International Journal of Research and Review
Volume 11; Issue: 5; May 2024
Website: www.ijrrjournal.com
Review Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Literature Review on the Association between Cerebral Large Artery Disease and Cerebral Microbleeds

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DOI: https://doi.org/10.52403/ijrr.20240552

ABSTRACT

CMBs are small areas of hemorrhage in the brain, often seen on neuroimaging studies, that have been associated with various cerebrovascular pathologies. Large-artery atherosclerosis and resulting vascular stenosis are major contributors to ischemic stroke. Given the structural continuity between intracranial large and small vessels, their susceptibility to hemodynamic influences, and their shared risk factors, they may coexist in the same individual. This article reviews recent advances in understanding the interplay between large artery atherosclerosis (LAA) and cerebral microbleeds (CMB).

Methods: A comprehensive search of electronic databases including PubMed, MEDLINE, and Google Scholar was conducted using relevant keywords such as "cerebral large artery disease," "cerebral microbleeds," "arterial stenosis," and "atherosclerosis." Articles published in English between [2010] and [2024] were considered for inclusion. Studies investigating the relationship between LAA and CMBs through neuroimaging, pathological examination, or clinical correlations were selected for review.

Results: The review identified a range of studies exploring the association between LAA and CMBs. Several cross-sectional imaging studies have demonstrated a significant correlation between LAA severity and the presence, number, and distribution of CMBs. Histopathological investigations have revealed microvascular alterations in regions affected by LAA, potentially contributing to CMB formation. The evidence indicates a correlation between cerebrovascular microbleeds (CMBs) and large artery diseases, impacting the prognosis of individuals with cerebral infarction resulting from large artery atherosclerosis (LAA).

Key words: Cerebral infarction; Large-artery atherosclerosis; Cerebral microbleeds.

INTRODUCTION

Cerebral large artery disease (CLAD) encompasses various pathological conditions affecting the major arteries supplying the brain, such as atherosclerosis, arterial stenosis, and arterial dissection.(1) Cerebral microbleeds (CMBs) manifest as small, circular regions of decreased signal intensity on T2*-weighted gradient-recalled echo (GRE) sequences.(2)

Common vascular risk factors have important effects on both large and small arteries.(3,4) Chronic inflammatory factors such as hypertension, dyslipidemia,

diabetes, smoking, obesity, physical inactivity, and various viral infections are associated with vascular endothelial dysfunction.(5)

Cerebral microbleeds (CMBs) are not unique to individuals diagnosed with cerebral small vessel disease (CSVD). They can also be observed in the general population and in patients with lesions of the large intracranial arteries.(6,7) One study correlates cerebral microbleeds with carotid plaque in patients with severe stenosis. (10) The role of inflammation in vascular disease, including microbleeds and plaque.

In addition, as neuroimaging techniques continue to evolve, the detection of cerebral small vessel disease (CSVD) is increasing, highlighting the importance of exploring the relationship between CSVD and large artery atherosclerosis (LAA) to better understand disease mechanisms and personalized interventions. Of particular interest is whether existing prevention and treatment strategies for LAA are effective in the management of CSVD, as well as addressing concerns about the safety of antithrombotic therapy in individuals with cerebral microbleeds (CMBs). This article provides a comprehensive review of recent advances in understanding the relationship between LAA and CMBs.

EPIDEMIOLOGY AND PREVALENCE

Stroke is the most common cerebrovascular disease, and is also one of the main causes of disability and death. Among them, patients with ischemic stroke account for up to 86.8%.(8) Ischemic stroke, also known as cerebral infarction, is the result of inadequate blood supply to brain tissue, initiating a cascade of events beginning with loss of electrical function and progressing to membrane dysfunction, influx of calcium ions leading to generation of reactive oxygen species, and ultimately causing damage to the cell membrane resulting in cell lysis. Over time, reversible tissue dysfunction progresses to irreversible apoptosis of neurons and supporting structures (9). Despite a decrease in mortality rate from being the second leading cause of death to the fifth in the United States, globally it remains the second leading cause of death and a primary contributor to acquired disability, necessitating prompt intervention.(10) Globally, the number of stroke events increased by 70.0%, and the mortality rate increased by 43.0%, with a significant increase in the number of stroke events and stroke deaths each year .(11)

In 2002, a study was conducted by scholars to investigate the detection rate of different subtypes of cerebral infarction, revealing that the prevalence of CMBs in LAA patients was 20.8%.(12) In a trial involving 459 patients with acute ischemic stroke in China, it was observed that the prevalence of cerebral microbleeds (CMBs) was 40.74%.(13)A retrospective study showed that the detection rate of CMBs in patients with LAA stroke was 24.8%, mainly distributed in deep brain regions.(14) Different studies have shown that the detection rate of CMBs in LAA patients is between 9% and 41.3%, and the difference may be related to different research populations and detection methods.(15)

Cerebral Microbleed:

The CMB is a subtype of cerebral small-vessel disease (CSVD).(16) Cerebral microbleeds, identified through magnetic resonance imaging (MRI), are considered as an imaging biomarker for cerebral small vessel disease.(17) They manifest as uniform, round or round-like low-signal lesions on T2* gradient echo sequence and susceptibility weighted imaging (SWI), with a diameter ranging from 2 to 5 mm (<10 mm), and without surrounding edema.(18) As a microvascular lesion with a tendency to hemorrhage, CMBs can significantly affect the quality of life and prognosis of patients. They are not only closely associated with the occurrence of intracranial hemorrhage, but also with ischemic stroke, leukoaraiosis, vascular dementia, Alzheimer's disease, cerebral

amyloid angiopathy, and other conditions..(19) Studies have shown that the prevalence of cerebral microbleeds (CMBs) in patients with ischemic stroke ranges from 35% to 71% (20). Using conventional MR sequences, the prevalence of microbleeds is approximately 5% in healthy individuals, but increases with age, reaching approximately 34% in patients with ischemic stroke and 60% in patients with hemorrhagic stroke.(18)

A meta-analysis of 642 non-stroke patients with cerebral microbleeds (CMBs) found that the lobar type accounted for approximately 42.79% of cases, while the deep, subtentorial, and mixed types together accounted for 57.21%. The prevalence of lobar CMBs was approximately 26.76% in Western populations and 16.03% in Eastern populations, indicating a relatively lower incidence in the latter compared to the former.(20)

Typically, microbleeds in the deep and infratentorial regions are considered to be indicative of hypertensive arteriopathy.(21) In contrast, lobar cerebral microbleeds are associated with cerebral amyloid angiopathy (CAA), which is characterized by the accumulation of beta-amyloid in the cortical and subcortical vessels of the brain, potentially leading to small infarcts or vessel rupture.(22) The development of CMBs may be related to various factors, such as surgery, medications, cerebral amyloid angiopathy (CAA), hypertension, advanced age, vascular endothelial dysfunction, and inflammatory responses.(23)

LAA stenosis:

Atherosclerosis of the large arteries is recognized as a systemic and persistent inflammatory condition that may contribute to the development of both cardiovascular and cerebrovascular disease.(24) Recent research has shown a positive correlation between atherosclerosis of the large arteries and CSVD.(4) Evidence suggests a possible association between Atherosclerosis in the large arteries and cerebral microbleeds (CMBs) are commonly associated with advanced age, hypertension, and diabetes mellitus, which are common risk factors for both large arteries and small vessels.(4)

Hashimoto et al. (24) showed that in symptomatic CSVD patients without severe cerebral artery stenosis (>50%), those with ≥5 CMBs had a more significant decrease in cerebral blood flow in the semioval center compared with those with <5 CMBs, suggesting a correlation between CMB severity and cerebral blood flow. Cortical CMBs were found to be associated with reduced cerebral blood flow in several brain regions, particularly the frontal lobe, parietal lobe, and occipital cortex, in 55 elderly subjects with normal cognition and a mean age of 86.8 years, suggesting possible stenosis of the large arteries supplying these lobes.(25) Romero et al. conducted a study which revealed that 8.3% of 1243 healthy individuals developed cerebral microbleeds (CMBs) over the course of long-term follow-up. The occurrence of CMBs was found to be associated with cerebral atherosclerosis, defined as carotid artery stenosis ≥25%, and showed a stronger association with deep and mixed-site CMBs.

A systematic review and meta-analysis showed a significant association between LAA stenosis >50% and the presence of CMBs in patients with cerebral artery stenosis, including both intracranial and extracranial arteries.(26)

In the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial, Kwon et al. observed cerebral microbleeds (CMBs) on baseline MRI in 9.0% of patients with intracranial arterial stenosis (ICAS).(3)

The endothelial inflammatory response is considered the primary process underlying atherosclerosis and is characterized by the recruitment of circulating immune cells.(27) The subjects with CMBs are known to have higher serum levels of several inflammatory markers such as TNF-a, myeloperoxidase, IL-6, and IL-18 than those without CMBs.(28)

The role of carotid plaque composition (lipid, calcification, or mixed) in stroke risk assessment is increasingly recognized (29) where vascular calcification is part of the LAA process and indicates that the aorta may be severely stenosed(30) Although this calcification is commonly seen in the LAA, there is evidence that it is associated with CSVD and may serve as a potential marker for CSVD.(31) and showed that intracranial large artery calcification in patients with ischemic stroke was associated with CMBs, especially deep CMBs. Saba et al. showed that CMBs and their severity were associated with increased plaque lipid volume.(29) However, further research is needed to confirm whether LAA plaque components (lipid/calcification) can become potential markers for CMBs.

Common risk factors for large vessel and small vessel disease

Common vascular risk factors have an important impact on both large and small arteries.(3) Chronic inflammatory factors such as hypertension, dyslipidemia, diabetes, smoking, obesity, physical inactivity, and various viral infections are associated with vascular endothelial dysfunction.(5)

The location of microbleeds varies, as does their pathogenesis. Lobar microbleeds suggest cerebral amyloid angiopathy, while deep patterns may suggest arteriosclerosis, and mixed patterns may suggest mixed pathological changes (32). Carotid plaques are also associated with microbleeds, with fatty plaques increasing the incidence of microbleeds, while calcified plaques have no effect on microbleeds. The increase in fat component of plaques also has a positive effect on the presence and number of microbleeds.(29)

One study showed that the location of microbleeds is associated with the presence of atherosclerotic markers, and deep and mixed microbleeds may be associated with carotid stenosis greater than 25%, with a low correlation with carotid intima-media thickness.(33). However, a separate study provided contrary results, indicating that microbleeds are correlated with an increase in carotid intima-media thickness and that the specific location of the microbleeds plays a critical role in determining this correlation.(34)

LAA may affect the incidence of microbleeds in the following ways: First, there are common risk factors between LAA and microbleeds. Age, hypertension, diabetes, etc. will lead to degeneration of the vessel wall, which will reduce its elasticity and compliance. The increased hemodynamic at the distal end will be transmitted to the distal small vessels, causing endothelial cells and smooth muscle cells to rupture, resulting in microbleeds. Second, long-term insufficient perfusion will accelerate the destruction of capillary structure, gradually develop into the destruction of blood-brain barrier, and change the permeability, resulting in extravasation of blood.(35)

Hypertension is a major risk factor for the onset and development of atherosclerosis. The effects of rapid blood flow during hypertension can damage vascular endothelial function, increase intimal permeability, and subsequently lead to changes in vascular structure. At the same time, damage to vascular endothelial function may activate inflammatory responses, thereby promoting the development of atherosclerosis. The detection rate of CMBs increases with age. Age and long-term hypertension may also cause hyalinization of intracranial small vessels and arteriolar sclerosis, which may lead to changes in microvascular tissue structure and increase the risk of microvascular rupture and hemorrhage.(36)

In addition, the pathogenesis of LAA and CSVD is thought to be related to an inflammatory response mediated by pro-inflammatory factors. Studies have shown that inflammatory markers such as interleukin-6 and interleukin-18 are associated with microbleeds.(37). In recent years, a large number of animal experiments have shown that matrix metalloproteinase-9

is closely related to the destruction of the blood-cerebrospinal fluid barrier, and its concentration and activity are significantly increased in atherosclerotic plaques. Therefore, it is speculated that matrix metalloproteinase-9 is closely related to the pathogenesis of cerebral microbleeds.(38)

Translational concepts and future direction.

While structurally and functionally connected, large arteries and cerebral small vessels are physiologically correlated. In the past, diseases of large vessels and small vessels were investigated separately. However, increasing evidence suggests that these two types of diseases are intertwined and should be considered together.The prevalence of cerebral microbleeds (CMBs) varies significantly across different populations, time periods, and imaging modalities. The prevalence of CMBs is notably higher in elderly patients compared to younger patients, and it is also higher in patients with cerebral hemorrhage than those with cerebral infarction. Furthermore, studies on different subtypes of cerebral infarction indicate that the prevalence of CMBs is highest in lacunar infarction (LI), followed by LAA.(12) Moreover, atherosclerosis in large extracranial((39) or intracranial Arteries(40) also leads to arteriolosclerosis in small cerebral vessels and to the development of CMBs.

Chronic inflammation may play a key role in developing both small and large arteries' diseases of the brain, including CMBs and vulnerable carotid plaque (7). Research suggests that individuals who experience ischemic strokes along with cerebral microbleeds (CMBs) may exhibit systemic atherosclerosis alongside arteriolosclerosis. This co-occurrence of CMBs and large-artery atherosclerosis could be attributed to the shared exposure of both small vessels and large arteries to similar vascular risk factors.(33,41)

Furthermore, the presence of CMBs in individuals with LAA may serve as a marker of disease severity, prognosis, and response to therapeutic interventions. Future research should focus on elucidating the temporal relationship between LAA and CMBs, exploring potential biomarkers, and evaluating targeted treatment strategies to mitigate cerebrovascular complications. Comprehending the potential relationship between large artery atherosclerosis and cerebral microbleeds (CMBs) is imperative for illuminating the fundamental mechanisms of cerebrovascular disorders and the involvement of persistent, systemic inflammation.(42) In the future, when conducting randomized clinical trials, it is essential to consider both large artery and cerebral microbleed damages as endpoints. These two diseases are interconnected, and in order to address one effectively, we must address both.

CONCLUSION

In conclusion, the literature suggests a significant association between cerebral large artery disease and cerebral microbleeds, indicating shared vascular pathology and clinical implications.

The association between LAA and CMBs implicates shared underlying pathophysiological mechanisms, including endothelial dysfunction, blood-brain barrier disruption, and chronic hypoperfusion. These vascular changes may promote microhemorrhages within the brain parenchyma, manifesting as CMBs on neuroimaging.(43)

Further studies are warranted to elucidate the mechanistic link between these entities and to guide clinical decision-making in the management of cerebrovascular diseases. Efforts aimed at preventing and treating LAA may have implications for reducing the burden of cerebral microvascular pathology, ultimately improving patient outcomes and quality of life.

Declaration by Authors

Ethical Approval: Not Applicable
Acknowledgement: None
Source of Funding: None

Conflict of Interest: The authors declare no conflict of interest.

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How to cite this article: Abdirahman Mohamed Ali, Xiaobo Li. Literature review on the association between cerebral large artery disease and cerebral microbleeds. *International Journal of Research and Review*. 2024; 11(5): 440-447. DOI: *https://doi.org/10.52403/ijrr.20240552*

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