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Original Investigation

The Effect of Matrix Metalloproteinase-3 on the Prognosis and Biological Behaviour of Meningiomas

Numan KARAARSLAN[1], Mehmet Sabri GURBUZ[2], Tezcan CALISKAN[1], Erdogan AYAN[1], Fugen VARDAR AKER[3], Mehmet Zafer BERKMAN[4]

[1]Namık Kemal University, Faculty of Medicine, Department of Neurosurgery, Tekirdağ, Turkey
[2]Ağrı Public Hospital, Neurosurgery Clinic, Ağrı, Turkey
[3]Haydarpaşa Numune Training and Research Hospital, Pathology Clinic, Istanbul, Turkey
[4]Acıbadem Hospital, Neurosurgery Clinic, Istanbul, Turkey

ABSTRACT

AIM: To analyse the effect of MMP-3 (Matrix Metalloproteinase Enzyme-3)-one of the extracellular matrix proteins- on the prognosis and biological behaviour of meningiomas.

MATERIAL and METHODS: 79 cases of meningioma that were operated in our clinic between 2005 and 2010 were retrospectively analysed. Age, sex, preoperative peritumoral edema, histological subtype, grade, Ki-67 expression, MMP-3 staining pattern and recurrence rate were analysed. Pathological preparations were graded according to the WHO (World Health Organisation) 2007 grading system.

RESULTS: Of the MMP-III positive cases; 24 cases (60%) were grade I, 16 cases were grade II. The MMP-3 staining pattern was significantly positive (80%) in grade II meningioma. 14 of the MMP-3 positive cases were atypical meningiomas. Of the 20 cases with high Ki-67 proliferation index (PI), 12 cases (60%) were MMP-3 positive and 8 cases (40%) were MMP-3 negative. Rates of recurrence and preoperative peritumoral edema were high in cases with MMP-3 positivity.

CONCLUSION: In this study it was determined that MMP-3 positivity has a strong relationship with meningiomas having an aggressive character. MMP-3 may be used as a proliferation marker for biological behaviour, recurrence rate and prognosis of meningiomas.

KEYWORDS: Grade, Ki-67 Proliferation index, Matrix Metalloproteinase-3, Meningioma

■ INTRODUCTION

Meningiomas are the most commonly seen primary benign tumors of the central nervous system. They are generally benign tumors but there are some subtypes that have aggressive characters although they are histopathologically benign. Parallel to the advances in the areas of molecular biology, immunohistochemical techniques and the use of the electron microscope, it has become possible to identify the structure of the extracellular matrix and the structure and functions of the proteins existing in the extracellular matrix. Studies have been performed on some extracellular matrix proteins such as SPARC, Tenascin, matrix metalloproteinase (MMP)-2, MMP-9, MMP-11 (21). MMP-3 was identified as an enzyme found in the extracellular matrix and synthesized from keratinocytes and was found to have crucial roles in tumor angiogenesis and cellular proliferation (7).

To our knowledge, this is the first study dealing with the expression of the MMP-3 in meningiomas. The relationship between MMP-3 and subtypes, grade, Ki-67 proliferation index (PI) and recurrence of meningioma was analysed.

Corresponding author: Numan KARAARSLAN
E-mail: numikara@yahoo.com

MATERIAL and METHODS

A total of 79 cases of meningioma that were operated on at our institution between 2005 and 2010 were retrospectively analysed. Hematoxylin-eosin (H&E) stained pathological preparations were examined under the light microscope and meningiomas were graded according to WHO 2007 tumor grading system. 59 cases were grade I and the remaining 20 were grade II. Sections were prepared to determine the immunohistochemical expression of MMP-3 and Ki-67. Immunohistochemical staining was done using the method of streptavidin-biotin 3 indirect immunoperoxidase. Ki-67 (Ki-67 Rabbit Monoclonal, Biocare Medical Laboratories, Memphis, Tennessee, U.S.A.) and MMP-3 antibody (Matrix Metalloproteinase 3 Mouse anti-Rabbit Monoclonal Antibody, Lampire Biological Laboratories, Pennsylvania, U.S.A.) were used (Figure 1A, B).

Ki-67 PI was determined as the ratio of nuclear stained neoplastic cells to total neoplastic cells in the same area. 2% were graded as low Ki-67 PI, 3-5% were graded as intermediate Ki-67 PI and higher than 5% were graded as high Ki-67 PI. To identify the expression of MMP-3, all tumoral areas were examined under x400 magnification. In the cases that showed MMP-3 expression, all areas of staining were low-intermediate-high stained areas together, so it was called MMP-3 staining positive. The cases that did not showed MMP-3 expression were called MMP-3 stainig negative.

Statistical analysis was done using the Number Cruncher Statistical System (NCSS) 2007&PASS 2008 Statistical Software (Utah, USA). Mean values, Standard deviation, chi-square, Fischer's exact test were used to analyse the data and $p<0.05$ was evaluated as statistical significance.

RESULTS

The mean age of the patients was 52.9 years (23-78 years). 70.9% of the cases (n= 56) were female and 29.1% of the patients (n= 23) were males.

Transitional meningioma was the most common subtype of meningioma among the patients (49.4%) and the second most common subtype was atypical meningioma (20.3%). 80% of grade II meningiomas were atypical, 10% were chordoid and remaining 10% were clear cell meningiomas (Table I).

Ki-67 PI was found low in 57%, intermediate in 17.7% and high in 25.3% of the patients. There was significant association between Ki-67 PI and histopathological grade ($p<0.01$). Ki-67 PI was found lower in grade I and higher in grade II meningiomas. Recurrence was higher in cases with intermediate and high Ki-67 PI (Table II). There was a significant association between Ki-67 PI and atypical meningiomas ($p<0.05$). Atypical meningioma constituted 60% of the cases with high Ki-67 PI. There were 2 cases of chordoid meningioma and Ki-67 PI was found intermediate in both which was statistically significant ($p<0.01$). Ki-67 PI was found significantly low in transitional type meningiomas ($p<0.01$). Transitional meningioma constitutes 64.4% of the cases with low Ki-67 PI (Table III).

MMP-3 was stained in 50.6% of the cases (MMP-3 positive) and 49.4% were MMP-3 negative. Of the MMP-3 positive cases; 60% were grade I and 40% were grade II. The rate of MMP-3 positivity among grade II meningiomas was 80%, which was statistically significant. MMP-3 positivity was found in 14 of 16 cases of atypical meningioma (87.5%), which was significant (Table IV). There was significant association between MMP-3 positivity and histopathological grade ($p<0.01$) (Table V). MMP-3 positivity was detected in 12 of 20 (60%) cases with high Ki-67 PI (Table VI). Nine of the 79 meningioma cases included in our study were recurrent cases. Of the 9 recurrent cases, 5 were grade II and 4 were grade I. Four of 5 recurrent grade II cases were MMP-3 positive (80%). On the other hand only 1 of 4 was MMP-3 positive in recurrent grade I cases (25%). Peritumoral edema was detected on preoperative MR images of 44 cases. Of these cases, 13 were grade II and 31 were grade I. Of 13 grade II cases with peritumoral edema, 12 were MMP-3 positive (92%), however only 14 of 31 grade I cases with peritumoral edema were MMP-3 positive (45%).

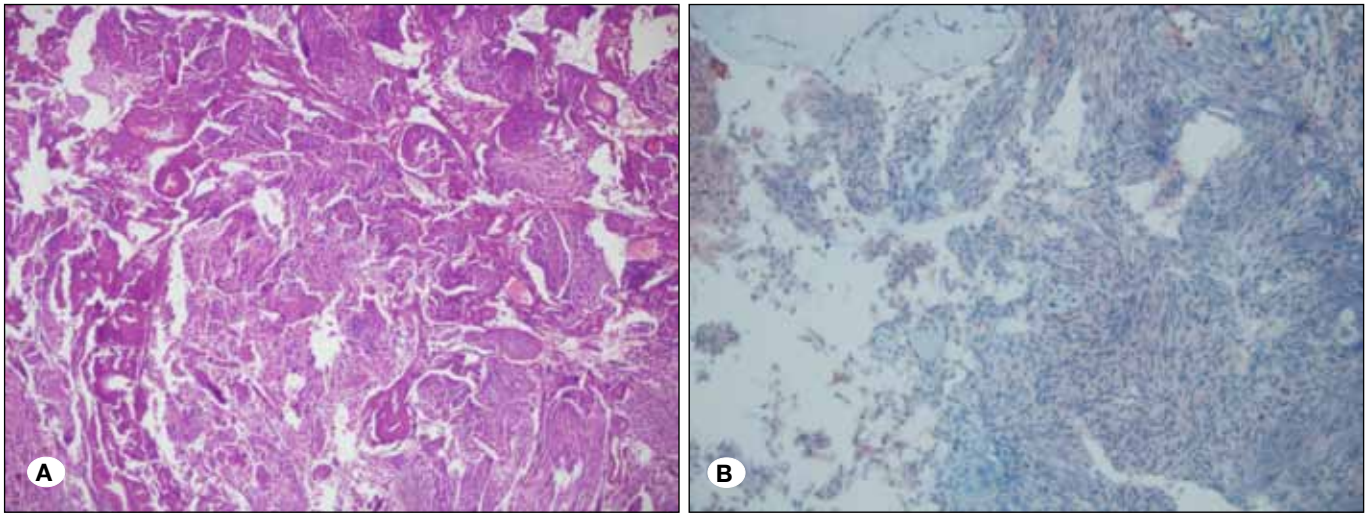

Figure 1: A) A grade II meningioma case. H&E (x400). **B)** A grade II meningioma case. MMP-3 staining positivity (x200).

As a result, the recurrence rate and presence of peritumoral edema were more prominent in MMP-3 positive cases (Table VII).

■ DISCUSSION

Meningiomas have a variety of biological, histopathological and genetic features and are the most common primary intracranial tumors (5). Recently, many studies have been

Table I: The Rates of Histopathological Subtypes and Their Grades

Histopathological subtype	Grade 1; n (%)	Grade 2; n (%)	Total; n (%)
Angiomatous	1 (1.7%)	0 (0%)	1 (1.3%)
Atypical	0 (0%)	16 (80%)	16 (20.3%)
Clear cell	0 (0%)	2 (10%)	2 (2.5%)
Fibroblastic	3 (5.1%)	0 (0%)	3 (3.8%)
Chordoid	0 (0%)	2 (10%)	2 (2.5%)
Meningothelial	13 (22%)	0 (0%)	13 (16.5%)
Microcystic	1 (7.1%)	0 (0%)	1 (1.3%)
Psammomatous	2 (3.4%)	0 (0%)	2 (2.5%)
Transitional	39 (66.1%)	0 (0%)	39 (49.4%)
Total	59 (100%)	20 (100%)	79 (100%)

Table II: The Association Between Ki-67 PI, Histopathological Grade and the Rate of Recurrence

		Ki-67 PI			p
		Low	Intermediate	High	
		n (%)	n (%)	n (%)	
Histopathological Grade	Grade I	43 (95.6%)	9 (64.3%)	7 (35%)	***0.001***
	Grade II	2 (4.4%)	5 (35.7%)	13 (65%)	
Recurrence		2 (4.4%)	3 (21.4%)	4 (20%)	***0.081***

Table III: The Association Between Histopathological Subtype and Ki-67 PI

Histopathological Type	KI-67 PI			p
	Low	Intermediate	High	
	n (%)	n (%)	n (%)	
Angiomatous	1 (2.2%)	0 (0%)	0 (0%)	***0.682***
Atypical	2 (4.4%)	2 (14.3%)	12 (60%)	***0.001****
Clear cell	0 (0%)	1 (7.1%)	1 (5%)	***0.238***
Fibroblastic	2 (4.4%)	0 (0%)	1 (5%)	***0.711***
Chordoid	0 (0%)	2 (14.3%)	0 (0%)	***0.009****
Meningothelial	8 (17.8%)	3 (21.4%)	2 (10%)	***0.633***
Microcystic	1 (2.2%)	0 (0%)	0 (0%)	***0.688***
Psammomatous	2 (4.4%)	0 (0%)	0 (0%)	***0.461***
Transitional	29 (64.4%)	6 (42.9%)	4 (20%)	***0.004****

Table IV: The Association Between Histopathological Subtype and MMP-3 Staining Pattern

Histopathological subtype	MMP-3		p
	Negative	Positive	
	n (%)	n (%)	
Angiomatous	1 (2.6%)	0 (%)	***0.494***
Atypical	2 (5.1%)	14 (35%)	***0.001****
Clear cell	1 (2.6%)	1 (2.5%)	***1.000***
Fibroblastic	1 (2.6%)	2 (5%)	***1.000***
Chordoid	1 (2.6%)	1 (2.5%)	***1.000***
Meningothelial	10 (25.6%)	3 (7.5%)	***0.030****
Microcystic	0 (0%)	1 (2.5%)	***1.000***
Psammomatous	0 (0%)	2 (5%)	***0.494***
Transitional	23 (59%)	16 (40%)	***0.034****

Table V: The Association Between Histopathological Grade and MMP-3 Staining Pattern

		MMP-3		p
		Negative	Positive	
		n (%)	n (%)	
Histopathological Grade	Grade I	35 (89.7%)	24 (60%)	***0.002****
	Grade II	4 (10.3%)	16 (40%)	

Table VI: The Association Between Ki-67 PI and MMP-3 Staining Pattern

Histopathological subtype		MMP 3		p
		Positive	Negative	
		n (%)	n (%)	
KI-67 PI	Low Ki-67 PI≤ %2	20 (50.0%)	25 (64.1%)	***0.206***
	Intermediate Ki-67 PI=%3-5	8 (57.1%)	6 (42.9%)	***0.808***
	High Ki-67 PI>%5	12 (60.0%)	8 (40.0%)	***0.477***

Table VII: The Association Between MMP-3 Staining Pattern, Recurrence and Peritumoral Edema

	MMP-3		p
	Negative	Positive	
	n (%)	n (%)	
Recurrence	4 (10.3%)	5 (12.5%)	***1.000***
Peritumoral Edema	18 (46.2%)	26 (65%)	***0.092***

conducted about the intra and extracellular molecules related to the histopathology and genetics of meningiomas in parallel to technological advances. Owing to advances in electron microscope and histopathological techniques, extracellular tissue was found to have special roles, although it had previously been thought to have only supportive functions (4). Matrisian (16) described MMP molecules as enzymes of protease group which is synthesized in an inactive form and inhibited by TIMP's. It has been found that, MMP's destroy normal tissue structure and have roles in tumor growth, angiogenesis, tumor invasion, apoptosis and metastasis (6,24,28).

Cellular proliferation potential is associated with tumor behaviour and prognosis of meningiomas (26). Cellular proliferation is determined by immunohistochemical analysis of Ki-67 antigen that is produced against nuclear protein (9). Akyildiz et al. (1), in their series of 245 cases, found that 201 cases (82%) are grade I with Ki-67 PI of 2.78%, 30 cases (12%) are grade II with Ki-67 PI of 7.23% and 14 cases (6%) are grade III with Ki-67 PI of 23.7%. Kayasu et al. (10) found Ki-67 PI as <3% in their series which included 240 grade I, 1 grade II and 1 grade III meningiomas, whereas they found Ki-67 PI as >3% in their series which included 56 grade I, 27 grade II and 17 grade III meningiomas. In our grade I cases, Ki-67 PI was low in 43 (72.8%), intermediate in 9 (15.2%) and high in 7 (12%) cases. In the grade II cases; Ki-67 PI was low in 2 (10%), intermediate in 5 (25%) and high in 13 (65%) cases. In the the cases with high Ki-67 PI; 13 cases (65%) were grade II and 7 cases (35%) were grade I. A significant relationship was detected between grade and Ki-67 PI in our study. Ki-67 PI was found high in 7 of 9 recurrence cases (77.7%) and low in 2 cases (22.3%) indicating that Ki-67 PI is associated with tumor recurrence which is consistent with literature (8,27).

Proteases are enzymes that degrade peptides, which are structural components of proteins and have crucial roles in many pathological and physiological processes (16). They consist of 6 groups, namely aspartic proteases, cystine proteases, serine proteases, threonine proteases, glutamicpeptidases and metalloproteinases (17). With respect to associations between MMP's and pathogenesis and behaviours of different tumor types, studies have been conducted to identify the roles of MMP's in the pathogenesis of meningiomas in particular (2,18).

MMP-3 is a member of the stromelysin group of metalloproteinases and is synthesized in 56 kDal single strand form from different cell types as proMMP-3 and turns into active MMP-3 after a variety of reactions. Substrates of MMp-3 are proteoglycans, fibronectin, procollagen type-I, collagen type III, collagen type IV, collagen type IX and laminin (12,15,23). MMP-3 was first described in the mammary gland of the lactation period and found to be synthesized from extracellular stromal cells (13). MMP-3 was also found to be expressed in pathologies of cartilage, inflammatory diseases, gastric cancers, cardiac diseases, endometrial cancers, endometriosis and invasive breast cancers (7,11,13). It functions in tumor angiogenesis, metastasis and has an antiapoptotic role in tumor tissue (14,23,28). Although many studies had been done on the association between MMP's, extracellular matrix and formation and prognosis of different types of tumors, there is no study in the literature dealing with the association between MMP-3 and the biological behaviour and histopathology of meningiomas. In the series of Okada et al. (18) including 56 cases of meningioma, 13 cases (23.2%) were MMP-2 positive. 8 of these 13 cases were grade I and the remaining 5 cases were grade II and III. 16.3% of grade I meningioma were MMP-2 positive whereas 71.4% of grade II and III meningioma were MMP-2 positive. In the same study, 32.7% of grade I meningiomas were MMP-9 positive whereas 85.7% of grade II and III were MMP-9 positive. Rooprai et al. (22) determined MMP-9 expression in all grade II meningiomas. In our study, 16 of 24 (66.6%) grade I cases that stained MMP-3 positive were transitional subtype and 10 of 13 (76.9) meningothelial subtype were MMP-3 negative. It was found that MMP-3 may be associated with transitional subtype of meningioma. Of grade II meningiomas; 14 of MMP-3 positive cases (87.5%) were atypical meningioma, one case (6.25%) was clear cell meningioma and one case (6.25%) was chordoid meningioma. MMP-3 was found positive in 14 of 16 (87.5%) atypical meningiomas, which is a significant rate of positivity.

In order to determine the association between MMP-3 and the proliferation capacity of the tumor cells we used Ki-67 PI, which is a widely used proliferation marker in neuropathology practice. Ki-67 PI is a monoclonal antibody synthesized against nuclear antigens of the tumor cells and marks the tumor cells other than the cells in the resting phase of the cell cycle. Significant association has been found between Ki-67 PI and MMP-2, MMP-9 and MMP-11 and it was stated that they could be used as proliferation markers in meningiomas (3,18,20). In our study, 12 of 20 cases (60%) with high Ki-67 PI were MMP-3 positive although there was no significant relationship between MMP-3 and Ki-67 PI. MMP-3 was found positive in 5 of 9 (55.5%) cases that recurred later. Of the 9 recurrent cases, 5 were grade II and 4 were grade I. Four of 5 recurrent grade II cases were MMP-3 positive (80%). Our study showed that MMP-3 could be used as a proliferation marker in meningioma.

■ CONCLUSION

MMP-3 enzyme might be associated with meningiomas that have aggressive characteristics. MMP-3 may play a role in the biological behaviour, recurrence and prognosis of meningiomas. The authors believe that MMP-3 may be used as a proliferation marker in meningiomas but further studies should be done to clarify the association between MMP-3 and the etiopathogenesis and biological behaviour of meningiomas.

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