Vascular parkinsonism—an important cause of parkinsonism in older people

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Abstract

Parkinsonism due to cerebrovascular disease (vascular parkinsonism, VP) is a distinct clinicopathological entity. It accounts for 4.4–12% of all cases of parkinsonism. Since there are no specific diagnostic criteria, true incidence and prevalence rates of VP are not known. Typically, parkinsonism in slow-onset VP tends to be bilaterally symmetrical, affecting the lower limbs more than the upper limbs (‘lower-body parkinsonism’), and resting tremor is usually absent. Commonly noted lesions on brain imaging in VP are lacunes, white matter changes and, rarely, territorial infarcts. As coincidental vascular lesions in idiopathic Parkinson’s disease (PD) are common, the mere presence of these lesions on brain imaging is not diagnostic of VP. Pathological evidence of a vascular disease in the absence of typical PD lesions (e.g. Lewy bodies) is the diagnostic ‘gold standard’. VP is generally considered to be poorly or non-responsive to L-dopa therapy. However, recent studies have shown a beneficial effect of L-dopa in a subset of patients. Despite great advances in overall understanding of the disease, there are several gaps in our knowledge.

Keywords: vascular parkinsonism, older people, Parkinson’s disease, elderly

Introduction

Parkinsonism can be caused by disorders other than idiopathic Parkinson’s disease (PD). Cerebrovascular disorders and drugs are the most important causes of secondary parkinsonism. Vascular parkinsonism (VP), a disorder caused by cerebrovascular disease, has gone through phases of introduction, rejection and then re-establishment.

In 1929, Critchley described a syndrome of ‘arteriosclerotic parkinsonism’, symptoms of which included rigidity, masked face and short-stepped gait in an elderly hypertensive person [1]. He suggested that older patients with arteriosclerosis and parkinsonism presented with most features of PD except that resting tremor was usually absent, the course of the disease was rapid and legs were more frequently involved than arms. He proposed that multiple vascular lesions in the basal ganglia were presumably responsible for producing the cardinal neurological symptoms of arteriosclerotic parkinsonism.

This concept was rejected by Schwab and England [2] and Parkes et al. [3]. It was argued that the evidence of vascular changes seen in some patients with PD could be an incidental finding. Critchley revised his original idea of arteriosclerosis as a cause of PD and agreed that the syndrome caused by arteriosclerosis was different from PD in clinical and pathological features [4]. He renamed it ‘arteriosclerotic pseudoparkinsonism’.

Although the concept of VP is still somewhat controversial, recent work has re-established it as a distinct entity [6]. In older patients a fairly common clinical dilemma is whether the patient has VP or PD. It is important to differentiate these conditions because of the differences in their speed of progression, response to treatment, potential strategies for secondary prevention and prognosis.

Epidemiology

In the UK Parkinson’s Disease Society Brain Bank clinicopathological series, 3 out of 24 cases were misdiagnosed by the specialist neurologists as idiopathic PD during life where there was post-mortem evidence of a lacunar state without characteristic PD pathology [7]. In a recent prospective study from Spain involving 5,160 parkinsonism-free older people, VP accounted for 4.4% of all cases of parkinsonism identified during the study period [8]. In a similar population-based Italian study, out of 68 incident cases of parkinsonism, 8 (12%) were diagnosed as VP [9]. Incidence
rates for parkinsonism and PD were higher in an older population and in men. When studies are limited to those with either imaging or pathological support for diagnosis, VP is estimated to account for 3–6% of all cases of parkinsonism [10]. It is likely that VP is underdiagnosed and that actual figures for incidence and prevalence are higher. In a recent pathological study of five patients with vascular disease at autopsy, none had a diagnosis of VP in life, though three patients had a history of stroke [11]. In a clinico-radiological study of gait disorders and parkinsonism in patients with stroke related to small deep infarcts [11], it was observed that nearly one-third of patients who had suffered a stroke and white matter lesions on brain imaging, it was observed that nearly one-third of patients who had suffered a stroke had 'one or more parkinsonian signs' one year after their stroke [12]. However, it is not known whether all of them had VP or whether some had developed a new onset of PD.

**Risk factors**

As the underlying cause for VP is a vascular disease, it is conceivable that VP has a risk factor profile similar to that of cerebrovascular disease. It should be pointed out that there is no clear-cut relationship between some of the vascular lesions causing VP (e.g. lacunar infarcts,Binswanger's subcortical vasculopathy and dilatation of perivascular spaces) and arteriosclerosis [13].

There is ample evidence that the incidence and prevalence of VP increase with age [9,10,14]. Patients with VP tend to be older than those with PD. In a given age group, men are more likely to suffer from VP than women.

In a recent study of parkinsonism using a vascular rating scale, out of 214 patients with a diagnosis of parkinsonism, 8 (3.74%) were shown to have VP [14]. Vascular risk factors are more common in VP than in PD [6]. Several studies have attempted to analyse the frequency of VP after strokes. Hypertension has been recognised as an important risk factor for VP since the original description of ‘arteriosclerotic parkinsonism’ by Critchley [1] and confirmed in a recent epidemiological study [8]. Diabetes mellitus is also associated with VP. The relationship of VP with hypercholesterolaemia, smoking and a family history of ischaemic heart disease has not been well studied.

VP has been associated with antiphospholipid antibody and anticardiolipin antibody [15].

The literature is somewhat conflicting regarding the relationship of PD and cerebrovascular disease. Some studies have reported lower or equal prevalence of stroke in PD than in controls [16]. The apparent protection of PD against stroke has been attributed to a decreased level of dopamine in the brain [17]. It is even proposed that treating PD patients with dopaminergic medications would increase the risk of endothelial dysfunction and atherosclerosis by raising levels of homocysteine [18]. However, other studies show an increased risk of stroke-related deaths in PD patients [19].

**Pathology of VP**

Any lesion involving the substantia nigra and/or its projections can theoretically produce ‘parkinsonism’. There are three different pathological states that produce typical clinical manifestations: (1) multiple lacunar infarctions in which parkinsonism is commonly associated with the pyramidal deficits, pseudobulbar palsy, cognitive impairment and a gait disorder; (2) subcortical arteriosclerotic encephalopathy (Binswanger’s disease) presenting on CT/MRI scans of the brain as periventricular or subcortical white-matter lesions (WML) and clinically as dementia and a progressive gait disorder; (3) rarely, an infarction (usually a lacunar type) involving basal ganglia can present with a clinical picture indistinguishable from PD.

In a consecutive autopsy series of 700 cases with a clinical diagnosis of parkinsonism, PD was confirmed by the presence of Lewy bodies in 80.7% of cases with co-existing cerebrovascular lesions in 19% [20]. In the remaining 135 (19.3%) cases of ‘secondary parkinsonism’, 27 (3.9%) brains showed subcortical vascular lesions in 32%, lacunar state in basal ganglia and brain stem in 20% and multi-infarct encephalopathy in 48% with no significant nigral lesions.

**Clinical aspects of VP**

Parkinsonism in slow-onset VP is typically bilaterally symmetrical, affecting the lower limbs more than the upper limbs (‘lower-body parkinsonism’), unassociated with resting tremors, and is generally considered to have a stepwise or rapid progression. There are usually additional features, such as pseudobulbar palsy, pyramidal signs and speech disturbance. Vascular risk factors (hypertension, history of transient ischaemic attacks (TIA)/stroke, diabetes mellitus, etc.) are commonly present. It is suggested that VP does not usually respond to dopaminergic (e.g. L-dopa) treatment.

Winikates and Jankovic have proposed a vascular rating scale (Table 1) based on the clinical and radiological/pathological features to aid the diagnosis of VP [14].

Acute onset is found only in about 25% of cases [14]. A history of stroke is common and was found in all patients in one study [14], and in more than half of the cases in another study [8]. Resting tremor of pill-rolling type characteristic of PD is typically absent (‘sine agitatione’), and a non-rolling type of resting tremor was found in only about 20% of the cases with possible VP [21]. Increased tone is usually of a ‘mixed’ type (a combination of spasticity and rigidity) with no cogwheeling. There is usually associated paraesthesia or

<table>
<thead>
<tr>
<th>Feature</th>
<th>Points</th>
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<tbody>
<tr>
<td>Pathological or angiographic evidence of diffuse vascular disease</td>
<td>2 points</td>
</tr>
<tr>
<td>Onset of parkinsonism within one month after stroke</td>
<td>1 point</td>
</tr>
<tr>
<td>History of two or more strokes</td>
<td>1 point</td>
</tr>
<tr>
<td>History of two or more of vascular risk factors for stroke</td>
<td>1 point</td>
</tr>
<tr>
<td>Neuroimaging evidence of vascular disease in two or more vascular territories</td>
<td>1 point</td>
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</tbody>
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Vascular parkinsonism = parkinsonism + vascular score of 2 or more.
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Table 2. Clinical syndromes associated with VP

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Lower-body parkinsonism</td>
<td>Classic type of VP, presenting with a prominent gait disorder, rarity of resting tremors and generally a poor response to L-dopa. MRI often shows subcortical arteriosclerotic encephalopathy</td>
</tr>
<tr>
<td>Parkinsonism associated with a multi-infarct state</td>
<td>Usually presents with additional features, such as pyramidal signs, pseudobulbar signs, dementia, incontinence and gait disorder. MRI shows multiple lacunar infarcts in cortex and subcortical regions</td>
</tr>
<tr>
<td>Parkinsonism indistinguishable from PD</td>
<td>Described in patients with basal ganglia infarcts, lacunes or dilatation of vascular spaces</td>
</tr>
<tr>
<td>(‘pure’ parkinsonism)</td>
<td>Rare occurrence, reported in infarcts of subcortical grey matter</td>
</tr>
<tr>
<td>Unilateral parkinsonism</td>
<td>Reported in patients with multi-infarct states</td>
</tr>
<tr>
<td>PSP-like syndrome</td>
<td>A combination of PD and VP in the same patient as a chance occurrence (‘double pathology’)</td>
</tr>
</tbody>
</table>

L-dopa = levodopa, MRI = magnetic resonance imaging, PD = Parkinson’s disease, PSP = progressive supranuclear palsy, VP = vascular parkinsonism.

‘gegenhalten’. The distribution of hypertonia is suggestive of an upper motor lesion involving antagonistic muscles rather than the extrapyramidal pattern seen in PD. Bradykinesia of varying degree is often seen with evidence of micrographia in some patients.

Gait abnormalities are characteristic and have been noted in most series [22]. Upper limbs are usually spared and hence the term ‘lower body parkinsonism’. Posture is mostly upright and the base is wide (cf. the stooped posture and narrow base of PD) with no loss of associated movements. There is marked retropulsion but anteropulsion and lateral pulsion are usually absent.

There may be clinical features of pseudobulbar palsy, such as dysarthria, dysphagia and emotional lability. Other recognised features include incontinence, pyramidal signs and cognitive impairment [14].

A syndrome of ‘pure’ parkinsonism, indistinguishable from idiopathic PD, has rarely been reported in patients with basal ganglia infarcts, lacunes or dilatation of vascular spaces [23].

A syndrome similar to progressive supranuclear palsy (PSP) has also been reported in patients with VP. Dubinsky and Jankovic reported that about one-third of their patients with PSP-like syndrome had a multi-infarct state [24].

A recent study examining correlation of L-dopa response and nigrostriatal pathology in patients with VP reported a beneficial effect of L-dopa in a subset of patients [25].

It should be remembered that VP and PD are both common in an older population and it is not unusual for them to present concomitantly. This so-called ‘overlap syndrome’ can pose a diagnostic and a therapeutic challenge, since the response to dopaminergic therapy may be suboptimal. Table 2 provides a summary of various clinical syndromes that can be found in patients with parkinsonism in association with a vascular disease of the brain.

**Imaging studies in VP**

The presence of vascular disease on brain imaging supports the diagnosis of VP but does not establish a cause and effect relationship. This issue is further complicated by observations that apparently similar vascular lesions noted on brain imaging may be associated with parkinsonism in some but not in others. Despite these limitations, it is useful to look for evidence of vascular disease on brain imaging. Imaging also helps to exclude other causes of secondary parkinsonism, e.g. normal pressure hydrocephalus, space-occupying lesions, etc.

MRI is more sensitive than CT in diagnosing ischaemic cerebrovascular disease. In a comparative MRI study, patients with suspected VP had significantly more subcortical lesions than those with PD or hypertension [26]. The cut-off point that best distinguished patients with suspected VP from the patients with PD was a 0.6% level of lesioned brain tissue volume. There are conflicting reports of the frequency of the association of isolated vascular lesions of the substantia nigra and VP. One study suggested that VP was rare in patients with basal ganglia infarcts, lacunes or dilatation of vascular spaces [23]. In another study, 38% of patients with lacunar infarcts of basal ganglia noted on MRI had parkinsonism [27].

**Functional imaging**

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) can be used to supplement morphological imaging with MRI/CT for diagnosis of various parkinsonian syndromes [28]. Use of dopamine transporter (DAT) ligands in the functional imaging techniques may help to differentiate PD (a pre-synaptic disorder) from VP. The technique defines integrity of the dopaminergic system and has its main clinical application in patients with mild, incomplete or uncertain parkinsonism [29]. DAT imaging is abnormal in PD, multiple system atrophy and progressive supranuclear palsy, and does not distinguish between these disorders. A normal scan suggests an alternative diagnosis such as essential tremor, VP (unless there is focal basal ganglia infarction), drug-induced parkinsonism or psychogenic parkinsonism. Imaging with specific SPECT ligands for DAT (FP-CIT, beta-CIT, IPT, TRODAT) provides a marker for presynaptic neuronal degeneration. In a study using this technique, the degree of striatal binding reduction was correlated with disease severity in PD, but not in patients with VP [30]. It should be noted that DAT imaging may be abnormal in VP owing to a focal...
infarction in the basal ganglia. A characteristic ‘punched out’ appearance of such a lesion on SPECT has been described [29].

In a PET study of patients with vascular dementia with or without parkinsonism, it was shown that local ischaemic changes in the striatum contributed to parkinsonism in vascular dementia patients [31]. PET results showed decreased regional blood flow (rCBF) and regional metabolic rate for oxygen (rCMRO) in the frontal and parietal cortices, and in the striatum of patients with dementia and parkinsonism compared with the group with vascular dementia without parkinsonism. In parkinsonism patients, rCBF and rCMRO were more decreased in the striatum contralateral to the most affected parkinsonian side. Though more sensitive than SPECT, PET is not as widely available.

Treatment of VP

Since VP is assumed to be caused by a vascular disease of the brain, it seems logical to apply the principles of primary and secondary prevention of cerebrovascular disease. Therefore, control of hypertension and diabetes mellitus, cessation of smoking, appropriate use of antplatelet drugs for ischaemic cardiac and cerebral disease, treatment of hyperlipidaemia, regular exercise, etc. would appear justified. However, there have not been systematic studies to ascertain the effectiveness of these approaches for VP.

Poor or no response to dopaminergic therapy should not come as a surprise since, unlike PD, VP is not caused by a disease restricted to the basal ganglia. However, a recent study examined a correlation of positive L-dopa response to a disease restricted to the basal ganglia. However, a recent study found L-dopa response to come as a surprise since, unlike PD, VP is not caused by a disease restricted to the basal ganglia. Therefore, control of hypertension and diabetes mellitus, cessation of smoking, appropriate use of antplatelet drugs for ischaemic cardiac and cerebral disease, treatment of hyperlipidaemia, regular exercise, etc. would appear justified. However, there have not been systematic studies to ascertain the effectiveness of these approaches for VP.

A norepinephrine precursor, L-threo-dops, was reported to be useful in VP in some open trials [32]. However, this has not been confirmed.

Gait disorder in normal pressure hydrocephalus (NPH) tends to improve with drainage of cerebrospinal fluid (CSF) by lumbar puncture (LP). Based on the similarity between VP and NPH in the presence of subcortical white matter lesions, Ondo et al. [33] carried out an interesting study. They removed 35–40 ml of CSF from 40 patients with VP symptoms and compared responders with non-responders for a variety of demographics and clinical features, and blinded interpretation of MRI. Fifteen patients (37.5%) reported ‘significant and irrefutable’ gait improvement after LP. Twelve (30.0%) reported no effect and 13 (32.5%) reported mild or very transient improvement. Timed gait in a subset of patients improved immediately after LP. Clinically, improvement after CSF removal was predicted by any positive response to levodopa, lack of vertical gaze palsies, absence of a pure freezing gait and lack of hypotensive episodes. MRI interpretation did not find features which clearly predicted response. Clinically, the responders tended to resemble idiopathic PD, whereas non-responders more closely resembled progressive supranuclear palsy (PSP). This study, if confirmed, would bring an interesting option of CSF drainage for patients with VP and idiopathic PD.

Rehabilitation of patients with a dominant gait disorder employing a multidisciplinary team approach is highly important. Some patients are helped by the use of visual cues, e.g. walking with upturned walking sticks. Many patients are limited by fear of falling, and can be helped by behaviour therapy. In an observational study, to identify predictors of functional recovery after an intensive rehabilitation training in patients with gait disturbances and refractory parkinsonism, subcortical cerebrovascular load was reported as a predictive factor for the successful rehabilitation of patients with L-dopa refractory parkinsonism [34]. Higher subcortical cerebrovascular vascular load was associated with less successful rehabilitation.

Conclusions

VP is an important cause of parkinsonism, particularly in an older population. It can be caused by a variety of vascular insults to the brain. Typically, parkinsonism in VP tends to be bilaterally symmetrical, affecting lower limbs more than the upper limbs (‘lower-body parkinsonism’), and resting tremors are usually absent. MRI of the brain is a useful test to define vascular lesion load. Functional imaging with SPECT and PET helps in differentiating PD from VP. Though generally considered to be ineffective, L-dopa has been recently shown to be beneficial in a subset of patients with VP. At present it remains unexplained why some patients develop VP and others do not with a similar load of vascular lesions. There is a great need for further research into this field. Zijlmans et al. recently investigated the
importance of pathological findings (macroscopic cerebral infarcts and microscopic ‘small vessel disease’) in the aetiology and clinical picture of VP [35]. The clinical features at presentation varied according to the underlying vascular pathological state. They have proposed new clinical criteria for diagnosis of VP based on the clinicopathological findings. Further studies are needed to confirm these findings.

Key points

• Vascular parkinsonism is a distinct clinicopathological entity from the idiopathic Parkinson’s disease.
• It accounts for 4.4–12% of all cases of parkinsonism in older people. However, the disease is probably significantly underdiagnosed owing to the lack of reliable diagnostic criteria and the heterogeneity of the underlying lesions.
• The parkinsonism usually tends to be bilaterally symmetrical, affecting lower limbs more than the upper limbs, and resting tremors are usually absent.
• The main pathological lesions that underlie VP include lacunes, subcortical white matter lesions and, rarely, the territorial infarcts.
• MRI of brain is a useful morphological test to evaluate the vascular lesions.
• Functional imaging with SPECT and PET, particularly using dopamine transporter ligands, has greatly helped to understand and differentiate various forms of parkinsonism.
• Recently, L-dopa responsiveness has been reported in a subset of patients with VP.
• We still do not know why some people develop VP and others do not despite a similar apparent vascular load.

References


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