Magnetic Resonance Techniques for the Identification of Patients With Symptomatic Carotid Artery Occlusion at High Risk of Cerebral Ischemic Events

Catharina J.M. Klijn, MD; L. Jaap Kappelle, MD; Jeroen van der Grond, PhD; Ale Algra, MD; Cornelis A.F. Tulleken, MD; Jan van Gijn, FRCP

Background and Purpose—We sought to assess whether MRI, MR angiography, or 1H MR spectroscopy can be used to identify patients with symptomatic carotid artery occlusion (CAO) who are at high risk of recurrent ipsilateral cerebral ischemic events.

Methods—In 115 consecutive patients with transient or moderately disabling symptoms of cerebral or retinal ischemia and ipsilateral CAO, we studied the prognostic value of (1) presence of a border-zone infarct; (2) quantitative flow in the middle cerebral artery (MCA) ipsilateral to the CAO; and (3) metabolic ratios in the centrum semiovale ipsilateral to the CAO.

Results—Presence of a border-zone infarct and the rate of flow in the MCA did not have a significant relationship with recurrence of cerebral ischemic events. Patients with a low N-acetyl aspartate (NAA)/choline ratio had an annual risk of recurrent, ipsilateral, cerebral ischemic events of 16.0% (95% CI, 9.5 to 27.0), whereas this risk was 4.2% (95% CI, 2.2 to 8.0) in those with a normal NAA/choline ratio (hazard ratio, 0.43; 95% CI, 0.19 to 1.00). Patients who on entry had had only retinal symptoms had on average a higher NAA/choline ratio (mean difference, 0.25; 95% CI, 0.13 to 0.37) and a lower risk of recurrent cerebral ischemic events (odds ratio, 0.0; 95% CI, 0.0 to 0.6) than those with cerebral ischemic symptoms.

Conclusions—NAA/choline ratio measured by 1H MRS, but not the presence of a border-zone infarct or the amount of flow in the MCA, can identify patients with symptomatic CAO who are at risk of future ipsilateral cerebral ischemic events. (Stroke. 2000;31:3001-3007.)

Key Words: carotid artery occlusion ▪ outcome ▪ spectroscopy, nuclear magnetic resonance

After the negative results of the international Extracranial/ Intracranial (EC/IC) Bypass Study published in 1985, surgical treatment of patients with carotid artery occlusion (CAO) has remained subject to debate.1,2 Research has focused on the identification of patients with a low-blood-flow state of the brain because theoretically those patients would benefit most from surgical procedures augmenting the cerebral blood flow. Some studies have shown that patients with compromised cerebral blood flow have a higher risk of recurrent cerebral ischemic events than patients with normal cerebral blood flow,1–5 but others failed to confirm this.6,7 Likewise, patients with exhausted autoregulation of the cerebral blood flow, indicated by the inability to respond to vasodilatory stimuli, have been shown to have a higher risk of recurrent cerebral ischemic events than those with normal cerebrovascular reactivity.8–10 At this time positron emission tomography with measurement of the oxygen extraction fraction is probably the most valuable technique to identify patients with a CAO who are at high risk of recurrent stroke.11 However, major drawbacks of positron emission tomography are that it requires administration of radioactive tracers, it is expensive, and therefore it is not widely available.

In recent years noninvasive MR techniques have become increasingly important in the diagnosis of cerebral ischemia.12,13 In addition to assessment of the presence and extent of infarcts with MRI, MR angiography (MRA) can be applied to quantify flow in the middle cerebral arteries (MCAs),14 and 1H MR spectroscopy (MRS) has proven to be a valuable tool to study metabolic changes in the brain in both infarcted15,16 and noninfarcted areas.17,18

The purpose of this study was to assess whether MR can provide prognostic information about the recurrence of cerebral ischemic events in patients with symptomatic CAO. We investigated the prognostic value of 3 factors that on theoretical grounds12,19 may be related to the blood flow state of the brain: (1) presence of a relevant infarct of the border-zone

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Subjects and Methods

Patients

Between September 1995 and July 1998, 115 patients with recent (≤6 months) symptoms of transient or moderately disabling (modified Rankin grade 3) retinal or cerebral ischemia and an angiographically confirmed ipsilateral CAO were studied prospectively. The degree of stenosis in the contralateral carotid artery was measured according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.21 We excluded patients with a diagnosis of arterial dissection, patients who suffered a severely disabling stroke (modified Rankin grade 4 or 5),20 and patients in whom it was not possible to perform the MR investigation because of claustrophobia. All patients were interviewed by 1 of 2 investigators (C.J.M.K., L.J.K.) for the presence of risk factors, as listed in Table 1. Patients with a ≥70% stenosis of the contralateral internal carotid artery (ICA) were offered endarterectomy. Patients with recurrent symptoms that were of presumed hemodynamic origin were offered high-flow EC/IC bypass surgery according to the method of Tulleken.22,23 In all patients antithrombotic medication was prescribed (low-dose aspirin in the majority), and vascular risk factors were rigorously treated.

MRI, MRA, and 1H MRS

MR studies were performed on a 1.5-T whole body system (model ACS/NT-15; Philips Medical Systems). Details of the applied MR protocol have been described previously.14,24 MRI investigations consisted of a sagittal T1-weighted spin-echo sequence (repetition time [TR], 545 ms; echo time [TE], 15 ms; slice thickness, 4 mm with a 0.6-mm interslice gap; field of view, 225 mm; 256×256 matrix) and a transaxial T2-weighted spin-echo sequence (TR, 2000 ms; TE, 20 and 100 ms; slice thickness, 7 mm with a 1.5-mm interslice gap; field of view, 225 mm; 256×256 matrix). All MRI scans were reviewed independently by 2 investigators (C.J.M.K., L.J.K.).

Quantitative flow in the MCA ipsilateral to the symptomatic CAO was measured by MRA. On the basis of the reconstruction of a 3-dimensional time of flight of the circle of Willis, two 2-dimensional phase-contrast single slices were positioned perpendicular to the left and right MCA (TR, 17 ms; TE, 10 ms; flip angle, 8°; 24 signals acquired; slice thickness, 5 mm; field of view, 250 mm; 256×256 matrix; velocity sensitivity, 70 cm/s). Flow values were obtained by integrating across manually drawn regions of interest, which enclosed the vessel lumen as closely as possible.19

1H MRS was performed with a single-voxel technique (TR, 2000 ms; TE, 136 ms; 2048 time domain data points; 64 signals acquired). In each subject a volume of interest...
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retinal infarction, a cardiologist or ophthalmologist was consulted. (C.J.M.K.). In case of doubt about the diagnosis of myocardial or ECG, and laboratory findings was summarized by one of us ancillary investigations including imaging of the brain, perimetry, of the MR investigations. For each outcome event, relevant infor-

nonfatal myocardial infarction, and vascular death were assessed by rhagic. The outcome events recurrent stroke, retinal infarction, was obtained to assess whether the stroke was ischemic or hemor-

P

0.10) with an outcome event to deter-

iate analysis including all variables with an at least borderline risk factors for all outcome events, resulting in hazard ratios (HR)

outcome events recurrent stroke, retinal infarction, nonfatal myocardial infarction, or vascular death, whichever hap-

Outcome Events

All patients were followed until November 1, 1999. The primary outcome event was any recurrent cerebral ischemic event ipsilateral to the symptomatic CAO, including ischemic stroke and transient ischemic attacks (TIAs). Other outcome events were recurrent stroke (both ipsilateral and contralateral to the symptomatic CAO and including hemorrhage), recurrent ipsilateral ischemic stroke, and the composite outcome event of any recurrent stroke, retinal infarction, nonfatal myocardial infarction, or vascular death, whichever hap-

recurrent TIAs before inclusion in the study. In 1 of the 16 patients who underwent endarterectomy of a contralateral carotid stenosis subsequently had angioplasty because of a severe stenosis of the proximal part of the common carotid artery on the same side as the carotid siphon. One of the 22 patients who underwent endarterectomy of a contralateral carotid stenosis subsequently had angioplasty because of a severe stenosis of the proximal part of the common carotid artery on the same side as the carotid siphon. One of the 22

mean NAA/choline ratio minus 2

3

3

N

N-acetyl aspartate (NAA) and choline, of NAA and creatine, and of lactate and NAA.

The average interval between the last symptoms a patient had and the MR investigation was 74 days (SD 57).

The control group for the MR studies consisted of 31 subjects (22 men; mean age, 58 years; SD 12; age range, 28 to 83 years), who were treated in the departments of neurology or urology for other than intracranial disease. None of the control subjects had a history of ischemic neurological deficits, and none showed abnormalities on MRI of the brain. Because no differences were found between the quantitative flow and metabolic measurements of the right and left hemispheres, values from both sides were averaged.

Data Analysis

The annual rates of outcome events with 95% CIs were calculated. The continuous variable NAA/choline ratio was transformed into a dichotomized variable by calculating a cutoff point equivalent to the mean NAA/choline ratio minus 2×SD in normal controls. The Cox proportional hazards model was applied for univariate analysis of all risk factors for all outcome events, resulting in hazard ratios (HR) with 95% CIs. Patients who underwent endarterectomy of the contralateral ICA were included until the end of the study period, whereas patients who underwent EC/IC bypass surgery were censored at the time of surgery. Subsequently, we performed multivar-

We obtained informed consent from all patients. The Institutional Review Board of the University Medical Center Utrecht approved the study protocol.

Results

Of 119 eligible, consecutive patients, 2 patients refused participation in the study, and in 2 patients it was not possible to perform the MR studies because they were claustrophobic. None of these 4 patients suffered any recurrent vascular event until the end of the study period. Baseline characteristics of the 115 included patients are summarized in Table 1. Twenty-nine of the 115 patients had a severe (70% to 99%) stenosis of the contralateral carotid artery; of these, 22 underwent an uncomplicated endarterectomy. Six patients chose not to undergo endarterectomy, and in 1 patient this procedure could not be performed because the stenosis continued as distally as the carotid siphon. One of the 22


durations, data are expressed as ratios of peak intensities of N-acetyl aspartate (NAA) and choline, of NAA and creatine, and of lactate and NAA.

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outcome events recurrent stroke, retinal infarction, nonfatal myocardial infarction, and vascular death were assessed by a panel consisting of 2 neurologists and 1 neurosurgeon, none of whom were participating in the study and all of whom were unaware of the MR investigations. For each outcome event, relevant infor-

Mean follow-up time was 24.2 months (SD 14.8; range, 0.1 to 50.2 months). None of the patients was lost to follow-up. Twenty-three patients had a primary outcome event, resulting in an annual rate of recurrent ipsilateral cerebral ischemic events of 9.5% (95% CI, 6.3 to 14.3). Of these 23 patients, 15 patients had an ipsilateral cerebral TIA (annual rate, 6.2%; 95% CI, 3.7 to 10.3), and 8 suffered an ipsilateral ischemic stroke (annual rate, 3.3%; 95% CI, 1.7 to 6.6). Three patients had a recurrent stroke on the side contralateral to the symptomatic carotid artery. In all but 1 of the patients with a recurrent stroke, imaging of the brain was performed to exclude a hemorrhage. One patient had a fatal intracerebral hemorrhage, 3 cardiac deaths occurred, 5 patients had a nonfatal myocardial infarct, and 1 patient suffered an ipsilateral retinal infarct. The annual rate of any recurrent stroke was 4.6% (95% CI, 2.5 to 8.3), and that of the combined outcome event of any recurrent stroke, retinal infarction, nonfatal myocardial infarct, or vascular death was 9.0% (95% CI, 5.9 to 13.9).

The univariate analysis of baseline characteristics for the primary outcome event recurrent ipsilateral cerebral ischemic events (TIA or stroke) is summarized in Table 1, and that of the MR investigations is shown in Table 2. None of the 24 patients with retinal but no cerebral symptoms at baseline had

recurrent TIAs before inclusion in the study. In 1 of the 16 patients the EC/IC bypass operation was preceded by endar-

terectomy of a contralateral carotid stenosis (1 of the 22 procedures mentioned earlier).

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recurrent ischemic symptoms of the brain during follow-up (odds ratio, 0.0; 95% CI, 0.0 to 0.6). Table 2 shows that neither the presence of a relevant border-zone infarct nor the rate of flow in the MCA ipsilateral to the symptomatic CAO was associated with recurrence of cerebral ischemic events. In contrast, the NAA/choline ratio in the hemisphere ipsilateral to the symptomatic CAO did predict recurrence of cerebral ischemic events: a low NAA/choline ratio was associated with a higher risk of recurrent cerebral ischemic events (HR per unit increase in NAA/choline ratio, 0.2; 95% CI, 0.0 to 0.9). Adjustment for the time interval between the last symptoms and the MR investigation hardly changed the crude HR (HR, 0.2; 95% CI, 0.0 to 0.8). Figure 1 shows the Kaplan-Meier cumulative cerebral ischemic event-free survival curves for patients with a normal and those with a low NAA/choline ratio, with a cutoff point of 1.51 equivalent to the mean NAA/choline minus 2×SD in normal controls. Figure 2 shows a characteristic example of a 1H MR spectrum of a patient with a low NAA/choline ratio who suffered a recurrent stroke and of a patient with a normal NAA/choline ratio who did not. The HR for the NAA/choline ratio as a dichotomized variable above or below 1.51 (HR, 0.43; 95% CI, 0.19 to 1.00) corresponded to the HR found when the NAA/choline was analyzed as a continuous variable (Table 2). The annual rate of recurrent ipsilateral cerebral ischemic events of patients with a low NAA/choline ratio (<1.51) was 16.0% (95% CI, 9.5 to 27.0) and in those with a normal NAA/choline (>1.51) ratio was 4.2% (95% CI, 2.2 to 8.0). Neither the NAA/creatine ratio nor the lactate/NAA ratio in the hemisphere ipsilateral to the symptomatic CAO was associated with recurrence of ipsilateral cerebral ischemic events (Table 2).

Multivariate analysis including both the factor contralateral CAO and the NAA/choline ratio showed that a low NAA/choline ratio was independently associated with recurrence of ipsilateral cerebral ischemic symptoms (HR per unit increase in NAA/choline ratio, 0.2; 95% CI, 0.0 to 0.7), whereas the relation with the presence of a contralateral occlusion (HR, 0.3; 95% CI, 0.1 to 1.2) was not statistically significant. Because patients with only symptoms of the retina had a zero risk of recurrent ipsilateral cerebral ischemic events, this prognostic factor could not be included in the multivariate analysis. We therefore assessed the prognostic value of the NAA/choline ratio in the group of 91 patients with cerebral symptoms on entry of the study. In this subgroup the association between the NAA/choline ratio and recurrence of cerebral ischemic events was found as well but was no longer statistically significant (HR, 0.4; 95% CI, 0.1 to 1.8). Patients with retinal symptoms only had, on average, a higher NAA/choline ratio (mean±SD, 1.74±0.21) than those with symptoms of the brain (1.49±0.26; mean difference [t test], 0.25; 95% CI, 0.13 to 0.37).

The secondary outcome events recurrent stroke (both ipsilateral and contralateral to the symptomatic CAO, including hemorrhage), recurrent ipsilateral ischemic stroke, and the composite outcome event of any recurrent stroke, retinal infarction, nonfatal myocardial infarction, or vascular death were not significantly related with any of the baseline characteristics or MR measures.
Discussion

This study shows that in patients with a symptomatic CAO, a low NAA/choline ratio in the white matter of the centrum semiovale of the symptomatic hemisphere is associated with recurrence of cerebral ischemic events. In contrast, neither the presence of a relevant border-zone infarct nor low flow in the MCA on the side of the symptomatic CAO showed a statistically significant association with recurrence of cerebral ischemic events.

Several studies have shown that cerebrovascular reactivity measured by means of transcranial Doppler ultrasonography or single-photon emission CT is more severely reduced in patients with border-zone infarcts than in those with territorial infarcts. These findings suggest that the presence of a border-zone infarct may identify patients with a low-flow state of the brain. However, in agreement with a previous study that showed a similar annual stroke rate in patients with and without a border-zone infarct, we found no statistically significant association between the presence of a border-zone infarct and recurrence of cerebral ischemic events. The observed trend toward such association (HR, 1.7; 95% CI, 0.7 to 4.2) may indicate that the association could have been found if a larger number of patients would have been studied. Another explanation may be that the variability of vascular territories between patients may have resulted in misclassification of infarcts, thus confounding the analysis.

Patients with symptomatic CAO have lower flow in the MCA ipsilateral to the symptomatic hemisphere than control subjects, but our study shows that this lower MCA flow is not associated with recurrence of cerebral ischemic events. A low NAA/choline ratio can be attributed to either a low NAA or a high choline level or to a combination of both. Since the average NAA/creatine ratio of the symptomatic hemisphere was significantly lower than that of the asymptomatic hemisphere (data not shown), and under the assumption that the creatine peak is relatively stable, it is likely that a decrease in NAA is at least part of the reason for the low NAA/choline ratio. Although in ischemic lesions the creatine peak has been shown to decrease over time, we believe that in this study the creatine peak may be assumed to be fairly stable because the metabolic measurements were done in regions without infarcts or white matter lesions. The finding that the NAA/creatine ratio in the symptomatic hemisphere was not associated with the recurrence of ischemic events may indicate that, in addition to a low NAA, an increase in the choline peak also contributes to the low NAA/choline ratio. The amino acid NAA is found primarily in neurons and axons and is therefore considered a marker of their integrity and function, but its exact function remains unknown. A low NAA in cerebral infarcts has been associated with an unfavorable clinical outcome at the time of hospital discharge and at 3 and 6 months, but another study could not relate a reduced NAA to a poor clinical outcome at 6 months. An association between a low NAA in noninfarcted areas and recurrent cerebral ischemic events has not been investigated previously. Our preliminary findings need confirmation from other studies before MRS can be considered of additive value in clinical practice.

In patients with symptomatic CAO, a low NAA in noninfarcted areas may indicate that neurons and axons suffer from ischemia, which may reflect misery perfusion caused by the CAO. The relatively high NAA/choline ratio of patients with ischemic symptoms of the retina only, compared with those with symptoms of the brain, may indicate that a low NAA/choline ratio is especially associated with clinically manifest cerebral ischemia. Because patients with ischemic symptoms of the retina only also had a better outcome than patients with cerebral symptoms, this factor confounds the analysis for the prognostic value of the NAA/choline ratio. All metabolic measurements were performed in regions that showed no sign of infarction, but damage subsequent to ischemia may be more extensive than can be concluded from the presence of infarcts on brain imaging alone. Additionally, the total volume of lesions as well as their distance from the VOIs may be important, but these were not measured. Possibly a low NAA/choline ratio in the symptomatic hemisphere should be considered the result of ischemic brain damage rather than an indication of future risk of ischemia. The finding that the predictive value of the NAA/choline ratio for recurrence of cerebral ischemic events in the subgroup of 91 patients with symptoms of the brain (and not of the retina only) was less strong and no longer statistically significant may support this hypothesis but could also indicate that the subgroup of 91 patients was too small to render a statistically significant result. The interval between a patient’s last symptoms and the NAA/choline ratio measurement, another potential confounding factor because metabolic indices have been shown to change over time, did not affect the association between the NAA/choline ratio and recurrence of ipsilateral cerebral ischemic events.

There is still uncertainty about which compounds contribute to the choline peak, but water-soluble choline, phosphocholine, and glycerophosphocholine as well as the lipid-soluble phosphatidylcholine have been implicated. The concentration of choline is the limiting factor for the synthesis of acetylcholine in cholinergic neurons and is used to synthesize phosphatidylcholine, a major constituent of the cell membrane in all brain cells. An increase in choline has been shown in infarcts, developing over weeks to months, in areas of leukoaraiosis, and in noninfarcted regions of the brain in patients with severe carotid artery stenosis. Whether the observed increase in choline is caused by increased membrane breakdown, by a change in acetylcholine metabolism, or by other changes in the metabolism of choline-containing compounds is unknown.

In the acute stage of an infarct, lactate is thought to be a good marker of cell hypoxia, whereas persistent presence of lactate up to months after the stroke has been related to macrophage infiltration. The origin of lactate observed in noninfarcted areas of the brain of patients with carotid artery stenosis or occlusion has not yet been elucidated. In accordance with observations that lactate in the acute stage of ischemic stroke does not predict clinical outcome, we did not find an association between the presence of lactate in...
noninfarcted brain regions and recurrence of cerebral ischemic events in patients with CAO.

A potential limitation of our study is that a total of 16 patients underwent EC/IC bypass surgery and were censored at the time of the operation. This may have resulted in a decreased rate of recurrent ischemic stroke because the decision for EC/IC bypass surgery was guided by an estimated high risk of recurrent stroke in the operated patients. On the other hand, all but 3 of the 16 patients who underwent EC/IC bypass surgery had already reached a primary outcome event (recurrent ipsilateral TIA or ischemic stroke) before they underwent surgery. It is therefore unlikely that censoring of these patients influenced prognostic factors for the primary outcome event of any recurrent cerebral ischemic event.

We conclude that patients with a symptomatic CAO with a low NAA/choline ratio in the hemisphere ipsilateral to the CAO have a higher risk of recurrent cerebral ischemic events than patients with a normal NAA/choline ratio. This predictive value of the NAA/choline ratio is associated with, and possibly dependent on, whether patients initially had symptoms of ischemia of the eye only or symptoms of the brain as well.

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