Research Article

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Association of matrix metalloproteinase-3 with lesion localization and size in acute ischemic stroke

Ayşegül Özyılmaz[1], Füsun Mayda Domaç[2], Cemile Handan Mısırlı[3], Duygu Özkan[3]

[1]Clinic of Neurology, Düzce Atatürk State Hospital, Düzce, Turkey
[2]Clinic of Neurology, Health Sciences University, Erenköy Mental and Neurological Diseases Training and Research Hospital, İstanbul, Turkey
[3]Clinic of Neurology, Health Sciences University, Haydarpaşa Numune Training and Research Hospital, İstanbul, Turkey

Abstract

Objective: The importance of molecular markers as predictors of stroke risk and ischemic damage has been increasing. Various studies suggested the association of matrix metalloproteinases with destruction of the blood brain barrier, vasogenic edema, and tissue damage in cerebral ischemia. We aimed to investigate the role of matrix metalloproteinase-3 (MMP-3) in ischemic stroke and its association with the size and localization of the infarct.

Methods: The study included 30 consecutive patients who were admitted to Haydarpaşa Numune Training and Research Hospital, Istanbul, Turkey, with ischemic stroke within the 24 hours from stroke onset and 27 control subjects. In the patient group, blood samples for MMP-3 were determined at 3 different time points (within the first 24 h, between 48 to 72 h, and on the 7th day) using an enzyme-linked immunosorbent assay. Infarct size was measured using magnetic resonance imaging at 48-72 h. Statistical analyses of the data were performed using the SPSS 16.00 software package.

Results: Plasma MMP-3 levels were significantly higher than the control group at all three time points ($p<0.001$ for all). No difference was found for MMP-3 regarding age, sex, or any vascular risk factor ($p>0.05$) and there was no significant correlation between MMP-3 and other laboratory parameters ($r>0.05$). No significant correlation was found between the lesion size and localization with serial measurements of serum MMP-3 levels ($p>0.05$).

Conclusion: Elevation of plasma MMP-3 seems to be a useful marker for acute ischemic stroke independent of risk factors, infarct size, and localization.

Keywords: Matrix metalloproteinase-3, ischemic stroke, infarct size

INTRODUCTION

Ischemic stroke is a heterogeneous condition in which different mechanisms are involved in the pathogenesis. Cerebral ischemia triggers the pathologic pathways of the ischemic cascade and causes irreversible neuronal injury in the ischemic core within minutes of the onset (1, 2). Matrix metalloproteinases (MMPs) were shown to be increased during the acute phase of ischemic stroke (3, 4). As is known, cerebral ischemia and reperfusion induce an inflammatory response, which is initiated in the microcirculation and leads to neuronal destruction (5, 6). In cerebral ischemia MMPs can degrade the laminin, collagen and fibronectin of the extracellular matrix, through which the structural integrity of the extracellular matrix is lost (4, 7). MMP-3 was also found to play a role in neuronal degeneration by promoting glial activation and neuronal apoptosis (8). MMPs contribute to tissue damage by destruction of the blood brain barrier, leading to vasogenic edema and also hemorrhagic transformation of infarction (9, 10). The initial damage in the blood brain barrier was demonstrated to be transient, and gross damage becomes evident in the following 24 to 48 h by expression and activation of MMP-3 and MMP-9 (11).

In our study, we investigated whether the MMP-3 serum levels of patients with acute cerebral ischemia differed over time and whether there was an association between serial measurements of MMP-3 levels with lesion size and localization.

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Corresponding Author: Füsun Mayda Domaç **E-mail:** fusundomac@yahoo.com.tr **Submitted:** 14 September 2017 **Accepted:** 30 January 2018

METHODS

Thirty consecutive patients with acute ischemic stroke who were admitted to Haydarpaşa Numune Training and Research Hospital within 24 hours after the initiation of symptoms and from whom serial measurements of MMP-3 were available were included in this study. The diagnosis of stroke was made using the criteria of the World Health Organization. Etiology was sub-typed according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) system. Patients with intracerebral or subarachnoid hemorrhage, transient ischemic attack, history of any infection within the last 2 weeks an acquired an infection after admission, autoimmune and inflammatory disorders or use of immunosuppressive drugs, malignancy, newly acquired heart disease, rheumatic, hepatic, renal or vasculitic disease were excluded. The age-matched control group was chosen from healthy subjects who met the inclusion and exclusion criteria. All patients or their caregivers signed informed consent and the study was approved by the local ethics committee.

All patients were examined by a neurologist, and routine biochemical and hematologic tests, cranial tomography imaging and cranial magnetic resonance (MRI) at admission and on the 7th day, electrocardiography, echocardiography, and high-resolution B-mode Doppler ultrasonography of the carotid and vertebral arteries were applied.

All patients received subcutaneous low-molecular-weight heparin as prophylaxis for deep venous thrombosis. Neither intravenous heparin nor tissue plasminogen activator was administered during the study period.

Venous blood samples for MMP-3 measurement were taken from the patients at three time points, within 24 h, at 48-72 h, and on the 7th day; blood samples were taken only once from the control group. Samples were collected in Vacuette gel tubes with clot activator. After 15 minutes, they were centrifuged for 15 minutes at 4000 rpm and stored at -80°C until required for analysis. Samples with lipidemia or hemolysis were excluded. MMP-3 levels were studied using anenzyme-linked immunosorbent assay (ELISA) (Human MMP-3 Elisa Kits; Ray-Biotech, Norcross-GA, USA). Plasma MMP-3 levels were determined by a biochemistry doctor blinded to clinical and radiologic data.

Based on the diagnostic tests, patients were grouped as: 1) cardioembolic, 2) large artery disease, and 3) small artery disease,depending on the etiology. Any association between plasma MMP-3 levels and age, sex, vascular risk factors, other laboratory parameters, and etiology was investigated.

Infarct volume was measured using MRI at 48-72 h. Based on imaging results, infarcts ≥5 cm^3 were grouped as large infarcts and infarcts <5 cm^3 were grouped as small infarcts (12). Infarct locations were grouped according to arterial locations as middle cerebral artery (MCA), posterior cerebral artery (PCA), basilar artery (BA), and middle cerebral artery-anterior cerebral artery borderzone (MCA-ACA), and also as cortical, subcortical, cortical+subcortical regions. The correlation between plasma MMP-3 levels and infarct volume and location was investigated.

Statistical Analysis

The Statistical Package for the Social Sciences statistical package, (SPSS Inc.; version 16.0, Chicago, IL, USA) was used to perform descriptive and frequency statistical analyses and comparisons. Statistical significance for intergroup differences was assessed using the Chi-square(χ^2) or Fisher's exact test for categorical variables and the *t*-test and ANOVA for continuous variables (a post hoc analysis was conducted by means of Tukey's test). MMP-3 values were normally distributed (Kolmogorov-Smirnov and P-P plot). A *t*-test was performed for paired data using Bonferroni correction for multiple comparisons to compare MMP levels for the different time points. The correlation between MMPs and other continuous variables was assessed using Pearson's test. P<0.05 was considered statistically significant.

RESULTS

Although 55 patients were recruited to the study initially, 25 patients were excluded because they did not meet the inclusion criteria. There were 20 (66.7%) male and 10 (33.3%) female patients (mean age, 60.6±12.4 years) in the patient group and 17 (62.9%) male and 10 (37.1%) female subjects in the control group with a mean age of 58.6±9.1 years. The demographic features and laboratory findings of the patient group are shown in Table 1.

The mean plasma MMP-3 levels at 24 h, 48-72 h, and day 7 time points in the patient group were 16.02±9.94 ng/mL, 16.46±9.69 ng/mL, and 15.65±10.2 ng/mL, respectively. The mean plasma

Table 1. Laboratory parameters of patient group

	Mean±SD
Blood glucose level, (mg/dL)	117.46±57.63
WBC (k/uL)	5858.21±3430.45
Hct, (%)	38.93±3.8
Hemoglobin, (g/dL)	13.42±1.44
Sedimentation, (h)	11.77±6.01
C-reactive protein, (mg/dL)	0.54±0.2
High density lipoprotein, (mg/dL)	42.86±9.88
Total cholesterol, (mg/dL)	185.3±40.35
Triglyseride, (mg/dL)	141.43±72.92
Low density lipoprotein, (mg/dL)	123.13±40.1
HbA1c, (%)	6.7±1.29

SD: standard deviation; WBC: white blood cell; Hct: hematocrit

Table 2. Comparison of mean matrix metalloproteinase-3 (MMP-3) levels based on arterial localization

MMP-3 (ng/mL)	MCA	PCA	BA	MCA-ACA
24 h	12.77±8.53	20.95±17.04	21.22±10.40	17.30±10.19
48-72 h	15.93±10.25	27.55±9.25	15.41±8.63	14.89±9.18
7th day	12.55±7.03	18.73±19.04	20.43±13.09	18.41±12.74

MCA: middle cerebral artery; PCA: posterior cerebral artery; BA: basilary artery; MCA-ACA: middle cerebral artery and anterior cerebral artery border zone infarction; MMP: matrix metalloproteinase

Table 3. Comparison of mean matrix metalloproteinase-3 (MMP-3) levels due to cortical, subcortical, cortical+subcortical infarctlocalization

MMP-3 (ng/mL)	Cortical	Subcortical	Cortical+Subcortical	p
24 h	14.33±7.48	17.57±10.87	14.87±10.48	0.737
48-72 h	16.23±10.42	16.38±9.76	16.71±10.22	0.995
7th day	17.31±8.97	18.44±11.37	11.74±8.27	0.179

MMP: matrix metalloproteinase

Table 4. Comparison of mean matrix metalloproteinase-3 (MMP-3) levels with NIHHS scores

	MMP-3^{24h} p	MMP-3$^{48\text{-}72\ h}$ p	MMP-3$^{7th\ day}$ p
$NIHSS_1$ (admission)	0.456	0.281	0.804
$NIHSS_2$ (7th day)	0.456	0.281	0.804

MMP: matrix metalloproteinase; NIHSS: National Institute of Health Stroke Scale

Table 5. Comparison of matrix metalloproteinase-3 (MMP-3) levels due to infarct size

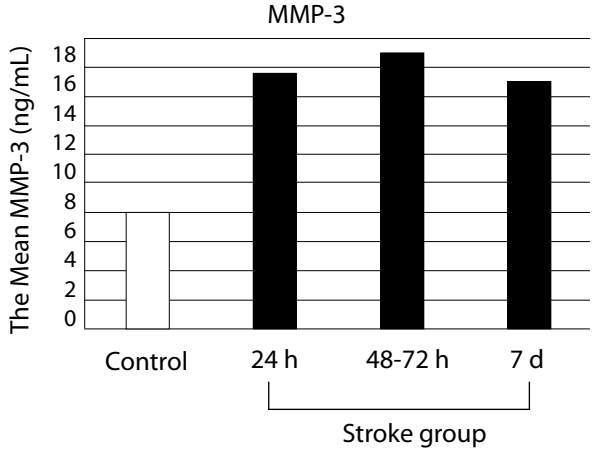
MMP-3 (ng/mL)	Large	Small	p
24 h	14.98±9.89	16.72±10.20	0.648
48-72 h	18.53±10.54	15.08±9.13	0.365
7th day	13.18±9.84	17.29±10.51	0.285

MMP: matrix metalloproteinase

MMP-3 level was 6.55±2.02 ng/mL in the control group. When compared with the control group, MMP-3 levels in the patient group were significantly higher at 24 h (p<0.001), 48-72 h (p<0.001), and the day 7 time points (Figure 1). No difference was found for MMP-3 regarding age, sex or any vascular risk factors (p>0.05) and there was no significant correlation between MMP-3 and other laboratory parameters (p>0.05).

Based on arterial localization, 15 (50%) patients had MCA infarcts, 8 (27%) had BA, 4 (13%) had PCA, and 3 (10%) had MCA-ACA borderz one infarcts. MMP-3 levels at 24 h and 48-72 h were higher in the PCA group compared with other arterial groups, but the difference was not statistically significant (p>0.05) (Table 2). Based on the cortical, subcortical, and cortical subcortical regions, 6 (20%) patients had cortical, 14 (46.7%) had subcortical,and 10 (33.3%) had cortical+subcortical infarcts. MMP-3 levelson the 7th day in the cortical-subcortical infarct group were lower than in the other groups, but the difference was not statistically significant (p>0.05) (Table 3).

Figure 1. Comparison of serum matrix metalloproteinase-3 levels between patient and control groups



The median National Institute of Health Stroke Scale (NIHSS) score evaluated at admission was 5.37±2.52, and 2.86±2.60 on the 7th day. There was no correlation between the admission and 7th day NIHSS scores and MMP-3 levels at any time point (Table 4).

Regarding infarct volume, 12 patients had large infarcts and 18 patients had small infarcts (Table 5). The etiology was

cardioembolic in 10 patients, large artery disease in 10 patients, and small artery disease in 10 patients. No significant difference was found for MMP-3 levels according to etiology ($p>0.05$). No correlation existed for MMP-3 levels and infarct volume at any time points.

DISCUSSION

MMP-3, known also as stromelysin-1 expression, in the adult brain is generally low and undetectable. However, when tissue damage occurs, neurons, astrocytes, oligodendrocytes, microglia cells and endothelial cells express MMPs in response to damage and the levels of MMPs increase (13). In an experimental study, the main source of MMP-3 was found to be a new population astrocytes at the 3rd day after stroke and proliferating pericytes in the peri-infarct areas at the 3rd week (14). Sole et al. observed MMP-3 immunoreactivity in oligodendrocytes of white matter on post-ischemic day 4 and in microglia/macrophages of the infarct site between 4 and 7 days. They also reported that MMP-3 expression was dense in ischemic neurons in accordance with infarct progression (15). The production of MMPs may also be influenced by genetic polymorphisms. The MMP-3-1612 5A/6A polymorphism was shown to be a risk factor for stroke and the MMP-3 gene to be effective in the development of ischemic stroke (16, 17). Jickling et al. (18) suggested that microRNA-19a regulated MMP-3, which has an angiogenic role in vascular remodeling after stroke-induced BBB destruction.

MMPs have been implicated in tissue remodeling during tissue repair and morphogenesis and growth. The maintenance of physiologic mechanisms depends on the balance between MMP activity and their specific endogenous tissue inhibitors (TIMP) (19). When MMP production exceeds TIMP production and the balance changes in favor of MMP activity, control of matrix degradation is lost and pathophysiologic events occur (19, 20). The disruption of balance between MMP-3 and TIMP and also genetic factors that predispose to reduced matrix remodeling (stromelysin 6A allele) increase the susceptibility for intima-media thickening in the carotid artery and for atherosclerosis (21, 22). The MMP-3 gene was found in rupture-prone regions of plaque and their adjacent tissues (23). Lien et al. reported that blood levels of active MMP-3 were associated with the extent of carotid atherosclerosis based on plaque formation but not intima-media thickness (24). The MMP-3-1612 6A6A genotype was associated with higher levels of blood-active MMP-3. In another experimental model, acute MI caused an early reduction in MMP-3 levels, and plasma fluctuation in MMP-3 levels were considered for use as an independent predictor of cardiovascular events in patients with stable coronary artery disease (25). The MMP-3 polymorphism was studied in ischemic stroke subtypes and MMP-3 levels were found high both in the acute period of large artery atherosclerosis and in small artery disease (26). In our study, there was no significant association between the stroke subtype and MMP-3 levels.

There were conflicting results with MMP-3 levels in ischemic stroke in various studies (27-29). In an experimental study that investigated the effect of TIMP-3 in focal cerebral ischemia, pro- and active MMP-3 levels were found to be significantly higher in wild-type mice when compared with knock out mice (27). In an animal model of MCA occlusion, MMP levels were measured at 6, 12, and 24 hours, and 5, 15, and 30 days after occlusion. MMP-3 levels showed no significant alterations through the entire follow-up period (9). In another study, mean serum MMP-3 levels collected from consecutive patients with acute stroke were found to be reduced compared with healthy controls and patients with other neurological diseases. The authors suggested that this was due to thromboembolic mechanisms and MMP-3 consumption may be the cause of the low MMP-3 concentrations seen in acute stroke (28). In our study, we found an upregulation of serum MMP-3 levels in patients with acute ischemic stroke at days 1, 3, and 7, suggesting the participation of MMP-3 in acute ischemia.

Increased MMPs after cerebral ischemia may lead to basal laminar destruction around micro vessels and to parenchymal damage, which may be related to infarct size and hemorrhagic transformation (29). In an experimental stroke model, animals treated with MMP inhibitors for 1 week after stroke had larger infarction size than those treated for 2 weeks after stroke, indicating that MMPs might play a pro-ischemic role during the early stages of stroke and a constructive role during the repair phase after stroke (3, 30). Rosell et al. studied MMP-3 levels of patients with middle cerebral artery occlusion and found no correlation between MMP levels and size of hypoperfused regions in MRI within the first 3 hours after stroke (31). In our study, there was no significant difference in the mean MMP-3 levels of large- and small-sized infarct groups, which suggests that MMP-3 levels are independent of the size of the infarcted area.

Adair et al. investigated MMP-2, MMP-9, TIMP-1, and TIMP-2 levels as possible diagnostic markers in the cerebrospinal fluid (CSF) of patients with vascular dementia or Alzheimer's disease (32). They found that cortical and subcortical changes in MRI of patients with multi-infarct cerebral vascular dementia were correlated with CSF MMP-9 levels, whereas MMP levels in Alzheimer's disease remained comparable with the control group (32). Candelario-Jalil et al. found increased MMP-3 activity in vascular cognitive impairment compared with controls and they hypothesized that MMPs were associated with white matter damage, particularly in subcortical ischemic vascular disease (33). We investigated the localization in relation with affected arteries and to cortical, subcortical, and cortical-subcortical regions. MMP-3 levels were lower than in the other groups on day 7 in the cortical-subcortical infarct group, and higher in the PCA group than in other arterial groups at 24 h and 48-72 h time points; however, the differences were not statistically significant, which implies that MMP-3 elevation is also independent from localization.

The prognostic value of MMP levels has also been studied. MMP-2 was not correlated with NIH stroke scale scores in the first 48 hours, whereas MMP-9 was correlated (31). Patients with a NIH stroke scores lower than 8 had lower MMP-9 levels when compared with patients with a score between 8 to 20 or patients who scored higher than 20. Lower MMP-9 levels were related to better neurologic improvement, whereas higher MMP-9 levels were related to poor neurologic outcomes (31). The effect of modest hypothermia on acute ischemic stroke was investigated, and MMP-3 expression was found increased in parallel to poor neurobehavioral outcomes in animals that underwent ischemia/reperfusion. Modest hypothermia suppressed MMP-3 expression and showed beneficial effects on neurological deficit (34). In our study, all patients had a good early prognosis and there was no significant correlation between MMP-3 levels and NIH stroke scores.

The main limitation of the present study is the small size of the study group. The importance of molecular markers as predictors of stroke risk and ischemic damage has been increasing. Although in animal models or postmortem studies, an association between brain damage and MMP overexpression has been suggested, it is not clear whether MMP overexpression contributes to the development of infarct or only represents a marker of brain ischemia (28). Our study also does not elucidate this controversy. We found that MMP-3 levels were elevated during the acute phase and remained high in the early subacute phase of ischemic stroke,independent from lesion size and localization. According to our results, because no difference was found for plasma MMP-3 levels regarding age, sex, vascular risk factors, and stroke subtype, elevation of plasma MMP-3 seems to be a useful marker for acute ischemic stroke and a good tool for further research into this field.

Ethics Committee Approval: Ethics committee approval was received for this study from the Noninvasive Clinical Researcher Ethics Committee of Düzce University School of Medicine (2010/32, 29.07.2010).

Informed Consent: Written informed consent was obtained from patients relatives or patients who participated in this study.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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