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Original Article

Patterns and Risk Factors of Cerebral Microbleeds and Cognitive Impairment in Patients Incidentally Detected with Cerebral Microbleeds on M.R.I. Brain

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Abstract

Background: Cerebral microbleeds (CMBs) act as markers of small vessel disease. Specific topographic patterns of microbleeds are representative of particular underlying vasculopathies mainly hypertensive vasculopathy and cerebral amyloid angiopathy. Mortality has also been strongly predicted by microbleeds. Deep and infratentorial microbleeds have been found to be associated with cardiovascular mortality whereas lobar microbleeds are associated with stroke related mortality.

Aim: The aim is to estimate the prevalence of CMBs in patients undergoing magnetic resonance imaging (MRI) brain for suspicious neurological symptoms, to find the risk factors of CMBs and association of cognitive impairment with the number and location of microbleeds.

Methods: This was a cross-sectional and observational study of 200 patients (>50 years of age) undergoing MRI brain for suspicious neurological symptoms. Cardiovascular risk factors (hypertension, smoking, diabetes, and dyslipidemia) were examined by interview and laboratory and physical examination. MRI examinations were assessed for the presence of CMBs. Subsequently, the patients detected with CMBs were evaluated for the presence of cognitive impairment.

Results: Overall prevalence of CMBs was 26%. A high prevalence of CMBs was found in patients with ischemic cerebrovascular disease with a higher prevalence found in patients with intracerebral hemorrhage. Increasing age was associated with higher prevalence of CMBs. Hypertension, smoking, and diabetes turned out to be important cardiovascular risk factors of CMBs. CMBs were associated with cognitive impairment with increase in number of microbleeds related to lower cognitive assessment scores.

Conclusion: CMBs act as markers of small-vessel disease and their topographical patterns are suggestive of underlying vasculopathies such as hypertensive vasculopathy, with cognitive impairment being one of the clinical manifestations of CMBs.

Key words: Cerebral microbleeds, Magnetic resonance imaging brain, Neurological symptoms

INTRODUCTION

Cerebral microbleeds (CMBs), also referred to as cerebral microhemorrhages, are small hypointense foci with maximum size up to 5 mm or even up to 10 mm detected using susceptibility-weighted magnetic resonance imaging (MRI).[1-5] Histopathologically, CMBs are tiny deposits of blood degradation products (mainly hemosiderin) contained within macrophages and lying in close spatial relationship with structurally abnormal vessels. Hemosiderin being a strong paramagnetic material allows its detection when a magnetic field is applied.[6] This phenomenon, called susceptibility effect, is the basis of T2*-gradient recalled echo (GRE) imaging.[7] Further sequences have been developed over time which include three dimensional T*-GRE[8] and the most sensitive one to date is susceptibility-weighted imaging (SWI).[9] Susceptibility effects scale

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linearly with field strength; hence, the detection rate of CMBs at MRI increases markedly even between 1.5 T and 3.0 T.[10,11]

Microbleeds might cause acute transient focal neurological episodes[12,13] which may resemble TIA or seizures depending on negative or positive character of symptoms. Cumulative microbleeds highlight the progression of underlying small vessel disease. Mortality has also been strongly predicted by microbleeds. Deep and infratentorial microbleeds have been found to be associated with cardiovascular mortality whereas lobar microbleeds are associated with stroke related mortality.[14] Other main neurological outcomes that have been associated with microbleeds are gait disturbances and cognitive impairment.[15]

Aims and Objectives

The objectives of the study are as follows:

- To estimate the prevalence of CMBs in patients undergoing MRI brain for suspicious neurological symptoms (headache, vertigo, dizziness, numbness, subjective memory impairment, syncope).
- To find the risk factors of CMBs and association of cognitive impairment with the number and location of microbleeds.

MATERIALS AND METHODS

This study was carried out in the postgraduate Department of Radiodiagnosis and Imaging, Government Medical College, Srinagar, over a period of 18 months (2020-2021), after obtaining clearance from the ethical committee of the college. After explaining the study details, written informed consent was taken. Patients aged more than 50 years were selected. Patients (aged ≥50 years) undergoing MRI brain for suspicious neurological symptoms (headache, dizziness, vertigo, numbness, syncope, and subjective memory impairment) were included in the study. Patients with contraindications for MRI, brain trauma, acute CNS infection, and intracranial space occupying lesion were excluded for the study. The risk factors included in our analysis were age, hypertension, smoking, diabetes, and dyslipidemia. Cardiovascular risk factors (hypertension, smoking, diabetes, and dyslipidemia) were examined by interview and laboratory and physical examination. Hypertension was diagnosed if, when it was measured on 2 different days, the systolic blood pressure readings on both days was ≥140 mmHg and/or the diastolic blood pressure readings on both days was ≥90 mmHg.[16] The diagnosis of diabetes mellitus was based on repeated pathological blood tests indicating fasting values ≥126 mg/dl or value loads ≥200 mg/dl 2 h after oral glucose administration or HbA1c level of ≥6.5%.[17] Dyslipidemia was determined when total cholesterol was ≥200 mg/dl or when low-density lipoprotein cholesterol was ≥130 mg/dl.[18]

A history of smoking was noted if the patient smoked during 3 months before the most recent neurological event. The patients were then subjected to MRI brain. On MRI brain, the patients were assessed for the presence of CMBs. CMBs were identified using Greenberg's criteria.[1] All the patients then subsequently detected with CMBs on MRI brain were assessed for the presence of cognitive impairment. Cognitive impairment was evaluated using Montreal Cognitive Assessment (MOCA) scale. A MOCA score of ≥26 was considered to be normal and MOCA <26 was suggestive of cognitive impairment. MRI examination was done on 3 TESLA equipment (MAGNETOM SKYRA 3T). For brain following sequences and slice thickness were obtained: (i) T1-weighted axial sequence-3mm, (ii) T2-weighted axial sequence-3mm, (iii) Fluid-attenuated inversion recovery axial sequence-4mm, (iv) Diffusion-weighted imaging sequence-5 mm, and (v) SWI sequence The SWI sequence used in our study was a 3-dimensional, T2*-weighted, GRE sequence with a high resolution used for microbleed detection. The parameters of SWI were as follows TR/TE 28/20 ms, flip angle 15®, matrix 448 × 364, number of excitations 1, field of view 18.68 × 23.0 cm, and slice thickness 2.0 mm.

Statistical Methods

The recorded data were compiled and entered in a spread sheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean ± SD and categorical variables were summarized as frequencies and percentages. Chi-square test or Fisher's exact test, whichever appropriate, was applied for comparing categorical variables. $P<0.05$ was considered statistically significant. All P-values were two tailed.

RESULTS AND DISCUSSION

This study included 200 patients undergoing MRI brain for suspicious neurological symptoms. Out of 200 subjects, 111 were males while as 89 were females. The mean age of our study subjects was 63 years. Out of 200 patients, 11 were detected with intracerebral hemorrhage (ICH), among which three patients had lobar hemorrhage and eight patients had hemorrhage in deep and infratentorial location. Thirty-one patients were detected with ischemic cerebrovascular disease (acute and chronic lacunar infarcts and large vessel infarcts). Out of 200 study subjects, 94 were diagnosed with hypertension, 26 had diabetes, 44 were smokers, and 26 were suffering from dyslipidemia [Tables 1-6].

Table 1: Prevalence of microbleeds in study subjects

Status and Location of Microbleeds	Number	Prevalence (%)
Prevalence of microbleeds		
Present	52	26
Absent	148	74
Total	200	100
Location of Microbleeds		
Present	45	86.5
Absent	7	13.5
Total	52	100

Overall prevalence of CMBs=26%, Percentage of patients with deep and infratentorial microbleeds=86.5%, Percentage of patients with strictly lobar microbleeds=13.5%

Table 2: Prevalence of microbleeds as per gender

Gender	Microbleeds		No Microbleeds		*P*-value
	No.	age%	No.	age%	
Male	29	26.1	82	73.9	0.964
Female	23	25.8	66	74.2	
Total	52	26.0	148	74.0	

Prevalence of microbleeds in males=26.1%, Prevalence of microbleeds in females=25.8%

Table 3: Prevalence of microbleeds in patients with ischemic cerebrovascular disease and intracerebral hemorrhage (ICH)

Microbleeds	Number of patients with ischemic cerebrovascular disease	Prevalence (%)
Ischemic cerebrovascular disease		
Present	11	35.5
Absent	20	64.5
Total	31	100
Intracerebral hemorrhage		
Present	8	72.7
Absent	3	27.3
Total	11	100

Prevalence of microbleeds in patients with ischemic cerebrovascular disease=35.5%, Prevalence of microbleeds in patients with ICH=72.7%

Prevalence of CMBs

Microbleeds were detected in 52 with an overall prevalence of CMBs found to be 26%. According to Rotterdam scan study (performed by using 1.5T MRI), the prevalence of CMBs in healthy older individuals can be as high as 23.5%.[19] The higher prevalence of CMBs detected in our study can be attributed to higher field strength MRI (3T) used to perform the study (apart from the differences in the study populations which may be present). This finding has also been seen by Stehling *et al.*[11] who have reported that the detection rate and visibility of CMBs benefit from the higher field strength, resulting in a significantly improved depiction of iron-containing brain structures (CMBs) at 3.0T compared to that at 1.5T.

In our study, the prevalence of CMBs among males was found to be 26.1%, while as the prevalence of microbleeds among females was found to be 25.8%. No significant difference in CMBs prevalence between males and females

Table 4: Age, hypertension, smoking, dyslipidemia, and diabetes in relation to cerebral microbleeds among study patients

Relation with cerebral microbleeds	Microbleeds		No Microbleeds		*P*-value
	No.	%age	No.	%age	
Age in years					
<60	17	13.8	106	86.2	<0.001*
≥60	35	45.5	42	54.5	
Hypertension					
Present	46	48.9	48	51.1	<0.001*
Absent	6	5.7	100	94.3	
Smoking					
Smoker	19	43.2	25	56.8	<0.003*
Non smoker	33	21.2	123	78.8	
Dyslipidemia					
Present	8	30.8	18	69.2	<0.723
Absent	44	25.3	130	74.7	
Diabetes					
Present	11	42.3	15	57.7	0.042*
Absent	41	23.6	133	76.4	

*Statistically Significant (*P*-value<0.05), Increase in age was associated with increase in prevalence of microbleeds, Hypertension turned out to be an important risk factor of CMBs, Smoking was a risk factor of CMBs, No association was found between dyslipidemia and occurrence of CMBs, Diabetes was a risk factor of CMBs

Table 5: Association of location of microbleeds with hypertension, diabetes, and smoking

Correlation	Deep and infratentorial		Lobar		*P*-value
	No.	Age%	No.	Age%	
Hypertension					
Present	42	93.3	4	57.1	0.031*
Absent	3	6.7	3	42.9	
Diabetes					
Present	10	22.2	1	14.3	0.632
Absent	35	77.8	6	85.7	
Smoking					
Smoker	17	37.8	2	28.6	0.631
Non smoker	28	62.2	5	71.4	

*Statistically Significant (*P*-value<0.05), Hypertension, diabetes and smoking was associated with deep and infratentorial microbleeds

Table 6: Association of cognitive assessment score (MOCA) with number and location, of microbleeds

Association of MOCA with number and location of microbleeds	18≤ MOCA ≤22		26> MOCA >22		*P*-value
	No.	%age	No.	%age	
Number of bleeds					
Few (<5)	4	15.4	16	61.5	0.002*
Multiple (≥5)	22	84.6	10	38.5	
Total	26	100	26	100	
Location of bleeds					
Deep and infratentorial	23	88.5	22	84.6	0.685
Lobar	3	11.5	4	15.4	
Total	26	100	26	100	

*Statistically Significant (*P*-value<0.05), Increase in number of CMBs was associated with lower cognitive assessment scores, Both deep and infratentorial microbleeds and lobar microbleeds were associated with lower cognitive assessment score was found. Similar findings were reported by Poels *et al.*[20] in the update of Rotterdam scan study. The prevalence of cerebral microbleeds in patients with ischemic cerebrovascular disease (like acute and chronic lacunar infarcts and large vessel infarcts) was found to be 35.5%. Similar results were found by Naka *et al.*[21] and Tsushima *et al.*[22] The prevalence of microbleeds in patients having suffered from ICH was found to be 72.7% which was in concordance with the finding reported by Jeong *et al.*[23] evaluated 102 patients with deep and lobar ICH (27% lobar, 73% deep) and found that 70% had microhemorrhages and they were frequently multiple. A wide range in the prevalence of CMBs in different clinical conditions like ischemic stroke and ICH has also been reported by Naka *et al.*,[21] Lee *et al.*[24] and Kato *et al.*[25]

Risk Factors

In our study, age was found to be an important risk factor of CMBs as increase in age was associated with increase in the prevalence of CMBs. In the age group of 50–60 years 13.8% of the study subjects had microbleeds, while as in the age group of ≥60 years, 45.5% had CMBs. Similar findings were seen by Poels *et al.*[20] in the update of Rotterdam scan study wherein it was reported that increasing age was associated with a higher prevalence of CMBs, as well as presence of multiple microbleeds.

In our study, hypertension was found to be an important risk factor of CMBs. Among the hypertensive patients presenting with microbleeds, it was found that about 93% had microbleeds in deep and infratentorial location. Thus, the presence of hypertension was found to be related to deep and infratentorial microbleeds. Similar findings were reported by Poels *et al.*[20] and Vernooij *et al.*[19] These cross-sectional studies found the association between cardiovascular risk factors such as systolic blood pressure, hypertension, smoking, and microbleeds in a deep or infratentorial region. In another study conducted by Jia *et al.*,[26] it was found that hypertension increases the risk of CMBs in the deep and infratentorial locations and also in the territory of the posterior cerebral artery.

Smoking was also found to be an important cardiovascular risk factor of CMBs in the present study. Among the smokers who presented with microbleeds, about 89% had microbleeds in deep and infratentorial location; however, a statistically significant relation between smoking and presence of microbleeds in deep and infratentorial location could not be established possibly because of a smaller sample size. Smoking was also reported to be an important cardiovascular risk factor of CMBs by Poels *et al.*[20] They also found a strong association between smoking and microbleeds in deep or infratentorial region. Smoking was also found to be a risk factor of CMBs by Tsushima *et al.*[27] who performed a study on neurologically healthy adults and found that microbleeds detected among these subjects were strongly related to hypertension and heavy smoking.

Diabetes also turned out to be a risk factor of CMBs. Out of 26 diabetics in our study, 11 (43%) had CMBs. Out of 11 diabetics who presented with CMBs, 10 had microbleeds located in deep and infratentorial location in comparison to one with strictly lobar microbleeds. Diabetes was reported as a cardiovascular risk factor of CMBs in the update of Rotterdam scan study by Poels *et al.*[20] who also found cardiovascular risk factors such as diabetes related to deep and infratentorial microbleeds.

In our study, no association was found between dyslipidemia and occurrence of CMBs.

CMBs and Effect on Cognition

In this study, it was found that majority of the subjects who were detected with multiple CMBs (22 out of 32/85%) scored lower on MOCA scale (MOCA). Thus, 85% of the subjects with multiple CMBs had lower cognitive assessment score (MOCA ≤22) in comparison to 4 subjects (15%) with multiple microbleeds who scored relatively better (MOCA >22). Further it was found that majority of the subjects who had few microbleeds (16 out of 20/62%) performed better on MOCA scale in comparison to 4 subjects who scored poorer. Thus, in our study, it was revealed that the presence of multiple CMBs (≥5) was associated with the lower MOCA total scores. Similar findings were reported by Zhang *et al.*[28] who performed a study on patients with essential hypertension and found that the presence of and a greater number of CMBs independently correlate with mild cognitive impairment in these patients without a history of transient ischemic attack or stroke. In another study performed by Yakushiji *et al.*,[29] presence and number of CMBs were related to reduced Mini-Mental State Examination scores (MMSE cognitive assessment scale).

In our study, while assessing cognitive scores in subjects with cerebral microbleeds, it was found that subjects with deep and infratentorial microbleeds (with or without lobar microbleeds) as well as those subjects with strictly lobar microbleeds had mild cognitive impairment. No statistically significant difference in the cognitive impairment score was seen between those with deep and infratentorial microbleeds and those with strictly lobar microbleeds. Similar findings were reported by Zhang *et al.*[28] They also found that both lobar microbleeds and deep and infratentorial microbleeds were related to mild cognitive impairment.

CONCLUSION

There was no significant gender-based difference in CMBs prevalence. The prevalence of microbleeds in patients with ischemic cerebrovascular disease was high (35.5%) with even higher prevalence seen in patients of ICH (72.7%). A larger proportion of patients presented with deep and infratentorial microbleeds (86.5%) in comparison to those with strictly lobar microbleeds (13.5%). Increasing age was associated with higher prevalence of CMBs. Hypertension, smoking, and diabetes turned out to be important cardiovascular risk factors of CMBs. CMBs were associated with cognitive impairment with increase in number of microbleeds related to lower cognitive assessment scores.

Inference of this study is that CMBs may act as markers of small-vessel disease and their topographical patterns are suggestive of underlying vasculopathies such as hypertensive vasculopathy, with cognitive impairment being one of the clinical manifestations of CMBs.

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