Factors Associated with Leukoaraiosis Severity in Acute Stroke Patients

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Objective: Age-related cerebral white matter abnormalities, commonly termed leukoaraiosis (LA), are frequent manifestation of cerebral microvascular disease. Aging and hypertension are well linked to LA. We compared additional vascular risk factors and socioeconomic factors with LA severity in acute stroke patients. *Methods:* We analyzed 271 patients with acute ischemic or hemorrhagic stroke from a hospital registry. We collected clinical and socioeconomic data prospectively with a standardized questionnaire during acute stroke hospitalization. We scored LA severity on all available head computed tomography and magnetic resonance imaging (MRI) scans with the Wahlund LA scale. Mean response modeling analyzed for associations between LA severity and multiple potential predictors. *Results:* Among 238 patients with CT LA scores, ageing and history of hypertension emerged as independent predictors of LA severity in multivariable analysis. Among 186 patients with MRI LA scores, ageing and severe left ventricular hypertrophy emerged as independent predictors of LA severity in multivariable analysis. We did not find an independent significant association between LA severity and the other factors we tested. *Conclusions:* Our study confirms the association of LA severity with ageing, and with hypertension. However, other vascular and socioeconomic factors we tested were not independently associated with LA severity.

Key Words: Leukoaraiosis—stroke--hypertension—aging

Introduction

The term leukoaraiosis (LA) implies a nonspecific, primarily age-related, abnormality of the cerebral white matter seen on computed tomography (CT) and magnetic resonance imaging (MRI) scans.[1] LA is associated with other vascular risk factors and is one of the manifestations of cerebral small vessel disease.[1,2] On CT, LA appears as abnormal hypodensities in cerebral white matter and on MRI, fluid attenuated inversion recovery or T2 sequences it appears as abnormal hyperintensities. The histopathology of LA includes various degrees of demyelination, with axonal loss in more severe cases, astrogliosis, dilated perivascular spaces, and small infarcts.[1,3]

LA has been firmly linked to aging and hypertension. A link between LA and other vascular risk factors is less well established. Associations between LA and socioeconomic factors have rarely been studied. To understand better the clinical correlates of LA, we analyzed LA severity in relation to traditional vascular risk factors, as well as multiple socioeconomic factors in acute stroke patients.

Patients and Methods

We studied patients from a vascular risk factor stroke registry at an academic Comprehensive Stroke Center, Augusta University Medical Center. This registry contains 300 acute stroke patients hospitalized with acute ischemic stroke or acute intracerebral hemorrhage within 7 days

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from onset. Six medical students in groups of 2, supervised by a vascular neurologist (A.B.) administered a standardized questionnaire about demographics and traditional vascular risk factors in 2 stages; first 100 patients between July 2010 and April 2011, and the remaining 200 patients between August 2012 and February 2014.[4] We collected the questionnaires Monday through Friday excluding holidays. We interviewed patients when possible, family members, and caregivers, and reviewed medical records to optimize data accuracy.

We classified race based on the designation in the medical record as white, African American, or other. Neuroimaging and all other clinical tests were done as standard of care.

We collected verifiable and quantifiable vascular risk factors. For consistent analysis, we categorized all variables. We classified left ventricular hypertrophy (LVH) severity based on left ventricular mass indexed to body surface area according to standard definition[5]; for woman: mild 96-108 g/m^2, moderate 109-121 g/m^2, severe $\geq$122 g/m^2; for men: mild 116-131 g/m^2, moderate 132-148 g/m^2, severe $\geq$149 g/m^2. The standard linear method and the cube formula determined left ventricular mass based on transthoracic echocardiograms. We categorized obesity per the National Heart, Lung, and Blood Institute, based on body mass index (in kg/m^2)[6]: normal 18.5-24.9, overweight 25.0-29.9, obesity class I 30.0-34.9, obesity class II 35.0-39.9, and extreme obesity (class III) $\geq$40.0.

For this analysis, we included all subjects who had a head CT or MRI during hospitalization. One medical student (K.V.) supervised by the vascular neurologist (A.B.) scored the available CTs and MRIs with the Wahlund LA scale.[7] We scored only the cerebral hemisphere contralateral to the acute stroke to avoid confounding by large strokes. We excluded subjects with bilateral nonlacunar strokes. The Wahlund LA scale has been validated with moderate interrater reliability on CT and good reliability on MRI.[7] We used standard brain window settings on CT and standard fluid attenuated inversion recovery MRI sequences.

The raters were blinded to all clinical data and to each other's scores. We first scored all the CTs. We then scored all the MRIs blinded to the CT scores. The vascular neurologist also scored a random sample of 69 CTs and 25 MRIs, for inter-rater agreement analysis with the student.

Our Institutional Review Board approved this study and all subjects or their legally authorized representatives gave valid informed consents to participate in the registry.

Statistical Analysis

For consistency, we classified and analyzed all the independent variables as dichotomized or ordinal. We categorized age into 6 categories, obesity into 5, the following variables into 3 (formal education level, LVH severity, HbA1c, low-density lipoprotein cholesterol, and triglycerides), and the remaining variables into 2 categories (Table 1).

Mean response modeling (MRM),[8] a type of ordinal regression, analyzed the univariate associations of each independent variable with the dependent variable, the Wahlund LA score on CT and MRI separately. The advantage of the MRM is that it models the mean of the dependent variable (in this case, the LA score) without requiring any assumptions about its distribution.

Multiple ordinal regression with forward stepwise variable selection identified factors independently and significantly associated with the LA score. Due to the exploratory nature of this study, we made no adjustment for multiple testing.

Using a significance level of .05, a sample of 185 patients would yield 90% power to detect an effect size of .24 on the Wahlund LA score with the MRM analysis, using the chi-square statistic with one degree of freedom. This effect size is "small to medium" using Cohen's guideline,[9] in which .1 is small, .3 is medium, and .5 is large. Under these same assumptions, a sample of 185 patients would yield 85% power to detect an effect size of .22, and 80% power to detect an effect size of .21.

The weighted kappa statistic (κ_w) with quadratic weights measured the LA score agreements between the student and the vascular neurologist. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, 2012).

Results

From the 300 patients in the registry, we excluded 29 due to missing or poor-quality CT and MRI scans, or bilateral nonlacunar strokes. We analyzed the remaining 271 patients, 238 with CT, and 186 with MRI (163 had both scans). Of these 271 patients, 63 (23%) had an acute intracerebral hemorrhage, 123 (45%) were white, 143 (53%) were African American, and 5 (2%) had race classified as other. Because the number of subjects with other race was too small for meaningful statistical analysis, we combined this race group with African American race.

The mean unilateral LA score on CT was 2.0, SD 1.9, median = 1, interquartile range 0-3, range 0-7. The mean unilateral LA score on MRI was 3.1, SD 2.3, median = 2, interquartile range 1-5, range 0-9. Table 1 shows the unadjusted associations of the patient characteristics with unilateral LA scores.

On CT, the unadjusted LA scores were significantly higher among patients that were older, women, less obese, and had a history of hypertension (Table 1). In multiple ordinal regression analysis, only age and history of hypertension remained as significant independent predictors of LA severity (Table 2).

On MRI, the unadjusted LA scores were significantly higher among patients that were older, had an annual household income <$50,000, and had lower triglyceride

Table 1. *Unadjusted leukoaraiosis severity scores for each categorical variable*

Variable	Patients with CT	Mean ± S.D. Wahlund CT score (n = 238)	*P* value	Patients with MRI	Mean ± S.D. Wahlund MRI score (n = 186)	*P* value
Age (years)			<.001			<.001
≤40	13	.7 ± .8		9	1.6 ± 1.6	
41-50	32	1.0 ± 1.5		20	2.2 ± 2.0	
51-60	65	1.6 ± 1.7		54	2.5 ± 2.0	
61-70	63	2.3 ± 2.0		57	3.5 ± 2.1	
71-80	36	2.4 ± 1.8		28	4.1 ± 2.8	
>80	29	3.5 ± 1.9		18	4.4 ± 2.6	
Race			.50			.10
Non-White	136	2.1 ± 1.9		99	3.4 ± 2.4	
White	102	1.9 ± 1.9		87	2.8 ± 2.3	
Gender			.01			.44
Female	121	2.3 ± 2.0		101	3.2 ± 2.5	
Male	117	1.7 ± 1.8		85	3.0 ± 2.1	
Education			.21			.22
Less than HS	85	2.2 ± 1.9		62	3.5 ± 2.5	
HS only	113	1.9 ± 1.9		95	2.9 ± 2.3	
College	39	1.9 ± 1.9		29	3.0 ± 2.1	
Annual household			.86			.01
income	156	1.9 ± 1.9		129	3.3 ± 2.3	
<$50,000	36	1.9 ± 2.0		24	2.0 ± 2.3	
≥$50,000						
Obesity category			.03			.12
Normal	62	2.3 ± 2.1		46	3.4 ± 2.5	
Overweight	79	2.2 ± 1.9		67	3.4 ± 2.1	
Class I	47	1.6 ± 1.6		34	2.8 ± 2.5	
Class II	31	1.5 ± 1.6		27	2.7 ± 2.3	
Class III	19	1.9 ± 2.4		12	2.8 ± 2.5	
History of hypertension			.002			.11
Yes	186	2.2 ± 1.9		136	3.3 ± 2.3	
No	52	1.4 ± 1.7		50	2.7 ± 2.3	
Severe LVH			.61			.001
Yes	38	2.1 ± 1.9		26	3.7 ± 2.4	
No	152	1.8 ± 1.8		141	3.0 ± 2.3	
History of diabetes			.11			.51
Yes	91	2.3 ± 1.9		69	3.3 ± 2.4	
No	147	1.9 ± 1.9		117	3.0 ± 2.3	
HbA1c Tertiles			.87			.38
≤5.7%	72	1.9 ± 1.8		57	2.9 ± 2.2	
5.8%-6.8%	76	2.2 ± 2.0		56	3.1 ± 2.2	
≥6.9%	68	1.8 ± 1.8		62	3.2 ± 2.4	
History of hyperlipidemia						.90
Yes	117	2.0 ± 1.9	.89	93	3.1 ± 2.3	
No	121	2.0 ± 2.0		93	3.2 ± 2.4	
LDL cholesterol Tertiles			.28			.06
≤88	74	2.1 ± 2.0		59	3.5 ± 2.4	
89-125	75	2.0 ± 1.9		63	3.1 ± 2.3	
≥126	70	1.8 ± 1.9		58	2.7 ± 2.2	
Triglycerides Tertiles			.89			.02
≤87	73	2.0 ± 1.8		54	3.9 ± 2.5	
88-138	68	1.7 ± 2.0		60	2.8 ± 2.1	
≥139	76	2.1 ± 1.9		66	2.8 ± 2.3	
Stroke type			.10			.31
Ischemic	176	1.9 ± 1.9		166	3.1 ± 2.3	
ICH	62	2.4 ± 1.9		20	3.7 ± 2.8	

Abbreviations: HbA1c, hemoglobin A1c; HS, High School; ICH, intracerebral hemorrhage; LVH, left ventricular hypertrophy.

Table 2. *Multiple ordinal regression of factors significantly associated with leukoaraiosis severity on CT and on MRI*

	CT subgroup (n = 238)			MRI subgroup (n = 186)		
Predictor	β	SE	*P* value	β	SE	*P* value
Age	.46	.06	<.001	.62	.09	<.001
History of hypertension	.89	.18	<.001	-	-	-
Severe LVH	-	-	-	1.19	.36	.001

Abbreviations: LVH, left ventricular hypertrophy; SE, standard error.

levels (Table 1). In multiple ordinal regression analysis, only age and severe LVH emerged as significant independent predictors of LA severity (Table 2).

The inter-rater agreements on the LA scores between the student and the vascular neurologist were excellent on both, CT (κ_w = .89, 95% confidence interval .84-.94) and on MRI (κ_w = .92, 95% confidence interval = .85-.98).

Discussion

We analyzed for associations between LA severity and multiple socioeconomic and clinical factors available in our registry. In patients with acute stroke, we confirmed that the 2 strong predictors of LA severity are ageing and hypertension.[2,10,11] However, we could not confirm the previously reported positive association between LA and HbA1c,[12-15] or the negative association between LA and hypertriglyceridemia.[16] In addition, none of the socioeconomic factors we tested where independently associated with LA.

Our results with CT differed somewhat than with MRI. In multivariable analysis, on CT LA severity was significantly associated with age and history of hypertension, while on MRI LA severity was significantly associated with age and LVH severity. Perhaps the greater sensitivity of MRI than CT in detecting small LA lesions determined this outcome.

An association of LA with hypertension or LVH as an index of uncontrolled hypertension has been reported in multiple studies.[17-20] Reports linking LA to diabetes mellitus type 2 are conflicting. In a recent review of 49 studies on this topic,[21] 20 reported a significant association of LA with diabetes. Fewer studies assessed LA severity and diabetes control as indicated by HbA1c levels. Four studies reported a significant positive association of MRI LA severity with HbA1c levels.[12-15] One study mentioned a significant positive association of MRI LA severity with HbA1c, but did not present these data.[22] Two studies reported no significant association of MRI LA severity with HbA1c.[23,24]

Reports linking hyperlipidemia and LA are also limited. In an international hospital-based study of 1135 acute ischemic stroke patients, history of hyperlipidemia was associated with less severe LA.[16] Specific lipid fractions were not analyzed in that study.

A combined analysis of 2 population-based studies totaling 2608 people found a significant negative association between MRI LA volume and hypertriglyceridemia, but not with other lipid fractions.[16] In our study, higher triglyceride levels are also significantly associated with lower MRI LA severity in univariate analysis (Table 1), but not in multivariable analysis (Table 2). Possibly this association is weak and our study was underpowered to confirm this association.

Our study differs from many previous studies on this topic by inclusion of subjects with intracerebral hemorrhage (23%) and a relatively large proportion of African Americans (53%). It is unknown at this time how these differences affected our results compared to other studies. However, in our multivariable analysis, there were no significant associations of LA severity with stroke type or race.

Although the LVH measure indexed to body mass that we used correlates well with uncontrolled hypertension, it remains an imperfect marker. Also, we used a LA scale with some subjectivity and imperfect interrater reliability.[7] A volumetric LA measure would have likely been more objective. Also, in this study we did not have data on some additional risk factors for LA, such as genetic markers[25] and autoimmune disorders.[26]

In conclusion, aging and uncontrolled hypertension being the strongest determinants of LA severity may overshadow weaker contributing factors in multivariable analysis. For additional LA risk assessments in future studies, it might be best to utilize LA volume measurements, assess levels of risk factor control, perform relevant genetic testing, and include a sufficient sample size to enable detection of small differences in LA severity.

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