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Letter to Editor

# Antiplatelet in Cerebral White Matter Hyperintensities: Are we under-using it?

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## DEAR EDITOR,

Cerebral small vessel disease (CSVD) is a progressive, age-related disorder involving cerebral small arteries, arterioles, veins, and capillaries. It is characterized by typical radiological changes detected on magnetic resonance imaging (MRI), including white matter changes, lacunes, cerebral microbleeds (CMBs), microinfarcts, enlarged perivascular spaces, and brain atrophy.

Periventricular ischaemia or white matter changes represent chronic small vessel ischemia or demyelination. This imaging finding is common and appears as a smooth rim around the ventricles; it is not considered a true "cavitated" infarction but rather a rarefaction of the white matter (leukoaraiosis), and the use of antithrombotics in this context is controversial. This is because antithrombotics increase the risk of intracranial hemorrhage, particularly when CSVD burden is high (sarcastically, in these patients' case, the chance of lacunar infarct is also high). Thus, CSVD is a double-edged sword, and identification of an infarct amongst all the consequent imaging findings becomes of utmost importance for starting of antithrombotic therapy (a single antiplatelet lowered the relative risk of recurrent stroke by 22% compared to placebo).

Chronic stroke/lacunar infarcts are usually larger than three millimetres, show clear cavitation on T1 and T2 sequences of MRI, and have sharp, well-defined borders indicating structural damage, often irregular, angular, or cystic cavities with ex vacuo dilatation. T2 susceptibility-weighted imaging is advantageous for identifying microbleeds associated with small vessel disease and differentiating them from lacunar infarcts. T1-weighted imaging is crucial to differentiate between myelination changes (periventricular ischemia) and actual cystic cavities or tissue loss (chronic stroke), as old strokes will have cerebrospinal fluid -like low signal on T1. Thus, careful evaluation of the MRI is important for identifying these infarcts.

It is important to distinguish recent subcortical or lacunar infarctions from silent cerebral ischemia. Silent cerebral ischemia is often detected on neuroimaging, and careful history and examination should be completed to ensure there are no prior transient or current neurologic deficits that localize to the lesion.

But, due to a lack of eyewitnesses, the clinical history of the vascular event is frequently missing, and these patients typically have underlying dementia that makes them forget these events.

Despite the fear of initiating antiplatelet therapy in these patients due to the risk of intracerebral hemorrhage, the gradual progression of "silent" cerebral ischemia over time can have equally devastating consequences. As the burden of CSVD accumulates over time, the connections between different areas of the brain are weakened, leading to cognitive impairment and ultimately dementia (vascular disease is thought to contribute to up to 50% of all dementias). CSVD is also thought to worsen all other forms of dementia.

Cerebral small vessels are at high risk from the effects of hypertension given their immediate proximity to large arteries, and occlusion of a small vessel is likely to result in downstream infarction given the lack of overlapping perfusion. These small vessel strokes are often caused by microatheroma at the origin of perforating arteries, meaning platelet-dependent thrombus formation. Both LAA (large artery atherosclerosis) and SAO (small artery occlusion) contribute to cerebrovascular damage at different vascular levels, and there may be interaction between these types during disease progression, which can jointly exacerbate CSVD. Thus, SAO may be a precursor of LAA or a continuum, and the slightest evidence warrants antiplatelet administration to prevent further disease progression.

For patients with hypertension, arteriolar lesions caused by hypertension are high-risk factors for ischemic stroke and cerebral hemorrhage. Atherosclerosis often co-occurs with hypertension and further increases the risk of ischemic stroke. Therefore, even if a patient has deep or subtentorial microbleeds, the benefit of oral antiplatelet therapy outweighs the risk of complications.

In fact, the RESTART trial revealed antiplatelet therapy might have reduced the recurrence of intracerebral hemorrhage (for example by decreasing chances of haemorrhagic infarcts) [1]. Though antiplatelets caused only a modest increase in the risk of recurrent intracerebral hemorrhage, it seemed too small to exceed the established benefits of antiplatelet therapy for secondary prevention of major vascular events [1].

In fact, white matter hyperintensity (WMH) progression is significantly associated with the occurrence of lacunar infarcts within a certain time frame, and this progression may serve as an independent indicator of lacunar infarct occurrence [2]. Hence, WMH should be addressed at the early stages of evolution in clinical practice.

When it becomes difficult to identify hidden lacunar strokes in the white matter changes, we can utilize biomarkers like IL-6, PTX3, and sTWEAK (more characteristic of acute lacunar infarctions) and more research is required in this regard [3]. However, WMH progression is better tracked by structural MRI changes.

It is noted that increased mean diffusivity and reduced fraction anisotropy on diffusion tensor images (DTI) are observed in white matter changes and also in normal-appearing white matter in MRI distant from the lesion, indicating secondary tract degeneration [4]. Thus, DTI needs to be a regular part of vascular imaging in stroke evaluation.

**Thus, to Conclude:**

1. We should maintain a low threshold for initiating antithrombotic treatment if there is uncertainty about the possibility of an impending vascular event in the context of CVSD, while justifying our decision and balancing the risks of ischemic events (both intracranial and systemic) against potential future bleeding complications.
2. We need to search for lacunar strokes by utilizing all MRI sequences, differentiating them from other causes of WMHs such as microbleeds and periventricular changes. We need to employ less commonly used imaging modalities like diffusion tensor imaging (DTI) and biomarkers for deep lacunar infarcts to predict and manage unacceptable events in the future. Follow-up brain imaging may help in decision-making. Extensive future research is required in this regard, as Asian populations often exhibit a higher burden of WMHs and other CSVDs.

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**Permissions**: NIL

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