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Risk factors of cerebral microbleeds in young and middle-aged patients with hypertension

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Abstract

Background & Objectives: This study aimed to explore the incidence and potential risk factors of cerebral microbleeds (CMBs) in young and middle-aged patients with hypertension. *Methods:* We retrospectively analyzed the clinical data of young and middle-aged patients with hypertension in the Department of Neurology, General Hospital of Western Theater Command, Chengdu, China between August 2018 and December 2020. The demographic baseline, laboratory parameters and clinical imaging data were collected. Microbleed anatomical rating scale (MARS) was applied to evaluate the presence, amount, and topographical distributions of CMBs. *Results:* Among 196 young and middle-aged patients with hypertension, 84 (42.9%) patients had CMBs. CMBs were more likely to occur in the deep brain tissue regions (41.8%), followed by lobar or infratentorial region. White matter hyperintensity (OR, 5.262; 95%CI, 1.314-21.075; P=0.019), abnormal lipid metabolism (OR, 3.832; 95%CI, 1.578-9.306; P=0.003), usage of anti-platelet aggregation drugs (OR, 2.947; 95%CI, 1.138-7.632; P=0.026), smoking history (OR, 3.218; 95%CI, 1.073-9.651; P=0.037), and hyperhomocysteinemia (OR, 1.415; 95%CI, 1.018-1.967; P=0.039) were independently associated with deep or infratentorial CMBs in young and middle-aged patients with hypertension. However, the occurrence of strictly lobar CMBs was only independently associated with abnormal lipid metabolism (OR, 4.162; 95%CI, 1.685-10.282; P=0.002). *Conclusions:* The rate of CMBs was high in young and middle-aged patients with hypertension, most commonly occurring in the deep brain tissue region. While multiple risk factors were identified to be associated with deep or infratentorial CMBs, the occurrence of strictly lobar CMBs was only associated with abnormal lipid metabolism.

Keywords: Cerebral microbleeds, hypertension, susceptibility weighted imaging, young and middle-aged patients

INTRODUCTION

Cerebral microbleeds (CMBs) are asymptomatic brain parenchymal damage, with small amount of bleeding.[1] The pathological manifestations are single or multiple CMB lesions and hemosiderin deposits, most of which are distributed in cerebral cortex, subcortical white matter and basal ganglia. In cerebral magnetic resonance imaging (MRI) susceptibility-weighted imaging (SWI), CMBs appear as circular and uniform density low signal or signal loss within a small region (diameter is 2-10 mm), and no edema could be observed around the lesions.[1] With the development of imaging technology, the detection rate of CMBs has gradually increased.

Currently, CMBs have been confirmed to be associated with a number of clinical conditions, such as cognitive dysfunction, abnormal gait and recurrence of cerebrovascular disease.[2,3] Kim *et al*.[4] reported that the incidence of CMBs in the general population was approximately 10.4%. Angelidis *et al*.[5] reported that CMBs could be detected in 35-60% patients with cerebral hemorrhage, 18-29% patients with ischemic stroke and 5% healthy elderly subjects with SWI scanning. Many studies have confirmed that CMBs not only increase the risk of acute cerebrovascular diseases, but also result in deterioration of cognitive dysfunction,[6-10]

Previous studies have shown many risk factors are associated with CMB, including age, hypertension, atrial fibrillation, low total cholesterol levels, apolipoprotein E (APOE) genotypes, and some medications (antithrombotic drugs, antidepressants, statins).[11] Among these age is the dominant risk factor. However, the presence of CMBs is also commonly observed

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during imaging screening in young and middle-aged patients with hypertension.[12] Many previous studies about CMBs focused on patients aged ≥ 60 years old, especially those with transient ischemic attack or ischemic stroke. Age, hypertension, atrial fibrillation, low total cholesterol levels, APOE genotypes, some medications (antithrombotic drugs, antidepressants, statins) have already been established as the main risk factors. As some of the young patients with hypertension may also develop CMBs this study aimed to investigate the incidence and risk factors of CMBs in young and middle-aged patients with hypertension.

METHODS

This single-center study retrospectively analyzed the clinical data of inpatients and outpatients with hypertension in the Department of Neurology, General Hospital of Western Theater Command (Chengdu Military General Hospital), Chengdu, China between August 2018 and December 2020. The inclusive criteria were: 1) age between 18 and 60 years old; 2) in accordance with the diagnosis criterion of hypertension[13]; 3) complete head MRI scan. Exclusion criteria were: 1) medical history of cerebral hemorrhage or cerebral arteriovenous malformation; 2) previous traumatic brain injury; 3) cerebral tumor or cardio-embolic stroke; 4) genetic syndrome, inflammatory demyelination, degenerative diseases associated with central nervous system; 5) patients with severe hepatic and renal dysfunction or coagulopathy; 6) incomplete medical records and MRI data. The study was approved by the ethics committee of Chengdu Military General Hospital and the informed consent of patient was waived by the ethics committee due to the retrospective nature of the study design.

Clinical data collection

Clinical data of all patients were retrospectively collected from the medical records. The demographic baseline (age, gender, medical history of diabetes mellitus, body mass index [BMI]), vascular risk factors (medical history of heart disease, ischemic cerebrovascular disease, duration of hypertension, smoking and/or alcohol history), laboratory biochemical indicators (blood lipid metabolism, blood urea nitrogen, blood creatinine, uric acid, and homocysteine), usage of anti-platelet aggregation drugs and clinical imaging data (plaque formation in cervical vessels, white matter hyperintensity) were recorded.

Cerebral MRI examinations

Cerebral MRI examination was performed in each patient using a 3.0 T MRI scanner (Achieva TX, Philips Healthcare, Best, The Netherlands). The scanning sequences included T_1WI, T_2WI, FLAIR and DWI sequences. Venous blood oxygen level dependent sequence from Philips Company was applied for SWI. The field of view was 22 cm×22 cm, flip angle was 30°, repetition time was 50 ms, recovery time was 25 ms, matrix was 224×384, and the number of acquisition was 1. The number and existence of CMBs lesions were assessed based on SWI, which was defined as homogeneous quasi-circular, circular or quasi-circular signal defect with 2 to 10 mm in diameter with clear boundary.[14,15] Surrounding edema, flow void effect, calcium/iron deposition, diffuse axonal injury and arteriovenous malformations should not be present. The presence, amount, and topographical distributions of CMBs in each patient was evaluated by two radiologists who were blinded to the clinical data. CMBs were identified and counted based on microbleed anatomical rating scale (MARS).[15] Microbleeds were categorized as deep, lobar, or infratentorial. Lobar topography included cortical and subcortical regions (including subcortical U-fibers). Lobar CMBs were assessed in the frontal, parietal, temporal, and occipital regions. Deep regions included the basal ganglia, the thalamus, the internal capsule, the external capsule, the corpus callosum, and the deep/periventricular white matter. Infratentorial regions included the brain stem and the cerebellum. Deep/periventricular white matter was defined as white matter adjacent to or within ≈10 mm of the lateral ventricular margin. We classified patients with CMBs into two different groups based on the locations of their CMBs: (1) deep or infratentorial CMBs and (2) strictly lobar CMBs, respectively.

Statistical analysis

The distribution of continuous data was assessed using the Kolmogorov-Smirnov test. Normally distributed data were presented as mean ± standard deviation and analyzed using the Student t test. Non-normally distributed data are presented as median (interquartile range [IQR]) and analyzed using the Mann-Whitney U test. Categorical variables are presented as frequencies and were analyzed using Fisher's exact test. Logistic regression model was performed to analyze the potential risk factors of CMBs presence in young and middle-aged patients with hypertension,

with the calculation of corresponding odds ratio (OR) and 95% confidence intervals (CIs). The presence or absence of CMBs in the deep/infratentorial regions or strictly lobar regions were also considered as dependent variables, respectively. Independent variables, including age, gender, medical history of diabetes mellitus or heart disease, abnormal lipid metabolism, ischemic cerebrovascular disease, smoking or drinking history, white matter hyperintensity, plaque formation in cervical vessels, usage of anti-platelet aggregation drugs, BMI, blood urea nitrogen, blood creatinine, uric acid, and hyperhomocysteinemia. Multivariate Logistic regression was further conducted to determine potential related risk factors of CMBs in different regions. SPSS 20.0 (IBM, Armonk, NY, USA) was used for all analyses. Two-sided P-values <0.05 were considered to be statistically significant.

RESULTS

Baseline characteristics

Among 196 young and middle-aged patients with hypertension, there were 84 patients (42.9%) with CMBs. The mean age was 53.65 ± 6.28 and 52.47 ± 5.18 years in patients with CMBs and those without CMBs, respectively (P=0.151). The proportion of male patients with CMBs was higher than that in patients without CMBs (76.2% *versus* 58.0%; P=0.008). In addition, compared to the patients without CMBs group, patients with CMBs had higher proportions of abnormal lipid metabolism, smoking history, white matter hyperintensity, usage of anti-platelet aggregation drugs, plaque in the cervical vessels, and higher homocysteine level (All P values <0.05). However, there was no statistically significant differences in terms of age, medical history of diabetes mellitus, medical history of heart disease, ischemic cerebrovascular disease, alcohol history, BMI, duration of hypertension, blood urea nitrogen, blood creatinine, and uric acid. (All P values >0.05; Table 1).

Risk factors of CMBs in young and middle-aged patients with hypertension

As illustrated in Table 2, multivariate Logistic

Table 1: Baseline characteristics between patients with CMBs and those without CMBs in young and middle-aged hypertensive patients

Characteristics	CMBs (n=84)	Without CMBs (n=112)	P value
Age, years, mean ± SD	53.65 ± 6.28	52.47 ± 5.18	0.151
Male, n (%)	64 (76.2)	65 (58.0)	**0.008**
Medical history of diabetes mellitus, n (%)	25 (29.8)	29 (25.9)	0.549
Abnormal lipid metabolism, n (%)	57 (67.9)	44 (39.3)	**<0.001**
Medical history of heart disease, n (%)	6 (7.1)	4 (3.6)	0.261
Ischemic cerebrovascular disease, n (%)	73 (86.9)	87 (77.7)	**0.099**
Smoking history, n (%)	49 (58.3)	41 (36.6)	**0.003**
Drinking history, n (%)	31 (36.9)	33 (29.5)	0.272
White matter hyperintensity, n (%)	76 (90.5)	73 (65.2)	**<0.001**
Plaque formation in cervical vessels, n (%)	60 (71.4)	56 (50.0)	**0.003**
Usage of anti-platelet aggregation drugs, n (%)	57 (67.9)	49 (43.8)	**0.001**
Duration of hypertension, years, median (IQR)	5 (2-9)	3 (2-7)	0.082
BMI, kg/m^2, mean ± SD	24.7 ± 2.9	24.6 ± 2.7	0.804
Blood urea nitrogen, mmol/L, median (IQR)	4.8 (4.1-6.1)	4.8 (4.1-5.8)	0.527
Blood creatinine, mmol/L, median (IQR)	74.8 (61.5-84.8)	70.1 (56.4-82.5)	0.077
Uric acid, mmol/L, mean ± SD	359.47 ± 92.21	362.23 ± 93.87	0.838
Homocysteine, mmol/L, median (IQR)	15.8 (10.7-22.1)	13.3 (7.6-16.8)	**0.003**

Data are shown as mean ± SD or n (%).
Note: CMBs=cerebral microbleeds; BMI=body mass index; SD=standard deviation; IQR=interquartile range.

Table 2: Risk factors for CMBs presence in young and middle-aged patients with hypertension

Variable	Multivariable analysis		
	OR	95% CI	P
Gender	1.216	0.551-2.682	0.628
Age	1.051	0.882-1.252	0.578
Medical history of diabetes mellitus	0.611	0.083-4.509	0.629
Ischemic cerebrovascular disease	1.370	0.633-2.964	0.424
Medical history of heart disease	1.315	0.458-3.777	0.611
Smoking history	1.021	0.962-1.083	0.492
Drinking history	0.774	0.436-1.373	0.381
White matter hyperintensity	4.632	1.170-18.340	**0.029**
Abnormal lipid metabolism	2.834	1.257-6.388	**0.012**
Hyperhomocysteinemia	1.221	1.028-1.450	**0.023**
Uric acid	0.658	0.449-0.965	**0.032**
Plaque formation in cervical vessels	1.725	0.894-3.329	0.104
Blood creatinine	1.052	0.982-1.127	0.147
Usage of anti-platelet aggregation drugs	1.762	0.450-6.899	0.416

Note: OR=odds ration; CI=confidence interval.

regression analysis revealed that white matter hyperintensities (OR, 4.632; 95% CI, 1.170-18.340; P=0.029), dyslipidemia (OR, 2.834; 95% CI, 1.257-6.388; P=0.012); hyperhomocysteinemia (OR, 1.221; 95% CI, 1.028-1.450; P=0.023) and uric acid (OR, 0.658; 95% CI, 0.449-0.965; P=0.032) were independently associated with presence of CMBs in the young and middle-aged hypertensive patients.

Risk factors of CMBs in different brain regions

Some patients had multiple CMBs lesions located in different brain regions. CMBs were most commonly seen in the deep brain tissue regions (188 lesions), followed by the lobar regions (151 lesions) and the infratentorial regions (142 lesions). The CMBs were seen in the deep brain tissue regions in 82 (41.8%) patients, the lobar regions in 69 (35.2%) patients, and infratentorial regions in 45 (23.0%) patients.

Multivariate Logistic regression showed that white matter hyperintensity (OR, 5.262; 95%CI, 1.314-21.075; P=0.019), abnormal lipid metabolism (OR, 3.832; 95%CI=1.578-9.306, P=0.003), usage of anti-platelet aggregation drugs (OR, 2.947; 95%CI, 1.138-7.632; P=0.026), smoking history (OR, 3.218; 95%CI, 1.073-9.651; P=0.037), and hyperhomocysteinemia (OR, 1.415; 95%CI, 1.018-1.967; P=0.039) were independently risk factors for deep or infratentorial CMBs in young and middle-aged patients with hypertension. As for the strictly lobar CMBs, abnormal lipid metabolism was the only significant associated risk factor (OR, 4.162; 95%CI, 1.685-10.282; P=0.002, Table 3).

DISCUSSION

The prevalence of CMBs was approximately 30-40% in elderly patients with ischemic stroke, and about 60-68% in patients diagnosed as initial cerebral hemorrhage, respectively.[16] As for the younger patients, previous studies have shown that the proportion of CMBs was about 17%[17] in young patients with ischemic stroke and up to 56% in populations with hypertension.[17,18] Our study showed that the occurrence rate of CMBs in young and middle-aged patients with hypertension was 42.9%, which was slightly higher than the incidence in patients accompanying with ischemic stroke and lower than that observed in patients with cerebral hemorrhage[16], and a similar study on a group of young patients with hypertension reported from Guizhou and Anhui, China (49.6%).[12]

White matter hyperintensity, a manifestation of cerebral small vessel disease, is also associated with CMBs.[19] In our study, white matter hyperintensity was independently associated with deep or infratentorial CMBs in young and middle-aged patients with hypertension. The

Table 3: Potential related risk factors of CMBs in different regions of middle-aged and young patients with hypertension

Potential risk factors	Deep or infratentorial CMBs*			Strictly lobar CMBs*		
	P	OR	95% CI	P	OR	95% CI
White matter hyperintensity	0.019	5.262	1.314-21.075	0.482	1.337	0.595-3.004
Abnormal lipid metabolism	0.003	3.832	1.578-9.306	0.002	4.162	1.685-10.282
Usage of anti-platelet aggregation drugs	0.026	2.947	1.138-7.632	0.230	2.315	0.588-9.116
Smoking history	0.037	3.218	1.073-9.651	0.632	1.174	0.609-2.264
Hyperhomocysteinemia	0.039	1.415	1.018-1.967	0.438	1.318	0.656-2.648
Age	0.368	1.126	0.870-1.458	0.792	1.262	0.224-7.115
Gender	0.744	0.758	0.144-3.998	0.561	1.052	0.887-1.248
Blood urea nitrogen	0.651	1.228	0.504-2.990	0.117	0.542	0.252-1.166
Blood creatinine	0.273	0.893	0.729-1.093	0.317	0.502	0.130-1.936
Uric acid	0.358	0.847	0.594-1.207	0.201	1.703	0.752-3.851
BMI	0.235	1.098	0.941-1.281	0.544	1.022	0.953-1.096
Medical history of diabetes mellitus	0.338	0.683	0.313-1.490	0.287	0.465	0.114-1.904
Medical history of heart disease	0.479	1.394	0.556-3.497	0.361	1.439	0.659-3.142
Ischemic cerebrovascular disease	0.853	0.891	0.263-3.020	0.157	0.279	0.048-1.635
Drinking history	0.174	0.195	0.018-2.059	0.623	1.125	0.703-1.799
Plaque formation in cervical vessels	0.082	2.625	0.885-7.789	0.211	1.136	0.930-1.387

*Patients without CMBs group was considered as the reference.

Note: CMBs= cerebral microbleeds; OR=odds ration; CI=confidence interval.

reasons may be speculated that the terminal branches of the intracranial arteries with little inter-arterial anastomosis undergo pathological changes, resulting in microcirculation ischemia and hypoperfusion, followed by endothelial cell dysfunction, blood-brain barrier damage and microaneurysm formation.[20] The ischemia result in white matter hyperintensities, while erythrocyte extravasation or aneurysm rupture results in CMBs. Thus, the coexistences of white matter hyperintensity and CMBs. However, the relationships between white matter hyperintensity and CMBs require further studies.

Our study indicated that smoking was an independent risk factor for the deep and infratentorial CMBs in young and middle-aged patients with hypertension. It has been known that long-term smoking could result in extensive damage and dysfunction of vascular endothelial cells from chronic oxidative stress, which may contribute to CMBs development and progression. For young and middle-aged patients with hypertension, lifestyle modification is advisable.[16,21]

Homocysteine, a vital intermediate product of methionine metabolism has been found to be strongly associated with cardiac-cerebral vascular diseases[6] and increased risk of stroke.[22] Elevated homocysteine level could damage the structure and function of the endothelial cells, reduce vascular elasticity, promoted the proliferation of vascular smooth muscle cells through oxidative stress, thereby synergistically aggravate the arteriosclerosis process, ultimately resulted in the increased bleeding risk of small blood vessel.[23,24] Thus, monitoring and control of homocysteine level is advisable.

Our results also showed that usage of anti-platelet aggregation drugs were independently associated with deep/infratentorial CMBs, which were consistent with findings observed in similar studies[25,26], and this relationship may be affected by ethnic factor.[27] Previous study also indicated that multiple CMBs were independently associated with prior usages of antithrombotic (antiplatelet or anticoagulant) agents.[28] Wilson *et al*.[29] proposed that less than 5 CMBs should not affect usage of anti-platelet aggregation drugs in patients with ischemic stroke or transient ischemic attack. Nevertheless, the increased risks of future

intracranial hemorrhage in patients with ≥ 5 CMBs should be taken into consideration in clinical decision making.

Remarkably, despite the association of multiple risk factors with deep and infratentorial with CMBs in our study, the only independent risk factor of strictly lobar CMBs was abnormal lipid metabolism, and this observation could not be explained by hypertensive arterial disease. Prior studies had demonstrated that abnormal lipid metabolism was associated with APOE genotypes. A meta-analysis involving 7,351 patients with CMBs indicated that APOE ε4 elevated the risk of CMBs occurrence.[30] This gene has been confirmed to be closely associated with increased amyloid deposits.[31] Prior study indicated that the excessive burden of brain amyloid protein was associated with lobar CMBs, especially occipital CMBs[32]; with the associated increased risk of spontaneous intracerebral hemorrhage. Therefore, our study is consistent with the hypothesis that hypertension, lipid metabolism related factors such as amyloid deposition and unidentified genotype variations might play the synergistic effect on the development of lobar CMBs in young and middle-aged patients.

This study had several limitations. First, due to the limited sample size, the role of other cerebral small-vessel diseases and ischemic cerebrovascular diseases could not be explored extensively. In addition, risk factors for single versus multiple CMBs were not explored. Second, there also existed selection biases and other confounding factors. Third, the causal connections among CMBs, hypertension and dyslipidemia could not be derived from this cross-sectional study, prospective longitudinal study with long-term follow up is required to elucidate the relationship of these factors.

In conclusion, our study has shown that the occurrence of CMBs in young and middle-aged patients with hypertension was common (42.9%). CMBs were more commonly found in the deep brain tissue regions, followed by the lobar regions and the infratentorial regions. White matter hyperintensity, abnormal lipid metabolism, usage of anti-platelet aggregation drugs, smoking history, and hyperhomocysteinemia were independently risk factors for deep/infratentorial CMBs in young and middle-aged patients with hypertension. However, the occurrence of strictly lobar CMBs was only associated with abnormal lipid metabolism.

DISCLOSURE

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REFERENCES

1. Liu S, Utriainen D, Chai C, *et al*. Cerebral microbleed detection using Susceptibility Weighted Imaging and deep learning. *NeuroImage* 2019;198:271-82.
2. Moulin S, Cordonnier C. Role of cerebral microbleeds for intracerebral haemorrhage and dementia. *Curr Neurol Neurosci Rep* 2019;19(8):51.
3. Wadi LC, Grigoryan MM, Kim RC, *et al*. Mechanisms of Cerebral Microbleeds. *J Neuropathol Exp Neurol* 2020;42(2):1093-9.
4. Kim BJ, Lee SH. Cerebral microbleeds: their associated factors, radiologic findings, and clinical implications. *J Stroke* 2013;15(3):153-63.
5. Angelidis C, Deftereos S, Giannopoulos G, *et al*. Cystatin C: an emerging biomarker in cardiovascular disease. *Curr Top Med Chem* 2013;13(2):164-79.
6. Akoudad S, Wolters FJ, Viswanathan A, *et al*. Association of cerebral microbleeds with cognitive decline and dementia. *JAMA Neurol* 2016;73(8):934-43.
7. Cannistraro RJ, Badi M, Eidelman BH, Dickson DW, Middlebrooks EH, Meschia JF. CNS small vessel disease: A clinical review. *Neurology* 2019;92(24):1146-56.
8. He D, Liu CF, Chu L, Li Y, Xu DF, Jiao L. The risk factors and pattern of cerebral microbleeds in Parkinson's disease. *Int J Neurosci* 2017;127(10):909-14.
9. Ozbek D, Ozturk Tan O, Ekinci G, Midi I. Risk of hemorrhage in ischemic stroke and its relationship with cerebral microbleeds. *Clin Neurol Neurosurg* 2018;168:112-7.
10. Romero JR, Beiser A, Himali JJ, Shoamanesh A, DeCarli C, Seshadri S. Cerebral microbleeds and risk of incident dementia: the Framingham Heart Study. *Neurobiol Aging* 2017;54:94-9.
11. Shuaib A, Akhtar N, Kamran S, Camicioli R. Management of cerebral microbleeds in clinical practice. *Transl Stroke Res* 2019;10(5):449-57.
12. Ni R, Chu L, Xu D, *et al*. Risk factors of cerebral microbleeds in young and middle-aged patients with hypertension. *Neurol Res* 2018;40(5):413-18.
13. James PA, Oparil S, Carter BL, *et al*. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014;311(5):507-20.
14. Hachinski V, Iadecola C, Petersen RC, *et al*. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. *Stroke* 2006;37(9):2220-41.
15. Gregoire SM, Chaudhary UJ, Brown MM, *et al*. The Microbleed Anatomical Rating Scale (MARS): reliability of a tool to map brain microbleeds. *Neurology* 2009;73(21):1759-66.

16. An SJ, Kim TJ, Yoon BW. Epidemiology, Risk factors, and clinical features of intracerebral hemorrhage: An update. *J Stroke* 2017;19(1):3-10.
17. Charidimou A, Turc G, Oppenheim C, *et al*. Microbleeds, cerebral hemorrhage, and functional outcome after stroke thrombolysis. *Stroke* 2017;48(8):2084-90.
18. Lee SH, Park JM, Kwon SJ, *et al*. Left ventricular hypertrophy is associated with cerebral microbleeds in hypertensive patients. *Neurology* 2004;63(1):16-21.
19. Gao Z, Wang W, Wang Z, *et al*. Cerebral microbleeds are associated with deep white matter hyperintensities, but only in hypertensive patients. *PloS one* 2014;9(3):e91637.
20. Litak J, Mazurek M, Kulesza B, *et al*. Cerebral small vessel disease. *Int J Mol Sci* 2020;21(24):9729.
21. Li Z, Cao L, Dong W, *et al*. Prevalence and risk factors of cerebral microbleeds in patients with nonvalvular atrial fibrillation: An enhanced T2*-weighted angiography imaging study. *Eur Neurol* 2019;81(3-4):112-9.
22. Lehotský J, Tothová B, Kovalská M, *et al*. Role of homocysteine in the ischemic stroke and development of ischemic tolerance. *Front Neurosci* 2016;10:538.
23. Ji Y, Li X, Teng Z, Li X, Jin W, Lv PY. Homocysteine is associated with the development of cerebral small vessel disease: Retrospective analyses from Neuroimaging and Cognitive Outcomes. *J Stroke Cerebrovasc Dis* 2020;29(12):105393.
24. Wang BR, Ou Z, Jiang T, *et al*. Independent correlation of serum homocysteine with cerebral microbleeds in patients with acute ischemic stroke due to large-artery atherosclerosis. *J Stroke Cerebrovasc Dis* 2016;25(11):2746-51.
25. Yamashiro K, Tanaka R, Okuma Y, *et al*. Associations of durations of antiplatelet use and vascular risk factors with the presence of cerebral microbleeds. *J Stroke Cerebrovasc Dis* 2014;23(3):433-40.
26. Vernooij MW, Haag MD, van der Lugt A, *et al*. Use of antithrombotic drugs and the presence of cerebral microbleeds: the Rotterdam Scan Study. *Arch Neurol* 2009;66(6):714-20.
27. Liu S, Li C. Antiplatelet drug use and cerebral microbleeds: A meta-analysis of published studies. *J Stroke Cerebrovasc Dis* 2015;24(10):2236-44.
28. Lau KK, Lovelock CE, Li L, *et al*. Antiplatelet treatment after transient ischemic attack and ischemic stroke in patients with cerebral microbleeds in 2 large cohorts and an updated systematic review. *Stroke* 2018;49(6):1434-42.
29. Wilson D, Werring DJ. Antithrombotic therapy in patients with cerebral microbleeds. *Curr Opin Neurol* 2017;30(1):38-47.
30. Maxwell SS, Jackson CA, Paternoster L, *et al*. Genetic associations with brain microbleeds: Systematic review and meta-analyses. *Neurology* 2011;77(2):158-67.
31. Knol MJ, Lu D, Traylor M, *et al*. Association of common genetic variants with brain microbleeds: A genome-wide association study. *Neurology* 2020;95(24):e3331-e3343.
32. Graff-Radford J, Botha H, Rabinstein AA, *et al*. Cerebral microbleeds: Prevalence and relationship to amyloid burden. *Neurology* 2019;92(3):e253-e262.