Vascular Parkinsonism: A Review on Management updates

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Abstract

"Vascular parkinsonism (VP)" is a condition which presents with the clinical features of parkinsonism that are presumably caused by cerebrovascular disease. It is classically described as symmetrical lower-body parkinsonism with gait unsteadiness and absence of tremors and is usually associated with pyramidal signs. Treatment for VP remains challenging as available data on the efficacy of current treatment options are contentious. VP is generally considered to be poorly responsive to levodopa, the most effective of the current treatment modalities for parkinsonism. However, there is evidence that some patients benefit from therapy with levodopa. This article reviews the place of levodopa in the treatment of VP.

Keywords: Atypical parkinsonism, response to levodopa, vascular parkinsonism

Introduction

What is vascular parkinsonism?

Parkinsonism is a hypokinetic movement disorder characterized by akinesia/bradykinesia, resting tremors, and extrapyramidal rigidity. "Vascular parkinsonism (VP)" is a form of atypical parkinsonism, in which the parkinsonian features are of vascular origin in contrast to typical Parkinson's disease (PD) which is neurodegenerative in etiology. It accounts for 4.4%–12% of all cases of parkinsonism.[1]

What are the clinical features of vascular parkinsonism?

VP is classically described as an entity characterized by predominant lower-body parkinsonism, postural instability, shuffling or freezing gait, absence of rest tremor, absent or poor response to dopamine, and presence of corticospinal tract signs.[2] Gait abnormalities predominate with VP –the base (distance between the feet) is not always as narrow in lower-body parkinsonism as it is in idiopathic PD and posture is unstable, with postural responses to maintain balance being poor. The occurrences of dementia, pseudobulbar palsy, and incontinence are other recognized features.

Clinical features that resemble the pattern seen in idiopathic PD have also been described as being attributable to lacunar infarcts in the basal ganglia. Although the parkinsonism is often only clinically evident on the contralateral side of the body to the brain lesion, ipsilateral clinical features have also been reported.

Diagnosis is supported by the history of prior stroke and vascular risk factors, namely hypertension, diabetes mellitus, hypercholesterolemia, or carotid stenosis.

Are there diagnostic criteria for vascular parkinsonism?

Zijlmans *et al*.[3] proposed possible criteria for the clinical diagnosis of VP and they are as follows:

a. Parkinsonism, defined as bradykinesia, and at least one of the following: rest tremor, rigidity, or postural instability
b. Cerebrovascular disease, defined as evidence of relevant cerebrovascular disease by brain imaging or the presence of focal signs or symptoms consistent with stroke
c. A relationship between (a) and (b): acute or delayed progressive onset of parkinsonism ≤1 year after stroke with evidence of infarcts on imaging in or near areas that increase the basal ganglion motor output or decrease the thalamocortical drive directly (i.e., basal ganglia lacunae), or an insidious onset of parkinsonism with extensive subcortical white matter lesions, bilateral symptoms at the onset, and the presence of early shuffling gait or early cognitive dysfunction.[4]

Based on the above criteria, two forms of VP are suggested: one with acute onset, related to basal ganglia infarcts, and another one with insidious progression, possibly associated with more diffuse subcortical white matter ischemia.[5,6]

Winikates and Jankovic have also suggested a two-step process[7] in identifying VP. Step 1 involves identifying the parkinsonian syndrome and requires the presence of at least two of the four cardinal signs of parkinsonism (tremor at rest, bradykinesia, rigidity, and loss of postural reflexes). Step 2 involves assigning a vascular score. Two points or more are essential to diagnose VP. The points are assigned as follows:

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a. Two points: Pathologically or angiographically proven diffuse vascular disease
b. One point: Onset of parkinsonism within 1 month of clinical stroke
c. One point: History of two or more strokes
d. One point: Neuroimaging evidence of vascular disease in two or more vascular territories
e. One point: History of two or more risk factors for stroke (hypertension, smoking, diabetes mellitus, hyperlipidemia, presence of heart disease associated with stroke [coronary artery disease, atrial fibrillation, congestive heart failure, valvular heart disease, mitral valve prolapse, and other arrhythmias], family history of stroke, history of gout, and peripheral vascular disease).

What are the imaging findings in vascular parkinsonism?

The literature in neuroimaging in VP is scarce. Computer tomography, magnetic resonance imaging (MRI), and cerebral angiography can be performed to delineate lesions. Even though imaging findings in VP are nonspecific and poorly defined, there are certain findings that would suggest VP over idiopathic PD. Ischemic changes in multiple vascular territories, periventricular white matter ischemia, global subcortical ischemic white matter involvement, ischemia in the basal ganglia and brain stem, and cortical atrophy are significant and more commonly seen in patients with VP[7]

Are there caveats of diagnosing vascular parkinsonism?

The diagnostic criteria for VP as suggested by Zijlmans *et al*., which is widely used, were based on a study that compared the brains of 17 patients with suspected VP to those of 10 age-matched controls who had hypertension and other vascular risk factors in life, but no evidence of parkinsonism. The study observed macroscopically visible lacunar infarcts or lacunae caused by enlarged perivascular spaces which were seen in the caudate, putamen, globus pallidus, and thalamus in 11 of the parkinsonian brains, compared to only one control brain. It was also noted that the severity of microscopic small-vessel disease pathology was substantially greater in the VP cohort compared to controls.

However, there are several commonitions,[8] worth highlighting about these observations which include the following: (1) severity of microscopic small-vessel disease did not differ between frontal, temporal, parietal, occipital, and striatal regions and suggest lack of regional specificity; (2) 12/17 patients had nigral cell loss suggestive of underlying neurodegenerative parkinsonism; and (3) proposed VP criteria could be acute, delayed, or insidious in onset, with unilateral or bilateral parkinsonism, with or without gait impairment, and with focal or diffuse lesions, located anywhere in the parenchyma. Such imprecise clinical and neuroimaging criteria have contributed to less defined diagnostic boundaries, resulting in misrepresentation of other entities as VP.

Furthermore, diagnosing parkinsonism (an essential criterion to diagnose VP) requires the presence of true bradykinesia, which is defined as a progressive decrement in the speed and amplitude of movement over repetitive tasks, not mere slowness of movement. This is often overlooked and misdiagnosed with several other conditions affecting corticospinal tracts which clinically present similarly.

The clinical and imaging correlation in VP has been challenged. A case–control study[9] which compared patients with enlarged striatal perivascular spaces on MRI (n = 27) with age-, sex-, and examination year-matched controls (n = 52) with minimal or no enlarged striatal perivascular spaces demonstrated similar rates of clinical parkinsonism (19% vs. 17%; odds ratio, 1.09 [95% confidence interval (CI), 0.28–4.16]). Thus, the author concluded that "scepticism is called for when attributing clinical symptoms (e.g., parkinsonism) to MRI findings described with VP."

It is also worth highlighting that parkinsonism rarely follows stroke. In a study of 220 consecutive brain autopsies of patients with cerebral infarcts, only five had a clinical history of parkinsonian symptoms.[10] Moreover, silent infarcts in the basal ganglia were identified in 40.2% of 219 consecutive adults "requesting medical evaluation for possible cerebrovascular diseases."[11]

Is there a proposed mechanism of vascular parkinsonism?

Ischemic basal ganglia or subcortical white matter lesions disrupt interconnecting fiber tracts between the basal ganglia, thalamus, and motor cortex leading to disruption of sensory-motor integration as well as descending reticular pathways to major centers of the brain stem.

Infarctions affecting basal ganglia lacunae, including the thalamus, external globus pallidus, and putamen, that extend into the caudate and internal capsule, can mimic features of idiopathic PD.[12] The second form with subcortical white matter lesions often produces clinical features resembling the classical lower body parkinsonism and has a more relentless rather than step-wise progression.[8]

How do you treat vascular parkinsonism?

There are several treatment options for parkinsonism including dopamine substitutes such as levodopa, dopamine agonists such as ropinirole, monoamine oxidase B inhibitors such as selegiline, and catechol-O-methyltransferase inhibitors such as entacapone, anticholinergics, and amantadine. Of all, levodopa, or syndopa, which is a combined preparation of levodopa with carbidopa, remains the most effective and widely used drug treatment in PD, possibly owing to the major neuropathological finding of degeneration of dopaminergic neurons in substantia nigra pars compacta leading to dopamine depletion in the striatum in PD.

However, the effectiveness of levodopa in VP is still an area under discussion. In a recent meta-analysis[13] which included 14 cross-sectional studies, two case-control studies, two cohort studies, and two clinicopathological studies (17 studies were used in the analysis, supplementary file), it was concluded that the calculated event rate of levodopa response (odds ratio for positive response to levodopa) in VP patients was

0.304 (95% CI of 0.230–0.388), thus having a low response rate to levodopa. The analysis revealed that approximately only 30% of VP patients respond to levodopa therapy.

The overall odds ratio for good response to levodopa in VP with lesion in the nigrostriatal pathway versus no lesion in the nigrostriatal pathway was 15.15 (95% CI: 5.2–44.17), concluding a good response to levodopa therapy in VP with nigrostriatal lesion. Out of the studies included, three studies with sample sizes of 20, 76, and 42 demonstrated that nigrostriatal dopaminergic denervation as evidenced by an abnormal fluoropropyl-2b-carbomethoxy-3b-(4-iodophenyl)-tropane single-photon emission computer tomography (SPECT) predicted a favorable response to levodopa.

Zijlmans' criteria[3] were used for the diagnosis of VP in ten studies, while Winikates'criteria[7] were used for five studies in the above meta-analysis. The rest did not have clear definitions of VP.

There are several draw backs of the above study. Definitions of VP used in the study are less well defined as elaborated above. It is important to note that the evidence retrieved came from observational studies and not from prospective and controlled studies. Thus, potential bias and inaccurate conclusions are possible concerning the efficacy of treatment. Most of the studies retrieved had a small sample size which could also imply bias. The analysis of dose–response relationship was not done in this meta-analysis, and therefore, the study does not assess whether the dosage had any influence on clinical response.

Some recent studies which have shown positive levodopa response in a subset of patients are highlighted here. L-dopa response in 20 parkinsonian patients who had CT evidence of basal ganglia lacunae was analyzed in a study, in which all but one out of 17 treated patients were L-dopa responders.[14] Mark *et al*. presented that a patient with a history of resting and postural tremor, rigidity, and cerebrovascular disease had improvement on L-dopa; autopsy showed cerebrovascular disease and no Lewy bodies.[15] A study performed by Zijlmans *et al*.[16] in 17 patients with VP demonstrated that L-dopa treatment (mean dose 450 mg/day, range 100–1000 mg/day) induced an excellent response in three patients, a good response in nine patients, and a moderate improvement in two patients during the 1st year, while three patients showed no response to L-dopa doses of 300–400 mg/day [Table 1].

A sufficient response to levodopa in this study could not be predicted by the type of disease onset (acute or insidious) or by the localization (upper and lower limbs and uni- or bilateral) or any of the dominant clinical features (tremor, rigidity, akinesia, and gait abnormality). It was also observed that this positive response was related to the presence of lesions in or near the nigrostriatal pathway, that is, macroscopically visible lacunar infarcts or lacunae caused by enlarged perivascular spaces in the putamen, caudate nucleus, and globus pallidus, or microscopic substantia nigra cell loss. This result was also demonstrated in the above meta-analysis which included this study.

A positive response in VP patients has been demonstrated in the aforesaid study by the presence of a remaining pool of striatal dopaminergic nerve terminals in a dysfunctional nigrostriatal pathway that remains adequate to convert exogenous L-dopa into dopamine and thus to restore the intrinsic dopaminergic drive. The absence of an L-dopa response in other patients with a nigrostriatal lesion may be because of the increase of basal ganglia output by L-dopa which was unable to compensate for the dysfunctional thalamocortical drive.[16]

There is a dearth of literature on the appropriate dosage of levodopa in VP. Due to the high frequency of cognitive and behavioral problems in this population, they do not tolerate antiparkinsonian agents as well as patients with PD. Clinicians should bear in mind that there is a risk of worsening of confusion, agitation, and even postural instability.[18]

Increased doses of levodopa (50% extra), albeit with apparent clinical benefit in bradykinesia and rigidity, do not necessarily translate into an equivalent benefit in gait profile. Nondopaminergic networks may be differently

Table 1: Studies demonstrating dose-response relationship

Study	Number of patients in the study	Dose of L-dopa	Measure of outcome	Outcome
Zijlmans *et al*.[16]	17	Mean dose 450 mg/day for 1 year	QSBBND	Number of responders/nonresponders
			Excellent (70%-100% improvement of motor symptoms)	3
			Good (50%-70% improvement)	9
			Moderate (25%-50%)	2
			Absent (<25%)	3
Gago *et al*.[17]	13	150% of L-dopa morning dose (L-dopa challenge)	MDS-UPDRS-III	+12%
			Rigidity	+25%
			Gait velocity	+9.9%/+8.3%*
			Stride length	+8.3%/+5.9%*
			Foot-flat	−1.5%/−1.3%*
			Pushing	+6.3%/+3.8%*
			Peak angle velocity	+5.1%/+4.1%*

*Statistically significant median change % in the left/right foot. QSBBND=Queen Square Brain Bank for Neurological Disorders

affected by vascular pathology and therefore be less responsive to dopamine. Gait can be a complementary tool in the individualized decision of levodopa dose in VP. Gago *et al*.[17] demonstrated improvements in various aspects of gait including gait velocity, stride length, pushing, and peak angle velocity, following a supramaximal dose ≥150% of the morning dose.

Conclusion

The above observations concluded that patients with VP whose clinical features mimic PD and patients with imaging evidence of nigrostriatal lesions rather than subcortical white matter lesions tend to benefit more by treatment with levodopa. The available data showed that no clinical or imaging evidence can predict the levodopa response accurately. However, functional imaging demonstrating dopamine-transporter deficiency measured with SPECT predicts a much better response to levodopa therapy.

The current evidence, therefore, suggests that pure dopa-responsive VP is due to ischemic or hemorrhagic lesions in the substantia nigra, globus pallidus pars externa, thalamic ventral lateral nuclei, or nigrostriatal pathway, leading to presynaptic dopamine transporter deficiency as measured by SPECT.

The adequate dose of levodopa for a favorable clinical outcome has not yet been defined, with only one study in literature suggesting a dose of 450 mg/day. Improvement of motor symptoms and improvement of gait profile can be used as tools for measuring the clinical outcome of levodopa therapy. Worsening of confusion, agitation, and postural instability may limit increments of drug doses.

In clinical practice, all patients with clinically suspected VP, particularly those with lesions in or close to the nigrostriatal and other dopaminergic pathways evidenced by MRI, irrespective of the disease onset or dominant clinical features, should receive a trial with L-dopa in adequate dosage >450 mg/day, at least 450 mg/day, for a sufficiently long period of time, at least 1 year, before concluding an absence of response.

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Conflicts of interest

There are no conflicts of interest.

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