Leukoaraiosis is independently associated with naming outcome in poststroke aphasia

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Abstract

Objective

To test the hypothesis that severity of leukoaraiosis in the noninfarcted hemisphere at onset is associated with poorer language outcome after poststroke aphasia independently of volume of infarct, damage to 3 critical language areas (left inferior frontal gyrus, superior longitudinal fasciculus, and superior temporal gyrus), comorbid conditions, and time since stroke.

Methods

In this cross-sectional study, we evaluated naming outcome (>3 months after stroke) in 42 individuals who initially had aphasia after stroke. We rated leukoaraiosis in the right hemisphere 1 to 4 weeks from onset of stroke using the Cardiovascular Health Study rating scale. We evaluated associations between severity of leukoaraiosis and each measure of naming using Spearman correlations and evaluated the independent contributions of leukoaraiosis, lesion volume, months since onset, comorbid conditions, and damage to critical nodes of the language network on language outcomes using logistic regression. We also evaluated associations between dichotomously defined leukoaraiosis and language outcomes using χ^2 tests.

Results

Severity of leukoaraiosis at onset correlated with object naming ($\rho = -0.56$, $p = 0.0008$) and word fluency ($\rho = -0.37$, $p = 0.01$) outcomes. Severe leukoaraiosis was associated with failure to achieve the highest quartile of object naming and word fluency. Severity of leukoaraiosis was associated with degree of naming outcome with the use of both measures after controlling for lesion volume, months since stroke, comorbid conditions, and damage to specific locations.

Conclusion

Naming outcome after poststroke aphasia is influenced by the initial severity of right hemisphere leukoaraiosis independently of other variables. Degree of recovery from aphasia may depend on the integrity of the noninfarcted brain tissue.

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Glossary

CHS = Cardiovascular Health Study; **FLAIR** = fluid-attenuated inversion recovery; **JHU-MNI** = Johns Hopkins University-Montreal Neurological Institute; **pIFG** = posterior inferior frontal gyrus; **RH** = right hemisphere; **SLF** = superior longitudinal fasciculus; **STG** = superior temporal gyrus; **WAB** = Western Aphasia Battery.

Aphasia is among the most common and disabling sequelae of stroke. The degree of recovery from aphasia is highly variable and difficult to predict at onset. One study indicated that improvement depends on initial severity except in severe initial aphasia.¹ Another found that time since onset, lesion volume, and damage to 35 brain regions were associated with outcome.² There are conflicting data on the influence of age, handedness,^{3,4} and sex.^{3,5}

The health of noninfarcted regions may also be critical to outcome, particularly outcome of complex tasks such as naming that depend on a network of brain regions. Connections between undamaged nodes of the network are likely to be essential for reorganization of these networks. Although studies have shown that disruption of specific white matter tracts affects language,^{6–12} we are not aware of previous studies that have examined the role of leukoaraiosis (diffuse white matter disease) in the right hemisphere (RH) on language outcome after stroke.

Leukoaraiosis is a nonspecific imaging finding that seems to reflect the health of the brain tissue. It is strongly associated with aging, hypertension, diabetes mellitus, hypercholesterolemia,¹³ and atherosclerosis.¹⁴ Leukoaraiosis is associated with cognitive impairment in otherwise healthy older adults¹⁵ and after stroke.^{16,17}

We hypothesized that severe leukoaraiosis at onset is associated with poor naming outcome after stroke independently of the infarct volume, time since onset, comorbid conditions, and damage to 3 critical language sites. We focused on naming outcome because naming deficits are among the most common and disabling residual deficits in chronic aphasia.

Methods

Participants

We carried out a cross-sectional study of a convenience sample of a consecutive series of 42 adults who had sustained a single left hemisphere ischemic stroke resulting in aphasia, were at least 3 months after the onset of stroke, and were evaluated at Johns Hopkins Hospital or Johns Hopkins Bayview Medical Center between December 2007 and July 2011. We selected 3 months as the minimal time since stroke because the greatest recovery takes place in the first 3 months.¹ Additional inclusion criteria were as follows: right-handed, fluent speaker of English before stroke, and had fluid-attenuated inversion recovery (FLAIR) sequence MRI 1 to 4 weeks from stroke onset. We excluded patients with previous neurologic disease involving

the brain, including dementia. We evaluated for dementia by asking the family detailed questions about the level of independent functioning and memory for events. We also excluded participants with known visual or hearing loss, unless the loss was corrected to normal acuity with glasses or hearing aids, and those receiving sedation. Participants were studied 3 to 157 (mean $\pm$ SD 39 ± 36 , median 28, mode 12) months after stroke. The mean $\pm$ SD age was 56.1 ± 15.0 years, and the mean $\pm$ SD education was 14.8 ± 3.1 years, which is representative of the age of stroke patients admitted to our hospital. The relatively young average age reflects the high proportion of our patients who are black/African because the mean age at initial stroke is younger in blacks than in whites.¹⁸ A total of 17 (40.5%) were black/African American, 24 (57.1%) were white/Caucasian, and 1 (2.4%) was Asian; of these, 2 (1 black, 1 white) were of Hispanic ethnicity. Women represented 52.4% of the population. Most had ≥ 1 risk factors for stroke, including 26.2% with diabetes mellitus, 71.4% with hypertension, and 9.5% with current tobacco use. All patients received language rehabilitation, although treatment varied in type, duration, and frequency; therefore, we did not evaluate the effect of language treatment.

Standard protocol approvals, registrations, and patient consents

All participants or their legally authorized representative provided informed consent using methods approved by the Johns Hopkins Institutional Review Board (protocol NA_00042097).

Language testing

Participants were administered the Western Aphasia Battery (WAB)–Revised.¹⁹ Our primary outcome measure was the WAB object naming score (0–60 points). A secondary outcome variable was the WAB word fluency score (rapid naming of items in a category). We did not use the WAB aphasia quotient (a summary score ranging from 0–100 based on fluency: articulation, melody, grammar, rate of speech) and content of spontaneous speech, auditory comprehension, naming, and repetition because 11 participants did not complete the entire battery. In addition, we were specifically interested in naming outcome because it is the most common residual deficit in aphasia. Furthermore, naming is objectively evaluated (unlike fluency and content of speech, which are rated subjectively on the WAB and have poor interrater reliability, even among experienced speech-language pathologists²⁰).

Imaging and image analysis

Because previous studies have indicated that damage to particular locations—left superior temporal gyrus

(STG),^{2,21–23} superior longitudinal fasciculus (SLF)/arcuate fasciculus,^{2,21,24,25} and posterior inferior frontal gyrus (pIFG)²—might affect naming outcome, we evaluated damage to these areas. Damage to the left STG, pIFG, or SLF was determined by methods described in previous publications.^{26–28} In brief, for each participant, the boundary of the stroke lesion(s) was identified on FLAIR images (standard 5-mm whole-brain axial slices) by a neurologist or radiologist without knowledge of the language outcome. The FLAIR sequence was transformed to the Johns Hopkins University-Montreal Neurological Institute (JHU-MNI) atlas using affine transformation, followed by large deformation diffeomorphic metric mapping.^{29,30} The JHU-MNI Brain Parcellation Map (cmrm.med.jhmi.edu) was then overlaid on the normalized lesion map to determine the percentage damage to each of the 3 regions of interest using DiffeoMap (MRIfstudio.org). Total infarct volumes were also calculated using the normalized lesion on FLAIR sequences. We have previously reported that our intraclass correlation coefficient for interrater reliability for these volumetric measurements was 0.98 for both within and across observers.²⁷

FLAIR images were also rated for the severity of leukoaraiosis in the noninfarcted hemisphere by a neurologist and a technician masked to the language scores using the Cardiovascular Health Study (CHS) white matter rating scale (ranging from 0–9, with 9 being most extensive).¹⁴ Participants' images were compared to templates corresponding to each rating on the CHS scale, from 1 (minimal) to 8 (severe and confluent white matter changes). Studies with no white matter hyperintensities were graded as 0, and those with more extensive white matter hyperintensities than the 8 template were rated as 9. There was excellent interrater agreement in rating leukoaraiosis ($\kappa = 0.83$). We defined severe white matter changes as a CHS scale rating of ≥ 5 . This value represented approximately the top quartile of white matter ratings.

Statistical Analyses

We used Stata version 13 for Macintosh (College Station, TX) for all analyses. We tested the relationships between severity of RH leukoaraiosis and language scores (object naming and word fluency) using Spearman correlations. We also dichotomized good outcome (highest quartile of each naming score). This cutoff was somewhat arbitrary, but quartiles are often selected as outcome measures.^{31–33} We compared participants who achieved the highest quartile of naming to those who did not with *t* tests for continuous variables and χ^2 tests for binary variables. We compared dichotomized outcomes for individuals with severe (CHS score ≥ 5) vs milder or no RH leukoaraiosis using Pearson χ^2 tests. There were no missing data in the primary outcome measures because participants were included only if the primary outcome measure of interest and the dependent variables were available. The 11 participants with missing data for WAB aphasia quotient were excluded from the secondary analyses of WAB aphasia quotient outcome.

Multivariable logistic regression models were created to evaluate the association between severity of residual language deficits and severity of RH leukoaraiosis, including infarct volume, months since onset, damage to 3 nodes of the language network that reportedly influence outcome (left STG, SLF, and pIFG), and comorbid conditions (hypertension, diabetes mellitus, and depression) as covariates. We chose these comorbid conditions because hypertension and diabetes mellitus are strongly associated with leukoaraiosis and depression has been shown to influence stroke outcome.³⁴ We controlled for comorbid conditions to evaluate whether leukoaraiosis itself affects outcome, rather than the comorbid conditions. Although they are associated with leukoaraiosis, they were not collinear with leukoaraiosis in this study because all 3 comorbid conditions were more common than severe leukoaraiosis. We repeated analyses to include race and estimated atrophy (ratio of brain volume to CSF volume in the RH only) to determine whether race or estimated brain atrophy, which might be related to leukoaraiosis, could account for the effects of leukoaraiosis.

Finally, the difference in severity of leukoaraiosis between those who achieved the highest quartile of naming and those who did not was evaluated with the Wilcoxon rank-sum (Mann-Whitney) test.

Data availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Median and range of language outcomes, demographics, and CHS white matter ratings for participants who achieved the highest quartile of object naming are given in table 1. There was no significant difference in these 2 outcome groups by *t* tests in age, education, lesion volume, or months since onset of stroke. Those who achieved the highest quartile of object naming also achieved higher WAB aphasia quotient ($t = -2.8$, $df = 30$, $p = 0.0079$) and higher word fluency ($t = -7.9$, $df = 40$, $p < 0.00001$). There were no significant differences in the percentage of each group who were non-Hispanic white/Caucasian or non-Hispanic black/African American by χ^2 tests. In univariate analysis, severity of RH leukoaraiosis correlated with both object naming ($\rho = -0.56$, $p = 0.0026$) and word fluency ($\rho = -0.36$, $p = 0.019$). When we dichotomized both RH leukoaraiosis and naming outcomes, severe RH leukoaraiosis (CHS score ≥ 5) was associated with failure to achieve the highest quartile of object naming ($\chi^2 = 4.7$, $p = 0.031$) and word fluency ($\chi^2 = 5.3$, $p = 0.022$).

In multivariable analysis, when severity of RH leukoaraiosis, lesion volume, months since onset, 3 comorbid conditions, and the 3 lesion sites were all included, achievement of the best outcome (highest quartile of object naming) was completely determined ($\chi^2 = 57.36$, pseudo- $r^2 = 1.0$, $p < 0.00001$). Including only damage to left STG, months since onset, and

Table 1 CHS leukoaraiosis ratings, demographics, and language outcomes in participants who did and did not achieve the primary outcome measure

	Participants who achieved highest quartile of naming (n = 11)		Participants who did not achieve highest quartile naming (n = 31)	
	73		48	
Non-Hispanic white/Caucasian, %	Median	Range	Median	Range
CHS rating	1	0–7	3	0–7
Age, y	50.5	29–84	50.5	20–85
Months since stroke	21	3–95	37	3–157
Stroke volume, cm ³	17.7	1.0–539.5	196.7	4.6–679.7
Object naming score	60/60	60–60/60	49/60	0–59/60
Word fluency score	14	5–26	5	0–17
WAB-R aphasia quotient score	98	49.4–100	56.5	1.6–94.6

Abbreviations: CHS = Cardiovascular Health Study; WAB-R = Western Aphasia Battery–Revised (obtained in a subset of 32 participants).

severity of RH leukoaraiosis together predicted outcome of object naming ($\chi^2 = 39.16$, $p < 0.00001$, pseudo- $r^2 = 0.68$), and severity of RH leukoaraiosis was independently associated with outcome (95% confidence interval -2.23 to -0.13 , $p = 0.027$) (table 2 for details). Similar results were obtained if total lesion volume was included in place of damage to left STG (table 2). All of the independent variables together also predicted highest quartile of word fluency [$\chi^2 (9) = 16.73$, $p = 0.05$, pseudo- $r^2 = 0.35$], although severity of RH leukoaraiosis and damage to left STG were the only independent (negative) predictors of word fluency outcome (table 2).

Adding white or black race or estimated atrophy as an independent variable in logistic regression did not improve the models, and none of these variables were independently associated with outcome. There was no significant effect of race on severity of leukoaraiosis ($F_{4,37} = 1.10$, $p = 0.37$) or naming outcome ($F_{4,37} = 1.74$, $p = 0.16$). Although estimated atrophy (lower scores indicating more atrophy) weakly correlated with severity of leukoaraiosis ($r = -0.41$, $p = 0.02$), it did not correlate with naming outcome ($r = 0.20$, $p = \text{NS}$). Not surprisingly, estimated atrophy correlated strongly with age ($r = -0.67$, $p < 0.00001$), with worse atrophy (lower scores) in older people.

Finally, leukoaraiosis was more severe in participants with stroke who failed to achieve the highest quartile of naming ($z = 2.0$, $p = 0.048$).

Discussion

Results indicate that severe RH leukoaraiosis is associated with poorer outcome of naming. Furthermore, severity of leukoaraiosis is associated with naming outcome independently of infarct volume, months since onset of stroke, comorbid conditions, and damage to key language areas.

Results are consistent with previous studies indicating that leukoaraiosis is associated with poor outcome of other functions. For example, results from 1 study showed that at 90 days after stroke, survivors who had severe leukoaraiosis had a modified Rankin Scale score that was 0.47 points higher (more impairment) than those without leukoaraiosis.³⁵ Another study showed that stroke survivors in the top quartile of leukoaraiosis had a 6-month modified Rankin Scale score that was 0.8 points higher (worse) than those in the lowest quartile.³⁶ Furthermore, our results are consistent with a reported association between damage to white matter tracts and performance on word fluency in healthy controls.³⁷

Many studies using diffusion tensor imaging have shown that damage to particular white matter tracts disrupts specific speech and language tasks.^{6–12} Three studies showed that outcome of naming in poststroke aphasia depends on the integrity of the arcuate fasciculus.^{24,25,38} Others have demonstrated the importance of specific white matter connections in explaining how damage to different areas can cause the same language impairment²² or syndrome.³⁹ However, these studies have not evaluated the role of leukoaraiosis in the RH on language outcome after stroke. One study did not find a significant effect of current leukoaraiosis (rated in both hemispheres) on the presence of aphasia, dysarthria, or dysphagia independently of damage to gray matter areas, lesion volume, and demographics.⁴⁰ However, leukoaraiosis in that study may have reflected wallerian degeneration caused by the stroke, which would not have been independent of damage to gray matter regions. Another study showed that leukoaraiosis in both hemispheres is associated with lower scores on a cognitive screening test and the NIH Stroke Scale⁴¹ 90 days after stroke.⁴²

Although the pathophysiology underlying leukoaraiosis is still debated, there is widespread agreement that it is associated with a higher risk of stroke and dementia.^{42,43} In acute stroke,

Table 2 Results of logistic regression for each language outcome

	Coefficient	Standard Error	p Value	95% Confidence interval
HQ object naming				
Left STG infarct	-8.23	3.09	0.008 ^a	-14.30 to -2.17
Months since stroke	0.021	0.03	0.96	-0.02 to 0.066
RH leukoaraiosis: CHS	-1.19	0.54	0.027 ^a	-2.23 to -0.14
HQ object naming				
Lesion volume	-0.000006	0.0000024	0.012 ^a	-0.000011 to -0.000013
Months since stroke	-0.0066	0.0097	0.49	-0.026 to 0.012
RH leukoaraiosis: CHS	-0.44	0.19	0.021 ^a	-0.82 to -0.066
HQ word fluency				
Left STG infarct	-4.62	2.23	0.038 ^a	-8.99 to -0.26
Left SLF infarct	2.26	1.70	0.18	-1.07 to 5.60
Left pIFG infarct	0.38	1.16	0.74	-1.90 to 2.66
Months since stroke	0.03	0.020	0.12	-0.0081 to 0.069
RH leukoaraiosis: CHS	-0.73	0.31	0.020 ^a	-1.35 to -0.12
Hypertension	1.16	1.22	0.34	-1.22 to 3.55
Diabetes mellitus	-0.92	1.30	0.48	-3.47 to 1.63
Depression	0.46	1.17	0.70	-1.84 to 2.75
Infarct volume	-0.0000027	0.0000046	0.56	-0.000012 to 0.0000064

Abbreviations: CHS = cardiovascular health study score; HQ = highest quartile; pIFG = posterior inferior frontal gyrus; RH = right hemisphere; SLF = superior longitudinal fasciculus; STG = superior temporal gyrus.

^a Alpha level $p < 0.05$

severe leukoaraiosis is associated with higher rates of hemorrhage after thrombolysis⁴⁴ and more severe neglect.¹⁶ It is thought to reflect small vessel cerebrovascular disease in most cases⁴³; other causes include demyelination and repeated head trauma. It is associated with aggressive small vessel diseases such as cerebral amyloid angiopathy, as well as hypertensive small vessel vasculopathy. It is unclear whether RH leukoaraiosis directly hinders recovery of naming or is a more general marker for poor brain health that in turn hampers recovery. However, accumulating evidence indicates that leukoaraiosis is 1 contributor to poor outcome after stroke.

Results contribute to the accumulating data on demographic and stroke variables associated with aphasia outcome. One large aphasia outcome study showed that damage to 35 gray and white matter regions contributed to speech outcome in 270 left hemisphere and RH stroke survivors at various times after onset.² Another study showed that the integrity of the left SLF was associated with phonologic encoding in speech production.¹² A recent longitudinal study revealed that recovery of naming was hindered by damage to the left STG or SLF,⁴⁵ 2 regions found to be important also in the large outcome study reported by Hope and colleagues.² The SLF in the JHU-MNI atlas (natbrainlab.co.uk/atlas-maps) is

essentially identical to the arcuate fasciculus in the Catani atlas (natbrainlab.co.uk/atlas-maps); as noted, the integrity of the arcuate fasciculus has been found to be important for recovery of naming.^{24,25,38} Another study identified the left pIFG as influencing speech production outcome.² Results of this study also confirmed the importance of damage to the left STG in naming and overall language outcome, consistent with other studies.^{2,21,22,45}

Our study population was relatively young for stroke patients, and approximately half were white/Caucasian and half were black/African American, with few Asian or Hispanic/Latino participants. It is unclear whether our results are generalizable to Asian and Hispanic/Latino participants.

Limitations of the study include the relatively small sample size, which limited our ability to comprehensively evaluate the effect of lesion location and all possible comorbid conditions that can affect outcome. We also were not able to control for the amount or type of language rehabilitation. Certainly, other comorbid conditions and language rehabilitation can influence outcome. Although we excluded anyone with documented dementia, we did not evaluate the influence of other cognitive impairments (e.g., in memory,

executive functions) that are often associated with leukoaraiosis because it is very difficult to evaluate cognitive functions in people with aphasia. Standard dementia screening tests are very sensitive to aphasia; anomia can impede naming of the month, year, and location, and recall of words. Aphasia can also interfere with comprehension of directions for tests of executive function. The study population was also heterogeneous in time since stroke; we chose beyond 3 months because of evidence that most recovery of language occurs in the first 3 months.¹ Nevertheless, many individuals show further recovery of language skills after 3 months, particularly with language rehabilitation. Therefore, we adjusted for time since onset in our logistic regression analyses. We also found no significant difference in time since onset between those who did and those who did not show good recovery of naming. Finally, the absence of information about initial severity is a limitation. All individuals had language assessment at onset, but various tests were used to identify aphasia. Therefore, we used stroke volume (and damage to 3 critical language areas) as a proxy for aphasia severity because these imaging variables are strongly associated with initial aphasia severity.⁴³

Despite its limitations, our study indicates that severity of leukoaraiosis may aid in prognosis of naming outcome. The significant effect of leukoaraiosis on naming outcome was independent of both lesion volume and time since onset. However, further studies are needed to determine whether the severity of leukoaraiosis can prospectively predict language outcome in larger, independent samples.

Author contributions

Ms. Wright: acquisition of data, critical revision of the manuscript for important intellectual content. Ms. Tippet: analysis and interpretation, critical revision of the manuscript for important intellectual content. Ms. Saxena: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Sebastian and Dr. Breining: analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. Hillis: study concept and design, drafting of the manuscript draft, statistical analysis, study supervision.

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