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REVIEW

Cerebral microbleeds: hearing through the silence—a narrative review

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ABSTRACT

Objective: The term *cerebral microbleed* (CMB) refers to lesions documented as unexpected findings during computed tomography or magnetic resonance imaging examination of the brain. Initially, a CMB was thought to represent hemosiderin-laden macrophages marking an area of a tiny hemorrhage. Recently, histopathologic studies have shown that the structure of a CMB can be variable. To aid in dealing with this finding and judging its clinical significance, this review addresses important aspects of a CMB, including the definition, prevalence, and incidence in various populations, end-organ damage, associated conditions, and whether any action or treatment by the clinician might be indicated.

Methods: PubMed Medline, EMBASE, BIOSIS, Current Contents, and Derwent Drug Files databases were searched for the keywords "microbleeds-detection-damage", "silent bleeds", "microbleeds", or "silent bleeds AND hemophilia" from 2011–2016. References of retrieved articles were also reviewed and included if applicable.

Results: The published data are found primarily in the imaging literature and focus on diagnostic techniques. Some publications address relationships with diverse, co-existing clinical conditions and implications for treatment, especially in stroke, intracranial hemorrhage, and antithrombotic therapy.

Conclusions: It is critical for non-radiologist clinicians (primary care, internists, neurologists, hematologists) to be aware of the potential importance of the finding of a CMB, and the fact that these lesions are not always truly silent or without important clinical consequences. As additional studies appear, clinicians may be able to "hear" more clearly through the silence of the CMB and understand potential clinical implications in patients.

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Introduction

Why is it important that a narrative review of microbleeds be considered at this time? There is a burgeoning literature on this topic. A recent literature search yielded 186 citations, primarily in the neuroimaging sectors (see Methods). Over 30 conditions, including laboratory and genetic abnormalities, have been associated with the magnetic resonance imaging (MRI) finding of microbleeds. Therefore, it seems important to review the literature, especially with respect to associated conditions and clinical findings, to help clinicians determine if a report of microbleeds warrants action on their part. Are microbleeds truly "silent", or are they speaking to us? This paper will define microbleeds and their etiologies; it will also describe current methods used to detect them, where they are found in the brain or in other organs, incidence in various populations, their predictive value, and any steps a clinician should consider when they are documented.

Methods

PubMed Medline, EMBASE, BIOSIS, Current Contents, and Derwent Drug Files were searched using the following search terms: microbleeds-detection-damage, silent bleeds, microbleeds or silent bleeds + hemophilia. The search was limited to 5 years (2011–2016) and in English. In total, 186 citations were retrieved. References in these citations were reviewed, and additional papers were selected. Papers were selected in the following priority: reviews, meta-analyses, clinical studies, and methodologic papers. Whenever possible, full papers were favored over meeting abstracts, except when the latter addressed important aspects not otherwise covered. Case reports and pre-clinical studies were excluded, except in rare instances where their value was considered highly relevant to the review. Abbreviations used may be found in Table 1.

Results

What is a microbleed?

A cerebral microbleed (CMB) is a lesion documented as an unexpected finding during a computed tomography or MRI examination of the brain. Microbleeds are suspected to also occur in other tissues, but most of the literature deals with those in the brain. CMBs have been thought to represent small collections of hemosiderin appearing as round, well-defined foci of low signal intensity by various

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Table 1. Conditions associated with the detection of cerebral microbleeds.

Aging
Alzheimer's disease (AD)
Apolipoprotein E4 presence
Arthritis
Atrial fibrillation (AF)
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL; hereditary microangiopathy)
Cardiac surgery
Cerebral amyloid angiopathy (CAA)
Chronic hemodialysis
Cnm gene + *Streptococcus mutans* infection
Chronic obstructive pulmonary disease (COPD)
Cognitive dysfunction
Coronary artery disease (CAD)
Diabetes, type 1
Dementia
Fabry disease (FD)
Glioma, post-irradiation
Hemophilia
High pulse pressure
Hypertension
Infective endocarditis (IE)
Intracranial hemorrhage (ICH)
Lacunar infarcts
Lewy body dementia
Low cholesterol
Low high-density lipoprotein cholesterol (HDL-C)
Microalbuminuria
Reverse nocturnal dipping (of blood pressure)
Serotonin antidepressants
Small-vessel disease
Stroke
Subcortical vascular dementia (SVaD)
Traumatic brain injury (TBI)

MRI sequences[1]. Histopathology of CMBs is variable, including iron-positive siderophages, erythrocytes, and vasculopathy[2]. A current unifying concept is that CMBs tend to be found in hemorrhage-prone states and/or in conditions with small-vessel disease.

Microbleeds have also been proposed as the etiology of progressive joint damage, seen by MRI in persons with hemophilia (PWH) who have not reported any signs or symptoms of a bleed in the joint(s) involved, as well as in those with septic arthritis and elbow prostheses[3–6]. Small-vessel disease and possibly microbleeds have also been suspected in the kidney in hemodialysis patients[7]. Patients with microalbuminuria have also been shown to have an association with CMBs[8].

MRI detection methods

There is extensive literature on MRI techniques used to detect CMBs. The imaging pulse sequences most reported and compared are T*-weight magnitude imaging and susceptibility-weighted imaging (SWI)[9–13]. There is consensus that SWI is the preferred method for detecting the greatest number of CMBs in a given patient[12]. The imaging studies are reported using 1 Tesla (T), 1.5T, and more recently, 3T and 7T MRIs[9,10]. Manual rating of CMBs is time consuming and has inconsistencies. This has led to the development of computer-aided diagnosis systems, shown to improve sensitivity and specificity[10,11,13]. Because the intention of this narrative was not to present a detailed review of MRI techniques used to document CMBs, the reader is referred to an excellent review by Greenberg *et al.*[14] for more complete details.

Prevalence and incidence

Numerous population-based studies of the prevalence of CMBs, and one study assessing incidence, have been published[14–20]. These include "healthy" populations (although not necessarily ones without comorbidities or other risk factors) and specific disease cohorts such as those with intracranial hemorrhage (ICH), stroke, Alzheimer's disease (AD), and other neurologic diseases. Overall, it appears that, in healthy populations, as described above, the prevalence of CMBs ranges from 3–15%[14–20]. In cohorts with neurologic diseases, prevalence can range from 83–94%[20–23].

In the important and ever-growing Rotterdam Scan Study[18,19], the incidence of CMBs was investigated in 831 patients, with a mean age of 68.5 years over a period of ~3 years. The incidence increased from 24% to 28%, and 10.2% of patients developed new CMBs[18]. In the largest series of patients with CMBs reported to date ($n = 3879$), prevalence was shown to increase with age, from 6.5% at 40–45 years of age to 35.7% for those aged ≥80 years[19].

Comorbidities reported in the prevalence/incidence series included hypertension, wide pulse pressure, smoking, and diabetes. Age, male sex, hypertension, and apolipoprotein E4 (ApoE4) were often significantly increased in the CMB groups in these series[14,16,18,19]. Many of the 30 conditions associated with the finding of CMBs (Table 1) and their clinical implications (Table 2)[3–7,21–50] will be addressed subsequently in this manuscript.

Literature review

Cerebral microbleeds have been reported to be associated with over 30 conditions, including specific disease states, physical and laboratory findings, and genetic traits (Table 1). As expected, a majority of the literature stems from diseases in which MRI is frequently used. These include stroke, ICH, AD, cerebral amyloid angiopathy (CAA), and traumatic brain injury (TBI). Table 2 outlines the important clinical implications of CMB presence, based on current knowledge.

Neurologic states

ICH and stroke

Significant take-home messages about CMBs and associated risks exist for ICH and stroke. In a study of 202 patients with ICH, CMBs were found in 69.3% of the ICH group vs 26.5% of controls ($p < .0001$). CMBs were shown to be a risk factor associated with ICH, leading the authors to conclude that they may be an independent risk factor for first-onset ICH[23]. This conclusion is supported by additional studies[24,25]. However, there is a study of 717 acute ischemic stroke patients after intravenous thrombolysis in which CMB presence, burden location, and presumed underlying vasculopathy were not independently associated with ICH[51].

Table 2. Clinical implications of conditions associated with microbleeds.

Condition	Clinical implications	References
ICH	CMBs are a strong independent predictor of first-onset ICH. CMBs, especially if in the basal ganglia, warrant evaluation of stroke risk in ICH.	Sun *et al.*[23]; Lin *et al.*[24]; Okazaki *et al.*[25]
Stroke	Presence of CMBs can predict hemorrhagic and ischemic stroke, even in healthy persons. Low HDL levels suggest increased risk of hemorrhagic transformation after ischemic infarcts. Caution is advised for aggressive lipid-lowering treatment. Management of HDL-C levels may be a target for preventing recurrent stroke. The distribution of CMBs may be helpful in distinguishing between stroke (deep brain) and degenerative diseases (lobar). CMBs after IV thrombolysis may indicate recanalization.	Lin *et al.*[24]; Bokura *et al.*[26]; Igase *et al.*[27]; Yang *et al.*[29]
Atrial fibrillation (AF) and antithrombotic therapy	CMBs, especially $\geq$5, appear to increase the risk of ICH and its mortality with antithrombotic therapy in chronic AF. Newer agents are favored over warfarin. New CMBs were found over 2 years in 26% of AF patients taking warfarin with CMBs at baseline vs 12% in those without baseline CMBs. An algorithm has been suggested to decrease risks of anticoagulation in AF.	Fisher[30]; Wang *et al.*[31]
Cerebral amyloid angiopathy (CAA)	CMBs as a marker for CAA are peripheral in location vs infratentorial or in the basal ganglia in hypertensive arteriopathy. CAA may carry a higher risk of hemorrhage after antiplatelet, antithrombotic, and thrombolytic treatment. Total CMBs and lobar CMBs are risk factors for remote parenchymal bleeding after IV thrombolysis.	Jäger[32]; Prats-Sanchez *et al.*[33]
Traumatic brain injury (TBI)	The number and extent of traumatic CMBs correlate with severity of injury and may expand 1-week post-injury. In mild TBI, there were more CMBs vs controls and greater short-term memory loss.	Huang *et al.*[34]; Toth *et al.*[35]
Radiation therapy	CMBs are increased after radiation therapy, increasing in incidence with a latency of 3 months to 9 years. Anti-angiogenic therapy slowed formation. The frequency of CMBs was dose related in high-dose radiation.	Tanino *et al.*[28]; Lupo *et al.*[37]
Alzheimer's disease (AD) and cognitive dysfunction	In AD and other forms of dementia, the number of CMBs ($\geq$10 most marked) correlated with decreasing cognitive function. Cases positive for apolipoprotein E4 had more CMBs than those without this marker. CMBs and cortical infarcts are apparent risk factors for dementia.	Nagata *et al.*[38]; Ueda *et al.*[39]
Coronary artery disease (CAD)	CMBs occur in CAD during antiplatelet therapy and progress when blood pressure is poorly controlled.	Iwamoto[40]
Nocturnal blood pressure 'dipping'	Stroke patients with reversal of nocturnal blood pressure "dipping" had greater risk of CMBs than those with normal dipping. Most ambulatory blood pressure parameters were higher in patients with CMBs.	Kwon *et al.*[41]; Shimbo *et al.*[42]
Infective endocarditis (IE)	CMBs were found in 94% of patients with IE, suggesting a worse prognosis. CMBs were correlated with major ICH in post-operative IE patients and may be an independent predictor of ICH in IE patients.	Ohira *et al.*[21]; Schrag *et al.*[22]
Chronic obstructive pulmonary disease (COPD)	COPD increases risk of CMB development, suggesting COPD is a risk factor for cerebral small-vessel disease.	Lahousse *et al.*[36]
Chronic renal disease and hemodialysis	CMBs are independently associated with a lower eGFR. CMBs showed significantly higher prevalence and faster progression in hemodialysis patients vs controls. These findings may suggest a risk factor for stroke. Microalbuminuria (UACR $>$30–$\leq$300 mg/g) is significantly associated with CMBs.	van Overbeek *et al.*[7]; Naganuma *et al.*[43]; Necioglu Orken *et al.*[44]; Zurru *et al.*[45]
Type 1 diabetes	CMBs were more prevalent in patients with proliferative diabetic retinopathy vs two control groups.	Woerdeman *et al.*[46]
Hemophilia	Joint MBs are suspected as a cause of MRI findings without a history of prior symptoms. Joint MBs may contribute to septic arthritis. In PWH with bacteremia. CMBs in 44 PWH were inversely correlated with overall cognitive performance.	Manco-Johnson *et al.*[3]; Seuser[4]; Staritz *et al.*[5]; Zanon *et al.*[6]

(*continued*)

Table 2. Continued.

Condition	Clinical implications	References
Subcortical vascular dementia (SVaD)	90% of SVaD patients (MMSE = 13 and CDT = 2.7/5.0) had CMBs vs two control groups without dementia. A high prevalence of thalamic lesions was noted.	Nagata *et al.*[47]
Lewy body dementia (LBD)	There is a specific distribution of CMBs in LBD that differs from AD and CAA.	De Reuck *et al.*[48]
Fabry disease	In young adults without a CVA or history and CMBs, FD, a treatable disease, should be considered.	Marchesoni *et al.*[49]
Serotonin antidepressant use	Incidence of CMBs in patients taking serotonin-specific antidepressants was 3.7% over 3.9 years. Median age = 58.7 years. This may support findings of increased bleeding risk with antidepressant use.	Akoudad *et al.*[50]

Abbreviations. CDT, clock-drawing test; CMB, cerebral microbleed; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; ICH, intracranial hemorrhage; IV, intravenous; MB, microbleed; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; PWH, persons with hemophilia; UACR, urinary albumin creatinine ratio.

Regarding the stroke literature and CMBs, 2201 healthy individuals (mean age = 62.1 years) were monitored over a mean period of 3.6 years[26]. CMBs were detected in 4.4%, and strokes occurred in 2.1%. CMBs were strongly associated with deep brain hemorrhage, but their association was less marked with ischemic stroke. The authors concluded that CMBs can be used to predict risks of hemorrhagic and ischemic stroke, even in healthy individuals.

Antithrombotic therapy and ICH

As the literature continues to support the fact that CMBs indicate a hemorrhage-prone pathologic state, there is increasing concern about the risk-benefit ratio of administering antithrombotic therapy in patients with ischemic stroke, transient ischemic attack (TIA), and non-valvular atrial fibrillation (AF). Wang *et al.*[31] addressed major aspects of this dilemma and how one might minimize the risk of ICH. Because there is a high prevalence of CMBs in ischemic stroke and TIAs (18–68%), understanding the risk of ICH in these patients is very clinically relevant. The large Rotterdam study showed that CMBs were more prevalent in clopidogrel users and anti-platelet users as a whole than anticoagulant users[31]. A pooled review of 1460 ICH patients and 3817 ischemic stroke/TIA patients found that the prevalence of CMBs was higher in the ICH group and that the risk increased from 2.8 in non-antithrombotic users to 5.7 in anti-platelet users and to 8.0 in warfarin users[31].

A meta-analysis of 10 prospective cohorts, including 3067 ischemic stroke/TIA patients, found that ICH risk increased over 8-fold (odds ratio [OR] = 8.52; CI = 4.23–17.8) in those with CMBs vs those without CMBs. This was much higher than with overall stroke (OR = 1.55) or ischemic stroke risk (OR = 2.25). In a meta-analysis of five studies, the presence of CMBs was related to an increased risk of ICH post-thrombolysis. The quantity of CMBs was significantly associated with symptomatic ICH and increased with >10 CMBs[31].

In 908 ischemic stroke patients, the risk of ICH and mortality increased significantly with the number of CMBs found (ICH risk 7.5% for ≥5 CMBs [$p < .001$]; mortality increase, 3.8% [$p = .054$]). This extra bleeding risk for ≥5 CMBs seems to outweigh the benefit of treatment, and the mortality of 3.8% exceeds the 1.3% mortality for recurrent ischemic stroke[31].

Fisher[30] has published an algorithm addressing the risk of anticoagulation in AF. This suggested approach is based on age, number and location of CMBs, and neurologic changes during anticoagulation. For patients aged <60 years who have either no CMBs or <5 sub-cortical CMBs, the algorithm suggests to anticoagulate as usual. For patients aged ≥60 years who have lobar microbleeds or ≤5 subcortical CMBs, a neurologic consult is recommended, and anticoagulation, avoiding warfarin, can proceed.

Lipid levels and thrombolysis

In 116 ischemic stroke patients (mean [SD] age = 70 [10] years), CMBs were present in 64%[27]. High-density lipoprotein cholesterol (HDL-C) levels were significantly lower in those with CMBs. The authors suggest that management of HDL-C levels might be a therapeutic target to prevent stroke recurrence in elderly patients. The prevalence of hemorrhagic transformation (HT) was studied in 348 patients after acute ischemic infarction[29]. Compared with the non-HT group, HT patients had lower prevalence of CMBs; lower levels of triglyceride, HDL, and low-density lipoprotein (LDL); higher National Institutes of Health Stroke Scale (NIHSS) score; and higher rates of diabetes, AF, and urokinase thrombolysis. A multivariant analysis defined risk factors for HT as cardioembolic or undetermined infarction, diabetes, and high NIHSS scores. A protective factor was maintaining existing LDL levels. To prevent incident HT, the authors concluded that aggressive lipid-lowering treatment be used with caution in patients with acute ischemic infarction.

A higher incidence of CMBs (40.7%) was seen in 162 patients with super-acute ischemic stroke treated with recombinant tissue plasminogen activator intravenous thrombolysis vs 18.4% in a non-thrombolysis group[52]. The thrombolysis group also showed significantly better NIHSS scores at 24 h. The conclusion was that CMBs may indicate vascular recanalization and/or reperfusion.

CAA

MRI markers of CAA were studied in 408 patients after intravenous thrombolysis with tissue plasminogen activator to ascertain risk factors for remote parenchymal hemorrhage[33]. The groups compared were 18 patients with remote parenchymal hemorrhage without concomitant local hemorrhage and 364 patients without either type of hemorrhage. Both total CMBs and CMBs of lobar localization were independently associated with remote parenchymal hemorrhage, suggesting that CAA is an important risk factor in this group of patients. CMBs associated with CAA may be differentiated from those of hypertensive arteriopathy by location[32]. The authors state that treatment with antiplatelet, antithrombotic, and thrombolytic agents may carry a higher risk of symptomatic hemorrhage in these patients.

TBI

In 111 patients with mild TBI compared with the same number of controls, the TBI group had 86.7% of cortical or subcortical CMBs vs 20% in the controls ($p = .0001$). Short-term memory function using digit span scores was lower in CMB patients ($p = .017$) than in controls without CMBs[34]. In TBI patients who had a repeat MRI at 1 week, interval changes were seen in some CMBs[35]. This included confluence and expansion of the CMBs, which led to a decrease in CMB count, but with a corresponding volume expansion.

Postcranial radiation

Two studies have evaluated the frequency of CMB postcranial radiation therapy. In one retrospective study of 34 patients, the frequency of CMBs varied from 21–47% depending on the MRI techniques used[28]. The latency of CMB appearance varied from 3 months to 9 years post-radiation. The frequency of CMBs was significantly associated with radiation dose in high-dose irradiation patients. In a second study of 17 patients with high-grade glioma, CMBs also increased over time, with a latency of 8–22 months[37]. The rate of CMB formation significantly increased 2 years after treatment ($p < .001$), and was decelerated by concomitant anti-angiogenic therapy.

Alzheimer's disease

Cerebrovascular lesions and vascular risk factors were studied in 120 elderly patients (mean age = 75.6 years) with probable AD by accepted criteria[38]. Vascular risk factors evaluated were hypertension, diabetes, dyslipidemia, congestive heart failure, AF, and hypotension. BNP and ApoE4 were also evaluated. Overall, 43% of patients had $\geq$3 risk factors. CMBs occurred in 17.5% of patients with ApoE4 vs 10.1% of those without. CMBs and cortical infarcts were found to additively decrease MMSE scores in 109 AD patients[39]. Patients with >10 CMBs showed significantly lower scores in several psychological screens. CMBs and cortical infarcts were thought to be risk factors for dementia.

Cardiovascular and respiratory states

Coronary artery disease

Intracranial hemorrhage is a serious complication of antiplatelet therapy in coronary artery disease (CAD) in patients undergoing percutaneous coronary intervention. In a small study of 14 patients, new CMBs were seen over a period of 8 months[40]. Blood pressure increased significantly from baseline values in CMB patients after 8 months. The authors advise strict coronary risk control, especially blood pressure, in this group of patients.

Infectious endocarditis

Two papers propose that MRIs should be performed in patients with infectious endocarditis (IE) to alert physicians to a worsening prognosis due to brain involvement. In 66 cases of IE, 94% had CMBs (the highest prevalence seen in this review), with an average of 22 CMBs per patient[22]. In another study, the concurrent presence of CMBs and acute brain infarction in IE appeared to be an independent predictor of ICH in IE[21].

Blood pressure phenomena

The diurnal pattern of blood pressure as documented by ambulatory blood pressure monitoring shows that blood pressure normally falls to its lowest level during the night, termed "nocturnal dipping"[42]. Individuals whose blood pressure does not fall by $\geq$10% at night are known as "non-dippers". Non-dipping has been associated with an increased risk of cardiovascular events and all-cause mortality[42]. The nocturnal dipping status and relationship to CMBs were investigated in 162 hypertensive stroke patients[41]; CMBs were seen in 40.1%. Most ambulatory blood pressure parameters except morning surge were higher in those with CMBs. Patients whose nocturnal dip reversed ("reverse dippers") had a higher risk of CMBs.

Chronic obstructive pulmonary disease

Another paper from the Rotterdam study explores the relationship between chronic obstructive pulmonary disease (COPD) and cerebral small-vessel disease[36]. In this report, the prevalence of CMBs in 165 subjects with COPD was compared with 645 subjects with normal lung function. In the same paper, a longitudinal MRI analysis of CMB incidence of 553 participants was reported. The prevalence of CMBs was significantly higher in those with COPD than those with normal lung function (44.8% vs 31.3%; $p = .001$). CMB prevalence was also significantly higher in smoking subjects than smoking subjects without COPD, even after controlling for age, sex, and pack-years (47.8% vs 32.8%; $p = .003$). Over a median interval of 3.42 years, of 46 COPD subjects without a CMB at the initial MRI, 10.9% developed a CMB vs 2.6% in 507 subjects without COPD. This study demonstrated for the first time that COPD increased the risk of developing CMBs both cross-sectionally and longitudinally.

Metabolic and renal diseases

Chronic renal disease

Several publications have investigated CMB prevalence and potential implications in chronic renal disease and hemodialysis patients[7,43–45]. In 808 ischemic stroke patients (mean [SD] age = 77 [11] years), estimated glomerular filtration rate (GFR) and the burden of microvascular brain damage were evaluated. GFR was inversely related to age, hypertension, and AF. Microvascular brain damage (CMBs, white matter hyperintensities, and silent lacunar infarcts) was inversely related to GFR. The conclusion was that decreased GFR indicates small-vessel disease both in the kidney and brain. An independent association between estimated GFR and CMB progression over a 2-year interval was found in a group of 89 lacunar stroke patients, further supporting the above findings[7]. Two studies have documented the presence of CMBs in hemodialysis patients. In 179 hemodialysis patients compared with 58 healthy controls, the prevalence of CMBs was 25.1%, vs 0% in the control group[43]. Independent and significant factors associated with CMB presence included age and hypertension. In another study, the prevalence of CMBs in hemodialysis patients was compared with healthy controls and hypertensive patients[44]. The prevalences were 64.7%, 11.5%, and 8.6%, respectively. The urinary albumin creatinine ratio and estimated GFR were studied in 285 hypertensive subjects[8]. CMBs were seen in 16.8%, a higher percentage than the prior study. Microalbuminuria, but not GFR, was significantly associated with a higher prevalence of deep or infratentorial CMBs. The specific causal relationship is suspected to be microvascular disease in the kidney.

Diabetes

Proliferative diabetic retinopathy is another example of a microangiopathy associated with CMBs. Diabetes type 1 patients with and without proliferative retinopathy and a control group were studied for CMB evidence[46]. CMBs were more prevalent in proliferative retinopathy patients vs the other two groups ($p < .05$).

Hemophilia

Microbleeds are suspected of occurring in the joints of PWH. This was first proposed after the publication of the US Joint Outcome Study, in which MRI findings of joint damage were documented in patients who had not reported joint bleeding[3]. In the absence of appropriate prophylaxis therapy with factor VIII, this early evidence of synovitis may progress and lead to rebleeding and further adverse joint outcomes[4]. Joint microbleeds were also thought to contribute to septic arthritis in a series of case reports in PWH[5]. Regarding CMBs in PWH, there is a concerning report of cognitive dysfunction in PWH in whom CMBs were detected[6]. In 49 adults with severe, moderate, or mild hemophilia, 73% presented with a reduction in overall cognitive performance. MRIs were conducted in 44/49 PWH. Although the number with CMBs was small (3/44), CMBs were inversely related to overall cognitive performance ($p < .05$) and were associated with cardiovascular risk factors ($p = .018$).

Other conditions

Subcortical vascular dementia

Subcortical vascular dementia (SVaD) is one of a group of dementias characterized by small-vessel disease in the brain. MRI findings were studied in 31 patients with SVaD and compared with 36 patients without dementia who had asymptomatic cerebral infarction and 49 patients without dementia with symptomatic lacunar infarcts to serve as disease controls[47]. Mean MMSE score was 13 (moderate dementia) and in the clock-drawing test was 2.7/5.0 (moderate impairment). The mean number of lacunar infarcts was highest in the SVaD group. CMBs were seen in 90% of SVaD patients (the second highest prevalence seen in this review). The mean number of microbleeds per patient was 5.8 for SVaD patients vs 1.3 and 2.1 for the control groups, respectively. Thalamic lesions were found in 96.8% of SVaD patients and were bilateral in 66.7%. The high prevalence of thalamic lesions may be a key factor in this dementia.

Lewy body dementia

The cerebrovascular pathology of Lewy body dementia (LBD) was studied in a post-mortem series of LBD brains with and without AD and CAA[48]. CMBs in this series were predominantly seen in the frontal sections, and the location did not differ in brains with and without AD and CAA. This location is different from locations of CMBs in other neurodegenerative diseases.

Fabry disease

Stroke is a major complication of Fabry disease (FD), affecting 11% of female and 15% of male FD patients. Multi-system defects are caused by the buildup of globotriaosylceramide (GL-3) due to a defect in the function of alpha-galactosidase that metabolizes GL-3. FD has also been identified in 4% of unexplained strokes in young patients. MRIs were conducted in 73 FD patients without a TIA or stroke history[49]. In this group, 33.3% of adult FD patients had evidence of small-vessel disease, and 21.05% had CMBs. These patients were older than those without MRI findings (51.3 vs 30.6 years; $p = .0001$). This study supports investigating for FD, a treatable disease, in cases of CMBs in young adults.

Antidepressant use

An association between serotonin antidepressant use and CMBs was investigated in 2559 people aged $\geq$45 years in the population-based Rotterdam study via two MRIs $\sim$3.9 years apart[50]. A higher incidence of CMBs was associated with antidepressant use vs non-use. Intermediate serotonin affinity carried an increased risk of developing CMBs, as did both selective reuptake and non-selective reuptake inhibitor use. The authors concluded that the incidence of

CMBs may support findings from clinical studies of increased intracranial and extracranial bleeding in antidepressant users.

Discussion

This narrative review introduces the reader to CMBs and describes more than 30 conditions that have been associated with this finding in MRI examinations. The data describing these associations and proposing clinical consequences extend from very large population-based datasets such as the Rotterdam Scan Study[18,19] and the Framingham Study[16] to smaller disease- and site-specific observations. The prevalence of CMBs ranges from 3–15% in healthy populations (albeit those with comorbidities, especially age-related), to extremely high prevalences of 90% and 94% in SVaD and IE, respectively. An excellent primer in CMBs has been published, and the reader is referred to Greenberg *et al.*[14].

The authors in many of the papers reviewed come to similar conclusions that CMBs do have clinical implications, especially in stroke, ICH, and anti-thrombotic therapy. The common thread that seems to link most conditions associated with CMBs is that CMBs indicate a hemorrhage-prone state related to underlying microangiopathy involving small vessels in the brain and possibly in other organs. Cerebral small vessel disease (SVD) is a term grouping microangiopathies including CMBs, recent lacunar infarcts (lacunes), and white matter changes, all of which can be seen in the MRIs of patients with lacunar infarcts[53]. SVD may contribute to the cognitive impairment associated with lacunar infarcts[53], SVaD[47], and Alzheimer's disease[38]. Overall, it appears that the presence of CMBs represents an independent risk factor for ICH, including first-onset ICH and ICH after thrombolysis therapy. CMBs can also predict the level of risk in patients receiving antithrombotic therapy. In CAA, total CMBs and lobar CMBs also represent an independent risk factor for remote ICH. Although the prevalence of CMBs in one study in hemophilia was low, the association with decreased cognitive performance is of concern.

Conclusions

CMBs are not silent, unexpected findings on an MRI, but speak to us in clinical terms, suggesting risk factors across a spectrum of conditions. Despite the limitations inherent in small disease-specific trials, many controlled studies suggest risk factors warranting clinical awareness and follow-up. This is especially apparent in stroke, ICH, and antithrombotic therapy such as in AF. In the future, large population-based studies such as the Rotterdam Scan Study[18,19] and the Rhineland Study[54] may help us further understand all the clinical implications of CMBs. Implications of CMBs and microbleeds in PWH also need further study.

Transparency

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PM is an employee of Bayer. CMRO peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

TJH wrote the paper, and PM reviewed and edited all drafts. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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