
Serum MMP-2 and MMP-9 in patients with Behçet's disease: Do their higher levels correlate to vasculo-Behçet's disease associated with aneurysm formation?

S. Pay¹, T. Abbasov², H. Erdem¹, U. Musabak³, I. Simsek¹, A. Pekel³,
A. Akdogan⁴, A. Sengul², A. Dinc¹

¹Division of Rheumatology, ²Department of Internal Medicine and ³Division of Immunology, Gulhane Military School of Medicine, Ankara; ⁴Division of Rheumatology, Hacettepe University School of Medicine, Ankara, Turkey.

Salih Pay, MD, Associate Professor in Rheumatology; Tarlan Abbasov, MD, Resident in Internal Medicine; Hakan Erdem, MD, Associate Professor in Rheumatology; Ugur Musabak, MD, Associate Professor in Immunology; Ismail Simsek, MD, Specialist in Rheumatology; Aysel Pekel, Biologist in Immunology; Ali Akdogan, MD, Specialist in Rheumatology; Ali Sengul, MD, Professor in Immunology; Ayhan Dinc, MD, Professor in Rheumatology.

Please address correspondence and reprint requests to: Dr. Salih Pay, GATA Romatoloji BD, 06018, Etlik, Ankara, Turkey.

E-mail: salihp@yahoo.com

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ABSTRACT

Objectives. Basic and clinical studies have revealed a strong correlation between matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, and the formation of abdominal aortic aneurysms. In addition, previous studies have clearly shown that MMP-2 and MMP-9 play an important role in the pathogenesis of vasculitis characterized by aneurysm formation such as Kawasaki disease, temporal arteritis and Takayasu arteritis. Depending on those findings, we hypothesized that circulating MMP-2 and MMP-9 could be useful markers to demonstrate vascular aneurysmatic involvement in patients with Behçet's disease (BD).

Methods. Fifty-eight patients with BD, and 20 healthy controls were enrolled in the study. We assessed the disease activity of patients according to the Leeds activity score system. We compared the Leeds activity scores of patients with their serum levels of MMP2 and MMP-9. Patients with BD were categorized as active (total activity score ≥ 5) or inactive (total activity score < 5). Patients were further categorized with respect to their extent of involvement as mucocutaneous or systemic. Patients with systemic involvement were subdivided into ocular or vascular involvement. Patients with vascular involvement were subgrouped as thrombotic or aneurysmatic involvement. The levels of MMP-2 and MMP-9 were measured by ELISA.

Results. Serum MMP-9 but not MMP-2 levels were significantly higher both in patients with active and inactive disease as compared to healthy controls ($p = 0.008$ and 0.013 respectively). We found positive correlation between Leeds activity score and serum MMP-2 levels in patients with vascular involvement ($p = 0.035$ and $r = 0.485$), and

serum MMP-9 levels in active BD patients ($p = 0.003$ and $r = 0.599$). The serum levels of MMP-2 and MMP-9 in patients with systemic involvement were higher than those of healthy controls but not patients with mucocutaneous involvement ($p = 0.046$ and 0.002 respectively). The serum levels of MMP-2 in patients with vascular involvement were found to be higher than those of healthy controls and patients with mucocutaneous involvement ($p = 0.001$ and 0.003 , respectively) but not different in those with ocular involvement. The serum levels of MMP-9 in patients with vascular involvement were found to be higher than those of healthy controls and ocular disease ($p = 0.001$ and 0.033 respectively) but not different in those with mucocutaneous involvement. The serum levels of MMP-2 in patients with aneurysmatic involvement were found to be higher than those of healthy controls, mucocutaneous and ocular involvement ($p = 0.004$, 0.008 and 0.004 respectively). The serum levels of MMP-2 in patients with thrombotic involvement were found to be higher than those of healthy controls and mucocutaneous ($p = 0.018$ and 0.033 respectively) but not ocular involvement. The serum levels of MMP-9 in patients with aneurysmatic involvement were found to be higher than those of healthy controls, mucocutaneous and ocular involvement ($p = 0.001$, 0.048 and 0.007 respectively). The serum levels of MMP-9 in patients with thrombotic involvement were found to be higher than those of healthy controls but not mucocutaneous and ocular involvement ($p = 0.046$).

Conclusions. We concluded that serum MMP-2 and MMP-9 levels can be used as an activity indicator for vasculo-Behçet's or active Behçet's patients, respectively. But they can not be used

Competing interests: none declared.

as a marker reflecting the systemic involvement of patients with BD. The systemic expressions of MMP-2 and MMP-9 were strongly associated with vasculo-Behçet's disease, particularly aneurysmatic involvement, suggesting their pathogenetic roles in vasculo-Behçet's disease complicated with aneurysm formation.

Introduction

Behçet's disease (BD) is a chronic inflammatory multisystem disease of unknown etiology characterized by oral and genital ulcers and by cutaneous, ocular, arthritic, vascular, and neurological involvement. Vasculitis is thought to underlie the clinical manifestations of BD. Vascular involvement of BD affects arteries, veins and blood vessels of all sizes and is called "vasculo-Behçet's disease". Large vessel involvement is observed in about 15-35 % of patients with BD. Vasculo-Behçet's disease may present three major manifestations: venous occlusion, arterial occlusion and aneurysm formation. The venous lesions are more frequent compared to arterial involvement (88 vs. 12%) (1).

As reviewed recently by Calamia *et al.*, the venous involvement of patients with BD may be seen in the form of superficial thrombophlebitis (the most frequent type), deep vein thrombosis (DVT), thrombosis of vena cava (inferior or superior vena cava syndrome), thrombosis of suprahepatic veins (Budd-Chiari syndrome), portal vein thrombosis, cerebral venous thrombosis (superior sagittal or transverse sinus thrombosis), and right ventricular thrombi (2). The arterial occlusions in patients with BD may appear in all arteries including aorta, with their prevalence being about 1.5% (1). Aneurysm formation in patients with BD is the most frequently seen in aorta and pulmonary arteries. However, others such as femoral, popliteal, subclavian, carotid, renal, coronary and inferior mesenteric arteries could also be affected (1-3). Pulmonary arterial aneurysms are one of the life threatening complications of patients with BD with the reported short-term mortality being around 50% (4).

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases which degrade the components of extracellular matrix (ECM) such as collagen, fibronectin and laminin. As reviewed by Corbel *et al.* recently, depending on substrate specificity, amino acid similarity, identifiable sequence modules, the MMP family can be classified into 6 subclasses: collagenases (MMP-1, -8, -13), gelatinases (MMP-2, MMP-9), stromelysins (MMP-3, -10, -11), membrane-type MMPs (MMP-14 to 25), matrilysin (MMP-7) and macrophage metallo-elastase (MMP-12) (5). Because MMP-2 and MMP-9 have a unique elastinolytic activity, they can degrade subendothelial basement membrane (6, 7). Destroyed subendothelial basement membrane may play a crucial role in arterial instability, excessive cell migration and proliferation.

Basic and clinical studies have revealed a strong correlation between MMPs (particularly MMP-2 and MMP-9) and the formation of abdominal aortic aneurysms (8-10). In addition, previous studies have clearly shown that MMP-2 and MMP-9 play an important role in the pathogenesis of vasculitis characterized by aneurysm formation such as Kawasaki disease (11-14), temporal arteritis (15, 16) and Takayasu arteritis (17). Depending on those findings, we hypothesized that circulating MMP-2 and MMP-9 could be useful markers to demonstrate the vascular aneurysmatic involvement in patients with BD. In the present study, we examined the serum concentrations of MMP-2 and MMP-9, and further investigated whether the concentration of MMP-2 and MMP-9 were related to the disease activity and clinical presentations in patients with BD.

Material and methods

Patients

In this study, serum MMP-2 and MMP-9 levels from patients with BD were investigated. Fifty-eight patients with BD, and 20 healthy controls were enrolled in the study. Diagnosis of patients with BD was made using criteria of the International Study Group for Behçet's Disease (18). We evaluated the disease activity of patients according to the Leeds activ-

ity score system (19). We compared the Leeds activity scores of patients with their serum levels of MMP2 and MMP-9. Patients with BD were categorized as active (total activity score ≥ 5) or inactive (total activity score < 5). Patients were further categorized with respect to their extent of involvement as muco-cutaneous or systemic. Patients with systemic involvement were subdivided into ocular or vascular involvement. Patients with vascular involvement were subgrouped as thrombotic or aneurysmatic involvement. Serum samples were obtained from patients for diagnostic purposes at the time of admission to out-patient clinic or the clinic. Informed consent of the patients was obtained, and all procedures were performed in accordance with the principles of the Declaration of Helsinki. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) of patients were studied in the same day of venopuncture. Ten millilitres of venous blood was drawn and centrifuged at 3000 rpm for 30 minutes for the measurement of MMP-2 and MMP-9 levels. The specimens were stored at -70°C until analysis.

Measurements of MMP-2 and MMP-9

The levels of MMP-2 and MMP-9 were measured by MMP-2 and MMP-9 ELISA kit (Calbiochem Inc. San Diego, CA), respectively. Absorbance readings were carried out on an EL_x 800 Universal Microplate Reader (Bio-Tek Instruments, Inc., USA). Concentrations of unknown samples were determined from a curve obtained with the standards.

Statistical analysis

All of the statistical analysis were performed by using SPSS (SPSS 10.0 FW, SPSS Inc., Chicago, USA) statistical package. For the tests of normality, Kolmogorov-Smirnov test were used. For multiple comparisons, Kruskal-Wallis test were used. The differences between two groups were evaluated by Mann-Whitney U test or Chi-Square test. To investigate the relations among the variables, Spearman rank correlation test was performed. *P* values less than or equal to 0.05 were considered as statistically significant.

Results

The demographic features and laboratory parameters of the study and control groups were presented in the Table I. Twenty-three out of 58 patients were considered as having active disease. Although serum MMP-2 levels were not significantly higher both in patients with active and inactive disease as compared to healthy controls (Fig. 1a), serum MMP-9 levels were significantly higher both in patients with active and inactive disease as compared to healthy controls (Fig. 1b).

We found positive correlation between the Leeds activity score and serum MMP-2 levels in patients with vascular involvement (Fig. 2a). Similar correlation was also found between serum MMP-9 levels and active Behçet's patients (Fig. 2b). There is no additional correlation neither between the Leeds activity score and serum MMP-2 or MMP-9 in other clinical situations, nor among other parameters.

Thirty-seven patients had systemic involvement while 21 patients had mucocutaneous involvement. The serum levels of MMP-2 and MMP-9 in patients with systemic involvement were higher than those of healthy controls but not mucocutaneous involvement (Fig. 3a and Fig. 3b, respectively).

Patients with systemic involvement are subgrouped as ocular ($n = 18$) and vascular ($n = 19$) involvement. The serum levels of MMP-2 in patients with vascular involvement were found to be higher than those of healthy controls, while no such difference was found when patients with systemic involvement were compared with patients having mucocutaneous involvement. (Fig. 4a). The serum levels of MMP-9 in patients with vascular involvement were found to be higher than those of healthy controls and patients with ocular disease, but not mucocutaneous involvement (Fig. 4b).

Patients with vascular involvement are grouped as thrombotic ($n = 10$) and aneurysmatic ($n = 9$) involvement. The serum levels of MMP-2 in patients having aneurysmatic involvement were found to be higher than those of healthy controls, mucocutaneous and ocular involvement. The serum levels of MMP-

Table I. Demographic characteristics and laboratory findings of patients with Behçet's disease and healthy controls.

	Number (n)	Age (year)	Leeds activity score	Sex F/M	MMP-2 (ng/ml)	MMP-9 (ng/ml)
Healthy controls ^a	20	22 (16)	-	4/16	4.3 (6)	19 (50)
Inactive cases ^b	35	23 (28)	3 (7)	4/31	6.8 (61)	33 (76)
Active cases ^c	23	21 (44)	6 (13)	4/19	4.3 (47)	31 (77)
Mucocutaneous involvement ^d	21	23 (23)	4 (12)	3/18	3.7 (43)	33 (76)
Systemic involvement ^e	37	22 (44)	3 (11)	5/32	6.4 (61)	32 (72)
Ocular involvement ^f	18	26 (28)	4 (11)	2/16	6.4 (47)	29 (72)
Vascular involvement ^g	19	21 (44)	3 (7)	3/16	11 (60)	38 (55)
-Aneurysmatic involvement ^h	9	21 (44)	3 (6)	1/8	21 (60)	51 (43)
-Thrombotic involvement ⁱ	10	21 (11)	3 (7)	2/8	7.9 (25)	31 (55)

Values are presented as median (range).

F: female, M: male.

*Multiple comparisons were done by using Kruskal-Wallis test.

$p = 0.293$, $p = 0.015$ for MMP-2 and MMP-9 in comparisons of ^{a, b, c}.

$p = 0.072$, $p = 0.011$ for MMP-2 and MMP-9 in comparisons of ^{a, d, e}.

$p = 0.004$, $p = 0.007$ for MMP-2 and MMP-9 in comparisons of ^{a, d, f, g}.

$p = 0.007$, $p = 0.007$ for MMP-2 and MMP-9 in comparisons of ^{a, d, f, h, i}.

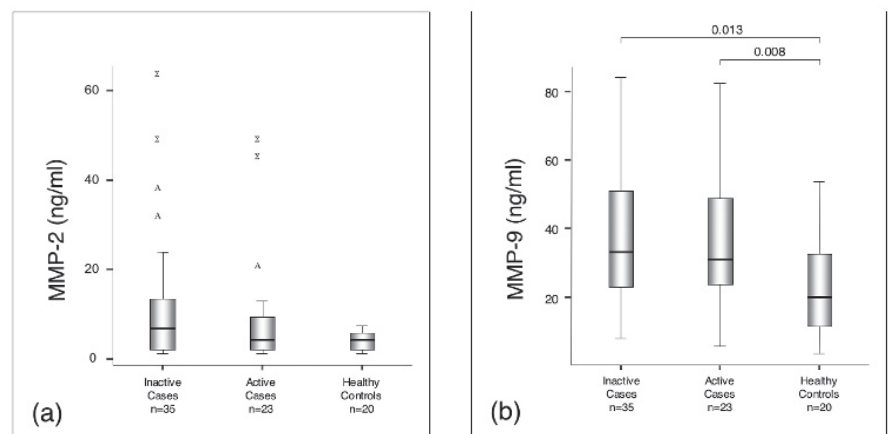


Fig. 1. The Comparisons of MMP-2 (a) and MMP-9 (b) levels from patients with inactive and active Behçet's disease and healthy controls. Boxes show the ranges of 1st and 3rd quartiles and extreme values. Horizontal bars represent median values. The differences between two groups were evaluated by Mann-Whitney U test. *P* values were indicated above the boxes when a level of significance < 0.05 was reached in comparisons of study groups.

2 in patients with thrombotic involvement were found to be higher than those of healthy controls and mucocutaneous but not different as compared to patients having ocular involvement (Fig. 5a). The serum levels of MMP-9 in patients with aneurysmatic involvement were found to be higher than those of healthy controls, mucocutaneous and ocular involvement. The serum levels of MMP-9 in patients with thrombotic involvement were found to be higher than those of healthy controls but not different than those of mucocutaneous and ocular involvement (Fig. 5b).

Discussion

In addition to venous involvement, the arterial occlusive lesions and aneurysms, which sometimes coexist (20), are also observed in patients with BD. The vascular supply disordered by the inflammatory process in vaso vasorum may result in the necrosis of vessel wall, or the detachment and the dissection of the vessel layers leading the formation of true or false (pseudo) aneurysm, respectively (21). It is possible to observe both types of aneurysms in patients with BD (22).

In basic and clinical studies, MMPs

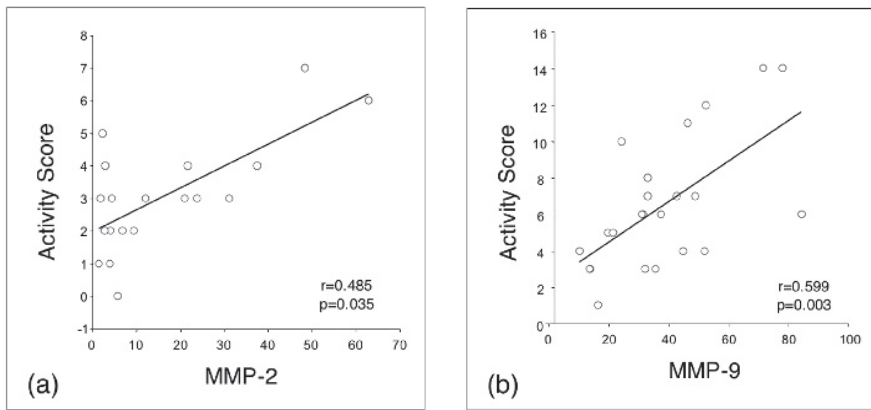


Fig. 2. Positive correlations between MMP-2 (a) or MMP-9 (b) levels and Leeds activity score in patients with vascular involvement or active cases, respectively. Spearman rank correlation test was used to investigate the relations among the variables. *P* value was indicated on the figure.

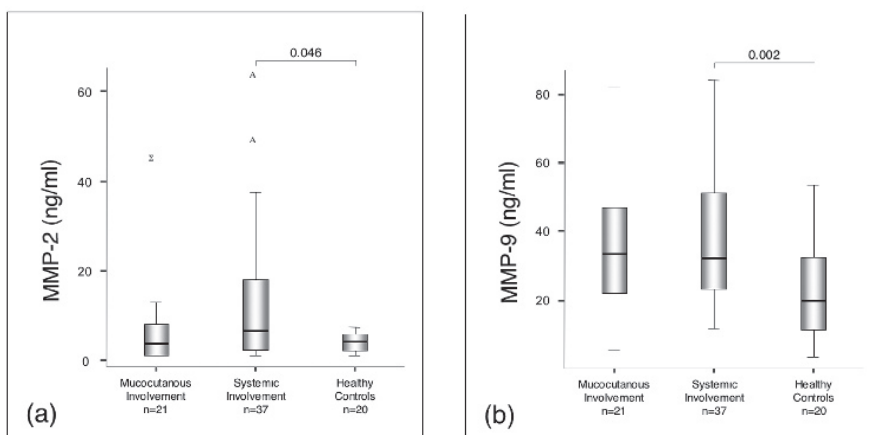


Fig. 3. Comparisons of MMP-2 (a) and MMP-9 (b) levels from patients with Behçet's disease (BD) and healthy controls. The comparisons were done among patients with mucocutaneous and systemic involvements and healthy controls. Boxes show the ranges of 1st and 3rd quartiles and extreme values. Horizontal bars represent median values. The differences between two groups were evaluated by Mann-Whitney U test. *P* values were indicated above the boxes when a level of significance < 0.05 was reached in comparisons of study groups.

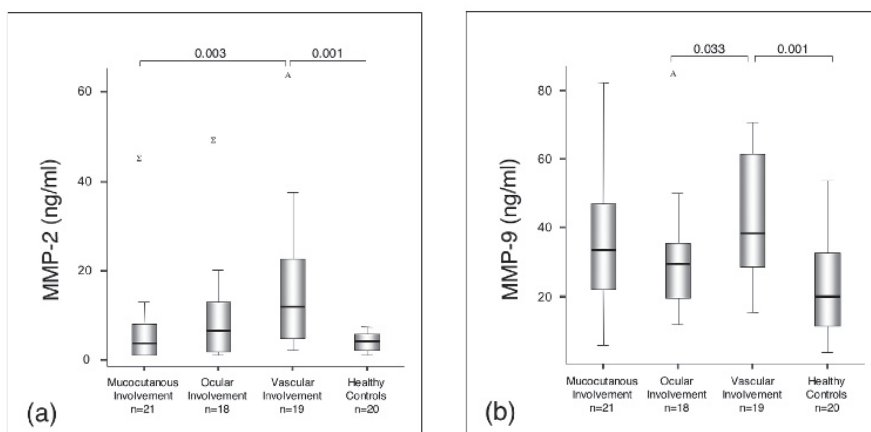


Fig. 4. Comparisons of MMP-2 (a) and MMP-9 (b) levels from patients with Behçet's disease (BD) and healthy controls. The comparisons were done among patients with mucocutaneous, ocular and vascular involvements and healthy controls. Boxes show the ranges of 1st and 3rd quartiles and extreme values. Horizontal bars represent median values. The differences between two groups were evaluated by Mann-Whitney U test. *P* values were indicated above the boxes when a level of significance < 0.05 was reached in comparisons of study groups.

(particularly MMP-2 and MMP-9) have been shown to play a crucial role in the formation of abdominal aortic aneurysms. Those studies obviously revealed that cells expressing MMP-2 and MMP-9 were localized at the intima and adventitia of abdominal aortic aneurysm and their expression were associated with the developmental process and the size of aneurysm (23, 24). Furthermore, MMP-9 C-1562T functional polymorphism was reported to have represented a genetic component contributing to susceptibility to abdominal aortic aneurysm (25).

MMP-2 and MMP-9 also play an important role in the pathogenesis of vasculitis characterized by aneurysm formation. Senzaki *et al.* demonstrated that levels of MMPs including MMP-2 and MMP-9 were significantly higher in patients with Kawasaki disease (KD) before treatment as compared to controls, and with the levels of MMP-9 in KD patients with coronary artery lesion being higher than those without coronary artery lesion (12). Similarly, higher serum levels of MMP-9 in patients with acute KD than those with sepsis and healthy controls were reported by other authors (11, 14). Takeshita *et al.* revealed that MMP-9 was generated from circulating leukocytes as they found more expression of MMP-9 mRNA in those patients with acute KD than control groups (11). The relationship between the expression of MMP-9 and the formation of aneurysm in KD were not addressed in these studies. MMP-2 and MMP-9 were also investigated with immunohistochemical methods in coronary arteries of patients with fatal acute KD and controls. Gavin *et al.* reported that the expression of MMP-2 was prominent in the thickened neo-intima and in endothelial cells of new capillaries in areas of angiogenesis in KD coronary aneurysms while MMP-9 was expressed in coronary artery aneurysm, non-aneurysmal coronary and non-coronary but not control coronary arteries (13). They concluded that MMP-2 contributes to the remodeling of arterial wall, and MMP-9 plays a part in the development of coronary aneurysm in patients with acute KD. Besides KD, MMP-2 and MMP-9 were investigated in patients with giant cell

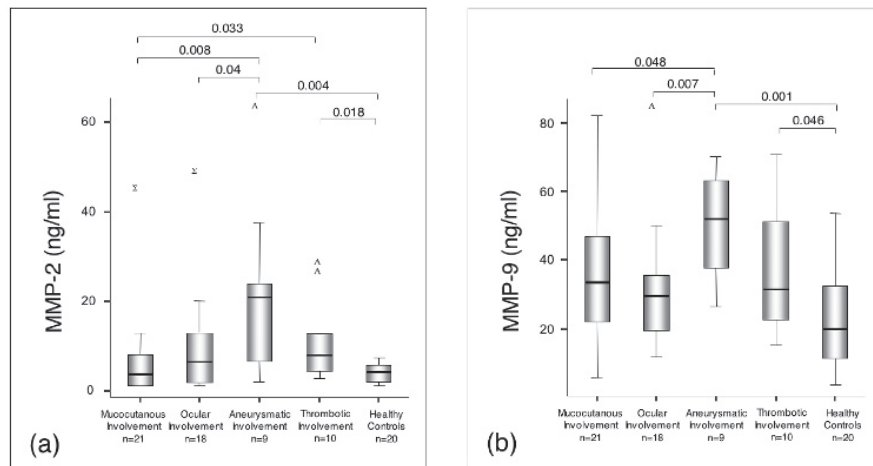


Fig. 5. Comparisons of MMP-2 (a) and MMP-9 (b) levels from patients with Behçet's disease (BD) and healthy controls. The comparisons were done among patients with mucocutaneous, ocular, aneurysmatic and thrombotic involvements and healthy controls. Boxes show the ranges of 1st and 3rd quartiles and extreme values. Horizontal bars represent median values. The differences between two groups were evaluated by Mann-Whitney U test. *p* values were indicated above the boxes when a level of significance < 0.05 was reached in comparisons of study groups.

arteritis (GCA). Sorbi *et al.* detected high serum levels of MMP-9 and the MMP-9 mRNA in the lamina media of inflamed vasculature in patients with GCA, and suggested its possible pathogenetic role in GCA (16). Furthermore, by histochemical staining, moderate staining for MMP-2 were found in both diseased and normal artery specimens although the enhanced staining for MMP-9 compared with normal arteries were detected in GCA specimens (15). These findings were interpreted as MMP-9 contributes to the pathogenesis of GCA.

MMP-2 and MMP-9 were also studied in patients with Takayasu arteritis (TA). Matsuyama *et al.* reported that the levels of MMP-2 and MMP-9 were higher in patients with TA than in controls, but only MMP-9 was found to be correlated with disease activity score (17). They concluded that MMP-2 and MMP-9 can be used as a diagnostic and an activity marker for TA, respectively.

Depending on those findings, we hypothesized that circulating MMP-2 and MMP-9 may play an important role in vasculo-Behçet's disease, particularly in patients with aneurysmatic formation. In order to prove our suggestion, we measured the serum levels of MMP-2 and MMP-9, and further investigated whether the concentration of MMP-2 and MMP-9 were related to the disease activity and clinical

presentations in patients with BD. For this purpose, we examined the disease activity of patients according to Leeds activity score system, and compared the activity scores of patients with their serum levels of MMP2 and MMP-9. Patients with BD were categorized as active (total activity score ≥ 5) or inactive (total activity score < 5). Although serum MMP-2 levels were not significantly higher both in patients with active and inactive disease as compared to healthy controls, serum MMP-9 levels were significantly higher both in patients with active and inactive disease as compared to healthy controls. We also did the correlation analysis between Leeds activity score and serum MMP-2 or MMP-9 levels. We found positive correlation between Leeds activity score and serum MMP-2 levels in patients with vascular involvement, and serum MMP-9 levels in active Behçet's patients. These findings indicated that serum MMP-2 and MMP-9 levels can be used an activity marker for vasculo-Behçet's or active Behçet's patients, respectively.

Patients were also categorized with respect to extent of their involvement as mucocutaneous or systemic. The serum levels of MMP-2 and MMP-9 in patients with systemic involvement were higher than those of healthy controls but not found to be different comparing with those of mucocutaneous involve-

ment. These findings can be interpreted as MMP-2 and MMP-9 may not reflect the systemic involvement in patients with BD.

Overall, we demonstrated increased levels of both MMP-2 and MMP-9 in patients with vascular involvement, thrombosis and aneurysm formation. Those results showed that the systemic expressions of MMP-2 and MMP-9 were strongly associated with vasculo-Behçet's disease, particularly patients having aneurysmatic involvement. We proposed that MMP-2 and MMP-9 may play a pathogenetic role in vasculo-Behçet's disease complicated with aneurysm formation.

In order to compare our results, we could not find any research investigating the role of MMPs in the pathogenesis of BD except our previous studies which investigated the synovial MMP-1 and MMP-3 levels in inflammatory arthritides including BD (26, 27). We found similar levels of synovial MMP-1 but relatively small quantities of MMP-3 in Behçet's synovitis compared to those of the patients with RA. We interpreted our findings as MMP-1 might be a marker of a cytokine-driven inflammation and the lower levels MMP-3 might explain the non-erosive character of Behçet's arthritis.

In conclusion, serum MMP-2 and MMP-9 levels could be used an activity marker for vasculo-Behçet's or active BD patients, respectively. However, they can not be used as an indicator of systemic involvement in patients with BD. The systemic expressions of MMP-2 and MMP-9 were strongly associated with vasculo-Behçet's disease, particularly aneurysmatic involvement, suggesting their pathogenetic roles in vasculo-Behçet's disease complicated with aneurysm formation.

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