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Original Article

Radiology Section

Correlation between Cerebral Microbleeds and White Matter Changes on MRI using Microbleed Anatomical Rating and Fazekas Scales: A Cross-sectional Study

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ABSTRACT

Introduction: Cerebral Microbleeds (CMBs) are small perivascular haemosiderin deposits in the brain that indicate bleeding events. The location of CMBs can provide insights into their underlying causes. CMBs found in peripheral lobar locations are often associated with cerebral amyloid angiopathy, while those occurring in deeper brain regions are more likely linked to hypertensive arteriopathy. White matter changes, known as Leukoaraiosis, have been linked to adverse cognitive functions, share risk factors with hypertension and microbleeds, and are associated with the severity of CMBs.

Aim: To determine the correlation between CMBs and white matter changes on Magnetic Resonance Imagning (MRI) using the Microbleed Anatomical Rating Scale (MARS) and Fazekas scales.

Materials and Methods: An analytical cross-sectional study was conducted in the Department of Radiodiagnosis, MS Ramaiah Hospitals, Bengaluru, Karnataka, India between November 2019 and June 2021, involving 65 subjects who underwent MRI brain scans at a tertiary care institute and were found to have microbleeds. Brain MRIs were performed using a 1.5 Tesla MRI Scanning Unit. Microbleeds were graded using the MARS, while white matter changes were graded using the Fazekas scale. The Chi-square test was employed to assess the significance of categorical data, and Spearman's correlation was used to determine the correlation between MARS and Fazekas scale variables.

Results: The subjects had a mean age range of 61 to 70 years, with a male-to-female ratio of 2:1. There was a significant correlation between MARS grade and Fazekas scale ($p<0.001$) with a correlation coefficient (r-value) of 1. The most commonly associated stroke subtype was lacunar infarct.

Conclusion: There is a significant correlation between Leukoaraiosis (LA) and CMBs, indicating the end results of small vessel ischaemia and bleeding.

Keywords: Cerebral amyloid angiopathy, Cognitive dysfunction, Hypertension, Magnetic resonance imagning, Stroke

INTRODUCTION

The Cerebral Microbleeds (CMBs) are defined as small, well-defined low signal lesions in the lobar or deeper cerebrum observed on T2* Gradient Recalled Echo (GRE) MRI brain studies. They are bleeding events associated with cerebral Small Vessel Disease (SVD), occurring as small perivascular haemosiderin deposits (usually within macrophages) in the brain [1,2].

Risk factors associated with CMBs include age, hypertension, a history of stroke (both ischaemic and haemorrhagic), imaging markers of SVD including white matter changes/Leukoaraiosis (LA), and lacunar infarcts [3-5]. Smoking, alcohol, and Chronic Obstructive Pulmonary Disease (COPD) have also been proposed as risk factors for CMBs. Impaired kidney function and Chronic Kidney Disease (CKD) are associated with CMBs, mostly of the deep and infratentorial types [3-5]. Some other recently discovered associations include Alzheimer's disease, multiple sclerosis, and Parkinson's disease. Genetics also play a role and are linked to sporadic microbleeds and, less commonly, mutations seen in familial conditions. The most common gene polymorphism associated with sporadic microbleeds is the Apolipoprotein E (APOE) gene on chromosome 19 [5]. The location of CMBs may indicate the underlying aetiology, with those occurring in peripheral lobar locations more likely to be associated with cerebral amyloid angiopathy, and those in deeper brain locations more likely linked to hypertensive arteriopathy [1-6].

On MRI, white matter changes or LA are defined as areas of high signal on the T2WI and FLAIR sequences, which may be seen in the periventricular location or in the deep white matter. They are hypothesised to be caused by reduced blood supply (ischaemia) or dilation of the perivascular spaces surrounding normal arterioles [7].

The presence of LA has been previously shown to be related to adverse cognitive functions and shares risk factors with hypertension and microbleeds [8]. It is also associated with the severity of Cerebral Microbleeds (CMBs) [5,9,10]. These findings in the literature may indicate a relationship between the different locations, aetiologies, and demographic factors of patients with CMBs in relation to the presence of LA. However, only a few studies [1,9] have been conducted to establish a relationship between Fazekas grading of SVD and the MARS scale of CMBs, if any. Among these studies, there have been no attempts to quantitatively correlate the severity of microbleeds with that of the white matter changes. Therefore, present study aimed to determine if, such a correlation exists between the two scales.

MATERIALS AND METHODS

An analytical cross-sectional study was conducted at the Department of Radiodiagnosis, MS Ramaiah Hospitals, Bengaluru, Karnataka, India from November 2019 to June 2021. The study obtained approval from the Ethics Committee (ECR number-MRMC/EC/AP-32/10-2019), and informed consent was obtained from the participants. The sample population consisted of patients who underwent brain magnetic resonance imaging and were diagnosed with CMBs.

Sample size calculation: The sample size was calculated based on a previous study conducted by Yamada S et al., which

reported a correlation of 0.48 between CMBs and periventricular hyperintensities [9]. In the present study, considering a 1% alpha error and 90% power, the minimum sample size was determined to be 50 subjects.

Inclusion criteria: Patients who underwent magnetic resonance imaging of the brain and showed evidence of CMBs were included.

Exclusion criteria: Patients with head trauma and post-traumatic haemorrhage, and with intracranial space-occupying lesions, vascular malformations, and cerebral vasculitis and patients with a previous history or imaging evidence of cerebral parenchymal surgery.

Study Procedure

The study included 65 patients. Detailed clinical history, including admission details, clinical symptoms, medication details, and reports of various blood investigations and other imaging data, were obtained.

The MRI images were acquired using a 1.5T, 18-channel Magnetic Resonance (MR) scanner (Magnetom, Avanto, Siemens, Erlangen, Germany) with a matrix coil. T1, T2, Fluid Attenuation Inversion Recovery (FLAIR), Diffusion-Weighted Imaging (DWI), and Susceptibility Weighted Imaging (SWI) sequences were performed for all patients, with additional MR Time of Flight (TOF) angiography and venography performed for selected patients.

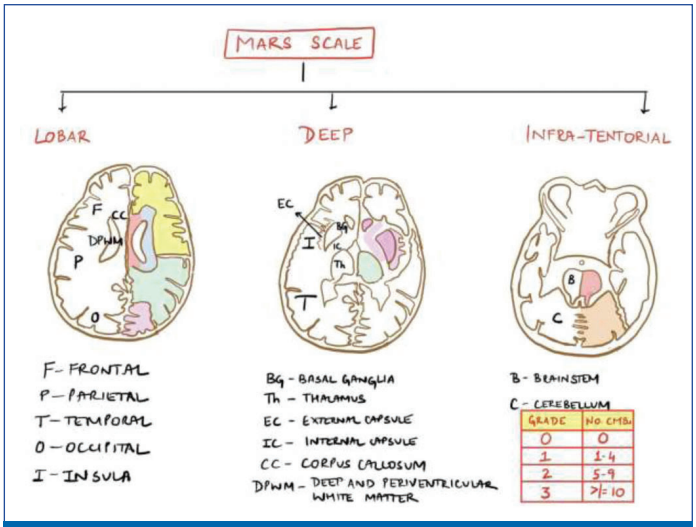
The presence of CMBs was evaluated on SWI, and grading was performed according to the Microbleed Anatomical Rating Scale (MARS) by three independent observers, as shown in [Table/Fig-1-3]. The severity of white matter changes or LA was assessed on FLAIR images using the Fazekas scale, with guidelines provided in [Table/Fig-4,5]. The severity of MARS was then correlated with the Fazekas scale. All results were correlated with clinical presentations, patient co-morbidities, and laboratory investigations.

Microbleed location (MARS scale)		Number	
		Right	Left
Lobar	Frontal		
	Parietal		
	Temporal		
	Occipital		
	Total		
Deep	Basal ganglia		
	Thalamus		
	Internal capsule		
	External capsule		
	Corpus callosum		
	Deep and periventricular white matter		
	Total		
Infratentorial	Brain stem		
	Cerebellum		
	Total		

[Table/Fig-1]: Anatomical division of the brain in MARS grading of CMBs [1].

Variables	
Degree 0	0 CMBs
Degree 1	1-4 CMBs
Degree 2	5-9 CMBs
Degree 3	>/=10 CMBs

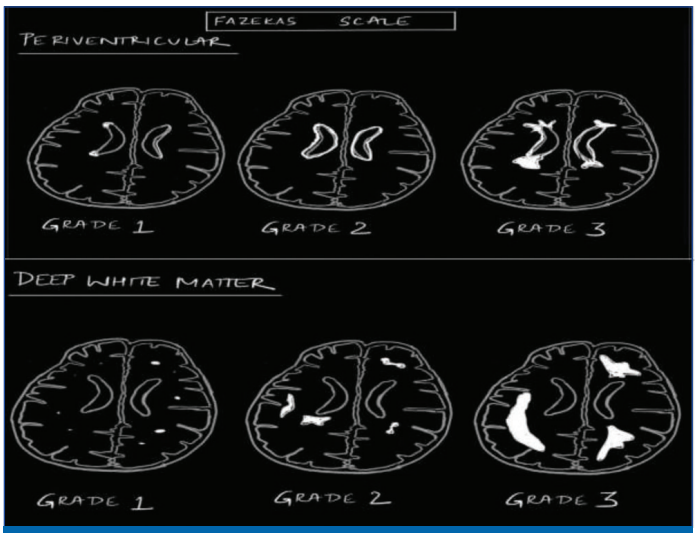
[Table/Fig-2]: CMB grading on MARS scale [1].



[Table/Fig-3]: Microbleed Anatomical Rating Scale (MARS) illustration [14].

Fazekas grading	Periventricular Hyperintensities (PVH)	Deep White Matter Hy (DWMH)
Grade-0	Absence	Absence
Grade-1	Caps or pencil thin lining	Punctate foci
Grade-2	Smooth 'halo'	Initial confluence of foci
Grade-3	Irregular PVH extending into the deep white matter	Large confluence of foci
Total	3	3

[Table/Fig-4]: Fazekas grading of white matter hyperintensities on brain MRI used in present study [1].



[Table/Fig-5]: Fazekas scale illustration for white matter changes [15,16].

STATISTICAL ANALYSIS

The data were entered into a Microsoft Excel spreadsheet and analysed using Statistical Packages for Social Sciences (SPSS) version 22.0 software. Categorical data were presented as frequencies and proportions. The Chi-square test was used as a significance test for categorical data. Continuous data were presented as mean and standard deviation. Spearman's correlation was performed to determine the correlation between two variables. A p-value of <0.05 was considered statistically significant, assuming all the rules of statistical tests. MS Excel and SPSS version 22.0 (IBM SPSS Statistics, Somers NY, USA) were used for data analysis [11-13].

RESULTS

The majority of subjects were in the age group of 61 to 70 years, 33 (50.8%). A total of 43 (66.2%) were males, and 22 (33.8%) were females [Table/Fig-6]. The most common clinical presentation was altered sensorium in 31 (47.4%) subjects.

Variables		Count	%
Age (years)	<50 years	4	6.2%
	51 to 60 years	6	9.2%
	61 to 70 years	33	50.8%
	71 to 80 years	17	26.2%
	>80 years	5	7.7%
	Total	65	100.0%
Gender	Female	22	33.8%
	Male	43	66.2%
	Total	65	100.0%

[Table/Fig-6]: Gender and age distribution of subjects.

Co-morbidities were observed in most subjects, with 61 (93.8%) having Hypertension (HTN), 44 (67.7%) having Diabetes Mellitus (DM), 18 (27.7%) having previous Transient Ischaemic Attack (TIA)/ Stroke, and 12 (18.5%) having a previous cardiac event [Table/Fig-7]. There were 30 (46.2%) smokers, and 37 (56.9%) were alcoholics.

Parameters	Yes	
	Count	%
HTN	61	93.8%
DM	44	67.7%
Previous TIA/Stroke	18	27.7%
Previous cardiac event	12	18.5%
Smoking	30	46.2%
Alcohol	37	56.9%

[Table/Fig-7]: Co-morbidities among subjects.

These patients were on common medications, with 47 (72.3%) on statins, 61 (93.8%) on antihypertensives, 43 (66.2%) on Oral Hypoglycemic Agent (OHA)/insulin, and 47 (72.3%) on aspirin/ anticoagulant.

The distribution of microbleeds showed 6 (9.2%) in the basal ganglia, 12 (18.5%) in the deep region, 18 (27.7%) in the lobar region, and 29 (44.6%) with a mixed distribution of CMBs [Table/Fig-8].

Variable		Count	%
Type	Basal Ganglia	6	9.2%
	Deep	12	18.5%
	Lobar	18	27.7%
	Mixed	29	44.6%
	Total	65	100.0%

[Table/Fig-8]: Distribution of microbleeds.

Based on Fazekas grading, 4 (6.2%) had Grade-1, 18 (27.7%) had Grade-2, 6 (9.2%) had Grade-3, 17 (26.2%) had Grade-4, 16 (24.6%) had Grade-5, and 4 (6.2%) had Grade-6 [Table/Fig-9].

		Count	%
Fazekas	1	4	6.2%
	2	18	27.7%
	3	6	9.2%
	4	17	26.2%
	5	16	24.6%
	6	4	6.2%
	Total	65	100.0%

[Table/Fig-9]: Fazekas grading distribution.
Fazekas grading is 6 as periventricular and deep white matter are each graded out of 3 and added up

In the study, among subjects with MARS Grade-1, the majority had Fazekas Grade 2 (47.8%); among subjects with MARS Grade-2, the majority had Fazekas Grade-4 (72.7%); and among subjects with MARS Grade-3, the majority of them had Fazekas Grade-5 (41.9%) [Table/Fig-10].

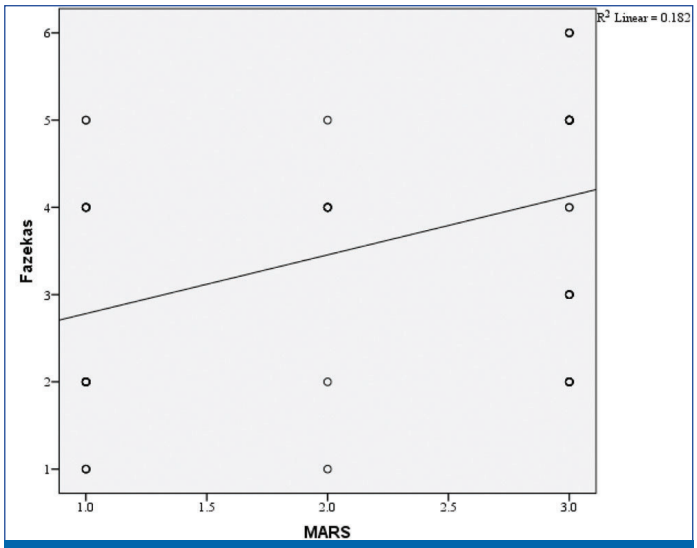
Parameter		MARS					
		Grade-1		Grade-2		Grade-3	
		Count	%	Count	%	Count	%
Fazekas	1	3	13.0%	1	9.1%	0	0.0%
	2	11	47.8%	1	9.1%	6	19.4%
	3	0	0.0%	0	0.0%	6	19.4%
	4	7	30.4%	8	72.7%	2	6.5%
	5	2	8.7%	1	9.1%	13	41.9%
	6	0	0.0%	0	0.0%	4	12.9%
	Total	23	100.0%	11	100.0%	31	100.0%

[Table/Fig-10]: Concordance between MARS and Fazekas.

There was a significant correlation between MARS grade and Fazekas, i.e., an increase in MARS corresponded to an increase in Fazekas and vice versa (p<0.001) [Table/Fig-11,12]. No significant interobserver variability was found among the three independent observers (Kappa value=0.95).

Parameter			MARS	Fazekas
Spearman's rho	MARS	Correlation coefficient	1.000	0.439**
		S (2-tailed)		<0.001*
		N	65	65

[Table/Fig-11]: Correlation between MARS and Fazekas.
**Correlation is significant at the 0.01 level (2-tailed); S: Significant



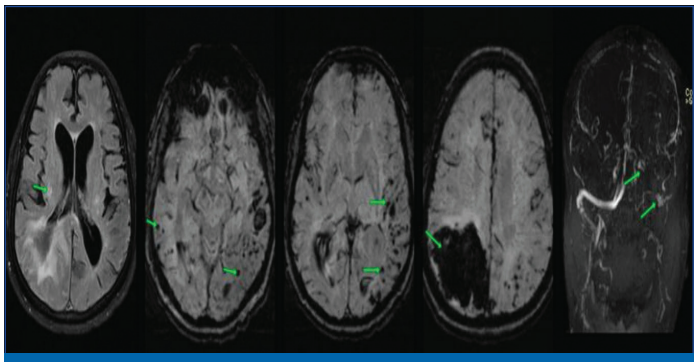
[Table/Fig-12]: Scatter plot showing correlation between MARS and Fazekas.

Periventricular white matter hyperintensities were associated more with cognitive dysfunction than deep white matter hyperintensities. Cognitive dysfunction was observed in 24 (36.9%) of patients in present study, of which 2 (4.6%) had a significant loss of memory. In those with cognitive dysfunction, predominantly lobar microbleeds followed by a mixed distribution of lobar and deep microbleeds were found [Table/Fig-13]. A higher systolic blood pressure was found in patients with deep and infratentorial microbleeds [Table/Fig-14]. The predominant stroke subtype in present study is the ischaemic subtype, with lacunar infarct being the most common [Table/Fig-15]. Patients with higher serum creatinine showed predominantly deep and infratentorial CMBs [Table/Fig-16].

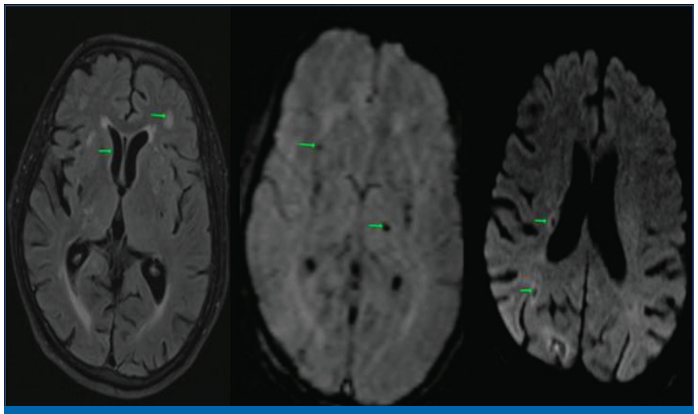
DISCUSSION

The majority of subjects were aged between 61 and 70 years, with 66.1% being males. In a prospective study on stroke outpatients by Yang Q et al., 1289 consecutive patients were screened. The mean age of these patients was 60.49 years, and the proportion of male patients was 53.7% [1]. This suggests that age is an independent risk factor for cerebral microbleeds. Among the ischaemic stroke subtypes, microbleeds occur more often in those with lacunar

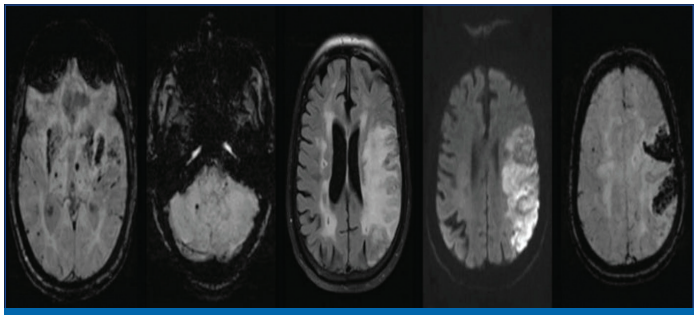
infarction (26-62%). Higher rates of CMBs are found in patients with recurrent ICH [17]. In present study, 18 (27.7%) had a previous history of stroke, predominantly of the ischaemic type.



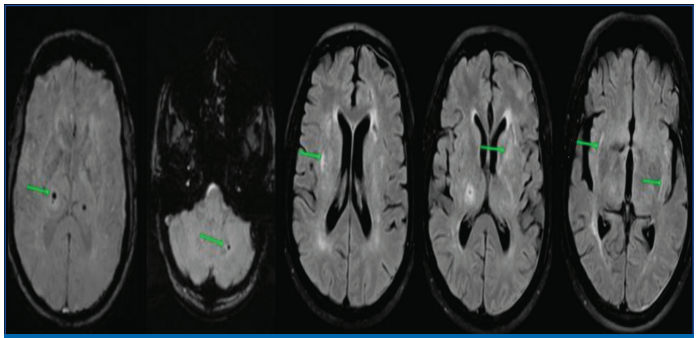
[Table/Fig-13]: Lobar CMBs-Axial FLAIR and SWI sequences in a 68-year-old male with dementia showing disproportionate lobar only CMBs as compared to subtle WMCs. Right parietal haematoma with chronic superior sagittal, left transverse and sigmoid sinuses seen on the SWI and coronal MR venogram.
References: Department of Radiology, MS Ramaiah hospital 2021



[Table/Fig-14]: Deep CMBs-Axial FLAIR, SWI and DWI sequences in a hypertensive 73 year male showing periventricular and deep white matter hyperintensities (Fazekas PVH-2 and DWMH-1) and predominantly deep CMBs. Chronic lacunar infarcts are seen in the right parietal white matter.
References: Department of Radiology, M. S. Ramaiah hospital 2021



[Table/Fig-15]: Acute stroke-Axial SWI, FLAIR and DWI sequences in a 72-year-old male with severe hypertension showing predominantly deep, infratentorial CMBs and predominantly deep white matter hyperintensities. Acute left middle cerebral artery territory infarction with haemorrhagic transformation seen on DWI/SWI.
References: Department of Radiology, MS Ramaiah hospital 2020



[Table/Fig-16]: Chronic kidney disease (CKD)-Axial SWI and FLAIR sequences in a 52-year-old male with CKD showing predominantly deep and infratentorial CMBs and few deep white matter hyperintensities. 'Lentiform fork sign' i.e., bilateral basal ganglia hyperintensities are seen on FLAIR sequence.
References: Department of Radiology, M. S. Ramaiah hospital 2020

The incidence of microbleeds among the stroke outpatients screened in the study by Yang Q et al., was 14.6% [1]. The distribution of CMB locations in their study was as follows: 23.4% strictly lobar, 12.2% strictly deep, 6.4% strictly infratentorial, and 58.0% mixed. In the present study, the distribution was 9.2% strictly in the basal ganglia, 18.5% deep and infratentorial, 27.7% lobar, and 44.6% mixed cerebral microbleeds. Mixed CMBs had the highest incidence in both studies.

In recent years, there has been increasing interest in the relevance of CMBs for cognition. Cerebral amyloid angiopathy associated with lobar Intracerebral Haemorrhage (ICH) and CMBs has long been known. In the Rotterdam study [18], a higher number of microbleeds was associated with a lower Mini Mental State Examination (MMSE) score and worse performance on tests of information processing speed and motor speed. These associations were most robust in participants with strictly lobar microbleeds. In present study, cognitive dysfunction was observed in 24 (36.9%) of patients, of which 2 (4.6%) experienced significant memory loss. Among these subjects, strictly lobar cerebral microbleeds were found in 9 (37.5%), and a mixed distribution of CMBs was found in 15 (62.5%).

In another prospective study by Valenti R et al., it was found that the total number of CMBs was associated with attention/executive and fluency domains. Considering their locations, a significant correlation was found between deep CMBs and attention/executive domains, while lobar CMBs showed a significant correlation with the fluency domain [19].

Hypertension is a major risk factor for microbleeds. In present study, 61 subjects (93.8%) were hypertensive, which is consistent with the findings of other research [3,4,20,21]. In a study by Liu W et al., systolic blood pressure variability was found to be an independent risk factor for deep and infratentorial CMB progression, while diastolic blood pressure variability was independently associated with CMB development in deep regions [21].

In studies by Kakar P et al., Yates PA et al., and Kim BJ and Lee SH, it was found that microbleeds are more frequently associated with intracerebral haemorrhage (prevalence 19-83%) than with ischaemic stroke (15-35%) [2,5,22].

According to Yang Q et al., the severity and number of CMBs at any location (graded on the MARS scale) correlated with the severity of white matter changes (graded on the Fazekas scale) [1]. In another study by Yamada S et al., evidence was found to indicate that white matter hyperintensities-related brain aging is more significantly associated with cerebral microbleeds than actual aging [9]. Additionally, the grade of PVH showed a stronger correlation with the number of microbleeds than the grade of DWMH. In a study by Gao T et al., both microbleeds (>grade 2) and LA in severity (>grade 2) were higher in the recurrent stroke group (14.5% and 48.4%) compared to the primary stroke group (3.8% and 7.7%) in a study by Gao T et al., [10].

In present study, a statistically significant correlation was found between the grades of cerebral microbleeds and white matter changes. As the severity of microbleeds increased, so did the grade of white matter changes.

In a recent study by Liu JY et al., involving 982 participants with CMBs, Diffusion Tensor Imaging (DTI) correlation was conducted. The study found that the presence of CMBs influenced the destruction of microstructural integrity of white matter, as indicated by lower fractional anisotropy, higher mean diffusivity, and higher radial diffusivity in the internal capsule and corpus callosum in these subjects [23].

Limitation(s)

The correlation between anticoagulants/antiplatelets and the subsequent development of CMBs could not be determined in present study as the temporal evolution of the CMBs was not

assessed. The counting-based grading in the MARS scale was not always reproducible and may have led to small discrepancies between two observers. Many subjects with acute stroke did not undergo an MRI brain study based on the SWI protocol, and therefore had to be excluded from the study. As a result, the sample size does not represent the entire population with incidental cerebral microbleeds.

CONCLUSION(S)

The LA and CMBs show a significant correlation, reflecting the end results of small vessel ischemia and bleeding. The severity of white matter changes increases with an increase in the severity of cerebral microbleeds. Lacunar infarction, which is again a marker of SVD, is most commonly associated with CMBs. The association of CMBs with advanced age, hypertension, and stroke highlights the importance of being vigilant in their detection and reporting. The association of deep, infratentorial CMBs with hypertension and the predominance of lobar CMBs with cognitive dysfunction provide valuable clues for diagnosis.

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- Manual Googling: Nov 06, 2023
- iThenticate Software: Nov 11, 2023 (13%)

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