Plasma Metalloproteinase-9 Concentration Predicts Hemorrhagic Transformation in Acute Ischemic Stroke

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Background and Purpose—Matrix metalloproteinase-9 (MMP-9) activity has been associated with hemorrhagic transformation (HT) in experimental models of cerebral ischemia. Our aim was to investigate the relationship between MMP-9 concentrations in blood within 24 hours of stroke onset and subsequent HT of cerebral infarction.

Methods—We studied 250 patients with a hemispheric ischemic stroke of 7.8±4.5 hours’ duration. Early CT signs of cerebral infarction were evaluated on admission. The HT and infarct volume were analyzed from the CT performed on days 4 through 7. MMP-9 levels were determined by enzyme-linked immunosorbent assay in blood samples obtained on admission.

Results—HT was observed in 38 patients (15.2%); 24 (63.2%) had a hemorrhagic infarction, and 14 (36.8%) had a parenchymal hematoma. A total of 108 patients (43%) received anticoagulants before the second CT scan. Systolic and diastolic blood pressures, body temperature, frequency of early CT signs of ischemia (92% versus 22%), and treatment with anticoagulants (79% versus 37%) were significantly higher in the group with HT (P<0.001). Mean infarct volume was 126±60 cm³ in the HT group and 90±68 cm³ in the group without HT (P=0.003). Median (quartiles) plasma MMP-9 concentrations were higher in the HT group (193 [163, 213] versus 62 [40, 93] ng/mL, P<0.001), even in the 24 patients seen within 3 hours of symptom onset (P=0.014). MMP-9 levels ≥140 ng/mL had a positive and negative predictive value of HT of 61% and 97%, respectively. MMP-9 ≥140 ng/mL was associated with HT (odds ratio, 12; 95% confidence interval, 3 to 51; P<0.001) after adjustment for potential confounders and final infarct volume.

Conclusions—High plasma MMP-9 concentration in the acute phase of a cerebral infarct is an independent biochemical predictor of HT in all stroke subtypes. (Stroke. 2003;34:40-46.)

Key Words: metalloproteinases ■ stroke, acute ■ stroke, hemorrhagic ■ thrombolytic therapy

The risk of hemorrhagic transformation (HT) after cerebral ischemia is of great concern to the clinician. Although it may develop as part of the natural evolution of ischemic brain injury,1 HT frequently occurs as a result of the use of anticoagulants or thrombolytic therapy in the acute phase of stroke.2,3 Factors such as the severity of stroke,4 hypertension,5 age,4 the dosage of the thrombolytic agent administered,5–7 and the presence of early ischemic changes on cranial CT on admission4 have been related to HT after the ischemic event. However, the underlying mechanisms mediating the occurrence of the HT of an ischemic area are not completely understood.

The loss of integrity of the endothelial basal lamina seems to be the primary cause of hemorrhage after focal cerebral ischemia.8 Matrix metalloproteinases (MMPs), a group of proteolytic zinc-dependent enzymes whose expression has been shown to be significantly increased during stroke in humans9–11 and in experimental models of focal ische-

See Editorial Comment, page 45

mia,12–16 are able to degrade the endothelial basal lamina.17 In fact, it has been demonstrated that MMP-9 contributes to edema and hemorrhage after disruption of the basal lamina in an experimental model using bacterial collagenase,18 and a significant increase in MMP-9 levels has also been reported in nonhuman primates with HT of the brain infarction.12 Moreover, administration of an MMP inhibitor in rats significantly reduces the incidence19 and severity20 of tissue plasminogen activator (TPA)–induced hemorrhage after thromboembolic stroke without altering the rate of hemorrhage in the absence of TPA administration.19 This finding might suggest that increased expression of MMPs in cerebral ischemia may account, at least in part, for the increased rate of hemorrhagic events associated with the administration of TPA as a therapy in stroke patients.

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Montaner et al. have recently demonstrated an association between serum MMP-9 expression and late hemorrhagic infarction after human cardioembolic stroke. Given that thrombolysis has proved to be effective in the treatment of all stroke subtypes, our aim in the present study was to investigate the potential association between plasma MMP-9 concentrations and the subsequent HT of cerebral infarct in a large series of patients with all subtypes of acute ischemic stroke, particularly in those patients seen within 3 hours of symptom onset, given the time frame for TPA infusion.

Subjects and Methods
Between March 1999 and February 2000, we prospectively studied 250 patients with a first episode of hemispheric ischemic stroke admitted within the first 24 hours of symptom onset to the stroke unit of a university hospital. A control group of 34 healthy subjects (male, 56%; mean age, 59±13 years) without neurological disorders or inflammatory diseases was also studied. All patients had a persistent focal neurological deficit and an absence of cerebral hemorrhage on the cranial CT performed before inclusion. Patients with inflammatory or infectious diseases, cancer, hematological diseases, and severe renal and liver failure and those who were previously dependent were excluded. The study was approved by the ethics committee, and informed consent was obtained from the patients or their relatives. The time from symptom onset to neurological attention (inclusion delay) was 7.8±4.5 hours (range, 1 to 23 hours). Medical history and stroke risk factors were recorded for all patients. Clinical examination, blood and coagulation tests, 12-lead ECG, chest radiography, and cranial CT were carried out on admission. Stroke subtype was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. Stroke severity was quantified by an experienced neurologist using the Canadian Stroke Scale (CSS) on admission and at 72 hours. Early neurological deterioration was defined as a drop of ≥1 points in the CSS score between the 2 evaluations. After admission to the stroke unit, only patients who had a systolic blood pressure ≥220 mm Hg or a diastolic blood pressure ≥120 mm Hg received antihypertensive treatment. Subcutaneous low-dose heparin was given as prophylaxis against pulmonary thromboembolism, and antiplatelet drugs (aspirin or clopidogrel) were prescribed during hospitalization in atherosclerotic and lacunar infarctions. Intravenous heparin was administered only to patients with a major cardioembolic source and when cranial CT and clinical examination excluded a large cerebral infarction. The activated partial thromboplastin time was maintained below 2.0 times the control value. No patients received thrombolytic therapy.

Early CT signs of infarction, which included 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 and/or shifting of the structures of the median line, were evaluated in the first radiological examination. To measure the infarct volume and to evaluate the presence of HT, a second cranial CT was performed between days 4 and 7 of hospitalization or earlier in the case of neurological deterioration. Infarct volume was determined by the formula 0.5×a×b×c, where a and b are the largest perpendicular diameters measured on CT and c is the slice thickness. The type of HT was classified according to the European Cooperative Acute Stroke Study (ECASS)-II criteria. Hemorrhagic infarction type 1 (HI-1) was defined as small petechiae along the margins of the infarct, and HI type 2 (HI-2) was defined as more confluent petechiae within the infarcted area but without a space-occupying effect. Parenchymal hemorrhage type 1 (PH-1) was defined as hematoma in ≤30% of the infarcted area but with some slight space-occupying effect; PH type 2 (PH-2) was defined as dense hematoma >30% of the infarcted area with substantial space-occupying effect or as any hemorrhagic lesion outside the infarcted area. All CT evaluations were made by the same neuroradiologist (J.M.P.) who was blinded to the clinical and analytical results. For the purpose of this investigation, we considered symptomatic HT those associated with early neurological deterioration.

Laboratory Tests
Blood samples were collected on admission to the Emergency Department in glass test tubes containing potassium edetate. Suspensions of plasma were centrifuged at 3000 rpm for 5 minutes and immediately frozen and stored at −80°C. Plasma MMP-9 was measured with commercially available quantitative sandwich enzyme-linked immunosorbent assay kits obtained from Biotrack, Amersham Pharmacia UK. MMP-9 determinations were performed by researchers blinded to clinical and radiological data.

Statistical Analysis
Proportions between groups were compared by use of the χ² test. Continuous variables are expressed as mean±SD and were compared by use of Student’s t test. Given that MMP-9 levels were not normally distributed, they were expressed as median (quartiles) and compared between the 2 groups by the Mann-Whitney test. Spearman’s correlation coefficient was used to analyze the association between MMP-9 concentration and baseline continuous variables, including age, time from onset to inclusion, CSS score, systolic and diastolic blood pressures, and body temperature. We used cutoff values, as described by Robert et al., to estimate the sensitivity, specificity, and predictive values of a specific concentration of plasma MMP-9 for HT. Logistic regression analysis was used to determine the importance of MMP-9 for HT after adjustment for those variables related to HT in the univariate analysis. To test whether the odds of HT for MMP-9 were substantially modified by the stroke subtype effect, we performed 2 different logistic models: Model A was not adjusted for stroke subtype, whereas model B included the selected variables in model A plus the stroke subtype. MMP-9 was included as a categorical variable because the cutoff value meant that there was a lack of linearity of the odds ratios (OR; 1=high, 0=low).

Results
Thirty-eight (15.2%) of the 250 patients included in the study showed HT on the second cranial CT. Eight patients (21.1%) had HI-1, 16 (42.1%) had HI-2, 12 (31.6%) had PH-1, and 2 (5.3%) had PH-2. Table 1 shows the main characteristics of patients with and without HT. Cardioembolic stroke and treatment with anticoagulants were significantly more frequent, and systolic and diastolic blood pressures and body temperature were significantly higher in patients with HT. Early CT signs of cerebral infarction were more frequent in the group with secondary bleeding, and these patients showed larger infarct volumes than those without HT. Neurological deterioration was observed in 41% of patients with HT and in 22% of those without (P=0.013). Fifty-seven percent of PH were symptomatic compared with 33% of HI (P=0.18). Systolic and diastolic blood pressures on admission showed a trend to be higher in PH than in HI (P<0.01), whereas anticoagulant treatment and early signs on CT were not different between the 2 types of HT (data not shown).

Plasma MMP-9 concentrations on admission were significantly higher in patients with subsequent HT (193 [163, 213] ng/mL) than in those without HT (62 [40, 93] ng/mL) and in the control group (56 [39, 79] ng/mL; P<0.001). This effect was found for each stroke subtype (Table 2). Among the 24 patients (9.6%) who arrived at the hospital within the first 3 hours from symptom onset, MMP-9 concentrations on admission were also significantly higher in patients with HT than in those without HT (P=0.028) (Figure 1). We did not find
significant differences in MMP-9 levels between each subtype of HT (Figure 2) or between symptomatic and asymptomatic HT (186 [165, 206] versus 204 [156, 215] ng/mL; \( P = 0.23 \)). The sensitivity, specificity, positive predictive value, and negative predictive value of plasma MMP-9 levels of \( 140 \) ng/mL for HT were 87%, 90%, 61%, and 97%, respectively.

A highly significant correlation was found between plasma MMP-9 levels and systolic and diastolic blood pressures on admission (\( r = 0.70 \), \( P < 0.001 \) and \( r = 0.63 \), \( P < 0.001 \), respectively) but not between MMP-9 concentrations and other prognostic variables such as body temperature, serum glucose, and stroke severity (all \( r < 0.05 \)). Early signs of ischemia on cranial CT were associated with high levels of MMP-9 (163 [110, 193] versus 54 [38, 74] ng/mL; \( P < 0.001 \)), but MMP-9 did not correlate with the ultimate infarct volume (\( r = 0.01 \)).

Plasma MMP-9 \( \geq 140 \) ng/mL was significantly associated with subsequent HT in the logistic regression analysis after adjustment for body temperature, systolic and diastolic blood pressures, treatment with anticoagulants, presence of early signs of infarction on cranial CT, and ultimate infarct volume (OR, 12; 95% CI, 3 to 51; \( P < 0.001 \)). Further adjustment for stroke subtype (cardioembolic or cryptogenic versus atherothrombotic or lacunar) did not substantially change the OR.
for plasma MMP-9 $\geq$140 ng/mL (OR, 16; 95% CI, 3 to 79; $P<0.001$; Table 3).

**Discussion**

Although thrombolytic treatment has proved to be the only effective therapy in acute ischemic stroke, the risk of cerebral hemorrhage often precludes its use in clinical practice. Therefore, it is extremely important to find early specific markers heralding HT in cerebral infarction. The present study has shown a significant association between high levels of MMP-9 in blood within 24 hours from stroke onset and subsequent HT in a large and nonselected series of patients. MMP-9 $<140$ ng/mL had a 97% negative predictive value, so this cut point might be used in clinical practice as an indicator of a low risk of secondary bleeding. Our findings also confirm the previously reported association between MMP-9 expression and HT in a small series of patients with cardioembolic stroke but extend this effect to those with large-artery atherosclerosis and cryptogenic stroke. Interestingly, the odds of HT for MMP-9 in the logistic model were even higher after adjustment for stroke subtype.

The role of MMP-9 in HT may be linked to its actions on microvascular integrity. It has been shown that the antigens of the basal lamina components such as laminin, collagen IV, and fibronectin disappear during experimental focal cerebral ischemia, and this effect has been associated with cerebral bleeding after middle cerebral artery occlusion in nonhuman primates. The activation of MMPs appears to play a primary role in basal lamina degradation and secondary HT of the ischemic area. Rosenberg et al reported that the intracerebral injection of MMP-2 provokes the disruption of the endothelial basal lamina and secondary necrosis and hemorrhage of the brain region that, in turn, are reduced by the administration of an MMP-2 inhibitor. Expression of MMP-9 but not MMP-2 occurs very early in the ischemic basal ganglia of nonhuman primates displaying HT. In rat stroke models, MMP-9 activity increases by 6 to 24 hours after cerebral ischemia, whereas MMP-2 activity increases by 5 days after the ischemic event. Clinical data have also demonstrated an association between MMP-9 in blood and HT but failed to obtain any association between MMP-2 and secondary bleeding. From these findings and the temporal profile of release of MMP-9 and MMP-2, we decided to analyze only plasma MMP-9 concentrations.

MMP-9 values in our patients did not discriminate between HI and PH, because we found similar levels in both types of HT (see Figure 2). Therefore, we hypothesize that other factors such as anticoagulant or thrombolytic treatment and high systolic blood pressure might contribute to the severity of the HT after basal lamina disruption. Interestingly, we found a highly significant correlation between MMP-9 concentrations and systolic blood pressure on admission. Hyper tension might lead to blood extravasation as a result of abrupt reperfusion, resulting in the enhanced generation of free radicals that damage the microvasculature, or simply as a result of the higher pressure of blood passing through microvessels debilitated by the ischemic process. This fact might be particularly important in patients treated with TPA, because it has recently been shown in an experimental model of thromboembolic stroke in rats that TPA-induced hemorrhage depends on blood pressure and that the risk of HT is reduced by pharmacologically decreasing hypertension during fibrinolysis. Hypertension, like other vascular risk factors related to atherosclerosis, is responsible for chronic endothelial activation secondary to a high level of inflammatory molecules that may attack the microvasculature, making the vessels much more vulnerable to the proteolytic action of MMPs. Moreover, a close relationship between the release of MMPs and cytokines, especially tumor necrosis factor-α, has been demonstrated, so the high correlation between systolic blood pressure and MMP-9 levels might reflect the interaction between inflammatory and proteolytic mechanisms, together leading to the HT of the ischemic area.

Although not supported by angiographic studies, recanalization of the occluded vessel and secondary reperfusion after embolic stroke have classically been accepted as the mechanisms responsible for HT. Other authors have suggested that HT might also occur through reperfusion via pial collaterals initially occluded by the pressure secondary to edema and reopened when the edema decreases. In agreement with this hypothesis, we have observed a significant relationship between the presence of early signs of cerebral ischemia on CT, which likely reflects cytotoxic and vasogenic edema, and HT. The strong association between MMP-9 and early signs
of ischemia but not between MMP-9 and the ultimate infarct volume suggests that increased MMP-9 is not an epiphenomenon of larger cerebral infarcts and that it may be responsible mainly for vasogenic edema. The lack of collateral circulation could also explain the lack of HT for small-vessel disease infarctions located in terminal areas of vascularization.

Because this study was conducted before the lack of data on the indication of anticoagulant treatment was pointed out, and in agreement with its extensive use in clinical routine for cardioembolic stroke, arterial dissections, intracranial stenosis, etc, a large number of patients in this study received intravenous heparin in the acute phase of stroke. Moreover, data from Adams et al were based mainly on the results of clinical trials with low-molecular-weight heparin and heparinoids published after 1999. Anticoagulant therapy was an independent predictor of subsequent HT, although this effect disappeared after adjustment for the stroke mechanism. In this study, we did not find an association between anticoagulants and PH or symptomatic HT, so a potential interaction of these drugs with MMP-9 on the severity of HT was unlikely. Anticoagulants were administered after the blood samples for MMP-9 determination were drawn, so we can reasonably exclude a drug effect on MMP-9 levels.

The present study has some limitations. First, we included 24 patients within 3 hours from symptom onset, but only 2 of them subsequently developed HT. These numbers are too small to conclude that MMP-9 is a good predictor for HT within this time frame. Second, although the effect of MMP-9 on HT was independent of other well-known risk factors for secondary bleeding, we cannot completely rule out an increase of plasma MMP-9 levels as a result of the acute-phase reaction or prior systemic causes. However, we hypothesize that high plasma MMP-9 concentrations were related to HT, because increased MMP-9 levels were detected on admission in patients who subsequently developed HT in whom initial stroke severity and final infarct volume were similar to those without HT. Therefore, we cannot attribute plasma MMP-9 increases to the extent of brain damage or to tissue destruction after HT. Although the origin of MMP-9 in plasma is difficult to assess, neutrophils and macrophages arriving at the ischemic area during reperfusion might release MMP-9, resulting in the degradation of the basement membranes and in high plasma concentrations of these molecules. On the other hand, because the generation of thrombin during hemorrhage may stimulate MMP release from myointimal smooth muscle cells, the increase of MMP-9 in patients with HT could be, at least in part, the consequence and not the cause of secondary bleeding after stroke. However, because MMP-9 concentrations were determined in blood samples taken on admission before HT appeared on CT scans, we can reasonably exclude high MMP-9 levels secondary to intracerebral bleeding. A further point of interest is that in contrast with a previous study, MMP-9 concentrations in patients without HT were similar to those in the control group, a fact that might indicate no or a minor pathophysiological role of MMP-9 in the early acute phase of cerebral ischemia. Prolonged arterial occlusions or a genetic susceptibility to overexpress MMP-9 in response to ischemia could explain increased concentrations in patients with secondary bleeding.

In conclusion, we have demonstrated that high plasma levels of MMP-9 are independently associated with HT in acute ischemic stroke. Importantly, MMP-9 <140 ng/dL had a very high negative predictive value for HT. Further studies are needed to clarify whether MMP-9 assessed within 3 hours from stroke onset may predict HT in patients treated with TPA. If this is confirmed, MMP-9 determination could be used in routine clinical practice to improve the risk-to-benefit ratio of thrombolytic treatment.

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Robust experimental data from various groups indicate that matrix metalloproteinases (MMPs) are highly relevant in the development of both blood-brain barrier damage and microvascular damage, which lead to subsequent brain edema and secondary hemorrhagic complications. More clinical evidence is needed to link these experimental findings with the clinical reality of our stroke patients.

Thanks to newly published work, the current gap between experimental and clinical data on the role of MMPs is slowly closing. Castellanos and colleagues found that the high MMP-9 concentrations in the acute phase of stroke in 250 patients were an independent predictor of subsequent hemorrhagic complications. Any bias resulting from patient selection was reduced by the large number of patients in their study. The authors have presented strong proof that enzyme-linked immunosorbent assay–measured MMP-9 levels exceeding 140 ng/mL in the peripheral blood on admission are predictive of a later hemorrhagic complication with an odds ratio of 12 (95% CI, 3 to 51).

Their findings, nevertheless, raise other questions. First, what is the time course of the MMPs? It is rather surprising that the initial, single measurement of MMP values proved significant for later hemorrhages. Secondary elevations in the later time course of the MMPs would logically seem more important. Because patients with hemorrhagic complications had a higher mean infarct volume than the stroke group without any bleedings, could the elevated MMP level be the result of a more severe disease that causes larger infarction? Does an elevation of the MMPs cause hemorrhagic complications, or is it the initial ischaemic stroke? Yes.

Unriddling the Role of Matrix Metalloproteinases in Human Cerebral Stroke

Castellanos et al Plasma MMP-9 and Hemorrhagic Transformation 45


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both hemorrhage and MMP elevation? Are the MMP levels in the authors’ patient population with acute ischemic stroke comparable to those seen in patients with myocardial infarction, intracerebral hemorrhage, or head trauma? Finally, is the relation between MMP-9 and hemorrhagic findings unique to ischemic stroke, or is this pathophysiological pattern also relevant for various brain diseases?

The experimental groundwork for the authors’ clinical findings has been well prepared. Other groups have shown that substantial damage of the microvascular basal lamina occurs in rats and nonhuman primates after transient cerebral ischemia and reperfusion. Secondary hemorrhagic complications are due to these losses of microvascular basal lamina. The implications of such findings are relevant not only for elucidating the proteolytic changes after ischemia but also for devising strategies to prevent edema or hemorrhage.

While providing a substructure for endothelial cells and astrocytes, the basal lamina constitutes the second element of the blood-brain barrier in addition to the well-known interendothelial cell tight junctions. Intact microvascular basal lamina and integrin-mediated matrix adhesion are required for cell survival. Once they are dissolved, hemorrhage can occur. During experimental focal cerebral ischemia, important changes in the microvascular basal lamina may also involve the plasmin system, the MMP system, and leukocyte activation. MMPs, especially MMP-2 and MMP-9, may also play an important role in the blood-brain barrier function and extracellular matrix remodeling after stroke. In a permanent middle cerebral artery occlusion model in the rat, MMP-2 and MMP-9 were shown to increase in neutrophils, endothelial cells, and macrophages. Activated MMP-9 (88 kDa) appeared as early as 3 hours after 60 minutes of transient focal cerebral ischemia. Pro-MMP9 (92 kDa) was significantly increased in endothelial cells in a time-dependent manner during reperfusion. A constitutive expression of pro-MMP-9 in the control specimens was evident. Activated MMP-9 further increased 23 hours after reperfusion. Pro–MMP-9 was shown to be significantly elevated 48 hours after 2 hours of middle cerebral artery occlusion; however, the activated form of MMP-9 was not detected.

On the one hand, systemic administration of neutralizing antibodies to MMP-9 appeared to reduce brain injury after middle cerebral artery occlusion, suggesting that MMP-9 is involved in neuronal damage after stroke. Also, the administration of BB-94, an MMP inhibitor, before recombinant tissue plasminogen activator produced a trend to reduced infarct rates and bleeding events. Newer data also showed that MMP-9 is involved in neuronal cell death cascades. Therefore, larger infarct volume in patients with higher MMP-9 levels can also be seen as a result of this proteolytic activation. On the other hand, a recent review draws attention to the Janus-faced nature of MMPs: They have potentially beneficial (eg, mediation of parenchymal and vascular recovery) as well as deleterious effects.

Despite the above-mentioned questions, the study of Castellanos and coworkers goes further than previous studies based on small patient groups. The authors have laid the groundwork for a better understanding of the role of proteolytic mechanisms in acute human stroke. Although their data would be expected in an experimental setting, the authors have finally provided sound clinical evidence for the important role of MMPs. Unfortunately, a marker for the risk of hemorrhage in thrombolysis still eludes us.

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