The Clinical Relevance of Cerebral Microbleeds

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Abstract

Despite their very recent discovery and only couple decade-long existence, cerebral microbleeds are progressively investigated, trending radiological concepts in today’s scientific era. In this paper, we are going to provide a short review on the most important details of cerebral microbleeds, with special focus on their clinical relevance and particular emphasis on their practical aspects with stroke prevention and therapy.

Keywords: Cerebral Microbleed; Magnetic Resonance Imaging; Stroke; Cognitive Impairment; Small Vessel Disease.

Introduction

In the last couple decades, the rapid evolution of imaging methods shed light on previously unknown entities. These findings confirmed discoveries from as early as the nineteenth century, when forms of small vessel disease were first documented.

Today, these entities have gained an important role in daily clinical practice, due to the fact that not solely the immensely developed technology can depict them, therefore clearing the way for expansive research. There has been numerous investigations for the better understanding of the radiological and histopathological concepts of cerebral microbleeds; but recently, most studies have been focusing on their clinical relevance such as cognitive impairment and a possible role as an imaging marker for brain hemorrhage.

Cerebral Microbleeds Definition and Imaging

Cerebral microbleeds are radiologically defined lesions visible on magnetic resonance imaging (MRI). They were first documented simultaneously by Chan, Greenberg and Offenbacher in 1996 [1]. The detailed pathology behind the lesions were described in 1999 by Fazekas as cerebral amyloid deposition and lipohyalinosis in cases of intracerebral hemorrhage [2], however the very same year Tanaka published another explanation pointing out the role of damaged arteriosclerotic microvessels [3]. Most studies agree that microbleeds indicate sites of accumulated hemosiderin-containing macrophages [2, 3] that arise owing to the submerged transport system from the iron-rich breakdown of minute hemorrhages from the damaged network of vessels [4]. Once they become visible, they scarcely disappear: the low rate of export of hemosiderin suggests a small number of true resorption and the dominance of possible artifacts [5]. Other suggestions of their origin include a hypothesis that they are results of parallel pro-inflammatory pathways activated by vasculopathy [6]; and a preposition presenting that age-related disorders of ferritin transport and storage might take notable part in microbleed pathomechanism [7].

Cerebral microbleeds are small, round, homogenous, hypointense lesions depicted by gradient recall echo (GRE) or susceptibility weighted (SWI) imaging (Figure 1) [8]. Both methods provide increased contrast between the paramagnetic material and brain tissue [9], however SWI is proved to be 50-70 percent more efficient than the GRE sequence, and currently the most sensitive in detecting microbleeds. Combining high-pass filtered phase information with images of multiplied magnitude [8, 10, 11]; contributes to augmented contrast and increased blooming effect [8, 10]. The appearance of cerebral microbleeds is highly dependent on imaging parameters including the sequence itself, the spatial resolution, magnetic field strength and the post-processing [8]. Studies have reported a 30 percent rise in identification of microbleeds with 3.0T field strength compared to 1.5T [12],...
Figure 1. Imaging of Cerebral Microbleeds with Susceptibility Weighted Imaging.

The small, homogenous, hypointense, round lesions are located in the lobar area in our patient from the Stroke Care Unit.

Moreover, the ultra-high resolution 7.0T field strength MRI seems to overcome these results [10]. Not solely the microbleed number but size is also contingent on these imaging parameters, and due to the blooming effect, MRI results are unable to measure the exact size of the lesions. Cerebral microbleeds are often bimodal in their size distribution, ranging from 2 mms to 5-10 mms with a cut-off at 5.7 mms [1, 8, 13].

The neuroimaging concensus criteria for detecting cerebral microbleeds involve the following key points: (1) homogenous foci on GRE or SWI, (2) round or ovoid in shape, (3) small in size - mainly 2-5 to 10 mms, (4) they present with blooming effect, (5) they devoid signal hyperintensities, (6) surrounded by brain parenchyma, (7) diffuse axonal injury and secondary causes are excluded and (8) microbleed mimics are ruled out [1, 8].

These microbleed mimics refer to various sites of calcification or iron deposition (mainly choroid plexus, basal ganglia and the pineal gland, cross-sectional vessels in the sulci, deoxyhemoglobin containing structures, air in the sinuses and bone artifacts along with secondary causes, particularly vascular malformations, metastatic tumors and diffuse axonal injury [8]. Differential diagnosis requires other imaging sequences to rule out the non-hemorrhagic lesions, artifacts and secondary phenomena that appear identically to microbleeds. In order to minimize misdiagnosis due to coexisting mimics, the standard imaging for cerebral microbleeds should include SWI or GRE, T1, T2, FLAIR and DWI sequences along with conventional head CT [1, 8].

Currently, manual rating scales, including Brain Observer MicroBleed Scale (BOMBS) and Microbleed Anatomical Rating Scale (MARS) are proved to be useful in clinical settings. BOMBS categorizes microbleeds by their size, side and location (deep, lobar, posterior) [14]. The MARS scale provides a slightly more sophisticated approach primarily classifying microbleeds as ‘definite’ or ‘possible’, then registering the side and the location similarly to the BOMBS method except for the size, which appears to be unnecessary in the scaling system (Figure 2). These alterations offer a good to very good inter- and intrarater variability of the microbleed assessment [15]. Automated detection methods are also available, however despite their very high sensitivity, they are overly deficient in specificity; making manual evaluation the gold standard [16]. However semi-automated methods requiring visual censor for false positives would reshape current time-consuming procedures [16, 17].

Cerebral Microbleeds in the General Population

The Rotterdam Study has been a pioneer in the research of cerebral microbleeds. Over twelve thousand brain scans have been processed since the beginning of the study in 1995 and almost 4000 scans were evaluated for cerebral microbleeds [18]. 15.3% of the study population had microbleeds, including 5.4% with multiple microhemorrhages. Age seems to play significant role in the appearance of microbleeds: they were detected in 6.5% of the patients between the age of 45 and 50, which increased to 35.7% among individuals over 80 years of age [18, 19].

This research group also suggested that microbleeds could demonstrate the worsening of the underlying brain lesions, therefore a longitudinal study including 831 patients was additionally performed. The mean interval between examinations was 3.4 years, whilst 10.2% of the patients developed new microbleeds, increasing the overall prevalence from 24.4% to 28%. If baseline microhemorrhages were present, new microbleeds appeared with the odds ratio of 5.36; moreover, this number escalated to 7.15 if multiple microhemorrhages were present. This study found that besides their number, microbleeds at baseline also predicted location; two thirds of the newly evolved microbleeds were strictly lobar [5, 18].

The preferential distribution of cerebral microbleeds reflect the primary pathology. Microhemorrhages are generally classified topographically as lobar, deep and infratentorial (Figure 3) [20, 21]. Lobar microbleeds are associated with cerebral amyloid angiopathy, β-amyloid deposition and certain APOE genotypes [2, 21]. Lesions in the deep or infratentorial regions are preferably relate to vascular risk factors, mainly hypertension [19, 21]. Areas above the corpus callosum are most presumably due to traumatic injuries, while lesions in the thalamus and the basal ganglia imply to non-traumatic sources [22].

The tremendous number of patients involved in the population-
Based studies produced information on the risk factors of cerebral microbleeds: age, gender, hypertension, low cholesterol levels, statin therapy, retinal microvascular lesions, left ventricular hypertrophy and APOE 4 genotype, the latter showing strong correlation to strictly lobar microhemorrhages [5, 19, 23, 24]. The role of the other alleles on APOE gene remain controversial as APOE 2 allele appears to cause fibrinoid necrosis, which contributes to the formation of microbleeds, however statistics do not verify this hypothesis [19, 25, 26]. Microbleeds are also commonly associated with genetic conditions including cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and Notch-3 protein mutation [27, 28]; polymorphisms of nephrilysin [9, 29] and the complement receptor-1 gene [30]; mutations of collagen 4 1-subunit [31], APP and presenilin [32]; Fabry's disease [33], familial multiple cavernoma syndrome and Tangier's disease [34]. Cerebral microhemorrhages may appear in cases of fat [35] and septic embolism [36], infective endocarditis [37], cerebral vasculitis [38], moyamoya disease [39] and they are also closely related to other subtypes of small vessel disease [40, 41].

Gregoire et al., suggested a new, reliable concept by the subdivision of the microbleeds to probable and definite lesions as the main concept of the scale. These microhemorrhages are then classified as deep, infratentorial or lobar on each side [15].

Location of the lesions indicate the underlying pathology, as deep microbleeds are results of hypertension or chronic vascular risk factors and deep microhemorrhages are caused by cerebral amyloid angiopathy [95].
Small Vessel Disease

Microbleeds, as the hemorrhagic margin of a spectrum disease, are often found together with other pathologies, such as subcortical microinfarcts, lacunes, white matter hyperintensities and focal brain atrophy [41, 42]. They are all key features of small vessel disease, one of the most common pathologies in the brain, a heterogenous systemic defect that affects various organs, commonly the small vessels in the brain [41]. Similarly to microbleeds, other parenchymal lesions are detectable by high-resolution MRI methods, however small vessel disease itself cannot be visualized in vivo, allowing imaging results to function as radiological markers [42].

A consensus for classification named STAndards for ReportIng Vascular changes on neuroimaging (STRIVE) was created to structure a clear system of neuroimaging protocols and consistent terminology. The new, standardized classification and reporting method relies on individual and clinical judgement besides strict imaging criteria, providing a useful guideline to both research and routine clinical practice [41].

Not only the appearance but the origin of these lesions is also heterogenous: main etiological categories include arteriolosclerosis (mainly associated with age, hypertension, diabetes mellitus), cerebral amyloid angiopathy, genetic factors (C3,4AD, and other inherited diseases), inflammatory or immunological disorders, venous collagensis and further secondary causes [42].

Major factors in the pathomechanism are vessel wall damage, change of cerebral blood flow and therefore chronic ischemia, disturbance of the blood-brain barrier, inflammation and apoptosis of oligodendrocytes [42]. Newer studies show importance of capillary disfunction as a shared marker of small vessel disease with special focus on pericytes, as key elements [43].

Cerebral amyloid angiopathy (CAA) is a condition of amyloidosis or amyloid deposition of the cerebrovascular system [44, 45]. Although several types of accumulating proteins have been described, amyloid β-protein is by far the most common type with major clinical relevance. CAA is associated with aging - appearing in half of the elderly population, it also plays an important role in Alzheimer's disease where amyloid β-protein deposition is found in more than 80% of the patients [46]. Its effect on intracerebral hemorrhage is still the focus of intensive research. CAA-associated cerebral vasculopathies contribute to microbleeds and intracranial hemorrhage in lobar, especially occipital location; indicating that microhemorrhages preferably occur where β-amyloid deposition is utmost [48]. In a study, cerebral microhemorrhages were present in almost half of the cases of confirmed CAA [49]. The inclusion of microbleeds into the Boston criteria [50], the validated clinical diagnostic approach of CAA in intracerebral hemorrhage appear to increase sensitivity of detecting CAA [8, 34, 40]. Nevertheless, recent data, based on 113 cases, has queried if this finding reflects the background of all microbleeds and presented results that show no significant correlation in distribution and the affected sites between CAA and lobar microbleeds, implying that no direct neuropathological association is present between the two entities [51].

Cerebral Microbleeds and Clinical Relevance

Although cerebral microbleeds have been described as asymptomatic lesions, emerging data points out that these lesions are able to generate clinical syndromes if appearing rapidly or manifesting at important sites [52]. Apart from their presence in healthy individuals [5, 19, 23], cerebral microbleeds are also related to ischemic and hemorrhagic strokes [2, 53], cognitive impairment and Alzheimer's disease [54] along with diffuse axonal injury associated with traumatic brain injury [55].

Cerebral Microbleeds and Stroke

Microhemorrhages reflect a bleeding prone state, therefore it is not unforeseen that they are found in 19-83% of cases of intracerebral hemorrhages [9]. Also, the number and location of the lesions are proportional to the risk and volume of hemorrhages [8, 56]. While a single microbleed merely means 14% risk of developing further symptomatic hemorrhages in three years, more than six microlesions increase the likelihood to 50%, serving as an indicator for the risk of recurrence [40, 57]. However, these facts do not suggest that micro- and macrohemorrhages are related; on the contrary, despite sharing features to some extent, they are entirely different entities [13].

Charidimou reported increased risk of intracerebral hemorrhage but not ischemic events when microbleeds were present [58], although several studies proved that they are not solely associated with conditions susceptible to bleeding, and they are also present in 15-35% of the ischemic strokes [9]. Findings remain controversial as a European investigation discovered no increased risk of hemorrhage risk but probability of future ischemic lesions, while a Japanese study stated strong relation to intracerebral bleedings rather than ischemic events [58]. Incident microbleeds point to the progression of ischemic vascular lesions, particularly if multiple lesions are present [59]. Moreover, they appear even in patients with transient ischemic attack (TIA) where they tend to emerge less [53], but they are linked to a higher risk of progression into stroke [60]. There is also a four-fold increased likelihood of detecting microhemorrhages in cases of recurrent stroke events. [9] Lim et al., reported that in TIA, recurrent strokes occured in only 4.2% in patients without microhemorrhages, and they were considerably associated with strictly lobar and mixed microbleeds, at rates 14.3% and 38.5%, respectively [61]. It has also been revealed that the lesions at mixed locations relate to increased risk of developing stroke after TIA in a manner independent of the number of the lesions [61].

The progression of the underlying pathologies are undeniably reflected by the number of microbleeds: 13% increase was recorded in the first four days and 23% in the next five years after a stroke event [62]. Another study measured the rate of the formation of new microbleeds in the three following years after TIA or ischemic stroke and found an extra 0.8 microlesions per year on average. Furthermore, the number of microbleeds were increased by 5.4 lesions per year in patients with more than five microbleeds at baseline [63].

The coexistence of ischaemic and hemorrhagic events in the presence of microbleeds implies that these microlesions function as markers of both first ever intracerebral hemorrhages and
ischemic strokes in healthy individuals [63, 64], as well as suggesting increased risk of recurrent hemorrhage after intracerebral hemorrhage [57] and among survivors of ischemic stroke [65]. Cerebral microbleeds are associated with higher risk to developing a future episode of stroke in general, representing both ischemic and hemorrhagic consequences; with a dose-dependent manner based on the number of microhemorrhagical lesions [57, 59, 66]. Cerebral microbleeds at regions generally affected by CAA imply an increased risk of intracerebral hemorrhage, while sites without CAA may reflect both ischemic and hemorrhagical alterations as the underlying stroke pathology [64].

Based on several previously mentioned studies, it has become undoubtful that presence and even number of microbleeds at baseline, along with radiological signs of previous cerebrovascular events mark a notable relation to the shaping of new microbleeds that contribute to recurrent strokes [67]. Therefore, cerebral microbleeds emerge as potential biomarkers for the increased risk of any types of cerebrovascular events [66], preparing the way for a possibly revolutionary method of diagnostics in clinical practice.

**Cerebral Microbleeds and Thrombolysis**

Thrombolytic therapy is proved to improve the three-month functional outcome if administered in a short time-window in acute stroke [68]. Despite its undeniable merit, secondary post-ischemic symptomatic intracranial bleeding generated dilemma in decision-making in the acute phase of ischemic stroke [69-72], leading to very strict inclusion criteria and a list of contraindications; even so these guidelines only contain standard radiological information without microbleeds [73]. Thrombolysis-associated hemorrhagic transformation was found in a one-week time period in 6.8% of patients receiving intravenous recombinant tissue plasminogen activator (rtPA) [72, 73].

Despite numerous attempts, there are no valid predictive scores able to filter patients more likely to develop secondary hemorrhagic transformation [72]. The risk of secondary hemorrhage might be related to age, blood pressure, early changes in diffusion imaging and ischemic signs on CT and severity of stroke [74], however cerebral microbleeds might serve as more reliable markers for risk associated with thrombolysis in stroke patients [69, 72] since their number increases rapidly after administration of rtPA [75]. However, it still remains unknown if microhemorrhages contribute to secondary bleedings after intravenous thrombolysis [76].

Numerous studies showed no significant relation even between multiple microbleeds and intravenous thrombolysis-related complications [69, 71, 76-79]. Until further data is available on their relation, the presence of cerebral microbleeds are not contraindication for the use of rtPA, therefore they are not included in thrombolysis guidelines [71-72].

**Cerebral Microbleeds and Antithrombotic Therapy**

Analogously to the previously discussed rtPA treatment, bleeding, especially intracranial hemorrhage is a rare, but the most feared complication of antithrombotic therapy [19, 80, 81]. These drugs have become the center of attention in acute clinical settings, since decision-making is extremely burdensome when cost-benefit balance is taken into consideration; emerging the need for risk stratification for potentially life-threatening intracerebral hemorrhages [82]. Besides pointing to the development of hemorrhagic strokes, cerebral microbleeds are also markers of antiplatelet and anticoagulant-related intracerebral bleedings [19, 42, 81, 83-85].

Antiplatelets are increasingly used medications in prevention and treatment of cardiovascular, cardiometabolic and cerebrovascular diseases. Presence of baseline microhemorrhages had a significant correlation with symptomatic brain hemorrhages in antiplatelet users, the relation was even more conspicuous when multiple lesions were present [81, 84, 86, 87]. New formation of cerebral microhemorrhages was indicated by baseline number of lesions [5], classic vascular risk factors including age, blood pressure, gender, diabetes mellitus and lipid status [21, 88] and microangiopathy [5, 88]. Lovelock et al reported relation between microbleeds and antiplatelet therapy in patients with intracerebral bleeding but not with TIA or ischemic stroke [83], however other studies revealed the same correlation regarding ischemic cerebrovascular lesions [58, 82]. The Rotterdam Study revealed that aspirin might be only associated with strictly lobar lesions, emphasizing the importance of the underlying small vessel disease [81]. Other studies investigating effects of clopidogrel demonstrated that clopidogrel use was associated with presence and even higher number of microbleeds in a stroke-free population [89], however, only a non-significant correlation was found in patients with stroke [90]. Moreover, in contrast to aspirin, clopidogrel was more related to deep and infratentorial lesions than lobar ones [90, 91].

Some investigations suggested that the increased risk of intracerebral hemorrhage might outweigh the benefit of antiplatelets as methods of secondary prevention [85, 88]. Nevertheless, the lack of significant association between microbleeds and antiplatelets in stroke-free population [82] questions the need for overriding current guidelines.

Vernooij et al. found in the Rotterdam study that microbleeds were only related to antiplatelet drugs but not to anticoagulants [81], that would be explained by a hypothesis suggesting that platelet aggregation is a more important factor in microbleed evolution than clot formation [81]. Other studies seems to be in contrast to this findings as they reported higher percent of patients developing new microbleeds when baseline lesions were present than in microbleed-negative cases [92]. Microhemorrhages have also been proved to increase in stroke patients with prior anticoagulant therapy [93]. Akoudad et al., located most of the microbleeds in the deep and infratentorial area in stroke-free patients on coumarin treatment [94], while other studies reported association with lobar lesions [95]. It has been verified that presence of microhemorrhages and prothrombin time, particularly high variability in international normalized ratio (INR) values are independent contributors to intracerebral hemorrhage in patients treated with warfarin [94, 96]. An impaired hemostatic system with inability to remain self-limited therefore causing microbleeds to expand, could be a general explanation for higher prevalence of both microbleeds and intracerebral hemorrhages [95, 97].

Novel oral anticoagulants (NOAC) have proved to lower risk of intracerebral bleeding by almost 50% [98-101]. Saito et al.,
found no new microbleeds in the NOAC group in contrast with the warfarin group, where the conventional anticoagulation was independently associated with the appearance of new lesions [102]. These results might be attributable to a more stable hemostatic state with NOAC, since studies focusing on conventional anticoagulation showed that warfarin treatment with well-balanced and optimal INR range have similar risk of hemorrhage to NOAC therapy [95].

Similarly to questions regarding antiplatelet-safety, the costs versus the benefits of anticoagulants are even more intensely argued, since they are key elements for treatment of cardiovascular diseases, especially for the primary and secondary stroke prevention in non-valvular atrial fibrillation, as they manage to lower risk by almost 70% [103]. Several study results raise awareness to the use of anticoagulants in patients with microbleeds, and therefore researchers argue whether oral anticoagulants still have the net benefit when the the risk of potentially disabling hemorrhage is so high [57] that statistically, prevention of a small number of cardioembolic strokes costs even higher number of hemorrhages in patients treated with warfarin [104]. Despite these findings, Haley et al., presented that based on a decision model, only as high as a 13-fold increased risk of intracerebral hemorrhage would balance benefits of conventional anticoagulant use [105]. Several suggestions have been published for a potential screening algorithm for high-risk patients (Figure 4), however in the absence of randomized trials, these proposals remained in the background [95, 106].

**Cerebral Microbleeds and Cognitive Impairment**

The relation between microbleeds and cognitive performance have been intensively researched [42]. Despite the fact that these lesions were believed to be silent, clinical and population-based studies have reported symptomatic manifestations of neurovascular damage [42, 107]. Small vessel disease is one the

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**Figure 4. Decision Algorithm for the Anticoagulation of High-Risk Patients.**

| MRI Screening for Anticoagulation |
|-----------------------------------|
| **Atrial Fibrillation Patient ≥ 60 years?** |
| Yes | MRI |
| No | MRI not needed |
| Microbleeds Present? |
| No |
| Yes |
| Cortial (Lobar) Microbleeds |
| or |
| ≥5 Subcortical Microbleeds |
| 1. Neurology Consultation |
| 2. For anticoagulation, avoid warfarin in favor of newer anticoagulants |
| Neurological changes during anticoagulation? |
| Yes |
| Repeat MRI |
| Microbleed Progression? |
| Yes |
| Discontinue Anticoagulation |
| No |
| Continue Anticoagulation |
| Anticoagulates as usual |
| Anticoagulates as usual |

High morbidity and mortality of the potential hemorrhagic complication of the antithrombotic drugs emerge the need for careful clinical decision-making. Flow charts and risk assessments before treatment might offer a safer but not profitable alternative. [Fisher M (2013) MRI screening for chronic anticoagulation in atrial fibrillation. Front. Neurol. 4:137. doi: 10.3389/ fneur.2013.00137.]
Most common source and also the marker of progression of vascular dementias, since underlying pathomechanisms might include CAA or hypertensive arteriopathy, especially that it has also been suggested that these lesions may be limited cerebral plasticity [42, 108].

Cerebral microbleeds are found in up to 19% in the cognitively unaffected population, however they are detected in higher percent in mild cognitive impairment, Alzheimer's disease and vascular dementia (20-43%, 18-32% and 65-85%, respectively) [9]. The presence of microhemorrhages was associated with lower scores on the Mini Mental State Examination (MMSE) or other neuropsychological testing methods [109, 110]. The RUN-DMC study however, revealed that microbleeds were linked to worse cognitive function without change in MMSE scores [111].

It was revealed in the Rotterdam Study that deep microbleeds are not significantly related to cognitive outcome, however they affect global cognition, psychomotor speed, gait and attention. Lobal lesions are associated with memory and executive functions besides global cognition [9]. The baseline number of microhemorrhages was proportional to risk of cognitive impairment: a single microbleed marked a 16% risk, while more than six lesions reflected a notable increase to 52% risk for cognitive dysfunction [57]. Presence of cerebral microbleeds reflected an overall two-fold risk for dementia [112]. Results from other studies do not support the relation between microhemorrhages and cognitive impairment [113].

Cerebral Microbleeds and Prognosis

Kim et al. investigated morbidity and prognosis among stroke patients with cerebral microhemorrhages. They documented a strong relation between poor functional outcome and microbleeds, especially the ones located in the infratentorial region [114]. They suggest that microbleeds and white matter hyperintensities indicate sites of chronic dysfunction in perfusion and reactivity, contributing to more critical damage in the penumbra area, leading to limited recovery [114, 115]. Prognosis is also influenced by the location affected by the lesions, since focal damages in important sites might worsen functional outcome [114].

Not only the location but the number of microhemorrhages are also related to prognosis, especially in bleeding-prone conditions: it was found in patients after thrombolysis that pre-existing microbleeds were associated with disease outcome [116], furthermore microbleed number was independently linked to increased score on the modified Rankin scale [117]. Besides direct effects of these microlesions on cognition and neurologic dysfunction, effects of secondary hemorrhages after thrombolysis or the administration of antithrombotic drugs worsen functional outcome in stroke patients [117].

The PROSPER study focuses on the connection between microhemorrhages and mortality in patients with cerebrovascular disease, antithrombotic therapy or cardio- and cerebrovascular risk factors. It is demonstrated that microbleeds are the most linked to overall mortality among imaging markers. They have found that overall mortality is higher in the group with more than one microbleed compared to the group without microbleeds present [118], analogously to a memory clinic study where the same result was found in patients with more than three microbleeds [119]. Multiple microbleeds also bear a six-fold increase in stroke-related mortality, and when investigating strictly lobar, CAA-related lesions, a 2.2-fold risk for stroke-associated deaths was revealed without any connection to cardiovascular mortality. Similarly to microbleed-related morbidity, their affect on mortality is also contingent of the number of cerebral microbleeds [118].

Conclusion

Along with the technical development of imaging methods, cerebral microbleeds are getting increasing attention both at scientific research and clinical practice. They have become particularly important for their increasing burden on health. Despite the intensive investigation, results remain highly controversial, thus relevant information for the treatment and clinical guidelines is missing. Our paper reveals highly inconsistent findings among recent studies of cerebral microbleeds. However, it has been proposed that these differences might no longer exist if all imaging and patient selection methods could be standardized. Methodological consistency is even more important considering that microbleeds are primarily radiological concepts, where slight differences in depicting could result in extreme divergence of results.

Emerging data on the relation between cerebral microbleeds and cognitive impairment is already in the spotlight as these lesions were previously believed to be related to no symptomatic complications. Ongoing trials, namely, the CROMIS-2 [120] or the CMB-NOW [121] might provide so far lacking data that expectantly contribute to further understanding of cerebral microbleed pathology, pathomechanism and clinical implications.

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