

## Editorial



# Cerebral Microbleeds and the Heterogeneity of Parkinson's Disease

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## OPEN ACCESS

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Parkinson's disease (PD) is the second most frequent neurodegenerative disease behind Alzheimer's disease (AD). The clinical manifestations of PD not only include cardinal motor symptoms such as bradykinesia, rigidity, and resting tremor but also nonmotor symptoms including depression, anxiety, constipation, dysautonomia, and dementia.<sup>1,2</sup> Consequently, a range of subtypes of PD with a wide spectrum of motor and nonmotor variables has been proposed and is awaiting validation by findings in genetics, neuroimaging, and clinico-pathological correlations. Neuroanatomically, PD is characterized by the accumulation of alpha-synuclein in brain as Lewy bodies and Lewy neurites, especially in the nigrostriatal dopaminergic system. However, while most clinico-pathological studies of PD have so far focused on cerebral synucleinopathy, there is now increasing recognition that the pathological spectrum of PD is more extensive and complicated. It includes tauopathy, amyloidopathy, vascular-origin pathology, and a range of neuroinflammatory processes, reflecting the clinical heterogeneity of PD.<sup>1</sup>

Cerebral microbleeds (CMBs) are radiologically defined as small and rounded hypointense lesions on T2\*-weighted gradient recalled echo (T2\*-GRE) imaging or susceptibility-weighted magnetic resonance imaging (MRI). CMBs have been established as being caused by the chronic microhemorrhagic product that is leaked from impaired small cerebral vessels and the neuroradiological distribution of CMBs is related to their histologic pathogenesis. Deep (basal ganglia and thalamus) and infratentorial (brainstem and cerebellar) CMBs are associated with hypertensive lipohyalinotic vasculopathy, while lobar (the frontal, temporal, parietal, occipital lobe, and periventricular area) CMBs are related to cerebrovascular amyloid depositions.<sup>2,3</sup> CMBs have previously been associated with various diseases including hypertension, ischemic stroke, spontaneous intracerebral hemorrhage, vascular cognitive impairment, cerebral amyloid angiopathy, and AD. However, few studies have investigated the relationship of CMBs with disease symptoms and subtypes of PD, and there have been substantial debates regarding whether CMBs impact the clinical features of patients with PD.

Several previous T2\*-GRE studies reported that patients with CMBs showed relatively more severe symptoms based on their cognitive performance and neuropsychiatric scores,<sup>2</sup> and the presence of strictly lobar CMBs was shown to be significantly related to PD dementia (PDD).<sup>3</sup> These results are in line with the findings of previous studies which showed that

patients with dementia with Lewy bodies have more lobar CMBs than patients with PDD or healthy controls.<sup>1</sup> In contrast, others have reported that the deep, lobar and infratentorial location of CMBs does not differ among patients with PDD, with PD-mild cognitive impairment, cognitively normal patients with PD, and healthy individuals.<sup>2</sup> Concerning the clinical subtype of PD, some investigators have reported that there were no differences in the frequencies of motor subtypes such as tremor-dominant, intermediate, and postural-instability gait disturbance (PIGD) between IPD with CMBs and without CMBs.<sup>4</sup> However, these prior studies were either limited by the presence of cognitively impaired patients with PD, or by their small sample size.

In this issue, Kim et al.<sup>5</sup> report that lobar CMBs, measured using 3-Tesla brain T2\*-GRE MRI, are more frequent in patients with the PI GD subtype than in healthy control with similar vascular risk factors, while lobar or other forms of CMBs are not significantly different from controls in patients with the tremor-dominant subtype and with the intermediate subtype. Their study is the largest investigation to date regarding the impact of CMBs on cognitively normal PD, with 205 non-demented patients with PD and 205 age-, sex-, and hypertension-matched healthy controls. This is the first report which statistically shows that the distribution of CMBs is a possible neuroimaging biomarker associated with the PI GD subtype of PD. The study by Kim et al.<sup>5</sup> has several limitations, such as their retrospective study design and their use of T2\*-GRE MRI, which can be inferior for the detection of CMBs compared to susceptibility-weighted brain MRI. Notwithstanding the above limitations, their findings demonstrate that the distribution of CMBs, which are thought to be the downstream neuroimaging markers of small vessel disease or cerebral amyloid angiopathy, differed in patients with different PD subtypes, and hence suggest a different pathogenic mechanism according to the clinical subtype of PD.

In conclusion, our knowledge of CMBs in patients with PD has improved substantially, and growing evidence suggests a link between CMBs and the heterogeneity of the pathogenesis of PD. Future studies will shed more light on the underlying factors that influence the development of CMBs in these disease processes, and will potentially provide the theoretical basis for tailoring individualized treatment for patients with PD.

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