Prediction of Malignant Middle Cerebral Artery Infarction by Diffusion-Weighted Imaging

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Background and Purpose—This study was designed to analyze whether early diffusion-weighted imaging (DWI) provides reliable quantitative information for the prediction of stroke patients at risk of malignant brain infarct.

Methods—We selected 28 patients with a middle cerebral artery (MCA) infarct and proven MCA or carotid T occlusion on DWI and MRI angiography performed within 14 hours after onset (mean 6.5 ± 3.5 hours, median 5.2 hours). Of these, 10 patients developed malignant MCA infarct, whereas 18 did not. For the 2 groups, we compared the National Institutes of Health Stroke Scale (NIHSS) score at admission, site of arterial occlusion, standardized visual analysis of DWI abnormalities, quantitative volume measurement of DWI abnormalities (volume_{DWI}), and apparent diffusion coefficient values. Univariate and multivariate discriminant analysis was used to determine the most accurate predictors of malignant MCA infarct.

Results—Univariate analysis showed that an admission NIHSS score >20, total versus partial MCA infarct, and volume_{DWI} >145 cm³ were highly significant predictors of malignant infarct. The best predictor was volume_{DWI} >145 cm³, which achieved 100% sensitivity and 94% specificity. Prediction was further improved by bivariate models combining volume_{DWI} and apparent diffusion coefficient measurements, which reached 100% sensitivity and specificity in this series of patients.

Conclusions—Quantitative measurement of infarct volume on DWI is an accurate method for the prediction of malignant MCA infarct in patients with persistent arterial occlusion imaged within 14 hours of onset. This may be of importance for early management of severe stroke patients. (Stroke. 2000;31:2175-2181.)

Key Words: brain edema ■ magnetic resonance imaging ■ middle cerebral artery ■ risk assessment ■ stroke, acute

Life-threatening middle cerebral artery (MCA) infarction occurs in up to 10% of all stroke patients.1,2 Within this group, the main cause of death is severe postischemic edema leading to raised intracranial pressure, clinical deterioration, coma, and death.3,4 Because the mortality rate is ~80% in such patients, the term malignant MCA infarction was coined.5 Aggressive treatments for malignant MCA infarction are currently being evaluated in ongoing trials. Decompressive hemicraniectomy has been shown to reduce the mortality rate while improving the clinical outcome of patients with malignant MCA infarction.3,5-7 Decompressive hemicraniectomy was first considered as a life-saving maneuver and was thus undertaken after clinical deterioration and CT signs of mass effects had occurred. Recent experimental studies8,9 and human stroke studies10 provide evidence that early rather than later decompressive intervention could lead to a better outcome while limiting the final volume of the infarction. This suggests that the decision to perform hemicraniectomy should be taken before clinical deterioration occurs. To this end, obscuration of the brain sulci or compression of the ventricle and pineal displacement may be relatively late signs of edema.5,11,12 Early CT predictors have been proposed for the early identification of patients at risk of fatal brain swelling; these predictors are the extent of tissular hypodensity13 and attenuated corticomedullary contrast.5 Unfortunately, these CT signs are relatively mild during the first few hours after stroke onset, and not only detection but especially a dependable quantification of subtle parenchymal hypodensity on CT scan can be difficult in the emergency setting.14

With the advent of diffusion-weighted imaging (DWI) in clinical MRI units, this technique is increasingly being used to image acute-stroke patients. Despite the thoroughly documented diagnostic power of DWI for diagnosing acute stroke,15-18 its ability to identify the extent of the so-called ischemic penumbra (by the combination of DWI and perfusion imaging),19 and its prognostic value on clinical outcome,20,21 the use of DWI for the early prediction of malignant MCA infarction has not been reported. We compared the DWI obtained within 14 hours after stroke onset in MCA infarction between a group of patients who subsequently
developed malignant MCA infarction and a group of patients who did not. We focused our attention on the volume of DWI abnormalities and on the values of the apparent diffusion coefficient (ADC) in the corresponding area.

Subjects and Methods

Patients
The present study consisted of 28 patients (20 men and 8 women) selected from a database of 367 consecutive patients from the stroke unit who were scanned with DWI between April 1998 and December 1999 for suspicion of stroke. In the present study, we included all patients who fulfilled the following criteria: (1) an acute hemispheric infarction involving the MCA territory, (2) a precisely established time of onset, (3) a National Institutes of Health Stroke Scale (NIHSS) score at admission, (4) a DWI performed within 14 hours after symptom onset, and (5) an MRI or digitized angiogram showing acute intracranial carotid artery or MCA occlusion.

All patients were admitted to the critical care unit of the stroke center and were treated according to standardized protocols. Seven patients were included in randomized thrombolytic or fibrinogenolytic therapeutic trials. One of the patients subsequently had a symptomatic nonfatal hemorrhage, but none developed malignant MCA infarction. The other patients received intravenous heparin as long as they had normal consciousness and no mass effect on the initial imaging. In the event of neurological or consciousness deterioration, heparin was interrupted, and a follow-up CT scan was rapidly performed. If the CT scan revealed brain swelling, the patient was treated by osmotherapy and mechanically ventilated if necessary. Hemicraniectomy was considered in the event of rapid neurological and consciousness deterioration, development of clinical signs of uncal herniation, and mass effect on the follow-up CT scan. The decision was taken by consensus between the stroke neurologist and the neurosurgeon, in accord with the patient’s relatives.

End Point
Patients were classified in the malignant MCA infarction group if they had deterioration of neurological and consciousness status with clinical signs of uncal herniation and mass effect leading to early death or hemicraniectomy.

Magnetic Resonance Imaging
All MRI examinations were performed with the use of a 1.5-T MRI unit (GE Signa Horizon Echospeed). All MRI examinations were obtained within 14 hours after the onset of acute neurological symptoms (mean 6±3.5 hours, range 2 to 14 hours).

Diffusion-Weighted MRI
The DWI sequence contained 16 slices (thickness 6 mm) with an interslice gap of 1.5 mm, a field of view of 280×210 mm, and a matrix of 96×64 pixels. Each axial slice was obtained with spin-echo multislice single-shot echo-planar imaging sequences (echo timer 92.6 ms, repetition time 2825 ms) with a baseline T2 acquisition (b=0 s/mm²) and b=1000 s/mm² (diffusion gradient 22 mT/m, active during 31 ms). The diffusion gradients were successively and separately set in the 3 orthogonal directions for a total acquisition time of 2 minutes 39 seconds. Maximum intensity projection views of MRI angiograms were analyzed on an Advantage Window workstation. In 2 patients, the image quality was insufficient because the patients were unable to lie still in the scanner. For one of them, a follow-up MRI angiogram at day 1 showed a persistent MCA trunk occlusion, lateral to the medial lenticulostriate arteries. From these data, the occlusion of the MCA at the acute phase was extrapolated. For the other patient, a digitized angiography performed at admission showed a distally occluded carotid artery.

Data Analysis
The initial MRIs were evaluated retrospectively by a neuroradiologist who was aware of the clinical diagnosis of MCA stroke but blinded in terms of acute clinical condition and individual subsequent course and also unaware of the results of imaging follow-up. For qualitative analysis of DWI, the neuroradiologist was asked to determine the extent of the infarction (ie, partial versus total MCA infarction) and whether additional acute lesions were visible in vascular territory other than the MCA. On angiograms, 3 types of occlusion were considered: (1) intracranial bifurcation of the internal carotid artery occlusion, the so-called carotid “T” occlusion; (2) MCA trunk occlusion proximal to the medial lenticulostriate arteries; and (3) MCA trifurcation occlusion distal to the lenticulostriate arteries. Because of the small sample, MCA trunk occlusion and more distally occluded MCAs were pooled in the MCA occlusion group for the final statistical analysis.

Quantitative measurements of the infarct volume and of ADC values were generated. The infarct volume (volumeDWI) was measured on the DWIs, ie, b=1000 s/mm². We first selected all images in which the infarcted area was displayed as areas of bright signal. On each of these slices, the area of hypersignal was delineated with a semiautomatic thresholding method as follows: A cursor was initially positioned on the most intense pixel. The intensity threshold was then progressively reduced (to select all contiguous pixels with an intensity superior to the set threshold) until the total selected area matched the intensity area that would have been manually contoured. Whenever ≥1 lesion was present, the additional lesions were manually contoured. The volumeDWI was obtained by multiplying the surface by the slice thickness plus the intersection gap, ie, 7.5 mm.

In a preliminary analysis, volume measurements were also calculated from the ADC color-coded maps. We used a semiautomatic thresholding method similar to that used for volumeDWI to outline the area of reduced ADC values. We then compared these volume measurements obtained from ADC maps with the volumeDWI. Because the results indicated an almost perfect colinearity between these volume measurements (r=0.99, P<0.00001), only volumeDWI, which is more straightforward to obtain, was selected for the present study. ADC values were calculated in both the infarcted and the contralateral hemispheres.

Infarcted Hemisphere
ADCinfarct corresponded to the mean ADC value of the whole ischemic lesion, which was delineated on DWI as described above. ADCpeak corresponded to the peak ADC decrease in the ischemic lesion as calculated in a 57-mm² circular region of interest (ROI), which was centered on the ischemic area with the lowest ADC value on color-coded ADC maps. ADCsuperficial values were calculated by positioning an ROI of 120 mm² in the superficial MCA territory, with care being taken to avoid cerebrospinal fluid. It should be noted that in patients whose hypersignal was initially limited to the deep MCA territory, this measurement concerned noninfarcted tissue. ADCdeep values were calculated by positioning an ROI of 120 mm² in the deep (lenticular nucleus) MCA territory. Note that in patients whose hypersignal was initially limited to the superficial MCA territory, this measurement concerned noninfarcted tissue.

Contralateral Hemisphere
Contralateral ADCsuperficial and ADCdeep values were calculated in mirror ROIs, ie, identically sized ROIs placed symmetrically in the contralateral hemisphere.

End Point
Patients were classified in the malignant MCA infarction group if they had deterioration of neurological and consciousness status with clinical signs of uncal herniation and mass effect leading to early death or hemicraniectomy.
In the 2 groups (malignant and nonmalignant MCA infarctions), we first compared demographic features (age, sex, side of infarction, and delay from onset to MRI) and potential predictors of malignant MCA infarction (initial NIHSS score; type of arterial occlusion, ie, carotid T versus MCA occlusion; infarct extent, ie, partial versus total MCA infarction; type of vascular territories, ie, MCA exclusive versus MCA1 anterior cerebral artery [ACA] or posterior cerebral artery [PCA]; volumeDWI; and ADC values). Categorical variables were compared with a 2-tailed exact Fisher test, and quantitative variables were compared with a 2-tailed Student t test.

Univariate discriminant analyses were then performed to determine which variables best predicted the occurrence of MCA malignant infarction. For each model reaching a \( P < 0.001 \) level of significance, the sensitivity, specificity, and positive and negative predictive values were calculated. Last, we tried to ascertain whether multivariate models improved prediction. Statistical analysis was performed with the use of GBstat V6.0 software (Dynamic Microsystems Inc).

### Results

#### Clinical and Demographic Results

There were 28 patients with a mean age of 54 ± 12.4 years (range 30 to 84 years) included in the present study. Of these, 10 (36%) developed major clinical and CT signs of brain swelling and constituted the malignant group. Six of these patients died from uncal herniation; one of them had undergone hemicraniectomy. Death occurred 2 to 4 days after stroke onset. The 4 other patients survived; all had hemicraniectomy performed 12 to 84 hours after stroke onset (mean 37 hours) because of the development of clinical and CT signs of life-threatening edema. They all had a modified Rankin score of 4 at 3 months after stroke onset. The 18 other patients did not experience malignant brain swelling. All of them survived, although 2 of them had a symptomatic hemorrhagic transformation. Three-month outcome was poor in 10 patients.
modified Rankin score 4 to 5), intermediate in 4 (Rankin score 3), and good in the remaining 4 patients (Rankin score 0 to 2).

**Group Comparison**

As shown in Table 1, patients in the malignant group were younger and had higher NIHSS score at admission than did those in the nonmalignant group. Total MCA infarction and those infarctions associated with a carotid T occlusion were significantly more frequent in the malignant than in the nonmalignant group. This was also true for MCA infarctions with additional lesions in the ACA or PCA territory. VolumeDWI was significantly greater in the malignant group than in the nonmalignant group. ADC infarct, ADC core, and ADC superficial values measured in the infarcted hemisphere were all significantly lower in the malignant than in the nonmalignant MCA group. In addition, mirror ADCdeep and ADC superficial values in the noninfarcted hemisphere were significantly lower in the malignant than in the nonmalignant MCA group. No statistical differences were found for the other studied variables.

**Discriminant Analysis**

**Univariate Models**

Three models reached the $P<0.0001$ significance level, indicating that 3 different variables were excellent predictors of the development of MCA malignant infarction. The most effective variable was volumeDWI ($F_{1,26} = 58.8$, cutoff value $145 \text{ cm}^3$), followed by NIHSS score ($F_{1,26} = 27.2$, cutoff value 20), and infarct extent ($F_{1,26} = 27.2$, total MCA infarction). As shown in Table 2, NIHSS score and infarct extent had a high sensitivity but only a moderate specificity. In contrast, volumeDWI achieved high sensitivity and specificity, with a cutoff value of $145 \text{ cm}^3$ (Figure 1). This model misclassified a single patient who was erroneously predicted to develop malignant MCA infarction. This patient was “borderline” because he developed mass effect but had no signs of uncal herniation and was therefore not considered for hemicraniectomy. Interestingly, the correlations between volumeDWI and delay to MRI were not significant (malignant group, $r=0.42$, $P>0.2$; nonmalignant group, $r=0.3$, $P>0.2$; all patients, $r=0.35$, $P>0.05$). MCA malignant infarction was also predicted at a slightly lower level of significance ($P<0.001$ to 0.0001) by 3 of the 4 ADC values of the infarcted hemisphere ($\text{ADC}_{\text{core}}$, $F_{1,26} = 17.8$; $\text{ADC}_{\text{superficial}}$, $F_{1,26} = 12.5$; and $\text{ADC}_{\text{infarct}}$, $F_{1,26} = 10.6$) and by 1 qualitative variable (ACA/CPA+MCA infarction, $F_{1,26}$

![Initial MRIs and follow-up CT scan in 2 patients with carotid occlusion and acute MCA infarction. Top rows, A 63-year-old man had a partial MCA infarction on initial DWI obtained 4 hours after stroke onset. The volumeDWI was $41 \text{ cm}^3$, which was below the $145\-\text{cm}^3$ cutoff value. The patient did not develop malignant MCA infarction, as shown on follow-up CT scan. Bottom rows, A 32-year-old woman had a total MCA infarction on DWI obtained 8 hours after stroke onset. The volumeDWI was $152 \text{ cm}^3$, which was above the $145\-\text{cm}^3$ cutoff value. She rapidly showed clinical signs of deterioration with CT signs of brain swelling. Life-saving hemicraniectomy was performed 26 hours after stroke onset.](image-url)
14.8). Predictors based on ADC_{deep} and ADC_{superficial} values of the noninfarcted hemisphere or on the site of arterial occlusion (F_{1,26} 6.49) had a lower level of significance (P<0.05 to 0.01) and very poor predictive values.

**Multivariate Models**

Four models were highly significant (P<0.0001) and reached 100% sensitivity and specificity in this sample of patients. The most significant model combined volume_{DWI} with non-infarcted side ADC_{deep} (F_{2,25} 45.9), as shown in Figure 2. Figure 3 compares the discriminant power of this bivariate model with that of 2 univariate models based on NIHSS score at admission and volume_{DWI}. The 3 other bivariate models combined volume_{DWI} with ADC_{infarct} (F_{2,25} 34.3), volume_{DWI} with noninfarcted side ADC_{superficial} (F_{2,25} 33.6), and volume_{DWI} with infarcted side ADC_{superficial} (F_{2,25} 31.0).

**Discussion**

Because DWI is increasingly used for the early management of acute stroke, we investigated whether it could help to predict the subsequent development of malignant MCA infarction. The present study was based on a simple pathophysiological hypothesis. Massive brain swelling is most likely to occur in patients with particularly severe ischemia and poor collateral circulation. We predicted that large DWI abnormalities would occur earlier in such patients because of the rapid transition from ischemia to infarction in most of the MCA territory. This rapid transition has been demonstrated by positron emission tomographic findings of an early and massive decrease in brain oxygen metabolism in a subset of severe MCA infarctions.\(^{22}\) In addition, a direct relationship between the development of malignant MCA infarction and the severity of ischemia has more recently been demonstrated with the use of xenon-enhanced CT or single-photon emission computed tomography.\(^{23,24}\) Our results confirm the hypothesis; an almost perfect prediction of malignant MCA syndrome can be achieved by the quantitative measurement of volume_{DWI}, and prediction may be further improved by ADC measurements.

**Patient Selection and Group Comparison**

We selected from our database of patients those with MCA infarction and persistent carotid T or MCA occlusion because most cases of malignant MCA infarction occur in such patients.\(^{5,14,25}\) As expected, a large proportion of the selected patients (36%) developed a malignant MCA infarction. In this group, the patients who survived may have owed their survival to the hemicraniectomy, which was performed only if clinical signs of life-threatening uncal herniation had occurred. Conversely, all other patients survived without hemicraniectomy, although a transient mass effect was observed in some cases. Therefore, the present study may be considered comparable to those studies that used fatal brain swelling as an outcome.\(^{13,14,23}\)

The comparison between the malignant and the nonmalignant groups confirms several known features of malignant MCA infarction. Patients were significantly younger in the malignant group,\(^{25,26}\) presumably because a certain degree of age-related cerebral atrophy protects from space-occupying brain swelling.\(^{3,13,14,27}\) As previously reported, the patients in the malignant group had a higher NIHSS score at admis-
Quantitative DWI indices also differed significantly among groups. The malignant group displayed significantly larger volume_{DWI} and lower ADC values in the ischemic area (ADC_{ischemic}) and in its core (ADC_{core}). In line with our pathophysiological hypothesis, these findings confirm that both large extent and severity of the early ischemic insult play a pivotal role in the development of malignant brain swelling. Interestingly, ADC also decreased in the noninfarcted hemisphere of the malignant group. This finding was unexpected but statistically significant in both deep and superficial MCA territory. It could simply be related to an α-type statistical error in a small group of patients and, thus, needs to be confirmed on a larger sample of patients. However, the decrease in ADC was considerably less marked in the noninfarcted hemisphere than in the ischemic focus. It may reflect subtle homeostatic changes related to neurochemical alterations in the noninfarcted hemisphere, such as abnormal glutamate release.

**Discriminant Analysis**

Univariate models identified 3 variables that were highly significant predictors of malignant MCA infarction: NIHSS score, extent of infarct (ie, total versus partial MCA infarction), and volume_{DWI}. High NIHSS scores and CT-based extent of infarction have previously been identified as predictors of poor outcome and of fatal brain swelling with a similar cutoff. Yet, as in earlier studies, NIHSS score and qualitative assessment of infarct extent were not perfect predictors. In the present study, these variables had high sensitivity but poor specificity and would therefore appear to be of limited clinical usefulness.

In contrast, the quantitative measurement of volume_{DWI} was an accurate predictor of malignant MCA infarction, inasmuch as it misclassified only 1 of the 28 patients. The model generated a cutoff value of 145 cm³. Interestingly, this value falls well within the ranges of the mean infarct volume in dependent patients (88 cm³) and in the patients who died (166 cm³) that were previously reported on T2-weighted MR sequences. However, the cutoff value is much lower than the 400-cm³ lesion volume reported in a large CT study. The latter study was carried out in patients imaged up to 48 hours after stroke (meaning that considerable edema has occurred), whereas our DWI-MRI studies were obtained before the development of mass effect.

The validity of the volume_{DWI} cutoff value may be questioned within the first 6 hours after stroke, because we included patients up to 14 hours after stroke. DWI abnormalities may increase with time, especially in patients with persistent arterial occlusion. However, we did not find a significant correlation between delay from onset to MRI and volume_{DWI}. This may be due to insufficient statistical power; it might also reflect the variability of collateral circulation, which affects both the kinetics of infarct constitution and its final size. This variability may mask the time-related growth of DWI abnormalities in the subset of patients with persistent ischemic penumbra.

The prediction of malignant infarction was further improved by bivariate models combining volume_{DWI} and ADC decrease, which achieved 100% accuracy of prediction in this sample of patients. The most significant model combined volume_{DWI} with ADC value in the deep MCA territory of the noninfarcted hemisphere. This was not predicted by our physiopathological hypothesis and therefore needs to be validated by further studies. Nevertheless, it suggests that metabolic and/or neurochemical changes in the noninfarcted hemisphere may not only be a consequence of malignant edema but may also be involved in its pathogenesis.

The present study has some limitations. First, although perfusion measurements are among the most accurate predictors of malignant MCA infarction, we did not analyze MRI perfusion data because they were not available for all patients. However, the present data suggest that DWI and ADC measurements are more effective predictors than the perfusion measurements previously reported. This seems logical because DWI abnormalities are one step downstream from perfusion abnormalities in the cascade of events starting with the sudden occlusion of a large intracerebral artery and eventual malignant edema. Second, we did not compare DWI with early CT scans because the CT scan was not systematically performed at the same time as DWI. The usefulness of early CT-based prediction of malignant infarction is still a subject of debate, although a recent study reported that a widespread attenuated corticomедullary contrast predicted malignant infarction with a relatively high sensitivity (87%) and an excellent specificity (97%) within 18 hours of the onset. Third, one could argue that the present results may have been biased by including some patients with NIHSS scores <15 in the nonmalignant group; however, we did verify that their exclusion would not have altered the statistical significance of univariate and multivariate predictions based on volume_{DWI} and ADC measurements. Fourth, some of the patients have been included in randomized trials and may have been reperfused shortly after MRI angiography. In such cases, some DWI lesions may have been partially reversible after early recanalization, which could have biased our results. Yet the cutoff value remained almost unchanged (volume_{DWI} 149 cm³ versus 145 cm³) after exclusion of these patients from the statistical analysis. Last, we must point out that this is a preliminary study, conducted with a relatively small number of highly selected patients. We are currently conducting a prospective study to test the reliability of the prediction models.

**Conclusions**

The present study was designed to identify potential MRI predictors of malignant MCA infarct. Therefore, it was conducted in a highly selected subgroup of patients at high risk to develop malignant MCA infarct. Our results suggest that quantitative measurement of volume_{DWI} is a reliable tool to predict malignant MCA infarction in stroke patients with persistent arterial occlusion imaged within 14 hours from onset. DWI is a noninvasive technique producing high-quality images even in most restless patients and is becoming more widely available. The high signal-to-background ratio
of DWI ischemic hyperintensity allows easy infarct volume measurement, which can be obtained in a few minutes with current image-processing tools. It is noteworthy that our results are also helpful in recognizing stroke patients who, despite a high NIHSS score at admission, are not high-risk candidates for malignant MCA if the infarction is too small on admission DWI. Indeed, in the studied population, none of the infarctions with volume_{DWI} < 145 mL became malignant. The early prediction of patients with MCA at risk of malignant edema is of practical importance. It should allow the physician to target a group of patients at high risk of brain swelling for a detailed discussion of management options, including surgical decompression, before the onset of neurological deterioration.

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