Original Article

Clinicoradiological features of cerebral microbleeds diagnosed on magnetic resonance neuroimaging

Jayaram Bharath[1], Mohan Amuthabharathi[1], Kulumani M. Sivasubramaniyan[1], Subathra Adithan[1], Sunil K. Narayan[2], Vellathussery C. Sunitha[1], Krishnan Nagarajan[1]

Departments of [1]Radio-Diagnosis and [2]Neurology, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India.

ABSTRACT

Objectives: Cerebral microbleeds (MBs) are recently described entity on magnetic resonance (MR) neuroimaging and are considered one of the markers of small vessel disease. We aimed to study the clinicoradiological features of cerebral MBs that were diagnosed in MR neuroimaging.

Materials and Methods: We studied 109 South Indian patients, who presented to a tertiary care institution for MR neuroimaging with cerebral MBs as diagnosed on MR neuroimaging based on either the gradient T2* imaging or susceptibility-weighted imaging. The clinical details and coexisting MR features of infarcts, macrohemorrhages, lacunar infarcts, and white matter leukoaraiosis were evaluated and analyzed.

Results: Of 109 patients, 79 were males and 30 were females. Associated clinical comorbidities noted include hypertension (62.39%), diabetes (23.85%), and alcoholism (31.19%) apart from the history of anti-platelet/anti-coagulant usage (15.5%), previous cardiac disease (12.84%), and previous stroke/transient ischemic attacks (9.17%). Other co-existing neuroimaging abnormalities noted include cortical infarcts (27.52%), old hemorrhages (29.36%), lacunar infarcts (56.88%), and white matter leukaraiosis (67.89%).

Conclusion: The clinicoradiological features of cerebral MBs in South Indian patients are similar to other Asian and Western studies with significant coexistence of clinical comorbidities and imaging features of small vessel changes. Further studies with a larger sample are needed to correlate the grade of MBs to the individual risk of these clinicoradiological characteristics.

Keywords: Microbleeds, Cerebral microbleeds, Magnetic resonance imaging, Gradient echo T2* imaging, Susceptibility-weighted imaging

INTRODUCTION

Cerebral microbleeds (MBs) are defined as small perivascular hemosiderin deposits, which are small, round or ovoid lesions of the cerebral parenchyma of low signal intensity on T2*-weighted and Gradient echo (GRE) magnetic resonance imaging (MRI) sequences, with a maximal diameter of 5–10 mm.[1,2] Several studies have been carried out in the recent past to identify the risk factors of cerebral MBs. Hypertensive vasculopathy, amyloid angiopathy, renal impairment with hyperuricemia, male gender, old age, smoking, heavy alcohol consumption, hyperlipidemia, diabetes mellitus, previous antithrombotic agents, and atrial fibrillation are among the risk factors recognized as associated with cerebral MBs.[3-5] Assessing the topographical distribution of cerebral MBs provides a diagnostic clue about the underlying disease. For example, both hypertensive small-vessel disease and cerebral amyloid angiopathy (CAA) contribute to the formation of lobar cerebral MBs while

cerebral MBs located in the basal ganglia or infratentorial brain regions are mainly associated with hypertensive vasculopathy.[4] With the advancement in MRI technology, there is a steady rise in the identification of cerebral MBs. From the clinical point of view, early detection and treatment of the underlying etiology of MB,s which will definitely improve, leading to better understanding and possible prognostication. Recent studies have shown that cerebral MBs are an independent predictor of stroke outcomes and recurrences.[5] We aimed in this study to describe the clinicoradiological features of MRI-diagnosed cerebral MBs.

MATERIALS AND METHODS

We included 109 patients, who were diagnosed to have cerebral MBs on MRI over 2 years (from January 2018 to December 2019) after approval from the Institute Research and Ethics Committees. All patients diagnosed with MBs in MRI were included and those without clinical details

were excluded from the study. Detailed history and clinical details including functional status and comorbidity were obtained from the case files maintained at the medical records department. The demographic characteristics of the study patients, including their vascular risk factors and previous use of antithrombotic agents (antiplatelet agents and anticoagulants), were also collected from medical records. The risk factors considered include hypertension, diabetes mellitus, previous cardiovascular disease, smoking, alcoholism, previous stroke or transient ischemic attacks (TIAs), anti-platelet or anti-coagulant use, history of head injury or neurosurgical procedures, radio- or chemo-therapy, and uremia (with or without dialysis).

MRI was performed with a routine 1.5 T MRI (Avanto Siemens, Erlangen, Germany) and included either GRE MRI sequences (TR/TE 900/26 ms, slice thickness 4 mm, flip angle 20°, matrix 256 × 192, FoV 230 mm, and No. of averages 1) or susceptibility-weighted imaging (SWI) sequence (TR/TE 49/40 ms, flip angle 15 o, matrix size 256 × 200, FoV = 230 × 180 mm, slice thickness 3 mm, and No. of averages 1). Thirty-nine patients had GRE sequence imaging and 70 patients had SWI imaging. About 78 patients had undergone MRI in 1.5T and the remaining 31 in 3T MRI.

Magnetic resonance (MR) brain images were analyzed in detail to detect cerebral MBs and their location. The lesions are divided based on the size and location (1. Lobar CMBs [a. frontal, b. parietal c. temporal, d. occipital] 2. Deep CMBs, 3. Cerebellar CMBs). All these details were entered in the data collection pro forma. Based on the total number of cerebral MBs, patients were classified as (a) <5 cerebral MBs – grade 1, (b) 6–10 cerebral MBs – grade 2, (c) 11–25 cerebral MBs – grade 3, and (d) >25 cerebral MBs – grade 4.[6] On magnetic resonance angiography (MRA), the cerebral vascular variants such as a hypoplastic vertebral artery and fetal posterior cerebral artery (PCA) were also documented. We subgrouped the MB patients into predominantly lobar and predominantly deep cerebral groups based on the topographical distribution of cerebral MBs and explored the association of these two major subgroups with various baseline clinicoradiological characteristics.

Statistical analysis

The data were tabulated and descriptive statistical analysis of the data was done using IBM Statistical Package for the Social Sciences software version 2.0. The association of the radiological profile with categorical variables such as gender and other risk and comorbidity factors, stroke subtypes, and outcome parameters was carried out using the Chi-square test/Fisher exact test. All analyses were done at a 5% level of significance with a $P < 0.05$ considered as statistically significant.

RESULTS

Out of 109 patients, there were 79 (72.5%) males and 30 (27.5%) females with the predominant age group of 18–65 years (79.8%). There were four patients of <18 years and 18 were older than 65 years. The comorbid factors were as follows; hypertension 62.4%, diabetes 23.8%, alcoholism 31.2%, and smoking 9.2%. The other predisposing factors were as follows: anti-platelet/anti-coagulant use 15.5%, cardiovascular disease including rheumatic valvular disease/atrial fibrillation 12.8%, previous stroke/TIAs 9.2%, history of radio- or chemo-therapy 8.3%, and previous neurosurgery and head injury 4.6% each. Uremia (+ dialysis) was seen in 5.5%, systemic infections (two out of three were hepatitis B) in 2.75%, suspected cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in 5.5%, and vasculitis in one patient [Table 1].

Imaging findings

Out of 109 patients, deep microbleeds were noted in 90 (82.6%), deep with cerebellar 105 (96.3%), and cortical and lobar in 91 (83.5%). The grades of these patients include; Grade 1 (<5 MBs) in 15 (13.8%) patients, Grade II (6–10 MBs) in 25 (22.9%), Grade III (11–25 MBs) in 36 (33%), and Grade IV (>25 MBs) in 33 (30.3%) patients [Figures 1-5, Table 2]. Cortical or territory infarcts were noted in 30 (27.5%), previous hemorrhages (basal ganglia or lobar) in 32 (29.4%) lacunar infarcts in 62 (56.9%), and white matter leukoaraiosis in 74 (67.9%). We also tried to see MRA which is done routinely for all patients with neurovascular/stroke work-up. Vessel narrowing/occlusions were noted in 7 (6.4%) patients and dolichoectasia (vertebra-basilar) in 26 (23.8%) apart from normal variants (including fetal PCA, hypoplastic vertebral artery + thin vertebra-basilar arteries) in 47 patients [Table 3].

The association of the MBs with a clinicoradiological profile including comorbidity factors was attempted using the Chi-square test/Fisher exact test. There was a statistically significant difference in number of deep MBs between hypertensive and non-hypertensive patients ($P < 0.05$). However, a comparison of the number of total or lobar cerebral MBs between hypertensive and non-hypertensive showed no statistically significant difference between the two groups. However, hypertension also showed significant association with lacunar infarcts ($P < 0.05$) and macrohemorrhages ($P < 0.05$) suggesting the common denominator small-vessel disease.

Similarly comparison of the number of cerebral MBs (lobar, deep, and total) between patients with lacunar infarcts and without lacunar infarcts showed no statistically significant difference between the two groups. Furthermore, a comparison of the number of cerebral MBs (lobar, deep, and
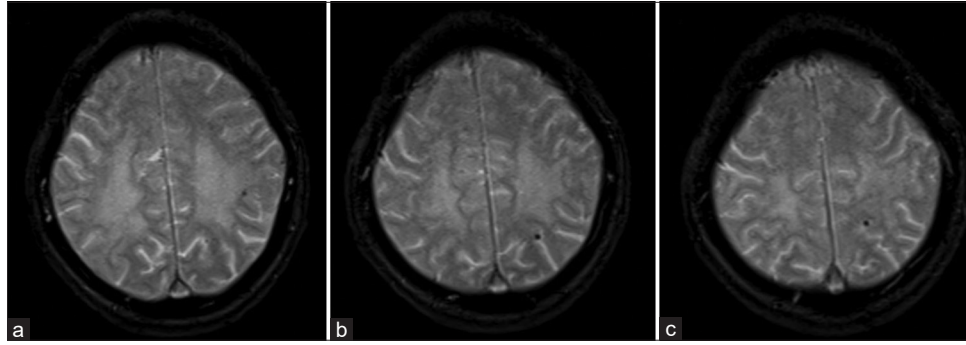
Figure 1: (a-c) GRE T2* axial images above the level of ventricles showing Grade I (<5) lobar microbleeds.
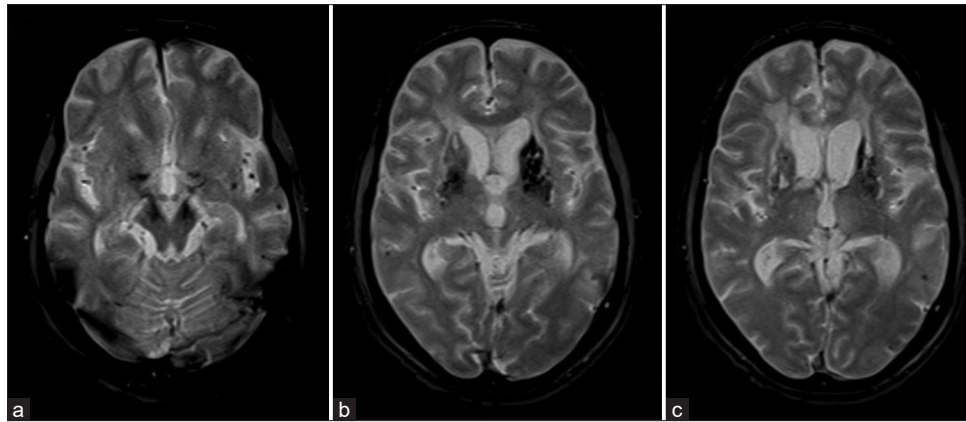
Figure 2: (a-c) The GRE T2* axial images at posterior fossa and basal ganglia level showing Grade II (6–10) deep and lobar microbleeds with the left putaminal old (macro) hemorrhage.
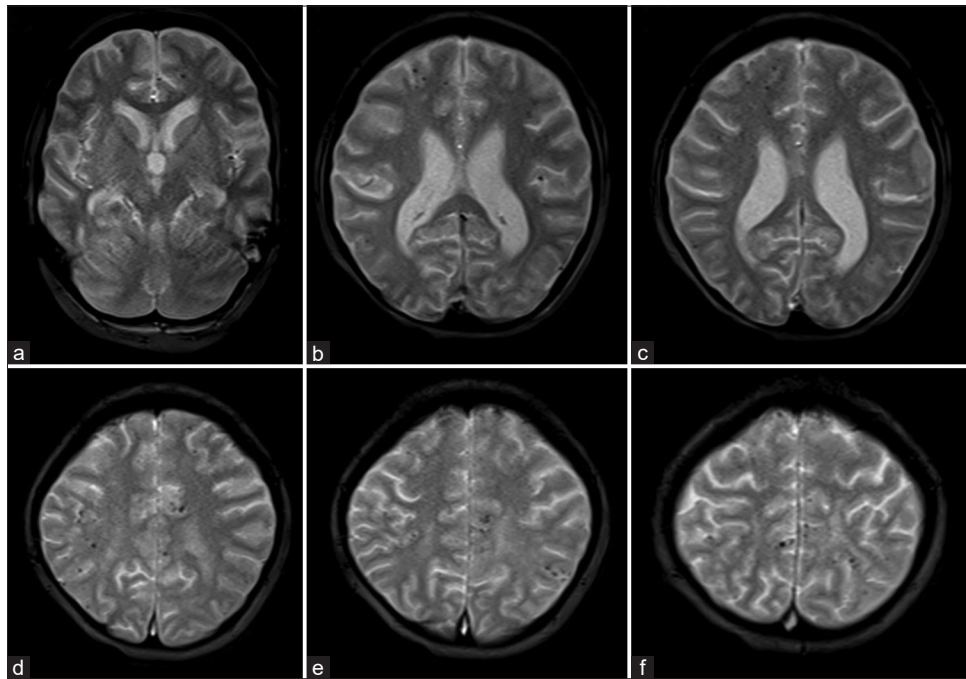
Figure 3: (a-f) GRE T2* axial images showing Grade III (11–25) microbleeds restricted to only lobar location without deep microbleeds.
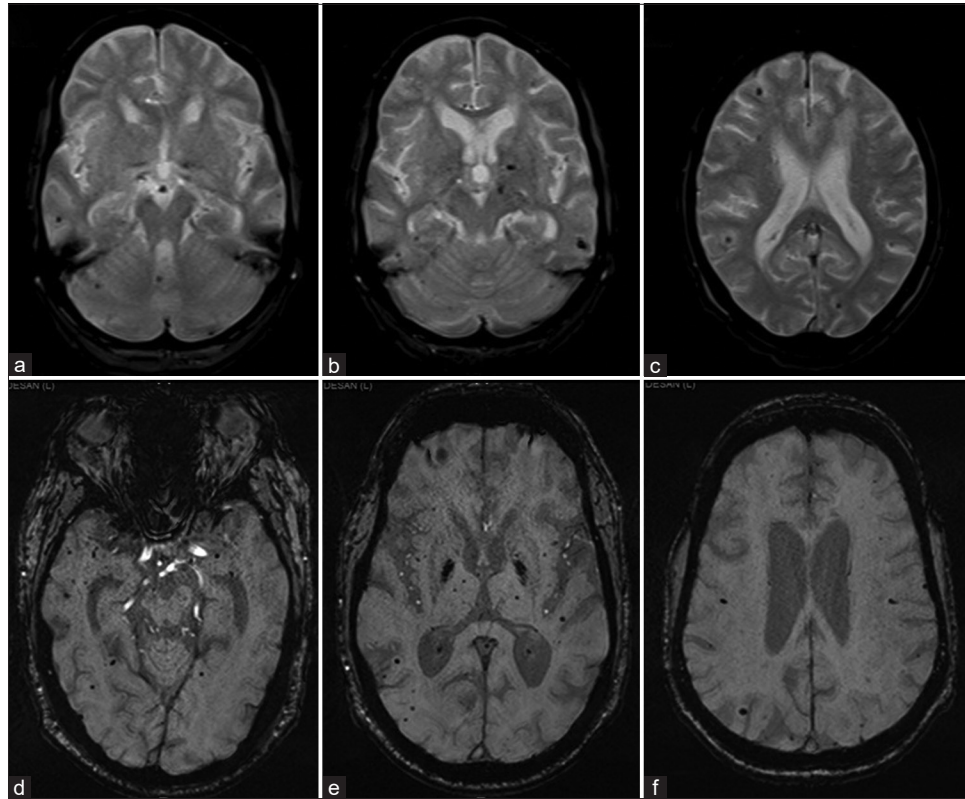
Figure 4: Two different patients with (a-c) GRE T2* axial and (d-f) susceptibility-weighted imaging axial images showing Grade III microbleeds of deep and lobar location.

total) between patients with various grades of leukoaraiosis did not show any statistically significant association. However, patients with Grade 3 leukoaraiosis were having more of Grade 4 cerebral MBs.

DISCUSSION

Nearly 5–6% of normal elderly are estimated to harbor cerebral MBs.[7,8] It may be slightly more in the Asian population both hypertensive and non-hypertensive.[9-11] Cerebral MBs are considered markers of not only for bleeding risk in those with macrobleeds or undergoing antithrombotic/ anticoagulant treatment but also as a marker of "diffuse microangiopathy."[9] There are not many studies about their incidence or association in our population. We tried to analyze the associated factors in those patients diagnosed with MBs on MR neuroimaging. Fazekas *et al.*[1] first described the histopathologic corroboration of GRE T2* hypointense foci as MBs and also found lipofibrohyalinosis in the underlying vessels. Greenberg *et al.*[2] refined the criteria so as to avoid the normal structures and other causes of such hypointense foci mimicking MBs. Later, these criteria were incorporated into standards for cerebral "small vessel disease."[4] There have been attempts to evolve scoring scales for the MBs such as the MB anatomical rating scale and the

brain observer MB scale.[12,13] The former uses each brain region – four lobes, cerebellum, brainstem, thalami, basal ganglia, internal and external capsule and insula – and the latter method divided them as lobar (cortical and subcortical white matter) and deep (basal ganglia and capsular tracts) for scoring.

MRI technique also has been shown the influence the visualization of MBs like 1.5 Tesla or 3T MRI, Gradient echo T2* imaging or the SWI, 3D acquisition of sub-millimeter spatial resolution with flow compensation, thinner sections (<5 mm), longer echo time (TE)/repetition time (TR), parallel imaging technique, and use of phase map in SWI and they are now part of standard sequence to improve the detection of MBs.[14-17]

The mimics of MBs include those with blood or blood degradation products (such as vessels and small type IV cavernomas)[2,18] and those without blood products such as calcifications, some micrometastases (such as melanoma).

The lobar and deep MBs have different clinical risk factors. The lobar is associated mainly with CAA including a stronger relation to the hereditary Dutch type of CAA. Other hereditary disorders featuring MBs include cerebral autosomal dominant arteriopathy with subcortical infarcts
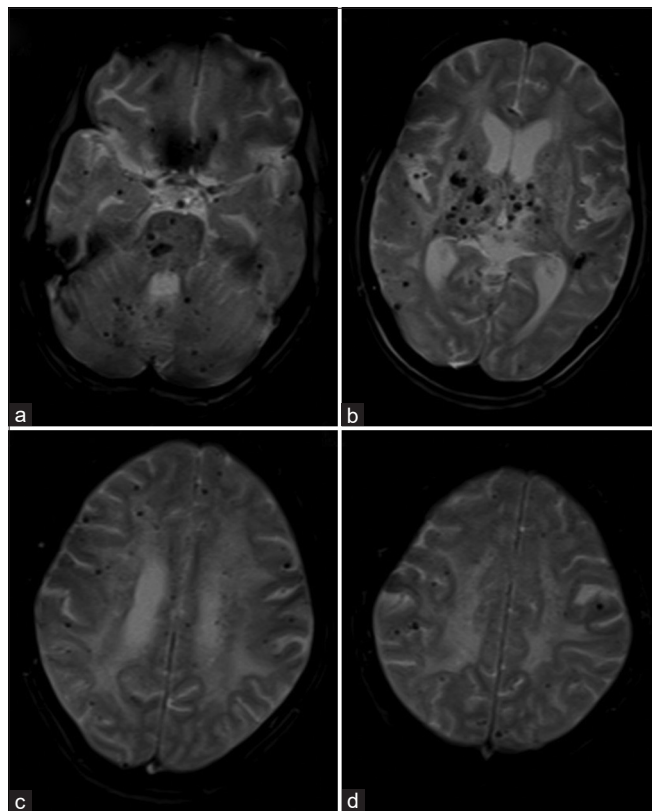
Figure 5: (a-d) The GRE T2* axial images showing Grade IV (>25) microbleeds of both deep and lobar location.

and leukoencephalopathy (CADASIL)/cerebral autosomal-recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), COL4A mutations, Fabry disease, Pompe disease, Tangier disease, retinal vasculopathy with cerebral leukodystrophy, and pseudoxanthoma elasticum.[3,19]

Lobar MBs have been shown to be an independent risk factor for cognitive impairment with higher MBs in baseline associated with risk of functional dependence with an odds ratio of 1.16 for every further MB.[20] Although the parieto-occipital region is the common location for lobar MBs in CAA, those in the frontal lobe and caudate are more associated with cognitive/executive impairment.[21] In fact, the lobar MBs are considered the link between amyloid and neurovascular factors of Alzheimer's disease. MBs also are important in those patients developing inflammatory syndrome of Amyloid-related imaging abnormalities (ARIA) and MBs more than 4 are considered a contraindication for anti-ARIA treatment using drugs such as bapineuzumab.[22]

The clinical associations for deep MBs include that of similar risk factors that are associated with other imaging markers of small-vessel disease such as hypertension, diabetes, dyslipidemia, smoking, apolipoprotein E genotype, and

Table 1: Clinical characteristics of patients with cerebral microbleeds.

Clinical characteristics	Number (Percentage)
Total patients	109
Male	79 (72.48)
Female	30 (27.52)
Age group <18 years	4 (3.67)
18–65 years	87 (79.82)
>65 years	18 (16.51)
Hypertension	68 (62.39)
Diabetes mellitus	26 (23.85)
Alcoholic	34 (31.19)
Smokers	10 (9.17)
Predisposing/risk factors	
H/o Head injury	5 (4.59)
H/o Neurosurgery	5 (4.59)
H/o Radio-/Chemo-therapy	9 (8.26)
H/o TIAs/Stroke	10 (9.17)
H/o Cardiovascular disease/Rheumatic heart disease/Atrial fibrillation	14 (12.84)
H/o Antiplatelet/anticoagulant use	17 (15.6)
Other associations	
Renal disease – Uremia/AKI	6 (5.5)
Infections	3 (2.75)
CADASIL (possible)	6 (5.5)
Vasculitis	1 (0.92)
Others (Postpartum, etc.)	21 (19.26)

AKI: Acute kidney injury, H/o: History of, CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, TIA: Transient ischemic attack.

Table 2: Imaging characteristics of patients with cerebral microbleeds.

Radiological profile	Number (percentage)	Average no. of MBs
Deep	90 (82.57)	8.1
Deep+cerebellar	105 (96.33)	10.2
Cortical/lobar microbleeds	91 (83.49)	19.9
Total	109	26
Microbleeds		
Grade I	15 (13.76)	4.4
Grade II	25 (22.94)	8.1
Grade III	36 (33.03)	16.7
Grade IV	33 (30.28)	60.3

MBs: Microbleeds

alcoholism apart from low cholesterol and atorvastatin use.[4,17,23] Although cerebellar and brainstem MBs are considered part of deep MBs, cerebellar superficial cortical MBs are also noted in CAA. In our study, the risk factor distribution is hypertension (62.39%), diabetes (23.85%), smoking (9.17%), and alcoholism (31.19%).

Table 3: Neuroimaging features of patients with cerebral microbleeds.

Radiological profile	Number (percentage)
Cortical infarcts	30 (27.52)
Macro hemorrhages	32 (29.36)
Lacunar infarcts <5	22 (20.18)
>5	40 (36.7)
WM changes (Fazekas)	
Grade I	28 (25.69)
Grade II	28 (25.69)
Grade III	18 (16.51)
MRA findings – Dolichoectasia	26 (23.85)
Vessel narrowing/occlusion	7 (6.42)
MRA variants – Hypoplastic vertebral artery, thin vertebrobasilar	28 (25.69)
Fetal PCA	19 (17.43)

MRA: Magnetic resonance angiography, PCA: Posterior cerebral artery, WM: White matter

There are some locations considered relatively specific for underlying disorder like thalami in CADASIL, occipital in post-radiation, frontal and corpus callosal in post-trauma, and periventricular and temporal regions in Moyamoya disease.[24] The other acquired disorders reported with MBs include traumatic brain injury (linear, corpus callosal involvement), uremia on dialysis (irrespective of mode of dialysis or heparin use), fat embolism, cardiac myxoma or valve replacement, post-carotid stenting, infective endocarditis, radiation therapy (particularly whole-brain of more than 25 Gy), and those on ECMO support and COVID-19 infection.[25,26] The radiation-induced MBs may partly benefit from anti-angiogenic therapy.[27] However, MBs have been shown to be less in those with TIAs than in complete ischemic stroke and those with cortical infarcts.[5,21] The associations in our study group are head injury (4.6%), previous neurosurgery (4.6%), radio-/chemo-therapy (8.3%), cardiovascular including valvular/infective (12.8%), anti-platelet/anticoagulant use (15.6%), previous TIAs/stroke (9.2%), and uremia (5.5%). Hypertension showed significant association with deep cerebral MBs. It is possible that there are fewer patients with head injury since MRI is not routinely used for the evaluation of trauma cases.

Imaging of cerebral MBs should at least give a semi-quantitative estimate (<5, 5–10, >10 or similar) and mention the numbers as they might have prognostic and management implications.[6] The risk of further recurrent bleed increases with the baseline number of MBs.[28] However, as per recent guidelines, MBs of <10 are not considered sufficient reason to withhold anti-thrombotic treatment in otherwise deserving/eligible patients with ischemic stroke and no recommendation for routine MRI before starting intravenous antithrombotic treatment.[29] Our study showed average bleed

in those mainly with deep and deep with cerebellar MBs was 8–10, but it was nearly 20 in those with lobar MBs.

CONCLUSION

In this descriptive study, 109 patients diagnosed with cerebral microbleeds on MR neuroimaging were analyzed for clinical predisposing factors and categorized by location (lobar, deep, cerebellar) and number (<5, 5 – 10, 11 – 25 and >25). The co-existing abnormalities that are also markers of small vessel disease like lacunar infarcts and white matter leukaraiosis were evaluated apart from cortical infarcts and macrobleeds. Vascular abnormalities and variants were also noted for association. Further structured studies with large sample population in each of the subcategory and risk factor may reveal more insights and better understanding of this important evolving marker of cerebral small vessel disease.

Ethical approval

The research/study approved by the Institutional Review Board at Institutional Ethics Committee (Human studies) JIPMER Puducherry, number JIP/IEC/2017/0396, dated May 26, 2018.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Fazekas F, Kleinert R, Roob G, Kleinert G, Kapeller P, Schmidt R, *et al*. Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: Evidence of microangiopathy-related microbleeds. AJNR Am J Neuroradiol 1999;20:637-42.
2. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, *et al*. Cerebral microbleeds: A guide to detection and interpretation. Lancet Neurol

2009;8:165-74.

3. Charidimou A, Krishnan A, Werring DJ, Rolf Jäger H. Cerebral microbleeds: A guide to detection and clinical relevance in different disease settings. Neuroradiology 2013;55:655-74.

4. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, *et al.* Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013;12:822-38.

5. Vernooij MW, Van der Lugt A, Ikram MA, Wielopolski PA, Niessen WJ, Hofman A, *et al.* Prevalence and risk factors of cerebral microbleeds: The Rotterdam scan study. Neurology 2008;70:1208-14.

6. Lee SH, Ryu WS, Roh JK. Cerebral microbleeds are a risk factor for warfarin-related intracerebral hemorrhage. Neurology 2009;72:171-6.

7. Roob G, Schmidt R, Kapeller P, Lechner A, Hartung HP, Fazekas F. MRI evidence of past cerebral microbleeds in a healthy elderly population. Neurology 1999;52:991-4.

8. Schrag M, Greer DM. Clinical associations of cerebral microbleeds on magnetic resonance neuroimaging. J Stroke Cerebrovasc Dis 2014;23:2489-97.

9. Werring DJ, Coward LJ, Losseff NA, Jäger HR, Brown MM. Cerebral microbleeds are common in ischemic stroke but rare in TIA. Neurology 2005;65:1914-8.

10. Koennecke HC. Cerebral microbleeds on MRI: Prevalence, associations, and potential clinical implications. Neurology 2006;66:165-71.

11. Yakushiji Y, Wilson D, Ambler G, Charidimou A, Beiser A, Van Buchem MA, *et al.* Distribution of cerebral microbleeds in the East and West: Individual participant meta-analysis. Neurology 2019;92:e1086-97.

12. Gregoire SM, Chaudhary UJ, Brown MM, Yousry TA, Kallis C, Jäger HR, *et al.* The Microbleed anatomical rating scale (MARS): Reliability of a tool to map brain microbleeds. Neurology 2009;73:1759-66.

13. Cordonnier C, Potter GM, Jackson CA, Doubal F, Keir S, Sudlow CL, *et al.* improving interrater agreement about brain microbleeds: Development of the Brain Observer MicroBleed Scale (BOMBS). Stroke 2009;40:94-9.

14. Nandigam RN, Viswanathan A, Delgado P, Skehan ME, Smith EE, Rosand J, *et al.* MR imaging detection of cerebral microbleeds: Effect of susceptibility-weighted imaging, section thickness, and field strength. AJNR Am J Neuroradiol 2009;30:338-43.

15. Goos JD, van der Flier WM, Knol DL, Pouwels PJ, Scheltens P, Barkhof F, *et al.* Clinical relevance of improved microbleed detection by susceptibility-weighted magnetic resonance imaging. Stroke 2011;42:1894-900.

16. Puy L, Pasi M, Rodrigues M, Van Veluw SJ, Tsivgoulis G, Shoamanesh A, *et al.* Cerebral microbleeds: from depiction to interpretation. J Neurol Neurosurg Psychiatry 2021;92:598-607.

17. Wu Z, Mittal S, Kish K, Yu Y, Hu J, Haacke EM. Identification of calcification with MRI using susceptibility-weighted imaging: A case study. J Magn Reson Imaging 2009;29:177-82.

18. Samarasekera N, Potter G, Al-Shahi Salman R. Cerebral microbleed mimics. In: Werring DJ, editor. Cerebal microbleeds: Pathophysiology to clinical practice. Cambridge: Cambridge University Press; 2011. p. 44-8.

19. Renard D. Cerebral microbleeds: A magnetic resonance imaging review of common and less common causes. Eur J Neurol 2018;25:441-50.

20. Viswanathan A, Guichard JP, Gschwendtner A, Buffon F, Cumurcuic R, Boutron C, *et al.* Blood pressure and haemoglobin A1c are associated with microhaemorrhage in CADASIL: A two-centre cohort study. Brain 2006;129:2375-83.

21. Werring DJ, Frazer DW, Coward LJ, Losseff NA, Watt H, Cipolotti L, *et al.* Cognitive dysfunction in patients with cerebral microbleeds on T2*-weighted gradient-echo MRI. Brain 2004;127:2265-75.

22. Sperling R, Salloway S, Brooks DJ, Tampieri D, Barakos J, Fox NC, *et al.* Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: A retrospective analysis. Lancet Neurol 2012;11:241-9.

23. Sveinbjornsdottir S, Sigurdsson S, Aspelund T, Kjartansson O, Eiriksdottir G, Valtysdottir B, *et al.* Cerebral microbleeds in the population based AGES-Reykjavik study: Prevalence and location. J Neurol Neurosurg Psychiatry 2008;79:1002-6.

24. Ishikawa T, Kuroda S, Nakayama N, Terae S, Kudou K, Iwasaki Y. Prevalence of asymptomatic microbleeds in patients with moyamoya disease. Neurol Med Chir (Tokyo) 2005;45:495-500.

25. Qian Y, Zheng K, Wang H, You H, Han F, Ni J, *et al.* Cerebral microbleeds and their influence on cognitive impairment in Dialysis patients. Brain Imaging Behav 2021;15:85-95.

26. Kakumoto K, Matsumoto S, Nakahara I, Watanabe Y, Fukushima Y, Yoshikiyo U, *et al.* Rapid formation of cerebral microbleeds after carotid artery stenting. Cerebrovasc Dis Extra 2012;2:9-16.

27. Lupo JM, Molinaro AM, Essock-Burns E, Butowski N, Chang SM, Cha S, *et al.* The effects of anti-angiogenic therapy on the formation of radiation-induced microbleeds in normal brain tissue of patients with glioma. Neuro Oncol 2016;18:87-95.

28. Soo YO, Yang SR, Lam WW, Wong A, Fan YH, Leung HH, *et al.* Risk vs benefit of anti-thrombotic therapy in ischaemic stroke patients with cerebral microbleeds. J Neurol 2008;255:1679-86.

29. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, *et al.* Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: A guideline for healthcare professionals from the American heart association/American stroke association. Stroke 2019;50:e344-418.