Educational Administration: Theory and Practice
2024, 30(4), 6248-6254
ISSN:2148-2403
https://kuey.net/

Research Article

MMP-3 And MMP-9 Concentrations In Alzheimer's Disease: A Cerebrospinal Fluid And Serum Analysis

Asma Perveen[1], Rayees Afzal Mir[1*], Mohd Gulfishan[1], Abdul Hafeez[2]

[1]Glocal School of Life Science, Glocal University, Saharanpur, Uttar Pradesh 247121, India.

[2]Glocal university Pharmacy college, Glocal University, Saharanpur, U.P 247121, India.

***Corresponding authors: Dr. Rayees Afzal Mir**

Glocal School of Life Science, Glocal University, Saharanpur, Uttar Pradesh 247121, India.

Email:- Rayees@theglocaluniversity.in

Citation: Dr. Rayees Afzal Miret al. (2024) MMP-3 And MMP-9 Concentrations In Alzheimer's Disease: A Cerebrospinal Fluid And Serum Analysis, *Educational Administration: Theory and Practice*, 30(4), 6248-6254
Doi: 10.53555/kuey.v30i4.2371

ARTICLE INFO

ABSTRACT

Matrix metalloproteinases (MMPs) constitute a group of proteins known for their pivotal role in the central nervous system, influencing process from growth and development to brain injury and repair. The specific MMPs targeting the amyloid precursor protein (APP) play a crucial role in influencing the aggregation of amyloid beta (Aβ), contributing to the onset of Alzheimer's disease (AD). While altered MMP expression has been implicated in the progression of AD, a definitive expression pattern remains elusive. Consequently, this study aims to establish the precise expression pattern of MMP-3 and MMP-9 in patients with AD. For this purpose, cerebrospinal fluid (CSF) and sera were collected from 31 patients with AD and 25 healthy normal controls. ELISA was employed to determine MMP-3 and MMP-9 quantities in both CSF and serum samples, followed by a comparative analysis to ascertain their expression patterns. Significantly different MMP-3 and MMP-9 levels were observed between patients with AD and healthy controls. Interestingly, a positive correlation emerged between the Mini Mental Status Examination (MMSE) score and concentrations of MMP-3 and MMP-9 in both CSF and serum, with MMP-9 demonstrating higher expression levels than MMP-3 in both compartments. These findings shed light on the distinct expression patterns of MMP-3 and MMP-9 in patients with AD and prompt further investigations into the potential utilization of these dynamic molecules as promising biomarkers for AD therapy.

Keywords: Alzheimer's disease, Biomarker, Matrix metalloproteinases, MMP-3, MMP-9

INTRODUCTION

Neurodegenerative disorders (NDDs), including Alzheimer's disease (AD), Parkinson's disease (PD), Mild Cognitive Impairement (MCI), Multiple Sclerosis (MS), and Amyotrophic Lateral sclerosis (ALS), stand as the primary etiological factors underlying dementia. These disorders are distinguished by cognitive impairments, encompassing deficiencies in memory retention and challenges in acquiring new information, fundamentally hampering the affected individuals' ability to autonomously navigate daily life (1). The etiology and progression of these NDDs have been correlated with an altered concentration of various proteins in the cerebrospinal fluid (CSF) and serum of the patients (2).

Matrix metalloproteinases (MMPs), also known as matrixins, distinguished by protein-domain structure and substrate preferences, form a family comprising at least 28 MMPs, are collectively capable of breaking down diverse components within the extracellular matrix (ECM). These MMPs can be further categorized into six primary subgroups. Gelatinases (e.g., MMP-2, MMP-9) are responsible for the degradation of molecules in the basal lamina around capillaries, facilitating several processes including angiogenesis, neurogenesis,

osteogenesis and wound healing. They also play pivotal role in inducing cell death and actively contribute to injury and repair mechanisms(3,4). The stromelysins group of MMPs [stromelysin-1(MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11)] has broad substrate specificity for components of the ECM. This group of enzymes degrades non-collagen connective tissue component including proteoglycans, fibronectin, laminin as well some other minor types of collagens. In addition, MMP-3 has the ability to cleave and activate pro-collagenase, thereby providing additional matrix-degrading capability. Collagenases (e.g., MMP-1, MMP-8, MMP-13, MMP-18) are specialized in degrading the triple helical fibrillar collagen found in bones and cartilage. Membrane-type MMPs (MT-MMPs, e.g., MT1, MT2, MT3, MT4, MT5, MT6), operate at the cell surface, wielding several functions, including the activation of other proteases and growth factors. Matrilysines (e.g., MMP-7) act on collagen type IV, glycoproteins, and gelatin. Other uncategorized MMPs (e.g., MMP-12, MMP-19, MMP-20, MMP-23, MMP-27, MMP-28) act on amelogenin, aggrecan, and elastin(5,6).Structurally, MMPs share four primary domains: catalytic, propeptide, transmembrane, and hemopexin-like domains, each essential for their distinct functions and enzymatic activities (7). MMPs are not only involved in a multitude of physiological processes, but their significance in the pathological progression of NNDs is also crucial, given their contribution to the intricate mechanisms of growth, injury, and repair within the central nervous system (CNS)(5,8–10). Within the CNS, notable MMPs involved in diverse processes comprise MMP-2, MMP-3, MMP-9, and MMP-14, each contributing significantly in the complex network of cellular events within the CNS, especially in the context of NDDs (11). Certain MMPs demonstrate functionality that induces the aggregation of amyloid beta (Aβ) by degrading amyloid precursor protein (APP), thereby contributing to the pathology of these disorders(12).

MMP-3 functions as a versatile matrix enzyme adept in degrading a spectrum of extracellular compounds, encompassing collagens, matrix proteins, and various proteoglycans. In mice devoid of MMP-3, observable alterations in neuromuscular junction manifested, characterized by augmented acetylcholine receptor (AChR) endplate staining and a higher count of functional folds. Additionally, a notable elevation in agrin concentration occurs at these neuromuscular junctions (13). Interestingly, during the creation of purified tau protein alongside active MMP-3 and MMP-9, minimal proteolysis was observed (14). Further insights are established through the correlation between CSF MMP-3 levels and the levels of T-tau and P-tau in older controls (15).

MMP-9 has emerged as a central participant in the pathogenesis of AD, as evidenced by its expression in diverse pathological hallmarks within AD patients. This includes senile plaques, neurofibrillary tangles, neuronal cytoplasm, cerebral cortex, and hippocampal vascular walls(16). Investigations correlating preventive brain blooming after immunotherapy with MMP-9 upregulation have shed light on its proinflammatory activity, suggesting its involvement in the disruption of blood-brain barrier (BBB)(17). A recent study has underscored the elevated levels of MMP-9 in neuronal extracellular vesicles in patients with AD, emphasizing the growing significance of MMP-9 in the pathogenesis of AD. The involvement of MMP-3 and MMP-9 in the pathophysiology of AD is depicted in Figure 1. Citing the increasing significance of MMP-3 and MMP-9 in AD, and scarcity of comprehensive studies on their conclusive expression patterns, our investigation delved into the analysis of these patterns in the CSF and serum samples of patients with AD patients. The primary objective was to unveil their potential role as biomarkers in the realm of AD.

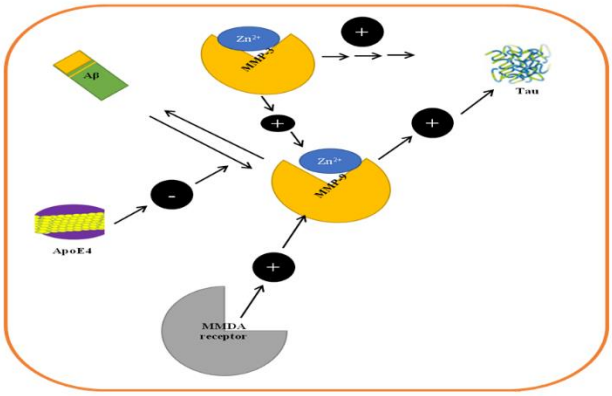

Fig. 1: MMP-9 and MMP-3 in AD pathology.

PATIENTS AND METHODS

Patients and Neuropsychological Assessment: The study enrolled a total of 56 participants, comprising 31 patients diagnosed with AD and 25 healthy individuals formingthe control group. Clinical severity of cognitive status was assessed using the Mini Mental Status Examination (MMSE) (18). The determination of

the MMSE cutoff score was based on considerations of education and age. Prior to formal diagnosis, a consensus was achieved by integrating all the laboratory and clinical data.

Ethical consideration: This study was conducted following the guidelines set forth by the National Institute of Neurological and Communicative Disorders and Stroke AD and Related Disorders Association and International Classification of Diseases, Tenth Revision, Diagnostic and Statistical Manual of Mental Disorders (Third Edition) (19). The research protocol was approved by ethical committee of King Abdulaziz University, Jeddah, Saudi Arabia. Additionally, written informed consent, in accordance with the Declaration of Helsinki, was obtained from each participating patient. All patients with AD included in this study had been diagnosed for a minimum of two years. Patients with AD and healthy control participants who reported habitual chain smoking were excluded from the study. Furthermore, patients with AD and healthy control individuals who reported the use of any medication that could potentially interfere with the study were also excluded.

Sample Collection: CSF and serum samples were meticulously collected from both patients and healthy controls and subsequently preserved at -80°C until the time of analysis. The collection of CSF involved lumbar puncture, performed under strict aseptic conditions, with an approximate volume of 5-8 ml, adhering strictly to the established inclusion and exclusion criteria.

Measurement of MMP-3 and MMP-9 concentrations in CSF ad serum samples:

To measure the concentrations of MMP-3 in CSF and serum samples from patients with AD, as well as healthy control samples, the Human MMP3 ELISA Kit (ab189572) by Abcam was utilized. Additionally, concentrations of MMP-9 in CSF and serum samples were quantified using Abcam's ab100610-MMP-9 Human ELISA™ kit. Briefly, each well of 96-well plate received 100 µL of the sample or standard, and incubation was carried for 2.5 hours. Subsequently, the solution was aspirated, and the plate was washed four times with 350 µL of wash buffer. Following the washes, 100 µL of biotinylated antibody was added to each well, and the plate was incubated at room temperature for one hour with gentle shaking. Afterward, the solution was aspirated, and the washing process was repeated. Next, 100 µL of HRP-Streptavidin solution was added to each well, and the plate was incubated at room temperature for 45 minutes with gentle shaking. The solution was then aspirated, and the washing step was repeated. Subsequently, 100 µL of TMP substrate was added to each well and incubated at room temperature for 30 min with gentle shaking in dark. Finally, 50 µL of stop solution was added to each well, and the absorbance was read at 450 nm.

Data Interpretation and Statistical Analysis. The differences in cognitive performance, sociodemographic characteristics, and MMP-3/MMP-9 concentrations were analyzed by MMSE test. Statistical analysis was carried out using Statistical Package for the Social Sciences Version 25 (SPSS Inc., Chicago, IL, USA). The Chi-squared test was employed to assess correlations among nonparametric data, encompassing demographic information. An unpaired t-test was utilized for the analysis of hematological parameters. Furthermore, a one-way ANOVA was performed to evaluate the association patterns among the tested parameters. Statistical significance was established at $P < 0.05$.

RESULTS

In the current study, a thorough analysis of the altered expression profiles of MMP-3 and MMP-9 was conducted, utilizing CSF and serum samples obtained from patients with AD and healthy normal controls. The control group exhibited a comparatively younger average age in contrast to patients with AD, resulting in higher scores on the MMSE test. Furthermore, the gender distributions and educational years between healthy control and AD groups displayed no significant differences. Table 1 depicts the demographic parameters and baseline characteristics of both groups.

Table 1. Demographic parameters and baseline characteristics.

Characteristics	AD	Controls	*p*
	n =31	*n = 25*	
Age (years)	66.8±7.8	65.71±6.5	0.05
Years of education	9.16±5.67	10.62±6.34	0.045
Males	18	13	0.04
Females	13	12	0.04
MMSE score	20.7±5.2	22.46±5.71	<0.001

MMSE, Mini-Mental State Examination.

CSF and serum concentrations of MMP-3

The MMP-3 concentrations in both CSF and serum showed a significant positive correlation (P < 0.001) with the MMSE score as in both healthy controls and AD groups as illustrated in Figure 2. In order to integrate age difference as a factor between healthy and AD groups, age was used as ANOVA covariate. The concentration of MMP-3 in CSF samples notably differed (P = 0.005) between the healthy controls and AD groups with a significant increase observed in AD patients compared to healthy controls (mean ± SD: 11.21±3.88ng/mL for healthy controls vs.17.31±4.02 ng/mL for AD patients; P = 0.025) (Figure 3).

Similarly, a noticeable difference in MMP-3 concentration was evident in serum samples between healthy controls and AD patients (P = 0.005). The concentration of MMP-3 was significantly higher in patients compared to controls (mean ± SD: 8.57±3.53 for healthy controls vs. 12.43±3.57 ng/mL for AD; P = 0.025) (Figure 4).

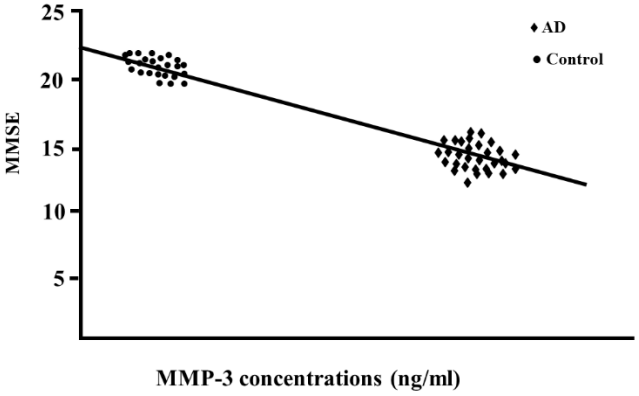

Fig. 2: MMSE and MMP-3 concentrations. A significant correlation was observed between MMSE score as a measure of cognitive status and MMP-3 levels P < 0.001) in AD patients as well as healthy controls (AD = 31, Controls = 25).

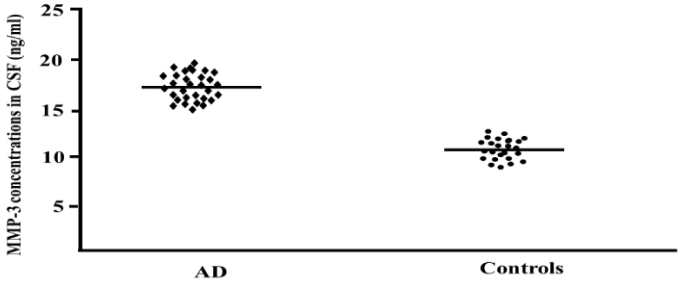

Fig. 3: The concentrations of MMP-3 in CSF of AD patients and healthy controls. AD patients showed enhanced MMP-3 concentrations in CSF as compared to the healthy controls [AD vs. controls (mean±SD) 17.31±4.02 vs. 11.21±3.88 ng/mL; P = 0.025].

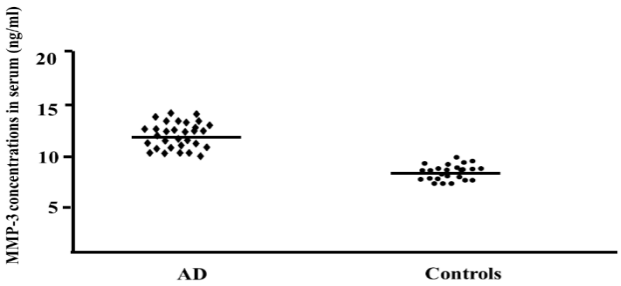

Fig. 4: The concentrations of MMP-3 in serum of AD patients and healthy controls. AD patients showed enhanced MMP-3 concentrations in serum as compared to the healthy controls [AD vs. healthy controls (mean ± SD) 12.43±3.57 vs. 8.57±3.53 ng/mL; P = 0.025].

CSF and serum concentrations of MMP-9

The concentrations of MMP-9 in CSF and serum form both healthy controls and patients with AD demonstrated a substantial positive correlation with the MMSE score (Figure 5). To account for age disparities between the healthy and AD groups, age was considered as a covariate in the ANOVA analysis. The concentration of MMP-9 in CSF samples exhibited a discernible difference (P = 0.005) between healthy controls and AD groups. A significant increase in MMP-9 concentration in CSF samples was observed in AD patients as compared to healthy controls (mean ± SD:13.43±4.18 for healthy controls vs. 18.56±4.32 ng/mL for AD patients; P = 0.025] (Figure 6). Similarly, a statistically significant difference in MMP-9 concentration was evident in serum samples between healthy controls and patients with AD (P = 0.005). A higher concentration of MMP-9 was observed in serum of patients with AD in comparison to healthy controls (mean ± SD: 13.61±3.96 for AD patients vs. 9.33±3.86 ng/mL for controls; P = 0.025] (Figure 7).

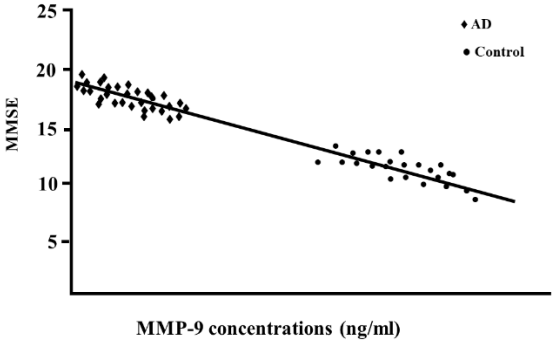

Fig. 5: MMSE and MMP-9 concentrations. A significant correlation was observed between MMSE score as a measure of cognitive status and MMP-9 levels P < 0.001) in all the patients (AD = 31, Controls = 25).

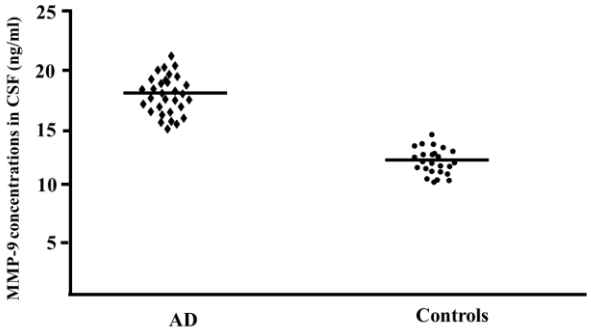

Fig 6: **The concentrations of MMP-9 in CSF of AD patients and healthy controls.** AD patients showed enhanced MMP-9 concentrations in CSF as compared to the healthy controls [AD vs. controls (mean±SD) 18.56±4.32 vs. 13.43±4.18 ng/mL; P = 0.025].

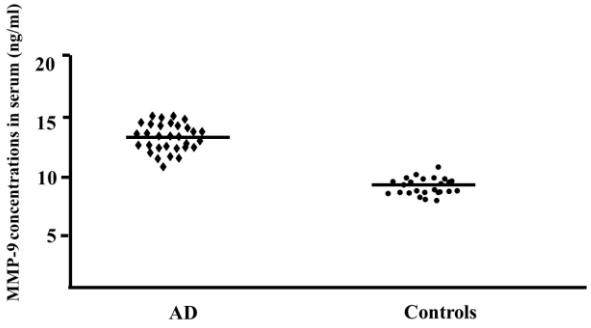

Fig 7: **The concentrations of MMP-9 in serum of AD patients and healthy controls.** AD patients showed enhanced MMP-9 concentrations in serum as compared to the healthy controls [AD vs. healthy controls (mean ± SD) 13.61±3.96 vs. 9.33±3.86 ng/mL; P = 0.025].

DISCUSSION

MMPs, a class of zinc-dependent endopeptidases, are initially secreted as inactive zymogens and require cleavage for activation, participating in the proteolysis of ECM (20).Moreover, they are integral to essential physiological processes, including wound healing, ovulation, angiogenesis, brain development and repair. Simultaneously, MMPs are implicated in pathological processes such as tumor progression and AD (9).

This investigation explored the concentration of MMP-3 and MMP-9 in CSF and serum samples from patients with AD and healthy controls. Our findings underscored a substantial positive correlation ($P < 0.001$) between MMP-3 levels and MMSE scores in both CSF and serum across both groups, suggesting the potential role of MMP-3 in cognitive status. To address age-related discrepancies between the healthy and AD groups, age was factored into the ANOVA analysis. Particularly, MMP-3 concentrations in CSF samples exhibited a pronounced disparity ($P = 0.005$) between the two groups, signifying a noteworthy elevation in MMP-3 levels among AD patients in comparison to their healthy counterparts. Similarly, this discernible difference in MMP-3 concentration was also evident in serum samples, reinforcing the higher MMP-3 levels observed in AD patients.

Upon examining MMP-9 concentration, a significant positive correlation ($P < 0.001$) between MMP-9 concentrations and MMSE scores was evident in both CSF and serum within both study cohorts. Notably, MMP-9 levels in CSF samples demonstrated a noticeable difference ($P = 0.005$) between the healthy controls and patients with AD, with the latter exhibited significantly elevated MMP-9 levels. This trend was consistently observed in serum samples as well, indicating significantly higher MMP-9 levels in patients with AD compared to healthy controls.

Our findings corroborate and contribute to the existing body of evidence highlighting the potential involvement of MMP-3 and MMP-9 in the pathophysiology of AD. MMPs, including MMP-3 and MMP-9, have been previously implicated in various NDDs, with specific emphasis on AD, owing to their involvement in neuroinflammatory responses, maintenance of BBB integrity, and remodeling of the extracellular matrix within the CNS(21,22).

Several studies have reported aberrant levels of MMPs, including MMP-3 and MMP-9, in the CSF and serum of patients with AD s(23–26). A study by *Lorenzl* et al. (27) demonstrated elevated MMP-9 levels in the CSF of patients with AD, suggesting a potential association between MMP-9 and AD pathology. In another study, *Lorenzl et al.* (28)reported increased MMP-9 levels in various types of dementia, reinforcing our observations of elevated MMP-9 concentrations in both CSF and serum samples of patients with AD. It has been demonstrated that modifying MMP-9 activity leads to an enhancement in specific neurobehavioral impairments in a mouse model of AD(29).Intriguingly, MMP-3 levels have shown correlations with the duration of AD and align with CSF T-tau and P-tau levels in elderly controls, suggesting their potential involvement in disease progression (30). Elevated cerebral MMP-3 levels may contribute to increased MMP-9 activity, indirectly facilitating tau aggregation.

In the aging brain, these enzymes experience increasing dysregulation, resulting in an imbalance between MMPs and their natural inhibitors, known as tissue inhibitors of metalloproteinases (TIMPs). This imbalance holds critical significance in the pathogenesis of AD for several reasons. MMPs, particularly MMP-9, are known for their ability to disrupt the integrity of the BBB. The disruption of BBB permits the influx of potentially neurotoxic substances and cells into the brain parenchyma, thereby contributing to AD pathology. The aging brain exhibit an increased permeability of the BBB, attributed in part due to enhanced MMP activity(22,31). The involvement of MMPs, including MMP-3 and MMP-9, in ECM remodeling and their impact on Aβ metabolism further emphasize their potential as key players in AD pathogenesis (26). MMP-3 and MMP-9 are involved in modulating the inflammatory response in the brain by acting on pro-inflammatory cytokines, facilitating their activation. In the context of aging, characterized by chronic low-grade inflammation, known as "inflammaging," the upregulation of MMPs can exacerbate this condition, thereby contributing to neurodegeneration(16). MMP-9, in particular, has been implicated in the cleavage and activation of cytokines such as interleukin-1β (IL-1β), contributing to the inflammatory response associated with AD. MMPs are crucial for synaptic remodeling and plasticity. In AD, the imbalance in MMP activity contributes to synaptic dysfunction, a key feature of cognitive decline(26). Moreover, excessive MMP activity can lead to neurodegeneration and neuronal loss by degrading extracellular matrix components and disrupting cell-matrix interactions(32).

While our findings highlight a significant increase in MMP-3 and MMP-9 concentration in the CSF and serum of patients with AD, the modest sample size emphasizes the necessity for additional research, especially larger cohort studies. Further investigations are warranted to validate and expand upon our findings. Understanding the multifaceted role of MMP-3 and MMP-9 in AD pathophysiology may pave the way for developing targeted therapeutic strategies and identifying reliable biomarkers for monitoring AD progression and assess treatment efficacy. To the best of our knowledge, the findings of this study, establishing elevated MMP-3 and MMP-9 concentrations in CSF and serum samples of patients with AD, represent a first of its kind reported from Saudi Arabia and the Middle East.

FUNDING

This work was funded by the Deanship of Scientific Research (DSR), King Abdulaziz University, Jeddah, Saudi Arabia under grant no. (KEP-3-140-42). The authors, therefore, acknowledge with thanks DSR technical and financial support.

REFERENCES

1. Doroszkiewicz J, Groblewska M, Mroczko B. Molecular biomarkers and their implications for the early diagnosis of selected neurodegenerative diseases. Int J Mol Sci. 2022;23(9):4610.
2. Pathak N, Vimal SK, Tandon I, Agrawal L, Hongyi C, Bhattacharyya S. Neurodegenerative disorders of Alzheimer, Parkinsonism, Amyotrophic Lateral Sclerosis and Multiple Sclerosis: An early diagnostic approach for precision treatment. Metab Brain Dis. 2022;37(1):67–104.
3. Ethell IM, Ethell DW. Matrix metalloproteinases in brain development and remodeling: Synaptic functions and targets. J Neurosci Res. 2007;85(13):2813–23.
4. Wang X, Khalil RA. Matrix Metalloproteinases, Vascular Remodeling, and Vascular Disease. Adv Pharmacol. 2018;81:241–330.
5. Zhang H, Adwanikar H, Werb Z, Noble-Haeusslein LJ. Matrix metalloproteinases and neurotrauma: Evolving roles in injury and reparative processes. Neuroscientist. 2010;16(2):156–70.
6. Zipfel P, Rochais C, Baranger K, Rivera S, Dallemagne P. Matrix Metalloproteinases as New Targets in Alzheimer's Disease: Opportunities and Challenges. J Med Chem. 2020;63(19):10705–25.
7. Cui N, Hu M, Khalil RA. Biochemical and Biological Attributes of Matrix Metalloproteinases. Prog Mol Biol Transl Sci. 2017;147:1–73.
8. Rivera S, Khrestchatisky M, Kaczmarek L, Rosenberg GA, Jaworski DM. Metzincin proteases and their inhibitors: foes or friends in nervous system physiology? J Neurosci Off J Soc Neurosci. 2010 Nov;30(46):15337–57.
9. Cabral-Pacheco GA, Garza-Veloz I, Rosa CCD La, Ramirez-Acuña JM, Perez-Romero BA, Guerrero-Rodriguez JF, et al. The roles of matrix metalloproteinases and their inhibitors in human diseases. Int J Mol Sci. 2020;21(24):1–53.
10. Rosenberg G. Metalloproteinases and neurodegenerative diseases: pathophysiological and therapeutic perspectives. Met Med. 2015;2:39–50.
11. Trentini A, Manfrinato MC, Castellazzi M, Bellini T. Sex-related differences of matrix metalloproteinases (MMPs): new perspectives for these biomarkers in cardiovascular and neurological diseases. J Pers Med. 2022;12(8):1196.
12. Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH, et al. The Amyloid-β Pathway in Alzheimer's Disease. Mol Psychiatry. 2021;26(10):5481–503.
13. VanSaun M, Herrera AA, Werle MJ. Structural alterations at the neuromuscular junctions of matrix metalloproteinase 3 null mutant mice. J Neurocytol. 2003 Nov;32(9):1129–42.
14. Nübling G, Levin J, Bader B, Israel L, Bötzel K, Lorenzl S, et al. Limited cleavage of tau with matrix-metalloproteinase MMP-9, but not MMP-3, enhances tau oligomer formation. Exp Neurol. 2012;237(2):470–6.
15. Stomrud E, Björkqvist M, Janciauskiene S, Minthon L, Hansson O. Alterations of matrix metalloproteinases in the healthy elderly with increased risk of prodromal Alzheimer's disease. Alzheimer's Res Ther. 2010;2(3):2–9.
16. Wang XX, Tan MS, Yu JT, Tan L. Matrix metalloproteinases and their multiple roles in Alzheimer's Disease. Biomed Res Int. 2014;908636.
17. Montaner J, Ramiro L, Simats A, Hernández-Guillamon M, Delgado P, Bustamante A, et al. Matrix metalloproteinases and ADAMs in stroke. Cell Mol Life Sci. 2019;76(16):3117–40.
18. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189–98.
19. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 2011 Jul 26;77(4):933–344.
20. Löffek S, Schilling O, Franzke C-W. Series "matrix metalloproteinases in lung health and disease": Biological role of matrix metalloproteinases: a critical balance. Eur Respir J. 2011 Jul;38(1):191–208.
21. Brkic M, Balusu S, Van Wonterghem E, Gorlé N, Benilova I, Kremer A, et al. Amyloid β oligomers disrupt Blood-CSF Barrier integrity by activating matrix metalloproteinases. J Neurosci. 2015 Sep;35(37):12766–78.
22. Gullotta GS, Costantino G, Sortino MA, Spampinato SF. Microglia and the blood-brain barrier: an external player in acute and chronic neuroinflammatory conditions. Int J Mol Sci. 2023 May;24(11):9144.
23. Bruno MA, Mufson EJ, Wuu J, Cuello AC. Increased matrix metalloproteinase 9 activity in mild cognitive impairment. J Neuropathol Exp Neurol. 2009;68(12):1309–18.
24. Gu D, Liu F, Meng M, Zhang L, Gordon ML, Wang Y, et al. Elevated matrix metalloproteinase-9 levels in neuronal extracellular vesicles in Alzheimer's disease. Ann Clin Transl Neurol. 2020;7(9):1681–91.
25. Hanzel CE, Iulita MF, Eyjolfsdottir H, Hjorth E, Schultzberg M, Eriksdotter M, et al. Analysis of matrix

metallo-proteases and the plasminogen system in mild cognitive impairment and Alzheimer's disease cerebrospinal fluid. J Alzheimers Dis. 2014;40(3):667–78.
26. Abe K, Chiba Y, Hattori S, Yoshimi A, Asami T, Katsuse O, et al. Influence of plasma matrix metalloproteinase levels on longitudinal changes in Alzheimer's disease (AD) biomarkers and cognitive function in patients with mild cognitive impairment due to AD registered in the Alzheimer's Disease Neuroimaging Initiative d. J Neurol Sci. 2020 Sep;416:116989.
27. Lorenzl S, Albers DS, Relkin N, Ngyuen T, Hilgenberg SL, Chirichigno J, et al. Increased plasma levels of matrix metalloproteinase-9 in patients with Alzheimer's disease. Neurochem Int. 2003;43(3):191–6.
28. Lorenzl S, Buerger K, Hampel H, Beal MF. Profiles of matrix metalloproteinases and their inhibitors in plasma of patients with dementia. Int psychogeriatrics. 2008 Feb;20(1):67–76.
29. Ringland C, Schweig JE, Eisenbaum M, Paris D, Ait-Ghezala G, Mullan M, et al. MMP9 modulation improves specific neurobehavioral deficits in a mouse model of Alzheimer's disease. BMC Neurosci. 2021;22(1):39.
30. Wang X-X, Tan M-S, Yu J-T, Tan L. Matrix metalloproteinases and their multiple roles in Alzheimer's Disease. Chang RC-C, editor. Biomed Res Int. 2014;908636.
31. Rivera S, García-González L, Khrestchatisky M, Baranger K. Metalloproteinases and their tissue inhibitors in Alzheimer's disease and other neurodegenerative disorders. Cell Mol Life Sci. 2019;76(16):3167–91.
32. Freitas-Rodríguez S, Folgueras AR, López-Otín C. The role of matrix metalloproteinases in aging: Tissue remodeling and beyond. Biochim Biophys Acta - Mol Cell Res. 2017;1864(11):2015–25.