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Subtype definition of vascular parkinsonism

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We thank Dr. Levin for his interest in our work. Dr. Levin applies a traditional clinico-anatomic perspective to interpret our proposed criteria. In this respect, he points out that our criteria do not exclusively require that vascular lesions need to be located within specific topographic regions, such as the nigrostriatal and striato-thalamo-cortical pathways. At the same time he points out the often observed clinical scenario that patients with extensive and confluent vascular lesions on brain MRI scans may be fully asymptomatic motor-wise despite the fact these some of these lesions may be located in regions of critical motor circuitry. This dilemma shows that factors other than the geographic location of vascular lesions in the brain may play a role in the pathogenesis of vascular parkinsonism (VaP).

Post-mortem studies have shown that the presence of parkinsonian signs in elderly who do not have Lewy body pathology is best explained by the presence of brain vascular lesions and nigral dopaminergic cell loss [1, 2]. We recently showed that the presence of mild parkinsonian signs in elderly with vascular brain lesions was dependent on specific genetic determinants of dopamine metabolism, in particular polymorphisms of the catechol-O-methyl transferase (COMT) enzyme [3]. These *ex vivo* and *in vivo* observations emphasize an important interaction effect between the presence of cerebrovascular lesions and the functional integrity of the dopaminergic system as it relates to the presence of parkinsonian motor symptoms in elderly subjects in the absence of Parkinson's disease (PD). In other words, the combination of age-related declines and/or genetic changes in dopaminergic system functions and the presence of vascular lesions may be a more important determinant of parkinsonism rather than the strategic location of vascular lesions alone. This multi-system interaction model may provide an explanation for the clinical observation that extensive leucoaraiosis can be fully asymptomatic in some individuals.

Dr. Levin warns about over-diagnosis of VaP using our criteria. The threshold for the emergence of motor symptoms in PD is at least 50% loss of dopaminergic nerve terminals in

the posterior putamen [4]. Normal aging is also associated with loss of nigrostriatal nerve terminals and can be as high as 6–8% loss per decade in adult life [5, 6]. Therefore, a septuagenarian may incur a loss of 30–40% of nigrostriatal nerve terminals, which is below but not far from the motor threshold in PD. The dopamine-vascular interaction model would predict that the additional presence of vascular lesions may lower the symptomatic threshold for parkinsonian motor symptoms to occur in the absence of PD. We believe that the current model of VaP is biased toward diagnosis in patients at the more severe end of the spectrum and hence - as pointed out by Dr. Levin - may actually under-diagnose this important condition. Despite this, we agree that the proposed criteria need to be appropriately applied. For example, we have specified that for the mixed neurodegenerative/VaP sub-type a clinical presentation characterized by postural instability and gait difficulties that appear out of proportion for the expected natural history of PD or for the degree of non-axial motor impairments would support a symptomatic manifestation of cerebrovascular disease in this mixed neurodegenerative disorder-VaP subtype. This is based on a previous head-to-head comparison of clinical correlates of PET measures of nigrostriatal dopaminergic losses versus MRI measures of vascular lesions in PD [7].

Dr. Levin also questioned the validity of cerebrovascular gait disorder as a sign of VaP. We agree with Dr. Levin's opinion that the term "lower body parkinsonism" is misleading. We suggested to replace the term "lower body parkinsonism" with "cerebrovascular gait disorder" in 2006 [8]. The gait in VaP is characterized by a wide-based mixed ataxic-parkinsonian gait pattern and differs from the purely parkinsonian gait pattern in PD. Gait disturbances cannot be omitted when defining VaP as is has been reported to be the initial symptom in up to 90% of VaP patients [9]. We described this higher level gait disorder as an early and often prominent manifestation of VaP preceding typical distal limb bradykinesia motor symptoms that are defining for parkinsonism. This is a similar situation as seen in idiopathic PD where an isolated tremor (a non-bradykinetic motor symptom) or isolated gait disorder may be the first sign of this condition. We have called for further testing and validation of our proposed criteria using appropriate biomarkers in well-designed clinical studies. Comments like those of Dr. Levin are very useful to start a productive academic dialogue and achieve these important goals.

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