Impact of Leukoaraiosis Burden on Hemispheric Lateralization of the National Institutes of Health Stroke Scale Deficit in Acute Ischemic Stroke

Johanna Helenius, MD, PhD; Richard P. Goddeau Jr, DO; Majaz Moonis, MD; Nils Henninger, MD

Background and Purpose—The National Institutes of Health Stroke Scale (NIHSS) awards higher deficit scores for infarcts in the dominant hemisphere when compared with otherwise similar infarcts in the nondominant hemisphere. This has been shown to adversely affect stroke recognition, therapeutic decisions, and outcome. However, factors modifying the association between infarct side and deficit severity are incompletely understood. Thus, we sought to determine whether age and age-related leukoaraiosis alter the relation between NIHSS deficit score and the side and volume of infarction.

Methods—We studied 238 patients with supratentorial, nonlacunar ischemic infarcts prospectively included in our stroke registry between January 2013 and January 2014. NIHSS deficit severity was assessed at the time of presentation. Infarct volumes were assessed by manual planimetry on diffusion-weighted imaging. Leukoaraiosis burden was graded on fluid-attenuated inversion recovery images according to the Fazekas scale and dichotomized to none-to-mild (0–2) versus severe (3–6). Multivariable linear regression with backward elimination was used to identify independent predictors of the admission NIHSS.

Results—Left-hemispheric infarction (P<0.001), severe leukoaraiosis (P=0.001), their interaction term (P=0.005), infarct volume (P<0.001), and sex (P=0.013) were independently associated with the NIHSS deficit. Analysis of the individual NIHSS components showed that severe leukoaraiosis was associated with an increase of the lateralizing components of the NIHSS in patients with right-hemispheric infarction (P<0.05).

Conclusions—Severe leukoaraiosis substantially attenuates the classic hemispheric lateralization of the NIHSS deficit by relating to greater NIHSS scores of components that are typically assigned to left hemisphere function. (Stroke. 2016;47:24-30. DOI: 10.1161/STROKEAHA.115.011771.)

Key Words: connectome • infarction • leukoaraiosis • magnetic resonance imaging • stroke • white matter

Ischemic strokes in the dominant hemisphere cause greater functional deficits than nondominant hemisphere strokes as assessed on the National Institutes of Health Stroke Scale (NIHSS).1–3 This hemispheric lateralization of the NIHSS deficit has been observed to adversely affect stroke recognition, therapeutic decisions, prediction of infarct-related disability, and outcome.4–6 Accordingly, a better knowledge of factors modifying the association between the side of infarction and NIHSS deficit severity is important to mitigate hemisphere-dependent outcome differences in patients with stroke by improving proper assessment and evidence-based treatment strategies as well as inform on clinical trial designs that rely on the NIHSS to assess stroke severity.

Substantial evidence exists for age- and sex-related alterations of lateralization of human brain functions and its structural connectome.7–9 However, whether age, or age-related phenomena, affect the hemispheric lateralization of the NIHSS deficit is presently unclear. In this respect, leukoaraiosis is of particular interest because it commonly present among the elderly,10–11 worsens functional deficit severity after ischemic stroke,12,13 and decreases white matter tract and functional network integrity.14,15 Accordingly, age-related leukoaraiosis could represent an easily accessible imaging marker that affects the association between deficit severity and side of infarction as assessed by the NIHSS. Considering its association with global cerebral white matter integrity we hypothesized that leukoaraiosis rather than chronological age per se modifies the known association between the side of infarction and NIHSS deficit severity.

To test this hypothesis, we investigated whether age and age-related leukoaraiosis alter the relation between NIHSS-deficit score and the side and volume of infarction, while adjusting for key confounders including the patient sex in a cohort of patients presenting with supratentorial, nonlacunar ischemic infarcts.

Methods

Study Population

This study was reviewed and approved by our Institutional Review Board. We retrospectively analyzed consecutive patients with acute ischemic strokes in the dominant hemisphere presenting with supratentorial, nonlacunar ischemic infarcts.
supratentorial ischemic stroke as shown on brain magnetic resonance imaging (MRI) that were prospectively included in our local stroke registry between January 2013 and January 2014.

Patient demographics, laboratory data, comorbidities, preadmission medications, and stroke pathogenesis (using the Trial of Org 10172 in Acute Stroke Treatment [TOAST] classification) after completion of diagnostic evaluation, were collected on all patients.12 NIHSS scores were assessed at the time of presentation by members of the stroke team certified in NIHSS. The modified Rankin Scale (mRS) score was assessed at 90 days by a stroke-trained physician or stroke study nurse certified in mRS via in-person or phone interview.14 We adhere to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (http://www.strobe-statement.org).

Neuroimaging Protocol

Brain MRI included T1-, T2-, and fluid-attenuated inversion recovery sequences as well as diffusion-weighted images (DWIs). MRI was performed on a 1.5 Tesla clinical scanner (GE Sigma; GE Medical Systems, Milwaukee, WI). DWI was obtained using echo-planar imaging with a repetition time of 8000 ms, an echo time of 102 ms, a field of view of 22x22 cm, image matrix of 128x128, slice thickness 5 mm with a 1-mm gap, and b values of 0 s/mm² and 1000 s/mm². Fluid-attenuated inversion recovery was obtained with a repetition time of 9002 ms, an echo time of 143 ms, a field of view of 22x22 cm, image matrix of 256x224, and slice thickness 6 mm with a 1-mm gap. All images were evaluated by a neuroradiologist for the presence of acute ischemic infarction.

Image Review and Analysis

DWI were reviewed independently by experienced readers (N.H., J.H.) blinded to both clinical data and any follow-up scans. Lesions that were hyperintense on DWI and hypo- or iso-intense on the apparent diffusion coefficient maps were considered acute ischemic infarcts. Ischemic infarcts on DWI were manually outlined using careful windowing to achieve the maximal visual extent of the acute DWI (b1000 trace weighted) infarct and with reference to the apparent diffusion coefficient image to avoid regions of T2 shine-through and to allow for reliable distinction from leukoaraiosis.12

Leukoaraiosis was defined as supratentorial white matter hypointen- tuation on fluid-attenuated inversion recovery MRI according to the STandards for ReportIng Vascular changes on nEuroimaging criteria17 and graded according to the Fazekas scale on the basis of visual assess- ment both periventricular (0=absent, 1=caps or pencil lining, 2=smooth halo, and 3=irregular periventricular hyperintensities extending into deep white matter) and subcortical areas (0=absent, 1=punctuate foci, 2=beginning confluence of foci, and 3=large confluent areas).12 The total Fazekas score was calculated by adding the periventricular and sub- cortical scores.12 Perivascular spaces and lacunes of presumed vascular origin were excluded. Leukoaraiosis was separately assessed in each hemisphere but only the score from the nonischemic hemisphere was considered after unblinding. All included patients had a symmetrical distribution of leukoaraiosis burden (ie, the assigned grade was identi- cal for the left and right hemisphere). We then dichotomized the degree of leukoaraiosis to Fazekas 0 to 2 (none-to-mild) versus 3 to 6 (severe). Using this approach, we have previously demonstrated high inter-rater reliability with an intraclass correlation coefficient of >0.95 for both the total and graded Fazekas score.12

Statistics

Unless otherwise stated, continuous variables are reported as mean±SD or as median (interquartile range). Categorical variables are reported as proportions. Normality of data was examined using Shapiro–Wilk test. Between-group comparisons for continuous variables were made with unpaired t test and Mann–Whitney U test. Categorical variables were compared using the χ² test or Fisher exact test. ANOVA on ranks with post hoc Dunn method was used to compare between-group differences in the NIHSS and infarct volume, respectively. Spearman rank correlation was used to determine the strength of association between the NIHSS and imaging volumes for right- and left-sided infarcts. ANCOVA investigated whether the association between NIHSS and infarct volume differed between hemispheres as stratified by leukoaraiosis severity.

To explore whether the infarct volume was independently associ- ated with the NIHSS after adjustment for other covariates, we con- structed a preplanned multivariable linear regression analysis with backward elimination adjusting for infarct side and leukoaraiosis as well as factors that have been associated with the outcome and stroke severity, namely: age, sex, use of antiplatelets and anticoagulants, and atrial fibrillation. Furthermore, we explored whether the associa- tion of leukoaraiosis with NIHSS depended on the side of infarction as well as the infarct volume by entering the following interaction terms into the multivariable model: (1) leukoaraiosis×infarct side, (2) leukoaraiosis×infarct side, (3) infarct side×infarct volume, and (4) leukoaraiosis×infarct side×infarct volume.

To achieve a more suitable distribution for ANCOVA and multivariable linear regression, we transformed the NIHSS and infarct volume on the basis of a cube-root transformation.12 For testing inter- actions in the multivariable linear regression analysis variables were centered. For ANCOVA, assumptions of homogeneity of variance as well as regression slopes was tested and met in all models. Collinearity diagnostics were performed (and its presence rejected). Two-sided significance tests were used throughout and a 2-sided P<0.05 was considered statistically significant. All statistical analyses were per- formed using IBM SPSS Statistics 20.0.0 (IBM, Armonk, NY).

Results

Patient Population

During the study period, 434 patients with a clinical diagno- sis of ischemic stroke or transient ischemic attack had a brain MRI allowing for reliable assessment of the leukoaraiosis burden and infarct volume. We excluded patients who had no ischemic infarct (n=61), infratentorial infarct location (n=55), small subcortical infarction (n=58), bihemispheric strokes (n=20), or because the admission NIHSS was not documented (n=2); leaving 238 patients for analysis. Small subcortical infarcts were excluded as they were not expected to impact the hemispheric lateralization of the NIHSS.1 Data were complete in included patients for all variables except for the 90-day mRS (9 patients were lost to follow-up) and detailed information on the NIHSS subcategories (n=32 patients had only the total NIHSS score documented).

To determine whether exclusion of patients without a brain MRI that otherwise fit the inclusion criteria for our study (n=70) may have introduced a significant bias we compared this subgroup with the included patients (n=238). Overall, patients without MRI more frequently had congestive heart failure (22% versus 10%, P=0.011), large-artery atherosclerosis (53% versus 27%, P<0.001), greater NIHSS deficit scores (median [interquartile range] mRS of 1 [2] versus 0 [1], P=0.001) as well as worse baseline functional defi- cits (median [interquartile range] mRS of 1 [2] versus 0 [0], P<0.001). All other baseline variables did not differ between groups (P>0.05, not shown).

Clinical Characteristics

Baseline characteristics of included patients as stratified by infarct side are summarized in Table 1. Patients with left- hemispheric infarcts had significantly greater NIHSS scores than subjects with right-hemispheric infarcts (P=0.008).
Otherwise, baseline variables were well balanced without significant between-group differences.

Factors associated with severe leukoaraiosis in unadjusted analyses included female sex (58% versus 39%, \( P = 0.004 \)), hypertension (87% versus 70%, \( P = 0.002 \)), history of stroke/transient ischemic attack (29% versus 15%, \( P = 0.11 \)), history of atrial fibrillation (26% versus 15%, \( P = 0.035 \)), no tobacco use (18% versus 37%, \( P = 0.002 \)), antihypertensives use (77% versus 62%, \( P = 0.017 \)), antiplatelets use (57% versus 44%, \( P = 0.039 \)), older age (77±11 versus 62±13 years, \( P < 0.001 \)), as well as a worse 90-day outcomes ( \( P < 0.001 \), not shown). There was no difference in the admission NIHSS (8±7 versus 9±7; \( P = 0.063 \)) and infarct volume (29±44 mL versus 22±36 mL, \( P = 0.183 \)) between patients with none-to-mild versus severe leukoaraiosis.

### Severe Leukoaraiosis Relates to Worse Functional Deficits With Right Hemisphere Infarction and Attenuated Hemispheric Lateralization of the NIHSS Deficit

There was a significant positive correlation between the NIHSS and DWI infarct size in the entire cohort (\( r = 0.607, P < 0.001 \)) as well as for both right hemisphere (\( r = 0.665, P < 0.001 \)) and left hemisphere (\( r = 0.571, P < 0.001 \)) infarcts, respectively (not shown).

Consistent with previous observations, we found significantly different associations between the DWI infarct volume and NIHSS of patients with right- versus left-hemispheric infarcts: left hemisphere infarcts caused relatively greater neurological deficits as assessed by the NIHSS (Figure 1A,
Intriguingly, hemispheric lateralization of the NIHSS was only present in patients with none-to-mild leukoaraiosis (Figure 1B; \( P<0.001 \)) but not in patients with severe leukoaraiosis (Figure 1C; \( P=0.957 \)). We further found that severe leukoaraiosis attenuated the hemispheric lateralization of the NIHSS by relating to worse NIHSS deficits rather than greater infarct volumes with right-hemispheric infarction (Figure 2A and 2B).

### Association Between Infarct Side and NIHSS Deficit Depends on Preexisting Leukoaraiosis Burden Rather Than Chronological Age

To assess whether infarct volume and side were independently associated with the NIHSS, we constructed a multivariable linear regression model to adjust for predictors of the admission NIHSS. As expected, we found that left-hemispheric infarcts and greater infarct volumes predicted a greater NIHSS deficit severity. Male sex was independently associated with a smaller NIHSS deficit. Finally, leukoaraiosis but not chronological age predicted the NIHSS deficit severity (Table 2; \( P<0.001 \)). Interestingly, there was a significant leukoaraiosis×side interaction. Conversely, the association of leukoaraiosis burden with NIHSS was not dependent on the infarct volume as indicated by absent association of the interaction term leukoaraiosis × infarct volume and leukoaraiosis × side × infarct volume with the NIHSS. These results show that the effect of infarct side on the admission NIHSS depends on the degree of preexisting leukoaraiosis burden.

### Impact of Leukoaraiosis Severity on Individual NIHSS Components

To gain a more granular understanding of the impact of leukoaraiosis burden on the hemispheric lateralization of the NIHSS deficit, we analyzed the distribution of functional deficits in each NIHSS component as stratified according to the side of infarction. This analysis was based on \( n=206 \) subjects (87% of the entire cohort) in whom the deficits within individual NIHSS components were detailed in the chart. We found that patients with left-hemispheric infarcts had a remarkably similar distribution of functional deficits when stratified according to leukoaraiosis severity (Figure 3A). In contrast, among patients with right-hemispheric infarction severe leukoaraiosis was associated with substantially greater NIHSS deficits in the NIHSS subcategories (Figure 3B).

When we categorized the NIHSS components according to their putatively lateralizing versus nonlateralizing contribution to the NIHSS,\(^{18} \) we noted that severe leukoaraiosis significantly increased only the lateralizing NIHSS components in patients with right-hemispheric infarction (\( P<0.05 \), not shown).

### Discussion

The NIHSS is routinely used to ascertain the severity of an ischemic infarct. Because the NIHSS awards 7 points for tests related to language function and only 2 points for neglect it is inherently skewed toward greater deficit scores with dominant (typically left) hemispheric infarctions. We found that the well-known phenomenon of hemispheric lateralization of the NIHSS deficit (NIHSS bias) is significantly affected by the burden of preexisting leukoaraiosis and that severe leukoaraiosis is associated with a remarkable attenuation of the NIHSS bias.

Loss of hemispheric functional lateralization is a well-documented phenomenon of the aging brain.\(^{7,8} \) Yet, we noted no association between chronological patient age and NIHSS.
in our study. Instead, leukoaraiosis, which is one of the most commonly noted abnormalities in the aging brain that relates to widespread loss of white matter tract and functional network integrity, significantly altered the association between infarct side and NIHSS deficit severity in our study. This is consistent with previous reports that functional task performance in the leukoaraiotic brain increasingly relies on recruitment of additional functional domains in bilateral hemispheres. Accordingly, patients with severe leukoaraiosis are expected to be more susceptible to develop functional deficits after an ischemic stroke irrespective of the involved hemisphere, consistent with our observation of a predominant effect on lateralizing NIHSS components. In addition, we made the intriguing observation that leukoaraiosis predominantly affected the association between NIHSS deficit severity and right hemisphere infarcts. Importantly, right- and left-hemispheric infarcts were similarly distributed among leukoaraiosis groups arguing against enrichment of our sample with more severe right-hemispheric strokes.

Our findings are important in several respects. For example, exclusion of patients with mild stroke from thrombolysis has been shown to result in a worse outcome, which is particularly true for right-hemispheric strokes because they often produce NIHSS deficit scores below the threshold for treatment despite a significant infarct size and worse outcomes. In addition, ongoing efforts are aimed at optimizing patient selection for endovascular stroke therapies based on imaging and clinical parameters. Our results emphasize that a single lower NIHSS inclusion threshold may be too restrictive for optimal treatment selection.

Table 2. Multivariable Linear Regression Analyses of Factors Independently Associated With the Admission NIHSS*

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Coefficient (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct volume*</td>
<td>0.326 (0.273 to 0.380)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left-hemispheric infarct</td>
<td>0.380 (0.189 to 0.571)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe leukoaraiosis†</td>
<td>0.795 (0.323 to 1.267)</td>
<td>0.001</td>
</tr>
<tr>
<td>Severe leukoaraiosis†×left-hemispheric infarct</td>
<td>−0.401 (−0.682 to −0.120)</td>
<td>0.005</td>
</tr>
<tr>
<td>Male sex</td>
<td>−0.178 (−0.318 to −0.038)</td>
<td>0.013</td>
</tr>
<tr>
<td>Oral anticoagulant use</td>
<td>0.177 (−0.034 to 0.387)</td>
<td>0.100</td>
</tr>
</tbody>
</table>

*Cube-root transformed.
†Entering leukoaraiosis as continuous variable did not meaningfully change the results (not shown).
particularly for patients with a right-hemispheric stroke and otherwise good brain health (as indicated by none-to-mild leukoaraiosis). Accordingly, future studies aimed at creating predictive tools for patient selection may be improved by adjusting for the side of infarction\textsuperscript{22} and degree of preexisting white matter injury; and one should not refrain from acute stroke therapy in patients particularly with right-hemispheric infarctions and a relatively low NIHSS score.

Limitations of our study relate the retrospective design of our research question. We did not quantify leukoaraiosis burden that may be more sensitive for detecting subtle inter-group differences and avoid a ceiling-effect in patients with severe leukoaraiosis.\textsuperscript{23} Furthermore, exclusion of patients without brain MRI may have introduced a bias. However, this was arguably small because key vascular risk factors associated with leukoaraiosis did not differ between included patients versus excluded patient. Conversely, MRI-based leukoaraiosis grading using the Fazekas scale is well established, frequently used in clinical research, and has been shown to correlate well with the leukoaraiosis volume and we have demonstrated

\textbf{Figure 3.} Distribution of the individual National Institutes of Health Stroke Scale (NIHSS) component scores as stratified by infarct side and leukoaraiosis burden. 
\textbf{A,} Among patients with right-hemispheric infarcts severe leukoaraiosis was associated with a shift to greater NIHSS scores in all subcategories (*P*<0.05; **<0.01; χ\textsuperscript{2} test). 
\textbf{B,} Among patients with left-hemispheric infarcts, there was no significant difference in the distribution of NIHSS subcategory scores as stratified by leukoaraiosis severity (P>0.05). Respective bar pairs indicate NIHSS score for none-to-mild (left) vs severe (right) leukoaraiosis.
high inter-rater reliability of leukoaraiosis assessment with its use.2,3 Furthermore, using a semiquantitative approach has the advantage that it does not require intensive postprocessing routines and can thus be more easily used in the clinical setting. Another limitation of our study protocol is that we cannot rule out the possibility that some patients may have had functional deficits predating their incident stroke. However, we recruited all patients that fit the study criteria from our consecutive database. This and the overall well-balanced baseline characteristics assuage concerns that potential preexisting deficits unduly influenced our results. Furthermore, although our approach to conceptually defining the left hemisphere as dominant is consistent with previous studies4–18 and has the advantage of greater clinical applicability, it may have resulted in misclassification of some patients. Finally, although our results are consistent with previous studies investigating the impact of infarct side and functional deficits our study design does not allow us to establish a causal relationship. Thus, and given the retrospective nature of our study, results should be considered hypothesis generating only that require confirmation in future studies.

Strengths of our study relate to (1) inclusion of consecutive patients with imaging confirmed, ischemic, supratentorial, stroke that were evaluated by clinicians certified in NIHSS, (2) exclusion of patients with small subcortical infarcts, (3) blinded assessment of DWI volumes and leukoaraiosis severity with respect to clinical variables, (4) rigorous adjustment for possible confounders, and (5) detailed assessment of the individual NIHSS components.

Conclusions
Severe leukoaraiosis substantially attenuates the classic hemispheric lateralization of the NIHSS deficit by relating to greater NIHSS scores of components that are typically assigned to left hemisphere function. This provides intriguing insight not only into how leukoaraiosis affects stroke-related deficits but also relate to phenomena of cerebral functional aging.

Acknowledgments
Dr Helenius involved in data acquisition, interpretation of data, and critical revision of the article for important intellectual content. R.P. Goddeau, Jr and Dr Moonis involved interpretation of data and critical revision of the manuscript for important intellectual content. Dr Henninger conceived study concept and design, data acquisition, statistical analysis, interpretation of data, and drafting the article.

Disclosures
None.

References
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On page 28, the second column, third line, “Our results emphasize that a wparticularly for patients with a right-hemispheric stroke and otherwise good brain health (as indicated by none-to-mild leukoaraiosis),” has been changed to read “Our results emphasize that a single lower NIHSS inclusion threshold may be too restrictive particularly for patients with a right-hemispheric stroke and otherwise good brain health (as indicated by none-to-mild leukoaraiosis).”

This correction has been made to the online and print version of the article, which is available at http://stroke.ahajournals.org/content/47/1/24.
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Abstract

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