Published in final edited form as:

Mov Disord. 2015 June ; 30(7): 886–894. doi:10.1002/mds.26263.

Vascular parkinsonism: Deconstructing a syndrome

Joaquin A. Vizcarra¹, Anthony E. Lang, MD, FRCPC², Kapil D Sethi, MD, FRCP(UK), FAAN³, and Alberto J. Espay, MD, MSc, FAAN⁴

¹ Facultad de Medicina “Alberto Hurtado”, Universidad Peruana Cayetano Heredia, Lima, Peru

² Movement Disorders Clinic and the Edmond J. Safra Program in Parkinson’s Disease, University Health Network, University of Toronto, Toronto, Canada

³ Georgia Regents University, Department of Neurology, Augusta, Georgia; and Merz Pharmaceuticals, Raleigh, North Carolina, USA

⁴ Gardner Family Center for Parkinson’s Disease and Movement Disorders, Department of Neurology, University of Cincinnati, Cincinnati, Ohio, USA

Abstract

Progressive ambulatory impairment and abnormal white matter signal on neuroimaging come together under the diagnostic umbrella of vascular parkinsonism. A critical appraisal of the literature, however, suggests that (1) no abnormal structural imaging pattern is specific to vascular parkinsonism; (2) there is poor correlation between brain magnetic resonance imaging hyperintensities and microangiopathic brain disease and parkinsonism from available clinicopathologic data; (3) *pure* parkinsonism from vascular injury (“definite” vascular parkinsonism) consistently results from ischemic or hemorrhagic strokes involving the substantia nigra and/or nigrostriatal pathway but sparing the striatum itself, the cortex, and the intervening white matter; and (4) many cases reported as vascular parkinsonism may represent *pseudovascular* parkinsonism (e.g., Parkinson disease or another neurodegenerative parkinsonism such as progressive supranuclear palsy with non-specific neuroimaging signal abnormalities), vascular *pseudoparkinsonism* (e.g., akinetic mutism due to bilateral mesial frontal strokes or apathetic depression from bilateral striatal lacunar strokes), or *pseudovascular pseudoparkinsonism* (e.g., higher-level gait disorders, including normal pressure hydrocephalus with transependymal exudate). These syndromic designations are preferable over *vascular parkinsonism* until pathology or validated biomarkers confirm the underlying nature and relevance of the leukoaraiosis.

Ischemic or hemorrhagic lesions in the substantia nigra or nigrostriatal pathway, leading to presynaptic dopamine transporter deficiency as measured by SPECT, are the only proven vascular lesions that consistently lead to parkinsonism, and might be considered “pure” or “definite” vascular parkinsonism (VaP). Virtually no other strategic vascular lesion directly

All correspondence to: Dr. Alberto J. Espay, University of Cincinnati Academic Health Center, 260 Stetson St., Suite 2300, Cincinnati, OH 45267-0525, USA, P: 513-558-4035 - F: 513-558-7015 - alberto.espay@uc.edu.

Author roles:

1. Research project: A. Conception, B. Organization, C. Execution;

2. Manuscript: A. Writing of the first draft, B. Review and Critique;

Vizcarra: 1B, 1C, 2A. Lang: 1C, 2B. Duker: 1C, 2B. Espay: 1A, 1B, 1C, 2B.

mediates the development of true parkinsonism but might lead to such disorders as akinetic mutism (bilateral anterior cerebral artery strokes, affecting the anterior cingulate gyrus)¹ or apathy or apathetic depression (left frontal and bilateral striatal lacunar strokes with dysfunction of the frontal-striatal network),² often mischaracterized as parkinsonism.

Nevertheless, the term “VaP” is applied to those whose impairments, predominantly in ambulation and posture, are associated with imaging abnormalities assumed to be of vascular origin. This concept has persisted minimally challenged since Critchley’s 1929 description of a tremorless disorder with rigidity, masked face, short-stepped gait and dementia, he referred to, without pathologic confirmation, as “arteriosclerotic parkinsonism.”³ Subsequently, two presumed cerebral vasculopathies, *Binswanger disease* and cribriform state or *état criblé* (enlarged perivascular [Virchow-Robin] spaces, also referred to as “Swiss cheese striatum”) were proposed based on computed tomography (CT)⁴ and magnetic resonance imaging (MRI) data,⁵ respectively. These imaging modalities are often relied upon to indicate “white matter disease” or leukoaraiosis, and suggested to be associated with, or render patients at risk for, parkinsonism. Thus, with virtually no pathology to support it, VaP became widely accepted as a nosological entity based on imaging abnormalities and a loosely defined syndrome of “lower body” parkinsonism.⁶ Given the hazy boundaries of VaP, its prevalence has been estimated to be as low as 2%⁷ and as high as 29%⁸ of all cases of parkinsonism, depending on population and criteria, which largely rests on studies variably combining features of ambulatory impairment and neuroimaging changes *suggestive* of vascular pathology –and some temporal connection between the two.

Even after admitting our inaccuracy in ascertaining the presence of true vasculopathy as underlying leukoaraiosis on neuroimaging, a major problem lies with the definition of parkinsonism itself. Slowness and reduction of amplitude of movement alone do not suffice to qualify as bradykinesia. (Indeed, stiff person syndrome and primary lateral sclerosis, two disorders that markedly reduce speed and amplitude of movement, are not classified as “parkinsonian”). Parkinsonism requires the presence of true bradykinesia, which is generally defined by the sequence effect, a progressive decrement in the speed and amplitude of movement over repetitive tasks.⁹ However, it is worth noting that the MDS-UPDRS in sections 3.4-3.8 accepts slowness without a decremental response as indicative of even severe bradykinesia. Thus, it is likely that unclear use of the term parkinsonism is contributing to the confusion in the nomenclature of *vascular parkinsonism*.

In this article, we intend to critically appraise both the *vasculopathy* and the *parkinsonian* components of this syndrome and propose that the use of the term VaP may be misguided, that vascular pathology is a rare cause of true parkinsonism, that the assumption of small-vessel ischemic disease from neuroimaging findings of abnormal white matter signals rests on scant clinicopathologic data, and that a variety of disorders associated with slow movement and abnormal imaging features may be pseudoparkinsonian and/or pseudovascular.

Sizing up the problem: Lessons from a clinico-pathologic case

An 80-year-old man with hypertension, hypercholesterolemia, Meniere's disease and a 60 pack/year accumulated history of smoking presented with a 2.5-year step-wise deterioration of gait and balance, with sudden-onset freezing-of-gait episodes, falls, and urinary incontinence (full case and video previously published.¹⁰). Examination was consistent with moderate cognitive impairment meeting criteria for mild dementia, in the context of a "lower-body predominant" parkinsonism, with wide-based gait on externally rotated feet, shortened stride length in the absence of festination, and impaired postural reflexes. A brain magnetic resonance imaging (MRI) was interpreted as demonstrating cortical atrophy, periventricular and deep white matter hyperintense lesions suggestive of small-vessel ischemic disease, and ventricular enlargement congruent with the extent of surrounding parenchymal atrophy (**Figure 1**). The clinical and imaging pictures met criteria for VaP.¹¹ However, a 3-day external lumbar drainage procedure, performed at the request of his general practitioner, unexpectedly demonstrated between 45% and 200% improvement over baseline walking and turning gait parameters, respectively, with corresponding milder but significant benefit in most cognitive measures. This degree of response to CSF drainage, associated with a high positive predictive value (80-100%) for optimal response to ventriculoperitoneal shunt placement,¹² provided the rationale for a diagnostic revision to normal pressure hydrocephalus (NPH). Unfortunately, the patient died in the immediate post-operative period due to colonic perforation at the abdominal end of the shunt, a rare complication. Post-mortem evaluation demonstrated that, despite the imaging interpretation, the brain was of normal weight (later volumetric analysis of the brain MRI confirmed normal volume; thus the MRI appearance was that of pseudoatrophy) and lacked any changes of microangiopathic vasculopathy (no perivascular pallor, gliosis, hyaline thickening, or enlargement of perivascular spaces). Only non-specific findings corresponding to those previously described for NPH (dilatation of lateral and third ventricles, fibrous thickening of the leptomeninges, gaps in ependymal lining) were observed.¹⁰

With all the caveats of a single case, the following observations can be made regarding the implications for clinical and imaging interpretation of cases suspected as VaP:

- 1) No clinical feature in the "classic" lower-body parkinsonism syndrome is adequate to distinguish VaP from NPH, entities commonly subsumed within this syndrome.
- 2) A history of step-wise decline in a patient with vascular risk factors does not necessarily imply vascular disease.
- 3) There is no clear burden of abnormal white matter signal intensity that can accurately distinguish between clinically diagnosed VaP and NPH.¹³
- 4) Hyperintense periventricular lesions on brain MRI are insufficient to indicate microangiopathic disease.¹⁴ Furthermore, substantial gait benefit to CSF shunting has been documented in patients with VaP without marked ventriculomegaly¹⁵ and in patients with presumed NPH but extensive burden of periventricular white matter abnormalities suggestive of microangiopathy.¹⁶

The boundaries of VaP are poorly defined

Only one clinicopathologic study, from the Queen Square Brain Bank for Neurological Disorders, has served to define what might be considered the modern or prevailing view of VaP.¹¹ This study compared the brains of 17 patients with suspected VaP to those of 10 consecutive age-matched controls who had hypertension and other vascular risk factors in life, but no evidence of parkinsonism. Parkinsonism was initially defined by the presence of bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) in *either upper or lower limb*, and at least one of the following: rest tremor, muscular rigidity, and postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction. The severity of microscopic small-vessel disease pathology (perivascular pallor, gliosis, hyaline thickening, and enlargement of perivascular spaces) was substantially greater in the VaP cohort compared to controls. A single large-vessel stroke was found in the territory of the middle cerebral artery. Macroscopically visible lacunar infarcts (type 1 lacunae) or lacunae caused by enlarged perivascular spaces (type 3 lacunae) were seen in the caudate, putamen, globus pallidus, and thalamus in 11 of the parkinsonian brains, compared to only 1 control brain which showed type 3 putaminal lacunae.¹¹ The onset of parkinsonism was acute progressive or progressive after a latent interval after a hemiparetic stroke in 4 patients, and insidious or step-wise in the remainder. The clinical picture was pleomorphic but included early shuffling gait, falls, cognitive impairment, urinary incontinence, and corticospinal or pseudobulbar signs.¹¹ Based on these data, the authors proposed that the diagnosis of VaP should apply to the presence of parkinsonism, although not as stringently defined as at the outset, developing within a year from CT, MRI, or clinical evidence suggestive of “strategic” strokes (in or near the globus pallidus pars externa, substantia nigra pars compacta, thalamic ventral lateral nuclei, or a large frontal lobe infarct) or “non-strategic” vascular lesions (“extensive subcortical white matter lesions”). In the latter case, the clinical association was with a symmetric parkinsonism, early shuffling gait *or* early cognitive dysfunction. Good response to levodopa was documented retrospectively in 12 of 17 patients from this cohort, 10 of whom had macroscopic infarcts or type 3 lacunae in the basal ganglia “or severe microscopic neuronal cell loss in the substantia nigra.”¹⁷ Neither onset (acute or insidious), nor localization (unilateral or bilateral, upper or lower limbs), nor clinical features (tremor, hypokinetic rigidity, or shuffling gait) predicted the presence or magnitude of levodopa response.¹⁷

Several caveats are worth highlighting about these observations: (1) the severity of microscopic small-vessel disease did not differ between frontal, temporal, parietal, occipital, and striatal regions, suggesting lack of regional specificity; (2) 12 of the 17 patients had nigral cell loss suggestive of underlying neurodegenerative parkinsonism (2 were thought to have multiple system atrophy, 1 progressive supranuclear palsy, and 9 Parkinson disease);¹¹ and (3) VaP criteria could be met with acute, delayed, or insidious presentations, with unilateral or bilateral parkinsonism, with or without gait impairment, and with focal or diffuse lesions, located anywhere in the parenchyma (“strategic” or otherwise). These tolerant clinical and neuroimaging criteria have contributed to ill-defined diagnostic boundaries, misrepresentation of other pathologies (**Table 1**), and alternative definitions

with wide estimates of prevalence (**Supplementary Table 1**). Indeed, a systematic review of 25 articles comparing VaP to Parkinson disease (PD), published up to 2010, concluded that there was no abnormal structural imaging pattern specific to VaP.¹⁸

Vascular disease is a rare cause of parkinsonism

Parkinsonism rarely complicates the recovery from strokes (**Figure 2**). While strokes of the basal ganglia and deep white matter are very frequent in the elderly, most are not followed by parkinsonism.¹⁹ Indeed, silent infarcts in the basal ganglia were identified in 40.2% of 219 consecutive adults “requesting medical evaluation for possible cerebrovascular diseases.”²⁰ Of 56 patients followed for at least one year after a stroke complicated with a movement disorder, only 6 developed parkinsonism with just 2 exhibiting a relatively symmetric, leg-predominant pattern of involvement.²¹

From 220 consecutive brain autopsies of patients with cerebral infarcts, only 5 had a clinical history of parkinsonian symptoms.²² In these 5 brains, there was no correlation between the location/size of the infarcts and the lateralization and severity of their parkinsonism. Nevertheless, the authors of this early influential study concluded that *status cribrosus* (enlarged perivascular spaces) of areas irrigated by paramedian branches of the mesencephalic arteries, “may be responsible for nigral degeneration and for the occurrence of parkinsonism.”²² This conclusion has been decisively challenged by a recent blinded study on patients from Mayo Clinic with striatal enlarged perivascular spaces (see *Pseudovascular parkinsonism*, below).²³

Although hemiparkinsonism is a recognized complication of unilateral strokes in the cerebral peduncle of the midbrain, even if exclusively involving the substantia nigra,²⁴ it rarely complicates large infarcts in the territory of the lenticulostriate arteries,²⁵ as might be expected. Indeed, from a cohort of 11 patients with striatal infarcts selected from 622 consecutive strokes (4.3% of all strokes), only 1 developed parkinsonism on follow up.²⁶ In apparently normal healthy adults, the prevalence of silent cerebral infarctions as measured by brain MRI, increases from 20% in those between 60-69 years to 44% between 70 and 79 years of age.²⁷ Forty-six lesions were found in the basal ganglia out of 121 total in this neurologically-normal population-based study.²⁷

A study comparing the brain pathology of 24 patients who had a premortem diagnosis of VaP with 22 age-matched brains with Binswanger’s disease but no clinical record of parkinsonism found that the extent of vascular lesions in the caudate nucleus, putamen, globus pallidus, and thalamus did not differ between these groups.²⁸ Only the density of oligodendrocytes in the frontal white matter was different: lower in the Binswanger’s disease group than in the VaP. This latter finding suggested, unexpectedly, that there was *less* severe white matter injury among those with parkinsonism.²⁸ The implications from this autopsy study are (1) there is no clear association between the burden of vascular pathology and parkinsonism; and (2) the clinical phenotype arose independently from, or could not be explained by, vascular or Lewy body pathology (indeed, absence of Lewy bodies was a criterion to “confirm” VaP). A final corollary is that the magnitude of leukoaraiosis bears no correlation with the clinical phenotype.

If we assume that vascular disease and parkinsonism are associated, one would expect the rate of parkinsonism prevalence to be congruent with the rates of stroke in the elderly, in whom there is an increasing prevalence of micro- and macro-angiopathic brain disease (**Figure 2**). However, the prevalence of “pathologically proven VaP” is only a fraction of a large PD-like cohort (1%).²⁹ Conversely, the frequency of ‘incidental’ cerebrovascular lesions occurring in pathology-proven PD is 20-30%, supporting the concept that vascular disease does not cause parkinsonism in these individuals.^{30, 31} Furthermore, in PD cohorts with white matter hyperintensities, gait dysfunction is not more common than in cases without this finding on MRI³².

Even relatively rare diseases that share a well-established vascular pathology, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)³³ and anti-phospholipid antibody³⁴ seldom have clinical features of parkinsonism. When assessed systematically, parkinsonism has been described in only 11% of patients from a cohort with the most common *NOTCH3* CADASIL mutation.³⁵ In the largest study to date of genetic leukoencephalopathies, a vascular pattern (defined by the occurrence of hyperintensities involving the deep grey matter, the pons and the external capsules, lacunes on T2/FLAIR sequences and presence of microbleeds on gradient echo sequence) identified in 55 patients, was determined to be due to *NOTCH3* mutation in 32, *COL4A1* mutation in 7, and leukoencephalopathy with calcifications and cysts in 2. Remarkably, none of these patients were reported to have parkinsonism, but exhibited, instead, depression, apathy, cognitive impairment, or migraine.³⁶ Some *non-vascular* leukodystrophies (e.g., hereditary diffuse leukoencephalopathy with axonal spheroids due to *CSF1R* mutations) are rarely associated with parkinsonism.^{36, 37} Even in some of these, parkinsonian-like phenotypes (e.g., apathetic depression, pyramidal weakness, i.e., “pseudo-parkinsonism”) may have been misinterpreted as parkinsonism.

VaP is often *not* vascular: Pseudovascular parkinsonism

Cerebrovascular disease, which by definition must be present in VaP, is one of the organ-specific consequences of hypertension and other vascular risk factors. A recent study found that the prevalence of vascular risk factors (including age, sex, hypertension, diabetes, previous stroke, cardiac disease, cigarette smoking, and serum levels of cholesterol and triglyceride) was not predictive of the burden of leukoencephalopathy in patients with a diagnosis of VaP, even if the extent of these white matter abnormalities correlated with the severity of their motor impairment.³⁸ These findings suggested that at least a substantial subset of their white matter lesions were not vascular in nature.

Importantly, the presence and duration of hypertension or other vascular risk factors do not always correlate with white matter abnormalities. A substantial proportion of the elderly with chronic hypertension either do not develop abnormalities or exhibit demyelinating changes rather than the perivascular pallor and gliosis typical of small-vessel disease.³⁹ The list of disorders causing multifocal or diffuse white matter changes on imaging that may not be vascular in nature include progressive multifocal leukoencephalopathy, human immunodeficiency virus encephalopathy, cerebral hyperperfusion syndrome, posttransfusion syndrome, proximal myotonic myopathy, trauma, radiotherapy, chemotherapy,

postinfectious demyelination, posthypoxic ischemic encephalopathy, cyclosporin or other immunosuppressants, vitamin B12 deficiency, and α -Galactosidase deficiency (Fabry disease).⁴⁰ Yet small-vessel disease tends to be our default etiologic impression upon identification of increased signal on brain MRI.

The vasculopathy-parkinsonism connection was severely challenged in a recent blinded, retrospective case-control study using the MRI database of residents 40 years of age or older of Olmsted County, Minnesota, who had extensive Mayo Clinic medical records and MRI reports of striatal enlarged perivascular spaces (“swiss cheese striatum” [SCS]).²³ Severe SCS cases ($n = 27$) were compared for presence of parkinsonism, dementia, and vascular risk factors with age-, sex-, and examination year-matched controls ($n = 52$) with minimal or no SCS. Both groups had similar rates of parkinsonism (19% vs. 17%; odds ratio, 1.09 [95% CI, 0.28-4.16]), dementia of any type (30% vs. 21%; odds ratio, 1.57 [95% CI, 0.48-5.13]), and vascular risk factors. The authors concluded that “skepticism is called for when attributing clinical symptoms [e.g., parkinsonism] to this MRI finding.”²³ Many of these patients thus, would have to be reclassified as “pseudovascular parkinsonism”.

Vascular disease can be suspected by history or imaging but it can only be confirmed by pathology. Seminal papers, including Thompson and Marsden’s description of 12 patients with CT-diagnosed Binswanger’s disease of whom 5 had “lower-half parkinsonism,”⁴ have not relied on pathologic confirmation of their cases. The diagnosis has often sufficed if hypertension or other vascular risk factors are identified in individuals with gait-predominant impairment, poor levodopa response, and white matter abnormalities on imaging.⁴¹⁻⁴³

Vascular pseudoparkinsonism

In addition to the difficulties establishing a vascular etiology, the literature on VaP has also been encumbered by reports of patients whose abnormal motor function does not meet the definition of parkinsonism.⁴⁴ Instead of a progressive reduction in amplitude and speed with rapid repetitive movements (the “sequence effect”, considered critical for the definition of bradykinesia, the core element of parkinsonism⁹), these patients may exhibit a reduction in amplitude and speed that varies but does not progressively diminish during a task. This pseudoparkinsonian state may be an expression of cognitive rather than primary motor impairment, and supports its classification under the rubric of a higher-level gait disorder (HLGD), meant to include such previous descriptors for gait impairment as frontal, magnetic, or “apraxic”, and encompassing varying degrees of slowed and short-stepped gait with freezing.⁴⁵ It is unclear how many of the patients categorized as parkinsonism exhibit, instead, motor abnormalities stemming from thalamo-striato-cortical-frontal involvement (i.e., executive dysfunction) or corticospinal involvement (i.e., spasticity, pyramidal weakness, pseudobulbar affect), which slow movement but do not qualify as true parkinsonism.

Adding further difficulties to our clinical interpretation, the core features of VaP and NPH, considered common expressions of HLGD, substantially overlap. Acknowledging that the definitions for VaP and NPH predated the MRI era and remain insufficiently supported by

clinicopathologic data, the recognition that most features of gait impairment can be found at similar rates in both (**Table 2**),⁴⁶ weakens the case of VaP as a distinct entity.

Conclusions

VaP has remained an outdated remnant of the CT era. The three decades since have confirmed that most patients with large-vessel or small-vessel strokes do not develop parkinsonism; that extensive basal ganglia imaging abnormalities can be present in normal or asymptomatic individuals²⁸ while, counterintuitively, parkinsonism rarely follows striatal infarcts;²⁶ and that ambulatory impairments suggestive of *lower-body parkinsonism* can occur with and without imaging abnormalities, with abnormalities in any part of the parenchyma, or with abnormalities that are not vascular. The terms *functional* VaP and *structural* VaP have more recently been suggested with the advent of dopamine transporter SPECT,⁴⁷ but neither clinical nor imaging data are adequate replacements for pathology-based diagnosis. Only ischemic or hemorrhagic strokes affecting the substantia nigra and/or nigrostriatal pathway but sparing the striatum and the cortex predicts “definite” vascular parkinsonism. It can be argued that many cases reported as VaP represent *pseudovascular* parkinsonism (e.g., Parkinson disease or another neurodegenerative parkinsonism such as PSP with non-specific neuroimaging signal abnormalities), vascular *pseudoparkinsonism* (e.g., akinetic mutism due to bilateral mesial frontal strokes or apathetic depression from bilateral striatal lacunar strokes), or *pseudovascular pseudoparkinsonism* (e.g., higher-level gait disorders, including normal pressure hydrocephalus with transependymal exudate) (**Figure 3**). Until a biomarker of vasculopathy is identified, we suggest using clinical descriptors instead of VaP to avoid assumptions of vascular pathology and pathogenesis for an individual’s gait-predominant impairment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

The authors thank Marcia Hartsock, MA, CMI, for creating Figure 3 for this manuscript.

Full financial disclosure for the previous 12 months:

Mr. Vizcarra has no disclosures to report.

Dr. Lang has served as an advisor for Abbvie, Allon Therapeutics, Avanir Pharmaceuticals, Biogen Idec, Boehringer-Ingelheim, Ceregene, Lilly, Medtronic, Merck, Novartis, NeuroPhage Pharmaceuticals, Teva and UCB; received honoraria from Medtronic, Teva, UCB, AbbVie; received grants from Brain Canada, Canadian Institutes of Health Research, Edmond J Safra Philanthropic Foundation, Michael J. Fox Foundation, the Ontario Brain Institute, National Parkinson Foundation, Parkinson Society Canada, Tourette Syndrome Association, W. Garfield Weston Foundation; received publishing royalties from Saunders, Wiley-Blackwell, Johns Hopkins Press, and Cambridge University Press; and has served as an expert witness in cases related to the welding industry.

Dr. Sethi is part-time employed as senior Medical expert with Merz Pharmaceuticals and has served as an advisor to Lundbeck, Synosia, Veloxis, Teva, Adamas, and Acadia; received honoraria from Lundbeck, Teva, and Veloxis; received grant support from Abbvie, Kyowa, Acadia, Pharma2B, and NIH and NPF; and has served as an expert witness in welding litigation.

Dr. Espay is supported by the K23 career development award (NIMH, 1K23MH092735); has received grant support from CleveMed/Great Lakes Neurotechnologies, and the Michael J Fox Foundation; personal compensation

as a consultant/scientific advisory board member for Abbvie, Chelsea Therapeutics, TEVA, Impax, Merz, Pfizer, Acadia, Cynapsus, Solstice Neurosciences, Eli Lilly, Lundbeck, and USWorldMeds; royalties from Lippincott Williams & Wilkins and Cambridge University Press; and honoraria from UCB, TEVA, the American Academy of Neurology, and the Movement Disorders Society.

References

1. Kumral E, Bayulkem G, Evyapan D, Yuntun N. Spectrum of anterior cerebral artery territory infarction: Clinical and mri findings. *Eur. J. Neurol.* 2002; 9:615–624. [PubMed: 12453077]
2. Hama S, Yamashita H, Shigenobu M, Watanabe A, Kurisu K, Yamawaki S, et al. Post-stroke affective or apathetic depression and lesion location: Left frontal lobe and bilateral basal ganglia. *Eur. Arch. Psychiatry Clin. Neurosci.* 2007; 257:149–152. [PubMed: 17131217]
3. Critchley M. Arteriosclerotic parkinsonism. *Brain.* 1929; 52:23–83.
4. Thompson PD, Marsden CD. Gait disorder of subcortical arteriosclerotic encephalopathy: Binswanger's disease. *Mov. Disord.* 1987; 2:1–8. [PubMed: 3504256]
5. Mehta SH, Nichols FT 3rd, Espay AJ, Duker AP, Morgan JC, Sethi KD. Dilated virchow-robin spaces and parkinsonism. *Mov. Disord.* 2013; 28:589–590. [PubMed: 23575640]
6. van Swieten JC, van den Hout JH, van Ketel BA, Hijdra A, Wokke JH, van Gijn J. Periventricular lesions in the white matter on magnetic resonance imaging in the elderly. A morphometric correlation with arteriolosclerosis and dilated perivascular spaces. *Brain.* 1991; 114:761–774. Pt 2. [PubMed: 2043948]
7. Savica R, Grossardt BR, Bower JH, Ahlskog JE, Rocca WA. Incidence and pathology of synucleinopathies and tauopathies related to parkinsonism. *JAMA Neurol.* 2013; 70:859–866. [PubMed: 23689920]
8. El-Tallawy HN, Farghaly WM, Shehata GA, Rageh TA, Hakeem NM, Hamed MA, et al. Prevalence of parkinson's disease and other types of parkinsonism in al kharga district, egypt. *Neuropsychiatr. Dis. Treat.* 2013; 9:1821–1826. [PubMed: 24379673]
9. Kang SY, Wasaka T, Shamim EA, Auh S, Ueki Y, Lopez GJ, et al. Characteristics of the sequence effect in parkinson's disease. *Mov. Disord.* 2010; 25:2148–2155. [PubMed: 20669182]
10. Espay AJ, Narayan RK, Duker AP, Barrett ET Jr. de Courten-Myers G. Lower-body parkinsonism: Reconsidering the threshold for external lumbar drainage. *Nat. Clin. Pract. Neurol.* 2008; 4:50–55. [PubMed: 18199997]
11. Zijlmans JC, Daniel SE, Hughes AJ, Revesz T, Lees AJ. Clinicopathological investigation of vascular parkinsonism, including clinical criteria for diagnosis. *Mov. Disord.* 2004; 19:630–640. [PubMed: 15197700]
12. Marmarou A, Bergsneider M, Klinge P, Relkin N, Black PM. The value of supplemental prognostic tests for the preoperative assessment of idiopathic normal-pressure hydrocephalus. *Neurosurgery.* 2005; 57:S17–28. discussion ii-v. [PubMed: 16160426]
13. Tullberg M, Hultin L, Ekholm S, Mansson JE, Fredman P, Wikkelsö C. White matter changes in normal pressure hydrocephalus and binswanger disease: Specificity, predictive value and correlations to axonal degeneration and demyelination. *Acta Neurol. Scand.* 2002; 105:417–426. [PubMed: 12027829]
14. Matsusue E, Sugihara S, Fujii S, Ohama E, Kinoshita T, Ogawa T. White matter changes in elderly people: Mr-pathologic correlations. *Magn. Reson. Med. Sci.* 2006; 5:99–104. [PubMed: 17008766]
15. Ondo WG, Chan LL, Levy JK. Vascular parkinsonism: Clinical correlates predicting motor improvement after lumbar puncture. *Mov. Disord.* 2002; 17:91–97. [PubMed: 11835444]
16. Krauss JK, Droste DW, Vach W, Regel JP, Orszagh M, Borremans JJ, et al. Cerebrospinal fluid shunting in idiopathic normal-pressure hydrocephalus of the elderly: Effect of periventricular and deep white matter lesions. *Neurosurgery.* 1996; 39:292–299. discussion 299–300. [PubMed: 8832666]
17. Zijlmans JC, Katzenschlager R, Daniel SE, Lees AJ. The l-dopa response in vascular parkinsonism. *J. Neurol. Neurosurg. Psychiatry.* 2004; 75:545–547. [PubMed: 15026493]

18. Kalra S, Grosset DG, Benamer HT. Differentiating vascular parkinsonism from idiopathic parkinson's disease: A systematic review. *Mov. Disord.* 2010; 25:149–156. [PubMed: 20077476]
19. Awad IA, Johnson PC, Spetzler RF, Hodak JA. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly. II. Postmortem pathological correlations. *Stroke.* 1986; 17:1090–1097. [PubMed: 3810706]
20. Uehara T, Tabuchi M, Mori E. Risk factors for silent cerebral infarcts in subcortical white matter and basal ganglia. *Stroke.* 1999; 30:378–382. [PubMed: 9933274]
21. Alarcon F, Zijlmans JC, Duenas G, Cevallos N. Post-stroke movement disorders: Report of 56 patients. *J. Neurol. Neurosurg. Psychiatry.* 2004; 75:1568–1574. [PubMed: 15489389]
22. de Reuck J, Sieben G, de Coster W, vander Ecken H. Parkinsonism in patients with cerebral infarcts. *Clin. Neurol. Neurosurg.* 1980; 82:177–185. [PubMed: 6260413]
23. Burnett MS, Witte RJ, Ahlskog JE. Swiss cheese striatum: Clinical implications. *JAMA Neurol.* 2014; 71:735–741. [PubMed: 24733660]
24. Ohta K, Obara K. Hemiparkinsonism with a discrete lacunar infarction in the contralateral substantia nigra. *Mov. Disord.* 2006; 21:124–125. [PubMed: 16229001]
25. Fenelon G, Houeto JL. Unilateral parkinsonism following a large infarct in the territory of the lenticulostriate arteries. *Mov. Disord.* 1997; 12:1086–1090. [PubMed: 9399244]
26. Peralta C, Werner P, Holl B, Kiechl S, Willeit J, Seppi K, et al. Parkinsonism following striatal infarcts: Incidence in a prospective stroke unit cohort. *J. Neural Transm.* 2004; 111:1473–1483. [PubMed: 15340870]
27. Lee SC, Park SJ, Ki HK, Gwon HC, Chung CS, Byun HS, et al. Prevalence and risk factors of silent cerebral infarction in apparently normal adults. *Hypertension.* 2000; 36:73–77. [PubMed: 10904015]
28. Yamanouchi H, Nagura H. Neurological signs and frontal white matter lesions in vascular parkinsonism. A clinicopathologic study. *Stroke.* 1997; 28:965–969. [PubMed: 9158634]
29. Hughes AJ, Daniel SE, Lees AJ. Improved accuracy of clinical diagnosis of lewy body parkinson's disease. *Neurology.* 2001; 57:1497–1499. [PubMed: 11673599]
30. Inzelberg R, Bornstein NM, Reider I, Korczyn AD. Basal ganglia lacunes and parkinsonism. *Neuroepidemiology.* 1994; 13:108–112. [PubMed: 8015663]
31. Jellinger KA. The neuropathologic diagnosis of secondary parkinsonian syndromes. *Adv. Neurol.* 1996; 69:293–303. [PubMed: 8615141]
32. Herman T, Rosenberg-Katz K, Jacob Y, Auriel E, Gurevich T, Giladi N, et al. White matter hyperintensities in parkinson's disease: Do they explain the disparity between the postural instability gait difficulty and tremor dominant subtypes? *PLoS One.* 2013; 8:e55193. [PubMed: 23383104]
33. Erro R, Lees AJ, Moccia M, Picillo M, Penco S, Mosca L, et al. Progressive parkinsonism, balance difficulties, and supranuclear gaze palsy. *JAMA Neurol.* 2014; 71:104–107. [PubMed: 24275943]
34. Huang YC, Lyu RK, Chen ST, Chu YC, Wu YR. Parkinsonism in a patient with antiphospholipid syndrome--case report and literature review. *J. Neurol. Sci.* 2008; 267:166–169. [PubMed: 17996905]
35. Ragno M, Berbellini A, Cacchio G, Manca A, Di Marzio F, Pianese L, et al. Parkinsonism is a late, not rare, feature of cadasil: A study on italian patients carrying the r1006c mutation. *Stroke.* 2013; 44:1147–1149. [PubMed: 23412372]
36. Aygnac X, Carra-Dalliere C, Menjot de Champfleury N, Denier C, Aubourg P, Bellesme C, et al. Adult-onset genetic leukoencephalopathies: A mri pattern-based approach in a comprehensive study of 154 patients. *Brain.* 2015; 138:284–292. [PubMed: 25527826]
37. Karle KN, Biskup S, Schule R, Schweitzer KJ, Kruger R, Bauer P, et al. De novo mutations in hereditary diffuse leukoencephalopathy with axonal spheroids (hdls). *Neurology.* 2013; 81:2039–2044. [PubMed: 24198292]
38. Chen YF, Tseng YL, Lan MY, Lai SL, Su CS, Liu JS, et al. The relationship of leukoaraiosis and the clinical severity of vascular parkinsonism. *J. Neurol. Sci.* 2014; 346:255–259. [PubMed: 25240444]

39. van Swieten JC, Geyskes GG, Derix MM, Peeck BM, Ramos LM, van Latum JC, et al. Hypertension in the elderly is associated with white matter lesions and cognitive decline. *Ann. Neurol.* 1991; 30:825–830. [PubMed: 1789694]
40. van Gijn J. Leukoaraiosis and vascular dementia. *Neurology.* 1998; 51:S3–8. [PubMed: 9744823]
41. FitzGerald PM, Jankovic J. Lower body parkinsonism: Evidence for vascular etiology. *Mov. Disord.* 1989; 4:249–260. [PubMed: 2779595]
42. Thanvi B, Lo N, Robinson T. Vascular parkinsonism--an important cause of parkinsonism in older people. *Age Ageing.* 2005; 34:114–119. [PubMed: 15713855]
43. Winikates J, Jankovic J. Clinical correlates of vascular parkinsonism. *Arch. Neurol.* 1999; 56:98–102. [PubMed: 9923767]
44. Sibon I, Fenelon G, Quinn NP, Tison F. Vascular parkinsonism. *J. Neurol.* 2004; 251:513–524. [PubMed: 15164182]
45. Nutt JG. Higher-level gait disorders: An open frontier. *Mov. Disord.* 2013; 28:1560–1565. [PubMed: 24132844]
46. Giladi N, Kao R, Fahn S. Freezing phenomenon in patients with parkinsonian syndromes. *Mov. Disord.* 1997; 12:302–305. [PubMed: 9159723]
47. Vaamonde J, Ibanez R, Garcia AM, Poblete V. [study of the pre and post-synaptic dopaminergic system by datscan/ibzm spect in the differential diagnosis of parkinsonism in 75 patients]. *Neurologia.* 2004; 19:292–300. [PubMed: 15199417]

Figure 1. Brain MRI in case of suspected vascular parkinsonism

Axial fluid-attenuated inversion recovery brain MRI of 80-year-old man with hypertension, hypercholesterolemia, and a 60 pack/year accumulated smoking history. Increased periventricular and subcortical white matter signal is suggestive of small-vessel ischemic disease. Ventricular dilatation appeared roughly proportionate to the assessment of parenchymal atrophy. However, apical cuts (lower row) did not support generalized atrophy. Increased signal intensity affecting subcortical and periventricular white matter suggested chronic small-vessel ischemic disease. Pathology showed normal brain weight, no micro- or macroangiopathy, and instead revealed changes consistent with normal pressure hydrocephalus.

Figure 2. No parkinsonian sequelae in classic vascular injury syndromes

A. Axial diffusion weighted brain MRI exemplifying acute stroke syndromes (clockwise from upper left): complete and partial middle cerebral artery [MCA] territory, exclusively in the caudate and putamen, and small infarcts in different vascular distributions (embolic etiology). B. Head CT of selected traumatic brain injury-associated vascular injury syndromes. Upon recovery, none of these patients manifested parkinsonism. Images courtesy of Drs. Achala Vagal (University of Cincinnati; panel A) and Alisa Gean (University of California, San Francisco; panel B).

Figure 3. Anatomical patterns in “vascular parkinsonism”

Vascular pseudoparkinsonism arises in the context of bilateral mesial frontal strokes due to anterior cerebral artery territory infarcts (A, akinetic mutism); bilateral striatal lacunar infarctions (B, apathetic depression); or small-vessel ischemic disease affecting the pons (C, pyramidal weakness and slowness). **Pseudovascular pseudoparkinsonism** occurs in the context of periventricular and deep white matter signal abnormalities in isolation (D, higher-level gait disorder) or in association with ventriculomegaly (E, higher-level gait disorder in normal pressure hydrocephalus). **Pseudovascular parkinsonism** can be documented in patients with Parkinson’s disease (with a pattern similar to D) or progressive supranuclear palsy (F, arrow point to atrophic midbrain). This diagrammatic representation does not include mixed-pathology parkinsonism (e.g., Parkinson’s disease with true microangiopathic brain disease), presumably accounting for a minority of patients with “vascular parkinsonism.”

Table 1

Most common causes of the syndrome of lower-body parkinsonism

Most common causes of lower-body parkinsonisms		
Clinical presentation	Suspected syndrome	Actual diagnosis
Acute onset of hemiparkinsonism + midbrain stroke/hemorrhage	VaP	Stroke (“definite” VaP)
LBP + diffuse and confluent hyperintensities on brain MRI	VaP (pseudobulbar palsy, pyramidal features)	Binswanger’s disease* Multiple lacunar infarcts
LBP + hyperintensities on brain MRI, esp. in striatum, external capsule, and temporal lobes	VaP	CADASIL (<i>NOTCH3</i>)
Porencephalic cavities, calcifications and microbleeds; sparing of temporal poles	Apathetic depression, abulia, migraine	<i>COL4A1</i> -related disorders
Frontal lobe predominance of white matter hyperintensities	Same as above VaP	Hereditary diffuse leukoencephalopathy with axonal spheroids (<i>CSF1R</i>)
LBP + enlarged perivascular spaces in striatum on MRI	VaP	“Swiss cheese striatum” (also common in CADASIL)
LBP + hydrocephalus	NPH	Idiopathic communicating hydrocephalus Secondary hydrocephalus (meningitis, head trauma)
LBP + hydrocephalus + periventricular and/or deep white matter hyperintensities	NPH + VaP	NPH or microangiopathic brain disease or both (scant clinicopathologic correlations)
LBP + falls + “unremarkable” MRI (early on)	Richardson syndrome	PSP
Primary progressive freezing of gait	Richardson syndrome VaP	PSP Striatonigroluysian degeneration Alzheimer disease
LBP + frontal lobe lesions	Akinesia, abulia, apathetic depression VaP	Tumors Ischemia Demyelination

Lower-body parkinsonism (LBP) has been defined of a syndrome of reduced gait mobility, with shortened stride length, diminished step height, increased step width, and freezing of gait episodes, with poor response to external cues and to levodopa. Abbreviations: CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; NPH: normal pressure hydrocephalus; VaP: vascular parkinsonism; PSP: progressive supranuclear palsy.

* Binswanger’s disease (most often defined by neuroimaging than pathology) has also been referred to as subcortical arteriosclerotic encephalopathy.

Table 2

Clinical features of gait in VaP and NPH

Common to NPH and VaP	Presumed Unique to NPH	Presumed Unique to VaP
Reduced gait velocity	Broad-based gait with outwardly-rotated feet ⁴⁴	None established in comparative studies
Reduced stride length		
Diminished step height		
Increased step width		
Freezing of gait (57%) ⁴²		
Gait apraxia ("frontal ataxia" or "magnetic foot")		
Preserved arm swing		
Poor response to external cues ^a		
Upright posture with "wooden appearance" ⁴		
Poor response to levodopa		

None of these have been based on studies with pathologic correlation.

^a Proprioceptive, visual, or auditory cues are highly effective in increasing stride length and cadence in Parkinson's disease, with which NPH and VaP can be confused. NPH, normal pressure hydrocephalus; VaP, vascular parkinsonism.