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Association of laterality and size of perfusion lesions on neurological deficit in acute supratentorial stroke

Meng Lee, MD, **Jeffrey L Saver, MD**, **Jeffry R Alger, MD**, **Qing Hao, MD, PhD**, **Noriko Salamon, MD, PhD**, **Sidney Starkman, MD**, **Latisha K. Ali, MD**, **Bruce Ovbiagele, MD, MSc**, **Doojin Kim, MD**, **J Pablo Villablanca, MD**, **Michael T Froehler, Md, PhD**, **Matthew S Tenser, MD**, and **David S Liebeskind, MD**
Stroke Center and Department of Neurology (M.L., J.L.S., J.R.A, J.R.A., Q.H., S.S., L.K.A, B.O., D.K., M.T.F.), the Department of Radiology (N.S., J.P.V.), and the Department of Emergency Department (S.S.), University of California, Los Angeles, CA, USA; the Department of Neurology, University of Southern California, CA, USA; and the Department of Neurology, Chang Gung Memorial Hospital at Chiayi, Chang Gung University College of Medicine, Taiwan (M.L.)

Abstract

Background—The influence of lesion size and laterality on each component of the National Institutes of Health Stroke Scale has not been delineated. The objective of this study was to use perfusion weighted imaging to characterize the association of ischemic volume and laterality on each component item and the total score of the NIHSS.

Methods—We analyzed consecutive right-handed patients with first-ever supratentorial acute ischemic strokes who underwent acute perfusion weighted imaging at a single center. Perfusion deficits were defined as mean transit time > 10 seconds. Ordinal regression was used to clarify the relationship between ischemic volume, laterality, and NIHSS scores.

Results—Among 111 patients, 58 were left hemisphere stroke, and 53 right hemisphere stroke. Median ischemic volume was 53 ml in left hand stroke and 65 ml in right hand stroke and median total NIHSS was 10 in left hand stroke and eight in right hand stroke. For individual NIHSS items, ischemic volume correlated most closely with commands and visual field and most weakly with ataxia and neglect. Left hand stroke predicted higher scores of total NIHSS and NIHSS items of questions, commands, right limb weakness, and language. Right hand stroke predicted higher scores of left limb weakness and extinction.

Conclusions—Larger perfusion defects contribute to higher scores on the total and most individual items of the NIHSS. However, lesion laterality contributes substantially to half the item scores, with greater association of left than right brain side. These findings indicate that imaging-deficit correlations will be improved by atlasing of lesions, taking into account side in addition to size.

Correspondence to David S Liebeskind, MD, UCLA Stroke Center, 710 Westwood Plaza, Los Angeles, CA 90095. Tel: 310-794-6379, Fax: 310-267-2063, davidliebeskind@yahoo.com.

Contributors JLS, JRA, DSL designed the study. ML, JLS, QH, SS, LKA, BO, DK, MTF, NS, JPV, MST participated in the data collection and extraction. ML processed the perfusion imaging with guidance from JRA and DSL. ML did the statistical analysis with guidance from JLS and DSL. ML wrote the first draft of the report, and JLS and DSL did the major revision. All other authors commented on the draft and approved the final version.

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Disclosures: None

Keywords

NIH Stroke Scale; perfusion weighted imaging; laterality; ischemic volume; acute ischemic stroke

Introduction

The National Institutes of Health Stroke Scale (NIHSS) is a widely used and validated tool for measurement of clinical stroke severity [1, 2]. The NIHSS is not only one of the most frequently used scales in stroke clinical trials [3, 4] but also a standard part of the clinical assessment of patients presenting with acute stroke in many stroke centers around the world [5, 6]. Ischemic lesion volume alone is known to account for only one-fifth to one-third of the variation in stroke-related neurologic deficits assessed on the NIHSS [7-9]. Because the human brain is organized into large-scale and lateralized functional networks, lesion location, especially side of lesion, has a substantial influence on degree of deficit. The relative influence of lesion size and laterality on motor, sensory, visual, wakefulness, language, neglect, and other functional components of the NIHSS have not been well delineated. Some component items of the NIHSS, such as language and extinction/ inattention, are widely recognized as highly related to laterality, but the strength of this association has not been quantified. The relationship to laterality of other items, such as gaze and dysarthria, are still inconclusive.

A decline in perfusion below the level needed to support synaptic transmission is the cause of neurological deficit in acute ischemic stroke. Perfusion weighted imaging, compared to diffusion weighted imaging has been demonstrated to have better correlation with NIHSS score in acute ischemic stroke [10]. Some patients who have an obvious neurological deficit may have negative diffusion weighted imaging but extensive perfusion defect [11]. It is therefore reasonable to use perfusion weighted imaging as a tool for investigating the neural substrates of functional deficits in acute ischemic stroke.

It is widely supposed that larger perfusion deficits are associated with higher total and component NIHSS scores and left hemisphere strokes affect more component NIHSS scores and are associated with higher total NIHSS score, but salient studies are sparse. The objective of this study was to use perfusion weighted imaging to characterize the association of ischemic volume and laterality on each component item and the total score of the NIHSS.

Methods

Study population

This is an analysis of a prospectively maintained database of consecutive ischemic stroke admitted to a single institution. All patients admitted within 12 h of stroke onset received NIHSS score evaluation by stroke fellow followed by PWI except a few patients had contraindication for MRI exam. The data of stroke patients were prospectively collected and maintained by a study nurse once stroke patients admitted and all the process was under supervision of the Stroke Center Director.

Criteria for inclusion in this study were:

- right-handed patients with first-ever supratentorial acute ischemic strokes who underwent acute perfusion weighted imaging, and
- NIHSS performed just before perfusion weighted imaging.

Patients received recanalization therapy (intravenous thrombolysis and/or intra-arterial mechanical or pharmacologic intervention) or conservative treatment. Among patients undergoing recanalization therapy, only NIHSS scores and perfusion weighted imaging obtained before intra-arterial intervention were analyzed. The study period was from January 1, 2007 to December 31, 2008. The study was approved by the local Institutional Review Board.

MRI methods and imaging analysis

Patients were imaged with a 1.5T Siemens Vision Scanner (Siemens Medical System) using a protocol detailed previously [12] including perfusion weighted imaging, diffusion weighted imaging, gradient-recalled echo, fluid attenuated inversion recovery imaging and magnetic resonance angiography. Perfusion weighted imaging was performed with a timed contrast-bolus passage technique (0.1mg/kg contrast administrated into an antecubital vein with a power injector at a rate of $5cm^3/s$). The processing of perfusion-weighted imaging was carried out on a Research System IDL computer program designed for analysis of perfusion data. Arterial input function was measured from vessel voxels with strong signal in the hemisphere contralateral to the ischemic lesion, generally from the contralateral middle cerebral artery. Measures of perfusion weighted imaging are semiquantitative; field inhomogeneities preclude absolute quantification of blood flow. The best perfusion metric and threshold for critical abnormality remain subjects of debate. In this study, perfusion lesion was defined as mean transient time (MTT) > 10 seconds. We MTT > 10 seconds as a study has shown this value correlates with cerebral blood flow < 20 ml/100g/min in Xenon Computed Tomography [13]. Perfusion lesion with MTT > 6 seconds and > 4 seconds were also applied since those thresholds could also outline the critical penumbra. Voxels meeting this threshold were identified and counted automatically using the Stroke Cerebral Analysis 2 (SCAN 2) software package. Voxels identified in this manner may include irrelevant areas, such as the ventricles or cerebellar diaschisis, and overestimate the real ischemic volume. However, it is unlikely to bias the laterality and the overall trend of ischemic volume.

Statistical analysis

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc). Continuous variables were compared with the Mann-Whitney Test. Comparison of right and left ischemic volume was made by stratifying patients according to five-point divisions of the NIHSS score [14]. Since NIHSS, total or item scores, are not continuous variables, an ordinal regression model was chosen to explore its association, direction and intensity, with other factors because ordinal regression is a statistical method developed for analyzing ranked outcome[15]. Ischemic volume (each 10 ml increase), laterality (left or right), gender, age, and factors shown statistical difference between left hemisphere stroke and right hemisphere stroke in Mann-Whitney Test were included in ordinal regression analyses to quantify their relationship with component and total NIHSS scores. $P<0.05$ was considered to indicate statistical significance and $P=0.05$ to 0.19 a statistical trend.

Results

The study population included 111 right-handed patients with first-ever unilateral supratentorial ischemic infarcts. Infarcts were within the middle cerebral artery in 100, posterior cerebral artery in five, anterior cerebral artery in one, and borderzone or multiple territories in five. Laterality was balanced with 58 left hemisphere stroke and 53 right hemisphere stroke. Median age was 64.5 years in left hemisphere stroke and 65 years in right hemisphere stroke. Median total NIHSS score was 10 in left hemisphere stroke and eight in right hemisphere stroke. Median ischemic volume was 53 ml in left hemisphere stroke and 65 ml in right hemisphere stroke when MTT > 10 seconds was used. When MTT > six seconds and MTT > four seconds were used, median ischemic volume was 57 ml and 59 ml, respectively, in left hemisphere stroke and 68 ml and 72 ml, respectively, in right hemisphere stroke. Median time interval between last know normal to perfusion weighted imaging was 350 minutes in left hemisphere stroke and 390 minutes in right hemisphere stroke. Vascular risk factors, pre-stroke medication, and etiology of stroke were similar between left hemisphere stroke and right hemisphere stroke, except a higher proportion of right hemisphere stroke patients had a history of hypertension and of taking antiplatelet agents at time of stroke onset (Table 1).

Table 2 showed the relation of perfusion weighted imaging ischemic volumes to NIHSS score in left hemisphere stroke and right hemisphere stroke patients. The trend of larger nominal values for median lesion volume were noted with right hemisphere stroke versus left hemisphere stroke in NIHSS strata 11-15 and 16-20. Above NIHSS score 20, only left hemisphere stroke cases were noted.

Ischemic volume, laterality, age, gender, hypertension, and antiplatelet use were included in ordinal regression analyses. Table 3 showed that each 10mL increase in perfusion deficits were associated most strongly with deficits of level of consciousness (LOC) commands, visual fields, and total NIHSS score and most weakly with deficits of ataxia, LOC questions, left leg weakness and extinction/inattention. Left brain stroke increased odds of NIHSS scoring on total NIHSS, LOC questions, LOC commands, right arm weakness, right leg weakness, and language. Right brain stroke increased odds of NIHSS scoring on left arm weakness, left leg weakness, and extinction/inattention. Age, gender, hypertension, and antiplatelet use were not significantly associated to component and total NIHSS score and were not shown on Table 3. The overall results was not different when we chose lower MTT thresholds, such as > four seconds and > six seconds, as cutoff points for ischemic lesion.

Discussion

Our study confirms an important lesion laterality influence on total scores of the NIHSS. Left hemisphere lesions had greater influence on total NIHSS score than did right. This finding accords with multiple previous reports [1, 14].

Moreover, our study extends prior investigations by dissecting this laterality effect at the item level. Among the 15 component items of the NIHSS 5 occurred more often with left-brain lesions (items 1b, 1c, 5b, 6b, and 9) and three more often with right brain lesions (items 5a, 6a, and 11). The strong lateralization of items of limb weakness, language processing, and hemispatial awareness is consonant with the known lateral dominance for limb motor control, language processing, hemispatial awareness. The lateralization of level of consciousness questions and commands likely reflects the substantial language component to these items. Since two more component items of NIHSS tend to be affected largely by left-brain lesion, left hemisphere stroke is likely to be associated with higher NIHSS score.

The modulation of the relation between lesion volume and NIHSS total score by lesion laterality was nonuniform over the range of the NIHSS. Laterality differences in lesion volume were minimal for NIHSS scores under 10 and marked for scores of 10 or higher. Likely this distribution is partially influenced by lacunar strokes, which produce fewer deficits in highly lateralized language and hemispatial neglect items and typically yield total NIHSS scores less than 10. At the higher end of the scale, ceiling effects appeared differentially with right and left brain lesions, with right hemisphere stroke patients reaching a ceiling at around 20 and left hemisphere stroke at around 30.

At the individual item level, lesion side exerted the greatest influence on functions known to have neural substrates that are highly lateralized, including language, hemispatial attention, and unilateral motor movements. Items showing strong relations to lesion size and low relation to lesion laterality either reflected the activity of diffusely distributed networks (dysarthria) or were not structured to distinguish sidedness (visual field deficits in either hemisphere and gaze deviation to either side each subsumed in a single item). Our result was different from a previous report, which suggested that several items, such as gaze, visual field, and sensory, to be categorized as right brain preference items [16]. However, the previous article did not take ischemic volume, which is usually larger in right hemisphere infarct, into account. The phenomenon of right brain preference in these items was not found when we consider laterality and ischemic volume at the same time.

The present study has several limitations. First, we only analyzed laterality rather than lesion location in the current study. Infarct location, assessed by diffusion weighted imaging, has been shown to be critical to stroke severity [8]. Further studies should clarify the impact of perfusion deficit at different location of brain in stroke patients. Seconds, the baseline characteristics of the left hemisphere stroke and the right hemisphere stroke patients were not completely identical in this study. Right hemisphere stroke patients had higher frequencies of hypertension history and pre-stroke antiplatelet use. However, these factors as well as gender and age did not show statistically significant influence on component and total NIHSS scores in ordinal regression analyses. Third, we did not implement diffusion weighted imaging data into the current study to directly explore the association of both results (PWI and diffusion weighted imaging) and NIHSS. Finally, although there is a trend toward larger lesion on the right hemisphere in the NIHSS 11-15 interval, a larger dataset is necessary to definitely clarify this issue. In conclusion, larger perfusion defects contribute to higher scores on the total and most components of the NIHSS. However, lesion laterality independently contributes substantially to half the component scores, with greater association of left than right brain side. These findings indicate that imaging-deficit correlations will be improved by atlasing of lesions, taking into account side in addition to size. Also, we may improve baseline NIHSS stratification and its correlation with functional endpoints in stroke trials by taking laterality into account.

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Table 1

Characteristics of first-ever right-handed left and right hemisphere stroke patients

Characteristics	Left hemisphere stroke, n=58	Right hemisphere stroke, n=53	P
Age, year	64.5 (interquartile range 50-79)	65 (interquartile range 59-78)	0.457
Male, n (%)	30 (52%)	19 (36%)	0.094
NIHSS score	10 (interquartile range 4-19)	8 (interquartile range 3-14)	0.103
Ischemic volume (ml)	53 (interquartile range 26-92)	65 (interquartile range 32-120)	0.222
Time interval between LNW to PWI (minutes)	350 (interquartile range 250-520)	390 (interquartile range 260-540)	0.912
Hypertension	47%	70%	0.017
Diabetes mellitus	21%	28%	0.406
Atrial fibrillation	32%	34%	0.790
Coronary artery disease	20%	26%	0.401
Other heart disease (valvular disease, CHF, PFO)	18%	21%	0.701
Hyperlipidemia	27%	42%	0.105
Current smoking	22%	12%	0.182
Pre-stroke medication			
Antiplatelet	19%	37%	0.038
Warfarin	15%	12%	0.704
Statin	20%	22%	0.797
ACE inhibitors or ARB	25%	29%	0.644
Etiology of stroke			
Large vessel atherosclerosis	28%	23%	0.549
Cardioembolism	41%	49%	0.417
Lacune	2%	9%	0.073
Other determined	10%	4%	0.181
Undetermined	19%	15%	0.589

NIHSS: National Institutes of Health Stroke Scale; LNW: last known well; PWI: perfusion weighted imaging; CHF: congestive heart failure; PFO: patent foramen ovale; ACE: Angiotension-converting enzyme; ARB: Angiotension receptor blockers; *P* indicates the difference between left hemisphere stroke and right hemisphere stroke by Mann-Whitney test

Table 2

Median ischemic volume according to stratified NIHSS score

NIHSS	Laterality	Number of patients (%)	Median ischemic volume, ml	*P*
1-5	Left hemisphere stroke	19 (33%)	32	0.555
	Right hemisphere stroke	20 (38%)	33	
6-10	Left hemisphere stroke	10 (17%)	54	0.510
	Right hemisphere stroke	12 (23%)	56	
11-15	Left hemisphere stroke	8 (14%)	37	0.069
	Right hemisphere stroke	11 (21%)	90	
16-20	Left hemisphere stroke	8 (14%)	68	0.110
	Right hemisphere stroke	10 (19%)	153	
>20	Left hemisphere stroke	13 (22%)	97	-
	Right hemisphere stroke	0	-	

NIHSS: National Institutes of Health Stroke Scale; *P* indicates the difference of ischemic volume between left hemisphere stroke and right hemisphere stroke by Mann-Whitney test

Table 3

Relationship between ischemic volume, laterality, and NIHSS scores in ordinal regression analyses

	Median scores of NIHSS (left, right)	**Increase of odds of NIHSS scoring if 10mL increase in ischemic volume**	**Increase of odds of NIHSS scoring if stroke at left brain**
1a. Level of consciousness	0, 0	1.09 (P=0.002)	1.36 (P=0.605)
1b. LOC Questions	1, 0	1.07 (P=0.042)	25.53 (P<0.001)
1c. LOC Commands	0, 0	1.23 (P=0.002)	80.40 (P=0.01)
2. Gaze	0, 0	1.10 (P=0.001)	1.15 (P=0.775)
3. Visual	0, 0	1.14 (P<0.001)	1.48 (P=0.395)
4. Facial palsy	2, 1	1.09 (P=0.002)	1.72 (P=0.176)
5 a. Motor arm, left	0, 2	1.15 (P=0.001)	0.001 (P<0.001)
5b. Motor arm, right	2, 0	1.09 (P=0.056)	222.07 (P<0.001)
6a. Motor leg, left	0, 1	1.05 (P=0.086)	0.05 (P<0.001)
6b. Motor leg, right	1, 0	1.10 (P=0.007)	97.13 (P<0.001)
7. Limb ataxia	0, 0	1.01 (P=0.925)	1.22 (P=0.841)
8. Sensory	0, 1	1.07 (P=0.008)	0.84 (P=0.668)
9. Language	2, 0	1.09 (P=0.007)	306.43 (P<0.001)
10. Dysarthria	1, 1	1.07 (P=0.005)	1.30 (P=0.513)
11. Extinction/inattention	0, 1	1.05 (P=0.057)	0.11 (P<0.001)
Total	10, 8	1.13 (P<0.001)	2.98 (P=0.004)

NIHSS: National Institutes of Health Stroke Scale; LOC: level of consciousness