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MATRIX METALLOPROTEINASE-9 AND INFLAMMATION IN DIFFERENT TYPES OF MULTIPLE SCLEROSIS

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Abstract

Analysis of the literature data on alcoholic addiction, poststress maladjustment and its combination revealed the significant number of common node moments in pathogenic mechanisms of its appearing and realization. It concerns biological mechanisms that are common for both processes and its activation at one of them provokes the development of the other. First of all it is stem structures of brain and neuroendocrine mechanisms of central and peripheral regulation and its activation is cross for stressor reaction and alcoholization. There was revealed the leading role of stressor reaction mechanisms and its association with poststress maladjustment in formation of psychological alcoholic addiction. There was constructed hypothetical model of development and functioning of association pathogenetic mechanisms with formation of comorbidity of analyzed pathological states.

Keywords: poststress maladjustment, alcoholic addiction, stressor reaction, psychic mechanisms, vegetative regulation, comorbidity.

1. Introduction

Data received in the recent years using morphological, immunological and neuroimaging research methods have greatly changed the traditional notion of multiple sclerosis (MS) as a remittent central nervous system (CNS) disease causing destruction of myelin of brain and spinal cord conductors only. It turned out that the pathological process continues even in the phase of clinical remission; axons are damaged from the initial stage of disease; besides the CNS white matter, grey matter of the cortex and subcortex is also damaged. However, a number of issues still remain unsolved. Different clinical courses of MS, heterogeneity of its clinical implications, different effect of immunomodulatory therapy for the same clinical forms implies various pathogenetic mechanisms of the CNS damage in this disease [1–5]. The scientific and practical objective in researching MS lies in studying mechanisms of neurodegenerative process development, assessment of interrelation between inflammatory, immunopathological and degenerative processes. There have not yet been established any informative immunobiochemical markers allowing the monitoring of pathological process activity at different MS courses using process activity estimates and prognosis; mechanisms that trigger exacerbations and remission are not clear either. Applicability of immunological and biochemical markers for the estimation of immunocorrecting and anti-inflammatory therapy efficacy is disputable [6–8]. Many of the proposed methods are complicated, laborious and costly. In this respect, it deems relevant to look for informative and widely available markers suitable for pathological process monitoring and prediction.

Search for new, more efficient MS treatment methods is closely related to the profound research of pathogenesis links of the disease, many aspects of which still unclear. In particular, the role of matrix metalloproteinase (MMP) which is normally a physiological mediator of tissues remodeling in MS pathogenesis has not been sufficiently studied. Most of the investigations are based on experiments on animals and MMP in vitro studies [9–12]. One of the main pathogenetic links in MS such as blood-brain barrier (BBB) disruption and as a result migration of plasma proteins to the brain parenchyma is MMP. MMPs form a series of enzymes whose principal activity is remodeling of the intercellular matrix. MMP-9 or gelatinase B is the most complicated metalloproteinase in terms of its domain structure and activity regulation. MMP-9 activity is strictly regulated at the different levels: regulation of genetic transcription by cytokines and various cellular interactions; regulation of proenzyme activation by the enzyme cascade including serine proteases and other MMPs; regulation by specific tissue inhibitors of MMPs (TIMPs) or non-specific inhibitors. MMP's main function is degradation of extracellular matrix components.

Matrix metalloproteinases are involved in multiple processes represented in **Table 1.**

Scholars attach great importance to MMPs when studying inflammations. It is known that most cells involved in immune reactions and inflammation (T-lymphocytes, macrophages, eosinophils and neutrophils) produce certain MMPs [13–16]. MMP production depends on different inflammatory mediators. MMP synthesis in macrophages for example is induced by contact with collagen and is further intensified by T-lymphocyte membrane determinants. Through matrix damage MMPs prepare the vascular wall to the adhesion of immune cells and facilitate migration of cells, proteins, antibodies, complement, etc. through the basal membrane to tissues [17–19]. According

to the latest publications MMPs are very important for CNS development and differentiation and may be produced by neurons [20, 21]. Besides through ECM remodeling it can influence different functions of the nerve tissue and growth factor concentration as well as impact synapse formation and stabilization and further interneuronic and neuroglia interaction.

Table 1
MMP's role in remodeling extracellular matrix (ECM) [6]

PHYSIOLOGICAL PROCESSES	PATHOLOGICAL PROCESSES
Ovulation	Growth/metastatic dissemination of tumors
Trophoblast and blastocyst implantation	
Embryogenesis	Rheumatoid arthritis, osteoarthritis
Morphogenesis of salivary glands	Periodontium disease
Development/involution of mammary glands	Pulmonary fibrosis
	Liver cirrhosis
Dilatation of cervix uteri	Gastric and stercoral ulcer
Uterine involution	Dilatational cardiomyopathy
Development/alteration of bones	Atherosclerosis
Healing of wounds/fractures	Arterial aneurism
Angiogenesis	Glomerulonephritis
Functioning of macrophages/ neutrophils	Encephalomyelitis

There are studies dedicated to MMP's role in metastatic dissemination of CNS tumors, stroke, neurodegenerative and demyelinization diseases. Some studies deal with MMPs' activity and intensity in infectious diseases of the CNS. MMP's role in bacterial meningitis is paid special attention to. The fundamental pathogenetic mechanism causing secondary damage at demyelinization diseases is BBB disruption. There are a lot of inflammation mediators that are known to play a certain role in BBB disruption. These are above all radicals of oxygen, nitrogen oxide, metabolites of arachidonic acid (E2 prostaglandines) and cytokines such as TNF-α, interleukin (IL)-1 β, IL-6 and IL-10 [22, 23]. However mechanisms of BBB disruption have not yet received comprehensive examination.

Thus on the one hand MMPs are physiological mediators important for CNS growth, development and functioning and on the other hand they are proteolytic enzymes that actively interact with cellular and humoral factors of the immune system (epidermal growth factor, growth factor of thrombocyte origin, IL-1, IL-4, etc.) and trigger pathological processes.

This research aims at improvement of pathological process stages diagnostics at multiple sclerosis and further therapy optimization depending on the activity of inflammatory process.

2. Research materials and methods

135 patients (54 males and 81 females) of different age (from 18 to 67) with multiple sclerosis (diagnosed according to the McDonald criteria, 2010) of different course types and at different activity stages of the pathological process were examined.

Quantitative determination of MMP-9 concentration was performed in the blood serum using an immune-enzyme test kit (Human MMP-9 ELISA, Bio Tech Lab-S).

3. Results and discussion

The highest MMP-9 rate was observed in patients with relapsing-remittent multiple sclerosis (RRMS) (average rate $MMP\text{-}9_{av}=212.37\pm17.51$). The lowest rate was in patients with primary progressive MS (PPMS) ($MMP\text{-}9_{av}=135.33\pm6.87$). The medium rate was in patients with secondary progressive (SPMS) ($MMP\text{-}9_{av}=252.19\pm10.36$). Obtained factor is $F=5.238$; its statistical significance is $p<0.01$. ANOVA variance analysis was used to determine interrelation between the clinical course type and MMP-9 rate; graphic results are provided in **Fig. 1.**

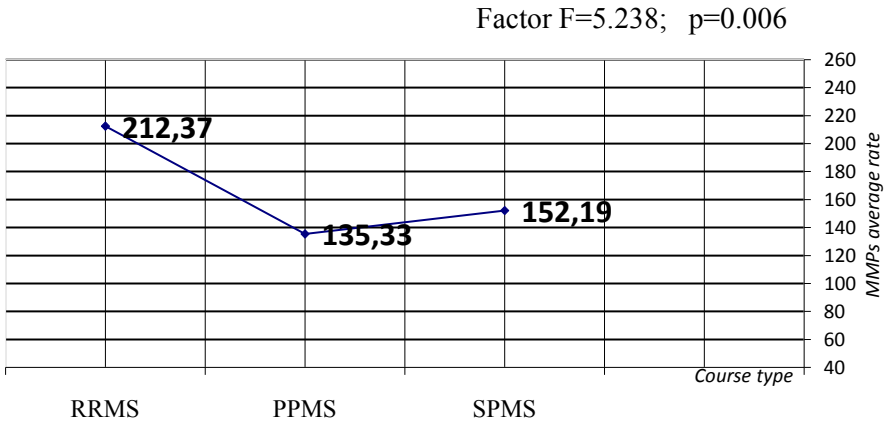

Fig. 1. Dependence of MMP-9 rate on the clinical course type

Besides the metalloproteinase rate was analyzed at different activity stages of the pathological process (exacerbation and remission in RRMS, progression and stabilization in progredient course types). Average ММП-9_{av} rates for the groups under examination were as follows: in RRMS at the remission stage – 122.05±7.82, at the exacerbation stage – 378.68±21.54. In progredient course types: at the stage of progression – 164.73±12.21, at the stage of stabilization – 114.64±8.43. The data obtained can be found in **Fig. 2.**

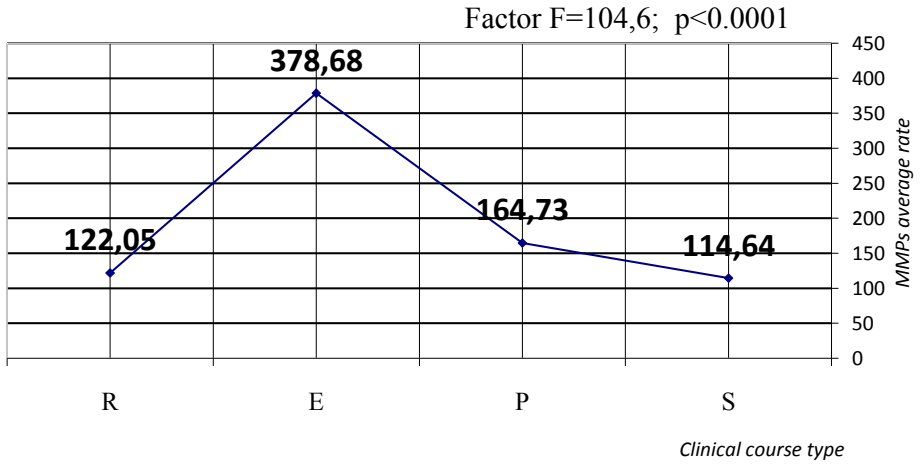

Fig. 2. Dependence of MMP-9 rate on the clinical course type

The value of factor F is so high that probability of error was almost equal to zero (p<0.0001). It is shown on the graph that the highest MMP-9 rates were observed at the exacerbation and progression stages of the pathological process. At the stages of remission and stabilization MMP-9 rates were within the normal range. Thus it was proved with a high degree of confidence that the average MMP-9 rate depends on the stage of disease.

MMP-9 rate is influenced by all of the factors collectively but not individually. Therefore clinical course types and disease stages as factors influencing MMP-9 rate most of all were analyzed using the multi-factor variance analysis. The results obtained are given in **Table 2.**

According to **Table 2**, the highest MMP-9 rates were observed in the RRMS group at the stage of disease exacerbation (381.54±22.19). MMP-9 rate was within the normal range at the stage of remission and reached 122.05±7.82. MMP-9 rates were high at the active stage in SPMS and PPMS: 169.98±15.64 and 147.03±6.78 respectively. The results obtained proved that inflammatory reactions in SPMS are more apparent than in PPMS when neurodegeneration processes are of primary importance. Unexpectedly MMP-9 rates at the stage of stabilization were higher in PPMS (121.96±10.90) than in SPMS (114.64±8.43). This may be accounted for by a considerable difference

between the number of patients in the respective groups – there were three times fewer patients in the PPMS group at the stage of stabilization than in the SPMS group at the same stage. The obtained results are represented graphically in **Fig. 3.**

Table 2
MMP-9 rate depending on the course type and stage of disease

Course type	Stage of disease	Number of patients	MMP-9 rate
RRMS	Exacerbation	26	381.54±22.19
	Remission	45	122.05±7.82
SPMS	Progression	28	169.98±15.64
	Stabilization	21	114.64±8.43
PPMS	Progression	8	147.03±6.78
	Stabilization	7	121.96±10.90

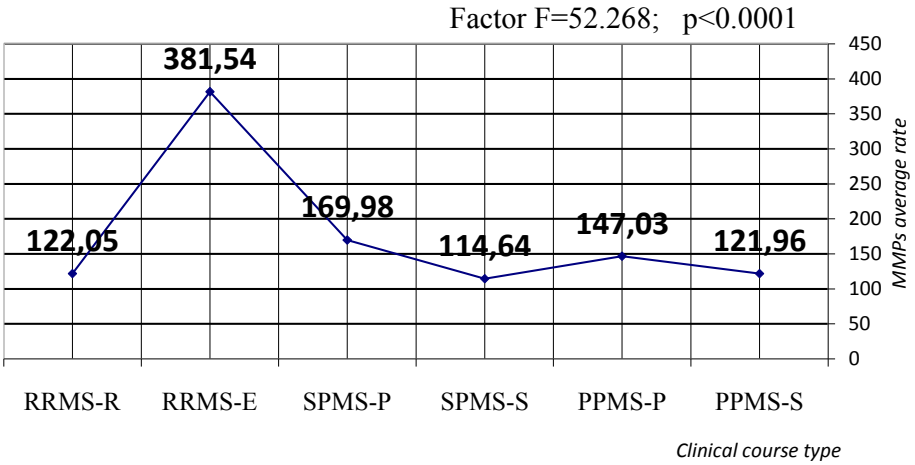

Fig. 3. Dependence of MMP-9 rate on the course type and stage of disease

4. Conclusions

1. Matrix metalloproteinase-9 may be considered as an activity marker of the inflammatory process, a marker of immunocompetent cells, and as a BBB state indicator at MS.

2. Determination of MMP-9 rate may contribute to the monitoring of therapy efficacy in MS patients at different stages of the disease.

3. Decrease of level of MMP-9 during exacerbations of MS may serve as unfovarable prognostic criterion and rate as predictor of chaging of types on progressive.

4. MMP-9 rate determination method may be recommended as part of diagnostic examination of MS patients in particular if neuroimaging is for some reasons not available.

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