

The Role of Cerebrovascular Disease in Parkinson's Disease Related Cognitive Impairment

Abstract

With the high prevalence rate of mild cognitive impairment (MCI) and dementia in Parkinson's disease (PD), there is an increasing need to establish biomarkers that could identify those at risk of dementia. Small vessel cerebrovascular disease (SVD), including white matter hyperintensities (WMH), lacunes, perivascular spaces (PVS), and microbleeds, has been associated with the motor functions and cognitive impairment in PD. This suggests that SVD could be one of the mechanisms underlying the pathophysiological alterations that occur in the course of PD. Despite its importance, there is a paucity of literature and a lack of consensus in findings on SVD in PD. Without a clear understanding of the interaction between SVD and PD, patient management and care could be compromised. As such, this review summarizes the findings from current literature of SVD in PD, highlighting the limitations that could drive the heterogeneity in results. We also examine the role of other factors, such as microinfarcts and genetics, in their associations with SVD and motor-cognition in PD. Lastly, we discuss the role of optimizing vascular risk factors and the role of antiplatelets in managing patients with concomitant SVD and PD. Consensus on the definition of what constitutes the individual markers of SVD is imperative to determine the method of standardized imaging strategies and for better care management for patients with concomitant SVD and PD.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that is typically characterized by its classical presentation of cardinal motor symptoms, including tremors, rigidity, bradykinesia, and postural instability [1]. However, non-motor symptoms, such as cognitive impairment and dementia, are increasingly recognized as a common feature of PD [2,3]. The prevalence of dementia in PD is between 20% and 30% and is associated with increased morbidity and mortality [4]. More significantly, it has been reported that up to 80% of patients with PD progress to mild cognitive impairment (MCI) and dementia (PDD) overtime [5]. Given the multitude of negative consequences associated with PD, it is imperative to establish biomarkers that could identify patients at risk of dementia and for subsequent patient management.

Cerebrovascular disease (CVD) has been demonstrated to be associated with cognitive impairment related to PD. Among the different subtypes of CVD, cerebral small vessel disease (SVD) is a term commonly used to describe all pathological processes that affect the perforating cerebral arterioles, capillaries, and venules resulting in atrophy in the cerebral white and deep gray matter [6-8]. Specifically, the ischaemic components of the pathological process of SVD, namely white matter hyperintensities (WMH), chronic lacunar infarcts, perivascular spaces (PVS), and microbleeds [6-9], have been implicated in the manifestations of motor and non-motor symptoms in PD [10,11]. One study has shown that brains of PD patients that lacked evidence of a specific neurodegenerative process



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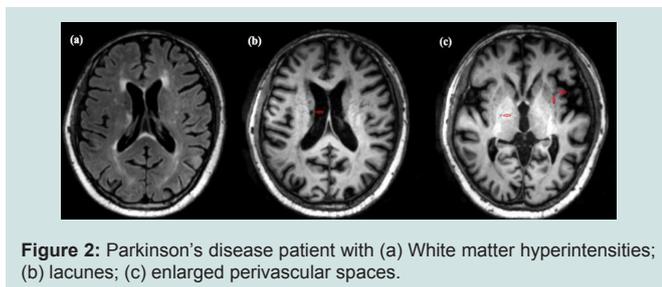
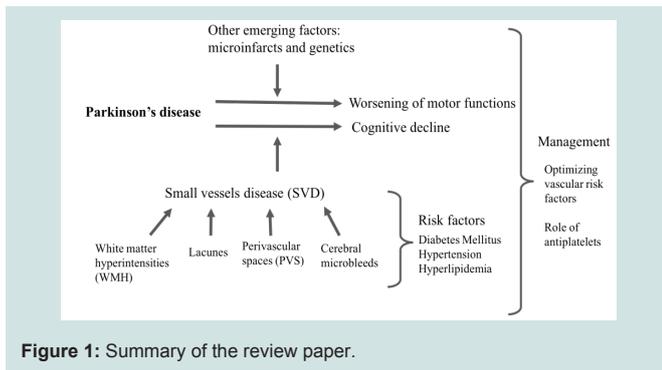
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demonstrated significantly more severe SVD-associated pathology compared to controls, which suggests that SVD may have a role in the pathophysiology of PD [12]. Another longitudinal study by Foo et al. demonstrated that progression of SVD was associated with significant cortical thinning in the frontoparietal regions with concomitant decline in memory, executive functions, and motor functions in PD patients [13]. This implies that the extent and progression of SVD could be associated with focal cerebral atrophy and domain-specific cognitive dysfunction. Furthermore, it could be possible that concomitant SVD in PD could alter the clinical-cognitive symptom presentation and treatment response of PD [14]. Additionally, Arena et al. showed that deep WMH burden was not only associated with worse performance on UPDRS, such as speech, facial expression, neck rigidity, postural stability, posture, and global spontaneous movements, but also worse response to L-Dopa [15]. This has important clinical relevance in patient management. Presence of WMH may impact response to L-dopa treatment and deep brain stimulation surgery (DBS), since evidence has established the correlations between response to L-Dopa and DBS [15]. Despite the consequence of SVD in PD, there is a paucity of literature investigating the impact of SVD as a whole in the pathophysiology of PD. Even within those who examined SVD in PD, the findings have been heterogeneous. This could be a result of the challenges to image and investigate small vessels *in vivo*, especially when imaging of small vessel disease are typically measured using subjective visual ratings instead of objective volumetric analysis; and the imprecise and inconsistent methods of classifying the lesions that could lead to under or over diagnosis of SVD [8]. In turn, it is imperative to establish the contributions of SVD to the underlying neuropathophysiology of PD in order to benefit subsequent patient management and treatment.

In this review, we provide the definition of the individual markers of SVD, suggest the importance of each in affecting the pathophysiology of PD, outline the current and emerging concepts of each SVD marker in relation to PD, and highlight the challenges faced in the present literature. We also examine other factors, such as microinfarcts and genetics, and their associations with SVD



and clinical-cognitive functions. We then conclude by suggesting potential management strategies (Figure 1).

White Matter Hyperintensities and PD

White matter hyperintensities (WMH) are abnormal areas of increased signal intensity on T2-weighted and fluid attenuated inversion recovery (FLAIR) images (Figure 2) [8]. Often, WMH are distributed in the periventricular and deep white matter of the cerebral hemispheres, in the basal ganglia and pons, and occasionally in the brainstem and cerebellar white matter [8].

The importance of WMH should not be undermined in PD: one systemic review emphasized the use of WMH as an indication of increased risk of stroke, dementia, and death [16] while another study has also showed associations between WMH accumulation and greater cognitive dysfunction and reduced gait performance overtime [17]. In addition, another paper has also shown that WMH could be a significant predictor of the conversion from MCI to dementia in PD patients [18]. It has also been shown in one study that WMH distribution was more widespread and extensive in PD-MCI compared to PD-NCI patients [19]. Taken together, the prominent role of WMH begets the need to use WMH as an intermediate marker in the diagnostic work-up of PD [16].

While WMH has been one of the more prominent feature of SVD that has been studied in the PD literature, there is still heterogeneity in findings - consensus as to whether WMH has a compounded effect on the PD pathology has yet to be fully elucidated. Previous studies have also shown the associations between WMH and motor symptoms [4,17]. Whereas de Laat et al. demonstrated the WMH, specifically in the frontoparietal cortices, were associated with increased risk of parkinsonian signs [4], Silbert et al. showed that periventricular WMH was associated with decreased gait performance overtime [17]. Although there is general consensus that WMH has an effect on the

presentation and severity of symptoms in PD, Dalaker et al. did not find similar results [20,21]. In their study, no significant differences were seen in whole brain volume and total WMH volume in PD patients compared to age-matched healthy controls, and associations between cognition and MRI variables did not survive after controlling for confounders [20,21]. While it could be argued that atrophy is not yet widespread in early stages of PD as seen by the results, it could be the corollary of the relatively small sample size that led to the results.

Besides the effects of WMH on motor symptoms in PD, negative associations between WMH and cognition of PD patients have been reported; PD patients with greater cognitive impairment had greater burden of WMH [3,21,22]. In addition, these studies also investigated the burden of WMH on the trajectory of cognitive decline and found that WMH contributed to the progression of dementia in PD patients [3,22,23]. Notably, evidence has demonstrated that PD patients with high burden of WMH showed poorer performance on frontal-lobe cognitive tasks compared to those with lower WMH; further investigations revealed that deep WMH was closely coupled with cortical thinning in the frontal cortices, which could have led to decline in executive functions [24]. In all, WMH could potentially have a compounded consequence on the pathogenesis of PD.

There are inherent challenges in determining the influence of WMH on the pathophysiology of PD. Firstly, there is a scarcity of longitudinal evidence in the WMH literature within PD, which hinders the interpretation of causality. Additionally, cross-sectional studies may also be less sensitive to subtle changes, which tend to be masked by the large interindividual variability in the brain size and structure. This warrants the need for more longitudinal studies in order to investigate the progression of WMH and its course on atrophy and clinical-cognitive outcomes. Secondly, few studies investigated regional WMH and concomitant grey matter atrophy in relation to clinical-cognitive outcomes. As Braak and Braak posited that atrophy is not widespread in early stages of PD, there could be localized atrophy that could be associated with localized WMH regions and in turn, affecting the domain-specific functions [25]. Lastly, the inherent challenge lies in the variability in the quantification of WMH. While some studies used validated semi-quantitative visual ratings, others used volumes; even within each, there are differing scales and methods to quantify WMH. This discrepancy creates mixed findings. Therefore, the current concepts of WMH in PD are limited and future studies should seek to address these limitations. As has been done in vascular dementia, a framework for quantifying and classifying CVD in the context of PD is timely.

Lacunes and PD

Lacunes are small cerebrospinal fluids- (CSF) containing cavities located in the deep grey matter or white matter [8]. To identify lacunes, the combination of the following image acquisitions such as FLAIR, magnetization prepared rapid-acquisition gradient echo (MPRAGE), and T2 are used [26]. Typically, lacunes have a hyperintense rim around the cavity on FLAIR images and hypointense foci on MPRAGE T1 images [6]. However, when present without a hyperintense rim in the basal ganglia and infratentorial regions on T2, they can be distinguished by their shape and size - they are defined as ovoid/spheroid cavities that are 3 mm to 15 mm (Figure 2) [6,8,26].

With evidence showing that striatal lacunar infarcts were three times more common than cortical infarction in pathologically confirmed PD, it could be postulated that lacunes are predominant stroke subtypes in PD [14,27]. Additionally, lacunes on MRI parallel a steeper rate of decline in psychomotor speed and executive functions, which suggests that lacunes play an important role in influencing the clinical-cognitive symptoms in PD. Despite its importance, the clinical significance of lacunes has received much lesser attention as compared to WMH.

Evidence has shown that Parkinsonian signs were found more frequently in lacunar than in territorial stroke patients: bradykinesia in 45% and 7%, rigidity in 13% and 7%, tremor in 6% and 7%, and gait disorder in 16% and 7%, respectively [28]. In agreement with this finding, it has also been shown that lacunar infarcts, particularly in the thalamus, were independently associated with an increased risk of mild parkinsonian signs, mainly due to the presence of bradykinesia [4].

While the clinical relevance of lacunes to motor symptoms is widely accepted, the degree to which cerebral lacunes affect cognition has been less clear [29]. The relative contribution of lacunes to cognitive functions has been contradictory. With uncertainty in previous cross-sectional studies, some showed a significant correlation between lacunes and cognitive symptoms [30,31] while others did not [32,33]. The few longitudinal studies have result in mixed findings [34-37]. Investigation of the associations between the presence of lacunes and cognitive dysfunction in the elderly population is paramount as it sheds light into the possible relationship they have in the PD population. Findings from the elderly population showed that cognitive performance was significantly poorer in elderly subjects with lacunes across cognitive domains such as memory, processing speed, motor functions, and executive functions compared to those without lacunes [38,39]. It has been posited that the mechanisms underlying the subcortical lacunes and executive dysfunction may be related to cortical hypometabolism: evidence from FDG-PET studies showed that lacunes are associated with frontal hypometabolism, particularly within the prefrontal cortex, which could explain the poorer executive functions [39,40]. Similar results were also seen in longitudinal studies [34,35]. Taken together, lacunes could contribute to impairment in different cognitive domains and identifying individuals with subclinical vascular brain changes could result in improved understanding of cognitive impairment in old age and potentially in PD [38].

The challenges in studying lacunes in PD patients include the definition of lacunes and the number of lacunes present to make considerable motor and cognitive impact. For the former, the terms lacunar infarcts and lacunes have been used interchangeably even though they are different; while lacunes refer to the abovementioned, lacunar infarcts should refer to a clinical stroke syndrome of lacunar type where the underlying lesion is an infarct on brain imaging [8]. The differentiation of these terms should be clear in order to specifically determine the vascular pathology that interacts with the neurodegenerative process of PD that results in motor and cognitive dysfunction. The latter is an issue as while dementia associated with multiple lacunes has been widely recognized, cognitive dysfunction resulting from one or few lacunes is often considered negligible [41].

This is an important issue that should be acknowledged based on the evidence that even a single lacune can produce cognitive deficits [42].

Perivascular Spaces and PD

Perivascular spaces (PVS), are fluid-filled spaces that are generally smaller than 3 mm in diameter, which surround the deep perforating arterioles as the arterioles pass through the deep grey and white matter (Figure 2) [8,43]. On MRI, these spaces are visible on either T2-weighted or T1 images as they have similar signal intensity similar to CSF [43]. As they follow the course of the vessel, they appear round in the basal ganglia and linear in the subcortical white matter of lateral parts of the lobes on axial images [43].

PVS have been postulated to have an important role in the brain's inflammatory and immunological response [41]. Rameirez et al. hypothesized the clearance pathways in explaining the essential role of PVS. Clearance of metabolic waste and fluid from the brain parenchyma may occur via various pathways, including degradation and clearance through the blood brain barrier, PVS, and CSF [44,45]. Collectively, these pathways maintain homeostasis within the brain. However, the contribution and importance of each pathway remains to be understood [41]. With disease, dysfunction of one or more of these pathways may result in further pathological compromise and further disrupting the removal of toxins and metabolic waste from the brain. As such, possibly, one of the pathological hallmark of compromised fluid and toxic clearance from the brain may be the enlargement of the PVS (ePVS), defined as dilated PVS with diameter equal to or more than 15 mm [46], which could represent a potential biomarker of clearance failure within the central nervous system [44]. Hence, ePVS could serve as a potential biomarker to neurodegenerative diseases, such as PD.

Enlarged PVS have been implicated with motor dysfunction as well as cognitive decline in PD [43,46]. While the exact pathological process leading to dilated PVS is still unknown, they have been associated with arteriolosclerosis, hypertension or other vascular risk factors, dementia, and reduced cognitive functions in elderly [46]. While it is still unclear whether ePVS should be recognized as normal or pathological ageing [47], reports from multiple case studies suggested that ePVS could contribute to observed atypical clinical features in patients who otherwise had clinical/imaging findings consistent with PD [48]. In one case study, it was reported that a patient with facial dystonia, chin tremor, and a postural and action-induced dystonic tremor with concomitant ePVS in the substantia nigra had partial response to levodopa dose, suggesting ePVS could also contribute to the postsynaptic changes as seen in this case [49]. In accordance with previous MRI studies, diffusion tensor imaging (DTI) studies, which examines water motion *in vivo*, showed correlations between changes in the corticospinal tracts and sensorimotor deficits and increased risk of dementia [50,51]. Additionally, findings from a previous study also demonstrated that increased basal ganglia/centrum semiovale ePVS is associated with worse non-verbal reasoning and typically, visuospatial cognitive ability [52].

Despite the promising results of ePVS, it is important to note that the etiology underlying the pathology of PD is probably multifactorial. As such, in order to demonstrate the causal relationship between ePVS and the clinical-cognitive symptoms in PD, further longitudinal

studies possibly with pathological correlations would be encouraged.

Cerebral Microbleeds and PD

Microbleeds are well defined small hypointense punctate on T2* gradient-recalled echo or susceptibility-weighted images that generally less than 10 mm in diameter [8,43]. Normally, they are located in the cortico-subcortical junction, and deep grey or white matter in the cerebral hemispheres, brainstem, and cerebellum [43].

With literature demonstrating that cerebral microbleeds are related to underlying cerebral small vessel diseases, increased risk of symptomatic intracerebral hemorrhage, incidence of cognitive impairment and dementia, it could be postulated that microbleeds contribute to the clinical manifestations and cognitive performance of PD patients [53]. In addition, it has been reported that cerebral microbleeds were found in 17.4% and 17.7% of PD patients in United Kingdom and Korea respectively [54,55]. Therefore, there is a growing need to regard microbleeds as a significant precursor to the motor and cognitive decline seen in PD.

Despite the importance of cerebral microbleeds in PD, there is a lack of literature and findings from these studies are also inconclusive. Cross-sectional studies have shown that microbleeds are not associated with motor symptoms in PD: frequencies of motor subtypes were similar in PD patients with microbleeds and those without; and the average Hoehn and Yahr did not differ based on the presence of microbleeds [54,55]. This suggests that the presence of microbleeds could have no associations with disease severity in PD. However, more studies with larger sample size and recruitment of early stage PD should be conducted in order to confirm the results.

Findings of microbleeds affecting cognition in PD were also mixed. On one hand, some cross-sectional studies found that microbleeds were associated with cognitive decline, typically in the executive function domain [56-60] others did not [54,55]. In addition, microbleeds were seen to occur more frequently in patients with PDD than in those with non-demented PD [61]. Furthermore, evidence has also shown that lobar microbleeds were also associated with regions of the brain associated with domain-specific cognitive decline [56]. Hence, microbleeds may contribute to an exacerbation of further cognitive decline in specific domains in PD patients.

More importantly, the presence of the number of microbleeds showed important relationship to cognition: some authors advocate the presence of 2 or more microbleeds in order to find an association with cognition [57] whereas others used 4 [62] or more [59] microbleeds as the benchmark. This inconsistency could generate conflicting results. Future studies should seek to clarify this issue. A longitudinal study is also necessary to clarify if the presence of microbleeds constitute an additive burden of ongoing cognitive dysfunction [61].

Other Factors Associated with SVD

Other factors, such as cerebral microinfarcts and genetics, which relates to SVD and affects motor-cognition symptoms in PD have not been fully explored. These are potential factors that if elucidated could have consequential impact on the management care of PD patients.

Cerebral microinfarcts are lesions that often result from small

vessel pathologies such as arteriolosclerosis and cerebral amyloid angiopathy (CAA). Typically, microinfarcts go undetected in clinical radiological studies relying on conventional structural imaging as they are very small lesions with approximately 0.2 mm in diameter [63]. Furthermore, thus far, the *ex-vivo* studies' examining microinfarcts have been cross-section and therefore, limits their ability to explore the incidence and consequence of microinfarcts [64-66]. Despite their limitations, these *ex-vivo* studies have postulated that the presence of numerous microinfarcts may be capable of causing clinical symptoms, specifically cognitive dysfunction, while accounting for other pathologies including macroinfarcts and lacunes [64-66]. However, it is important to note that the sample from these studies usually represent patients in the intermediate AD stage, which is not representative of the general population. In community studies, findings showed that cortical microinfarcts were significantly associated with episodic memory, semantic memory, and visual perception speed and not with subcortical microinfarcts [67]. In addition, the few studies investigating microinfarcts in Parkinsonism showed that the presence of multiple infarcts has been linked to gait impairment [68-70]. Taken together, there are promising results in relating microinfarcts to cognitive dysfunction as well as motor symptoms, however, there needs to be studies in larger longitudinal PD cohorts in order to confirm these results.

While there is some literature associating genetics with SVD, the exact pathogenesis is still uncertain. Results from one candidate gene study, which is an approach involving exploring genetic influence on complex trait by identifying candidate genes that might have a role in the etiology of the disease, showed that there were no associations between genes such as apolipoprotein E (ApoE) (e4+/-) [71]. However, this is in contrast with the established literature that the ApoE genotype relates to an increased risk of developing sporadic CAA, which could imply the underlying degenerative vascular changes similar to small vessels disease [72]. The variability in results suggests the need to study ApoE in a longitudinal large cohort. Moreover, novel genotyping methods have also showed promising results. One of the methods is the use of the genome-wide association study (GWAS), which measures and analyzes deoxyribonucleic acid (DNA) sequence variations from across the human genome in attempts to identify genetic risk factors for diseases and the biological underpinnings of disease susceptibility for developing prevention and treatment strategies [73]. One GWAS study has demonstrated that single nucleotide polymorphisms (SNPs) rs3744028 and rs1055129 contributed to cerebral WMH, however only about 4% to 8% of the overall mean WMH burden in the sample [74]. Although several SNPs have been identified, detailed information on the specific genes and functional variants should be investigated further to determine the exact role of the gene function in the underlying pathogenic mechanisms of SVD [75]. Other genetics of single gene disorders that cause cerebral SVD include CADASIL caused by mutations in the NOTCH3 gene on chromosome 19q12 and has been implicated in progressive cognitive decline [76,77]. Hence, these different genetic techniques have shown promising results in relating genetics to SVD. Future studies should look into the underlying pathogenesis of genetics of SVD in PD cohort. This could have important implications in clinical presentation and cognitive performance of PD patients and so influence the management of these patients.

Management

Therapeutic options in patients with concomitant SVD in PD are scarce. In this review, we evaluate a few management strategies, such as the role of optimizing vascular risk factors and the role of antiplatelets in cognition in PD, that have been reported to be useful in prevention of dementia and management of these patients.

Although the exact mechanisms of the individual markers of SVD differ, they have been associated with vascular risk factors, such as diabetes mellitus, hypertension, and hyperlipidemia, which have consequential implications on the cognitive status of patients with PD. As The Rotterdam study has reported that up to one-third of dementia cases could be prevented through optimal prevention and treatment of vascular risk factors, similar trend could also be projected onto patients with cognitive dysfunction in PD [78]. Community-based studies have consistently demonstrated the associations between WMH and hypertension [79]. It has also been reported that effective hypertension treatment was associated with lower risk of WMH; reduction in dementia cases were found in subjects treated for isolated systolic hypertension [80,81]. In addition, another study has also shown correlations that smaller lacunes were associated with diabetes mellitus whereas larger ones were associated with low-density lipoprotein (LDL) cholesterol suggesting that diabetes could be associated with fibrinoid necrosis and LDL cholesterol with microatheroma that have been implicated in the risk of lacunes [82]. One study has shown that by lowering the prevalence of diabetes by 25%, more than 200,000 dementia cases could potentially be prevented worldwide [83]. In the same respect, by managing diabetes in PD patients, cognitive impairment and dementia cases within PD could be reduced. Similarly, microbleeds have also showed correlations with systolic blood pressure and severe hypertension [84]. Taken together, managing potentially modifiable vascular risk factors could potentially lower the incidence of cognitive dysfunction in PD.

Antiplatelet drugs, such as aspirin and cilostazol, may also be beneficial to patients with SVD. Studies have demonstrated that vascular dementia and dementia patients on antiplatelet treatment were at lower risk of death [85]. Additionally, in a randomized clinical trial of low dose aspirin, it showed that aspirin played an important role in reducing the risk of myocardial infarction and stroke, and slowing the onset and progression of dementia [86]. Moreover, cilostazol has also been suggested to decrease beta-amyloid accumulation and protect beta-amyloid induced cognitive deficits [87]. Specifically, one study has shown that cilostazol seemed to be safer than aspirin in terms of the risk of hemorrhagic stroke in hypertensive patients with SVD [88]. However, the use of antiplatelet begets the problem of degree of benefit/risk ratio in patients with vascular dementia according to the risk of hemorrhage, which is increased by the presence of silent microhemorrhages on MRI frequently detected in the presence of ischemic white matter lesions and by gait disturbances and falls [89]. Despite so, due to the relatively low efficacy of available drugs to improve cognition in patients with SVD, which may lead to the development of dementia, antiplatelet drugs could be one of the key treatments to managing patients with SVD in PD and in minimizing the risk of dementia in these patients.

Conclusion

In conclusion, there is increasing evidence linking measures of SVD, such as WMH, lacunes, PVS, and microbleeds to motor and cognitive symptoms in PD. However, the lack of uniform criteria and standardized measurement techniques continue to hamper progress in research related to CVD and PD. As such, there is an urgent need to develop consensus criteria in order to ensure standardized imaging techniques to determine SVD and also for better patient management strategies to move this field forward.

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