

Review Article

Uncommon Causes of Cerebral Microbleeds

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Background: Cerebral microbleeds (CMBs) are small and round perivascular hemosiderin depositions detectable by gradient echo sequences or susceptibility-weighted imaging. Cerebral microbleeds are common among patients with hypertension, cerebral ischemia, or cerebral amyloid angiopathy. In this article, we describe uncommon causes of CMBs. *Methods:* We searched Pubmed with the keyword CMBs for relevant studies and looked for different uncommon causes of CMBs. *Results:* CMBs have several uncommon etiologies including posterior reversible encephalopathy syndrome, infective endocarditis, brain radiation therapy, cocaine abuse, thrombotic thrombocytopenic purpura, traumatic brain injury, intravascular lymphomatosis or proliferating angio-endotheliomatosis, moyamoya disease, sickle cell anemia/ β -thalassemia, cerebral autosomal dominant arteriopathy subcortical infarcts, and leukoencephalopathy (CADASIL), genetic syndromes, or obstructive sleep apnea. *Conclusions:* Understanding the uncommon causes of CMBs is not only helpful in diagnosis and prognosis of some of these rare diseases, but can also help in better understanding different pathophysiology involved in the development of CMBs. **Key Words:** Hypertension—cerebral ischemia—cerebral amyloid angiopathy—gradient echo sequence—disease—disorders.
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Introduction

Cerebral microbleeds (CMBs) are small perivascular hemosiderin depositions that can be seen in 5% of the healthy population.¹ CMBs can be detected on gradient echo sequence (GRE) or susceptibility-weighted imaging (SWI), characterized as small, round, hypointense foci, usually 2-5 mm and occasionally up to 10 mm in diameter.²

However, these sequences can often overestimate the exact diameter of a microbleed seen on light microscopy, a magnetic resonance imaging (MRI) artifact referred to as “blooming effect.”³ In a systematic review, Shoamanesh et al reported that CMBs seen on MRI pathologically correlate with hemosiderin deposition (49%), old hematomas (19%), intact erythrocytes (13%), vascular pseudocalcification (1%), and microaneurysm (1%).³ 15% of cases in this study had no associated specific pathology. Improvement in imaging modalities has allowed us to better appreciate the prevalence of CMBs in various cerebrovascular diseases. Up to 60% of patients with a history of ischemic stroke and hypertension have CMBs that are pathologically associated with focal hemosiderin deposition,⁴ mostly in deep gray matter and brainstem regions.^{2,5,6} CMBs are also associated with calcification of large vessels, white matter disease, and lacunar infarcts.² They can be markers of hypertensive end-organ damage, and have been associated with a number of diseases

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including cerebral amyloid angiopathy, atrial fibrillation, as well as ischemic and hemorrhagic strokes.⁷⁻¹¹ The rate of CMBs has been shown to increase by age and can be as high as 36% among people older than 80 years.^{12,13} Studies evaluating the prognostic value of CMBs have shown that elderly patients with greater than one CMB have a 6-fold risk of stroke-related death compared to subjects without CMB.¹⁴ While it remains unclear whether CMBs are merely a marker of disease, extrapolated data from studies such as PROMoting School-community-university Partnerships to Enhance Resilience have shown that both the presence and the location of microbleeds do correlate with loss in cognitive function and severity of ischemic insults.¹⁵⁻¹⁷ Therefore, further understanding of CMB pathological characteristics and clinical associates is crucial for primary and secondary prevention of cerebrovascular diseases. In this article, we review the uncommon etiologies of CMBs.

Uncommon Causes of Cerebral Microbleeds

Posterior Reversible Encephalopathy Syndrome (PRES)

PRES has been described to cause CMBs by three different mechanisms. Vasoconstriction as a response to increased blood pressure can cause hypoperfusion and cerebral ischemia, and subsequently cause CMBs formation. The second theory proposes that hypertension results in failure of autoregulation in the brain. Failed autoregulation causes hyperperfusion and forms CMBs. The third theory defines hypertension as a cause of imbalance between vasodilators (nitric oxide) and vasoconstrictors (thromboxane-A2 or endothelin).¹⁸ This imbalance leads to capillary bed injury and hyperpermeability. Studies on immunosuppressant medications (Cyclosporine/Tacrolimus) support the latter. It is believed that immunosuppressant medications cause blood-brain barrier impairment, which leads to cortical and subcortical vasogenic edema, and hemorrhage mostly in the parietooccipital region.¹⁹⁻²¹ PRES also increases the chance of intracerebral hemorrhage. In a study of 76 patients with PRES, 13 patients (17.1%) developed subarachnoid or parenchymal hemorrhages.²² McKinney et al²³ reported that more than half of their subjects diagnosed with PRES were found to have hemorrhage on SWI (64.5%), of which the majority (58%) showed evidence of CMBs. Hefzy and colleagues reported that the hemorrhage frequency was the highest among patients with PRES who had allogeneic bone marrow transplantation (46.6%) compared with solid-organ transplantation (11.7%), as well as patients on immunosuppression agents (22%). In this study, the rate of hemorrhage was independent of the blood pressure.²⁴

Infective Endocarditis

CMBs can be seen in more than half of patients with infective endocarditis.²⁵ They can be seen in any part of

the brain with variety in size and shape.² Klein and colleagues showed that CMBs related to infective endocarditis are predominantly located in cortical areas.²⁶ In another study, Okazaki and colleagues showed that the presence of CMBs in lobar territories is a strong predictor of impending intracerebral hemorrhage among patients with infective endocarditis.²⁷ They have considered vascular vulnerability as a possible mechanism of CMBs in patients with infective endocarditis.

Brain Radiation Therapy

Radiation can cause complications such as diffuse white matter injury, central nervous system atrophy, and vascular injury such as large arterial injury and telangiectasia.²⁸ The latter results in cerebral hemorrhage, including radiation-induced CMBs.²⁸ Cytotoxic and vasogenic edema can also cause endothelial damage and increased capillary permeability leading to CMBs.²⁹ Telangiectasia can be seen in up to 20% of pediatric patients who undergo radiation treatment.³⁰ In one study, the frequency of CMBs among patients who received radiation therapy was 47% with mean radiation latency of 33 months.³¹

Cocaine Abuse

Cocaine causes a sudden transient increase in blood pressure, resulting in rupture of leaky and weak vessels and subsequent CMBs. Intracerebral hemorrhage and ischemic stroke are frequent among cocaine users aged 65 years and older.³² A published study examining the progression of CMB burden on serial MRI studies in inner city young stroke patients concluded that patients who developed new microbleeds over time had a higher incidence of having a positive serum toxicology for cocaine compared to patients who did not develop new microbleeds (67% versus 13%).⁷ There are other mechanisms for cocaine-induced CMBs including cerebral arterial vasoconstriction, cocaine-induced vasculitis,³³ disruption of blood-brain barrier integrity and function, and neuroinflammation³⁴ (Fig 1).

Thrombotic Thrombocytopenic Purpura (TTP)

There are only a few case reports describing the development of CMBs among patients with TTP.³⁵⁻³⁷ Thrombotic thrombocytopenic purpura causes excessive platelet thrombi and multisystem vasculopathy due to deficiency of ADAMTS13. Associated with a von Willebrand factor (vWF) cleaving protease, this defect is thought to cause platelet aggregation and microvascular thrombosis.³⁸ Initial central nervous system involvement is near 50% in TTP, and ultimately 90% of patients

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