Is the Association of National Institutes of Health Stroke Scale Scores and Acute Magnetic Resonance Imaging Stroke Volume Equal for Patients With Right- and Left-Hemisphere Ischemic Stroke?

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Background and Purpose—The National Institutes of Health Stroke Scale (NIHSS) is an established measure of neurological impairment; however, it can award more points for tests of presumed left-hemisphere function, such as language, than for tests of right-hemisphere function, such as neglect. This difference may be important if a low NIHSS score is used to exclude patients with right-hemisphere stroke from clinical trials or established treatments. The aim of this study was to investigate whether the relationship between acute NIHSS score and acute stroke volume as determined by acute diffusion- and perfusion-weighted MRI (DWI and PWI) differs between right- and left-sided stroke.

Methods—This was a retrospective study of 153 patients with acute stroke seen at Beth Israel Deaconess Medical Center between January 1995 and March 2000 who underwent an MRI examination and NIHSS within 24 hours of stroke onset. NIHSS score was recorded prospectively by the admitting stroke fellow at the time of acute presentation, immediately preceding imaging. Computerized volumetric analysis of the MRI lesions was performed by investigators blinded to clinical data.

Results—There were significant correlations between the acute NIHSS scores and acute DWI lesion volumes ($r=0.48$ right, $r=0.58$ left) and between acute NIHSS scores and perfusion-weight imaging hypoperfusion volumes ($r=0.62$ right, $r=0.60$ left). For patients with NIHSS scores of 0 to 5, the DWI volume of right cerebral lesions was greater than that of left-sided lesions (mean volume, 8.8 versus 3.2 cm^3; $P=0.04$). Among patients with DWI lesions larger than the median volume (9 cm^3), 8 of 37 with right-sided stroke had an NIHSS score of 0 to 5 compared with 1 of 39 patients with left-sided stroke ($P=0.01$). Multiple linear regression analysis revealed a significantly lower acute NIHSS on the right compared with the left side when adjusted for stroke volume on chronic T2 imaging ($P=0.03$).

Conclusions—Patients with right-sided stroke may have a low NIHSS score despite substantial DWI lesion volume. Acute imaging information, such as that available with multimodal MRI, may be useful to identify patients for inclusion in acute stroke protocols when there is clinical uncertainty about eligibility. Prospective evaluation of criteria incorporating acute imaging data is required. **(*Stroke*. 2002;33:954-958.)**

Key Words: cerebral infarction ■ magnetic resonance imaging

The National Institutes of Health Stroke Scale (NIHSS) is a widely used and validated tool for assessment of clinical stroke severity.[1–3] The NIHSS score in the acute phase of stroke is a powerful predictor of final clinical outcome[4,5] and has been used to include or exclude patients from trials of acute stroke therapy, including thrombolysis.[6–9] The use of the NIHSS is not confined to clinical trials and is now a standard part of the clinical assessment of patients presenting with acute stroke in many stroke centers.[10–12] One potential weakness of the NIHSS, however, is its greater emphasis on deficits associated with left-hemisphere lesions than those associated with right-hemisphere stroke.[1,13,14] Although cognitive deficits associated with right-hemisphere stroke may be less clinically obvious and more difficult to test than aphasia associated with the left hemisphere, the ultimate functional outcome of patients with right-hemisphere stroke is no more favorable than for left-hemisphere stroke.[15] The NIHSS score could introduce bias against patients with right-hemisphere stroke when it is used to determine enrollment in clinical trials or in clinical decision-making protocols. This may be of particular importance if a low NIHSS score is used to exclude right-hemisphere stroke patients from treatment.

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The volume of right-hemisphere strokes determined by chronic CT scan has been shown to be larger than the volume of left-hemisphere strokes for a given NIHSS score; however, the clinical implications of this finding remain uncertain.[13] A difference between hemispheres in the relationship of NIHSS score and imaging parameters in the hyperacute phase of stroke might be of greater importance for clinical decision making. The combination of DWI and PWI can predict progression of cerebral infarction and clinical outcome in the early stages of stroke.[16–23] MRI, including diffusion- and perfusion-weight imaging (DWI and PWI) is a routine part of acute stroke assessment at our center. The aim of this study was to investigate whether the relationship between NIHSS score and stroke volume assessed acutely with DWI and PWI differs between right- and left-hemisphere lesions, particularly in patients awarded low NIHSS scores.

Subjects and Methods

This was a retrospective study of patients with acute stroke who were seen by the stroke service at Beth Israel Deaconess Medical Center between January 1995 and March 2000. Patients were identified from a prospectively collected computerized stroke registry of consecutive patients. Patients were eligible for inclusion in the study if they met the following criteria: (1) ischemic stroke presenting to hospital within 24 hours of symptom onset, (2) MRI (including DWI) within 24 hours of symptom onset, and (3) NIHSS score obtained just before the MRI. Patients with symptoms and signs lasting >24 hours (transient ischemic attack) who had negative DWI and patients with brainstem or cerebellar infarctions were excluded.

Prospectively recorded data for each patient in the stroke registry included demographic details, stroke risk factors, time of stroke onset (defined either as time of symptom onset or as time the patient was last seen well, if the patient woke with a deficit), time of hospital evaluation, NIHSS score at acute presentation immediately before imaging, type and time of imaging studies performed, treatments given, and final stroke diagnosis, including anatomic stroke localization and presumed stroke mechanism. The NIHSS score was recorded by stroke fellows who had accreditation in the performance of this test. As required for assessment of item 1c of the NIHSS, level of consciousness commands, gestures were used when aphasia was present. During the study period, multimodal MRI, including DWI and PWI, was a routine part of the evaluation of all acute stroke patients unless contraindications to MRI existed, including medically unstable or excessively restless patients. Follow-up clinical data at 3 to 6 months after stroke were obtained from hospital records for the subgroup of patients with large acute DWI lesions and low NIHSS scores. Modified Rankin scores and major neurological disabilities were determined by an independent observer who was unaware of the major hypothesis of this study.

Imaging Protocol

MRI studies were performed on a Siemens Vision 1.5-T echo-planar imaging system (Siemens Medical Systems). The imaging protocol included DWI, susceptibility-weighted (T2*) images, conventional spin-echo T1- and T2-weighted images, and magnetic resonance angiography. Perfusion MRI was also performed on some patients. Details of the imaging parameters have been published previously.[16,21]

Volumetric assessment of lesion size was performed with custom software implemented in the Advanced Visualization Systems software package running on a Hewlett-Packard workstation. DWI lesion volumes were measured on the image of maximum contrast between lesion and normal brain regions (ie, DWI with the highest b value). DWI lesion volumes were measured by an experienced, blinded observer on 2 occasions; the mean value was used. The volume of the perfusion abnormality was assessed on relative mean transit time maps that were calculated as previously described.[21]

TABLE 1. Summary of Presenting Characteristics

	Right	Left	*P*
Patients, n	72	81	0.26*
Mean age (range), y	71.4 (34–91)	69.9 (22–94)	0.47†
Mean time from symptom onset to MRI (range), h	7.4 (1–21)	8.0 (0.5–23)	0.53†
Median NIHSS score	7	8	0.54‡
Mean DWI volume (median), cm^3	23.7 (10.0)	21.3 (7.8)	0.98‡

*Binomial distribution; †Student's *t* test; ‡Wilcoxon rank-sum test.

Measurements were made by an experienced observer who was blinded to the clinical scores and DWI lesion volumes. Volumes for the regions of interest drawn on the diffusion images and relative mean transit time maps were computed by multiplying the measured area per slice by section thickness; there was no interslice gap. Total lesion volume was defined as the larger of the DWI or PWI lesion volume for each patient for whom PWI was performed to control for cases in which recanalization had occurred before imaging to get a better estimate of the total volume of functionally impaired cerebral tissue.

Statistical Analysis

The Spearman correlation was used to determine the strength of association between the NIHSS and imaging volumes for right- and left-sided lesions. The Pearson correlation was used for continuous variables. Correlations were compared by *z* test. Student's *t* test was used for comparison of continuous variables, Wilcoxon rank-sum test for nonparametric data, and Fisher's exact test for 2×2 tables. An analysis of covariance was used to control for imaging volume in assessments of the effect of right- versus left-sided stroke on NIHSS. Categorical comparison of right and left lesions was made by stratifying patients according to 5-point divisions of the NIHSS score, as has been done previously by others.[13] Because it was expected that most patients with small lesions from either hemisphere would have low NIHSS scores, a right-left NIHSS comparison of patients with lesion volumes above the median value was planned. A subgroup analysis was performed for patients imaged within 6 hours of stroke onset, simulating an "acute decision" group.

Results

One hundred fifty-three patients fulfilled the study entry criteria. Baseline features of the patients are summarized in Table 1. There was no significant difference in baseline characteristics between patients presenting with right or left cerebral lesions. In particular, there was no difference overall in NIHSS score or lesion volume measured by DWI

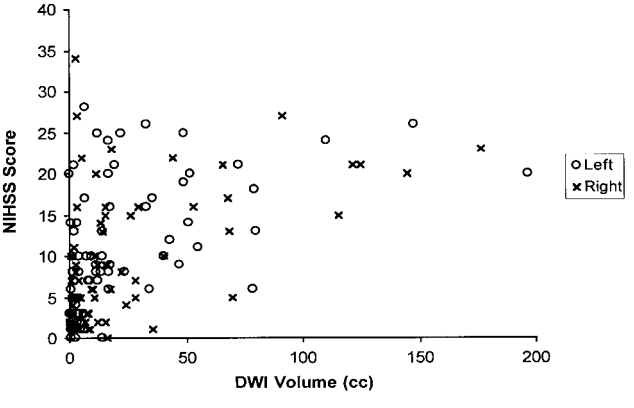

Figure 1. NIHSS score and DWI lesion volume.

TABLE 2. DWI Lesion Volume According to Stratified NIHSS Score

	Right		Left		
NIHSS Score	DWI Lesion Volume (Mean)	n	DWI Lesion Volume (Mean)	n	*P*
0–5	8.8	32	3.9	27	0.04
6–10	12.1	16	15.9	26	0.39
11–15	38.1	6	31.1	8	0.75
16–20	48.6	7	48.7	10	1.0
>20	71.0	8	38.0	8	0.23

between patients presenting with right or left cerebral lesions (Table 1).

Acute DWI Lesion Volume and NIHSS Score

There was a significant correlation between the DWI lesion volume and NIHSS score for both right and left cerebral lesions (r=0.48 and 0.58, respectively; P<0.0001 for both); however, considerable variability was present, as demonstrated by the scattergram in Figure 1. There was no difference in the strength of these correlations between patients with right- or left-sided lesions (P=0.40). Analysis of covariance revealed no difference overall in NIHSS score adjusted for DWI lesion volume between the hemispheres (P=0.41). When stratified according to 5-point NIHSS categories, the DWI lesion volume of right cerebral lesions was greater than of left-sided lesions for patients with NIHSS scores of 0 to 5 (mean volume, 8.8 versus 3.2 cm^3; P=0.04) but was no different between right and left for any of the other NIHSS strata (Table 2).

Large Acute Lesion Volume and Low NIHSS Score

The median DWI lesion volume was 9 cm^3. When patients with DWI lesions larger than the median were stratified according to NIHSS score, 8 of 37 patients with right-sided stroke had an NIHSS score of 0 to 5 compared with 1 of 39 patients with left-sided stroke (P=0.01, Fisher's exact test). Most patients with both right and left cerebral lesion volumes less than the median had an NIHSS score of 0 to 5 (24 of 35 right, 25 of 42 left; P=0.63). Neglect, constructional or dressing apraxias, anosognosia, or other cortical signs usually associated with right-hemisphere lesions were present in 4 of the 8 right-hemisphere stroke patients with DWI lesion volume >9 cm^3 and low NIHSS scores. Mild to moderate disability (modified Rankin score of 2 to 3) remained present at 3- to 6-month follow-up for 3 of the 8 patients despite the initial low NIHSS scores (Table 3). Figure 2 shows a DWI from a patient with a large right-hemisphere lesion and an NIHSS score of 5.

There was no change in any of these results if 28 patients with subcortical strokes <1.5 cm in diameter were excluded from the analyses. If the motor component of the NIHSS score was subtracted from each patient's score, the median remaining scores were 4.5 for right- and 6 for left-hemisphere lesions (P=0.08); there was no change in the statistical significance of any of the other comparisons.

Patients Within 6 Hours of Stroke Onset

Stroke imaging was performed within 6 hours of symptom onset for 72 of the 153 patients. Of these, 34 had right and 38 had left cerebral lesions. The Spearman correlations between NIHSS and DWI lesion volume remained significant for patients imaged within 6 hours (right cerebral lesions: r=0.50, P=0.002; left: r=0.58, P=0.0001); there was no significant difference between right and left (P=0.65). Within 6 hours, the mean DWI lesion volume of patients with NIHSS scores of 0 to 5 was double for patients with right-sided lesions than those on the left, but the difference was not significant (5.8 versus 2.3 cm^3, P=0.065). Of patients with DWI lesions greater than the median volume (>7 cm^3) within 6 hours of stroke onset, none with left cerebral lesions had NIHSS scores of 0 to 5 compared with 3 patients with right cerebral lesions (P=0.06).

Perfusion MRI

PWI was performed for 113 of 153 patients. The mean total lesion volume was 88.5 cm^3 on the right and 82.0 cm^3 on the left (P=0.69). There was an equally strong correlation between total lesion volume and NIHSS score for right- and left-sided lesions (r=0.62 right, r=0.60 left). When adjusted for total lesion volume, however, there was a trend for the NIHSS score to be lower for patients with right-hemisphere lesions than for those with left-hemisphere lesions (P=0.07).

Chronic T2 Lesion Volume

T2-weighted MRI between 7 days and 3 months after stroke onset was available in 86 patients (39 right, 47 left). Thrombol-

TABLE 3. Patients With Low NIHSS Score and DWI Lesion Volume >9 cm^3

Case	Age, y	Sex	NIHSS Score	Clinical Features	DWI Volume, cm^3	Stroke Location	Outcome (mRS)
Left 1	67	M	2	Aphasia	14	Left ICA occlusion: watershed infarcts	1
Right 1	58	M	3	Left-side weakness, memory and attention impairment	11	Right ACA territory	2
Right 2	67	M	2	Left-side sensory loss, neglect	12	Right parietal and posterior frontal	3
Right 3	78	M	2	Mild left-side weakness, cortical sensory loss	15	Right high parietal	1
Right 4	74	F	0	TIA: dysarthria, mild left-side weakness	16	Right frontoparietal	0
Right 5	59	M	4	Anosognosia, aprosody, mild left-side weakness, cortical sensory loss	24	Right temporal	1
Right 6	72	M	3	Left-side neglect and sensory loss, apraxia	28	Right temporoparietal	1
Right 7	34	M	1	Mild left-side weakness	35	Right insular	1
Right 8	60	M	5	Left-side neglect with minimal weakness	70	Right frontotemporal	2

mRS indicates modified Rankin score; ICA, internal carotid artery; ACA, anterior cerebral artery; and TIA, transient ischemic attack.

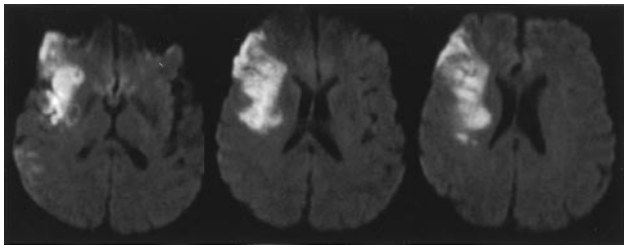

Figure 2. DWI from 1 patient with a large right-hemisphere lesion and low NIHSS score. Patient presented with neglect and minimal weakness (NIHSS=5).

ysis with tissue plasminogen activator (tPA) was received by 9 patients with right-sided stroke and 12 patients with left-sided stroke ($P=1.0$). Acute DWI lesion volume strongly correlated with the chronic T2 lesion volume for both right and left-sided lesions ($r=0.82$ right, $r=0.71$ left). The Spearman correlation between acute NIHSS and chronic T2 lesion volume was $r=0.53$ on the right and $r=0.60$ on the left (no difference; $P=0.65$). When adjusted for chronic lesion volume, the acute NIHSS score was significantly lower on the right (intercept=5.56) than on the left (intercept=8.45; $P=0.03$), but there was no difference between regression slopes.

Discussion

This study shows that among patients awarded a low NIHSS score (0 to 5), the acute DWI lesion volume is greater for those with right-sided stroke than those with left-sided lesions. The NIHSS score at presentation was significantly associated with the acute DWI and ischemic lesion volumes and chronic T2 lesion volumes of both right and left cerebral lesions. A subgroup of patients with right-sided stroke who had low NIHSS scores despite a substantial lesion volume on acute diffusion MRI was evident. Some of these patients appeared to have a good clinical outcome despite the size of the cerebral lesion, but others had significant residual disability at long-term follow-up. Such a group was not seen among patients with left cerebral stroke. These results apply to patients imaged within 24 hours of stroke onset. Similar trends were apparent within the subset of patients imaged within 6 hours; however, the number of patients was inadequate to achieve a statistically significant result.

The NIHSS is an important tool for clinical stroke research and is a routine part of clinical practice for many neurologists who treat acute stroke patients.[10–12] It has been shown to be a good predictor of poor outcome after stroke,[4,5] is superior to simpler clinical stroke scales,[3] and is a powerful measure of the effectiveness of stroke treatment.[24] Analysis of the underlying structure of the NIHSS has shown that it closely represents the 4 primary clinical factors of left and right motor function plus left and right cortical function.[25] However, as noted by others, the NIHSS may award up to 7 of a possible maximum of 42 points for tests directly related to language function (orientation questions, 2 points; commands, 2 points; aphasia, 3 points) and only 2 points related to neglect.[1,13] The lower possible number of points for right cortical dysfunction is likely to explain the larger lesion volumes seen on that side for patients with low NIHSS scores. That this difference in lesion volume between hemispheres for a given NIHSS score was less evident for patients with higher NIHSS scores probably reflects the reduction in the proportion of the given NIHSS score that may be contributed by lateralizing cortical functions as scores increase, as well as the variability of acute lesion volumes for a given stroke severity.

Apart from the subset of patients with right-hemisphere stroke and low NIHSS score, there were no important differences in the relationships of acute MRI lesion volumes and NIHSS score between hemispheres. However, a nonsignificant trend for a larger absolute acute total ischemic lesion volume on the right for a given NIHSS score was seen. Failure to detect a difference between sides in these correlations reflects the broad variation in the relationship between acute lesion volume and clinical deficits between individuals with stroke on either side. Despite the significant associations between acute DWI or perfusion lesion volumes and NIHSS score found in this study and reported previously by us and others,[16,18,20,23] we found that there was substantial variability in clinical score among patients with similar lesion volumes on either hemisphere. The clinical variability seen may be the result of several factors, including the neuroanatomy of the lesion involving more or less eloquent areas of the brain, the underlying structure of the NIHSS,[13,25] and the dynamic nature of early stroke pathophysiology, whereby not all hypoperfused tissue identified will become irreversibly damaged and not all dysfunctional tissue is abnormal on DWI.[26] Our finding that there was only a significant difference between the hemispheres for NIHSS after adjustment for lesion volume when chronic T2 lesions were studied parallels the findings of a previous study that used chronic CT lesion volumes.[13] DWI lesion volume has been shown to be an independent predictor of functional outcome within 48 hours of stroke onset,[22] but in the very early phase of stroke, such markers as diffusion-perfusion mismatch and persistent vascular occlusion may be important additional indicators of higher risk of infarct progression and poor outcome.[18–21,23,26–28]

The finding of a subgroup of patients with substantial right-hemisphere lesions yet low NIHSS score may have implications for future research or clinical protocols that include the NIHSS. Some studies have used an NIHSS score of <4 or <5 to exclude patients from enrollment.[6–9] It is possible that some patients with right-hemisphere stroke excluded by this criterion may have had large lesion volumes, significant neurological deficits not assessed by the NIHSS, and impaired functional outcome. Such patients would otherwise have been good candidates for randomization and might have demonstrated improved functional recovery after successful treatment with thrombolytics. The exclusion criteria for patients with mild or improving neurological deficits used in the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study[29] and recommended by the American Heart Association[30] emphasize the use of careful clinical examination and clinical judgment, not the NIHSS score, to determine eligibility for treatment with tPA. However, a recent review of the application of these criteria in an experienced stroke center revealed that one third of patients excluded from treatment with tPA for this reason were left either dead or dependent (modified Rankin score, ≥ 3) after their stroke, bringing into question the initial decision not to treat.[31]

In conclusion, the present study suggests that the NIHSS score may not be the optimal criterion for defining the lower limit of eligibility for acute stroke research or treatment protocols because of the risk of excluding patients with moderate-sized right-hemisphere lesions. Acute imaging information, such as that available with multimodal MRI, may be useful in identifying patients for inclusion in acute stroke protocols when there is clinical uncertainty about eligibility, such as patients with right-hemisphere syndromes associated with little motor deficit. Prospective evaluation of enrollment and eligibility criteria incorporating acute imaging data are required.

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