Vascular parkinsonism

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Vascular parkinsonism (VP), resulting from cerebrovascular disease, is a rare disorder showing a variety of clinical and pathological presentations distinct from sporadic Parkinson's disease (PD). It accounts for 3–6% of all parkinsonian syndromes, and is difficult to diagnose with clinical certainty. Clinical features include: bilateral symmetrical rigidity; bradykinesia, predominantly involving lower limbs; postural instability; shuffling gait; falls; dementia; and corticospinal findings. Neuropathology shows multiple subcortical ischemic lesions owing to small vessel disease in striatum, globus pallidus, white matter and, less often, substantia nigra, involving cortico-striato-pallidal (nigral), thalamofrontal and other loops, without evidence of Lewy bodies. Cranial computed tomography and magnetic resonance imaging are useful tests to evaluate the vascular lesions. Functional imaging of presynaptic dopamine transporter may be useful in the differentiation of VP from PD. Response to levodopa treatment has been reported in up to 50% of VP patients, particularly in those with lesions in or close to nigrostriatal pathways, although only a few patients demonstrate long-term efficacy. There are no data on the efficacy of dopamine agonists; deep-brain stimulation appears to be ineffective. Major risk factors for VP are principally the same as those for cerebrovascular disease, and their prevention and treatment are of utmost importance. Higher cerebrovascular load is associated with less successful rehabilitation.

Parkinsonism, clinically defined by the presence of akinesia/bradykinesia, plus one of the following signs: 4–6 Hz resting tremor, extrapyramidal rigidity and postural instability not owing to other causes [1,2], can be caused by a variety of neurodegenerative disorders including sporadic Parkinson's disease (PD) or Lewy body disease of the brainstem predominant type [3–5]. Cerebrovascular disorders and drugs are the most important causes of 'secondary' or atypical parkinsonism. Vascular parkinsonism (VP), vascular parkinsonian syndrome (VPS) or vascular pseudoparkinsonism [6,7], also known as arteriosclerotic parkinsonism [8] or 'lower body' parkinsonism [7,9], is one of the most controversial concepts in the field of neurology, mainly owing to imprecise terminology and because the concept encompasses a heterogeneous set of clinical and neuropathological conditions [10]. There is no doubt that cerebrovascular disease (CVD) can cause parkinsonian signs and symptoms, but the extent of this spectrum, the possible criteria for its clinical diagnosis, the impact of functional neuroimaging markers and successful treatment options remained imprecise until recently. However, based on careful examination of clinical history, symptoms, neuroimaging and response to therapy, it has been concluded that VP and PD are two distinct clinicopathological entities, although the coexistence of PD and CVD in elderly patients is not uncommon and can complicate the diagnosis.

This review summarizes the history, epidemiology, risk factors, clinical aspects, image studies, functional imaging, pathophysiology and treatment options of VP.

History

Marie described the 'état lacunaire' [11], in which many signs and symptoms resemble parkinsonism, and French and German neurologists and neuropathologists reported cases reminiscent of PD that were owing to arterial disease, or lacunar disintegration or cribriform state [12–14]. This was the historical context in which Critchley drew attention to 'a variety of parkinsonism owing to cerebral arteriosclerosis' [8]. He described a syndrome of arteriosclerotic parkinsonism, symptoms of which included rigidity, masked face and short-stepped gait in an elderly hypertensive person. He suggested that older patients with arteriosclerosis and parkinsonism presented 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 defined five types of

Keywords: differential diagnosis, multi-infarct state, Parkinson's disease, subcortical arteriosclerotic encephalopathy, treatment options, vascular parkinsonian syndrome

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arteriosclerotic parkinsonism: type 1 characterized by rigidity, hypomimia, a small-step gait, no resting tremor and usually bilateral signs. Other types were associated with pseudobulbar palsy (type 2), dementia and incontinence (type 3), pyramidal signs (type 4) and cerebellar symptoms (type 5). He proposed that multiple vascular lesions in the basal ganglia were responsible for producing this disorder [8]. Although many pertinent clinical observations were provided in his work, this concept was rejected by others [15,16]. It was argued that the evidence of vascular changes seen in some patients with PD could be an incidental finding, and epidemiological and pathological studies, plus increasing knowledge regarding the pathophysiology of PD, provided evidence that vascular disorders are not the cause of PD, and are not even a common cause of parkinsonism mimicking PD [16–20]. In this context, Critchley [7] revised his original idea of arteriosclerosis as a cause of PD and admitted that the syndrome caused by CVD was clinically and pathologically different from PD; he renamed it 'arteriosclerotic pseudoparkinsonism', stating that it can be defined as the presence of signs superficially suggestive of parkinsonism, but not fulfilling the full criteria above [21]. The somewhat arbitrary classification of the different types of arteriosclerotic parkinsonism was a matter of discussion and the syndrome was later referred to as VPS or VP [22,23]. It occurs with subcortical white-matter lesions (WMLs), lacunes or multiple lacunary infarcts and isolated infarcts of the basal ganglia, appearing on neuroimaging studies, although these occur frequently in elderly persons with no parkinsonism [24,25]. Furthermore, cerebrovascular lesions are a common, incidental finding in pathologically confirmed PD [26–28].

Although the concept of VP is still controversial, recent work has re-established it as a distinct clinicopathological entity [10,29–34].

Epidemiology

Due to the problem of definitions and the clinical heterogeneity of VP, it is difficult to determine its epidemiology. Clinical, neuroradiological and some autopsy studies suggest that 3.0–12.5% of cases of parkinsonism, more or less resembling PD, may be owing to CVD [23,28,35–39]. Patients diagnosed as having PD during life, who were reclassified pathologically as VP, constituted 3% (1987–1993) and 1% (1996–1998) in the UK Parkinson's Disease Society Brain Bank series [2,40]. However, 12.5% of 235 deceased cases of parkinsonism in Olmsted County, MN, USA, with an autopsy rate of 17%, were classified as VP, none of whom had been clinically diagnosed as such [36]. Comparing the incidence of VP in various autopsy series of patients with parkinsonism reveals an incidence of between 0 and 5.5% [39–42], while among 200 cases in the UK Parkinson's Disease Society Brain Bank, only seven (3.5%) were found who had VP lacking the pathological hallmarks of PD and who had fulfilled clinical diagnostic criteria for PD during life [2,43]. Among 600 brains of parkinsonian patients collected at the Queen Square Brain Bank for Neurological Disorders in London (UK) between 1989 and 2000, only 17 cases (2.8%), fulfilled the criteria of VP [44]. In a 40-year study of 900 autopsy cases with the clinical diagnosis of parkinsonism in Vienna, Austria (1957–2006), VP owing to cerebrovascular lesions (subcortical leukoencephalopathy, multi-infarct lesions, lacunes and so on) accounted for 3.7%, compared with 84.8% primary Lewy body disease, including 16% PD with cerebrovascular lesions and 11.5% other secondary parkinsonian syndromes [45]. Separating this study into three periods revealed slightly increasing data for the incidence of VP in autopsy cohorts: among 110 cases between 1957 and 1970, the incidence of VP was 3.0%; among 380 cases between 1971 and 1988 it was 4.2%, and among 360 cases between 1989 and 2006 it was 5.0%, as compared with 76–85% of Lewy body disease (PD plus dementia with Lewy bodies). This incidence of VP is less than 10–30% as common as the frequency of incidental cerebrovascular lesions occurring in true PD, which is 20–44% [18,26–28,46]. Among 4000 consecutive necropsy cases of elderly persons in Japan, clinicopathologically confirmed cerebrovascular parkinsonism was found in 24 patients with a mean age of 80 years [47]. Population-based epidemiological studies, using stringent (but not generally accepted) diagnostic criteria for VP found that it constituted only 1.4% of incident cases of parkinsonism in Rochester (USA) [48] and 3% amongst the elderly in Europe (prevalence 7/1000 aged over 65 years) [49]. Among 2071 patients with parkinsonism, VP was clinically diagnosed in 133 (6.4%) [23]. In a recent Spanish door-to-door study of parkinsonism among subjects aged 65 years and over, 4.4% were found to suffer from VP [50]. The same incidence of ischemic brain lesions accounting for parkinsonism was reported among 250 parkinsonian patients in Hong Kong [6]. In another clinical series, 69 among 369 patients with parkinsonism (almost

20%) suffered from parkinsonism with strong evidence of CVD [23]. In a large, retrospective study of clinical movement disorders following vascular basal ganglia lesions, parkinsonian syndromes were reported in 9%; all of these cases showed bilateral lesions in putamen or globus pallidus [51], while in another study, eight (3.74%) among 214 patients clinically diagnosed as PD were suggested to be so because of CVD [52]. In a recent study of five patients with vascular disease, none had been given the clinical diagnosis of VP, although three of them had a history of stroke [53]. On the other hand, van Zagten *et al*. found that a third of patients who had suffered a stroke had 'one or more parkinsonian signs' 1 year after the vascular event, and 10% clinically had a parkinsonian syndrome that differed from Lewy body parkinsonism [54]. However, it is not known whether or not all of them had true parkinsonism, and how many had developed VP, true PD or both. Among 1000 consecutive patients' cranial computed tomography (CCT) scans showing isolated lacunar lesions in caudate and lentiform nuclei, only 38% presented a parkinsonian syndrome and a further 20% showed a combination of contralateral hemiparesis and parkinsonian symptoms [55], whereas in a retrospective series of 622 patients in a stroke unit, 27 (4.3%) met the criteria for striatal brain infarct, and 11 patients were available for follow-up. However, only one person presented with a bilateral rigid-akinetic parkinsonian syndrome starting contralateral to the infarct, with slowly progressive course. β-CIT-single photon emission computed tomography (SPECT) showed a decrease of the ligand uptake following the limits of the vascular lesions [56]. Among five patients with subacute hemicorporal parkinsonism and infarcts of the basal ganglia, DatSCAN findings were concordant with the size and location of the vascular lesionin only three of them [57]. In other patient series with striatocapsular infarcts and/or hemorrhages, no signs of parkinsonism have been reported [58,59]. In summary, modern epidemiological and autopsy studies indicate that CVD accounts for 3–6% of parkinsonism [10,28,60,61].

Clinical features

The clinical picture of VP is heterogeneous. It is dominated by lower-limb bradykinesia, gait disturbances, postural instability, absence or rare occurrence of resting tremor (absence of pill-rolling tremor) and, very rarely, impairment of eye movements. It may be associated with additional signs, such as transient deficits, pyramidal signs, pseudobulbar palsy, speech disorders, dysphagia, urinary incontinence and cognitive dysfunctions/dementia [23,29,44,53,62,63]. Older age at onset, acute but occasionally also insidious onset, more rapid or stepwise progression of the disease, multiple vascular risk factors and poor or absent long-term response to dopaminergic therapy also distinguish VP from PD. Comparison of the clinical data of eight recent studies revealed:

- Insidious onset in 54–75%
- Asymmetric onset in 35–88%
- Bradykinesia in 82–100%
- Rigidity in 29–100%
- Rest or postural tremor in 0–42%
- Gait disorders in 69–95.8%
- Postural instability in 69–77%
- Lower body predominance in 60–73.7%
- Upper body predominance in 0–4%
- Falling in 31–46%
- Freezing in 36.8–62%
- Pyramidal signs in 25–70%
- Pseudobulbar palsy in 10–54%
- Dementia in 23–71%
- Incontinence and autonomic dysfunction in 9–15%
- Presence of vascular risk factors in 27–100%
- Response to levodopa therapy in 0–38% [6,23,29,30,62,64–66]

All these data were significantly different from PD [64,66].

To describe the spectrum of VP, a recent review used the terms vascular atypical parkinsonism (defined as true parkinsonism with unusual or additional features not present in PD) that are rather rare, and vascular pseudoparkinsonism (predominant gait disorders called 'lower body' parkinsonism with postural instability that are reminiscent of, but distinct from, those found in PD) [10,31].

Winikates and Jankovic have proposed a vascular scoring system derived from the Hachinski ischemic scale, based on the clinical and radiological/pathological features, to aid the diagnosis of VP [23,67] (**Box 1**). When a vascular score of 2 or higher was used as a designation of VP, such patients could be clearly differentiated from PD. The authors concluded that VP is a distinct clinical entity, and suggested that there are two types of VP: one with acute onset, probably related to infarction or other lesions affecting the basal ganglia; the other with insidious onset and slower progression, associated with a more diffuse impairment of the subcortical white matter, although there are also reports of insidious onset

Box 1. Vascular parkinsonism rating scale.

- Pathologically or angiographically proven diffuse vascular disease (2 points)
- Onset of parkinsonism within 1 month after stroke (1 point)
- History of two or more strokes (1 point)
- History of two or more vascular risk factors for stroke* (1 point)
- Neuroimaging evidence of vascular disease in two or more vascular territories (1 point)

Vascular parkinsonism: parkinsonism + vascular score of 2 or more.
**Vascular 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 or other arrythmias), and other risk factors for stroke (family history of stroke, history of gout or peripheral vascular disease).*
Adapted from [23].

of VP in patients with basal ganglia lesions [55,68]. Another group proposed four types according to their clinical manifestation [22]:

- VP manifesting itself in a manner identical to PD
- Unilateral parkinsonism following a contralateral vascular lesion
- Atypical parkinsonian syndromes
- Parkinsonian gait disorders.

In a recent critical discussion of these different groups, Rektor *et al.* suggested that in rare cases described as VP 'imitating' PD, the etiopathogenetic role of vascular lesions can not be considered to have been proven [69]. Patients who meet the following criteria should be included into type 2: appearance of unilateral parkinsonism following a stroke; neuroradiological evidence of contralateral vascular lesions in striopallidal, nigral or thalamus regions. The presence of atypical parkinsonian symptoms and CVD may lead to differential diagnostic difficulties, since there are no specific signs for the diagnosis of VP, although there are clusters of symptoms more or less typical for VP. If the clinical picture correlates with the criteria recently proposed [44], the diagnosis of VP appears as probable, otherwise the diagnosis may be considered as possible. However, it should be considered that the presence of CVD, being a frequent incidental finding in aged patients with PD, may considerably aggravate and influence the clinical features and severity of parkinsonian symptoms [70].

The category of parkinsonian gait disorders as a dominant clinical sign, also termed 'lower half parkinsonism' [71], lower body parkinsonism [9] or 'vascular pseudoparkinsonism' [31], shows a heterogenous clinical picture (**Table 1**) and various pathophysiology, frequently associated with cerebrovascular lesions. In contrast to other gait disorders, cerebrovascular gait disorder has been suggested to present a clearly detectable entity with a characteristic clinical picture and the presence of cerebrovascular lesions documented by neuroimaging [69].

Another summary of clinical syndromes in patients with parkinsonism in association with a CVD was proposed by Thanvi *et al.* [33] (**Table 2**).

Table 1. Comparison of gait characteristics in various disorders.

	Parkinson's disease	Gait ignition failure	Frontal gait disorders
Standing from seated position	Impaired	Normal	Impaired
Posture during standing/walking	Flexed	Upright	Upright or flexed
Stance and stride base	Narrow	Narrow	Wide
Equilibrium	Normal (early)	Normal	Abnormal
Postural reflexes	Normal (early)	Normal	Abnormal
Protective/rescue reactions	Normal (early)	Normal	Abnormal
Retropulsion	Present	Absent	Present (may fall)
Start/turn hesitation	Marked	Marked	Marked
Stride length	Short (shuffling)	Normal	Short (shuffling)
Freezing	Yes	Yes	Yes
Festination	Yes	No	No
Arm swing	Reduced	Normal	Variable
Leg movement when seated	Slow	Normal	Variable
Apraxia	No	No	Variable

Modified from [173].

Table 2. Clinical syndromes associated with vascular parkinsonism.

Syndrome	Comments
Lower-body parkinsonism	Classical type of VP, presenting with a prominent gait disorder, rarity of resting tremors and generally poor response to L-dopa. MRI often shows subcortical arteriosclerotic encephalopathy or multilacunar state
Parkinsonism associated with a multi-infarct state	Usually presents with additional features, e.g., pyramidal signs, pseudobulbar signs, dementia, incontinence and gait disorder. MRI shows multiple lacunar infarcts in cortex and subcortical regions
Parkinsonism indistinguishable from PD ('pure' parkinsonism)	Described in patients with basal ganglia infarcts, lacunes or dilatation of vascular spaces
Unilateral parkinsonism	Rare occurrence, reported in infarcts of subcortical grey matter
PSP-like syndrome	In patients with multi-infarct states with poor/no L-dopa response
An 'overlap syndrome'	Incidental combination of PD and VP in the same patient ('double pathology') – occurring in 20 to more than 40% of autopsy-proven PD

L-dopa: Levodopa, MRI: Magnetic resonance imaging, PD: Parkinson's disease; PSP: Progressive supranuclear palsy; VP: Vascular parkinsonism. Modified from [33].

Based on a clinicopathological study of 17 patients with VP, Zijlmans *et al.* proposed inclusion and exclusion criteria for the possible clinical diagnosis of VP (**Box 2**) [44].

Zijlmans *et al.* emphasized that these criteria would need to be evaluated both prospectively and retrospectively against patients with other pathologically established forms of parkinsonism to analyze sensitivity, specificity and positive and negative predictor values. In this systematic clinicopathological study, they gave a sensitivity of 94% (16 out of 17 patients).

Cognitive dysfunction is frequently associated with VP. In a comparative study, dementia occurred in 45% of the patients with VP compared with only 10% in the PD group [23]. In other clinical studies, the incidence of cognitive dysfunction/dementia ranged from 23 to 71% [31]. It may be possible that a part of VP and subcortical dementia are manifestations of a common underlying disorder, namely Binswanger's disease (BD), whereas Alzheimer-type pathology in these cases appears to be rare [44].

Recent studies have shown that, in contrast to PD, most patients with VP and without associated dementia have a preserved sense of smell [72]. However, it remains possible that some of the hyposmic VP patients had subclinical or comorbid Lewy body changes or dementia in addition to CVD [73]. Despite these limitations, testing olfactory function may help with the differential diagnosis between VP, PD and other parkinsonian syndromes [74].

Not only do cerebrovascular lesions rarely masquerade as PD, but they can also cause some clinical features of other neurodegenerative diseases associated with parkinsonism, such as progressive supranuclear palsy (PSP), multisystem atropy (MSA) or corticobasal degeneration (CBD). The differential diagnosis between VP, 'vascular PSP' [67,75] and other neurodegenerative parkinsonian syndromes has been summarized by Sibon *et al.* [31].

Imaging studies

While usefulness of several ancillary investigations in the diagnosis of VP and its differentiation against other parkinsonian syndromes is questionable, for example, encephalography showing less slowing of background activity in VP than in PD [76] and transcranial magnetic stimulation (TMS) giving conflicting results [77,78], the presence of CVD on brain imaging supports the diagnosis of VP, but does not establish a cause-and-effect relationship. However, it helps to exclude other causes of parkinsonism, for example normal-pressure hydrocephalus, space-occupying lesions and so on. MRI is more sensitive than CCT in diagnosing CVD. MRI studies have generated data on the use of density and frequency of lacunes or white-matter intensities as means for the differential diagnosis between VP and PD, but these are controversial owing to frequent lack of subsequent neuropathological confirmation. In patients with suspected VP, the number and intensity of subcortical lesions is greater than in those with PD or hypertension [54,79], although the frequency and extent of periventricular hyperintensities have been shown to be significantly higher in patients with PD than in controls. They are correlated with increased gait disorders, less levodopa responsiveness and shorter survival, suggesting a more rapid neurodegeneration process [80,81], whereas other studies showed no relationship

Box 2. Possible criteria for the clinical diagnosis of vascular parkinsonism.

- Parkinsonism: bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions in either upper limb or lower limb, including reduced step length) and at least one of the following: resting tremor, muscular rigidity, or postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction. In contrast to PD, a preserved sense of smell is apparent.
- Cerebrovascular disease, defined by evidence of relevant cerebrovascular disease by brain imaging (CT or MRI) or the presence of focal signs or symptoms that are consistent with stroke or transitory ischemic attacks ('silent' stroke).
- A relationship between the above two disorders. In practice: (1) an acute or delayed progressive onset with infarcts in or near areas that can increase the basal ganglia motor output (external GPe or substantia nigra pars compacta) or decrease the thalamocortical drive, directly (VL of the thalamus, large frontal lobe infarct). Parkinsonism at onset consists of a contralateral bradykinetic-rigid syndrome or shuffling gait, within 1 year after a stroke (VPa). (2) An insidious onset of parkinsonism with extensive subcortical white matter lesions, bilateral symptoms at onset, and the presence of early shuffling gait or early cognitive dysfunction (VPi).
- Exclusion criteria for VP: history of repeated head injury, definite encephalitis, neuroleptic treatment at onset of symptoms, presence of cerebral tumor or communicating hydrocephalus on CT or MRI scan, or other alternative explanation for parkinsonism.

CT: Computed tomography; GPe: External globus pallidus; MRI: Magnetic resonance imaging; VL: Ventrolateral thalamus; VP: Vascular parkinsonism; VPa: Acute onset VP; VPi: Insidious onset VP.
Modified from [44].

between WMLs and motor impairment in PD [82]. A comparison between pathologically confirmed cases of VP, PD and BD showed that most VP patients had diffuse WMLs, as well as basal ganglia lesions; VP might be related to frontal WMLs [83]. There are conflicting reports on the frequency of the association of isolated vascular lesions in substantia nigra (SN) and VP [55,84], which are also frequently seen in patients with PD [85]. Three patterns of ischemia on CCT or MRI, including frontal lobe, deep subcortical and basal ganglia infarction, have been associated with steady progression. Autopsy of one of the patients in this study confirmed a multi-infarct state without any evidence of Lewy bodies [6], while in another case with a clinical syndrome indistinguishable from PD, postmortem examination revealed extensive lacunar infarction of the basal ganglia without evidence of coexistent PD of the Lewy body type [86]. MRI findings in three series of VP patients revealed normal findings in 0%, basal ganglia ischemic lesions in 27–50%, subcortical WMLs in 36–87.5%, cortical ischemic lesions in 0–27% and brainstem or cerebellar lesions in 18.7–21.7% [6,23,29].

Several neuroimaging-based studies related parkinsonism to basal ganglia or thalamic infarcts [6,23,38,54,55,79,84,87–96], striatal lacunes because of enlargement of perivascular spaces [97,98] or frontal infarcts [6].

The correlation of MRI abnormalities (lacunes, WMLs and width of SN) with clinical features suggested that patients with parkinsonism and a lacunar state in putamen or confluent white-matter hyperintensities may have VP but also PD (as defined by reduced SN width) [99], but measurements of SN using conventional MRI remain inexact. Frequently, SN is preserved, but it can also be affected by ischemic changes [84] or, very rarely, by lacunar infarction, associated with acute onset of parkinsonism [100], while parkinsonism has been reported following larger infarcts of the basal ganglia or the anterior cerebral artery territory, and in association with cribriform state of the striatum [31]. Recent studies examined the effects of lacunar infarcts, WMLs and cortical atrophy in 268 subjects aged 65–83 years on the risk and severity of mild parkinsonian signs (MPS) [101]. Lacunar infarcts and large subcortical WMLs were associated with an elevated risk and severity of resting tremor but not with other signs; severe cortical atrophy correlated with the severity of rigidity and bradykinesia, while the severity of brain atrophy was correlated with the degree of either cardinal symptoms. Determining the presence of cerebral small-vessel disease (SVD) using brain imaging may help to identify persons at risk for developing MPS. Transcranial color-coded sonography imaging SN echodensity and transcranial

Doppler for intracranial hemodynamics may also be useful tools for differentiating between PD and VP [102].

However, the relationship between the observed vascular lesions and parkinsonism may be coincidental in some of these, and some studies could not find a relationship between VP and basal ganglia lesions in their clinicopathological study [62].

Functional imaging

Functional imaging studies, such as positron emission tomography (PET), SPECT or magnetic resonance (MR) spectroscopy may also be useful in the diagnosis and differential diagnosis of VP. Imaging with specific SPECT ligands for dopamine transporters (DAT, FP-CIT, β-CIT, IPT and TRO-DAT) providing a marker for presynaptic neuronal degeneration defines the integrity of the dopaminergic system, and is useful for differentiating VP from other parkinsonian syndromes [103–106]. Using this technique, the degree of striatal binding reduction was correlated with disease severity in PD, but not in patients with VP [107]. Whereas vascular lesions that do not directly affect the striate components do not induce significant presynaptic alterations [56], DAT imaging may be abnormal in VP if there is focal basal ganglia infarction, giving a characteristic 'punched-out' SPECT deficit [108]. In the same way, dopamine D2 receptor binding at the striatal level with C^{11}/*N*-methylpiperone PET is not severely affected in patients with VP and shows no correlation with clinical impairment [109]. In VP related to basal ganglia infarcts, previous studies showed an abnormally decreased ligand binding, delineating the limits of vascular lesions [56,57]; this distribution usually differs from the classical pattern in PD [110,111]. A recent study of (123)FP-CIT SPECT in 13 patients fulfilling operational clinical criteria for VP showed a significantly lower uptake in the basal ganglia than in healthy controls and, in comparison with the PD group, the mean asymmetry index was significantly lower in VP patients. None of the parameters measured were significantly different between VP patients with acute or insidious onset of disease, but there was a significant correlation between the bilateral basal ganglia FP-CIT uptake and the Unified Parkinson's Disease Rating Scale (UPDRS) motor scores. The data suggest that in most VP patients, presynaptic dopaminergic function is reduced, and that the presence of a rather symmetrical uptake in the basal ganglia may help to distinguish VP from PD [105].

A proton MR spectroscopy study in VP has shown a particular profile with a decrease in the *N*-acetyl-aspartate (NAA):creatine (CRE) ratio in the frontal cortex and putamen not observed in PD [112], but preservation of dopaminergic neurons [113].

Boecker *et al.* [95] first reported results of a [^{18}F]-fluorodeoxyglucose (FDG) and [^{18}F]-L-6-fluorodopa (FDOPA) PET in a woman aged 71 years with right-sided parkinsonism of sudden onset without tremor. MRI depicted bilateral SN lesions, but was more pronounced on the left side. FDOPA uptake reductions were similar to those in idiopathic PD; FDG PET shows reduced regional cerebral metabolic rate of glucose (rCMRG) in putamen.

A recent comparative study of patients with extensive WMLs, with and without gait disorders suggestive of VP, using PET scan, showed significant reduction of cerebral blood flow (CBF) in the striatum and inversal relationship between striatal/C^{11}/fluazenil (FMZ) volume values and motor UPDRS scores as well as association with gait disturbances, suggesting impaired neuronal integrity in the striatum of patients with VP [114]. These data sugggest that striatal FMZ binding could be a reliable diagnostic marker of VP.

Myocardial iodine-123 metaiodobenzylguanidine (MIBG) SPECT, which usually shows significantly reduced uptake in patients with PD suggesting myocardial postganglionic sympathetic dysfunction [115,116], has been shown to be normal in both VP and controls, thus being useful to help distinguish between VP and PD [66].

However, it should be emphasized that none of the current clinical and imaging criteria taken alone are specific for the diagnosis of VP. A combination of convergent clinical and imaging clues are therefore necessary to improve the accuracy of the diagnosis, which is only definite when neuropathology excludes Lewy body disease and other disorders associated with parkinsonism.

Neuropathology

Any lesions involving the SN and/or its projections can induce parkinsonism. Interpretation of various autoptic and histological findings is difficult, owing to the heterogeneity, variable location, extent and histological features and anatomoclinical correlations.

Cerebrovascular lesions associated with VP include SVD pathology with multiple lacunar infarctions or lacunes in basal ganglia and/or white matter, Binswanger's subcortical arteriosclerotic leukoencephalopathy and tiny infarctions in the

basal ganglia and brainstem regions, usually with either minimal or no degenerative changes in the SN. The character and pathogenesis of pathological lesions is heterogenoeus-ischemic, hemorrhagic or demyelination. However, simultaneous occurrence of Lewy bodies has been found in 10% of such brains, which was higher than in an age-matched control group, suggesting the possibility of a simultaneous occurrence of VP and PD in some patients [18].

In many cases of multiple subcortical lacunar infarctions, parkinsonism is usually associated with pyramidal deficits, pseudobulbar palsy, cognitive impairment and gait disorders, subcortical arteriosclerotic leukoencephalopathy Binswanger's type or BD presenting on CCT/MRI scans as periventricular or subcortical WMLs, and clinically as dementia and a progressive gait disorder, rarely associated with parkinsonian signs and symptoms [43,62]. To our knowledge, there are only two reports, of three cases each, of levodopa-responsive parkinsonism with associated focal signs owing to pathologically proven BD without associated Lewy pathology [94,117]. While there was no significant difference in the extent of vascular lesions in the basal ganglia between patients with VP and BD without parkinsonism, the extent of frontal white-matter pallor tended to be less broad in VP, where the number of oligodendrocytes in the frontal white matter was significantly less than in age-matched controls and significantly more than in those with BD. These data suggested that VP might be related to frontal WMLs [62].

Patients with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) may rarely present with parkinsonism [32], and a single case of VP with imaging and biopsy-proven moyamoya syndrome has been reported [118].

Rarely, an infarction, usually of lacunar type, involving basal ganglia can present with a clinical picture mimicking PD [98]. Other vascular lesions associated with VP syndrome were found in the thalamus or in the external capsule and inferior part of the putamen [119]. Intracerebral hemosiderosis has been observed in three patients with stroke-related parkinsonism [120].

A systematic clinicopathological study of 17 cases of VP showed significantly more serve microscopic SVD pathology findings, including gliosis, perivascular myelin pallor, hyalinosis of arteries and enlargement of perivascular spaces, together with lacunar infarcts in the basal ganglia, in the parkinsonian brains, compared with controls [44]. Three of four patients with acute or delayed progressive onset of parkinsonism after a hemiparetic stroke had lacunar or cystic infarcts contralaterally in or near the external globus pallidus (GPe) or ventrolateral thalamus (territory of the left tuberothalamic artery), while another patient showed a cystic infarct in the posterior part of the left putamen reaching the border with the GPe. These findings were in agreement with most neuroimaging studies in which a vascular cause for parkinsonism was acceptable when there was a single lesion in the basal ganglia and thalamus; only infarcts in the contralateral hemisphere [6,55,90,92,96,97] or in the contralateral brainstem [91,93,95] may cause parkinsonism. Zijlmans *et al.* [113] could not confirm a causal relationship between VP and lesions caused by enlarged perivascular spaces in basal ganglia or infarcts in the frontal lobe or SN.

Lacunar infarcts and lacunes caused by enlarged perivascular spaces in seven patients with insidious onset were located in the entire putamen with or without extension into the head of the caudate nucleus, internal capsule and internal globus pallidus (GPi) [44]. These findings are in agreement with those of Fisher [121], who concluded that lacunar infarcts in the head of the caudate nucleus and putamen may be silent. The other six patients with insidious onset did not show any of these lesions in the basal ganglia or thalamus on macroscopic examination. Almost all VP patients with insidious onset had a bilateral onset of their motor signs, and none had lacunar infarctions in strategic areas. This finding raises the possibility that their parkinsonism was caused by diffuse microscopic SVD pathological states in deep gray nuclei and white matter, unrelated to specific areas of infarction. Several authors attributed lower body parkinsonism to periventricular and frontal white-matter damage [9,23,62,71,79,86,90,122]. Only three of ten controls had a microscopic SVD score comparable with that of the VP patients [44], which is in keeping with data of previous imaging studies, showing that 10–30% of asymptomatic elderly patients with vascular risk factor had partially or widely confluent subcortical lesions [79]; for review see [123].

In the series of Zijlmans *et al.* [44], one brain showed mild cerebral amyloid angiopathy, while in another, even in the absence of dementia, the diagnosis of possible Alzheimer's disease according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria was made. Two patients showing involvement of supranuclear eye movements, similar to the vascular

subgroup of progressive supranuclear palsy (PSP) [124], could otherwise not be clinically or pathologically differentiated from the other VP patients, with the exception of additional lesions in the dorsal pons in both, and in the thalamus in one of them. In four of the patients, parkinsonism was associated with nigral cell loss, which was severe in two, and in common with PD [125,126]. Medial cell groups of the rostral portion of the SN were only slightly involved, while there was severe damage to the lateral cell groups. All patients had extensive vascular damage to putamen, globus pallidus or thalamus, which may cause transneuronal degeneration [127], and degenerative changes in the ipsilateral SN after a stroke, as a possible result of excessive excitatory influence resulting from loss of inhibitory GABA input [128], confirmed by experimental occlusion of the middle cerebral artery in the rat [129].

Subgroups suggested by Critchley [8] could not be confirmed by Zijlmans *et al.* [44], and most patients showed signs of overlap with these subgroups. They suggested two types of onset of VP: one with acute onset, associated with basal ganglia infarctions, and the other with insidious onset, associated with diffuse subcortical WMLs.

Experimental models

There are only a few experimental models of extrapyramidal motor symptoms related to CVD. Examination of dopaminergic neurons of SN pars compacta in the rat brain following striatal infarction subsequent to transient focal cerebral ischemia showed a transitory reduction of tyrosine hydroxylase immunoreactivity in the ipsilateral SN, suggesting that striatal infarction causes a transient deficit of dopaminergic function [130]. Methamphetamine (MP)-induced rotation test for the detection and quantification of extrapyramidal motor symptoms induced by striatal infarction in gerbils after focal ischemia showed biased rotation contralateral to the lesioned side, associated with significant reduction of dopaminergic nigral neurons after 20 min of left common carotid artery occlusion (CCAO), which was not observed after short-time CCAO [131]. Thus, biased rotation behavior is a sensitive parameter of the extent of striatal injury after focal cerebral ischemia, provided the lesion is not extended to the ipsilateral cortex. MP-induced rotation in rodents probably coordinates with extrapyramidal dysfunction after striatal infarction in patients with VP. Transient focal ischemia of 1-h duration induced marked depletion of Parkin protein levels to 60, 36, 33 and 25% of controls after 1, 3, 6 and 24 h of reperfusion, respectively, with Parkin depletion preceeding neuronal cell death [132]. Ischemia-induced depletion of Parkin protein may contribute to the pathological process resulting in cell injury by increasing the sensitivity of dopaminergic neurons to endoplasmic reticulum dysfunction and the aggregation of ubiquitinated proteins during the reperfusion period. Hypoxic–ischemic mechanisms may lead to both presynaptic (SN), postsynaptic (striatal outflow pathways) and pallido–thalamo–cortical loop dysfunction. Changes in vascularization in SN pars compacta have been observed in monkeys rendered parkinsonian by chronic MPTP injection, a frequently used model of PD [133].

Risk factors

Most patients with VP have a risk-factor profile similar to that of CVD, although there is no clear-cut relationship between some of the cerebrovascular lesions causing VP and arteriosclerosis [31].

There is evidence that the incidence and prevalence of VP increases with age [23,35,60], and patients with VP tend to be older at disease onset than those with PD [29,31,64,65]. Men are more likely to suffer from VP than women [31]. Among vascular risk factors, in particular, hypertension, the most important risk factor for developing SVD has been recognized as an important risk factor for VP [29,44,50] and is significantly more common in VP than in PD. Diabetes mellitus is also associated with VP, although SVD may occur in the absence of diabetes and hypertension [134,135], suggesting that factors other than hypertension are probably also involved in the development of 'hypertensive' SVD [135]. On the other hand, Type 2 diabetes mellitus is associated with parkinsonian signs in older persons, especially postural reflex impairment–gait disturbance, suggesting that vascular factors may play a role in this association [136]; however, the mechanism behind the association between diabetes and increased risk for incident PD is not known [137].

A recent study of the relationship between mild parkinsonian signs occurring in 16.4% of 2286 older people without dementia revealed a higher prevalence of diabetes mellitus, heart and peripheral vascular disease and stroke in participants with MPS, whereas nonvascular diseases (cancer and thyroid disease) were not of higher prevalence [138]. The presence of MPS in elderly individuals, therefore, might reflect, in part, the accumulation of vascular pathological changes in basal ganglia and/or white matter caused by preventable vascular diseases.

The relationship between hypercholesterinemia, smoking and a familial history of ischemic heart disease has not been well studied [33].

VP has been asssociated with antiphospholipid and anticardiolipin antibodies (ACLA) [139], usually associated with hypercoagulable states and increased stroke risks, but no significant differences in clinical features or other risk factors (hypertension, diabetes, coronary artery disease or clinical stroke) were evident between $ACLA^+$ and $ACLA^-$ groups [140].

Elevated plasma homocystein levels have also been associated with ischemic events resulting in VP, as well to increased risk of dementia associated with PD, but this abnormality has been attributed to levodopa therapy [141–144], influenced by the B vitamin status [145], and may not be specific for movement or neurodegenerative disorders [146]. Patients with homocysteine levels in the higher quartile have an increased risk of coronary disease [143] and dementia [147], while other researchers observed no association with neuropsychiatric disorders (depression and cognitive impairment), enhanced disease severity or vascular comorbidity [148].

There are conflicting data regarding the relationship of PD and CVD. Some studies have reported lower or equal prevalence of stroke in PD than in controls [149], related to reduced vascular disease risk factors attributable to reduced autonomic activity [150], and a decreased dopamine level in the brain [151]. It has even been proposed that treating PD patients with dopaminergic drugs would increase the risk of endothelial dysfunction and atherosclerosis by raising levels of homocysteine [152]. However, several clinical studies showed that the presence of CVD in PD patients may aggravate the severity of late-onset disease, and treatment of vascular riks factors may contribute to control the natural course of PD, particularly in older patients [70]. Other studies showed an increased risk of stroke-related deaths in PD patients [28].

Pathophysiology

The pathophysiology of VP varies according to the type and extent of lesions and symptoms observed. An abrupt-onset parkinsonism owing to a large infarct in the basal ganglia may differ from that of insidious forms owing to lacunar or chronic ischemic damage affecting the subcortical white matter.

The combination at onset of unilateral parkinsonism or shuffling gait with a hemiparesis contralateral to the involved basal ganglia or thalamus suggests coexistent damage to the nigrostriatal dopaminergic pathway and to corticospinal fibers in the internal capsule. Lesions in the posterior part of the putamen might lead to a shift of balance toward the indirect pathway if it mainly reduces inhibition by D1 dopamine receptors, thereby increasing the excitation of GPi/SN pars reticulata further (**Figure 1**). It was suggested that parkinsonism after acute stroke related to damage of the strategic areas near to the internal capsule may be caused by a decrease in the thalamocortical drive [153], causing a contralateral hypokinetic rigid syndrome or shuffling gait [30], but the interpretation of fairly discrete lesions in strategic areas causing parkinsonism needs confirmation by further pathological studies.

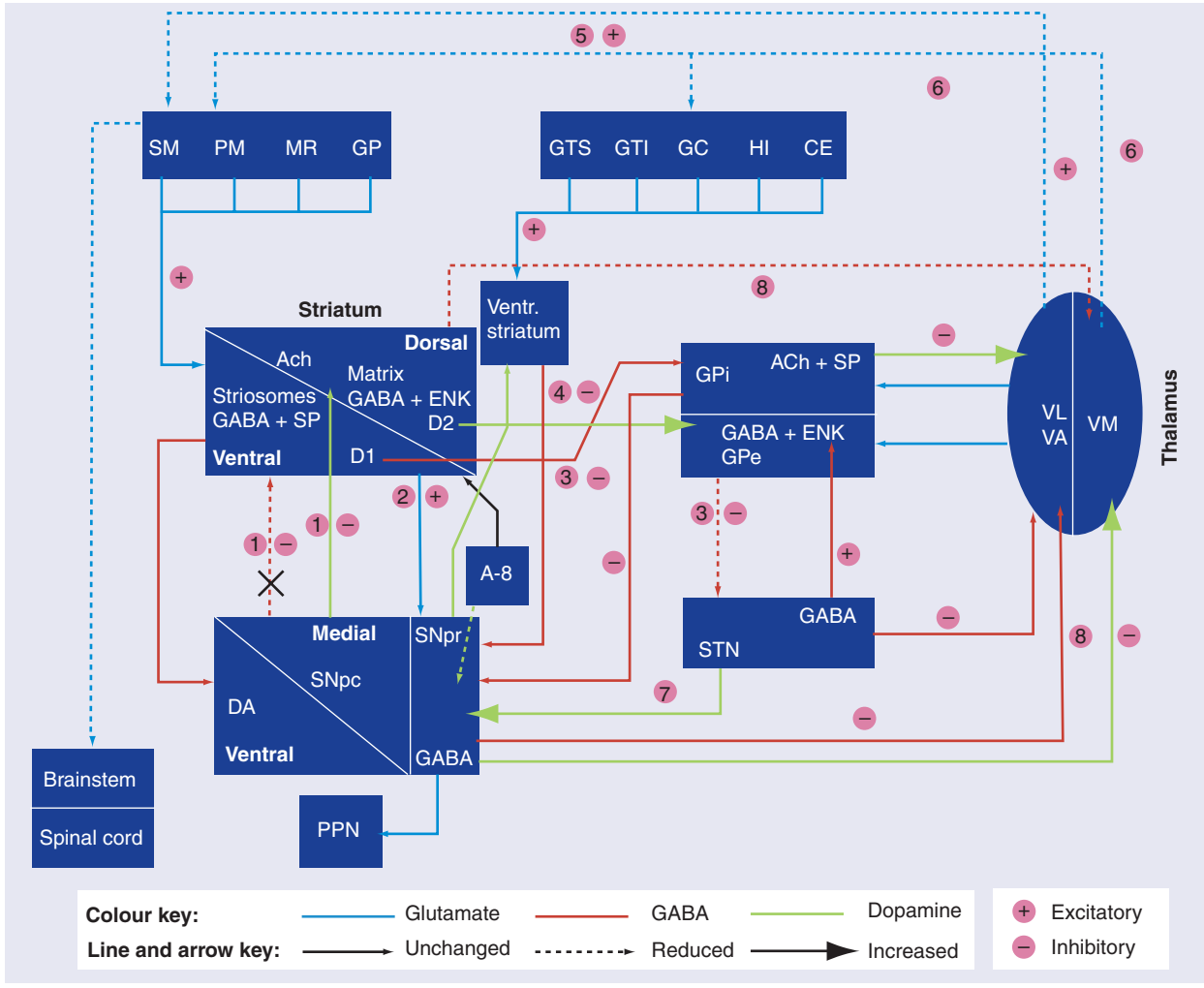
Lacunar lesions in the rostral or entire putamen with or without extension into the head of the caudate nucleus and GPi are not expected to reduce the thalamocortical drive and, therefore, may be silent. However, diffuse microscopic SVD pathological states in the deep gray and white matter, unrelated to specific areas of infarction, may cause disconnection of thalamocortical fibers to the supplementary motor area and cerebellar fibers to the leg area as a pathophysiological mechanism [71].

Frontal gait disorders and gait ignition failure are thought to result from impairment of executive and planning functions of the basal ganglia–frontal lobe circuitry, owing to combined lesions of the subcortical white matter and caudate-putamen [154]. These pathophysiological concepts are in accordance with MRI and histopathological studies demonstrating that in cases of acute-onset parkinsonism, lesion load is greater in the gray nuclei than in cases with insidious onset [44].

In summary, coexisting damage to the nigrostriatal dopaminergic or striatal outflow pathways, either ischemic or owing to underlying subclinical PD, may be crucial in the pathogenesis of parkinsonism related to CVD. Chronic ischemia could lead, by hypoxia or secondary excitotoxic mechanisms, to WMLs and to a loss of D1 striatal dopaminergic receptors, related to a marked imbalance in the ratio of β-preprotachykinin-D1:preproenkephalin-D2 striatal outflow pathways in human postmortem brains of patients with lacunar stroke compared with older controls [155]. Chronic ischemia decreases the expression of β-2 and α-4 subunits of nicotinic acetylcholine receptors, which in turn activate the dopaminergic pathway [156].

One patient with VP showed an isolated ischemic focal lesion in the left cerebral peduncle between SN and nucleus ruber, as evidenced by

Figure 1. Schematic diagram of basal ganglia–thalamocortical circuitry under normal conditions and in Parkinson's disease.



Cortex: CE: Entorhinal cortex; GC: Gyrus cinguli; GP: Postcentral gyrus; GTI: Gyrus temporalis inferior; GTS: Gyrus temporalis superior; HI: Hippocampus; MR: Motor cortex; PM: Premotor field; SM: Supplementary motor field.
Basal ganglia: 1: Nigrostriatal dopaminergic pathway; 2: Striato–nigral pathway; 3: Indirect loop; 4: Direct loop; 5: Motor or complex loop; 6: Thalamocortical pathway; 7: Pallido–subthalamic pathway.
A-8: Retrorubral field; Ach: Acetylcholine; CS: Superior colliculus; DA: Dopamine; ENK: Enkephalin; GPe: External globus pallidus; GPi: Internal globus pallidus; MPT: Mesopontine tegmentum; PNN: Pedunculopontine nucleus; SN: Substantia nigra; SNpc: SN pars compacta; SNpr: SN pars reticulata; SP: Substance P; STN: Subthalamic nucleus; VA: Ventro-anterior thalamus; VL: Ventrolateral thalamus; VLM: Ventro-lateral/medial thalamus; Vm: Medioventral thalamus.
Adapted from [3].

MRI, suggesting an interruption of nigrothalamic projections, not causing a striatal dopamine deficiency pathognomonic of PD. Nonresponse to levodopa therapy in this patient was suggested to be the consequence of ischemic destruction of subcortico-cortical axons, suggesting an alternative pathophysiological explanation for the nature of the disease [157].

However, the elucidation of pathophysiological concepts of VP is limited by the following facts [31]:

- Most patients with subcortical ischemic lesions, even if very extensive, will never develop parkinsonism;
- Among patients with cerebrovascular lesions, there is no clear difference in the extent of vascular damage to the basal ganglia and subcortical white matter between patients with and without parkinsonism [62];
- Infarction or hemorrhage in the subthalamic nucleus, the motor ventro-oral thalamus and

the ipsilateral cerebellum have also been described to improve pre-existing parkinsonism [46,158–163].

Treatment options

Since VP is assumed to be caused by CVD, it seems logical to apply the principles of primary and secondary prevention of vascular disorders of the brain. Therefore, control of hypertension and diabetes mellitus, cessation of smoking, appropriate use of antiplatelet drugs for ischemic cardiac and cerebral disease, treatment and prevention of hyperlipidemia, regular exercise and corrections to lifestyle would appear justified. However, to the best of the reviewer's knowledge, there are no systematic studies available to ascertain the effectiveness of such approaches for VP.

Poor or only transient response to dopaminergic therapy appears unsurprising, since, unlike PD, VP is not caused by a disease predominantly involving the dopaminergic system, although PD is undoubtedly a multisystem disorder [3,164]. However, a recent study examined correlations of positive levodopa response with the presence of a nigrostriatal pathology owing to either vascular disease or neuronal loss [30]. A total of 17 patients with pathologically confirmed VP were selected and their L-dopa response during life was compared with the presence of vascular lesions in the nigrostriatal pathway and nigral cell loss. The response was graded excellent (70–100% improvement of motor symptoms), good (50–70% improvement), moderate (25–50% improvement) or absent (<25%). Ten out of 12 patients with a good or excellent response had macroscopic infarcts or lacunes in the basal ganglia or neuronal loss in the SN. By contrast, only one of five patients with moderate or no response had lacunes in the putamen; none had lacunar infarcts or nigral cell loss. It was concluded that a substantial number of patients with clinically suspected VP may respond to dopaminergic therapy, especially those with lesions in or close to the nigrostriatal pathway, as demonstrable by modern neuroimaging methods. These data are at variance to several other studies reporting that 38 up to approximately 50% of patients with VP show a sufficient response to levodopa [9,29,32,71,87]. In clinical practice, all patients with suspected VP, particularly those with lesions in or close to the nigrostriatal and other dopaminergic pathways documented by MRI, 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 [33]. A sufficient response to levodopa in this study should 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). A possible explanation for the positive L-dopa response in VP patients is the presence of a remaining pool of striatal dopaminergic nerve terminals in a dysfunctional striatonigral pathway that remains adequate to convert exogenous levodopa into dopamine and thus to restore the intrinsic dopaminergic drive [165]. A norepinephrine precursor, L-threo-dops, was reported to be useful in VP in some open trials [165], but this has not been confirmed.

Occasionally, gait disorder and other symptoms of VP may transiently improve with cerebrospinal fluid (CSF) drainage by lumbar puncture, similar to that seen in normal-pressure hydrocephalus [166]. Clinical improvement after CSF removals was predicted by any positive response to L-dopa, lack of vertical gaze palsy, absence of pure freezing gait and lack of hypotensive episodes. MRI did not find any features with predicted response. Clinically, these symptoms resembled PD, whereas nonresponders more closey resembled PSP. If this study is confirmed, it could bring an interesting option of CSF drainage in patients with VP and PD. However, this improvement is rarely sustained and is not predictive of response to CSF shunting.

There are only very few data on the efficacy of subcortical stimulation in patients with VP. In a patient with parkinsonism caused by hypoxic striatal lesions secondary to hypoxic encephalopathy, posteroventral pallidotomy showed positive effects [167], whereas in patients with postischemic parkinsonism owing to a combination of SN striatal and external and internal pallidal lesions, subthalamic nucleus stimulation has been reported to be ineffective [168].

Depending on the identification of stroke risk factors, patients with VP should be treated with antiplatelet therapy, or anticoagulation in those with atrial fibrillation and valvular heart disease with high risk of embolization [32]. Furthermore, reduction of plasma homocysteine levels should be tried by using folate and other medication [169,170]. Plasma levels of antioxidant vitamins C and E are decreased in VP but normal in PD, stressing the necessity of maintaining sufficient dietary intakes of these agents in the elderly [171].

Rehabilitation of patients with dominant gait disorder employing a multidisciplinary team approach is extremely important. Some patients can be helped by the use of visual cues, for example, walking with upturned walking sticks. Behavior therapy may help patients limited by fear of falling. 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 a successful rehabilitation of patients with L-dopa-refractory parkinsonism; higher subcortical cerebrovacular load was associated with less successful rehabilitation [172].

Conclusion

Parkinsonism can be caused by CVD, particularly in an older population. It can result from a variety of vascular insults to the brain. The clinical situations are heterogenous, ranging from the exceptional situation of unilateral or bilateral parkinsonism, mimicking PD, to the more common pseudoparkinsonism, tending to be bilaterally symmetrical, affecting lower limbs more than the upper limbs (lower-body parkinsonism), mainly affecting gait, and usually with the absence of resting tremors. The diagnosis of VP should be based upon the convergence of clinical and imaging clues, but any of the following may be specific: history of vascular risk factors; history of stroke; parkinsonism with

Table 3. Differential diagnosis of vascular parkinsonism.

	Acute/subacute VP	VP with insidious onset	Gait disorder in SAE	Coincidence of PD and SAE
Vascular risk factors	Constant	Constant	Constant	Frequent
Onset	Acute/subacute	Insidious	Insidious	Insidious
Laterality	Mainly contralateral to lesion	Bilateral	Bilateral	Usually lateralized symptoms, axial disorders often predominent
Gait disorder	Frequent	Always	Always	Almost constantly
Falls	Occasional	Frequent	Frequent	Frequent
Resting tremor	Occasional	Rare, no typical pill-rolling tremor	No	Frequent
Akinesis upper limbs	Frequent	Almost constantly	No	Almost constantly
Dementia	Possible	Frequent	Frequent	More frequent than in isolated PD
Course	Variable: progressive/ remittent; frequently transition to progressive	Progressive or stationary; stepwise progression possible	Progressive or stationary; stepwise progression possible	Chronically progressive; stepwise progression possible
CCT/MRI	Local lesions in GPe, VL, SN, frontal regions	Subcortical microangiopathy with frequent frontal predominance	Some	Some
FP-CIT-SPECT*	'Punch-out' lesions	Occasional diminished radionuclide binding	Nothing abnormal	Reduced radionuclide binding
Cardiac MiBG scintigraphy‡	Negative	Negative	Unknown	Positive
Olfactory testing§	Normal	Normal	Normal	Pathologic
Levodopa response	Frequent	Possible	No	Present, often incomplete

**From [105].*

‡From [66].

§From [72].

CCT: Cranial computed tomography; GPe: External globus pallidus; MiBG: [123I]Metaiodobenzylguanidine; MRI: Magnetic resonance imaging; PD: Parkinson's disease; SAE: Subcortical arteriosclerotic encephalopathy; SN: Substantia nigra; VL: Ventrolateral thalamus; VP: Vascular parkinsonism.

Modified from [34].

Executive summary

- Vascular parkinsonism (VP) is a rare clinicopathological entity distinct from classical (Lewy body) Parkinson's disease (PD) and other predominantly neurodegenerative disorders associated with parkinsonism.
- VP accounts for 3–12% of all cases of parkinsonism in older people. However, because of problems with definition and the clinical and pathological heterogeneity of VP, its epidemiology is difficult to determine. Modern epidemiological and autopsy studies indicate that cerebrovascular disease accounts for 3–6% of parkinsonism.
- The parkisonism usually tends to be bilaterally symmetrical, with rigidity and bradykinesia, affecting lower limbs more than upper limbs ('lower-body parkinsonism'), postural instability, shuffling gait, falls and resting tremors being very rare or absent. Frequent additional signs include transient deficits, pyramidal signs, speech disorders, pseubobulbar palsy, dysphagia, urinary incontinence and cognitive dysfunction/dementia (atypical or 'pseudoparkinsonism'). In contrast to PD, most patients with VP without associated dementia have a preserved sense of smell and, therefore, olfactory function tests are helpful.
- The main pathological lesions underlying VP are multiple subcortical ischemic changes owing to small-vessel disease (microinfarcts and lacunes) in the basal ganglia (globus pallidus, thalamus, striatum and, rarely, substantia nigra), white matter lesions and, rarely, territorial infarcts. The lesions involve cortico–striato–pallidal (nigral), thalamofrontal and other circuitries.
- Recent studies suggested two types of onset of VP: one with acute onset, associated with basal ganglia infarctions/lacunes, and the other with insidious onset, mainly associated with diffuse subcortical white-matter lesions.
- Neuroimaging, in particular magnetic resonance imaging, is a useful morphological method to evaluate cerebrovascular lesions and to exclude other CNS lesions.
- Functional imaging with single photon emission computed tomography (SPECT) and positron emission tomography (PET), particularly using dopamine transporter ligands, have greatly helped to understand and differentiate various forms of parkinsonism. Presynaptic dopaminergic function is reduced in most VP patients and those with basal ganglia infarction give a charactristic 'punched-out' deficit. Reduced striatal fluazenil uptake may also be a reliable marker for VP. In contrast to PD, myocardial [123I]Metaiodobenzylguanidine SPECT is normal in VP.
- Although neuropathological demonstration of cerebrovascular disease in the absence of Lewy body and other pathologies causing parkinsonism is still the diagnostic 'gold standard', modern diagnostic clinical criteria proposed by Zijlmans *et al.*, including testing of olfactory function, and a differential diagnostic scheme proposed by Ebersbach and Poewe will increase the diagnostic accuracy of VP, which is currently based upon the convergence of clinical, anamnestic and imaging clues.
- Major risk factors of VP are principally the same as those of cerebrovascular disease and their prevention and treatment is of great importance.
- VP is generally considered to be poorly responsive to dopaminergic therapy, but recent studies have shown a beneficial effect in at least a subset of patients. However, at present there are no clinical or imaging clues that may predict levodopa responsiveness. Deep-brain stimulation is generally ineffective.
- Cerebrovascular lesions are a frequent incidental finding in neurodegenerative PD, and may influence its severity and natural history. However, it is still poorly understood why some people develop VP and others not, despite apparently similar vascular pathologies.

atypical signs and levodopa response; and evidence of cerebrovascular lesions on MRI and normal dopamine transporter SPECT. Although generally considered as poorly effective, levodopa has recently been shown to be beneficial in a subset of patients with VP. At present it remains unexplained as to why some patients with a similar load and distribution pattern of cerebrovascular lesions develop VP and others do not. Both the mode of onset and the type and distribution of lesions involved are heterogenous. Moreover, it should not be forgotten that vascular lesions may also frequently coexist with PD and could modify the spontaneous evolution of natural history of the disease. New diagnostic criteria (**Box 2**) [44] should be used, to which testing of the olfactory function should be added [72]. Although pathological evidence of CVD in the absence of Lewy body and other pathologies causing parkinsonism still represents the diagnostic 'gold standard', a differential diagnostic scheme proposed by Ebersbach and Poewe [34] might help to clinically diagnose VP and to distinguish it from other parkinsonian syndromes (**Table 3**).

VP is generally considered to be poorly responsive to dopaminergic therapy, but recent studies have shown a beneficial effect in a

subset of patients. As in other cerebrovascular disorders, treatment of vascular risk appears to be of utmost importance.

Despite considerable advances in the understanding of the disease, many 'black holes' in our knowledge of the pathogenesis, clinical diagnosis, pathophysiology and treatment of VP will hopefully be clarified by future research.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

No writing assistance was utilized in the production of this manuscript.

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