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Original Research

Is Matrix Metalloproteinase-9 Associated with Post-Stroke Cognitive Impairment or Dementia?

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Abstract

Background: Matrix metalloproteinase-9 (MMP-9) is a significant protease required for synaptic plasticity, learning, and memory. Yet, the role of MMP-9 in the occurrence and development of cognitive decline after ischemic stroke is not fully understood. In this study, we used clinical data experiments to further investigate whether MMP-9 and genetic polymorphism are associated with post-stroke cognitive impairment or dementia (PSCID). **Materials and Methods**: A total of 148 patients with PSCID confirmed by the Montreal Cognitive Assessment (MoCA) 3 months after onset (PSCID group) were included in the study. The MMP-9 rs3918242 polymorphisms were analyzed using polymerase chain reaction coupled with restriction fragment length polymorphism, and the serum level of MMP-9 was measured using enzyme-linked immunosorbent assay (ELISA). The same manipulations have been done on 169 ischemic stroke patients without cognitive impairment (NCI group) and 150 normal controls (NC group). **Results**: The expression level of serum MMP-9 in the PSCID group and NCI group was higher compared to the NC group, and the levels in the PSCID group were higher than that in the NCI group (all $p < 0.05$). Diabetes mellitus, hyperhomocysteinemia, and increased serum MMP-9 levels were the main risk factors of cognitive impairment after ischemic stroke. The serum level of MMP-9 was negatively correlated with the MoCA score, including visual-spatial executive, naming, attention, language, and delayed recall. Genetic polymorphism showed that TC genotype with MMP-9 rs3918242 and CC genotype were associated with a significantly increased risk of PSCID; moreover, the TC genotype significantly increased the risk of cognitive impairment. In the TCCC genotype of MMP-9 rs3918242, diabetes mellitus and hyperhomocysteinemia were associated with the increased risk of PSCID; also, hyperhomocysteinemia could increase the risk of cognitive impairment. **Conclusions**: MMP-9 level and MMP-9 rs3918242 polymorphism have an important role in the occurrence and development of post-stroke cognitive impairment or dementia (PSCID).

Keywords: ischemic stroke; post-stroke cognitive impairment or dementia (PSCID); matrix metalloprotenase 9; genetic polymorphism; cognitive function

1. Introduction

Vascular cognitive impairment (VCI) is a heterogeneous disease that involves cognitive decline characterized by disturbance of frontal or executive dysfunction [1]. VCI is usually a consequence of cerebrovascular disorders (cerebral infarction, cerebral hemorrhage, chronic cerebral hypoperfusion) and their risk factors (hypertension, diabetes, hyperlipemia, hyperhomocysteinemia, etc.) [1,2]. Post-stroke cognitive impairment or dementia (PSCID; VCI after cerebral ischemic stroke) is very common and can affect different cognitive domains. Executive functions are the most commonly affected funtions [3]. Impairment in cognitive, especially executive functions, commonly appears within 3 months after stroke. According to various hospital-based studies [4–6], the prevalence of PSCID varies from 11.6% to 56.3%. Therefore, neurorestoration of cognitive impairment has gained increasing interest among researchers [7–9].

Matrix metalloproteinase-9 (MMP-9) is a member of the MMP family with 26 extracellular and intracellular matrix-degrading enzymes that regulate many zinc-binding proteolytic enzymes physiological processes, including activation of growth factors, tumor growth and metastasis, cleavage of zymogens, and remodeling of the extracellular matrix [7,8]. MMP-9 is mainly produced by neurons, and its expression and activity have been detected in adult brain structure, such as the hippocampus, cortex, striatum, and cerebellum [9,10]. In neurons, the MMP-9 expression is induced by neuronal activity under both physiological and

pathological conditions, such as stroke [11,12] and epilepsy [13]. Abnormalities and typically excessive MMP-9 gene expression have been associated with several central nervous system diseases [14–16]. Moreover, MMP-9 is involved in blood-brain barrier destruction [17], inflammatory reaction [18], atherosclerosis, and ischemic stroke [19], as well as in synaptic plasticity [20], learning, and memory [21]. Yet, the role of MMP-9 in the occurrence and development of PSCID is not fully understood.

So far, only a few studies reported on the role of MMP-9 in VCI and its progression to dementia [22–24]. Even some studies have not found correlation with MMP-9 polymorphism and cognition [25–27]. In this study, we use enzyme-linked immunosorbent assay (ELISA) to detect serum MMP-9 levels and their association with PSCID. Furthermore, genotyping assays were performed to determine the relationship between the MMP-9 rs3918242 polymorphism and susceptibility of PSCID in a Chinese population.

2. Materials and Methods

2.1 Study Population

A total of 2351 acute ischemic stroke patients consecutively enrolled in the Department of Neurology, the First Affiliated Hospital of Xinxiang Medical University, Henan, China, between June 2013 and September 2018 were screened. The main inclusion criteria were: (1) ischemic stroke confirmed by imaging (computed tomography (CT) or magnetic resonance imaging (MRI)) within 72 hours of symptom onset, according to the criteria of the 10th Edition of International Classification of Diseases (ICD-10); (2) unrelated Han Chinese people and a Mini-Mental State Examination (MMSE) score of illiterate >17, primary >20, and secondary or higher >24 out of 30. MMSE scores were based on the cultural level of the subjects. Patients with brain tumors, brain trauma, thyroid dysfunctions, alcoholism, severe medical conditions, or neurological condition with consciousness were excluded. Also, those with severe stroke with NIHSS (National Institute of Health stroke scale) >25 or patients unable to complete assessment were excluded from this study. Exclusion criteria and the exact number of patients for each study stage are shown in Fig. 1.

After the onset of 3 months [28], 583 patients underwent a follow-up evaluation, and 486 patients were assessed with global cognitive functions by Changsha version of the Montreal Cognitive Assessment (MoCA-CS) [29] and according to the flow chart [30,31]. Yu K.H's protocol was referred (Fig. 1) [32]. Age- and gender-matched cognitively normal patients after ischemic stroke (MoCA $\geq$26) were used as a control. In addition, age- and gender-matched 150 healthy control subjects unrelated Han people with no ischemic stroke and cognitive dysfunction were randomly selected from the outpatients for health check-ups.

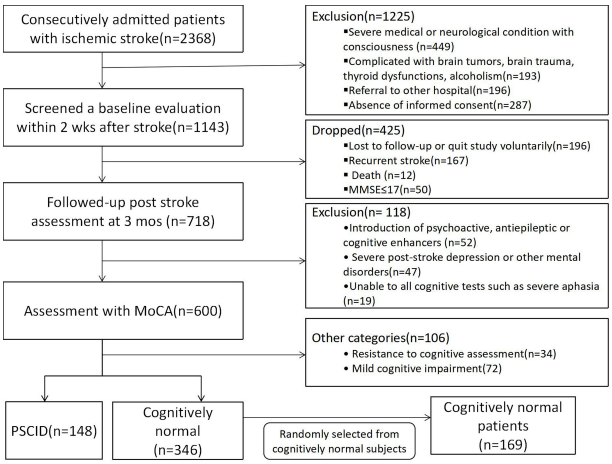

Fig. 1. Flow chart of participants' selection.

2.2 Cognitive Screening Measures

All subjects were evaluated based on MMSE and MoCA (Fig. 1). MoCA was scored based on a 30-point scale with 7 cognitive subtests: visual-spatial executive, naming, attention, language, abstraction, delayed recall, and orientation. The MoCA test was conducted to rectify the educational level of the bias correction, and subjects with education <12 years were given an additional 1 score on their test results. A higher score indicates the better cognitive function, and $\geq$26 were divided into normal [33]. MoCA-CS in China was used in this study [29].

Unified and standardized survey questionnaire terminologies were used in a quiet environment without interferences. The neuropsychological assessments for each patient were completed by one psychological surveyor on the same day.

2.3 DNA Extraction

The blood samples were collected during cognitive assessment between three months and half a year after stroke. And the blood sample were collected in EDTA-containing tubes and separated the serum immediately and frozen at –80 °C until further use. Genomic DNA was isolated using the TIANamp Blood DNA Kit (Tiangen, Beijing, China) according to the kit's protocol. The lab technician performing the test was blinded to all patients and clinical information, and all lab work was carried out in the First Affiliated Hospital of Xinxiang Medical University.

2.4 Genotyping Assays

The MMP-9 rs3918242 polymorphisms were performed by polymerase chain reaction (PCR) coupled with restriction fragment length polymorphism, as described in our previous studies [19].

2.5 MMP-9 Level in Serum

The collection, processing and storage of blood sample are same as DNA extraction. The process of measuring MMP-9 is according to the MMP-9 ELISA Kit's (Wuhan Fine Biotech Co., Ltd.; Wuhan; China) protocol.

2.6 Statistical Analysis

SPSS 24.0 (SPSS Inc., Chicago, IL, USA) was used for statistical processing. The measurement data in the results were expressed as mean $\pm$ SD, and the count data were expressed as a percentage. Analysis of variance and two independent samples *t*-test were used for normally distributed data; rank-sum test was used for non-normally distributed data, and the χ^2 test was used for the count data to compare the statistical differences of demographic and clinical data between groups. Spearman correlation analysis was used to analyze the correlation between MMP-9 and MoCA score. Logistic regression analysis was used to analyze the risk factors of PSCID by estimating the odds ratio (OR) and 95% confidence interval (95% CI). The Hardy-Weinberg equilibrium of MMP-9 rs3918242 genotype was tested by Chi-square (χ^2) goodness-of-fit test. The associations between the MMP-9 rs3918242 polymorphisms and PSCID risk were determined by logistic regression. The major homozygous genotype of MMP-9 rs3918242 was used as a reference, two-tailed, and $p < 0.05$ was considered statistically significant.

3. Results

3.1 Comparison of Baseline Demographic Features, Vascular Risk Factors, and Location of Cerebral Infarction in the Three Groups

There were significant differences in diabetes, hyperhomocysteinemia, serum MMP-9 levels, and MoCA scores between the three groups (all $p < 0.05$). Compared with the NC group, the serum MMP-9 expression level in the PSCI group and the NCI group was significantly increased; yet, the MMP-9 expression level in the PSCI group was significantly higher than that in the NCI group (all $p < 0.05$). Moreover, the MoCA scores of the PSCI group and the NCI group were significantly reduced compared with the NC group, and the MoCA scores of the PSCI group were significantly lower than that of the NCI group ($p < 0.05$) (Table 1).

3.2 Logistic Regression Analysis of PSCID

With diabetes mellitus, when hyperhomocysteinemia and serum MMP-9 level were used as independent variables, and PSCID as dependent variables, logistic regression analysis showed that diabetes mellitus, hyperhomocysteinemia, and elevated serum MMP-9 level were the main risk factors of PSCID (OR = 1.77, 95% CI: 1.07–2.93; OR = 1.88, 95% CI: 1.18–3.56; OR = 1.01, 95% CI: 1.01–1.02) (Table 2).

3.3 Correlation between Serum MMP-9 Level and MoCA Score in Patients with PSCID

The Spearman correlation analysis showed that the serum MMP-9 level was negatively correlated with the total score of MoCA scale in patients with PSCID ($p < 0.05$), and the serum MMP-9 level was negatively correlated with visual-spatial executive, naming, attention, language and delayed recall ($p < 0.05$), but not with abstraction and orientation ($p > 0.05$) (Table 3).

3.4 The Polymorphism Distribution of MMP-9 rs3918242 in Each Group

The genotype frequency of MMP-9 rs3918242 in the NC group conformed to Hardy-Weinberg equilibrium ($p > 0.05$), while the genotype frequency of MMP-9 rs3918242 in the PSCID group and the NCI group did not ($p < 0.05$). The χ^2 test showed that the genotypes of the three groups were significantly different ($\chi^2 = 14.57, p < 0.05$) (Table 4).

3.5 Association between MMP-9 rs3918242 and Risk of PSCID

The logistic regression analysis showed TC genotype carrying MMP-9 rs3918242 (OR = 3.91, 95% CI: 1.63–9.38) and CC genotype (OR = 2.79, 95% CI: 1.12–7.00) were associated with a significantly increased risk of PSCID ($p < 0.05$). Also, in PSCID and NCI groups, TC genotype carrying MMP-9 rs3918242 (OR = 2.03, 95% CI: 1.02–4.05) significantly increased the risk of PSCID using TT genotype as a control ($p < 0.05$) (Table 5).

3.6 Association between MMP-9 rs3918242 and Risk of PSCID Stratified by Demographic Characteristics

The relationship between MMP-9 rs3918242 and PSCID risk of was further analyzed and stratified by demographic characteristics such as diabetes mellitus and hyperhomocysteinemia (Table 6). The logistic regression analysis showed that diabetes mellitus and hyperhomocysteinemia in the TCCC genotype of MMP-9 rs3918242 were associated with increased risk of PSCID (OR = 1.26, 95% CI: 1.14–2.66; OR = 1.24, 95% CI: 1.02–2.69). In addition, hyperhomocysteinemia increased the risk of PSCID (OR = 1.19, 95% CI: 1.10–2.38).

4. Discussion

Our data suggested that TC and CC genotypes of MMP-9 rs3918242 polymorphism were associated with a significantly increased risk of PSCID in a Han Chinese population, further suggesting an association between rs3918242 variation in the MMP-9 gene and PSCID. We also found that the TC genotype of rs3918242 increased the risk of PSCID compared to the TT genotype. Our results support the hypothesis that MMP-9 gene polymorphisms are associated with PSCID. In addition, our data suggested that diabetes mellitus, hyperhomocysteinemia, and MMP-9 serum levels were associated with PSCID. However, there

Table 1. Comparison of baseline demographic features, vascular risk factors, and location of cerebral infarction in the three groups.

Variables	Groups			$F/Z/\chi^2$	p
	PSCID	NCI	NC		
	(n = 148)	(n = 169)	(n = 150)		
Age [years]					
≤60	73 (49.32)	88 (52.07)	73 (48.67)		
>60	75 (50.68)	81 (47.93)	77 (51.33)	0.42	0.81
Gender					
Females	98 (66.22)	107 (63.31)	100 (66.67)		
Males	50 (33.78)	62 (36.69)	50 (33.33)	0.47	0.79
Educations [years]					
≤24	102 (68.92)	118 (69.82)	102 (68.00)		
>24	46 (31.08)	51 (30.18)	48 (32.00)	0.12	0.94
NIHSS†	8.59 ± 5.27	8.37 ± 5.47	-	0.34	0.56
Hypertension					
No	52 (35.14)	63 (37.28)	54 (36.00)		
Yes	96 (64.86)	106 (62.72)	96 (64.00)	0.16	0.92
Diabetes mellitus					
No	94 (63.51)	129 (76.33)	113 (75.33)		
Yes	54 (36.49)	40 (23.67)	37 (24.67)	7.68	0.02
Hyperlipidemia					
No	128 (86.49)	154 (91.12)	141 (94.00)		
Yes	20 (13.51)	15 (8.88)	9 (6.00)	3.49	0.18
Hyperhomocysteinemia					
No	62 (41.89)	93 (55.03)	86 (57.33)		
Yes	86 (58.11)	76 (44.97)	64 (42.67)	8.36	0.02
Tobacco smoking					
Never	95 (64.19)	108 (63.91)	96 (64.00)		
Yes	53 (35.81)	61 (36.09)	54 (36.00)	0.00	1.00
Alcohol intake					
Never	78 (52.70)	102 (60.36)	90 (60.00)		
Yes	70 (47.30)	67 (39.64)	60 (40.00)	2.33	0.31
TOAST classification					
Large-artery atherosclerosis	52 (35.14)	59 (34.91)	-		
Small vessel occlusion	64 (43.24)	71 (42.01)	-		
Cardioembolism	10 (6.76)	12 (7.10)	-		
Other determined etiology	13 (8.78)	16 (9.47)	-		
Undetermined etiology	9 (6.08)	11 (6.51)	-	0.11	1.00
MMP-9 (mg/dL)†	299.07 ± 101.67*#	266.56 ± 98.23*	197.75 ± 86.92	88.14	<0.001
MoCA†	20.27 ± 3.54*#	28.62 ± 1.24*	29.50 ± 0.90	337.74	<0.001

*$p < 0.05$ compared with NC group; #$p < 0.05$ compared with NCI group.

†Use of the rank-sum test.

BMI, Body mass index; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Table 2. Logistic regression analysis of PSCID.

Variables	Beta value	Standard error	Wald value	OR	95% CI	p
Diabetes mellitus (%)	0.63	0.24	4.91	1.77	1.07–2.93	0.03
Hyperhomocysteinemia (%)	0.57	0.26	7.10	1.88	1.18–3.56	0.01
MMP-9 (mg/dL)	0.01	0.0003	51.31	1.01	1.01–1.02	<0.001

Table 3. Correlation between serum MMP-9 level and MoCA score in patients with PSCID.

Variables	Fraction (mean ± SD)	MMP-9 (ng/mL)	
		r	*p*
Visual spatial executive	2.74 ± 1.46	–0.401	0.000
Naming	2.59 ± 0.58	–0.230	0.005
Attention	4.27 ± 1.41	–0.470	0.000
language	1.99 ± 0.76	–0.255	0.002
Abstraction	1.18 ± 0.81	–0.006	0.944
Delayed recall	2.66 ± 1.09	–0.165	0.045
Orientation	4.84 ± 0.789	–0.130	0.116
Total	20.27 ± 3.54	–0.517	0.000

Table 4. The polymorphism distribution of MMP-9 rs3918242 in each group.

MMP-9 rs3918242	Genotype %			Allele %		Hardy-Weinberg equilibrium	
	TT	TC	CC	T	C	χ^2	*p*
PSCID (%)	77 (52.03)	45 (30.40)	26 (17.57)	199 (67.23)	97 (32.77)	14.22	0.001
NCI (%)	109 (64.50)	43 (25.44)	17 (10.06)	261 (77.22)	77 (22.78)	12.95	0.002
NC (%)	102 (68.00)	40 (26.67)	8 (5.33)	244 (81.33)	56 (18.67)	2.22	0.329
χ^2		14.57					
p		0.006					

Table 5. Association between MMP-9 gene rs3918242 and risk of VCI after ischemic stroke.

MMP-9 rs3918242	Groups		OR (95% CI) *	*p*	Groups		OR (95% CI) *	*p*
	PSCID (%)	NCI (%)			PSCID (%)	NC (%)		
TT	77 (52.03)	102 (68.00)	1.0 (Ref.)	-	77 (52.03)	109 (64.50)	1.0 (Ref.)	-
TC	45 (30.40)	40 (26.67)	3.91 (1.63–9.38)	0.002	45 (30.40)	43 (25.44)	2.03 (1.02–4.05)	0.044
CC	26 (17.57)	8 (5.33)	2.79 (1.12–7.00)	0.028	26 (17.57)	17 (10.06)	1.51 (0.71–3.22)	0.282

* Adjusted for Diabetes mellitus, Hyperhomocysteinemia.

Table 6. Association between MMP-9 rs3918242 and risk of PSCID stratified by demographic characteristics.

Variables	PSCID		NC		OR (95% CI)	*p*	PSCID		NCI		OR (95% CI)	*p*
	TT	TC+CC	TT	TC+CC			TT	TC+CC	TT	TC+CC		
Diabetes mellitus												
No	51	43	86	43	1.65 (0.87–3.14)	0.13	51	43	73	40	1.59 (0.84–3.02)	0.06
Yes	26	28	23	17	1.26 (1.14–2.66)	0.01	26	28	29	8	1.69 (0.90–3.56)	0.37
Hyperhomocysteinemia												
No	47	15	53	40	1.51 (0.71–3.16)	0.27	47	15	58	28	2.37 (0.86–4.82)	0.22
Yes	30	56	56	20	1.24 (1.02–2.69)	0.00	30	56	44	20	1.19 (1.10–2.38)	0.00

was no significant association between PSCID and other demographic features (such as age, gender, hypertension, hyperlipidemia, tobacco smoking, alcohol intake, as well as TOAST classification). Moreover, MMP-9 in the serum was negatively correlated with MoCA score, especially visual-spatial executive, naming, attention, language, and delayed recall.

Numerous studies have investigated the relationships between MMP-9 gene polymorphisms and ischemic stroke. However, these results remain debatable. A meta-analysis showed that MMP-9 (-1562C/T) gene polymorphism was not associated with ischemic stroke [34]. In addition, Wang *et al*. [35] showed that the MMP-9 gene rs3918242 and rs17577 polymorphisms are not significantly correlated with ischemic stroke risk. Contrary, another meta-analysis suggested that MMP-9 (-1562C/T) polymorphisms might be a risk factor for ischemic stroke [36]. Also, several recent studies have reported the significant association between MMP-9 and cerebral ischemic stroke [15,37,38]. Gao *et al*. [37] showed that the rs3787268 locus in the MMP-9 gene might increase the risk of ischemic stroke in a southern Chinese Han population. Moreover, Hao and colleagues [16] conducted a similar study with 317 patients and found that MMP-9 rs3918242 polymorphism is correlated with an elevated risk of ischemic stroke. In addition, Li *et al*. [15] observed a significant association between the

MMP-9 rs3918242 polymorphism and the risk of ischemic stroke, which is consistent with our previous study [19].

Preclinical studies showed that MMP-9 undergoes high expression and activation in brain tissue after a major complication of acute and chronic stroke [24,39], suggesting that MMP-9 may participate in the acute brain injury and edema resulting from neuroinflammation [40–42]. On the other hand, secondary disruption to the deep white matter, the blood-brain barrier (BBB), and demyelination at the cerebral brain [24,39,43,44], have an important role in the pathogenesis of vascular cognitive impairment and vascular dementia [22,43]. Some clinical trials have reported elevated MMP-9 levels in the serum of patients with stroke [45,46]. The high levels of MMP-9 in acute ischemic stroke confirm the involvement of this metalloproteinase in the regulation of inflammation in stroke [47,48]. Meanwhile, animal studies suggested that MMP-9 has a role in cognitive functions, especially learning and memory [21,49–51]. Therefore, the expression level of MMP-9 can be dispensable for PSCID. An increasing number of reports indicate that MMP-9 levels are in cerebrospinal fluid [22,39,41,52] and peripheral blood [23,53] of patients with PSCID. Furthermore, our data showed higher serum MMP-9 levels in patients with PSCID compared to normal controls and patients without cognitive impairment, which is consistent with the previous study. Furthermore, the serum level of MMP-9 was negatively correlated with the MoCA score, especially visual-spatial executive, naming, attention, language, and delayed recall.

This study has a few limitations. It has a relatively small sample size. Also, changes in MMP-9 expression at different development periods of PSCID were not analyzed. It is widely accepted that a large sample size is a key issue in genetic polymorphisms association studies of complex traits generally and cognitive dysfunction specifically [54]. In addition, it is unlikely that a polymorphism in a single gene would have a profound effect on the risk of PSCID which may be caused by many risk factors. Furthermore, the distribution and expression of MMP-9 in the pathogenesis and progression of post-stroke cognitive impairment or dementia are dynamic. According to the previous studies [21,22,53,55], MMP-9 expression levels are associated with PSCID, although they are not exactly equal in serum, cerebrospinal fluid, and brain tissue after BBB disruption. So, multi-center, multi-source, large sample size studies investigating PSCID and dynamic monitoring of MMP-9 are needed to further confirm these findings.

5. Conclusions

Our data and previous studies suggest that MMP-9 level and MMP-9 rs3918242 gene polymorphism are associated with post-stroke cognitive impairment or dementia (PSCID). MMP-9 has a role in the development of post-stroke cognitive impairment or dementia (PSCID); yet, the mechanisms of action need to be further explored.

Author Contributions

JZhao and SL designed the study and wrote the protocol. FY and XP enrolled the patients and wrote the paper. QingL, FW and ZX were in charge of follow-up of patients. RC, DJ, JZhang, MW and QiongL interpreted the patients' image data. SJ and SL help in manuscript revision and interpretation of the results.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the first affilicated hospital of Xinxiang Medical University. The ethical statement No. is EC-022-016. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Meng L, Zhao J, Liu J, Li S. Cerebral small vessel disease and cognitive impairment. Journal of Neurorestoratology. 2019; 7: 184–195.

[2] Zanon Zotin MC, Sveikata L, Viswanathan A, Yilmaz P. Cerebral small vessel disease and vascular cognitive impairment: from diagnosis to management. Current Opinion in Neurology. 2021; 34: 246–257.

[3] Levit A, Hachinski V, Whitehead SN. Neurovascular unit dysregulation, white matter disease, and executive dysfunction: the shared triad of vascular cognitive impairment and Alzheimer disease. GeroScience. 2020; 42: 445–465.

[4] Sachdev P, Kalaria R, O'Brien J, Skoog I, Alladi S, Black SE, *et al*. Diagnostic Criteria for Vascular Cognitive Disorders: A vascog statement. Alzheimer Disease and Associated Disorders. 2014; 28: 206–218.

[5] Rohde D, Gaynor E, Large M, Mellon L, Bennett K, Williams DJ, *et al*. Cognitive impairment and medication adherence post-stroke: A five-year follow-up of the aspire-s cohort. PLoS ONE. 2019; 14: e0223997.

[6] Sexton E, McLoughlin A, Williams DJ, Merriman NA, Donnelly N, Rohde D, *et al*. Systematic review and meta-analysis of the prevalence of cognitive impairment no dementia in the first year post-stroke. European Stroke Journal. 2019; 4: 160–171.

[7] Zhuang M, Wu Q, Wan F, Hu Y. State-of-the-art non-invasive brain–computer interface for neural rehabilitation: a review. Journal of Neurorestoratology. 2020; 8: 12–25.

[8] Huang H, Chen L, Mao G, Bach J, Xue Q, Han F, *et al*. The 2019 yearbook of Neurorestoratology. Journal of Neurorestoratology. 2020; 8: 1–11.

[9] Huang H, Chen L, Chopp M, Young W, Robert Bach J, He X, *et al*. The 2020 Yearbook of Neurorestoratology. Journal of Neurorestoratology. 2021; 9: 1–12.
[10] Chen H, Chen X, Li W, Shen J. Targeting RNS/caveolin-1/MMP signaling cascades to protect against cerebral ischemia-reperfusion injuries: potential application for drug discovery. Acta Pharmacologica Sinica. 2018; 39: 669–682.
[11] Turner RJ, Sharp FR. Implications of mmp9 for blood brain barrier disruption and hemorrhagic transformation following ischemic stroke. Frontiers in Cellular Neuroscience. 2016; 10: 56.
[12] Li H, Yue P, Su Y, Li C. Plasma levels of matrix metalloproteinase-9: a possible marker for cold-induced stroke risk in hypertensive rats. Neuroscience Letters. 2019; 709: 134399.
[13] Rempe RG, Hartz AMS, Soldner ELB, Sokola BS, Alluri SR, Abner EL, *et al*. Matrix Metalloproteinase-Mediated Blood-Brain Barrier Dysfunction in Epilepsy. The Journal of Neuroscience. 2018; 38: 4301–4315.
[14] Hayat S, Ahmad O, Mahmud I, Howlader MZH, Islam Z. Association of matrix metalloproteinase-9 polymorphism with severity of Guillain-Barré syndrome. Journal of the Neurological Sciences. 2020; 415: 116908.
[15] Li Y, Chen L, Yao S, Chen J, Hu W, Wang M, *et al*. Association of Polymorphisms of the Matrix Metalloproteinase 9 Gene with Ischaemic Stroke in a Southern Chinese Population. Cellular Physiology and Biochemistry. 2018; 49: 2188–2199.
[16] Hao Y, Tian S, Sun M, Zhu Y, Nie Z, Yang S. Association between matrix metalloproteinase gene polymorphisms and development of ischemic stroke. International Journal of Clinical and Experimental Pathology. 2015; 8: 11647–11652.
[17] Rempe RG, Hartz AM, Bauer B. Matrix metalloproteinases in the brain and blood–brain barrier: Versatile breakers and makers. Journal of Cerebral Blood Flow and Metabolism. 2016; 36: 1481–1507.
[18] Zhang S, Dong H, Zhang X, Li N, Sun J, Qian Y. Cerebral mast cells contribute to postoperative cognitive dysfunction by promoting blood brain barrier disruption. Behavioural Brain Research. 2016; 298: 158–166.
[19] Zhao JH, Xu YM, Xing HX, Su LL, Tao SB, Tian XJ, *et al*. Associations between matrix metalloproteinase gene polymorphisms and the development of cerebral infarction. Genetics and Molecular Research. 2016; 14: 19418–19424.
[20] Figiel I, Kruk PK, Zaręba-Kozioł M, Rybak P, Bijata M, Wlodarczyk J, *et al*. MMP-9 signaling pathways that engage rho gtpases in brain plasticity. Cells. 2021; 10: 166.
[21] Gorkiewicz T, Balcerzyk M, Kaczmarek L, Knapska E. Matrix metalloproteinase 9 (MMP-9) is indispensable for long term potentiation in the central and basal but not in the lateral nucleus of the amygdala. Frontiers in Cellular Neuroscience. 2015; 9: 73.
[22] Candelario-Jalil E, Thompson J, Taheri S, Grossetete M, Adair JC, Edmonds E, *et al*. Matrix Metalloproteinases are Associated with Increased Blood-Brain Barrier Opening in Vascular Cognitive Impairment. Stroke. 2011; 42: 1345–1350.
[23] Zhong C, Bu X, Xu T, Guo L, Wang X, Zhang J, *et al*. Serum Matrix Metalloproteinase-9 and Cognitive Impairment after Acute Ischemic Stroke. Journal of the American Heart Association. 2018; 7: e007776.
[24] Weekman EM, Wilcock DM. Matrix Metalloproteinase in Blood-Brain Barrier Breakdown in Dementia. Journal of Alzheimer's Disease. 2016; 49: 893–903.
[25] Vassos E, Ma X, Fiotti N, Wang Q, Sham PC, Liu X, *et al*. The functional MMP-9 microsatellite marker is not associated with episodic memory in humans. Psychiatric Genetics. 2008; 18: 252.
[26] Rybakowski JK. Matrix Metalloproteinase-9 (MMP9)-A Mediating Enzyme in Cardiovascular Disease, Cancer, and Neuropsychiatric Disorders. Cardiovascular Psychiatry and Neurology. 2009; 2009: 904836.
[27] Rybakowski JK, Borkowska A, Skibinska M, Kaczmarek L, Hauser J. The−1562 C/T polymorphism of the matrix metalloproteinase-9 gene is not associated with cognitive performance in healthy participants. Psychiatric Genetics. 2009; 19: 277–278.
[28] Pohjasvaara T, Erkinjuntti T, Vataja R, Kaste M. Dementia Three Months after Stroke. Baseline frequency and effect of different definitions of dementia in the helsinki stroke aging memory study (sam) cohort. Stroke. 1997; 28: 785–792.
[29] Tu QY, Jin H, Ding BR, Yang X, Lei ZH, Bai S, *et al*. Reliability, validity, and optimal cutoff score of the montreal cognitive assessment (changsha version) in ischemic cerebrovascular disease patients of hunan province, china. Dementia and Geriatric Cognitive Disorders Extra. 2013; 3: 25–36.
[30] Swardfager W, MacIntosh BJ. Depression, Type 2 Diabetes, and Poststroke Cognitive Impairment. Neurorehabilitation and Neural Repair. 2017; 31: 48–55.
[31] Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. MoCA, ACE-R, and MMSE Versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery after TIA and Stroke. Stroke. 2012; 43: 464–469.
[32] Yu K, Cho S, Oh MS, Jung S, Lee J, Shin J, *et al*. Cognitive Impairment Evaluated with Vascular Cognitive Impairment Harmonization Standards in a Multicenter Prospective Stroke Cohort in Korea. Stroke. 2013; 44: 786–788.
[33] Zhao J, Tian X, Liu Y, Yuan B, Zhai K, Wang C, *et al*. Executive Dysfunction in Patients with Cerebral Hypoperfusion after Cerebral Angiostenosis/Occlusion. Neurologia Medico-Chirurgica. 2013; 53: 141–147.
[34] Wen D, Du X, Nie S, Dong J, Ma C. Association between Matrix Metalloproteinase Family Gene Polymorphisms and Ischemic Stroke: a Meta-analysis. Molecular Neurobiology. 2014; 50: 979–985.
[35] Wang Y, Zhang L, Huang H, Qin X, Huang Z, Lan J, *et al*. Relationship between the matrix metalloproteinase-9 gene polymorphisms and ischemic stroke. International Journal of Clinical and Experimental Pathology. 2019; 12: 949–956.
[36] Misra S, Talwar P, Kumar A, Kumar P, Sagar R, Vibha D, *et al*. Association between matrix metalloproteinase family gene polymorphisms and risk of ischemic stroke: a systematic review and meta-analysis of 29 studies. Gene. 2018; 672: 180–194.
[37] Gao N, Guo T, Luo H, Tu G, Niu F, Yan M, *et al*. Association of the MMP-9 polymorphism and ischemic stroke risk in southern Chinese Han population. BMC Neurology. 2019; 19: 67.
[38] Wang B, Wang Y, Zhao L. MMP-9 gene rs3918242 polymorphism increases risk of stroke: a meta-analysis. Journal of Cellular Biochemistry. 2018; 119: 9801–9808.
[39] Ueno M, Chiba Y, Matsumoto K, Murakami R, Fujihara R, Kawauchi M, *et al*. Blood-brain barrier damage in vascular dementia. Neuropathology. 2016; 36: 115–124.
[40] Hannocks M-, Zhang X, Gerwien H, Chashchina A, Burmeister M, Korpos E, *et al*. The gelatinases, MMP-2 and MMP-9, as fine tuners of neuroinflammatory processes. Matrix Biology. 2019; 75-76: 102–113.
[41] Rosenberg GA, Bjerke M, Wallin A. Multimodal Markers of Inflammation in the Subcortical Ischemic Vascular Disease Type of Vascular Cognitive Impairment. Stroke. 2014; 45: 1531–1538.
[42] Jin X, Liao Y, Tan X, Guo J, Wang G, Zhao F, *et al*. Involvement of the p38 MAPK signaling pathway in overexpression of matrix metalloproteinase-9 during the course of brain edema in 1,2-dichloroethane-intoxicated mice. NeuroToxicology. 2018; 69: 296–306.

[43] Rosenberg G. Extracellular matrix inflammation in vascular cognitive impairment and dementia. Clinical Science. 2017; 131: 425–437.
[44] Salvadó G, Brugulat-Serrat A, Sudre CH, Grau-Rivera O, Suárez-Calvet M, Falcon C, *et al*. Spatial patterns of white matter hyperintensities associated with Alzheimer's disease risk factors in a cognitively healthy middle-aged cohort. Alzheimer's Research and Therapy. 2019; 11: 12.
[45] Petrovska-Cvetkovska D, Dolnenec-Baneva N, Nikodijevik D, Chepreganova-Changovska T. Correlative study between serum matrix metalloproteinase-9 values and neurologic deficit in acute, primary, supratentorial, intracerebral haemorrhage. Prilozi. 2014; 35: 39–44.
[46] Yang Y, Rosenberg GA. Matrix metalloproteinases as therapeutic targets for stroke. Brain Research. 2015; 1623: 30–38.
[47] Cojocarui IM, Cojocaru M, Sapira V, Socoliuc G, Hertea C, Paveliu S. Changes in plasma matrix metalloproteinase-9 levels in patients with acute ischemic stroke. Romanian Journal of Internal Medicine. 2012; 50: 155–158.
[48] Hijazi Z, Wallentin L, Lindbäck J, Alexander JH, Connolly SJ, Eikelboom JW, *et al*. Screening of Multiple Biomarkers Associated with Ischemic Stroke in Atrial Fibrillation. Journal of the American Heart Association. 2020; 9: e018984.
[49] Raz L, Yang Y, Thompson J, Hobson S, Pesko J, Mobashery S, *et al*. MMP-9 inhibitors impair learning in spontaneously hypertensive rats. PLoS ONE. 2018; 13: e0208357.
[50] Lebida K, Mozrzymas JW. Spike Timing-Dependent Plasticity in the Mouse Barrel Cortex is Strongly Modulated by Sensory Learning and Depends on Activity of Matrix Metalloproteinase 9. Molecular Neurobiology. 2017; 54: 6723–6736.
[51] Bozdagi O, Nagy V, Kwei KT, Huntley GW. In Vivo Roles for Matrix Metalloproteinase-9 in Mature Hippocampal Synaptic Physiology and Plasticity. Journal of Neurophysiology. 2007; 98: 334–344.
[52] Zhang Y, Fan F, Zeng G, Zhou L, Zhang Y, Zhang J, *et al*. Temporal analysis of blood–brain barrier disruption and cerebrospinal fluid matrix metalloproteinases in rhesus monkeys subjected to transient ischemic stroke. Journal of Cerebral Blood Flow and Metabolism. 2017; 37: 2963–2974.
[53] Zhu Z, Zhong C, Guo D, Bu X, Xu T, Guo L, *et al*. Multiple biomarkers covering several pathways improve predictive ability for cognitive impairment among ischemic stroke patients with elevated blood pressure. Atherosclerosis. 2019; 287: 30–37.
[54] Dichgans M, Markus HS. Genetic Association Studies in Stroke: Methodological issues and proposed standard criteria. Stroke. 2005; 36: 2027–2031.
[55] Zheng K, Li C, Shan X, Liu H, Fan W, Wang Z, *et al*. Matrix metalloproteinases and their tissue inhibitors in serum and cerebrospinal fluid of patients with moderate and severe traumatic brain injury. Neurology India. 2013; 61: 606–609.