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Editorial

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Strengthening the link between periodic leg movements during sleep and cerebral small vessel disease

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Sleep disruptions, especially periodic leg movements during sleep (PLMS), have long been implicated in cardiovascular and cerebrovascular conditions, albeit with mixed evidence. The recent study by Veitch et al. [1] presents a compelling exploration of the association between PLMS and cerebral small vessel disease (CSVD), focusing on patients with first-ever stroke or transient ischemic attack (TIA). By leveraging a larger cohort and refining methodologies, the study not only reinforces the link between PLMS and markers of CSVD but also opens new avenues for clinical and research discourse.

The study stands out by addressing key limitations in prior research, including small sample sizes and inadequate control for confounding variables. With 86 participants, this research is the largest of its kind to investigate PLMS in the context of CSVD. The authors used validated imaging markers, including Fazekas and age-related white matter changes scale (ARWMC) scores, to measure white matter hyperintensities (WMHs) and other CSVD indicators. Importantly, the incorporation of age- and sex-specific PLMS index cutoffs represents a methodological innovation that ensures more precise classification of abnormal PLM activity.

Unlike earlier studies, the authors adjusted for a broad spectrum of vascular risk factors, such as hypertension, diabetes, and obstructive sleep apnea (OSA), enhancing the robustness of their findings. This rigorous approach allowed them to isolate the impact of PLMS on WMHs, distinguishing it from confounding influences like OSA. Their findings—PLMS independently predicted higher WMH burden—add a crucial piece to the puzzle of how nocturnal physiological disruptions contribute to cerebrovascular pathology.

The relationship between PLMS and CSVD has been a topic of ongoing debate. Previous studies [2, 3] suggested an association between elevated PLMS and CSVD markers, including WMHs, lacunar infarcts, and enlarged perivascular spaces (PVSs). However, these studies often lacked statistical adjustments for comorbidities, limiting the generalizability of their conclusions.

Conversely, studies like those by Manconi et al. [4] and Del Brutto et al. [5] reported no significant association, underscoring the need for larger, well-controlled analyses. Veitch et al.'s study [1] bridges this gap by demonstrating consistent associations between PLMS and WMHs, even after controlling for potential confounders. This consistency aligns with the hypothesis that PLMS, through mechanisms such as nighttime sympathetic overactivity and systemic inflammation, may exacerbate endothelial damage and cerebrovascular dysregulation.

One of the study's strengths lies in its discussion of potential mechanisms linking PLMS and CSVD. The authors highlight that PLMS may disrupt sleep architecture, particularly slow-wave sleep, which is critical for neurovascular health. By impairing glymphatic clearance and exacerbating oxidative stress, PLMS could contribute to WMH development. Alternatively, the reverse causality hypothesis—wherein existing CSVD disrupts neural circuits governing motor activity—cannot be excluded.

PLMS have been linked to significant autonomic fluctuations during sleep, including transient increases in heart rate [6, 7] and blood pressure (BP) [8, 9], contributing to nighttime sympathetic overactivity. For instance, reported elevated plasma nitric oxide levels in patients with PLMS suggest endothelial dysfunction mediated by recurrent cardiovascular stress [10]. Similarly, higher nocturnal BP has been reported in individuals with frequent PLMS [11], underscoring their potential role in promoting vascular strain and exacerbating cerebrovascular disease. These repeated hemodynamic changes may lead to long-term consequences, such as impaired vascular compliance and small vessel damage [12], highlighting the need for further investigation into their role in CSVD progression.

Cerebral hemodynamic changes associated with PLMS have also been studied using advanced imaging techniques such as near-infrared spectroscopy (NIRS). NIRS has provided insights into the relative changes in cerebral oxygenation and perfusion during PLMS. Studies with NIRS demonstrated that PLMS disrupt regional cerebral oxygenation and autoregulatory capacity, further linking these movements to vascular dysregulation [13–15]. This impaired autoregulation may exacerbate the burden of CSVD by contributing to endothelial damage, WMHs, and other

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markers of CSVD [16]. Future studies leveraging NIRS and other imaging modalities could provide a deeper understanding of the temporal relationship between PLMS, cerebrovascular dysfunction, and associated clinical outcomes.

Furthermore, medications such as antidepressants—particularly selective serotonin reuptake inhibitors—may play a significant role in exacerbating sleep-related motor disturbances, including PLMS. Antidepressants have been shown to increase chin muscle tone across all sleep stages [17], and their potential contribution to PLMS, as highlighted by a meta-analysis linking antidepressant use with increased PLMS [18], warrants further investigation. Future studies should focus on disentangling the effects of these medications from the underlying pathophysiological mechanisms driving PLMS. Additionally, the duration of the presence of PLMS may be a critical factor in their impact on cerebrovascular health, as Ferri et al. [19] emphasized the challenges in assessing this variable in studies exploring the relationship between PLMS, restless legs syndrome (RLS), and silent CSVD.

Despite these advances, the study leaves critical questions unanswered. For instance, it remains unclear whether treating PLMS can mitigate WMH progression or improve clinical outcomes in stroke/TIA patients. Additionally, the role of systemic inflammation as a mediator between PLMS and CSVD warrants further exploration, particularly through biomarkers or longitudinal studies [20].

The findings have significant implications for both clinicians and researchers. For clinicians, the study emphasizes the importance of assessing PLMS in stroke and TIA patients, not merely as a symptom but as a potential marker of cerebrovascular burden. Polysomnography, often reserved for diagnosing OSA, could be expanded to include PLMS evaluations in high-risk populations. For researchers, the study underscores the need for longitudinal designs to determine causality and explore interventional strategies. Could therapies targeting PLMS, such as dopaminergic agents or nonpharmacological interventions, reduce the risk of CSVD progression? Moreover, expanding the study to include diverse populations, such as stroke-free individuals or those with different CSVD phenotypes, could provide a more comprehensive understanding of this complex interplay.

Currently, there are no established clinical guidelines or indications for the treatment of PLMS, as their role in long-term health outcomes, including cerebrovascular disease, remains incompletely understood. While treatments such as anticonvulsants, dopaminergic agents, iron supplementation, and opioids are used to manage related conditions like RLS and periodic limb movement disorder [21], their utility in targeting isolated PLMS has not been systematically studied. The growing evidence linking PLMS to CSVD, including the findings by Veitch et al. [1], highlights the potential need for interventional trials. These studies could explore whether addressing PLMS, either through pharmacological or nonpharmacological approaches, might reduce the burden of CSVD or improve clinical outcomes in high-risk populations. However, until causality and the mechanisms of this association are better established, recommendations for routine treatment of PLMS remain premature.

Veitch et al.'s study [1] marks a significant step forward in elucidating the relationship between PLMS and CSVD. By addressing prior limitations and introducing methodological innovations, the research not only strengthens the evidence base but also highlights critical gaps for future exploration. As our understanding of the neurovascular impacts of sleep disruptions deepens, studies like this pave the way for integrated approaches to cerebrovascular health, linking sleep science with neurology and cardiovascular medicine.

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