Interaction effects between vascular factors, age-associated nigrostriatal dopaminergic losses and motor parkinsonism: a multisystem model of mobility impairments

N. Bohnen, MD, PhD
University of Michigan, Ann Arbor, MI, USA

Pure or non-Lewy body vascular parkinsonism (VP) can occur in at least two forms. First, the more rare and typically acute form of pure VP (primary VP or PVP) can manifest itself when a clear ischemic or hemorrhagic stroke occurs in the substantia nigra or nigrostriatal pathway that leads to a distinct presynaptic dopaminergic lesion (with or without post-synaptic dopamine receptor losses). Second, a more common form may occur when typically widespread extra-nigrostriatal white or gray matter vascular lesions associate with motor parkinsonism (secondary VP or SVP). Although there may not be a distinct focal nigrostriatal deficit in SVP, it is assumed that motor parkinsonism occurs when vascular lesions disrupt connectivity in widespread neural systems underlying bipedal stance and gait that include cortico-striatal-thalamo-cortical loops, interhemispheric fibers, striatothalamic-brainstem systems, and proper processing of multi-modal sensory information. The second type of VP develops more insidiously but it is debatable how primary the role of vascular lesions is in its etiopathogenesis. Aging appears to play a key role in the emergence of motor symptoms in this group of patients with more widespread cerebrovascular disease.

It is well known that the threshold for the emergence of motor symptoms in Lewy body parkinsonism (LBP) is at least 60% loss of dopaminergic nerve terminals in the posterior putamen. Normal aging is also associated with loss of nigrostriatal nerve terminals and can be as high as 8% loss per decade in adult life. Therefore, a septuagenarian may incur a loss of 40% or more of nigrostriatal nerve terminals, which is below but not far from the LBP motor threshold. Unlike the posterior-to-anterior (i.e., putaminal more than the caudate nucleus) and often asymmetric striatal denervation gradient in LBP, nigrostriatal dopaminergic losses of normal aging affect the striatum more diffusely and symmetrically.

Geriatric mobility problems are now being recognized as the result of deterioration of multiple physiological systems, including vascular or metabolic systems. In this conceptual model, a relatively isolated impairment of a single system may not manifest clinical impairments because of adaptive plasticity in remaining intact systems. Once multisystem impairments occur, the surviving components of these systems cannot adapt further and clinical mobility problems become manifest, often in nonlinear fashion as critical thresholds are exceeded. In this framework, increased brain vascular lesion burden in the presence of degraded striatal function due to age-associated nigrostriatal losses likely represents a critical interactive mechanism exceeding the threshold underlying motor parkinsonism in SVP. The comorbid presence of cerebrovascular disease and LBP would follow the same multisystem model of motor parkinsonism but in a more pronounced and explicit form due to significant lowering of the symptomatic motor threshold in the setting of an even more degraded striatal capacity and other neurodegenerations in LBP. This multisystem degeneration model would explain why SVP associates with a predominant postural instability and gait difficulties (PIGD) phenotype of motor parkinsonism. This model would explain also incremental motor effects of other conditions beyond pure vascular lesions in SVP, such as metabolic disorders like diabetes mellitus.