Vascular Parkinsonism—A Revisit

Vascular parkinsonism (VaP) is a form of atypical parkinsonism accounting for 4.4–12% of all parkinsonism cases in clinical practice.[1] Historically, Critchley in 1929, described this syndrome of parkinsonism and coined the term Arteriosclerotic Parkinsonism.[2] Still, the concept of this syndrome is controversial and needs a more consistent and updated definition. It requires a revisit as several contradictory views are put forward in understanding and management of various aspects of VaP.

The recent clinical study by Pal *et al*.[3] has explored the determinants of the levodopa responsiveness in patients with VaP. Different clinical and radiological and levodopa response were studied in this retrospective study of 44 patients. The levodopa responsiveness was positively correlated with neuroimaging and opine to give levodopa trials to all the patients presenting with VaP.

Clinically the presentation of VaP is heterogeneous with different Parkinsonian signs and symptoms. As conceptualized, it is often not vascular, other aetiologies need to be investigated and considered which cause pseudo VaP. The systemic medical disorders like hypertension, diabetes, and lifestyle factors are known to increase the risk of cardiovascular diseases (CVD) and are often present as comorbid conditions in VaP.[4] However, in the study by Chen *et al*.,[5] the known cardiovascular risk factors were not predictive of the leukoaraiosis burden and the severity of motor dysfunction. The neuroimaging-reliant diagnosis of VaP is not appropriate as there are instances when extensive basal ganglia hyperintensities are found in normal or in asymptomatic patients.[6] However, it is also evident that lacunar infarcts in basal ganglia, substantia nigra, thalamus, external globus pallidus, and putamen, caudate, and internal capsule, can mimic features of parkinsonism.

Recently, in 2018, recommendations from an expert working group on an updated approach to the subtype definition of VaP. Three subtypes have been classified—1. Acute or Subacute 2. Insidious onset 3.[7,8] Mixed idiopathic Parkinson's disease or other neurodegenerative parkinsonism and CVD. The whole range of primary neurodegenerative parkinsonism due to alpha synucleinopathy, i.e., Parkinson's disease (PD), Diffuse Lewy body disease (DLB), Multile system atrophy (MSA), and proteinopathies such as PSP or CBS are the differential diagnosis of mixed subtype of VaP.[9,10]

Leukoaraiosis has variable clinical presentation and complex aetiopathogenesis. It is important to understand that leukoaraiosis is not always vascular in origin and other causes need to be investigated. Immune system plays an important role in degenerative disease. The other causes of small vessel disease include inflammatory and autoimmune pathology. Systemic Immune dyshomeostasis is hypothesized for accelerating the pathogenesis in neurodegenerative disorders like Alzheimer's disease.[11] The hereditary diseases CADASIL and CARASIL present with leukoaraiosis and can present with parkinsonism.[8] There is a need of redefining leukoaraiosis.

Treatment for VaP is challenging as available data on the efficacy of current treatment options are controversial. Presently, except for controlling vascular risk factors, there is currently no first-line treatment for patients with VaP.[10] The critical unmet need to improve the management of VaP, different therapeutic interventions have been used in clinical practice.

Levodopa is being commonly used in VaP on the basis of the similarity of symptoms with PD. It has been widely characterized as parkinsonism. Levodopa use in the treatment of VaP patients has remained a matter of debate, the different studies have shown variable responses. Zijlmans *et al*.[12] in a retrospective clinicopathological study confirmed that VaP patients with vascular lesions in or near the nigrostriatal pathway showed good response to levodopa regardless of their parkinsonism onset type (acute or insidious) or their dominant clinical features.

In review of literature on levodopa, responsiveness in disorders with parkinsonism stated that VP was responsive to levodopa in 20–40% of patients.[13] The recent meta-analysis reported that approximately 30% of VP subjects do respond to levodopa therapy despite the heterogeneity in diagnostic criteria used in studies. They have also found that the probability of responsiveness to levodopa for a VP subject is 0.018 times the probability of a PD subject, further explained as, for every 55 PD subjects that respond to levodopa, only one VP subject responds to it.[14] The management and future therapeutics of VaP are summarized in a systematic review which concluded that a small number of patients have well responded to levodopa therapy. Adjuvant therapy with vitamin D and rTMS may be promising. The study using rTMS showed clinical improvement as validated by the timed 10-m walk test and UPDRS part 3. In the recent review by for Cerebro spinal fluid (CSF), drainage to treat patients with VaP has shown positive results while in systematic review only one study has shown the effect of lumber puncture.[14] It is mandatory to have a clear definition of VaP for conducting the randomized placebo-controlled clinical trials of available therapeutic interventions. At present, there is insufficient evidence to give recommendations for treatment for VaP patients.

The present updated diagnostic approach to subtype definition of VaP is helpful in the facilitation of future research and better clinical definition and possible management. As the boundaries of VaP have been poorly understood and defined, we need to explore the pathology and validated biomarkers to confirm the underlying nature and relevance of leukoaraiosis. The improvement in the definition of clinical syndrome of

VaP can be proposed depending on the understanding and the availability of the validated biomarkers in the future to guide the management.

Meena Gupta

Director Neurolohy, Paras Hospital, Gurugram, Haryana, India

Address for correspondence: Prof. Meena Gupta, MD, DM, Director Neurolohy, Paras Hospital, Gurugram - 124 001, Haryana, India.
E-mail: drmeenagupta@gmail.com

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