Risk Factors for Early Recurrent Cerebral Ischemia Before Treatment of Symptomatic Carotid Stenosis

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Background and Purpose—In patients with a recently symptomatic carotid stenosis, surgical or interventional treatment is often delayed for weeks to months. Because therapy should be instituted as early as possible in patients at highest risk for recurrent ischemia, the aim of this study was to identify these individuals using clinical data and serial diffusion-weighted imaging (DWI).

Methods—One hundred thirty-one patients (98 male; mean age 68±9 years) who had been referred to our department within 14 days (median; interquartile range, 4 to 36 days) after experiencing an ischemic event caused by a carotid stenosis were followed-up until carotid angioplasty and stenting. Risk factors predicting recurrent transient ischemic attack, stroke, or new DWI lesions were examined.

Results—During a median follow-up period of 7 days (interquartile range, 5 to 13 days) no patient experienced a stroke, 4 patients (3.1%) developed a hemispherical transient ischemic attack, and in 15 patients (12%) new asymptomatic DWI lesions were present in the territory of the treated artery. Multivariable regression analysis revealed that motor symptoms (odds ratio, 5.6; 95% CI, 1.2 to 26.3; P < 0.05) or the presence of a contralateral carotid occlusion (odds ratio, 4.6; 95% CI, 1.0 to 20.4; P < 0.05) were significant independent predictors of further cerebral ischemic events before carotid angioplasty and stenting.

Conclusions—In patients with a recently symptomatic carotid stenosis, the risk of early recurrent ischemia is highest in those with motor symptoms and in those with a contralateral carotid occlusion. In these high-risk patients urgent preventive treatment might be warranted. (Stroke. 2006;37:3032-3034.)

Key Words: brain ischemia ■ diffusion-weighted imaging ■ risk factors ■ symptomatic carotid stenosis ■ stroke recurrence

Patients with a recently symptomatic carotid artery stenosis have a high risk of early recurrent ischemia, so that preventive treatment such as carotid endarterectomy (CEA) or carotid angioplasty and stenting (CAS) should be performed as early as possible.1,2 However, CEA is often delayed because of logistics or a resource shortage for weeks to months.2 Therefore, it is necessary to identify those individuals at highest risk of early recurrent stroke, so that these can be treated in a more timely fashion. In this study we aimed to identify these patients by taking into account serial clinical and diffusion-weighted imaging (DWI) data.

Subjects and Methods

Patient Population
A total of 372 consecutive patients who had been treated with CAS at our institution between 1999 and 2005 after a prospective protocol were identified. Patients were included in this analysis if they met the following criteria: (1) presence of a symptomatic carotid stenosis (≥70% local degree of stenosis as assessed with ultrasound and symptoms within the past 6 months) and (2) DWI scans performed at presentation and immediately before CAS.

All patients gave written informed consent to participate in our prospective CAS study, which was approved by our Institutional Ethics Review Board.

Initially all patients were seen by a stroke neurologist at the outpatient department and underwent physical and neurological examinations. They were reevaluated immediately before CAS and at recurrence of an ischemic event. Moreover, a detailed history, including symptoms and timing of cerebral ischemic events was obtained in each patient and major cerebrovascular risk factors were recorded. During the study period all patients were treated with aspirin (100 mg/d) and at least 3 days (mean±SD, 4.5±4.6 days) before CAS with aspirin (100 mg/d) and clopidogrel (75 mg/d).

MRI
In all patients MRI (1.5 T) including DWI (mean of 5 runs in slice direction, b=1100 s/mm²) and fluid attenuated inversion recovery images were obtained at initial presentation and immediately before CAS. An intracranial/extracranial contrast-enhanced magnetic resonance angiography was also obtained initially.
**Image Analysis**

DWI images were analyzed (number, location, and maximal diameter) by 2 investigators (U.E., A.K.) blinded to the clinical data. The magnetic resonance angiographies were used to decide if the new DWI lesions were inside or outside the vascular territory distal to the carotid stenosis.

**Follow-Up End Points**

Patients were followed-up until CAS. Clinical end points included stroke or transient ischemic attack (TIA) and imaging end points the occurrence of new DWI lesions.

**Statistical Analysis**

Risk factors for recurrent ischemic events were first identified using $\chi^2$ statistics with Yates correction or the Fisher exact test. Variables achieving a $P<0.10$ were subsequently entered into a logistic regression model with a backward selection process using the combined outcome measure (TIA, stroke, new DWI lesion) as dependent variable. A value of $P<0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed with SPSS (Version 12; SPSS Inc).

**Results**

A total of 131 symptomatic patients (98 male; mean age $68\pm9$ years) were included in this analysis. The median delay
from symptom onset to the initial presentation and thus first DWI scan was 14 days (interquartile range, 4 to 36 days).

On the first DWI scan none of 21 patients with a retinal TIA, 18 of the 59 patients with a hemispherical TIA, and 33 of 51 patients with a minor stroke showed DWI lesion(s). The incidence of a positive first DWI scan was significantly associated with a shorter time period since the presenting event ($P<0.01$).

After a median follow-up period of 7 days (interquartile range, 5 to 13 days) no patient experienced a stroke, 4 patients (3.1%) developed an ipsilateral hemispherical TIA (1 DWI-positive case), and another 15 patients (12%) had single (n=4) or multiple (n=11) new DWI lesions (all <10 mm in diameter) located in the territory of the treated artery.

Factors associated with new ischemic events during follow-up are summarized in the Table. Multivariable regression analysis revealed that motor symptoms (odds ratio, 5.6; 95% CI, 1.2 to 26.3; $P<0.05$) or the presence of a contralateral carotid occlusion (odds ratio, 4.6; 95% CI, 1.1 to 19.3; $P<0.05$) were significant independent predictors of further ischemic events before CAS.

**Discussion**

The present study demonstrates that in patients with a recently symptomatic carotid stenosis the risk of early recurrent ischemia is highest in those with motor symptoms and in those with a contralateral carotid occlusion. Moreover, confirming published reports on mixed patient populations, our results show that the presence of a symptomatic carotid stenosis is associated with a high incidence of subsequent silent ischemia as detected with DWI.

Although it is unclear why those patients presenting with motor symptoms had an increased risk of ischemic events before CAS, a similar finding has recently been observed in acute TIA patients. In NASCET medically treated patients with symptomatic carotid stenosis on one side and a carotid occlusion on the other side were more than twice as likely to have an ipsilateral stroke at 2 years. Our results extend these long-term observations to the very early period of a carotid artery becoming symptomatic in these patients.

In contrast to previous studies that found a high rate of recurrent stroke in patients with symptomatic large artery atherosclerosis, clinically obvious new events were infrequent in our sample. This could partially be caused by the use of a dual antiplatelet therapy in our patients, which has recently been shown to significantly reduce asymptomatic embolization in this patient population. The fact that all of our patients received dual antiplatelet therapy during follow-up limits the generalizability of our results to other patient populations, for instance those on antiplatelet monotherapy while waiting for CEA. Additional limitations of this study include the small sample size, as well as the relatively long delay between first symptoms and CAS, which has likely lead to an underestimation of the true risk of recurrent ischemia in our study.

In conclusion, in patients with a recently symptomatic carotid stenosis the risk of early recurrent ischemia is highest in those with motor symptoms and in those with a contralateral carotid occlusion. Although preventive treatment should be instigated as soon as possible in all patients with a recently symptomatic carotid stenosis, urgent intervention might be warranted in these subgroups.

**Disclosures**

None.

**References**

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