The Prediction of Malignant Cerebral Infarction by Molecular Brain Barrier Disruption Markers

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Background and Purpose—Space-occupying brain edema is a life-threatening complication in patients with large hemispheric stroke. The aim of the study was to determine whether molecular markers of endothelial damage may help to predict secondary brain edema and, secondly, to identify patients who could benefit from aggressive therapies such as decompressive hemicraniectomy or hypothermia.

Methods—We studied 40 consecutive patients with malignant middle cerebral artery (MCA) infarction and 35 controls with massive MCA infarctions <70 years of age and matched by stroke severity on admission. Cranial computed tomography (CT) was performed at entry and repeated between days 4 and 7, or earlier if there was neurological worsening. Malignant MCA (m-MCA) infarction was diagnosed when follow-up CT detected a more than two-thirds space-occupying MCA infarction with midline shift, compression of the basal cisterns, and neurological deterioration. Plasma concentrations of glutamate, glycine, γ-aminobutyric acid, interleukin-6 (IL-6), IL-10, tumor necrosis factor-α, matrix metalloproteinase-9 (MMP-9), and cellular-fibronectin (c-Fn) were determined in blood samples obtained at admission.

Results—Mean time from stroke onset to blood sampling was 6.3±4.8 in m-MCA and 7.7±6.0 hours in the control group ($P=0.63$). Baseline characteristics were comparable in both groups. c-Fn and MMP-9 levels were significantly higher in patients with m-MCA than in controls (all $P<0.001$). c-Fn >16.6 μg/mL had the highest sensitivity (90%), specificity (100%), and negative and positive predictive values (89% and 100%, respectively) for the prediction of m-MCA infarction.

Conclusions—A plasma c-Fn concentration >16.6 μg/mL at admission is associated with the development of m-MCA infarction with high sensitivity and specificity, suggesting that c-Fn might be useful in therapeutic decision making. **(*Stroke*. 2005;36:1921-1926.)**

Key Words: brain edema ■ craniectomy ■ stroke

Massive middle cerebral artery (MCA) infarction accounts for 10% to 15% of all MCA infarctions,[1] and of these patients, malignant MCA (m-MCA) reaches 40% to 50%.[2,3] The syndrome of m-MCA infarction, which is attributable to brain edema, is more frequent in younger patients and has a poor prognosis both short and long term. In 80% of patients, it leads to death, and those patients who survive experience severe neurological deficits.[4]

Conservative treatments fail to improve mortality and disability. Early hemicraniectomy and hypothermia are feasible and have been proposed as effective treatments for this condition because they change the natural history of the disease.[5] However, those patients who will develop m-MCA syndrome are currently not revealed by clinical, neuroimaging, or biochemical markers sufficiently early and with sufficient accuracy as to indicate an aggressive management.

The loss of integrity of the endothelial basal lamina is believed to be the primary cause of edema after focal cerebral ischemia. Matrix metalloproteinase-9 (MMP-9), a proteolytic zinc-dependent enzyme for which expression is increased during stroke,[6–8] and in experimental models of focal ischemia,[9] it degrades the endothelial basal lamina[10] and plays an essential role in producing edema and hemorrhagic transformation.[8,11] In a recent study, serum cellular-fibronectin (c-Fn), a component of the basal lamina, was shown to be a more accurate predictor of hemorrhagic transformation than

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MMP-9 in acute ischemic stroke patients treated with tissue plasminogen activator (tPA).[12] Therefore, an increased expression of blood–brain barrier (BBB) disruption markers in cerebral ischemia may partially explain the syndrome of m-MCA infarction.

This retrospective study investigates the potential association between plasma concentrations of MMP-9, c-Fn, excitatory amino acids (EAAs), and inflammatory molecules with the development of brain edema and subsequent m-MCA syndrome in patients with complete MCA infarction.

Methods

Plasma glutamate, glycine, γ-aminobutyric acid (GABA), interleukin-6 (IL-6), IL-10, tumor necrosis factor-α (TNF-α), MMP-9 and c-Fn concentrations were determined in 75 patients <70 years of age experiencing a clinically massive MCA infarction <24 hours from stroke onset. Patients were consecutively included in a prospective register with the aim of evaluating serum markers of early and late clinical course. Of 408 acute ischemic stroke patients included during the 1-year study period, 75 patients experienced large/massive strokes (total anterior cerebral infarction [TACI]), met all eligibility criteria, and so were included retrospectively in the present study. Forty of these patients had fatal brain swelling and were designated as having m-MCA infarction. The remaining 35 patients with complete MCA infarction of comparable clinical severity to those of m-MCA infarction served as the control group.

Massive MCA infarction was diagnosed in patients with a clinically identifiable TACI syndrome at admission[14] and a cerebral infarction involving at least the anterior and posterior divisions of the MCA territory (with or without the deep MCA territory supplied by the lenticulostriate arteries), which is equivalent to two thirds or more of the MCA, as measured in a follow-up computed tomography (CT) scan.[13]

Malignant MCA infarction was diagnosed following the Schwab et al criteria:[5] clinical evidence of acute, massive MCA infarction demonstrated on follow-up CT including complete space-occupying MCA infarction with midline shift and compression of the basal cisterns, and further neurological deterioration consisting of a decrease in the level of consciousness to somnolence or stupor compared with the baseline clinical status on admission.

The protocol was approved by the ethics committees, and informed consent for inclusion in the stroke registry was given by patients or their relatives. Stroke severity was quantified by an experienced neurologist using the Canadian Stroke Scale (CSS) at admission and 24 hours, 48 hours, and 7 days after inclusion. Following already published criteria aimed at giving the highest sensitivity and specificity, early neurological deterioration (END) was diagnosed when the CSS score dropped ≥1 points during the first 48 hours after admission.[15]

Patients with potential infectious diseases or hyperthermia within the 15 days before stroke were excluded. Outcome at 3 months was evaluated using the modified Rankin scale and the CSS.

CT scan was performed at admission. Early signs of cerebral infarction (ESCIs) on CT, including the presence of focal hypodensity consistent with the clinical picture, obscuration of the lenticular nucleus, obscuration of the cortex, and mass effect with effacement of the cortical sulci (grade I), ventricular asymmetry (grade II), or shifting of the structures of the median line (grade III), were evaluated in the first radiological examination. To measure the infarct volume and evaluate the presence of hemorrhagic transformation or mass effect, a second CT was performed between days 4 and 7 of hospitalization, or earlier in the case of neurological deterioration. The infarct volume was determined by the formula $0.5 \times a \times b \times c$ (where a and b are the largest perpendicular diameters measured on CT and c is the slice thickness). Because the extent of MCA ischemia is not included in the prospective stroke registry, we have made a retrospective assessment using the Alberta Stroke Program Early CT Score (ASPECTS) method and blinded to molecular and clinical data.[16] Blood chemistry test, 12-lead ECG, chest radiography, and arterial supra-aortic trunk examination were also performed in all patients. The suspected etiology of brain infarction was classified as large-artery atherosclerosis, cardioembolism, and cryptogenic stroke, following the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[17] Patients included in clinical trials or treated with recombinant tPA were excluded.

Laboratory Tests

Blood samples were taken on admission at the emergency department in glass test tubes containing potassium edentate and centrifuged at 3000*g* for 5 minutes and stored at −80°C. Plasma IL-6, IL-10, TNF-α, MMP-9, and c-Fn were measured with commercially available quantitative sandwich ELISA kits (Quantikine, R & D Systems, Biotrack, Amersham Pharmacia UK, and Adeza Biomedical, respectively). Glutamate, glycine, and GABA were quantified by high-performance liquid chromatography as described previously.[18] These measurements were made by technicians blinded to the clinical outcome and neuroimaging findings at an independent laboratory.

Statistical Analyses

Proportions between groups were compared by the χ^2 test. Continuous variables have been expressed as the mean and SD, or median and quartiles in the case of distribution that was not normal, and compared by the Student's t test or the Mann–Whitney test as appropriate. We used cut-off values, as described by Robert et al,[19] to estimate the sensitivity, specificity, predictive values, and accuracy (with 95% CI) of a specific concentration of MMP-9 and of c-Fn for m-MCA. This method is a probabilistic technique based on Bayes' rules, which provides the maximum probability of a correct classification. The importance of c-Fn for the development of m-MCA infarction was assessed by logistic regression analysis adjusting for those baseline variables related to m-MCA infarction in the bivariate analysis. However, the model could not estimate the adjusted effect of c-Fn because of the high collinearity among age, MMP-9, and c-Fn. Because the c-Fn is one of the main components of the endothelial basal lamina and the target of MMP-9, and considering its high positive predictive value (PPV), we decided to focus the results and the discussion on the role of c-Fn in predicting m-MCA without taking into account the multivariate analyses.

Results

Forty of the 75 patients included in the study met the criteria of m-MCA infarction. The 35 patients consecutively admitted for a TACI who did not develop m-MCA were used as a control group. Table 1 shows the main characteristics of patients with and without m-MCA infarction.

Patients with m-MCA infarction were younger than non-mMCA infarction patients. There were no significant differences in clinical characteristics nor in vital signs or biochemical parameters at admission. Poor outcome was significantly more frequent in patients experiencing m-MCA syndrome. Twenty-seven of 40 patients (67.5%) with m-MCA died, and only 1 (2.5%) of the survivors was independent (modified Rankin ≤2) at 3 months. These same figures were 20% and 22.9% in the non-mMCA group (all $P \leq 0.01$; Table 1).

ESCIs on CT scan at admission were detected more frequently in patients who later developed m-MCA infarction, although without statistically significant differences compared with the non-MCA group (92.5% versus 74.3%; $P = 0.06$). Severe mass effect on CT scan at admission, extent of MCA infarction (ASPECTS), and final infarct volume in the second CT scan were significantly more frequent in the m-MCA group (Table 2).

TABLE 1. Baseline Clinical Characteristics and Biochemical Parameters in m-MCA and Non-mMCA Brain Infarction

	m-MCA Infarction (n=40)	Non-mMCA Infarction (n=35)	*P*
Sex, male, n (%)	28 (70)	21 (60)	0.47
Age, y	59.7 (7.2)	65.0 (6.5)	<0.01
Patients >60 y of age, n (%)	19 (47.5)	30 (85.7)	<0.001
Mean time from stroke onset to blood sampling, hours	5.3 (2.6, 9)	6.5 (2.5, 9)	0.63
Previous infectious disease or hyperthermia, n (%)	4 (10.0)	4 (11.4)	1.0
Clinical characteristics			
CSS on admission	3.5 (3,5)	3.5 (2.5,5)	0.75
Suspected etiology			0.81
Large-artery atherosclerosis	35.0%	42.9%	
Cardioembolism	55.0%	45.7%	
Cryptogenic stroke	10.0%	11.4%	
Biochemistry and vital signs at admission			
Plasma glucose, mg/dL	144.5 (49.0)	155.5 (48.0)	0.34
Plasma fibrinogen, mg/dL	546.0 (206.2)	485.5 (154.7)	0.17
Leukocyte count, no.$\times 10^3$/mm^3	9.9 (2.7)	9.0 (2.4)	0.12
Erythrocyte sedimentation rate, mm/hour	24.6 (22.4)	25.3 (16.4)	0.90
Systolic blood pressure, mm Hg	149.4 (20.1)	147.7 (26.4)	0.13
Diastolic blood pressure, mm Hg	85.1 (14.3)	80.0 (14.9)	0.17
Body temperature, °C	36.6 (0.7)	36.9 (0.7)	0.07
Outcome			
Early neurological deterioration	100%	25.7%	<0.001
Mortality	67.5%	20.0%	<0.001
CSS at 3 months	1.5 (1.5, 3.8)	5.5 (4.7)	<0.001
Modified Rankin scale >2 at 3 months	97.5%	77.1%	0.01

Continuous variables are expressed as mean (SD) or median values and quartiles as appropriate.

Table 3 shows the levels of molecular markers at admission. Plasma levels of glutamate were significantly higher in patients who went on to develop m-MCA infarction, whereas inflammatory molecules were not significantly different between the 2 groups. When focusing on markers of basal membrane disruption, baseline MMP-9 and c-Fn concentrations were significantly higher in patients with m-MCA infarction than in controls.

We calculated the c-Fn and MMP-9 cut-off values with the highest sensitivity, specificity PPV, and negative predictive value (NPV) for m-MCA infarction development. This analysis showed that plasma MMP-9 concentrations ≥140 ng/mL

TABLE 2. Neuroimaging Finding in m-MCA and Non-mMCA Infarction

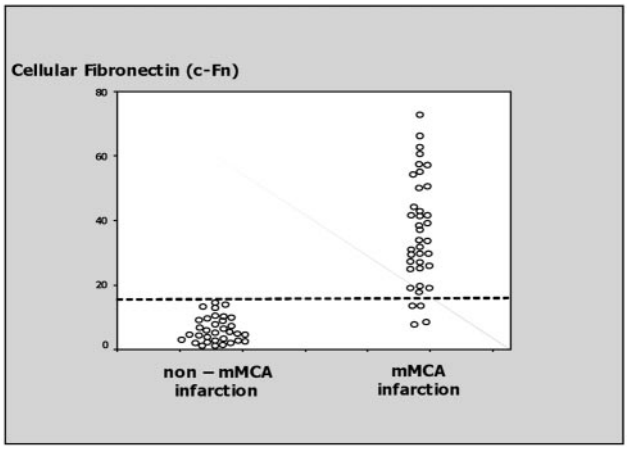
	m-MCA Infarction (n=40)	Non-mMCA Infarction (n=35)	*P*
CT scan at admission			
Early signs of brain infarction	37 (92.5%)	26 (74.3%)	0.06
Hypodensity	25 (62.5%)	25 (71.4%)	0.47
Mass effect	28 (70%)	19 (54.3%)	<0.001
Grade I	8 (20.0%)	17 (48.6%)	
Grade II	14 (35.0%)	3 (5.2%)	
Grade III	6 (15.0%)	0	
ASPECTS	5 (3–7)	7 (5–10)	<0.05
Ultimate infarct volume, cc	266.2 (107)	108.3 (104)	<0.001

Values are expressed as mean (SD) or median values and quartiles as appropriate.

TABLE 3. Molecular Markers in Plasma Samples at Admission in Patients With m-MCA Infarction and in Non-mMCA Infarction

	At Baseline		
	m-MCA Infarction (n=40)	non-mMCA Infarction (n=35)	*P*
Glutamate, μmol/L	147.2 (88–239.9)	84.6 (57.2–188.6)	0.02
Glycine, μmol/L	203 (98)	192 (77)	0.58
GABA, nmol/L	286 (131)	315 (144)	0.38
IL-6, pg/mL	18.9 (10.8)	18.2 (12.6)	0.82
IL-10, pg/mL	6.7 (2.1)	6.6 (2.3)	0.84
TNF-α, pg/mL	18.1 (6.8)	19.0 (6.6)	0.62
MMP-9, ng/mL	150 (66)	78 (59)	<0.001
c-Fn, μg/mL	25.3 (33.7, 50.2)	4.2 (6.7, 10.9)	<0.001

Values are expressed as mean (SD) or median values and quartiles as appropriate.



Plasma c-Fn ≥16.6 μg/mL for the prediction of m-MCA infarction.

predicted the development of m-MCA with a sensitivity of 64%, specificity of 88%, PPV of 85%, and NPV of 69%. The sensitivity, specificity, PPV, and NPV of plasma c-Fn ≥16.6 μg/mL for the prediction of m-MCA infarction were 90%, 100%, 100%, and 90%, respectively (Figure). Table 4 includes the sensitivity, specificity, PPV, and NPV of clinical, radiological and molecular markers of m-MCA infarction.

Discussion

Results for mortality rate and functional outcome after hemicraniectomy in massive MCA infarction have been contradictory.[5,20] This might be explained by the lack of reliable predictors of m-MCA infarction. Studies into the value of neuroimaging and clinical and biochemical markers of malignant brain edema have found few predictors to be sufficiently sensitive and specific as to be useful in clinical practice (Table 5). Clinical factors alone are not sufficient to identify patients with impending brain edema.[2,4,21] CT scan showed acceptable sensitivity in some studies but low specificity in identifying candidates for hemicraniectomy.[22,23] A recent approach has been to monitor biochemical markers and intracranial pressure (ICP) using a microdialysis probe inserted into the brain tissue.[3] However, this technique is complex, not widely available, invasive, and did not predict fatal outcome early enough for the successful implementation of invasive therapies because clinical deterioration often preceded the appearance of the analyzed biochemical markers and increased ICP. Promising results have been obtained with recent neuroimaging tests such as single-photon emission CT,[23] positron emission tomography of C-flumazenil,[3] and diffusion-weighted MRI[24,25] in the prediction of m-MCA infarction within the suggested time window for hemicraniectomy. These techniques evaluate infarct volume, the most reliable predictor of m-MCA, quickly and accurately but are unable to predict the development of massive brain edema directly.

Our study shows that a plasma c-Fn concentration >16.6 μg/mL at admission predicts the development of m-MCA infarction with a sensitivity of 90% and specificity of 100%, and therefore, it may be of use in therapeutic decision making.

The increase in vascular permeability and the subsequent extravasation of serum components leading to brain edema may be the result of several mechanisms including the activation of MMPs, which is secondary to ischemia.[28] MMP overexpression is associated with the loss of microvascular integrity and the disappearance of antigens of the endothelial components of the BBB.[26] Among these antigens, c-Fn is especially important because it mediates the interaction between the endothelium and blood cells as well as other blood components.[27] The disappearance of the c-Fn of the vascular endothelium secondary to ischemia might facilitate edema development. Although high c-Fn levels have been reported previously in patients with acute stroke and hemorrhagic transformation,[12] no previous data are available on the association between c-Fn levels and brain edema in cerebral ischemia. The present study confirms the significant association between MMP-9 levels and brain edema. However, the fact that c-Fn is almost exclusively located at the endothelium suggests that this molecule could be a more specific marker of a high risk of brain edema and hence of m-MCA infarction. This hypothesis is supported by the fact that the specificity and PPV for m-MCA is higher in the case of c-Fn than for MMP-9. In this study, we also analyzed EAAs and inflammatory molecules, which have been associated previously with END, increased infarct volume, and poor outcome. We found that EAA and inflammatory molecules were predictors of END and poor outcome (data not shown) but not of m-MCA infarction.

About 30% of all stroke patients experience END within the first 48 to 72 hours.[18] A significant proportion of END may be attributable to hemodynamic factors, recurrence, or biochemical mechanisms without the development of malignant brain edema, and hence, in these patients, aggressive treatments such as hemicraniectomy would not be indicated. In our series, 26% of patients in the non-mMCA group deteriorated within 48 hours.

In agreement with previous studies, we found CT scan at admission not to be a sensitive method for the prediction of m-MCA infarction. Because of the characteristics of our patients, prevalence of ESCIs was high in both groups, and although grade II mass effect was significantly more prevalent and ASPECTS was significantly lower in the m-MCA group, it was not sufficiently accurate as to be useful in clinical practice (Tables 2 and 4). Because age may be the

TABLE 4. Clinical, Radiological and Biochemical Predictors of m-MCA Infarction

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Age >50 vs <50 y	12.5	97.1	83.3	49.3
Age >60 vs <60 y	52.5	85.7	80.8	61.2
Early signs of brain infarction	93	75	93	26
Hypodensity	63	40	63	29
ASPECTS ≤7	56	31	56	55
ASPECTS ≤4	81	89	81	57
MMP (≥140 ng/mL)	64	88	85	69
c-Fn (≥16.6 μg/mL)	90	100	100	90

TABLE 5. Description of Studies Focused on Predictors of m-MCA

	No.	m-MCA %, (No.)	Predictors of m-MCA	Time From Stroke	Sensitivity for m-MCA, %	Specificity for m-MCA, %
von Kummer, 1994	53	...	Early CT findings for fatal outcome:			
			Hypodensity >50% MCA		61	94
			Any hypodensity		89	23
			Swelling		78	83
			HMCAS		44	41
Krieger DW, 1999	353*‡	6.5 (n=23)	CT scan: early hypodensity (OR, 6.1; 95% CI, 2.3–16.6)	<6 hours	ND	ND
			Early nausea or vomiting (OR, 5.1; 95% CI, 1.7–15.3) and			
			Systolic blood pressure >180 mm Hg after 12 hours (OR, 4.2; 95% CI, 1.4–12.9)			
Kasner SE, 2004	201†	47 (n=94)	History of hypertension (OR, 3.0; 95% CI, 1.2–7.6)	48 hours	ND	ND
			History of heart failure (OR, 2.1; 95% CI, 1.5–3.0)			
			Increased baseline white blood cell count (OR, 1.08; 95% CI, 1.01–1.14)			
			Major early CT hypodensity involving >50% of the MCA territory (OR, 6.3; 95% CI, 3.5–11.6)			
			Involvement of additional vascular territories (OR, 3.3; 95% CI, 1.2–9.4)			
Dohmen C, 2003	34†	50 (n=17)	PET parameters	12–34 hours	54–82	88–100
			Neuromonitoring parameters¶		96	100
			Microdialysis‖			
			ICP >26.6			
			Clinical parameters (NIHSS >20)	<12 hours	55	62
Berrouschot J§, 1998	108‡	10 (n=11)	99m Tc-ECD SPECT	<6 hours	82	98
			CT scan <6 hours		36	100%
			SSS <40		36–73	45–88
Oppenheim C, 2000	28†	36 (n=17)	DWI volume >145 cm^3	<14 hours (6.5±3.5)	100	94
Thomalla GJ, 2003	37	30 (n=11)	ADC <80% lesion volume >82 mL	<6 hours	87	91
			TTP >4 s lesion volume >162 mL		83	75
			NIHSS at admission >19		96	72
Present study, 2004	75†	53 (n=40)	Markers of BBB disruption	<24 hours	90	100

*The Lubeluzole-International-9 trial; †>50% MCA territory or carotid-T/MCA main stem occlusion; ‡MCA infarction, general population. §Only SPECT findings were independent predictors of m-MCA infarction/death; ¶did not predict fatal outcome early enough for implementation of invasive therapies; ‖glutamate >46.0 μmol/L, aspartate >4.2 μmol/L, GABA >9.0 μmol/L, glycerol >543 μmol/L; hypoxanthine >39 μmol/L.

SSS indicates Scandinavian Stroke Scale; PET, positron emission tomography; HMCAS, hyperdense middle cerebral artery sign; OR, odds ratio; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; TTP, time to peak; ND, not done.

most important factor when deciding on surgery, it has been suggested that future trials or standardized protocols should focus on hemicraniectomy in younger patients and early surgery before signs of herniation appear. Although this might seem a reasonable position to take given the complexity of conducting a clinical trial, our study found that although prevalence of m-MCA is higher in younger people, it was also high (40%) in patients >60 years of age (Tables 1 and 4). Furthermore, it should be noted that 19% of patients <60 years of age did not experience m-MCA. We also believe that stroke severity (National Institutes of Health Stroke Scale [NIHSS] >20) is not a good predictor of m-MCA. In our series, 50% of patients with severe stroke at admission did not develop m-MCA. Better tools of discrimination than age and neurological examination are clearly needed in deciding on surgery (Table 4).

As possible limitations of the study, we might consider the following: m-MCA infarction could be better detected if the

scan were consistently undertaken earlier, or repeated every 48 hours; a bias could conceivably have crept in during the process of retrospective selection because there is a nonstatistically significant difference in the prevalence of hypodensity on admission between patients who experience m-MCA and those who do not; and despite having demonstrated the accuracy of plasma c-Fn levels $\geq$16.6 μg/mL for the prediction of m-MCA infarction, these data were obtained from a post hoc analysis and so should be considered as hypothesis generating and requiring confirmation in a large-scale prospective study.

The state of investigation so far has not established the criteria for the routine use of decompressive surgery for patients with acute cerebral infarction complicated by edema, and patient selection by clinical evaluation and traditional neuroimaging are clearly insufficient. Diffusion-weighted MRI study has recently shown potential as a valuable tool in improving patient selection, although the series have been small,[24,25] and the present study suggests that the association of molecular markers of BBB disruption might also refine patient selection for aggressive treatments such as hemicraniectomy.

In conclusion, high plasma levels of markers of BBB disruption, and specifically of c-Fn, are found to be associated with malignant MCA infarction, and the high sensitivity provided by this marker, with a PPV value of 100%, suggests that it may be useful in clinical practice in indicating hemicraniectomy.

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