Can fall of blood pressure prevent falls in Parkinson disease?

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Idiopathic Parkinson disease (PD) is an α-synucleinopathy, one of several proteinopathies characterized by intracellular and extracellular accumulation of abnormal filament proteins.[1] Relentless progression of neuropathologic changes, consisting of α-synuclein-positive Lewy bodies and Lewy neurites, and widespread neuronal loss closely correlate with clinical worsening of motor and nonmotor PD symptoms. Typically, unilateral onset of tremor, rigidity, or bradykinesia, the cardinal motor features, is followed by contralateral spread of disease signs. The presence of midline problems, such as gait disorder and balance impairment, generally represents a more advanced phase of the disease, used as the central criteria in Hoehn & Yahr staging.

The emergence of postural problems is a milestone in the disease progression, with increased disability and a negative effect on quality of life. These problems also represent a therapeutic challenge because dopaminergic stimulation, the standard of PD motor symptom management, provides only limited benefit. The lack of improvement of the midline signs in response to dopaminergic medications suggests involvement of nondopaminergic pathways responsible for gait control or balance, broadening the concept of PD from nigrostriatal dopaminergic degeneration to a more widespread neurodegeneration.[1] The pathophysiology of postural impairment in PD is only emerging, but recent data support an important role of the cholinergic system, especially cholinergic neurons, in the pedunculopontine nucleus and their projections to the thalamus.[2] The degree of cholinergic denervation, detected by in vivo imaging using PET or by postmortem analysis, correlated with falls and other signs of postural impairment in PD and was independent of the degree of dopaminergic denervation.[3,4]

Successful modification of the natural course of PD remains the Holy Grail of the field. Similar to other neurodegenerative conditions, multiple preclinical and clinical studies have failed to produce slowing, stopping, or reversing of clinical progression.[5] These therapeutic approaches have been focused on prevention of cellular neurodegeneration based on theories of PD pathophysiology. However, the pathology of most common types of neurodegenerative disorders, such as Alzheimer disease and PD, is complicated by microvascular changes, which are common. This is also consistent with the fact that age is one of the most robust risk factors for both neurodegeneration and cerebrovascular changes. Vascular risk factors, most notably hypertension and diabetes mellitus, cause hyalinization of vessel walls leading to focal hypoperfusion and ischemia of cerebral white matter, detected by MRI as increased white matter signal or leukoaraiosis. Increased leukoaraiosis burden in patients with PD has been associated with a higher risk of cognitive decline and motor impairment, most notably axial problems.[6] Hypertension and diabetes, together with other vascular risk factors, are treatable with a plethora of effective therapies and treatment algorithms. Thus, convincing clinical evidence of consequences of modifiable vascular risk factors on both motor and nonmotor PD symptoms would underscore the need for active and aggressive management of these risk factors in patients with PD.

In this issue of *Neurology*®, Kotagal et al.[7] provide additional support for the hypothesis that an increased white matter disease burden due to cerebrovascular disease worsens the motor phenotype in patients with PD. However, rather than simply analyzing the extent of white matter changes as a final outcome, they first stratified their well-studied patients with PD based on their risk factors for vascular pathology using a simplified version of a 10-year Framingham General Cardiovascular Disease Risk Score. This allowed calculation of the 10-year likelihood of cardiovascular events and division of patients with PD into low and elevated risks groups, based on age, sex, smoking status, body mass index, systolic blood pressure, diabetes status, and use of antihypertensive medications. Patients with PD with an elevated risk for cardiovascular events had worse axial motor scores and a higher burden of frontal lobe white matter disease; however, the extent of frontal leukoaraiosis did not correlate with the total motor impairment as measured by the Movement Disorders Society–Unified Parkinson's Disease Rating Scale score, but instead correlated with impaired postural control. Systolic hypertension was the most significant contributing vascular risk factor to the overall extent of white matter disease.

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These results suggest that cerebrovascular disease, as reflected by the severity of vascular risk factors, may play a crucial role in the development or exacerbation of axial problems in PD that is out of proportion with the progression of nigrostriatal dopaminergic degeneration. However, a cross-sectional cohort study design at this point does not provide a definite answer to whether the actual accruement of axial symptoms correlates with the growing leukoaraiosis burden. Another important unanswered question is whether cerebrovascular pathology and neurodegeneration are completely independent processes.[8] α-Synuclein-related degeneration also disrupts autonomic regulation in PD, and blood pressure variability may be challenging in these patients. Symptomatic treatment of orthostatic hypotension may cause supine hypertension; nocturnal hypertension is common and closely correlates with the extent of white matter changes, suggesting that leukoaraiosis may be aggravated by circadian regulatory disturbances.[9]

This study involved 85 participants, included speech as an axial sign of PD, and excluded patients with large-vessel but not small-vessel strokes. Blood pressure was measured once and the use of antihypertensives was included as a risk factor. The results therefore must be considered preliminary. However, though we do not have definitive answers about the role of vascular changes in the progression of PD, it is prudent to consider very active management of existing vascular risk factors in patients with PD. Modifying risk factors should not substantially differ between patients with PD and other patients, with a notable exception of hypertension: orthostatic hypotension, common in PD and exacerbated by antihypertensives, itself contributes to the risk of falling. Thus, aggressive blood pressure management may be a double-edged sword: potentially lower white matter disease burden resulting in an improved axial control may be complicated by falls induced by iatrogenic hypotension. Prospective studies will be needed to determine the Goldilocks "just right" blood pressure values in patients with PD.

AUTHOR CONTRIBUTIONS

Peter Hedera: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision. Joseph Friedman: drafting/revising the manuscript.

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