Review

The place of dopamine substitution therapy in vascular parkinsonism

T B Udagedara[1], **I K Gooneratne**[2]

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Introduction

What is vascular parkinsonism?

Parkinsonism is a hypokinetic movement disorder characterized by akinesia/ bradykinesia, resting tremors and extra-pyramidal rigidity. "Vascular parkinsonism (VP)" is a form of atypical parkinsonism in which the parkinsonian features are of vascular cause rather than a neuro-degenerative process as in typical "Parkinson's disease(PD)". It accounts for 4.4-12% of all cases of Parkinsonism[1].

What are the clinical features of VP?

VP, is classically described as having: predominantly lower body parkinsonism, postural instability, shuffling or freezing gait, absence of rest tremor, absent or poor response to dopamine substitution therapy and presence of cortico-spinal tract signs[2]. Occurrence of dementia, pseudobulbar palsy and incontinence has also been described. Diagnosis is supported by history of prior stroke, and vascular risk factors namely hypertension, diabetes mellitus, hypercholesterolaemia, or carotid stenosis.

Are there diagnostic criteria for VP?

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 (ie:- basal ganglia lacunae), or an insidious onset of parkinsonism with extensive sub-cortical white matter lesions, bilateral symptoms at the onset and the presence of early shuffling gait or early cognitive dysfunction[4].

Thus two forms of VP may be suggested: one with acute onset, related to basal ganglia infarcts, and another one with insidious progression, possibly associated with more diffuse subcortical white matter ischaemia[5,6].

Is there a proposed mechanism of VP?

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

Infarctions affecting basal ganglia lacunae, including the thalamus, external globus pallidus (GPe) and putamen, that extend into the caudate and internal capsule, can mimic features of idiopathic PD[7]. 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 stepwise progression[8].

How do you treat VP?

There are several treatment options for parkinsonism including dopamine substitutes like levodopa, dopamine agonists like ropinirole, monoamine oxidase B inhibitors like selegiline, COMT inhibiters like entacapone, anticholinergics and amantadine. Of all, levodopa, (sinemet, syndopa), which is a combined preparation of levodopa with carbidopa remain the most effective and widely used drug treatment in PD possibly owing to the major neuropathologic 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. Overall, only a third to half of patients with VP improve with conventional dopaminergic therapy. Patients with vascular lesions in or close to the nigrostriatal pathway and rare cases with abnormal DAT SPECT imaging are more likely to improve with levodopa[1].

[1] *Teaching Hospital, Kegalle,* [2]*Institute of Neurology, Colombo, Sri Lanka.*
Correspondence: TB Udagedara E-mail: thiliniudagedara@gmail.com

According to Demikiran et.al; only 38% of VP patients will satisfactorily respond to levodopa treatment[9]. Another study found only 24.6% of the patients with VP treated with levodopa responded compared with 73.6% of patients with PD (P<.00001). The predominant neuroimaging finding in the VP group was diffuse areas of increased signal intensity in the subcortical white matter on T2-weighted MRI scans and the common clinical features were lower body parkinsonism, gait disorder and postural instability[10].

Although it is classically accepted that VP will not or only poorly respond to levodopa some recent studies have shown positive levodopa response in a subset of patients. L-dopa response in 20 parkinsonian patients who had CT evidence of basal ganglia lacunes was analyzed in a study, in which all but one out of 17 treated patients were L-dopa responders[11]. Mark et. al. reported 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[12]. A study performed by Zijlmans et al.[13] in seventeen older patients with VP, documented 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, and a moderate improvement in two patients during the first year, while three patients showed no response to L-dopa doses of 300-400 mg/day. 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, lower limbs, uni- or bi-lateral), 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[13].

A positive response in VP patients has been explained in this 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 a L-dopa response in other patients with a nigrostriatal lesion may be because the increase of basal ganglia output by L-dopa was unable to compensate for the dysfunctional thalamocortical drive[13].

There is 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 anti-parkinsonian 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[14].

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. Non-dopaminergic networks may be differently 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[15].

Conclusion

These observations conclude that patients with VP whose clinical features mimic PD, and patients with imaging evidence of basal ganglia infarcts rather that WML tend to benefit more by treatment with levodopa. However the available data show that no clinical or imaging evidence can predict the levodopa response accurately.

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 for a sufficiently long period of time, at least 3-6 months, before concluding an absence of response.

Conflicts of interest

None.

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