Notably, history of tobacco use is an independent predictor of WMH severity specific to the youngest IS patients (PEOS), while age loses its effect as a determinant of WMHv in the elderly (PLOS). The importance of these novel data is that they are derived from the largest-to-date, hospital-based cohort of IS subjects with WMH severity quantified on brain MRI using a volumetric method, and that they identify potential age-specific, modifiable targets for stroke prevention aimed at reduction of both symptomatic and clinically silent cerebral ischemia. Additionally, while age of stroke onset has been previously explored with respect to stroke risk factors[15,24,25] and variability in cerebral small vessel disease at the extremes of ages has been previously reported[26,27], this is the first analysis of traditional cerebrovascular risk factors for WMH burden that differentiates between patients with early, average, and late age of stroke onset.

Tobacco use is an established risk factor for stroke and WMH;[1,28] however, in our analysis, history of tobacco use emerged as an independent predictor of WMHv only among PEOS. This suggests that exposure to smoking may have the greatest effect on WMH progression in this group. Thus, the window of susceptibility to smoking-related small cerebral vessel disease may be at a younger age, in contrast to the many risk factors that appear to

contribute to WMHv in PAASO, which may be within the window of susceptibility to WMH burden for all traditional cerebrovascular risk factors. Overall, the effect of history of tobacco use translates into an increase of 1.5 cm^3 in WMHv among the youngest IS patients, which is the most powerful determinant linked to WMH, except for age, among all stroke patients, reported to date.[29]

Another distinct finding of this study is the lack of effect of age on WMH burden in the very old, which may be due to genetic protection against stroke risk factors, including WMH, in these patients who do not experience a stroke until their advanced years. However, we also note an interaction effect (p=0.049) between age and sex, as women are significantly older than men in this group (p=0.0004) but not in the other subpopulations (p=0.09 in PAASO, p=0.15 in PEOS). This interaction could explain the lack of effect of age and the unique predictive value of sex in this model as a "survivor paradox," previously described in cohorts demonstrating a protective effect of smoking.[30] Because WMH burden is highly correlated with age, regardless of sex, the apparent protective effect of male sex may be reflective of the difference in age distribution caused by greater mortality in older males than females.

The consistent, apparent protective effect of HL in all multivariable models of WMHv has been observed previously.[31] However, this effect is not replicated in the youngest stroke patients in this analysis, which may be a result of non-diagnosis in its subclinical stage; in fact, the prevalence of HL is notably lower in this population (28.5%) than any other (49.6% in PAASO, 49.5% in PLOS). The relationship between HL and WMH burden is not well understood, yet some data imply that a diagnosis of HL may be a marker of cerebrovascular disease that is diagnosed and treated (e.g. with statins), as opposed to that which is undetected until stroke onset.[9,31] Similarly, the apparent protective effect of prior TIA may reflect the benefits of risk factor management following a TIA diagnosis.

Finally, a protective effect of non-white race on WMH burden may be attributable to significantly lower WMHv in non-whites as compared to whites in our IS cohort (p=0.0003), a finding that is also evident in the Framingham Heart Study[32] and likely due to population bias in our region.

This study is limited by its retrospective nature and the homogeneity of the patient population, as the subjects were predominantly white and a majority had HTN and a history of tobacco use. However, higher incidence of stroke risk factors is appropriate, given the hospital-based, high-risk cohort described. Strengths of this study include the large sample size and quantitative measure of WMHv that provided power to detect significant, clinically relevant findings.

Summary

In this cohort, history of tobacco use is a strong independent predictor of WMH burden in patients who experience IS before the age of 55 years, whereas female sex, HL, and current alcohol use, but not age, independently contribute to severity of WMH in those with stroke onset after 75 years of age. These findings suggest that the major risk factors for WMH and stroke differ across age groups and are modifiable. Future studies that target age-specific

prevention strategies of symptomatic cerebrovascular disease as well as clinically silent but significant manifestations such as WMH are warranted.

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Table 1

Clinical characteristics of the ischemic stroke cohort (n=1008).

	PEOS n = 249	PAASO n = 448	PLOS n = 311	All n = 1008
Age, y, mean (SD)	46.1 (7.5)	65.4 (5.7)	82.3 (5.1)	65.9 (14.7)
Male sex, n (%)	170 (68.3)	311 (69.4)	141 (45.3)	622 (61.7)
WMHv,* cm^3, median (IQR)	2.4 (1.5 – 4.0)	6.1 (3.1 – 12.0)	11.3 (6.2 – 23.0)	6.0 (2.7 – 12.5)
Normalized WMHv,† mean (SD)	0.9 (0.9)	1.8 (1.0)	2.4 (1.0)	1.8 (1.1)
Creatinine, mg/dL, median (IQR)	0.9 (0.8 – 1.1)	1.0 (0.9 – 1.2)	1.0 (0.9 – 1.3)	1.0 (0.8 – 1.2)
Risk Factors, n (%)				
HTN	98 (39.4)	310 (69.2)	250 (80.4)	658 (65.3)
T2DM	41 (16.5)	109 (24.3)	60 (19.3)	210 (20.8)
HL	71 (28.5)	222 (49.6)	154 (49.5)	447 (44.3)
AF	14 (5.6)	55 (12.3)	97 (31.2)	166 (16.5)
CAD	18 (7.2)	94 (21.0)	88 (28.3)	200 (19.8)
Alcohol use	123 (49.4)	231 (51.6)	154 (49.5)	508 (50.4)
History of tobacco use	142 (57.0)	311 (69.4)	165 (53.1)	618 (61.3)
Prior TIA	13 (5.2)	34 (7.6)	29 (9.3)	76 (7.5)
Prior AIS	28 (11.2)	80 (17.9)	52 (16.7)	160 (15.9)
Race				
White	219 (88.0)	413 (92.2)	294 (94.5)	926 (91.9)
Black	13 (5.2)	25 (5.6)	7 (2.3)	45 (4.5)
Asian	6 (2.4)	4 (0.9)	3 (1.0)	13 (1.3)
Native American	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Multiple	4 (1.6)	1 (0.2)	1 (0.3)	6 (0.6)
Other	4 (1.6)	3 (0.7)	2 (0.6)	9 (0.9)

PEOS – patients with early-onset stroke; PAASO – patients with average age of stroke onset; PLOS – patients with late-onset stroke; SD – standard deviation; WMHv – white matter hyperintensity volume; IQR – interquartile range; HTN – hypertension; T2DM – type II diabetes mellitus; HL – hyperlipidemia; AF – atrial fibrillation; CAD – coronary artery disease; TIA – transient ischemic attack; AIS – acute ischemic stroke.

*Adjusted for head size.

†Adjusted for head size and natural log-transformed.

Table 2

Predictors of white matter hyperintensity volume* in ischemic stroke cohort.

	PEOS n = 249		PAASO n = 448		PLOS n = 311		All n = 1008	
	β	p-value	β	p-value	β	p-value	β	p-value
Age	0.02	0.002	0.05	8.36×10^{-8}	0.02	0.106	0.04	9.55×10^{-75}
Male sex	0.13	0.300	0.04	0.662	−0.25	0.023	−0.23	0.002
Creatinine	−0.09	0.433	0.25	0.024	−0.18	0.085	0.16	0.034
HTN	0.34	0.004	0.19	0.063	0.07	0.599	0.56	8.92×10^{-15}
T2DM	0.29	0.062	0.11	0.328	−0.07	0.634	0.13	0.119
HL	0.21	0.093	−0.17	0.080	−0.26	0.015	0.07	0.323
AF	0.09	0.718	0.17	0.226	0.13	0.277	0.51	5.90×10^{-8}
CAD	0.42	0.060	0.25	0.033	−0.25	0.037	0.34	0.0001
Alcohol use	0.20	0.084	0.23	0.015	0.23	0.035	0.24	0.0009
History of tobacco use	0.44	0.0001	0.12	0.231	−0.18	0.111	0.10	0.190
Prior TIA	−0.16	0.541	−0.35	0.049	0.17	0.356	0.003	0.979
Prior AIS	0.04	0.817	0.34	0.006	0.12	0.409	0.30	0.002
Non-white race	−0.13	0.483	−0.32	0.077	−0.49	0.072	−0.49	0.0002

PEOS – patients with early-onset stroke; PAASO – patients with average age of stroke onset; PLOS – patients with late-onset stroke; HTN – hypertension; T2DM – type II diabetes mellitus; HL – hyperlipidemia; AF – atrial fibrillation; CAD – coronary artery disease; TIA – transient ischemic attack; AIS – acute ischemic stroke

*Natural log-transformed.

Table 3

Multivariable linear regression model predictors of white matter hyperintensity volume* in ischemic stroke cohort.

	PEOS n = 242		PAASO n = 440		PLOS n = 292		All n = 974	
	β	p-value	β	p-value	β	p-value	β	p-value
Age	0.02	0.018	0.05	1.19×10^{-8}			0.04	2.88×10^{-58}
Male sex					−0.30	0.007		
Creatinine			0.27	0.011				
HTN	0.24	0.049	0.22	0.037			0.22	0.002
T2DM								
HL			−0.23	0.016	−0.27	0.015	−0.17	0.008
AF								
CAD			0.19	0.098				
Alcohol use	0.19	0.086	0.18	0.046	0.23	0.034	0.23	9.82×10^{-5}
History of tobacco use	0.38	0.001					0.11	0.075
Prior TIA			−0.41	0.017				
Prior AIS			0.24	0.040			0.18	0.029
Non-white race			−0.34	0.048	−0.49	0.065	−0.24	0.034

PEOS – patients with early-onset stroke; PAASO – patients with average age of stroke onset; PLOS – patients with late-onset stroke; HTN – hypertension; T2DM – type II diabetes mellitus; HL – hyperlipidemia; AF – atrial fibrillation; CAD – coronary artery disease; TIA – transient ischemic attack; AIS – acute ischemic stroke

*Natural log-transformed.