National Institutes of Health Stroke Scale Score Is Poorly Predictive of Proximal Occlusion in Acute Cerebral Ischemia

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Background and Purpose—Multimodal imaging is gaining an important role in acute stroke. The benefit of obtaining additional clinically relevant information must be weighed against the detriment of increased cost, delaying time to treatment, and adverse events such as contrast-induced nephropathy. Use of National Institutes of Health Stroke Scale (NIHSS) score to predict a proximal arterial occlusion (PO) is suggested by several case series as a viable method of selecting cases appropriate for multimodal imaging.

Methods—Six hundred ninety-nine patients enrolled in a prospective cohort study involving CT angiographic imaging in acute stroke were dichotomized according to the presence of a PO, including a subgroup of 177 subjects with middle cerebral artery M1 occlusion.

Results—The median NIHSS score of patients found to have a PO was higher than the overall median (9 versus 5, P < 0.0001). The median NIHSS score of patients with middle cerebral artery M1 occlusion was 14. NIHSS score ≥10 had 81% positive predictive value for PO but only 48% sensitivity with the majority of subjects with PO presenting with lower NIHSS scores. All patients with NIHSS score ≥2 would need to undergo angiographic imaging to detect 90% of PO.

Conclusions—High NIHSS score correlates with the presence of a proximal arterial occlusion in patients presenting with acute cerebral ischemia. No NIHSS score threshold can be applied to select a subgroup of patients for angiographic imaging without failing to capture the majority of cases with clinically important occlusive lesions. The finding of minimal clinical deficits should not deter urgent angiographic imaging in otherwise appropriate patients suspected of acute stroke. (Stroke. 2009;40:2988-2993.)

Key Words: acute stroke ■ angiography ■ CT ■ scales

In acute ischemic stroke, brain tissue may continue to infarct over many hours from initial stroke ictus.1 Noncontrast head CT is limited in its ability to characterize local tissue conditions in the acute phase,2 whereas other imaging techniques yield information about vascular patency, tissue viability, and regional perfusion that may be useful in predicting outcome or response to stroke therapies.3–7 Multimodal imaging for acute stroke is not without disadvantages. Additional image acquisition consumes time, exposes patients to risks such as contrast-induced nephropathy, and increases costs. Citing both potentially useful applications and limitations, current American Stroke Association guidelines for early stroke management call for a focused selection of diagnostic tests for the sake of minimizing time to intervention.8

Although multimodal imaging requires further validation, it is already being incorporated into selection criteria for clinical trials.9,10 The additional image sequences are of particular interest in cases of proximal arterial occlusion for which the use of interventional techniques and induced hypertension are under investigation. A correlation between National Institutes of Health Stroke Scale (NIHSS) score and the likelihood of encountering a proximal occlusion is described by several published reports.11–14 Use of NIHSS to predict the presence of a proximal occlusion as a method of triaging patients to further imaging studies or interventions is therefore of interest.

The aim of this study was to determine whether NIHSS score on admission predicts angiographic occlusion in a proximal artery using CT angiography in a broadly representative group of patients with stroke. The clinically interesting population of patients with proximal middle cerebral artery (MCA) occlusion was studied separately for the same rela-

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tionship. Finally, the question of using a NIHSS score threshold for performing angiographic imaging was explored.

Methods

Patient Selection
We analyzed data from 741 consecutive patients enrolled between March 2003 and January 2006 in a prospective cohort study at 2 university-based hospitals, part of the Screening Technology and Outcomes Project in Stroke (STOPStroke). All patients presenting with symptoms consistent with acute cerebral ischemia were considered eligible. Admission nonenhanced CT scans were obtained followed by CT angiograms. Institutional protocol calls for all patients presenting with signs of acute cerebral ischemia to undergo nonenhanced head CT and CT angiographic imaging unless specific contraindications are present. Patients were excluded from enrollment for contraindication to iodinated contrast agent administration (history of contrast agent allergy, pregnancy, congestive heart failure, renal insufficiency) or if the nonenhanced CT scan showed evidence of intracranial hemorrhage. NIHSS scores were obtained by direct examination of subjects at the prespecified time points of admission, 24 hours after admission, discharge, and at a 6-month follow-up. All study staff performing examinations to obtain NIHSS scores were certified through the American Stroke Association’s NIHSS training program. The study received Institutional Review Board approval at both participating institutions and was Health Insurance Portability and Accountability Act-compliant. At enrollment, all subjects gave informed consent for participation. Study subjects lacking all data requisite for the analysis described subsequently were excluded.

Neuroimaging Protocol
Nonenhanced CT and CT angiographic acquisitions were performed according to standard departmental protocols with 8- or 16-section multidetector CT scanners (LightSpeed; GE Healthcare, Milwaukee, Wis). Nonenhanced CT was performed with the patient in a head holder in the transverse plane. Representative sample parameters, with minimal variations between scanners and sites shown as ranges, were as follows: 120 to 140 kVp, 170 mA, 2-second scan time, and 5-mm section thickness. Imaging with these parameters was immediately followed by biphasic helical scanning performed at the same head tilt as nonenhanced CT. CT angiography was performed after a 25-second delay (40 seconds for patients in atrial fibrillation) and administration of 100 to 140 mL of a nonionic contrast agent (Iovue; Bracco Diagnostics, Princeton, NJ) at an injection rate of 3 mL/s by using a power injector (Medrad Power Injector; Medrad, Indianola, Pa) through an 18-gauge intravenous catheter. Parameters were 140 kVp, 220 to 250 mA, 0.8- to 1.0-second rotation time, 2.5-mm section thickness, 1.25-mm reconstruction interval, 3.75 mm per rotation table speed, and 0.75:1 pitch. Images were obtained from the C6 vertebral body level through the circle of Willis. Immediately afterward, a second set of images was obtained from the aortic arch to the skull base. Afterward, source images were reconstructed into standardized maximum intensity projection views of the intracranial and extracranial vasculature.

Image Review
Image review was independently performed on a picture archiving and communication system workstation (Impax; Agfa Technical Imaging Systems, Richfield Park, NJ) by a board-certified neuroradiologist and a clinical neurologist experienced in stroke imaging (M.H.L. and W.J.K., 15 and 25 years of neuroimaging review experience, respectively). Reviewers were blinded to follow-up clinical and imaging findings but had information in regard to the patients’ age, sex, and presenting clinical symptoms. Neither of the reviewers had participated in the selection of the patients. Variable window width and center-level settings were used for optimal ischemic hypodensity detection with nonenhanced CT and CT angiographic source images. In all cases, nonenhanced CT images obtained for acute stroke were reviewed first followed by CT angiographic source images, and finally, follow-up images for confirmation of true-positive or true-negative infarct regions. Disagreements in readings were resolved in consensus. Reviewers rated the ischemic lesion on the nonenhanced CT scans, CT angiographic source images, and follow-up images according to Alberta Stroke Programme Early CT Score (ASPECTS).15 Angiographic occlusions, with a 1 to 5 level of certainty rating, were recorded for 27 defined vessel segments. Lesions identified as subtotal or total occlusion of Level 4 and 5 certainty (probably or definite) were defined as an occlusion. Proximal occlusion was defined as occlusion of the basilar artery, internal carotid artery, MCA M1 and/or M2 segment, anterior cerebral artery A1 and/or A2 segment, posterior cerebral artery, or vertebral artery.

Analysis
Two analyses were performed. For the first, patients were dichotomized into those with a proximal arterial occlusion and those without. For a second analysis, patients with M1 segment MCA occlusions were studied. Given the use of NIHSS ≥10 for inclusion in recent interventional stroke trials, the positive predictive value and sensitivity are calculated at that threshold.

Time to imaging was calculated as the amount of time elapsed between the onset of symptoms and the acquisition of the CT angiography segment of the neuroimaging protocol. Time of onset was defined as time of symptom onset for witnessed events and time the subject was last known normal for unwitnessed events. For patients with unwitnessed events in which the time last known normal could only be estimated as “AM” or “PM,” a conservative estimate of midnight for AM and noon for PM was used. NIHSS was measured at the time of initial presentation. Student t test was used to compare means and the Wilcoxon rank sum test was used to compare medians.

Results
Of the 741 subjects enrolled in the study, 699 had requisite data for the primary analysis. For the secondary analysis, 177 subjects were identified. The characteristics of these individuals are summarized in the Table. The median (interquartile range [IQR], average) NIHSS score was 5 (2 to 12, 7.5), and 54% of all acute cerebral ischemia subjects studied had a proximal arterial occlusion identified on CT angiography (CTA). The average time elapsed between symptom onset and CTA imaging was 7.5 hours.

Although the distribution of NIHSS scores was higher for subjects with proximal arterial occlusions than for subjects without (median [IQR], 9.0 [4–16] versus 5.0 [2–12]; mean, 10.3 versus 7.5; both P<0.0001), there was considerable overlap as depicted in Figure 1. A high initial NIHSS score was associated with a proximal occlusion; however, many patients with low initial NIHSS scores were found to have clinically important occlusions. Nearly 90% of patients without proximal arterial occlusions presented with NIHSS scores ≥10, but so did 55% of all patients found to have occlusive lesions that may have been amenable for interventional therapy or inform management of blood pressure and other variables. Proximal occlusions were found in 90% of subjects presenting with an initial NIHSS score ≥16 and all subjects with an initial NIHSS score ≥27, but such high NIHSS scores were relatively uncommon. Figure 2 shows the percent of cases with a proximal occlusion that would go unidentified if NIHSS scores were used as a threshold for obtaining angio-
The negative predictive value of NIHSS score for proximal occlusion is poor, making it an unreliable screening instrument. Many physicians hesitate to obtain urgent imaging beyond a noncontrast head CT for patients presenting with symptoms of acute cerebral ischemia, especially for those with low NIHSS scores. One concern is whether the extra time required to obtain the imaging may delay important treatment. A study of patients admitted to Calgary, Alberta, area hospitals found that only 5.4% of patients presenting <3 hours from onset were unable to receive intravenous tissue plasminogen activator due to the time required for in-hospital evaluation, including obtaining a CT scan and other decision-making. The number of patients prevented from thrombolysis by in-hospital evaluation is small compared with a more fundamental problem of 75% of patients arriving beyond 3 hours. If a judicious and limited amount of additional imaging evaluation can safely extend the time window for thrombolysis as emerging data suggest, it is warranted.

Another rationale for limiting acute phase imaging to a nonenhanced CT for a patient with minor deficits is that there is a low probability of encountering a significant finding that would impact management. As observed in this group, the majority of patients presenting with symptoms of acute cerebral ischemia that are found to have proximal occlusions had low to moderate NIHSS scores. On average, the NIHSS scores of patients found to have proximal arterial occlusions was just 2.8 points higher than the average for all presenting patients. Although a NIHSS score threshold can be established that yields a high sensitivity for finding a proximal arterial occlusion, screening patients for angiographic imaging based on such a method would miss the vast majority of cases. In fact, patients with a proximal occlusion but lower NIHSS score are of particular clinical interest because they are more likely to have a large penumbra of at-risk tissue and therefore be ideal candidates for further interventions or other treatment trials.

The analysis presented here is directly relevant to the design of current interventional stroke trials. For example, the ongoing Interventional Management of Stroke Trial-III (clinical trial number NCT00359424) uses a NIHSS threshold of 10 and does not require noninvasive angiography for inclusion. Based on the representative sample of patients with acute ischemic stroke in this study, 52% of cases with lesions amenable to the intervention would be excluded. The same concept is relevant to the application of other stroke therapies. Patients with proximal occlusions may respond differently to thrombolysis, induced hypertension, and other therapies than...
those with no occlusions. Finally, 29% of subjects in this study presenting with initial NIHSS score of 0 were found to have proximal occlusions. Patients with transient ischemic attack with intracranial occlusion on MR angiography have been found to have a 40% higher rate of second clinical stroke within 90 days and 17% higher rate of new silent diffusion-weighted imaging lesions at 30 days. Therefore, obtaining angiographic imaging for acute stroke or transient ischemic attack in the context of low NIHSS score yields information important for both management and prognosis.

The use of a NIHSS threshold as an inclusion criterion in new interventional trials is defended by relying on previously published reports of NIHSS predicting occlusions. These data provide a more accurate representation of the relationship between NIHSS and the probability of a proximal artery occlusion than prior reports. In one study, 54 patients who underwent MR angiography within 24 hours of stroke onset found that NIHSS score was highly predictive of an occlusion with no visualized occlusions in patients with a NIHSS score of 1 to 6 and in 78% of cases with a NIHSS score $\geq 15$. The Emergency Management of Stroke (EMS) Bridging Trial using digital subtraction angiography (DSA) on 35 patients with baseline NIHSS scores $\geq 5$ found occlusions in all patients with NIHSS scores $\geq 15$. Another study of 43 patients who underwent DSA found that 96.9% of cases with NIHSS scores $\geq 10$ had occlusions. A third study of 226 patients who underwent DSA with the intention of intra-arterial thrombolysis found that a NIHSS score $\geq 12$ had a 91% positive predictive value for a central (basilar, internal carotid artery, or M1/M2 MCA segment) occlusion. All of these series had smaller numbers of patients, used MR angiography (which may have lower sensitivity for detecting arterial occlusions with certainty), or reviewed cases of patients who underwent DSA. Interpretation of all of these studies is also limited due to selection of patients with unrepresentatively high baseline NIHSS score (mean, 13.5; mean, 14.1; mean, 14.7; and median, 14, respectively), whereas the median baseline NIHSS score of all presenting patients with stroke is closer to between 5 and 6. This undoubtedly represents a significant selection bias, especially in the interventional DSA studies in which a high likelihood of an occlusion was desirable. Furthermore, only the last mentioned study specifies whether the occlusions identified were central/proximal occlusions and therefore representative of a major source of perfusion impairment and amenable to an intervention. Another source of potential bias is time to imaging. A beneficial attribute of CTA is rapid image acquisition. Because MR angiography and DSA were used in prior studies, a longer delay to imaging may have occurred during which time occlusions may have resolved.

A potential for selection bias exists when drawing conclusions from a sample of patients who have undergone angiography for a clinical indication. Several facts mitigate the potential for such bias in this patient population. Institutional protocols in the sites patients were enrolled call for all patients with symptoms of acute cerebral ischemia to undergo nonenhanced CT and CTA imaging unless specifically contraindicated regardless of the type and magnitude of clinical deficits. This is reflected in the average NIHSS score of 7.5 and the fact that 12.2% of all enrolled patients had NIHSS...
scores of 0. The baseline attributes of this large, prospective study sample closely mirrors the age, sex, and average NIHSS scores reported in the literature for unselected patients presenting with cerebral ischemia; thus, these results should be generalizable to the broad population of patients with acute cerebral ischemia. The important limitation is the exclusion of patients unable to receive intravenous contrast. Although relevant to a minority of patients, excluded patients likely had greater medical comorbidities, which may have influenced the predictive relationship between NIHSS score and the presence of proximal occlusion in some way. Although contrast-related contraindications are an important limitation to the use of CTA, the widespread access to CT scanners in emergency departments and rapid image acquisition compared with other angiographic imaging modalities is a compelling benefit.

Conclusions

Although high NIHSS scores are predictive of a proximal arterial occlusion in patients presenting with acute cerebral ischemia, the large majority with such lesions present with low to moderate NIHSS scores. Despite the need to evaluate patients quickly and efficiently in the setting of acute stroke, angiographic and perfusion imaging yields potentially useful information that is increasingly relied on for decision-making. Excluding patients presenting with low NIHSS scores from such diagnostic techniques would lead to a failure to diagnose the majority of arterial lesions amenable for alternative therapies.

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