Current Neurology and Neuroscience Reports (2019) 19: 51
https://doi.org/10.1007/s11910-019-0969-0

STROKE (H.C. DIENER, SECTION EDITOR)

Role of Cerebral Microbleeds for Intracerebral Haemorrhage and Dementia

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Published online: 19 June 2019

Abstract

Purpose of Review Cerebral microbleeds (CMB)—small round or ovoid lesions detected in hyposignal on blood-sensitive MRI sequences—are promising radiological biomarkers of cerebral small vessel disease. Their relations with ischaemic or haemorragic stroke and their potential contribution to dementia have been extensively addressed. This article reviews recent research on the clinical significance of CMB that remains to be determined.

Recent Findings The presence, burden and location of CMB allow to obtain a more accurate estimate of intracerebral haemorrhage and ischaemic stroke risk. Most studies evaluating the association between CMB and dementia are hampered by methodological limitations and show conflicting results.

Summary CMB mainly reflect the severity of the underlying small vessel disease and should not be interpreted independently of the others neuroimaging biomarkers or the clinical setting. Future large prospective longitudinal studies and randomized controlled trials in various settings are required to determine whether specific therapies are beneficial in case of incidental findings.

Keywords Cerebral microbleeds · Intracerebral haemorrhage · Ischaemic stroke · Cognitive impairment · Dementia

Introduction

Cerebral microbleeds (CMB) are small round or ovoid lesions detected in hyposignal on paramagnetic sensitive MRI sequences including T2*-weighed gradient-recalled echo (T2*GRE) or susceptibility-weighted (SWI) [1]. The increasing use of MRI in clinical practice and in research leads to the frequent incidental detection of CMB in various populations or clinical settings involving questions on their clinical value. Although the pathophysiological mechanisms leading to CMB remain elusive, histopathological studies suggest that they reflect perivascular collection of blood-breakdown products leaked from damaged arterioles or capillaries. CMB have received a huge interest in the literature and are broadly recognized as biomarkers of small vessel disease in the ageing brain but their clinical significance remains to be determined. Over the past 10 years, their relations with ischaemic or haemorragic stroke and their potential contribution to dementia have been extensively addressed raising key issues on their clinical management.

This article is part of the Topical Collection on *Stroke*

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Prevalence

The prevalence of CMB differs across the population study but also the imaging techniques and strength fields [2, 3]. Using conventional MRI sequence, the prevalence of CMB is around 5% in healthy adults [2]. CMB are rarely detected in young adults (< 40 years) [4•], but their prevalence and numbers increase with age. In the Rotterdam Scan Study, the prevalence increased from 18% in 60–69 years old to 38% among 80 years and over [5]. Among stroke patients, CMB are detected in 34% (95% CI 31–36%) of ischaemic stroke patients and in 60% (95% CI 57–64%) of patients with intracerebral haemorrhage (ICH) [2]. The prevalence is lower in first ever than in recurrent ischaemic and haemorrhagic, suggesting that CMB are a maker of the severity of the underlying vascular disease. Among patients with dementia, the prevalence of

CMB is around 14% (95% CI 9–20%) in patients with mild cognitive impairment and reaches 23% (95% CI 17–20%) in patients with Alzheimer's disease (AD) [6, 7]. The increasing prevalence of CMB in the elderly mainly reflects the presence in this population of the two major underlying small vessel diseases: deep perforating vasculopathy and cerebral amyloid angiopathy (CAA).

Topographical Distribution and Underlying Small Vessel Disease

Although histopathological studies on the topic are scarce, it is commonly admitted that the distribution of CMB in the brain indicates the presence, the cause and the severity of the underlying small vessel disease. Recent consensus divides the topographical distribution of CMB into 'strictly lobar' and 'deep or infratentorial' CMB [1]. Strictly lobar CMB strongly predict underlying CAA pathology whereas strictly deep CMB seem to be associated with deep perforating vasculopathy (or arteriolosclerosis or hypertensive arteriopathy) [1] (Fig. 1). In many clinical situations, CMB can be found in lobar and deep locations. In this context, they are classified as 'diffuse' or 'mixed' CMB and the association with deep perforating vasculopathy seems strong [8••].

CAA is characterized by the progressive deposition of amyloid beta in the media and adventitia of small arteries, arterioles and capillaries in the cerebral cortex, overlying the leptomeninges and gray-white matter junction [9]. CAA is a major cause of spontaneous lobar ICH and cognitive impairment in the elderly. Deep perforating vasculopathy, mainly driven by vascular risk factors, typically affects the small perforating end-arteries of the deep gray nuclei and deep white matter and is a major cause of deep ICH [9]. The Boston criteria allows with the use of T2*-GRE a clinical diagnosis of CAA in living subjects [10]. The application of these criteria in Dutch-type hereditary CAA yielded a specificity approaching 100% and a much improved sensitivity when lobar CMB were included [11]. By contrast with CAA-related ICH, there are no criteria for deep perforating ICH. Beyond aging and hypertension, another major risk factor for CMB is the apolipoprotein E (ApoE) genotype [12]. To that extent, the Rotterdam Scan Study found an association with the ApoE e4 allele pertaining only to a subgroup with strictly lobar CMBs and provided evidence that strictly lobar CMBs often reflect the presence of advanced CAA [5]. In positron emission tomography studies using the amyloid radioligand Pittsburgh compound B (PiB), CMB are spatially correlated with areas of amyloid deposition [13] suggesting a close relationship to sites of highest CAA severity [14].

CMB are strongly associated with other small vessel disease markers such as lacunes, white-matter changes (periventricular hyperintensities and white-matter hyperintensities, perivascular spaces). However, few studies have simultaneously analysed these MRI markers which prevents from evaluating the level of contribution of each individual brain lesions to the occurrence of stroke or dementia.

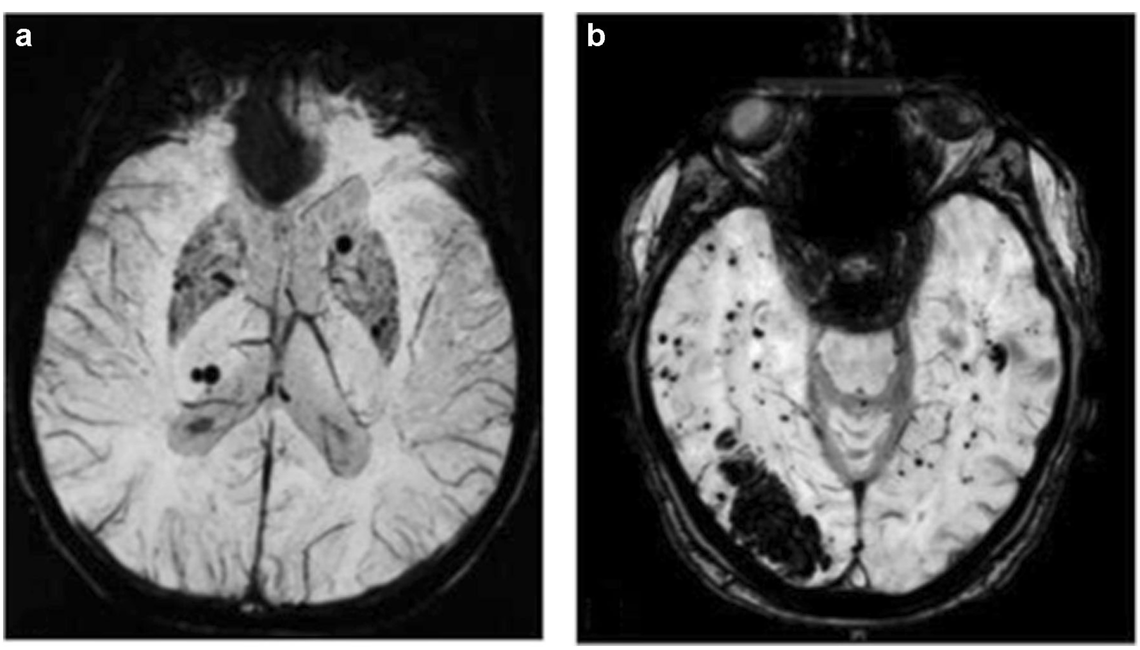

Fig. 1 Topographical distribution and underlying small vessel disease. Susceptibility-weighted Imaging (SWI). **a** Strictly deep CMB associated with deep perforating vasculopathy. **b** Strictly lobar CMB and right temporo-occipital intracerebral haemorrhage suggesting underlying cerebral amyloid angiopathy

Role of CMB for Intracerebral Haemorrhage

CMB and Risk of Subsequent Stroke

Although CMB are commonly associated as a marker of underlying haemorrhage-prone microangiopathies, deep CMB are associated with lipohyalinosis of deep small penetrating arteries related to deep perforating vasculopathy which also exhibits a frequent occlusive feature [15]. The presence of CMB increases the risk of both ischaemic and haemorrhagic strokes in participants from the general population. In the population-based Rotterdam Study including 4579 participants aged 45 or more, the risk of stroke was evaluated according to the presence, number and/or location of CMB on baseline MRI during a median follow-up of 4.9 years [16]. In this cohort, the presence of CMB and especially multiple CMB at baseline increased the risk of stroke up to twofold compared with those without CMB. Focusing on CMB location, deep CMB were associated with a twofold increase in the risk of first ever ischaemic stroke and a fivefold greater risk of first ever ICH whereas lobar CMB were only associated with a fivefold increase in the risk of first ever ICH, suggesting that the risk of stroke subtype possibly differ with underlying vasculopathy (CAA versus deep perforating vasculopathy).

The Weight of Antithrombotics on CMB in Secondary Prevention

In primary prevention, the use of antiplatelet agents in older adults does not result in a significantly lower risk of cardiovascular disease than placebo but in a significantly higher risk of major haemorrhage [17••]. Thus, antiplatelet agents should be avoided in this low-risk population and particularly when lobar CMB are detected on brain MRI. In the setting of secondary prevention, this haemorrhagic risk is counterbalanced by the decrease in recurrent ischaemic events [18], implying that the decision of withholding antiplatelet agents even in patients at higher risk of bleeding should be accurately balanced [19•].

Studies have shown that long-term use of antiplatelet agent was associated with a higher in prevalence of CMB compared with people who were not treated with antiplatelet agents [20, 21]. The risk of developing CMB was almost 3 times higher for antiplatelet medication and 8 times higher with the use of warfarin [20]. In observational studies, the risk of ICH seems higher in patients with CMB in whom antithrombotic drugs are used [22] but randomized clinical trials are ongoing.

More recently, during a median of follow-up of 2 years, the CROMIS 2 study showed a higher risk of subsequent ICH in ischaemic stroke or TIA patients treated with oral anticoagulation for atrial fibrillation [23••]. Although the risk of subsequent ICH in this study was low, it remains at least 3 times higher in patients with CMB than in patients without CMB (9.8 [95% CI 4.0–20.3] versus 2.6 [95% CI 1.1–5.4] per 1000 patient-years follow-up). The presence of CMB was associated with an increased hazard of symptomatic ICH but not with recurrent ischaemic strokes. These results support the hypothesis that CMB are a neuroimaging biomarker of a bleeding-prone arteriopathy relevant for ICH associated with anticoagulation. However, even in patients with CMB the absolute incidence of symptomatic ICH was lower than that of recurrent ischaemic stroke. Among the 40% of patients treated with direct oral anticoagulants (DOACs), the risk of ICH was lower than in patients treated with warfarin which supports previous findings, suggesting that DOAC may be a better option than warfarin to prevent long-term risk of ischaemic stroke in patients with atrial fibrillation [24, 25]. The low rate of events in this observational study limited the ability to determine how increasing CMB burdens (reflecting a more severe diffuse vascular frailty) and CMB locations (reflecting the nature of the underlying small vessel disease) might mitigate the risk of future ICH.

CMB and the Risk of Haemorragic Transformation in Acute Stroke Management?

Haemorrhagic transformation is a feared and commonly seen complication after ischaemic stroke thrombolysis. Recent studies have reported an increased risk of ICH in patients with CMB treated with recombinant tissue plasminogen activator (rtPA) [26, 27]. In a meta-analysis including 9 studies comprising 2479 patients, the presence of CMB and high CMB burdens were independently associated with symptomatic ICH in patients with acute ischaemic stroke treated with intravenous thrombolysis [28•]. However, whether this increased risk outweighs the benefit on functional outcome in rtPA-treated individuals remains unknown. There are no current data which justify withholding IV rtPA, from acute ischaemic stroke patients solely of the basis of CMB presence, number or location [29]. These observations imply that CMB burden may be included in individual risk stratification predicting the risk of symptomatic ICH following rt-PA for ischaemic stroke. In case of proximal occlusion of the circle of Willis, standards of care rely on combining thrombolysis and endovascular therapy but further data are needed to determine whether the presence of multiple CMB should imply endovascular treatment alone [30].

What about CMB in Patients with Spontaneous Intracerebral Haemorrhage?

Since CMB represent blood leakage from haemorrhage-prone small vessels and their prevalence is higher in recurrent versus first-ever ICH [1, 2], they have been hypothesized to predict increased recurrent risk [31•]. Moreover, their strictly lobar distribution is highly specific for CAA diagnosis—a major cause of spontaneous lobar ICH in the elderly [32]—and exposes patients to a risk of ICH recurrence as high as 10–15% per year [33–35]. A meta-analysis involving 1300 ICH survivors demonstrated a sevenfold increased risk of ICH recurrence after CAA-related ICH (according to the original Boston criteria) versus deep perforating vasculopathy related ICH [31•]. In the subgroup of non-CAA-related ICH, the presence of more than 10 CMB predicted recurrent symptomatic ICH. These results reinforce previous findings highlighting the strength of the association between ICH recurrence and the burden of CMB at baseline as well as the influence of the underlying vasculopathy [35–38]. While CMB, by predicting ICH recurrence, may appear as promising prognostic biomarkers, several points deserve to be further clarified. First, the pathophysiological relevance of 1 CMB is unclear and reflects a less severe microangiopathy than multiple CMB associated with other biomarkers of small vessel disease that represent diffuse cerebrovascular damage. Moreover, the cutoff for CMB subgroup used in studies is largely reliant on the magnetic field strength. Secondly, other haemorrhagic small vessel disease biomarkers other than CMB burden also play a role in recurrent ICH risk such as cortical superficial siderosis which has been recently identified as a specific biomarker of CAA [39]. In a cohort of spontaneous ICH survivors, disseminated cortical superficial siderosis seems to herald a high risk of recurrent ICH over and above CMB [40]. This finding reinforces previous work conducted in cohort of possible and probable CAA [39, 41] which implies that the recurrent ICH risk-related CMB previously described was partially confounded by cortical superficial siderosis that was not accounted for.

Finally, focussing on prognosis of ICH patients presenting with CMB at baseline, studies show conflicting results. A recent study suggests that CMB did not influence ICH-related death or disability at 3 months or haematoma expansion at 24 h [42]. Moreover, there were no differences in response to intensive acute blood pressure treatment in patients having ICH with versus without CMBs [43]. Conversely, it has been previously found that in the presence of CMB, ICH tends to be larger [44], leading to an increased length of stay in hospital [45] and an increased mortality [38].

Taken together, these data show that the presence, burden and location of CMB allow to obtain a more accurate estimate of ICH and ischaemic stroke risk. In the absence of randomized controlled trials, treatment decisions must imperatively be tailored for each patient at an individual level and mainly rely on indirect evidence.

Role of CMB for Dementia

CMB and Cognition: Not a Clear Link

At an early stage after their discovery, CMB have been suggested to confer a risk of incident dementia [1, 5]. Two hypotheses may be advanced as possible explanation for the link between CMB and dementia: on one hand, CMB may affect neurocognitive functioning due to disruptions of connections between strategic cerebral regions [46, 47], and on the other hand, their impact on cognition may mainly rely on the underlying microangiopathy—deep perforating vasculopathy or CAA [48]. Most studies reporting an effect of CMB on cognition are hampered by methodological limitations such as inclusion of patients with too few CMB to cause cognitive changes, analyses without adjustment on important confounders such as other small vessel disease biomarkers and heterogeneity in cognitive functions evaluation [49]. These limitations may explain the conflicting results regarding the impact of CMB on cognition. Moreover, association between number as well as location of CMB and cognition is somehow unreliable since the detection of CMB depends on MR sequence characteristics and at least half of CMB are missed in premortem MRI compared with histopathological examinations [50•, 51•].

What Does the Literature Tell Us?

A prospective study of consecutive adults without neurological disorders found that the presence and number of CMB were associated with a global cognitive dysfunction based on the MMSE score showing a 1.5 standard deviation below the age-related average [52]. In an another longitudinal study including 524 subjects with vascular risk factors, multiple or mixed CMB independently showed higher risk of all-cause of dementia suggesting that this association may be driven by vascular risk factors [53]. Accordingly, a recent meta-analysis pooling the 3 major population-based studies (Rotterdam study [54••], Framingham Heart study [55] and AGES Reykjavik Study [56]) found an association between CMB and dementia but with a marginal statistical association and considerable heterogeneity [38].

By contrast, a meta-analysis published the same year and including the same population based studies found no significant statistical association between the presence of CMB and the incidence of dementia [57]. The authors rightly pointed out that these discrepancies may be partly explained by the assessment of the presence or the absence of CMB which seems to be less relevant on a pathophysiological viewpoint than the total number of CMB. While previous meta-analyses focused on 1 biomarker at a time, a meta-analysis simultaneously gathered for the first time published data on the association of the 4 main MRI biomarkers of small vessel diseases (white matter hyperintensities, brain infarcts, CMB and perivascular spaces) with risk of incident dementia [58••]. Interestingly, they found that only white matter hyperintensity burdens were associated with incident dementia in general population as well as in high-risk individuals. The lack of association with CMB may be due to the small number of CMB in individuals reflecting a less severe underlying microangiopathy and therefore a weaker contribution to cognitive outcome [58••]. Extensive white matter hyperintensities in comparison to very few CMB is more likely to affect complex cortical–subcortical tracks, ultimately leading to damage of neural networks and seems to be mostly responsible for cognitive decline [59, 60] and dementia [61] in studies using advanced MRI techniques. The lack of association with CMB may be due to the small number of CMB in individuals reflecting a less severe underlying microangiopathy and therefore a weaker contribution to cognitive outcome [58••].

What About the Contribution of CMB in Alzheimer's Disease?

CMB are present in one in five patients with AD [62].Their anatomical distribution tends to be lobar with a posterior predominance [63]. The higher prevalence of CMB in AD can be explained by the presence of CAA and hypertension which both play a role in the pathophysiology of the disease [6]. It is still controversial whether CMB contribute to the pathophysiology of AD or are just bystanders in the aging brain [6]. In a recent meta-analysis, the prevalence of CMB in studies reporting probable AD was shown to be higher than in those reporting possible and probable AD (14 versus 27%) [3]. It is obviously tempting to confer to CMB a link between amyloid pathology and neurovascular changes. Their impact on cognitive prognosis in AD remains a matter of debate. The overall burden of CMB suggesting a more severe underlying small vessel disease may predict a more aggressive form of AD [48, 64]. Nevertheless, in a longitudinal study including 221 patients with AD, the presence and number of CMB were not associated with rate of cognitive decline after adjustment on age at onset, APOE genotype suggesting that CMB do not affect the downstream Alzheimer processes such as loss of synapses and neurodegeneration [65].

What About the Contribution of CMB in CAA?

CAA is frequently diagnosed in patients based on the presence of multiple strictly lobar CMB [64] and is recognized as a cause of vascular cognitive impairment and dementia [66] even in patients who never experienced ICH. While the association between CAA pathology and dementia has been increasingly reported, risk factors predicting cognitive decline in CAA are not fully understood. Previous studies focusing on dementia in ICH survivors have reported that CAA-related neuroimaging markers (such as CMB, cortical superficial siderosis, white matter hyperintensities) rather than ICH volume or location were predictors of long-term dementia suggesting the relevance of an underlying ongoing vascular or degenerative process [67••, 68••]. Lobar CMB have been identified as a strong predictor of cognitive decline in CAA patient or in general population [16, 69]. However, more than CMB taken in isolation, it is the overall small vessel disease burden (accumulation of ischaemic and haemorragic lesions) that seems to be the most robust predictor of incident dementia in CAA patients [70] due to microstructural alterations of brain networks in CAA [70, 71].

Conclusion

CMB can be observed in various settings with a high prevalence and draw considerable attention for clinicians since they may be a marker of future stroke or might contribute to dementia. CMB are often incidentally detected on MRI raising clinical dilemmas about the optimal management of these patients. CMB mainly reflect the severity of the underlying small vessel disease and should not be interpreted independently of the others neuroimaging biomarkers or the clinical setting. From a practical point of view, the presence of CMB should lead to a detailed assessment of an individual risk of stroke (either ischaemic or haemorragic) or of dementia to carefully evaluate the most appropriate preventive strategies. Future large prospective longitudinal studies and randomized controlled trials in various settings are required to determine whether specific therapies are beneficial in case of incidental findings. Multimodal neuroimaging assessments of fibre tract integrity, amyloid burden and brain metabolism may contribute to the understanding of the link between CMB and associated cognitive impairment by integrating coexisting vascular and neurodegenerative lesions.

Compliance with Ethical Standards

Conflict of Interest Solène Moulin and Charlotte Cordonnier each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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