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Research Paper: Expression of Matrix Metalloproteinase-2 and -9 in Meningioma

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Running Title: MMP-2 and -9 expression in Meningioma

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Bullet Points:

- MMP-2 and -9 might be involved in the patho-physiology of meningioma.
- Detection of MMP-2 and -9 in serum may be useful in classifying meningioma.

ABSTRACT

Background: Meningioma is one of the most common tumors of the central nervous system. It was shown that meningioma had up-regulated expression of Matrix Metalloproteinases (MMPs) that involved in cell growth, angiogenesis and metastasis.

Objectives: The aim of the study was the assessment of serum MMP-2 and -9 levels in patients with different grades of meningioma.

Materials & Methods: The study included the number of 66 normal control and 101 patients with different grades of meningioma (42 cases of grade I, 38 grade II and 21 grade III). The serum samples was recruited between March 2013 and August 2017 at the Departments of neurology and neurosurgery, in an academic hospital affiliated to Guilan University of Medical Sciences, in the north of Iran. MMP-2 and -9 levels determined by Enzyme Linked Immunosorbent Assay (ELISA). All data presented are expressed as mean±Standard Error of the Mean (SEM). Statistical analysis was done using one-way ANOVA by SPSS software, version: 24.0 and only values with $P \leq 0.05$ were considered as significant

Results: We showed that the level of MMP-2 and -9 in the serum samples of patients with meningioma was higher than in controls ($P<0.01$). We also showed that all serum samples from patients and controls, presented MMP-2 and -9 expression, whereas, starting from grades I to III meningioma, a significant increase of MMP-2 and -9 protein expression was observed ($P<0.05$).

Conclusion: It is concluded that MMP-2 and -9 are a constant composition of human serum. It is also concluded that MMP-2 and -9 might be involved in the pathophysiology of meningioma and their detection in serum may be useful in classifying meningioma.

Keywords: Matrix metalloproteinases, Gene expression, Meningioma

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Introduction

Meningioma accounts for more than 30% of all intracranial tumors. The prevalence peaks between the age of 60 and 70 years, at a male: female ration of 2: 3. Nevertheless, the tumor may also occur in children [1]. According to the World Health Organization (WHO), meningioma is categorized into 3 grades. Criteria include cell type, mitotic activity, cellularity, necrosis, and brain invasion. WHO grade I or benign meningioma represent approximately 90% of all meningiomas. WHO grade II (atypical meningioma) represents approximately 5%-7% of all meningiomas. They show a mitotic index of ≥4 mitosis per 10 Higher-Power Fields (HPF). WHO grade III or anaplastic meningioma accounts for 3% of all meningiomas, show a mitotic index of ≥20 mitosis per 10 HPF [2].

A critical step in tumor progression and recurrence is the infiltrative invasion into the contiguous tissue. Tumor invasion and metastasis formation are major obstacles for successful cancer therapy. Metastasis is a complex multistep process that requires sequential interactions between the invasive cell and the Extracellular Matrix (ECM). The remodeling of the ECM is carried out by a family of enzymes known as Matrix Metalloproteinases (MMP). MMPs are the family of endopeptidases, present in normal healthy tissue and constitute a large group of multidomain, zinc dependent endopeptidases capable of hydrolyzing all protein components of the ECM [3]. They can collectively degrade any component of ECM and basement membrane, and their excessive activity has been linked to numerous pathologies mainly including, but not limited to, tumor invasion and metastasis [4]. The tumor microenvironment can be regulated by MMPs. It has been shown that increased expression of MMPs plays a crucial role in the development of several human malignancies [5].

MMPs are grouped into the following categories on the basis of their substrate specificity: 1. Interstitial collagenases (MMP-2 and MMP-9); and 2. Stromelysins (MMP-3, MMP-10 and MMP-11), which contain a unique transmembrane domain in their COOH terminal that localizes these MMPs on the cell surfaces [6]. Among them, MMP-2 and MMP-9 are expressed as pro-forms, activated by cleavage of their amino terminal, and are consequently involved in proteolysis of the ECM and basement membrane. The activation of MMP is regulated by gene expression, pro-enzyme activation and inhibition of active enzymes by their endogenous Tissue Inhibitors of Metalloproteinases (TIMPs). Specifically, TIMP1 inhibits MMP-9 activity while TIMP2 controls MMP-2 activity [7]. TIMPs are also involved in the regulation of angiogenesis in brain tumor progression [8, 9]. It was documented that MMPs play a pivotal role in the process of malignant progression and that inhibition of MMP-9 activity results in the reduction of tumor invasion and metastasis in animal models [10]. MMP-2 and MMP-9 were shown to play a direct role in angiogenesis which require for tumor growth and metastasis [11]. MMPs and TIMPs are extensively studied in the field of tumor invasion and metastasis. Of the MMP family, MMP-2 and MMP-9 also known as gelatinase A and gelatinase B, respectively, are frequently mentioned in brain tumor biology [12].

It was shown that biochemical brain modifications could be reflected in the biological fluids including serum, therefore, measurement of peptides and amino acids in the serum might identify biomarkers of meningioma and disease progression. Thus, it is important to analyze serum biochemistry to find a reliable biomarker. The aim of this study was to evaluate the concentration of MMP-2 and MMP 9 in the serum of patients with different grades of meningioma.

Materials and Methods

Patient samples

The study included the number of 66 normal control and 101 patients with different grades of meningioma (42 cases of grade I, 38 grade II and 21 grade III). The serum samples was recruited between March 2013 and August 2017 at the Departments of neurology and neurosurgery, in an academic hospital affiliated to Guilan University of Medical Sciences, in the north of Iran. Meningioma cases were confirmed by Magnetic Resonance Imaging (MRI) and histopathology according to the World Health Organization (WHO) classification [2]. Patients who had any history of cancer/intracranial surgery, and received either radiotherapy or chemotherapy before surgery were excluded. The physical examination and imaging results of the patients at presentation and follow-up were recorded. Clinical information was collected and regularly updated for the patients through follow-up and questionnaires.

One hundred and thirty two healthy volunteers were randomly selected from annual check-up visitors at the same hospital during the similar time period. The controls with a self-reported history of central nervous system-related diseases or cancer and previously receiving radiotherapy/chemotherapy were excluded. The research

protocol was performed in accordance with the Declaration of Helsinki 1964 (revised 2013) and approved by the Ethics Committee of the Guilan University of Medical Sciences for Approval of Research Involving Human Subjects. Informed consent was obtained from all study subjects after explanation of the nature and possible consequences of the study. Samples of serum from normal subjects (controls) and patients with meningioma were collected and stored at -70°C until used.

Protein analysis: Total protein concentration and ELISA

The total concentration of proteins in serum and Cerebro-Spinal Fluid (CSF) was determined by the Bio-Rad protein assay based on the Bradford dye procedure. MMP-2 and MMP-9 in serum was measured using the sensitive two sided ELISA and antiserum against Human MMP2 ELISA Kit (ab100606), Human MMP9 ELISA Kit (ab100610), (Cambridge, UK) were first coated with 80 ng primary antibody per well in 0.1 M Tris buffer. After overnight incubation, the plates were blocked with EIA buffer (50 mM Tris, pH 7.5, 0.3 M NaCl, 0.1% Triton X-100, 1% BSA and 1% Gelatine). The samples and standards were placed in triplicate wells and incubated overnight at room temperature. After washing a biotinylated secondary antibody (8 ng/mL) was added per well and the incubation was carried out for 24 hours at room temperature. b-Galactosidase coupled to Avidin was then added and after 2 hours was followed by washing. Finally 200 lM 4-methylumbelliferyl-b-galactoside (Sigma, Poole, UK) in 50 mM sodium phosphate and 10 mM $MgCl_2$ buffer were added and the amount of fluorescence was measured after 40 min incubation at 37°C using a fluorimeter (Dynatech).

Statistical analysis

All data presented are expressed as mean±Standard Error of the Mean (SEM). Statistical analysis was done using one-way ANOVA and only values with P≤0.05 were considered as significant (SPSS software Version: 24.0).

Results

Total protein concentrations

The total concentration of proteins in serum samples from patients with different grades of meningioma and normal subjects was measured by the Bio-Rad protein assay. Results obtained demonstrated that no significant changes in all serum samples, starting from grades I to III meningioma, was observed (0.36±0.02, 0.35±0.06, 0.36±0.06 g/l as compared to controls (0.35±0.06 g/l) (P=0.58, 0.87 and 0.71, respectively) (Figure 1).

Analysis of MMP-2 and MMP-9 concentrations in the serum by ELISA

Using ELISA, it was shown that the levels of MMP-2 and MMP-9 in the serum samples of patients with meningioma were higher than in normal controls. The results showed that all serum samples, presented MMP-2 and MMP-9 expression, whereas, starting from grades I to III meningioma, a significant increase of MMP-2 and MMP-9 protein expression was observed (MMP-2 serum levels of 296.27±54.78,

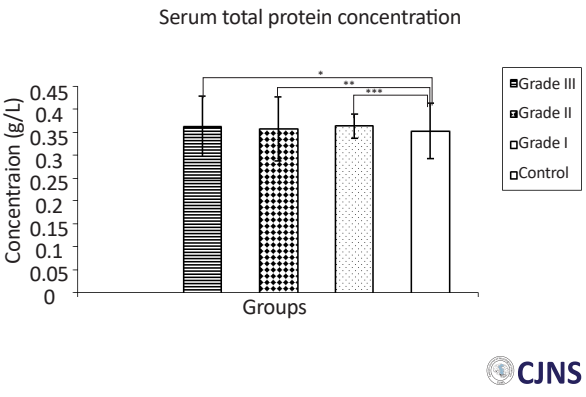

Figure 1. Total protein concentration in the serum of normal subjects and patients with various grades of meningioma (g/L)

Results demonstrated that no significant changes in all serum samples, starting from grades I to III meningioma, was observed (0.36±0.02, 0.35±0.06, 0.36±0.06 g/L as compared to controls (0.35±0.06 g/L) (***: P=0.58, **: 0.87 and *: 0.71, respectively).

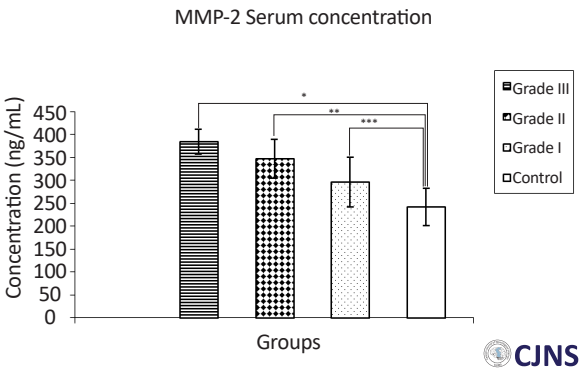

Figure 2. MMP-2 concentration in the serum samples from controls and patients with different grades of meningioma (ng/mL)

Starting from grades I to III meningioma, a significant increase of MMP-2 protein expression was observed (MMP-2 serum levels of 296.27±54.78, 346.90±41.77, 384.18±2742 ng/mL) as compared to controls (242.18±40.93) (***: P=0.01, **: 0.0001 and *: 0.00001, respectively).

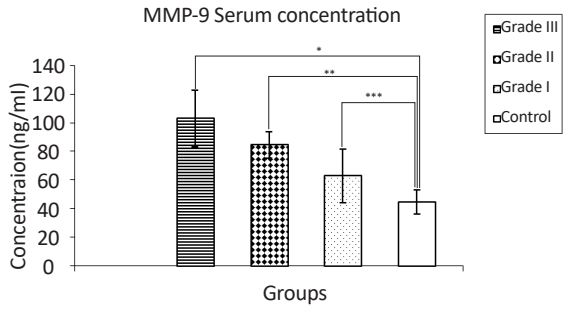

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Figure 3. MMP-9 concentration in the serum samples from controls and patients with different grades of meningioma (ng/ml). Starting from grades I to III meningioma, a significant increase of MMP-9 protein expression was observed (MMP-9 serum levels of 62.81±18.93, 84.45±9.21, 103±19.74 ng/ml) as compared to control group (44.54±8.45 ng/ml) (***: P=0.008, **: 0.000012 and *: 0.00017, respectively).

346.90±41.77, 384.18±2742 ng/mL as compared to controls (242.18±40.93) (P=0.01, 0.0001 and 0.00001, respectively) and MMP-9 serum levels of 62.81±18.93, 84.45±9.21, 103±19.74 ng/mL as compared to control group (44.54±8.45 ng/mL) (P=0.008, 0.000012 and 0.00017, respectively) (Figures 2 and 3). An increase concentration of MMP-2 and MMP-9 is correlated with advanced grades of meningioma (Table 1).

Discussion

Meningioma is an extra-medullary, intradural tumor arising from meningiothelial arachnoid cap cells which form the outer layer of the arachnoid matter. Multiple genes have been shown to be associated with meningioma [12]. Several studies have reported deletion of chromosome 22q and of its associated gene NF2 in case of meningioma [13]. In addition to chromosomal alterations, changes to individual genes have also been observed in meningioma. It was shown that meningioma had up-regulated expression of MMP family of proteins involved in cell growth, angiogenesis and invasion [12]. In addition, transfection of small interfering RNA (siRNA) constructs to reduce or silence expression of MMP-9 gene reduces meningioma migration and invasion in vivo [14]. It has been suggested that the increased ration of MMP-9 to TIMP-1 might be associated with the meningioma progression [15]. MMPs might be associated with meningioma that have aggressive characteristics. They may play a role in the biological behavior, recurrence and prognosis of meningioma [16]. It was demonstrated that MMPs and their TIMPs play key role in the pathogenesis of meningioma [17]. Increased levels of MMP-2 and MMP-9 in grade 1 meningioma were shown as prognostic or predictive factors of recurrence [18].

MMPs play a central role in different physiological and pathological conditions [19-22]. Changes in the MMPs Cerebrospinal Fluid (CSF) and serum concentration were shown in the patients with meningitis, Creutzfeldt Jacob Disease (CJD), hydrocephalus and seizure [23-27]. It has been shown that MMPs and TIMPs play key role in cell proliferation, invasion and migration in different cancers including laryngeal carcinoma cells and ovarian cancer [28, 29]. It has been demonstrated that MMP-9 and MMP-2 may be correlated with invasiveness of pituitary adenomas [30]. It was also shown that a balance between MMPs and TIMPs has an important role to play in human brain tumors and their expression may be valuable markers for tumor malignancy and the imbalance between MMP-2 and TIMP-2 may have an important role in glioblastoma invasion by degrading the extracellular matrix [31, 32].

Changes in the MMP expression in many cancer tissues have been demonstrated [33, 34]. In this study we found that the levels of serum MMP-2 and MMP 9 levels were significantly increased in patients with meningioma. Moreover, among patients with meningioma, the concentration of MMP-2 and MMP 9 were significantly higher in patients with advanced grade of the disease.

Table 1. Significance levels of serum MMP-2 and -9 concentrations between different grades of meningioma

Groups	MMP-2	MMP-9
	P	P
Grade I vs. grade II	0.024	0.002
Grade I vs. grade III	0.0001	0.0009
Grade II vs. grade III	0.022	0.01

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Meningioma demonstrate more complex cytogenetic and molecular profile with activation of oncogenes, inactivation of tumor suppressor genes, and alterations in other genes involved in several molecular pathways [35]. Multidrug Resistance-associated Proteins (MRPs) were shown to be utilized in the treatment of aggressive meningioma [36]. Increased expression of MRP5 was reported in anaplastic but not in benign meningioma [37]. Deletions on chromosome 22 map to 22q12, has been seen in meningioma [38]. Another common tumor suppressor genes that have been associated with the development of meningioma is DAL-1 (differentially expressed in adenocarcinoma of the lung) [39]. Increased expression of IGF2 transcripts, along with decreased expression of IGFBP2, has been shown to be associated with meningioma development, and anaplastic grade [40].

Conclusion

It is concluded that MMP-2 and MMP 9 are a constant composition of human serum. The result of this study suggests that MMP-2, MMP 9, TIMP1 and TIMP2 serum concentrations may provide a reliable and practical indicator of malignant potential and tumor progression. It is also concluded that MMP-2 and MMP 9 might be involved in the pathophysiology of meningioma and the detection of serum MMP-2 and MMP 9 may be useful in classifying meningioma.

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Conflict of Interest

The authors have no conflicts of interest.

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