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Activity of selected metalloproteinases in neurodegenerative diseases of the central nervous system as exemplified by dementia and schizophrenia

Aneta Tylec[1], Maciej Skałecki[2], Joanna Kocot[3], Jacek Kurzepa[3]

[1] 2nd Department of Psychiatry and Psychiatric Rehabilitation, Medical University of Lublin
[2] Independent Public Psychiatric Care and Treatment Center in Celejow
[3] Chair and Department of Medical Chemistry, Medical University of Lublin

Summary

Aim. The aim of the study was to determine and analyze the correlation between the concentrations of selected metalloproteinases and their inhibitors (TIMP-1 and TIMP-2) in patients with dementia and schizophrenia.

Method. The concentration of two collagenases and metalloendopeptidase was determined in the study. The study included 29 patients with late onset dementia, 25 patients with paranoid schizophrenia and 25 healthy controls who were age-matched with the study groups. Symptoms of dementia were evaluated using the Short Mental State Assessment Scale, whereas the symptoms of schizophrenia were assessed using the Positive and Negative Assessment Scale. Blood samples were collected from the participants and the concentrations of MMP-1, MMP-7, MMP-13, TIMP-1, and TIMP-2 in the blood serum were evaluated using ELISA method.

Results. A two-fold increase in the concentration of MMP-1 and a slight increase in MMP-13 was observed in dementia patients compared to other groups, as well as a lower level of MMP-7 and TIMP-1 and a higher level of TIMP-2 compared to the control group. Patients with schizophrenia showed lower MMP-7 and higher TIMP-2 serum level compared to the controls. No differences in the concentration of MMP-1, MMP-13 and TIMP-1 levels were noticed. In people with late onset dementia an increase in collagenolytic activity was demonstrated.

Conclusions. Increase in collagenolytic activity may indicate an increased remodeling within the central nervous system in late onset dementia. The difference in the fluctuation of the concentrations of the studied enzymes and their inhibitors in dementia and schizophrenia indicates their different involvement in the pathogenesis of these disorders.

Key words: extracellular matrix metalloproteinase, tissue metalloproteinase inhibitor, neurodegenerative disease

Introduction

The extracellular matrix (ECM) of all the tissues and organs in the human body is made up of collagen, elastin, glycoproteins, proteoglycans, and glycosaminoglycans. Composition of the matrix depends on the type of tissue [1]. In the central nervous system (CNS), chondroitin sulfate proteoglycans as well as glycosaminoglycan (hyaluronic acid) are the main components of the ECM [2]. The ECM undergoes reconstruction both during the physiological processes (embryogenesis, gestation and puerperium, cyclic endometrial changes, angiogenesis, wound healing, platelet aggregation) and pathological processes (inflammatory, degenerative, neoplastic processes) [1]. Various proteolytic enzymes are involved in the degradation and regeneration of the matrix components [3]. The matrix metalloproteinases (MMPs) are capable to degrade the ECM proteins and adhesive proteins, they also take part in the transmission of intercellular signals [1]. Depending on the type of substrate and their location, six subfamilies of MMPs are recognized as collagenases (MMP-1, MMP-8, MMP-13, MMP-18), gelatinases (MMP-2, MMP-9), stromelysins (MMP-3, MMP-10, MMP-11), matrilysins (MMP-7, MMP-26), membrane-type MMPs and other enamelysins – MMP-20, metalloelastases – MMP-12 [4]. Activity of MMPs is affected by specific and non-specific inhibitors (plasma inhibitors – alpha 2 macroglobulines and alpha 1 antiproteases) [5], however, the most significant inhibition is made by four natural tissue inhibitors of MMPs (TIMPs), the small proteins that block the active center of MMPs [6]. TIMPs are important factors in the CNS regenerative processes [7].

MMPs released by the residential cells (astrocytes, oligodendrocytes, microglia, and neurons) as well as by the inflow cells (lymphocytes, granulocytes and macrophages) play a role in the embryonic and postnatal development of the CNS, which has been confirmed by the results of the research into the dynamics of changes of the mRNA and metalloprotein expression [8]. Moreover, MMPs take part in the intracellular processes of information transfer, growth regulation, proliferation, and apoptosis. They are also involved in elongation and branching of dendrites (MMP-9, MMP-2, MMP-3, MMP-7, and MT5-MMP) and cell migration [9]. Activation of MMPs within the CNS triggers the onset of an inflammatory process in the infective and non-infective pathomechanism. Penetration of blood tissue morphotic elements into the nerve tissue takes place either directly, by breaking the blood-brain barrier [10] or indirectly, by stimulation of the cerebral vessels' endothelial cells and a release of the soluble vascular cell adhesion molecule-1 (VCAM-1) [11]. The only exception are the CNS regions deprived of the blood-brain barrier. These include periventricular organs: posterior hypophyseal lobe, vascular terminal plate, subfornical body, subcallosal area, Area postrema as well as the pineal body and choroid plexus [12]. ECM protein proteolysis plays an important role in the excessive MMPs activation [10] and the change in their structure affects the plasticity within the synapses, neurons and glial cells of the CNS. Brain plasticity means the ability of the neuronal networks to undergo structural and functional reorganization in response to external stimuli, which allows the body to adapt to the changing environment (through the processes of learning and remembering). The phenomenon of plasticity is indispensable in the process of recovery following the CNS

disorders resulting from various pathomechanisms, including injuries. The changes concern regulations on the molecular level (gene expression, accessibility and functions of proteins), the impact on the cellular physiology and the final effect in the form of changes in the behavior of an individual. Changes in the synaptic plasticity may contribute to the development of pathological conditions (e.g., epilepsy, drug dependency, autism spectrum disorder, schizophrenia, depression) or alleviate adverse effects of pathological changes (e.g., multiple sclerosis, Parkinson`s disease, deterioration of cognitive functions, Alzheimer`s disease) [13, 14].

MMPs, including MMP-1 and MMP-7, are capable to degrade the myelin basic protein (MBP). This results in degradation of the myelin sheath and exposure of immunogenic epitopes, which intensify the autoimmunological response, thereby intensifying the initiated process of destruction of the myelin sheath [15]. MMPs exert also an effect on cytokines and chemokines [16], participate in the formation and destabilization of the atherosclerotic plaque (MMP-1, – 2, – 3, – 7, – 9) [17], which reduces the blood supply to the brain, leading to the development of various types of pathological conditions within the CNS [18].

Aim

Our objective was to analyze the serum levels of two collagenases, MMP-1 and MMP-13 (the substrates are as follows: collagen type I, II, III, V, VII, VIII, and X, entactin, aggrecan) and matrilysin, MMP-7 (digests: collagen type IV, X, gelatin, laminin; affects the activity of other MMPs) in two groups of patients treated for late onset dementia and paranoid schizophrenia and in a control group. Together with MMPs, TIMP-1 and TIMP-2 serum levels were evaluated in both groups of patients and in the control group.

Material and methods

Clinical groups

Persons participating in the study agreed to carry it out. The approval of the Medical University of Lublin Bioethics Committee was also obtained for the implementation of the project.

The study included a group of 54 people chronically treated in psychiatric care and treatment center: 29 people being treated for late onset dementia and 25 treated for paranoid schizophrenia. In patients with dementia, Alzheimer's disease was indicated as the cause of dementia in 17 of them, and in other cases – vascular diseases. All patients – both those with late onset dementia as well as the ones suffering from paranoid schizophrenia – were examined and diagnosed by at least two trained psychiatrists, in accordance with diagnostic criteria for mental disorders, based on the Structured Clinical Interview for DSM-V Axis I Disorders (SCID–I) [19] and ICD-10 [20]. The study excluded people with coexisting disorders associated with the abuse of psychoactive substances or with mental retardation. Symptoms of dementia were assessed using the

Mini-Mental State Examination (MMSE) [21] and features of paranoid schizophrenia were assessed using the Positive and Negative Syndrome Scale (PANSS) [22]. People treated for late onset dementia taking pro-cognitive drugs in full doses: 18 patients took memantine (N-methyl-D-aspartate receptor antagonist, NMDA) and 12 took cholinesterase inhibitors: 10 people – donepezil and 2 – rivastigmine. In the discussed group, 8 patients were subjected to polytherapy – memantine with donepezil, 6 of them were also treated with olanzapine at a dose of 2.5–5 mg daily. Patients diagnosed with paranoid schizophrenia were treated with atypical neuroleptic monotherapy: 16 patients took olanzapine (10–20 mg daily), 6 – clozapine (400–600 mg daily) and 3 – risperidone (4–8 mg daily). The dose of antipsychotic medicine was converted to chlorpromazine equivalent (CPZ). Besides, no patient from the two groups has been given drugs for any other reason or used nicotine.

The control group consisted of 25 people without mental disorders, age-matched with the study groups. Characteristics of the studied groups have been described in Table 1.

Table 1. **Characteristics of patients and control group**

	Late onset dementia	Paranoid schizophrenia	Controls	Statistics
n	28	25	25	-
Sex (male/female)	9/19	12/13	11/14	$p>0.05$ (Chi^2 test)
Age (mean ± SD)	75.5 ± 10.1	61.6 ± 8.9	65.3 ± 4.8	$p<0.001$ (ANOVA)
Duration of illness (mean ± SD)	8.6 ± 4.1	32.6 ± 6.2	NA	NA
PANSS total	NA	111.9 ± 21.5	NA	-
PANSS positive symptoms	NA	22.8 ± 6.3	NA	-
PANSS negative symptoms	NA	32.9 ± 7.1	NA	-
PANSS general symptoms	NA	56.2 ± 11.4	NA	-
MMSE (min.-max.)	8.8 (0 – 22)	-	NA	-
CPZ dose (mg) (mean ± SD)		312 (83.7)	NA	

Biochemical procedures

Venous blood was collected into a sterile tube without the addition of anticoagulant. After clot forming and centrifugation, the serum was transferred to test-tubes and placed in a temperature of – 70°C. Commercially available ELISA kits (R&D Systems, USA) were applied to determine the serum levels of MMP-1, MMP-7, MMP-13 as well as TIMP-1 and TIMP-2. All procedures were performed according to the manufacturer's

instructions. For each assay, the double determination was performed. The results were read using an Epot microplate reader (BioTek, USA) at a wavelength of 450 nm (540 nm correction).

Statistics

The normality distribution was determined using the Lilliefors test. The analysis of determined variables in the studied groups (late onset dementia and paranoid schizophrenia) as compared to the control group was made by one-way ANOVA with Tukey-Kramer Multiple Comparisons Test. The results were expressed as mean ± standard deviation (SD). Significant differences were found at significance level of less than 0.05. Data base and statistics analyses were conducted with the use of the Statistica 12.0 (StatSoft, Poland) software.

Results

In people with late onset dementia we found the following: two-fold increase in MMP-1 and a slight increase in MMP-13 serum levels in comparison to the controls and paranoid schizophrenia patients (p <0.001; Figure 1 and 2); a lower MMP-7 and TIMP-1 serum levels (p <0.05; Figure 3 and 4) and higher TIMP-2 serum level (p <0.001; Figure 5) in comparison to the controls.

In contrast, in the group of people treated for paranoid schizophrenia compared to the control group, a lower MMP-7 serum level (p <0.001), a higher TIMP-2 serum level (p <0.001) and no differences in MMP-1, MMP-13 and TIMP-1 serum levels were found (Figure 1–5).

Discussion

MMPs play an important role in the pathological processes within the CNS [16]. Also, more and more evidence indicates their involvement in the pathogenesis of neurodegenerative diseases [23], including dementia and schizophrenia.

Dementia is one of the most common disorders of the old age. It affects approximately 10% of the elderly population. According to the results of histopathological studies, 60% of dementia cases in the individuals over 65 years of age is due to Alzheimer's disease (AD). The vascular form of dementia constitutes about 15%. It seems it is too frequently diagnosed as numerous cases of multi-infarct dementia turn out to be AD. These two forms of dementia usually coexist in about 20% of cases [24]. Overproduction of MMPs is associated with the development of many pathological conditions, including AD [25].

Schizophrenia affects approximately 1% of population and it often has its onset in early adolescence, although the risk of its development increases after the age of 45, especially in women [26]. At the very beginning of the 21st century a neurodevelopmental background of schizophrenia was commonly hypothesized. In the later years intense degenerative changes in the brain of individuals treated for schizophrenia were

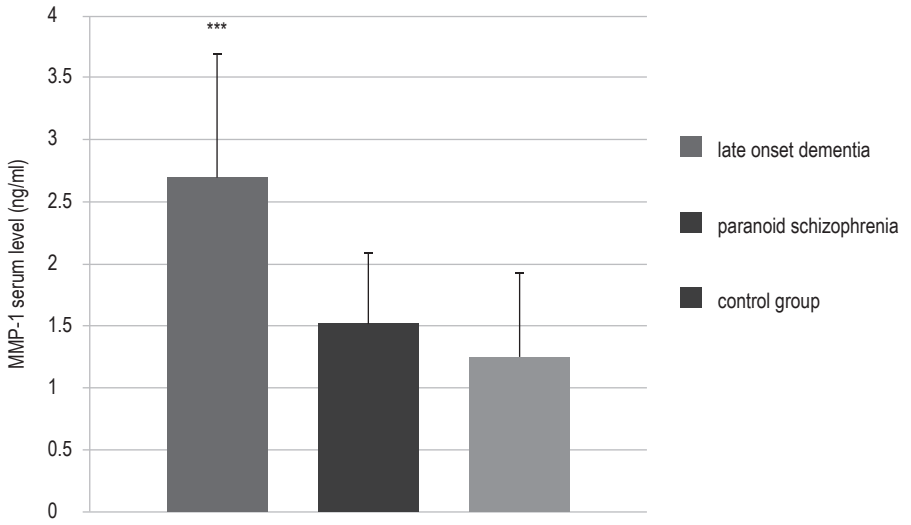

Figure 1. **MMP-1 serum levels in late onset dementia and paranoid schizophrenia patients compared to controls**

Mean and SD values. ANOVA p <0.0001; Tukey-Kramer Multiple Comparison Test ***p <0.001 late onset dementia vs. controls and late onset dementia vs. paranoid schizophrenia

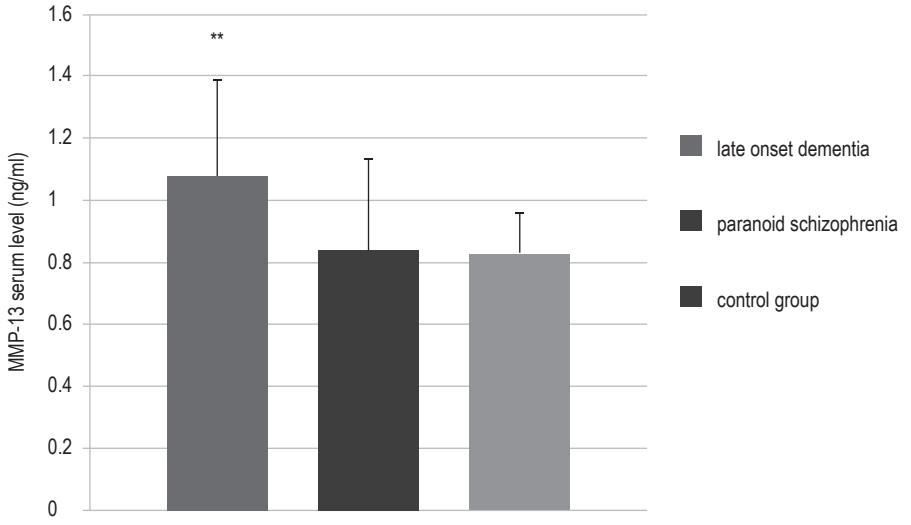

Figure 2. **MMP-13 serum levels in late onset dementia and paranoid schizophrenia patients compared to controls**

Mean and SD values. ANOVA p = 0.0008; Tukey-Kramer Multiple Comparison Test **p <0.01 late onset dementia vs. controls and late onset dementia vs. paranoid schizophrenia

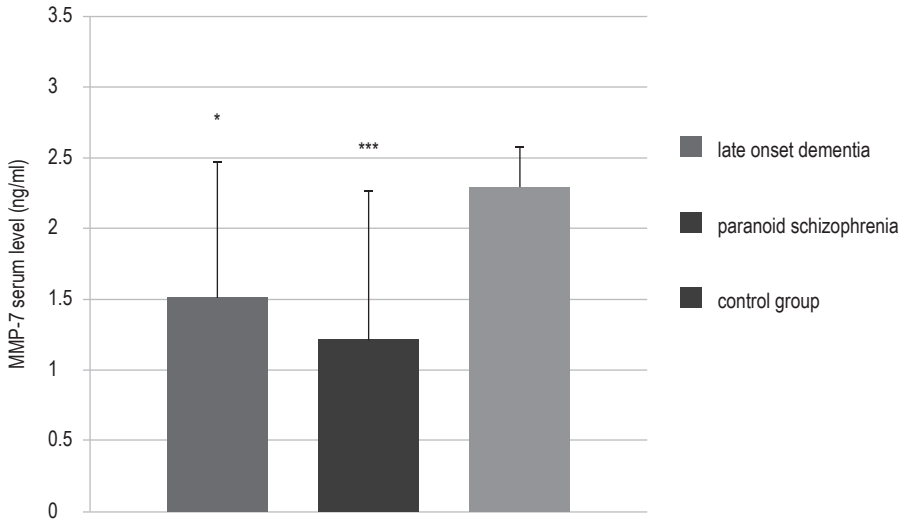

Figure 3. **MMP-7 serum levels in late onset dementia and paranoid schizophrenia patients compared to controls**

Mean and SD values. ANOVA p = 0.0007; Tukey-Kramer Multiple Comparison Test *p <0.05 late onset dementia vs. controls, ***p <0.001 paranoid schizophrenia vs. controls

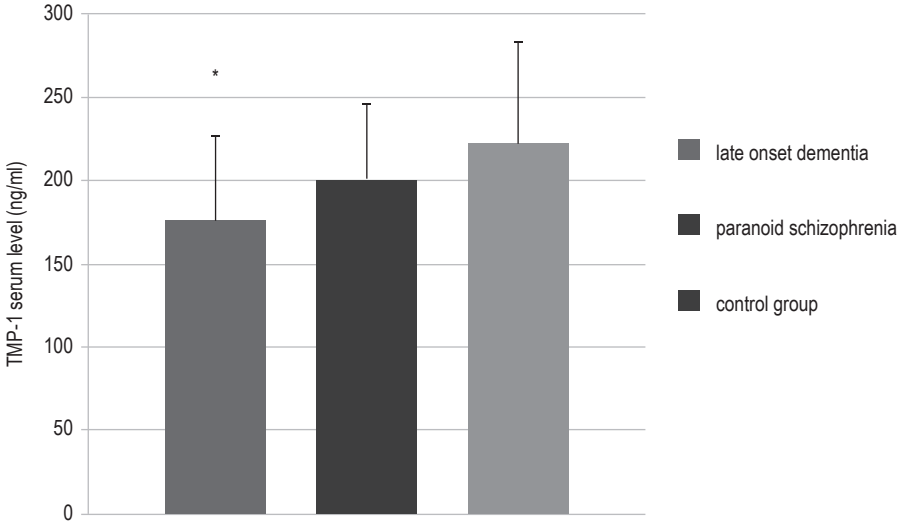

Figure 4. **TIMP-1 serum levels in late onset dementia and paranoid schizophrenia patients compared to controls**

Mean and SD values. ANOVA p = 0.0135; Tukey-Kramer Multiple Comparison Test *p <0.01 late onset dementia vs. controls

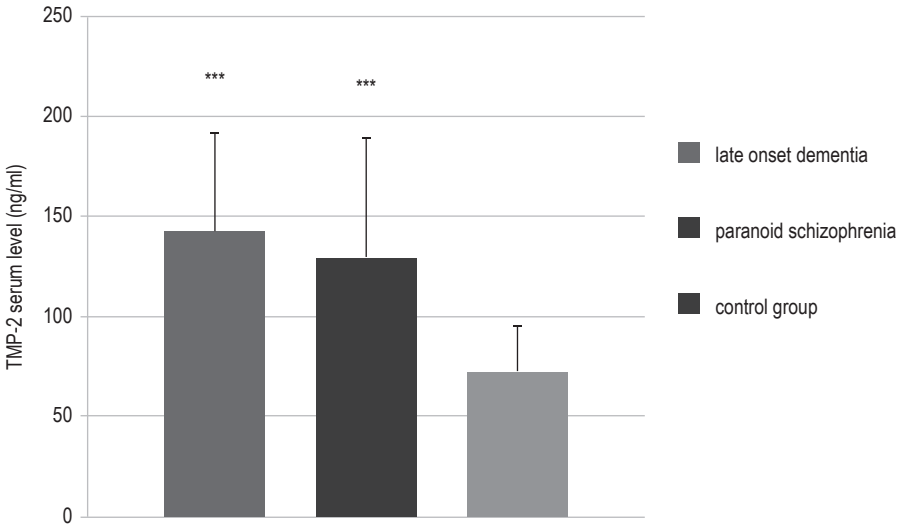

Figure 5. **TIMP-2 serum levels in late onset dementia and paranoid schizophrenia patients compared to controls**

Mean and SD values. ANOVA p <0.0001; Tukey-Kramer Multiple Comparison Test ***p <0.001 late onset dementia vs. controls and paranoid schizophrenia vs. controls

further demonstrated, which confirmed the hypothesis [27]. Undoubtedly, neurodegenerative and neurodevelopmental processes overlap in schizophrenia spectrum disorder.

According to the neurodevelopmental theory, an abnormal progress of genetically programmed processes, such as neuron migration, formation of nerve connections and synapses (reduced number and size of the synaptic vesicles, delayed release of their contents) or neuron selection (surviving neurons are unable to migrate to the appropriate regions of the brain and form connections), are observed in schizophrenia. The neurodegenerative hypothesis, however, points out to a process of destruction of synapses and neural projections (axons and dendrites) as a result of disturbances in the genetically programmed processes. Some researchers are of the opinion that increasing cognitive disturbances result from the neurotoxic effect of psychosis or external factors [28]. An advancing process of neuronal degeneration and an increase in residual (negative) symptoms in schizophrenia may be a result of an excessive transmission within the glutamatergic system. This may lead to the neurodegenerative and toxic stimulation of the NMDA receptors. According to this hypothesis, a pathological process is responsible for the chaotic and toxic neuronal activation. At this stage the calcium channels open up, secondary activation of intracellular enzymes gets started and production of free radicals is launched. All these toxic factors affect the cell membranes and intracellular structures, thereby leading to a slow CNS neurodegeneration [29]. Primary cognitive deficits are overlapped by secondary cognitive disturbances, which is associated with the phenomenon of excitotoxicity and neurodegeneration.

The results of neuroimaging studies of individuals with a long course of the disease seem to confirm the neurodegeneration hypothesis: a decreased volume of the gray matter, especially within the frontal cortex and thalamus, and the white matter, especially in the frontal, temporal and parietal regions; widening of the lateral ventricles of the brain as well as widening of the fluid spaces in the frontal, temporal and parietal regions of the brain [30]. These changes correlate with the impairment of cognitive functions, however, they had little impact on other clinical parameters [31]. The correlations were found between schizophrenia, polymorphism of some of metalloproteinases and occurrence of acute positive symptoms manifested by thought content disorder [32–35] – among other things, an increase in TIMP-1 level was indicated [36], although Jeffries et al. [37] did not confirm this correlation.

The study conducted by the authors of this paper is innovative since there are very scarce reports in the literature on the scientific analysis of concentrations of selected metalloproteins (MMP-1, MMP-13 and MMP-7) as well as their inhibitors (TIMP-1 and TIMP-2) in patients treated for dementia or schizophrenia [12]. The specialist literature does not provide much information about the expression of collagenase-1 in the CNS [38]. The latter showed MMP-1 immunoreactivity in the olfactory lobes, the entorhinal cortex, bridge nuclei, and periarterial gray matter [39], also in the brain of people treated for AD [40]. It seems that mainly glia cells are responsible for the expression of MMP-1 [41], although neurons are also pointed out to [39]. MMP-1 increases the proliferation and differentiation of neurons from hippocampal stem cells [42]. In contrast, studies on an animal model have shown that its increased concentration causes learning and memory deficits [43].

In our studies we observed an apparent increase in the MMP-1 concentration in the serum of the studied AD patients, which is in line with animal models. Moreover, in the AD patients an increase in the other studied collagenase, MMP-13, as well as a decrease in the TIMP-1 concentration was observed, which is suggestive of intense processes of protein modeling in the extracellular matter in that group of patients. In the brain, MMP-1 acts mainly through the receptor activated by the proteinase 1 (PAR1) and an increase in the citoplasmatic Ca^{2+} concentration, also in the platelets. As for collagenase 3, the studies performed so far have analyzed its relationship with PAR1 in the heart muscle. Similarly to the research into collagenases, the MMP-7 expression is hardly reported in the specialist literature. The microglial cells are responsible for the expression of this metalloproteinase. The study results indicate the high level of matrilysin in the hippocampal region, and its increase in multiple sclerosis, experimental, autoimmune encephalomyelitis, dementia or brain tumors. Among the substrates of MMP-7 in the brain the most important are as follows: the pro-nerve growth factor (proNGF), SNAP-25, NMDA receptor NR1 subunit, and myelin-associated glycoprotein [13].

MMP-7 may directly affect functioning of the NMDA receptor and its downregulation, which is essential for synaptic plasticity. Moreover, application of the recombinant MMP-7 at the presynaptic terminal on cultured hippocampal neurons reduced easily released bulk of the synaptic vesicles, it reduced the dimension of the active zones and hindered recycling of the vesicles. The effect of MMP-7 on vesicle recycling may be

partially explained by the split of SAP-25 protein (a protein bound with a synaptosome of 25kDa mass), which disrupts the complexity of vesicle docking [44].

Despite the scarcity of data concerning the studied issue, it is worth noting that pharmacotherapy of neurodegenerative diseases of the central nervous system (typical neuroleptics medication, memantine) also has an impact on the expression of metalloproteinase genes and their inhibitors. A correlation has been found between the dose of haloperidol and expression of mRNA MMP-9 and TIMP-1, with no effect on MMP-2 within the range of monocytes [45]. It has been observed that the MMP-9 polymorphism and severity of traumatic events in childhood have an effect on the response to flupentixol treatment in the population of patients with the first episode of schizophrenia [46]. In the case of anti-dementia drugs, it has been shown that memantine reduces the expression and activity of MMP-2, it does not affect MMP-9 after ischemia or endothelial cell reperfusion of the cerebral vessels, it intensifies the TIMP-2 expression [47].

A limitation of our work is the different age of the study groups. Patients with paranoid schizophrenia were the youngest of the analyzed groups. However, the results of previous studies do not indicate a significant relationship between the concentration of metalloproteinases and the age of the subjects or indicate such a relationship in the case of comparative analysis of their concentration in the population of very young people and the elderly [1, 48, 49].

The knowledge about properties and significance of MMPs in the central nervous system has progressed over the years. Modulation of the MMP function may be a promising alternative of the therapy of neurodegenerative diseases. Determination of these proteins in the bodily fluids may be of great diagnostic significance and application of specific inhibitors may lead to hampering of neurodegenerative processes.

Conclusions

1. In people with late-onset dementia, an increase in collagenolytic activity has been demonstrated, which may indicate an increased remodeling within the central nervous system in this group of patients.
2. The difference in the fluctuation of the concentrations of the tested enzymes and their inhibitors in dementia and paranoid schizophrenia indicates their different participation in the pathogenesis of these disorders.

References

1. Kucharska A. *Stężenie metaloproteinazy macierzy zewnątrzkomórkowej-9 (MMP-9) w schizofrenii i chorobach afektywnych a stan kliniczny i neuropsychologiczny*. Poznan: Poznan University of Medical Sciences, 2016.
2. Csoka A, Sternr R. *Hypotheses on the evolution of hyaluronan: a highly ironic acid*. Glycobiology 2013; 23: 398–411.
3. Larsen M, Artym V, Green J, Yamada K. *The matrix reorganized: extracellular matrix remodeling and integrin signaling*. Curr. Opin. Cell. Biol. 2006; 18: 463–471.

4. Mott J, Werb Z. *Regulation of matrix biology by matrix metalloproteinases*. Curr. Opin. Cell. Biol. 2004; 16: 558–564.
5. Pastuszka E, Pabin A, Radkowski M. *Metalloproteinases in meningoencephalitis*. Przegl. Epidemiol. 2008; 62: 401–406.
6. Nagase H, Visse R, Murphy G. *Structure and function of matrix metalloproteinases and TIMPs.* Cardiovasc. Res. 2006; 69: 562–573.
7. Chirco R, Liu X, Jung K, Kim H. *Novel functions of TIMPs in cell signaling*. Cancer Metastasis. Rev. 2006; 25: 99–113.
8. Leib S, Clements J, Lindberg R, Heimgartner C, Loeffler J, Pfister LA et al. *Inhibition of matrix metalloproteinases and tumour necrosis factor alpha converting enzyme as adjuvant therapy in pneumococcal meningitis*. Brain 2001; 124: 1734–1742.
9. VanSaun M, Matrisian L. *Matrix metalloproteinases and cellular motility in development and disease*. Birth Defects Res. C. Embryo. Today 2006; 78: 69–79.
10. Zalewska T, Ziemka-Nałęcz M, Sarnowska A, Domańska-Janik K. *Transient fore-brain ischemia modulates signal transduction from extracellular matrix in gerbil hippocampus*. Brain Res. 2003; 977: 62–69.
11. Hummel V, Kallmann B, Wagner S, Füller T, Bayas A, Tonn J et al. *Production of MMPs in human cerebral endothelial cells and their role in shedding adhesion molecules*. J. Neuropathol. Exp. Neurol. 2001; 60: 320–327.
12. Wright J, Harding J. *The brain angiotensin system and extracellular matrix molecules in neural plasticity, learning, and memory*. Prog. Neurobiol. 2004; 72: 263–293.
13. Beroun A, Mitra S, Michaluk P, Pijet B, Stefaniuk M, Kaczmarek L. *Cellular and Molecular Life Sciences MMPs in learning and memory and neuropsychiatric disorders*. Cellular and Molecular Life 2019; 76: 3207–3228.
14. Bitanihirwea B, Woo T. *A conceptualized model linking matrix metalloproteinase-9 to schizophrenia pathogenesis*. Schizophrenia Research 2020. https://doi.org/10.1016/j.schres.2019.12.015.
15. Svedin P, Hagberg H, Sävman K, Zhu C, Mallard C. *Matrix metalloproteinase-9 gene knock—out protects the immature brain after cerebral hypoxia-ischemia*. J. Neurosci. 2007; 27: 1511–1518.
16. Kurzepa J, Bartosik-Psujek H, Suchozebrska-Jesionek D, Rejdak K, Stryjecka-Zimmer M, Stelmasiak Z. *Role of matrix metalloproteinases in the pathogenesis of multiple sclerosis*. Neurol. Neurochir. Pol. 2005; 39(1): 63–67.
17. Fic P, Zakrocka I, Kurzepa J, Stepulak A. *Metaloproteinazy w miażdżycy naczyń krwionośnych*. Post. Hig. Med. Dośw. 2011; 65: 16–27.
18. Rodriguez-Feo J, Sluijter J, de Kleijn D, Paster-Kamp G. *Modulation of collagen turnover in cardiovascular disease*. Curr. Pharm. Des. 2005; 11: 2501–2514.
19. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorder (5th ed.).* Washington, DC: APA; 2013.
20. *Międzynarodowa Statystyczna Klasyfikacja Chorób i Problemów Zdrowotnych ICD-10*, ICD-10; World Health Organisation; 2009.
21. Foistein M, Foistein S, McHugh P. *MiniMental State: A practical method for grading and the cognitive state of patients for the clinician*. Journal of Psychiatric Research 1975; 12: 189–198.
22. Kay S, Oppler L, Fiszbein A. *The Positive and Negative Syndrome Scale (PANSS) for schizophrenia*. Schizophrenia Bull. 1986; 13: 261–276.

23. Wysocka A, Giziński S, Lechowski R. *Metaloproteinazy macierzy – ich struktura oraz znaczenie*. Życie Weterynaryjne 2014; 89(3): 34–45.
24. Small G. *Differential diagnosis and early detection of dementia*. Am. J. Geriatr. Psychiatry 1998; 6: 26–33.
25. Baker A, Edwards D, Murphy G. *Metalloproteinase inhibitors: biological actions and therapeutic opportunities*. J. Cell. Sci. 2002; 115: 3719–3727.
26. Hafner H, Van der Heiden W, Behrens S, Gattaz W, Hambrecht M, Löffler W et al. *Causes and consequences of the gender difference in age at onset of schizophrenia*. Schizophr. Bull.1998; 24: 99–113.
27. Murray R, Bhavsar V, Tripoli G, Howes O. *30 Years on: How the Neurodevelopmental Hypothesis of Schizophrenia Morphed Into the Developmental Risk Factor Model of Psychosis*. Schizophr. Bull. 2017; 43(6): 1190–1196.
28. Stahl S. *Stahl's essential psychopharmacology: neuroscientific basis and practical applications*. Cambridge: Cambridge University Press; 2008.
29. Gargiulo P, Landa De Gargiulo A. *Glutamate and modeling of schizophrenia symptoms: Review of our Findings: 1990−2014*. Pharmacol. Rep. 2014; 66: 343−352.
30. Andreasen N, Nopoulos P, Magnotta V, Pierson R, Ziebell S, Ho B. *Progressive brain change in schizophrenia: a prospective longitudinal study of first-episode schizophrenia*. Biol. Psychiatry 2011; 70: 672−679.
31. Andreasen N, Liu D, Ziebell S, Vora A, Ho B. *Relapse duration, treatment intensity, and brain tissue loss in schizophrenia: a prospective longitudinal MRI study*. Am. J. Psychiatry 2013; 170: 609−615.
32. Rybakowski J, Skibinska M, Kapelski P, Kaczmarek L, Hauser J. *Functional polymorphism of the matrix metalloproteinase-9 (MMP-9) gene in schizophrenia*. Schizophr. Res. 2009; 109(1–3): 90–93.
33. Han H, He X, Tang J, Liu W, Liu K, Zhang J et al. *The C(-1562)T polymorphism of matrix metalloproteinase-9 gene is associated with schizophrenia in China*. Psychiatry Res. 2011; 190(1): 163–164.
34. Kucukali C, Aydin M, Ozkok E, Bilge E, Orhan N, Zengin A et al. *Do schizophrenia and bipolar disorders share a common disease susceptibility variant at the MMP3 gene?* Prog. Neuropsychopharmacol. Biol. Psychiatry 2009; 33(3): 557–561.
35. Lepeta K, Purzycka K, Pachulska-Wieczorek K, Mitjans M, Begemann M, Vafadari B. et al. *A normal genetic variation modulates synaptic MMP-9 protein levels and the severity of schizophrenia symptoms*. EMBO Mol. Med. 2017; 9(8): 1100–1116.
36. Domenici E, Wille D, Tozzi F, Prokopenko I, Miller S, McKeown A et al. *Plasma protein biomarkers for depression and schizophrenia by multi analyte profiling of case-control collections*. PLoS One 2010; 5(2): 9166.
37. Jeffries C, Perkins D, Fournier M, Do K, Cuenod M, Khadimallah I et al. *Networks of blood proteins in the neuroimmunology of schizophrenia*. Transl. Psychiatry 2018; 8(1): 112.
38. Sharma N, Wang X, Majerciak V, Ajiro M, Kruhlak M, Meyers C et al. *Cell type – and tissue context-dependent nuclear distribution of human Ago2.* J. Biol. Chem. 2016; 291(5): 2302–2309.
39. Ierusalimsky V, Balaban P. *Type 1 metalloproteinase is selectively expressed in adult rat brain and can be rapidly upregulated by kainate*. Acta Histochem. 2013; 115(8): 816–826.
40. Leake A, Morris C, Whateley J. *Brain matrix metalloproteinase 1 levels are elevated in Alzheimer's disease*. Neurosci. Lett. 2000; 291(3): 201–203.

41. Vos C, Sjulson L, Nath A, McArthur J, Pardo C, Rothstein J et al. *Cytotoxicity by matrix metalloprotease-1 in organotypic spinal cord and dissociated neuronal cultures*. Exp. Neurol. 2000; 163(2): 324–330.
42. Valente M, Allen M, Bortolotto V, Lim S, Conant K, Grilli M. *The MMP-1/PAR-1 axis enhances proliferation and neuronal differentiation of adult hippocampal neural progenitor cells*. Neural. Plast. 2015: 64: 65–95.
43. Allen M, Ghosh S, Ahern G, Villapol S, Maguire-Zeiss K, Conant K. *Protease induced plasticity: matrix metalloproteinase-1 promotes neurostructural changes through activation of protease activated receptor 1*. Sci. Rep. 2016; 6: 354–397.
44. Szklarczyk A, Oyler G, McKay R, Gerfen C, Conant K. *Cleavage of neuronal synaptosomal-associated protein of 25 kDa by exogenous matrix metalloproteinase – 7*. J. Neurochem. 2007; 102(4): 1256–1263.
45. Lee Y, Hsiao C, Lin F, Jan J, Chou Y, Lin Y et al. *Haloperidol Abrogates Matrix Metalloproteinase-9 Expression by Inhibition of NF-κB Activation in Stimulated Human Monocytic Cells*. Mediators Inflamm. 2018; 2018: 9541459.
46. McGregor N, Thompson N, Sean O'Connell K, Emsleyb R, van der Merwe L, Warnich L. *Modification of the association between antipsychotic treatment responseand childhood adversity by MMP9 gene variants in a first-episode schizophrenia cohort.* Psychiatry Research 2018; 262: 141–148.
47. Liu Y, Huang Y, Xu Y, Qu P, Wang M. *Memantine protects against ischemia/reperfusion-induced brain endothelial permeability*. IUBMB Life 2018; 70(4): 336–343.
48. Tayebjee M, Lip G, Blann A, Macfadyen R. *Effects of age, gender, ethnicity, diurnal variation and exercise on circulating levels of matrix metalloproteinases (MMP)-2 and – 9, and their inhibitors, tissue inhibitors of matrix metalloproteinases (TIMP)-1 and – 2*. Thromb. Res. 2005; 115(3): 205–210.
49. Weber K, Alipui D, Sison C, Bloom O, Quraishi S, Overby M et al. *Serum levels of the proinflammatory cytokine interleukin-6 vary based on diagnoses in individuals with lumbar intervertebral disc diseases*. Arthritis Res. Ther. 2016; 18: 3.

Address: Aneta Tylec
2nd Department of Psychiatry and Psychiatric Rehabilitation
Medical University of Lublin
20-439 Lublin, Głuska Street 1
e-mail: anetatylec@wp.pl