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Background and Purpose—Acute ischemic stroke with mild or rapidly improving symptoms is expected to result in good functional outcome, whether treated or not. Therefore, thrombolysis with its potential risks does not seem to be justified in such patients. However, recent studies indicate that the outcome is not invariably benign.

Methods—We analyzed clinical and radiological data of patients with stroke who presented within 6 hours of stroke onset and did not receive thrombolysis because of mild or rapidly improving symptoms. Univariate and logistic regression analyses were performed to define predictors of clinical outcome.

Results—One hundred sixty-two consecutive patients (110 men and 52 women) aged 63±13 years were included. The median National Institutes of Health Stroke Scale score on admission was 2 (range, 1 to 14). All patients presented within 6 hours of symptom onset. After 3 months, modified Rankin Scale score was ≤1 in 122 patients (75%), indicating a favorable outcome. Thirty-eight patients (23.5%) had an unfavorable outcome (modified Rankin Scale 2 to 5) and 2 patients (1.3%) had died. Baseline National Institutes of Health Stroke Scale score ≥10 points increased the odds of unfavorable outcome or death 16.9-fold (95% CI: 1.8 to 159.5; $P<0.013$), and proximal vessel occlusion increased the odds 7.13-fold (95% CI: 1.1 to 45.5; $P<0.038$).

Conclusions—Seventy-five percent of patients with mild or rapidly improving symptoms will have a favorable outcome after 3 months. Therefore, a decision against thrombolysis seems to be justified in the majority of patients. However, selected patients, especially those with proximal vessel occlusions and baseline National Institutes of Health Stroke Scale scores ≥10 points, might derive a benefit from thrombolysis. **(*Stroke*. 2007;38:2531-2535.)**

Key Words: acute stroke ■ mild or rapidly improving symptoms ■ outcome predictors ■ thrombolysis

Intravenous recombinant tissue plasminogen activator is currently the only treatment approved by health authorities to reestablish cerebral blood flow within 3 hours of ischemic stroke onset.[1] A local delivery of the thrombolytic agent to the site of vessel occlusion and more precise patient selection based on newer imaging technologies have successfully pushed the time window out to 6 or even 9 hours.[2,3] However, a number of stroke victims arriving within the time window do not receive thrombolysis for several reasons.[4–8] One of the most common reasons to withhold thrombolytic treatment is stroke presenting with mild or rapidly improving symptoms (MRIS).

It is assumed that patients with MRIS have an excellent prognosis, even when left untreated. Therefore, the risks of thrombolysis seem to outweigh potential benefits in this patient group. Yet, a significant number of patients have persistent neurological deficits, deteriorate, or cannot be discharged home.[4,8] This raises doubt about the decision not to treat. A recent study found a strong association between unfavorable outcome and persistent large-vessel occlusions in patients with MRIS,[9] although other studies failed to identify predictors of outcome.[4,8,10]

We assessed the clinical outcome of patients who presented within 6 hours of stroke onset but did not receive thrombolysis because of MRIS. Our aim was to identify predictors of clinical outcome.

Patients and Methods

From January 2000 to January 2006, 876 patients with acute ischemic stroke (<24 hours after symptom onset) were admitted to our university-based stroke center, 461 patients (53%) within 0 to 3 hours and 246 patients (28%) within 3 to 6 hours. Eventually, 24 patients (3%) underwent intravenous and 264 (30%) intraarterial thrombolysis. Intravenous (<3 hours of onset) or intraarterial thrombolysis (<6 hours of onset) was administered according to international guidelines and institutional protocols.[11,12] In 588 patients (67%), thrombolysis was not performed for the following reasons: delayed presentation to the stroke center (n=169), clinical and radiological findings suggesting lacunar stroke in patients presenting within 3 to 6 hours after symptom onset (n=85), limiting

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comorbidities (n=57), no occlusion on angiography (n=56), extracranial carotid artery occlusion or high-grade stenosis (n=40) or vertebral artery occlusion and contralateral vertebral hypoplasia (n=2) preventing endovascular access to the occluded intracranial artery, aortic dissection (n=3), time window elapsed while trying to reach the intracranial occlusion in angiography (n=4), multiple reasons (n=10), and mild or rapidly improving symptoms (n=162). Data of the 162 patients with MRIS were analyzed and are the subject of this study.

Demographic data, stroke risk factors, and baseline National Institutes of Health Stroke Scale (NIHSS) scores were recorded prospectively by a stroke neurologist. Mild neurological symptoms were defined as a NIHSS score of ≤3. We defined early rapid improvement as a ≥4-point NIHSS score improvement from time of initial evaluation to time of thrombolysis decision.[1] Stroke pathophysiology was assigned using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria after a complete diagnostic workup.[13]

After initial clinical evaluation, patients underwent either nonenhanced CT followed by CT angiography (n=124) or multimodal MRI, including axial T1-, T2-, and intermediate-weighted images, diffusion-weighted images, perfusion-weighted images, time-of-flight magnetic resonance angiography, and gadolinium-diethylenetriamine-pentaacetic acid enhanced T1-weighted images (n=38). A stroke neurologist analyzed retrospectively the images. Early parenchymal CT signs of ischemia were defined according to the criteria by von Kummer et al[14] Diffusion-weighted image–perfusion-weighted image mismatch was considered present when visual inspection indicated that the volume of the perfusion abnormality on the time-to-peak map exceeded the volume of diffusion abnormality on the $b=1'000$ image by 20% or more. Vessel occlusions at the time of initial CT angiography, time-of-flight magnetic resonance angiography, or catheter angiography were classified into: (1) proximal (internal carotid artery, M1 and M2 segments of the middle cerebral artery, A1 segment of the anterior cerebral artery, V4 segment of the vertebral artery, basilar artery, and P1 segment of the posterior cerebral artery) and (2) distal occlusions (the more distal branches of middle cerebral artery, anterior cerebral artery, and posterior cerebral artery, as well as cerebral infarcts without any visible vessel occlusions).

Outcome was assessed at 3 months after the stroke by clinical examination or telephone interview using the modified Rankin scale (mRS).[15] The mRS scale scores of 0 to 1 were defined as "favorable" and mRS scores of 2 to 6 as "unfavorable" outcome. Neurologists or physicians in neurology training certified for NIHSS and mRS assessment performed the follow up.

Statistical Analysis

Quantitative data are expressed as mean values±1 SD. The NIHSS score for each patient at admission is given as a median value. Data are reported in frequency tables. Differences between groups and the effect of patient characteristics on clinical outcome were assessed using the Fisher exact test (for comparison of proportions), Student *t* test (for comparison of continuous variables), and Mann-Whitney *U* test (for comparison of ordinal variables). A logistic regression analysis, which included variables that showed statistical difference ($P\leq0.2$ on univariate comparison) was performed. To calculate the sensitivity and specificity of baseline NIHSS score to predict unfavorable outcome, a receiver operator characteristic curve was configured, and cutoff values with the highest sensitivity and specificity were included in the final logistic regression analysis.

Results

Demographic, Clinical, and Radiological Data

Demographic, clinical, and radiological characteristics of 162 patients with acute stroke with mild (n=123) or rapidly improving symptoms (n=39) are presented in Table 1. There were no significant differences between the 2 groups with respect to gender, age, prevalence of vascular risk factors, stroke etiology, or radiological findings. Patients with mild symptoms were more likely to receive a CT scan only, whereas patients with rapidly improving symptoms underwent more frequently both a CT and an MR examination on admission ($P<0.007$).

Outcome 3 Months After Stroke

Clinical outcome at 3 months after the ictus was favorable in 122 patients (75%) and unfavorable in 40 patients (25%) (Table 2). Of the patients with unfavorable outcome, 26 (16%) were slightly disabled (mRS 2), 12 (7%) were dependent (mRS 3 or 4), and 2 (1%) patients had died. Two transient ischemic attacks and 2 ischemic strokes occurred during follow up. One of the recurrent strokes was fatal (mRS 6) and the other one was disabling (mRS 0 after the index stroke, mRS 2 at 3 months follow up).

Clinical outcome at 3 months did not differ significantly between the groups with mild and with rapidly improving symptoms ($P=0.063$).

Predictors of Clinical Outcome

A receiver operator characteristic curve provided a cutoff point of baseline NIHSS score ≥10 (sensitivity, 83%; specificity, 78%) that was the best predictor of unfavorable outcome at 3 months. There were no other significant predictors of unfavorable outcome in the univariate analysis (Table 3). Logistic regression analysis included patients with baseline NIHSS score ≥10 ($P=0.001$), proximal vessel occlusion ($P=0.14$), and early CT signs of cerebral ischemia ($P=0.15$). It showed that NIHSS score ≥10 and proximal vessel occlusion independently predicted unfavorable outcome (Table 4).

A subgroup analysis of patients with rapidly improving symptoms revealed a significant association between NIHSS score ≥10 and unfavorable outcome at 3 months ($P=0.008$ in the univariate and $P=0.026$ in the logistic regression analysis). There were no other predictors of outcome in this patient subgroup.

In the subgroup of patients with mild symptoms, there were no predictors of clinical outcome either in the univariate or in the logistic regression analysis.

Discussion

Seventy-five percent of patients with stroke who do not undergo thrombolysis because of MRIS have a favorable clinical outcome 3 months after the stroke. Nevertheless, a significant minority of patients faces permanent neurological deficits (23.5%) or death (1.5%). This is the main result of the present study.

Stroke presenting with MRIS is the most common reason to withhold thrombolysis from patients arriving within 3 hours of stroke onset. Current guidelines advise against treatment with intravenous recombinant tissue plasminogen activator in patients with MRIS.[16] The pivotal studies on reperfusion treatment also excluded such patients. The National Institute of Neurological Disorders and Stroke rt-PA Stroke study did not enroll 13% of the screened patients because of rapid improvement of their symptoms.[1] In the Prolyse in Acute Cerebral Thromboembolism (PROACT) II

TABLE 1. Demographic, Clinical, and Radiological Characteristics of 162 Patients With Acute Stroke With Mild or Rapidly Improving Symptoms

Characteristics, n (%)	Mild Symptoms (n=123)	Rapidly Improving Symptoms (n=39)	Total
Male sex	82 (67)	28 (71)	110 (68)
Age, y (SD)	63 (14)	63 (12)	63 (13)
Vascular risk factors			
Hypertension	75 (61)	24 (62)	99 (61)
Diabetes mellitus	12 (10)	6 (15)	18 (11)
Current smoking	32 (26)	15 (38)	47 (29)
Hypercholesterolemia	77 (63)	27 (69)	104 (64)
Coronary artery disease	49 (40)	16 (41)	65 (40)
History of transient ischemic attack	26 (21)	6 (15)	32 (20)
History of amaurosis fugax	4 (3)	0	4 (2.5)
NIHSS score on admission, median (range)	2 (1 to 3)	6 (4 to 14)	2 (1 to 14)
Stroke etiology			
Large artery arteriosclerosis	26 (21)	9 (23)	35 (21.6)
Small artery disease	28 (23)	7 (18)	35 (21.6)
Cardioembolism	30 (24)	14 (36)	44 (27.2)
Other determined etiology	7 (6)	2 (5)	9 (5.6)
Unknown etiology	29 (24)	5 (13)	34 (21)
Multiple causes	3 (2)	2 (5)	5 (3.1)
Brain imaging			162 (100)
CT alone	72 (59)	12 (31*)	84 (52)
MRI alone	26 (21)	11 (28)	37 (23)
Both CT and MRI	25 (15)	16 (41*)	41 (25)
Early CT signs of cerebral ischemia	18 (15†)	7 (18†)	25 (20†)
Dense artery sign	3 (2†)	0	3 (2†)
Diffusion-weighted image–perfusion-weighted image mismatch	6 (5‡)	4 (10‡)	10 (13‡)
Proximal vessel occlusion	11 (9)	7 (18)	18 (11)

*$P<0.007$ difference between the groups.
†Percent of patients who underwent CT.
‡Percent of patients who underwent MRI.

study, the most common reason for exclusion among patients presenting within the 6-hour time window were mild (12% of excluded patients) and rapidly improving symptoms (10% of excluded patients).[2] Stroke presenting with MRIS is routinely excluded from thrombolytic treatment at many stroke centers.[4–8]

The consideration behind the exclusion of patients with MRIS from reperfusion therapy is the assumption of a favorable natural course, even if left untreated. However, earlier studies suggest that the outcome of patients with MRIS is not invariably benign. In a large study from the region of Calgary, Canada, 32% of the patients who were considered "too good to treat" remained either dependent at hospital discharge or died during hospital admission.[4] A study from the Massachusetts General Hospital in Boston found that patients with rapidly improving symptoms were 4 times more likely to have subsequent neurological worsening than patients presenting with mild symptoms.[8] In a more recent series from the UCLA Medical Center, approximately 10% of patients who were eligible for, but were excluded from, thrombolysis based on MRIS showed early neurological deterioration, and approximately 20% showed poor outcome at discharge.[9] We found that 25% of patients presenting with MRIS had permanent neurological deficits 3 months after stroke onset (Table 2). Most of them (26 of 40 patients) were slightly disabled (mRS 2), ie, they were able to look after their own affairs without assistance. Twelve patients were dependent and 2 had died.

TABLE 2. Clinical Outcome 3 Months After Stroke

	Favorable		Unfavorable				
mRS Score	0	1	2	3	4	5	6
Number (%)	72 (44)	50 (31)	26 (16)	10 (6)	2 (1)	0 (0)	2 (1)

The question arises whether it is justified to exclude patients with MRIS from thrombolytic therapy. To date, the answer cannot be derived from randomized, controlled trials. In the present series, the majority of patients had a favorable clinical outcome without treatment. However, we identified a subset of patients who may have had a better outcome if

TABLE 3. Variables Predicting Clinical Outcome at 3 Months by Univariate Analyses

Variable, n (%)	mRS 0 to 1 (n=122)	mRS 2 to 6 (n=40)	*P* Value
Male sex	83 (68)	27 (67)	0.71
Age, mean (SD)	62 (13)	65 (13)	
Vascular risk factors			
Hypertension	73 (60)	26 (65)	0.37
Diabetes mellitus	11 (9)	7 (18)	0.41
Current smoking	34 (28)	13 (33)	0.37
Hypercholesterolemia	79 (65)	25 (63)	0.56
Coronary artery disease	49 (40)	16 (40)	0.37
History of transient ischemic attack	25 (21)	7 (18)	0.30
History of amaurosis fugax	3 (3)	1 (3)	0.99
NIHSS scale on admission ≥10	1 (1)	5 (13)	0.001
Stroke etiology			
Large artery arteriosclerosis	24 (20)	11 (28)	0.30
Small artery disease	29 (24)	6 (15)	0.24
Cardioembolism	32 (26)	12 (30)	0.64
Other determined etiology	8 (7)	1 (3)	0.33
Unknown etiology	25 (20)	9 (23)	0.80
Multiple causes	4 (3)	1 (3)	0.80
Brain imaging			
Early CT signs of cerebral ischemia	16 (17*)	9 (29†)	0.15
Dense artery sign	3 (3*)	0 (0)	0.32
Diffusion-weighted image–perfusion-weighted image mismatch	8 (15‡)	4 (17§)	0.47
Proximal vessel occlusion	11 (9)	7 (18)	0.14

*Percent of 93 patients with favorable outcome who underwent CT.
†Percent of 32 patients with unfavorable outcome who underwent CT.
‡Percent of 55 patients with favorable outcome who underwent MRI.
§Percent of 23 patients with unfavorable outcome who underwent MRI.

thrombolysis had been given. Patients with persisting proximal vessel occlusions were 7 times (95% CI: 1.1 to 45.5; $P<0.038$) more likely to have an unfavorable outcome at 3 months. Previous sonographic and MR studies found that persisting large-vessel occlusions were strongly associated with deterioration of patients with acutely resolving symptoms of cerebral ischemia.[9,17–19] We identified an additional independent predictor of unfavorable outcome: rapidly improving but still severe symptoms (NIHSS scores ≥10 points on admission) increased the odds of unfavorable outcome 17-fold (95% CI: 1.8 to 159.5; $P<0.013$). Our findings suggest that patients with persisting large-vessel occlusions and those with baseline NIHSS score ≥10 points might benefit from thrombolysis despite mild or rapidly improving symptoms at presentation. A recent study evaluated the clinical course of 19 patients with acute stroke with MRIS who were treated with intravenous thrombolytics within the 3-hour time window.[20] At 3-month follow up, clinical outcome was favorable (mRS 0 or 1) in 15 of 19 patients (79%). Three patients regained functional independence (mRS 2), and one patient with intermittent atrial fibrillation and insufficient oral anticoagulation died from recurrent ischemic strokes.

TABLE 4. Variables Predicting Clinical Outcome at 3 Months by Multivariate Analysis

Variable	Odds Ratio	95% CI	*P* Value
NIHSS scale on admission ≥10	16.9	1.8–159.5	0.013
Proximal vessel occlusion	7.13	1.1–45.5	0.038

Our study has several limitations. It is a retrospective analysis of prospectively acquired data. The outcome assessment was not blinded because the treating physician had access to all clinical and radiological data. Furthermore, it is a hospital-based series, thus not necessarily representing the patients with acute stroke with MRIS in a whole population. On the other hand, the relatively large sample size is one of the strengths of the present study. As a result, subgroups with unfavorable outcome could be identified. Moreover, clinical outcome was assessed at 3 months follow up as is customary in acute stroke trials. Previous studies reported functional outcomes at discharge only, which may not reflect functional outcomes at 3 months.

In conclusion, the decision not to thrombolyze patients with MRIS seems to be justified in the majority of cases with 75% exhibiting excellent functional outcome at 3 months follow up. However, a small subgroup of patients with MRIS might benefit from thrombolysis: those with proximal vessel

occlusions and those with baseline NIHSS score ≥10 points. Hopefully, future prospective studies will clarify optimal treatment for this patient group.

Disclosures

None.

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