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## Clinical and Imaging Outcomes after Stroke with Normal Angiograms

Andrew P. Slivka, Greg A. Christoforidis, Eric C. Bourekas, Philip E. Calendine, and Margaret A. Notestine

**BACKGROUND AND PURPOSE:** Information about the prognosis of patients with acute ischemic stroke and normal angiography is limited. We report clinical and imaging outcomes of patients seen within 6 hours of symptom onset who were considered candidates for thrombolysis.

**METHODS:** Between November 1994 and December 1999, patients with stroke onset of less than 6 hours who were thrombolytic candidates underwent cerebral angiography. Patients with normal angiograms (defined as no sign of occlusive disease in the head or neck in the symptomatic artery) were included. Admission National Institutes of Health Stroke Scale (NIHSS) scores and discharge modified Rankin scores (mRS) were obtained. CT or MR images were obtained 24 hours or longer after symptom onset. Good outcome was defined as an mRS score  $\leq 2$ . For analysis, follow-up CT or MR imaging findings were classified as showing cortical infarct, subcortical infarct  $\geq 1.5$  cm, subcortical infarct  $\leq 1.5$  cm, or no new infarct. The mechanism of the normal angiogram was assumed on the basis of these results.

**RESULTS:** Twenty-one patients with stroke had normal angiograms. About 43% (9/21) of the patients had a favorable hospital discharge clinical outcome, and an additional 33% (7/21) had favorable clinical outcomes at subsequent follow-up. New infarct on follow-up imaging was seen in 71% (15/21). Discharge mRS scores were not correlated with admission NIHSS scores or the mechanism of the normal angiogram.

**CONCLUSION:** Approximately 76% of acute stroke patients with normal angiograms have a favorable clinical outcome, and 71% have associated new infarctions. Given these outcomes, further study is needed before recommendations regarding thrombolytic treatment can be made in this population.

Cerebral arterial occlusion is present in 70–80% of patients undergoing angiography within 8 hours of stroke symptom onset (1–3). Information about the prognosis of patients with acute stroke without vascular occlusion is limited (4). The purpose of our study was to assess the clinical and CT or MR imaging outcomes of patients presenting with acute stroke who 1) were considered candidates for thrombolysis after clinical, laboratory, and CT evaluation and 2) had normal cerebral angiograms within 6 hours of symptom onset.

### Methods

#### Patients

Between November 1994 and December 1999, all patients who were seen within 6 hours of the onset of symptoms of a stroke and who were considered candidates for thrombolysis underwent screening cerebral angiography after providing informed consent. Patients with clinical signs and symptoms in the carotid or vertebral distributions were included in this study; otherwise, the clinical, laboratory, and CT inclusion and exclusion criteria of Prolyse in Acute Cerebral Thromboembolism (PROACT I) were used to determine their eligibility for thrombolysis (5). Specifically, CT exclusion criteria included evidence of hemorrhage, significant mass effect with midline shift or presence of an intracranial tumor (5). This study included patients examined as part of an intra-arterial thrombolytic treatment protocol that was reviewed and approved by the Institutional Human Subjects Review Board at our facility.

#### Data Collection and Analysis

Times from symptom onset until cerebral angiography were determined. All patients underwent repeat CT or MR imaging at 24 hours or longer after admission. A neuroradiologist (G.A.C.) retrospectively reviewed all angiograms, admission CT scans, and follow-up CT or MR images. Patients were

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From the Departments of Neurology (A.P.S., M.A.N.) and Radiology (G.A.C., E.C.B., P.E.C.), Ohio State University Medical Center, Columbus.

Address reprint requests to Andrew Slivka, MD, Department of Neurology, Ohio State University Medical Center, 1654 Upham Drive, Columbus, OH 43210.

**TABLE 1: Stroke etiologies by TOAST classification**

| Etiology               | Number | Comment  |
|------------------------|--------|--|
| Cardioembolic          | 7*     | 5 high-risk sources, 2 medium-risk sources   |
| Small-vessel occlusion | 2      | Possible   |
| Unknown                | 2      | Probable   |
| Other                  | 1      | Postcoronary catheterization   |
| Multiple               | 9      | Small-vessel occlusion and cardioembolic (1 high-risk source, 8 medium-risk sources) |

\*Cardiac sources included: atrial fibrillation ( $n = 3$ ), left ventricular thrombus ( $n = 1$ ), akinetic left ventricular segment ( $n = 1$ ), nonbacterial thrombotic endocarditis ( $n = 1$ ), and atrial septal aneurysm with patent foramen ovale ( $n = 1$ ).

divided into the following categories on the basis of the findings of follow-up CT and MR imaging results: subcortical infarct (single or multiple and  $\leq 1.5$  cm or  $>1.5$  cm), cortical infarct (single, multiple, or with subcortical infarct), and no new infarct. A new infarct was defined as the development of a new low-attenuating lesion on CT or a new lesion on fluid-attenuated inversion recovery or T2-weighted MR imaging. A normal angiogram was defined as one showing no evidence of occlusive disease in the head or neck in the symptomatic artery. The mechanism of the normal angiogram was assumed on the basis of follow-up imaging studies. Patients with cortical infarcts, subcortical infarcts  $>1.5$  cm, or multiple subcortical infarcts  $\leq 1.5$  cm were thought to have spontaneous lysis of an occluded vessel, and those with single subcortical infarct  $\leq 1.5$  cm or no new infarct were presumed to have occlusion of a nonvisible arteriole.

On the basis of their clinical presentation, laboratory evaluation, follow-up CT or MR images, angiograms, and echocardiograms, patients were also classified by stroke subtype by using Trial of ORG10172 in Acute Stroke Treatment (TOAST) criteria (6). One neurologist (A.P.S.) performed this classification after the retrospective radiologic review.

All patients had a screening National Institutes of Health Stroke Scale (NIHSS) score and were categorized as having lacunar or cortical presentations by using the Oxford Community Stroke Project clinical classification system at admission. A modified Rankin score (mRS) was obtained before discharge. Favorable clinical outcomes were defined as a mRS of  $\leq 2$ . Clinical outcomes after hospital discharge were retrospectively obtained by reviewing the discharge summaries from the rehabilitation hospital or the clinic follow-up notes.

#### Statistical Analysis

Admission NIHSS scores were correlated with discharge mRS scores by using the Spearman correlation coefficient. The relationship of favorable outcomes to the mechanism of the normal angiogram was analyzed by using the Fishers exact test.

### Results

Eighty-eight patients who were potential candidates for thrombolysis underwent cerebral angiography. The mean time from symptom onset until angiography was 4 hours 47 minutes. All patients but one, who had a catheterization-related stroke, underwent angiography 4 hours or longer after stroke onset. None received thrombolytic therapy before angiography. Twenty-five had normal angiograms. Four of these patients were excluded from further analysis: Three had a nonstroke diagnosis, and one had a transient ischemic attack. The remaining 21 patients (16 men, 5 women) included in the study had a mean age of 62 years (range, 42–89 years).

The follow-up imaging study was CT in 13 patients

**TABLE 2: CT and MR imaging findings**

| Finding                 | Number |
|-------------------------|--------|
| No new infarct          | 6      |
| New abnormality         | 15     |
| Cortical infarct        | 7      |
| Single                  | 5      |
| Single with subcortical | 1      |
| Multiple                | 1      |
| Subcortical infarct     | 8      |
| Single, $\leq 1.5$ cm   | 5      |
| Single, $>1.5$ cm       | 2      |
| Multiple                | 1      |

and MR imaging with or without CT in eight. Table 2 shows the follow-up CT and MR imaging results. Initial CT scans were normal in 15 and abnormal in six. Four had subcortical infarcts, and two had cortical infarcts. None of the initial CT scans demonstrated early ischemic changes.

Only two of the six patients with no new infarct underwent MR imaging as the follow-up imaging study. On the basis of these results, 10 (48%) of 21 likely had large-vessel occlusions that spontaneously recanalized, while 11 (52%) had nonvisible end-artery occlusions.

Eighteen patients underwent cardiac echocardiography. Table 1 shows the etiologies of stroke in the 21 patients. Two patients with small-vessel occlusion did not undergo echocardiography and might have been classified as having multiple etiologies if echocardiography had been done. The patient with a postcardiac catheterization stroke also did not undergo echocardiography.

Of 10 patients presenting with lacunar syndromes, seven had subcortical infarcts  $\leq 1.5$  cm or no new infarcts, one had a cortical infarct, and two had subcortical infarcts  $>1.5$  cm. Of the 10 patients who presented with cortical symptoms, six had cortical infarcts, while four had no new infarct. Six of the seven patients with cardioembolic strokes had cortical infarcts on follow-up CT or MR imaging, and the seventh patient had multiple infarcts  $<1.5$  cm.

The median NIHSS scale on admission was 9 (range, 4–19). Fifteen (71%) of 21 patients had NIHSS scores of 10 or less. Median mRS at discharge was 3 (range, 1–5). Nine patients (43%) had favorable outcomes, five patients had an mRS score of 3, six patients had an mRS score of 4, and only one patient had a score of 5. No patient died. Admission NIHSS

scores were not correlated with discharge mRS scores ( $P > .05$ , Spearman correlation coefficient,  $r = 0.29$ ). Of the 12 patients with an mRS score of  $>2$  at discharge, information from follow-up (range, 2 weeks to 7 months) was available in nine. Seven of these patients had an mRS score of  $\leq 2$  at the time of follow-up, one had a score of 3, and one had a score of 4.

Favorable discharge clinical outcomes were seen in three (30%) of 10 patients with spontaneous lysis as the mechanism of the normal angiogram and in five (45%) of 11 patients with end-artery occlusion ( $P > .05$ , Fisher exact test).

### Discussion

Among our population of patients, 28% had normal angiograms. This is similar to the 20–30% frequency others report (1–3). We found that 43% of stroke patients with normal angiograms had favorable clinical outcomes at discharge, and an additional 33% had favorable clinical outcomes at subsequent follow-up.

New infarcts on CT or MR imaging were seen in 71%. Derex et al (4) reported clinical and CT outcome results in 10 patients from the Emergency Management of Stroke trial who had no occlusion on angiograms obtained within 4 hours of symptom onset. Three of their patients were treated with intravenous tissue-type plasminogen activator before angiography. Four patients had a favorable 3-month outcome, with a Barthel score of 95 or 100 and an mRS score of 0 or 1. Eight had new infarcts on CT. Six patients had mRS scores of 0, 1, or 2 at 3 months. Our study differs in several ways from theirs. Our patients with normal angiograms were drawn from a population of patients examined within 6 hours of stroke symptom onset, and follow-up clinical outcomes were not prospectively measured. None of our patients were treated with thrombolytics before angiography. Nonetheless, our overall results regarding clinical and radiographic outcomes are similar.

The two most likely reasons for normal angiograms in patients with acute stroke are spontaneous lysis of an occluding thrombus or occlusion in a nonvisible arteriole. In our population, both mechanisms occurred with approximately equal frequency. These findings may have implications for treatment. In patients with complete spontaneous recanalization, thrombolytic therapy involves a risk of intracerebral hemorrhage without any potential additional benefit. Still, a percentage of patients with complete large vessel recanalization may have distal occlusions not visible on angiography that might be amenable to thrombolysis. Patients with nonvisible penetrating arteriole occlusions might also benefit from such treatment, if the occlusion is thrombotic in nature. However, autopsy evidence suggests this may not be the case.

Fisher (7) studied the arterial lesions causing 50 lacunes in four patients, only two of whom had a prior history suggestive of acute stroke. Most of the lacunes were asymptomatic. Forty-five of the lacunes were caused by total occlusion of the penetrating artery

supplying the territory of the infarct, but only two of those had thrombotic occlusion of the vessel. The other five lacunes were associated with occlusive lesions or no disease of the penetrating artery and thus could have been occluded with thrombus acutely. More relevant to patients with stroke was another autopsy study by Fisher (8). He studied 11 internal capsule infarcts in 10 patients who had a history of stroke. Obstructive lesions were seen in nine patients. In five, the vessel was occluded. Two had a thrombus, the third had an occlusion due to lipohyalinosis, and in the fourth, the cause of the occlusion was unknown. In the fifth patient, a penetrating artery was obstructed at its orifice by an atheroma in the parent vessel. In two infarcts, vessels were patent, suggesting an embolic source. At most, eight (73%) of the 11 infarcts could have been caused acutely by a thrombus, and at least two (18%) were caused by a thrombotic occlusion.

We found several clinical predictors of spontaneous lysis of an occlusion or arteriolar occlusion. Seven of 10 patients with presentations of lacunar syndrome had no new infarcts or subcortical infarcts  $\leq 1.5$  cm, which are suggestive of arteriolar occlusion. Six of seven patients with cardiac sources of emboli had cortical infarcts or subcortical infarcts  $>1.5$  cm suggesting spontaneous recanalization as an explanation for the normal angiogram. However, enough overlap occurs in these groups to suggest these should not be the sole criteria for determining the mechanism of a normal angiogram. Acute diffusion-weighted MR imaging or CT perfusion imaging might prove useful in this context. Clearly, further study is needed in this population before definite treatment recommendations can be made, particularly given their favorable clinical outcomes.

### Conclusion

Several limitations of this study should be mentioned. The lack of correlation between NIHSS score and discharge outcome, as well as the lack of correlation between mechanism for the normal angiogram and outcome, could be reflective of the small sample size. This group had relatively mild strokes on admission; 71% of those with NIHSS scores of 10 or less. Finding a correlation with outcome—if one exists—would likely require large numbers of patients. Follow-up clinical outcomes were not available in all patients and not collected in a routine prospective manner. Only two of the six patients who did not have a new infarct had MR imaging on the follow-up imaging study. A new infarct might have been seen in an even higher percentage of patients if MR imaging, rather than CT, was done in the other four patients. In addition, this study included a highly select group of patients, namely those seen within 6 hours of stroke onset who were potential candidates for thrombolysis. They may not be reflective of patients with normal angiograms who are evaluated at different times or who do not meet the clinical criteria for thrombolysis. Specifically, because all our patients

except one underwent angiography 4 hours after symptom onset, the results may not apply to patients with normal angiograms obtained more acutely after symptom onset. However, given the treatment potential for patients seen within 3 hours of onset and given the associated time constraints for performing angiography, outcomes in a large series of patients with normal conventional angiograms obtained soon are unlikely to be reported.

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