Vascular gait disorders
What’s the matter with the white and gray matter?

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Small vessel disease is the commonest known brain disorder, and, among its hallmarks, difficulty walking is a major cause of increased dependency and reduced quality of life, as well as death. Although gait problems relate to the presence and extent of various neuroimaging markers of small vessel disease (e.g., white matter hyperintensities, lacunes, and cerebral microbleeds), the exact mechanisms involved, and any additional role of neurodegenerative pathology, are not well-understood. A key question is how small vessel disease affects white matter integrity and ultimately motor and cognitive function to result in clinical symptoms.

Modern imaging techniques can reveal unprecedented information about vascular and neurodegenerative pathologies and how they interact. In this issue of Neurology, Kim et al. contribute important new data in a study of 129 patients with subcortical vascular cognitive impairment, representing a spectrum of patients from mild cognitive impairment to vascular dementia. Cerebral small vessel disease (CSVD) severity was quantified using global and regional white matter hyperintensities (WMH) volume, lacunes, and microbleeds. Brain amyloid burden, as a putative marker of amyloid-related neurodegenerative pathology, was assessed using Pittsburgh compound B (PiB)–PET. The authors measured gait function using the pyramidal and extrapyramidal scale, including selected items from the Unified Parkinson’s Disease Rating Scale and the Guideline for Disability Evaluation. White matter integrity was assessed by tract-based spatial statistics of diffusion tensor imaging parameters, including fractional anisotropy (FA). Cortical thickness was measured using surface-based methods. Path analysis—a statistical approach used to estimate the magnitude and import of hypothesized causal connections between sets of variables for gait score—was performed using regional CSVD markers as predictors, FA and cortical thickness as mediators, and gait function score as the outcome of interest.

The authors found that periventricular WMH (PWMH) volume was associated with gait score, but not the other CSVD markers, or PiB binding. Gait score was correlated with FA (a measure of microstructural integrity of tracts) in the frontal and parietal white matter and bilateral corpus callosum, and with cortical thinning in the bilateral frontal and lateral temporo-parieto-occipital regions. Path analysis suggested that PWMH contributed to gait disturbances, mediated via mean FA or cortical thickness. The authors conclude that gait disturbances are related to gray and white matter changes in the frontal and parietal regions, which mediate the effects of PWMH.

This study confirms previous observations implicating PVWM and the corpus callosum in gait disorders: periventricular changes, including those occurring in normal-pressure hydrocephalus, are associated with gait impairment. In CSVD populations, this fits with the vulnerability of the periventricular white matter areas to hypoperfusion, and with their rich connectivity critical to walking function. The most novel aspect is in the use of path analysis to link this process to reduced cortical thickness in frontal and parietal regions, which adds another potential mechanism for the clinical picture observed in CSVD: traditionally, vascular gait disorders have been linked to subcortical but not cortical pathology. The findings are also noteworthy in not linking amyloid burden to gait, suggesting a prime role for vascular rather than Alzheimer pathology in gait abnormalities, at least in this cohort with prominent vascular pathology. These findings are in apparent contrast to other studies showing a relationship between amyloid and falls, highlighting the complex relationship among falls, cognition, and gait.

A limitation is the uncertainty about the causal direction of the relationship between white and gray matter pathology: mediation analysis is suggestive but does not offer proof. However, it seems most plausible that white matter tract disruption could cause disconnection and volume loss in connected cortical areas, a phenomenon recently demonstrated using serial imaging of incident lacunar infarcts.
Serial imaging in other larger representative CSVD cohorts, for example population-based studies, could yield similar insights. There are other limitations: the population studied was cognitively impaired, so may not generalize to other populations with SVD or those with cognitive impairment without SVD. Moreover, the semiquantitative gait measures used by the authors may not fully capture the range of performance afforded by continuous measures such as gait speed, stride length, or other quantitative approaches, such as gait mats or gait laboratory assessments. In patients with advanced disease, as studied here, this approach likely captures clinically meaningful observations, as in the Leukoaraiosis and Disability (LADIS) study of older people with white matter changes, though further validation of the measures used is warranted. Finally, deep brain structures with potential relevance to gait were not specifically examined.

What are the implications for clinical neurologists and for future research? The key role of white matter disease in gait disturbance emerges once again, so presumably measures to limit progression of this process are welcome. The use of statins and intensive blood pressure lowering show promise to reduce white matter disease progression, and it will be interesting to determine whether these or other interventions have specific effects on gait function in future trials. The incorporation of measures of white matter structural integrity and cortical thickness may be of considerable interest in future intervention trials, including small studies of new interventions, such as cognitive and physical rehabilitation or pharmacologic strategies.

The role of the cortical thinning found in this study may have relevance to other populations at risk of gait disorders: for example, in individuals with or at risk of neurodegenerative conditions such as Alzheimer or Parkinson disease. Further study in such populations will be an important next step. Meanwhile, this article clearly shows that careful and focused study of measures of vascular and neurodegenerative pathology can help elucidate common and important clinical syndromes, with promise to monitor, prevent, and, ultimately, treat them more effectively.

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**REFERENCES**