Vascular parkinsonism: a case series of 17 patients

Parkinsonismo vascular: uma série de casos de 17 pacientes

Thiago Cardoso Vale¹, Paulo Caramelli¹,², Francisco Cardoso¹,³

ABSTRACT

Objective: To report the clinical and neuroimaging findings in a case series of vascular parkinsonism (VP). Methods: Seventeen patients with VP were evaluated with motor, cognitive, and neuroimaging standardized tests and scales. Results: All patients had arterial hypertension. Ten patients were male and the mean age of the whole sample was 75.8±10.1 years. The mean age of parkinsonism onset was 72.2±10.0 years. Common clinical features were urinary incontinence (88.2%), lower limb parkinsonism with freezing of gait and falls (82.3%), and pyramidal signs (76.4%). The mean Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn-Yahr scores were 72.5±21.6 points and 3.3±0.9 points, respectively. Sixteen (94.1%) patients had freezing of gait and executive dysfunction. Twelve (70.5%) patients had probable vascular dementia. The mean dose of levodopa was 530.9 mg/day. Unresponsiveness to the drug was confirmed by a 6.9 mean point reduction in the UPDRS score after the “practically defined off” test. Conclusion: This series provides a profile of VP with predominant lower-limb involvement, freezing of gait and falls, pyramidal signs, executive dysfunction, concomitant vascular dementia, and poor levodopa response.

Keywords: cerebrovascular disorders, dementia, movement disorders, parkinsonian disorders.

RESUMO

Objetivo: Relatar os achados clínicos e de neuroimagem em parkinsonismo vascular (PV). Métodos: Foram avaliados 17 pacientes com PV do ponto de vista motor, cognitivo e de neuroimagem através de testes e escalas padronizados. Resultados: Dos 17 pacientes, 10 (58,5%) eram homens; a média de idade média foi 75,8±10,1 anos. Todos os pacientes eram hipertensos; a média de idade do início do parkinsonismo foi 72,2±10,0 anos. Achados clínicos mais frequentes: incontinência urinária (88,2%); parkinsonismo de membros inferiores com bloqueio de marcha e quedas (82,3%); sinais piramidais (76,4%). A média dos escores UPDRS e Hoehn-Yahr foram, respectivamente, 72,5±21,6 e 3,3±0,9 pontos. Dezesseis pacientes (94,1%) apresentaram bloqueio de marcha e disfunção executiva. Doze pacientes (70,5%) preencheram critérios para demência vascular provável. A dose média de levodopa foi 530,9 mg/dia e os pacientes tiveram uma baixa resposta à droga, tendo havido redução de apenas 6,9 pontos em média no escore UPDRS após o teste “practically-defined off”. Conclusão: O perfil de PV encontrado neste estudo foi caracterizado por: envolvimento predominante de membros inferiores, com bloqueio de marcha e quedas; sinais piramidais; disfunção executiva; demência vascular concomitante e resposta pobre à levodopa.

Palavras-chave: demência, transtornos cerebrovasculares, transtornos do movimento, transtornos parkinsonianos.

Vascular parkinsonism (VP) is a form of secondary parkinsonism resulting from cerebrovascular disease. The clinical picture of VP is heterogeneous and may pose significant challenges to general neurologists and to movement disorders specialists¹. The diagnosis of VP has remained a controversial clinical concept since 1999 when Winikates and Jankovic first proposed its clinical criteria². It was only in 2004 that a clinicopathological study was performed that led the authors to suggest new and stricter clinical criteria for VP; these criteria are widely used today³. However, given the many overlapping features of parkinsonian syndromes, a definitive diagnosis can only be reached by autopsy.

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Conflict of interest: There is no conflict of interest to declare.

Financial support: Francisco Cardoso received research grants from Fundação de Amparo à Pesquisa do estado de Minas Gerais (FAPEMIG) and an honorarium from Roche and Moksha³. Paulo Caramelli receives research grants from CNPq (Bolsa de Produtividade em Pesquisa) and FAPEMIG.

Received 08 June 2013; Accepted 17 June 2013.
In various population-based studies and clinical series, VP reportedly accounted for 2.5% to 5.0% of all cases of parkinsonismo. In Brazil, Cardoso et al. reported that VP was present in 4.7% of 338 patients who were followed up in a tertiary care specialized movement disorder unit. In a more recent study, Munhoz et al. diagnosed VP in 3.9% of patients in a large clinically based series of 1,528 patients with parkinsonismo. In a community-based survey, called the Bambuí Study, 86 cases of parkinsonism were diagnosed among 1,186 study participants who were aged 64 years or older. The most frequent causes were Parkinson's disease (PD) and drug-induced parkinsonism. The third most frequent etiology was VP, which was diagnosed in 13 (15.1%) patients; it had a crude prevalence rate of 1.1% (95%CI 0.4–1.8).

The clinical features of VP were assessed by a recent systematic review that aimed to determine the characteristics that distinguish VP from PD. Seven clinical studies were selected and they showed that the mean age at symptom onset was four to ten times higher in patients with VP than in patients with PD. Patients with VP more commonly presented with symmetrical gait difficulties, postural instability, falls, dementia, pyramidal signs, pseudobulbar palsy, and urinary incontinence. Patients with PD were likewise more rigid and tremulous and tended to have more hypokinesia or bradykinesia. Vascular risk factors were more common in VP than in PD. This paper is the first Brazilian case series of VP that aims to provide a clinicoradiological profile of the disease from a university setting outpatient movement disorder clinic.

METHODS

Subjects

This was a cross-sectional study of 17 patients who had a diagnosis of VP and were regularly followed-up in the Movement Disorders Outpatient Clinic of the Hospital das Clínicas of the Federal University of Minas Gerais in Belo Horizonte, Minas Gerais, Brazil. Patients had their diagnosis confirmed by applying the criteria of Zijlmans et al. They were selected to participate in a structured interview to identify epidemiological and clinical data such as the age and mode of onset of their parkinsonism and dementia; its clinical course; the presence of comorbidities; past medical history (especially in regard to their past cerebrovascular event); family history; use of medication; presence of adverse medication effects; presence of levodopa fluctuations and dyskinesia; presence of visual hallucination; falls; urinary incontinence; freezing of gait (FOG); and difficulties in daily living activities. A retrospective medical chart review was eventually necessary to retrieve missing information.

Patients had to fulfill Zijlmans’ probable criteria for VP, which were (1) parkinsonism (defined as bradykinesia accompanied by at least one of following: rest tremor, muscular rigidity, or postural instability); (2) cerebrovascular disease, defined by evidence of relevant cerebrovascular disease, as indicated by brain imaging computed tomography (CT) or magnetic resonance imaging (MRI), or by the presence of focal signs or symptoms that are consistent with stroke; (3) a relationship between the parkinsonism and cerebrovascular disease, as ascertained by (i) an acute or delayed progressive onset with infarcts in or near areas that can increase basal ganglia motor output (e.g. the external segment of the globus pallidus or substantia nigra pars compacta) or a direct decrease in the thalamocortical drive (e.g. ventrolateral nucleus of the thalamus, large frontal lobe infarct) – the parkinsonism consists of a contralateral bradykinetic rigid syndrome or a shuffling gait that develops within one year after a stroke; or as ascertained by (ii) an insidious onset of parkinsonism with extensive subcortical white matter lesions, bilateral symptoms at onset, and the early onset of a shuffling gait or cognitive dysfunction.

Because of the heterogeneity of clinical pictures of VP, we used the Fénelon and Houéto classification of VP to divide it into four types, based on the clinical manifestation: (1) VP manifesting in a manner identical to PD; (2) unilateral parkinsonism after a contralateral vascular lesion; (3) “atypical” parkinsonian syndromes; and (4) “parkinsonian” gait disorders. Three categories were considered in regard to their clinical course: (1) rapidly progressive (i.e. worsening of symptoms to a nadir in less than a year after its onset); (2) stable; and (3) slowly progressive (i.e. worsening of symptoms to a nadir more than a year after its onset).

Other inclusion criteria were current use of levodopa and a Hoehn-Yahr stage of 1 to 4. Exclusion criteria included the following:

1. Evident and documented orthopedic, rheumatologic, or spinal cord disease that significantly impaired the application of motor scales and that may have otherwise posed challenges to the diagnosis;
2. Evident and documented visual abnormalities that significantly impaired the application of cognitive scales;
3. Past medical history of brain trauma or tumor;
4. Hoehn-Yahr stage 5 (i.e. wheelchair bound or bedbound), so that the patient is unable to perform the tests;
5. Diagnostic uncertainty from the medical charts review;
6. Inability of the patient to undergo neuroimaging;
7. Missing data or lack of adequate information from the patient and family; and
8. Patient’s refusal to give written consent.

Scales and tests

The first version of the Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) was used in the analysis of non-motor and motor symptoms of the disease. Patients were examined according to Part III
of the scale in the early morning after a 12-hour interruption from levodopa use (i.e. the "OFF" period). Immediately afterwards, the FOG scale by Giladi et al.\textsuperscript{12,13}, which was recently translated into Portuguese\textsuperscript{14}, was applied to all patients during the "OFF" period. Patients were instructed to use their regular diurnal dose of levodopa and were evaluated with the aforementioned scales after an hour. Response to levodopa was determined by this test – named the "practically defined off" test – initially described by the Core Assessment Program for Intracerebral Transplantations (CAPIT)\textsuperscript{15,16}, in which patients had a 12-hour interruption in levodopa use. Response was based on the percentage reduction in the MDS-UPDRS scale\textsuperscript{27} and the Hoehn-Yahr stage. Cognitive assessment was made by the Mini-Mental State Examination (MMSE)\textsuperscript{18,19}, the Frontal Assessment Battery (FAB)\textsuperscript{20,21}, and the Executive Interview (EXIT\textsuperscript{25})\textsuperscript{22,23}. Functional activities of daily living were assessed by the Pfeffer\textsuperscript{21} scale and the Katz scale\textsuperscript{22}. Probable vascular dementia was diagnosed based on the criteria of the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherché et l’Enseignement en Neurosciences (NINDS-AIREN)\textsuperscript{25} and supported by the Hachinski score\textsuperscript{27}. A 1.0 Tesla brain MRI was performed in all patients and fluid-attenuated inversion recovery (FLAIR), and T2- and T1-weighted sequences were used to measure the white matter burden by using the Fazekas scale\textsuperscript{26}.

**Cut-off values**

Lower limb parkinsonism predominance was determined by a two-point difference between the upper limb and lower limb scores of bradykinesia, rigidity, and/or postural instability from Part III of the MDS-UPDRS scale. The presence of FOG was assessed by Item 14 of the MDS-UPDRS scale and by one or more points of the Giladi FOG scale, Item 3. Responders to the levodopa diurnal dose were patients who reached a percentage reduction exceeding 25% in Part III of the UPDRS\textsuperscript{27}. The MMSE scores were correlated to the number of years of schooling. Patients were considered cognitively impaired when they scored less than 21 points (for 1–3 years of schooling), less than 24 points (for 4–7 years of schooling), and less than 26 points (for 8 years or more years of schooling)\textsuperscript{25}. The FAB scores (up to 18 points) were also subjected to variability in accordance with the formal years of schooling. Patients were considered executive dysfunctional when they scored less than 8.6 points (for 1–3 years of schooling), less than 10.1 points (for 4–7 years of schooling), less than 11.6 points (for 8–11 years of schooling), and less than 13 points (for more than 12 years of schooling)\textsuperscript{25}. Patients were assessed by the EXIT\textsuperscript{25} scale (up to 50 points) to determine if they had executive dysfunction. Points on this scale also varied in accordance with the formal years of schooling: 5.1 points (for 1–4 years of schooling), 3.3 points (for 5–8 years of schooling) and 2.9 points (for more than 8 years of schooling)\textsuperscript{21}.

**Statistics and ethics**

Statistical analysis consisted of descriptive univariate analysis (mean±standard deviation) by using SPSS 20.1 software (IBM Corporation Software Group, USA). The study was approved by the Ethics Committee of the Federal University of Minas Gerais (Belo Horizonte, Minas Gerais, Brazil). All procedures were performed with adequate understanding and written consent of the patients or their relatives (whenever necessary).

**RESULTS**

Ten patients (58.8%) were male and the mean ± standard deviation (SD) age of the whole sample was 75.8±10.1 years (expressed as the mean±standard deviation [SD]). The mean number of years of formal schooling was 2.9±2.5 years. All patients had arterial hypertension; 10 (58.8%) patients had dyslipidemia; and eight (47.0%) patients had type 2 diabetes. Three (17.6%) patients used tobacco and alcohol. Thirteen (76.4%) patients had a previous history of lacunar stroke and developed parkinsonism within less than a month from the event. The remaining patients had an insidious onset of parkinsonism with extensive subcortical white matter disease in areas adjacent to the basal ganglia and thalamus. The mean age of onset of parkinsonism was 72.2±10.0 years. Eight (47.0%) patients had a rapidly progressive course of symptoms, whereas five (29.4%) patients had stable symptoms and four (23.5%) patients had slowly progressive symptoms. According to the aforementioned Fénelon and Houéto\textsuperscript{7} classification, we encountered patients from all groups, except the one patient in which the VP manifested in a manner identical to PD. All patients had been using levodopa for a mean period of 2.9 years and the mean dose was 530.9±218.2 mg/day. No patient reported the usual complications of levodopa use such as dyskinesia and fluctuation.

The most common symptoms were urinary incontinence (88.2%), lower limb parkinsonism with falls and FOG (76.4%). The mean MDS-UPDRS total score was 72.5±21.6 points; the MDS-UPDRS Part III score was 46.3±8.0 points; the Giladi’s FOG score was 13.7±6.7 points; and the Hoehn-Yahr stage score was 3.3±0.9 points. The "practically-defined off" test determined a mean 6.9±4.8 point reduction in the UPDRS scale and a mean 5.8±4.4 point reduction in UPDRS Part III. There was no change in Hoehn-Yahr stages between periods when patients were examined when "ON" and when "OFF" levodopa.

Cognitive assessment by the MMSE, FAB, and EXIT\textsuperscript{25} scales resulted in mean values of 16.2±5.8 points, 3.8±3.5 points, and 35.4±11.5 points, respectively. Twelve (70.5%) patients fulfilled the criteria for probable vascular dementia and had a mean Hachinski score of 9.4±2.2 points. The mean Pfeffer’s Functional Activities Questionnaire score was
2.6±1.4 points and the mean Katz Index of Independence in Activities of Daily Living score was 15.7±7.0 points.

Except for one patient who had a strategic lacunar infarct in the contralateral substantia nigra and two patients with only periventricular white matter lesions, most (58.8%) patients had multiple lacunar infarcts and 23.5% of the patients had extensive white matter disease. The mean Fazekas scale of white matter burden was 2.47±0.7 points.

**DISCUSSION**

In this case series, VP was mostly characterized by lower limb parkinsonism with frequent FOG and falls, urinary incontinence, pyramidal signs, and executive dysfunction with concomitant probable vascular dementia. There was no response to levodopa and most patients had multiple infarcts or an extensive white matter disease burden, as indicated by brain MRI. The onset of the movement disorder occurred in patients who were in their seventies and symptom onset was preceded by an overt cerebrovascular event – mostly lacunar – in most patients.

Because of prognostic and therapeutic implications, the most important consideration when making a diagnosis of VP is differentiating it from PD. Based on a systematic review of seven clinical studies and 16 other comparative studies (which included an assessment of imaging data), patients with VP were older, had a shorter duration of the illness, presented with symmetrical gait difficulties, and were less responsive to levodopa. They were also more prone to postural instability, falls, and dementia. Pyramidal signs, pseudobulbar palsy, and urinary incontinence were also common. By contrast, patients with PD were presented with upper limb asymmetrical rest tremor or bradykinesia and they had a prominent response to levodopa. Vascular risk factors were more common in patients with PD presented with upper limb asymmetrical rest tremor or bradykinesia and two patients with Parkinson’s disease had multiple lacunar infarcts and 23.5% of the patients had extensive white matter disease. The mean Fazekas scale of white matter burden was 2.47±0.7 points.

### Table 1

<table>
<thead>
<tr>
<th>VP Symptoms</th>
<th>PD Symptoms</th>
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<tr>
<td>Lower limb parkinsonism</td>
<td>Upper limb parkinsonism</td>
</tr>
<tr>
<td>FOG, falls, and dementia</td>
<td>Pyramidal signs, pseudobulbar palsy, urinary incontinence</td>
</tr>
<tr>
<td>Symmetrical gait difficulties</td>
<td>Asymmetrical rest tremor</td>
</tr>
<tr>
<td>Less responsive to levodopa</td>
<td>Prominent response to levodopa</td>
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</tbody>
</table>

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Vascular risk factors were more common in patients with PD presented with upper limb asymmetrical rest tremor or bradykinesia and 23.5% of the patients had extensive white matter disease. The mean Fazekas scale of white matter burden was 2.47±0.7 points.

On brain MRI, the diagnosis of VP must be supported by the presence of diffuse white matter lesions and/or strategic subcortical infarcts. The exact pathophysiological mechanisms leading to VP are unknown, although diffuse white matter lesions may damage the basal ganglia on higher centers of motor planning and execution. All the same, strategic infarcts would cause parkinsonism by disrupting the putamino-pallido-thalamic loop. The clinical picture comprised lower limb parkinsonism with FOG and falls, pyramidal signs, executive dysfunction, and poor levodopa responsiveness. Most patients developed concomitant probable vascular dementia and had multiple infarcts or an extensive white matter burden on brain MRI. Physicians should keep this profile in mind when dealing with parkinsonism in the elderly population, especially in people with a history of stroke.
Table 1. Clinical characteristics of vascular parkinsonism obtained from seven clinical studies (adapted from Kalra et al.8).

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Design</th>
<th>Subjects</th>
<th>Diagnostic criteria</th>
<th>Clinical findings</th>
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<tbody>
<tr>
<td>FitzGerald and Jankovic29/1989</td>
<td>Hospital-based cross-sectional (tertiary referral center)</td>
<td>10 VP 100 PD</td>
<td>Marked gait difficulty with lack of or with only minimal upper limb involvement (i.e. lower body parkinsonism)</td>
<td>Patients with VP have a significantly shorter symptom duration, present with gait difficulty, have less levodopa responsiveness. There is no difference in risk factors, except for hypertension.</td>
</tr>
<tr>
<td>Zijlmans et al.30/1995</td>
<td>Cross-sectional</td>
<td>15 VP 15 DP</td>
<td>Parkinsonism with dominant frontal gait disorder, aged &gt;60 years, and the exclusion of other secondary parkinsonism types</td>
<td>There is no difference between patients with VP and patients with PD or hypertensive controls in age or BP. Patients with VP have more subcortical lesions than patients with PD. A cutoff of 0.6% lesioned ischemic brain volume is suggested. Clinical severity is not correlated with lesion volume or location.</td>
</tr>
<tr>
<td>Yamanouchi and Nagura31/1997</td>
<td>Clinicopathological</td>
<td>24 VP 30 PD</td>
<td>Parkinsonism with evidence of cerebrovascular lesions and lack of depigmentation or Lewy bodies in the substantia nigra</td>
<td>Of the patients with VP, 17% of the patients had tremor (versus 73% of the PD patients), 38% of the patients had hemiparesis, and 63% of the patients had pyramidal signs (versus 0% in the PD patients). One-half of the patients with VP had pseudobulbar palsy; 27% of patients with PD had dysphasia or dysarthria. Dementia was present in 71% of patients with VP and 43% of patients with PD. Only one-fifth of the patients with VP showed a transient response to levodopa. Asymmetry of limb rigidity was present in 29% of the patients with VP versus 73% of the patients with PD. There was no difference in gait disorders between VP and PD.</td>
</tr>
<tr>
<td>Winikates and Jankovic2/1999</td>
<td>Retrospective, cross-sectional, hospital-based</td>
<td>69 VP 277 PD</td>
<td>Patients with parkinsonism and a vascular score of 2 points or more on a vascular rating scalea</td>
<td>Patients with VP were significantly older and had gait difficulty, less levodopa responsiveness, asymmetrical predominant lower body involvement, postural instability, falls, dementia, corticospinal findings, incontinence, and pseudobulbar palsy.</td>
</tr>
<tr>
<td>Demirkiran et al.32/2001</td>
<td>Review of medical records, cross-sectional</td>
<td>16 VP 50 PD</td>
<td>Parkinsonism, presence of vascular lesions on brain MRI, and the exclusion of other causes of secondary parkinsonism</td>
<td>Patients with VP were significantly older, had a shorter disease duration, had a gait disorder as the most frequent initial symptom, and 38% of the patients were levodopa responsive. Vascular risk factors were more common in patients with VP. Postural instability, freezing, gait disturbance, pyramidal signs, postural tremor were significantly more prevalent in VP. Patients with VP have more prominent features in the lower limbs.</td>
</tr>
<tr>
<td>Rampello et al.33/2005</td>
<td>Hospital-based cohort</td>
<td>39 VP 28 PD</td>
<td>Parkinsonism with vascular lesions on brain MRI</td>
<td>Patients with VP were older and 29% of the patients were levodopa responsive. Vascular risk factors, postural tremor, gait disorder, pyramidal signs, and lower body predominance more frequent in VP. The UPDRS scores at baseline were higher in patients with VP than in patients with PD. After 2 years, patients with VP had greater lower limb involvement than patients with PD.</td>
</tr>
<tr>
<td>Okuda et al.34/2008</td>
<td>Cross-sectional</td>
<td>55 VP 132 PD</td>
<td>Lower body parkinsonism with frontal gait disorder, postural instability, lack of resting tremor, symmetrical progression, poor response to levodopa, and multiple basal ganglia or subcortical infarctions</td>
<td>There was no difference in age or MMSE score between patients with VP, PD, and hypertensive controls. Primitive reflexes (i.e. snout, palmomental), jaw jerk, Hoffmann's score, and extensor plantar response were significantly higher in VP.</td>
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aVascular rating scale: 2 points for pathologically or angiographically proven diffuse vascular disease; 1 point for the onset of parkinsonism within 1 month of clinical stroke; 1 point for a history of two or more strokes; 1 point for a history of two or more risk factors of stroke; and 1 point for neuroimaging evidence of vascular disease in two or more vascular territories. 

bOnly patients older than 70 years were included.

cThese patients included 22 age-matchedBinswanger’s disease patients without parkinsonism.

BP: blood pressure; MMSE: Mini-Mental State Examination; MRI: magnetic resonance imaging; PD: Parkinson’s disease; UPDRS: Unified Parkinson’s Disease Rating Scale; VP: vascular parkinsonism.
References