MRI in patients with suspected vascular parkinsonism

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Article abstract—To determine whether MRI can reveal more vascular lesions in patients clinically suspected of having vascular parkinsonism, we compared 15 such patients with 15 patients who had idiopathic Parkinson's disease and 10 hypertensive controls. Patients with suspected vascular parkinsonism had significantly more subcortical lesions than those with Parkinson's disease or hypertension. The cutoff point that best distinguished patients with suspected vascular parkinsonism from patients with Parkinson's disease was a 0.6% level of lesioned brain tissue volume. There were two types of vascular parkinsonism: one had an acute onset and lesions located in the subcortical gray nuclei (striatum, globus pallidus, thalamus); the other had an insidious onset and lesions diffusely distributed in the watershed areas.

Since Critchley popularized the concept of "arteriosclerotic parkinsonism" in 1929,1 many authors have challenged its existence.2-4 CT and MRI have provided support for the concept of vascular parkinsonism.7-10 Atypical parkinsonism (without tremor or levodopa response) occurs with subcortical white or gray matter lesions (SCLs)7-10 that correlate with arteriosclerosis, demyelination or...
loss of axons, and chronic infarcts on postmortem studies. Clinically, vascular parkinsonism—“lower-half parkinsonism” or “lower-body parkinsonism”—is dominated by “frontal gait disorder,” with characteristic shuffling, short steps, start-and-turn hesitation, variable base (narrow to wide), and moderate disequilibrium.

The multiple etiologies of frontal gait disorder make diagnosis of vascular parkinsonism difficult. Moreover, infarction of the basal ganglia and deep white matter (or SCLs on MRI and CT) occurs in elderly people who do not have parkinsonism. Since authors were unable to detect vascular lesions in patients meeting clinical criteria for idiopathic Parkinson’s disease (PD), the existence of vascular parkinsonism was denied. Calne et al and Rowe and Kahn emphasized the necessity of obtaining proper controls. Because of the heterogeneity in risk factors for SCLs among nondiseased elderly, care is needed in selecting a control group with full knowledge of the distribution of their individual risk factors. The best choice for controls are neurologically normal elderly persons with chronic hypertension, the main vascular risk factor for SCLs.

The aim of our study was to investigate whether MRI can yield evidence for vascular lesions in suspected vascular parkinsonism. Therefore, we attempted to determine whether (1) patients with clinically suspected vascular parkinsonism (SVP) have more SCLs on MRI than patients meeting clinical criteria for idiopathic PD; (2) SVP patients have more SCLs than hypertensive controls without parkinsonism or gait disorder; (3) SCLs in SVP patients with an acute onset are located differently from SCLs in SVP patients with an insidious onset; and (4) the severity of parkinsonian symptoms in SVP patients is related to the volume and location of SCLs.

Methods. Patients and controls. Fifteen PD patients (10 men and 5 women; mean age, 72 ± 8 years; mean duration of disease, 7 ± 7 years), 15 SVP patients (11 men and 4 women; mean age, 72 ± 4 years; mean duration of disease, 3 ± 3 years), and 10 hypertensive controls were examined clinically and with MRI. All PD and SVP patients were selected consecutively from the departments of neurology and geriatrics in our hospital; this was done without knowledge of any previous MRI or CT findings or of whether there was a history of vascular risk factors. PD was diagnosed in accordance with accepted clinical criteria. SVP was diagnosed in patients 60 years or older who had parkinsonism (hypokinesia and rigidity) associated with, or reversible ischemic neurologic deficit. Patients with other parkinsonism nor gait disorder and met the exclusion criteria as described above. All patients gave informed consent prior to the examination in accordance with institutional guidelines.

Procedures. All patients and controls were examined by one investigator (J.C.M.Z.), who assessed severity of arm and leg rigidity in accordance with the Unified Parkinson’s Disease Rating Scale, severity of hypokinesia using a pegboard test as described in a previous study, and gait velocity during free-speed walking by measuring the time needed to cover a distance of 10 meters. Blood pressure was measured with a legally stamped sphygmomanometer (Erka-meter 300) after 5 minutes of supine rest. At the time of clinical examination, no patient had taken levodopa during the preceding 12 hours.

MRI examination was performed with a 1.5-tesla Magnetom and a spin-echo sequence using proton-density and T2 weighting (TE = 20 and 80 msec; TR = 2,500 msec). Images through the whole brain were acquired in the transverse plane, parallel to the intercommissural line, with a slice thickness of 4 mm and a slice gap of 0.4 mm. Spatial resolution was 0.95 mm, corresponding to a 256 x 256 matrix. All images had an identical field of view. Two investigators (J.C.M.Z. and O.J.M.V.), blind to the identities of the imaged patients, interpreted the images for the volume and location of SCLs as evident from areas with increased signal intensity on both short- and long-TE images. Perivascular dilatations and hyperintense rims around the tip of the frontal horn were not scored, because they are of nonischemic origin.

SCL volume was determined with a stereologic estimation using a point-counting method (Gundersen and Jensen) and the Cavalieri theorem of systematic sampling. This method uses systematic sampling of parallel sections with a known, fixed interval (in this study, 4.4 mm—i.e., MRI slice thickness plus slice gap) and estimation of area using counting grids. It was applied to estimate the volume of cerebral ventricles in hydrocephalic patients on brain CT and to estimate the volume of several brain structures in Down’s syndrome on MRI. We estimated the total area of all SCLs (A SCL) on all MRI slices by superimposing a systematic array of test points on each slice. Giving random positioning of the test array on each slice, the total number of test points (AZ) that hit SCLs affords an unbiased estimator of A SCL. The exact relationship is expressed as

\[ A_{SCL} = \Sigma p \times a(p) \text{[in mm}^2\text{]} \]

where a(p) is the areal equivalent of one test point. Total volume of SCL (V SCL) is given by the formula

\[ V_{SCL} \text{[in mm}^3\text{]} = A_{SCL} \text{[in mm}^2\text{]} \times 4.4 \text{[in mm]} \]
The coefficient of error of the estimate of each individual SCL volume declines in direct proportion to the total number of MRI slices and to the total number of test points.53 In our study, a coefficient of error of less than 5% was obtained, because the number of MRI slices hitting SCLs was 10 or more and the number of test points was 50 or more.36 The systematic and random errors of the VGC estimates of the two investigators (interobserver variability), and also those of one investigator at two points separated by a 4-week interval (intraobserver variability), are described elsewhere.36 They were all approximately 10%. This indicates a high reproducibility of the method, especially when compared with the recently developed semiquantitative rating scales in which the severity of SCLs is expressed as a sum score of points awarded to subjective criteria, such as focal, multifocal, and confluent lesions.12,21,37 or punctate, nodular, and patchy lesions,38 yielding Cohen's kappa coefficient values of inter- and intraobserver agreement ranging from 0.34 to 0.73.37 The SCL volume was finally expressed as a percentage of total brain tissue volume: (V_SCL/V_brain tissue) × 100%, whereas V_brain tissue was obtained by a method similar to that for V_SCL.

SCLs were also scored with respect to location of (1) territories of the three main cerebral arteries (anterior, middle, and posterior); (2) territories of the three watershed areas (between the anterior and middle cerebral arteries, the middle and posterior cerebral arteries, and the deep and superficial middle cerebral arteries); and (3) the subcortical gray nuclei (putamen, caudate nucleus, globus pallidus, thalamus, and substantia nigra).

**Statistics.** To compare the SCL volume in the two SVP groups, PD patients, and hypertensive controls, the Mann-Whitney test with Bonferroni adjustment for multiple comparisons was used. To determine whether SVPa patients and SVPi patients could also be differentiated from one another by the presence of SCLs in the gray nuclei, Fisher's exact test (two-tailed) was used. Finally, the severity of the parkinsonian symptoms of the SVP patients and their relation to the volume and location of SCLs were examined with Spearman's rank correlation. For the unilateral tests (arm and leg rigidity, pegboard), the more severely affected side of the body was correlated with the total SCL volume in all test procedures, p values <0.05 were considered significant.

**Results.** SVP patients did not differ significantly from PD patients or hypertensive controls in age, systolic blood pressure, or diastolic blood pressure (table 1). The SVP group scored significantly lower than PD patients in rigidity in the upper and lower extremities (table 1). Pegboard score and walking velocity were not appreciably different between the two patient groups. SVP patients had a significantly higher pegboard score and a significantly lower walking velocity than controls (table 1). The four SVPa patients were not crucially different from the 11 SVPi patients in age, systolic blood pressure, diastolic blood pressure, pegboard test, arm and leg rigidity, or walking velocity (data not shown). Current blood pressure did not differ significantly by one-way ANOVA between the SVPi group and the controls (1152 ± 16/188 ± 11 mm Hg versus [166 ± 21]/[91 ± 8] mm Hg).

Figure 1 shows MRI studies of an SVPa and an SVPi patient. SVPi patients had markedly more SCLs than did patients with PD (p < 0.01; Mann-Whitney test) or hypertension (p < 0.05) (figure 2). SVPa patients had significantly more SCLs than did PD patients (p < 0.05), but not more than hypertensive controls (figure 2). The SCL volume was not significantly different between the two SVP groups. A cutoff point for SCL volume of 0.6% of brain tissue volume resulted in the best discrimination between the PD and SVP groups (figure 2). Three hypertensive controls had an SCL volume ≥0.6% (table 2).

All four SVPa patients had SCLs in the gray nuclei, but only two of the 11 SVPi patients did (p = 0.02; Fisher's exact test, two-tailed) (table 2). None of the PD patients or controls had gray nuclei SCLs (table 2). SCLs in the gray nuclei were located in the putamen or thalamus alone or in one of those two nuclei along with the globus pallidus or caudate nucleus.

The severity of clinical symptoms (gait velocity, arm and leg rigidity, pegboard score) was significantly correlated with neither the total SCL volume in the SVP patients nor the location of SCLs as seen from the subcores of the blood-supplying territories of the three main cerebral arteries, the three watershed areas between these three arteries, and the subcortical gray nuclei (Spearman's rank correlation). The SCLs were diffusely distributed, mainly in the three watershed areas, with only a small variation between the four patient groups. Of the total SCL load, 0 to 3% was located in the territories of the three main cerebral arteries; 40 to 50% in the watershed area of the anterior/middle cerebral arteries; 15 to 20% in the watershed area of the deep and superficial middle cerebral arteries; 30 to 40% in the watershed area of the middle/posterior cerebral arteries; and 0 to 14% in the subcortical gray nuclei.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>SVP (n = 15) (mean ± SD)</th>
<th>PD (n = 15) (mean ± SD)</th>
<th>Controls (n = 10) (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>72 ± 4</td>
<td>72 ± 8</td>
<td>70 ± 2</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>154 ± 18</td>
<td>145 ± 15</td>
<td>168 ± 21</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>91 ± 11</td>
<td>89 ± 15</td>
<td>91 ± 8</td>
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<tr>
<td>Pegboard test (sec)</td>
<td>10.8 ± 6.1</td>
<td>10.6 ± 6.1</td>
<td>5.7 ± 0.8*</td>
</tr>
<tr>
<td>Arm rigidity (UPDRS)</td>
<td>1.0 ± 0.8</td>
<td>2.0 ± 0.6†</td>
<td>—</td>
</tr>
<tr>
<td>Leg rigidity (UPDRS)</td>
<td>1.2 ± 0.9</td>
<td>1.9 ± 0.6*</td>
<td>—</td>
</tr>
<tr>
<td>Velocity of walking (cm/sec)</td>
<td>60 ± 26</td>
<td>69 ± 29</td>
<td>117 ± 24†</td>
</tr>
</tbody>
</table>

SVP Suspected vascular parkinsonism.
PD Parkinson's disease.
BP Blood pressure.
UPDRS Unified Parkinson’s Disease Rating Scale.
* p < 0.05; † p < 0.01 (t test): PD patients and controls compared with SVP group.
...suggests a causal relationship between the groups of neurologically normal hypertensive patients and patients with essential hypertension. The definite gold standard, ie, postmortem examination, was not available. Systemic vascular disease was assessed clinically through a neurological examination with accepted clinical diagnostic criteria for vascular disease. The presence of vascular disease was evaluated for determining the presence of vascular disease. The criteria were used for determining the presence of vascular disease. The criteria were used for determining the presence of vascular disease. The criteria were used for determining the presence of vascular disease. The criteria were used for determining the presence of vascular disease. The criteria were used for determining the presence of vascular disease. The criteria were used for determining the presence of vascular disease. The criteria were used for determining the presence of vascular disease. 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Table 2. Cross-tabulation of clinical and lesion groups

<table>
<thead>
<tr>
<th>Group</th>
<th>SCL+/SGN-</th>
<th>SCL/-SGN+</th>
<th>PD  (n = 15)</th>
<th>SVPi (n = 11)</th>
<th>SVPa (n = 4)</th>
<th>Controls (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>8</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Figure 1. Spin-echo proton density-weighted MRI studies showing acute onset of suspected vascular parkinsonism (A) and a patient with insidious onset of suspected vascular parkinsonism (B).
The difference in SCL volume between the SVP and control patients was influenced neither by hypertension history nor by current blood pressure. Only four of 15 SVP patients had a history of hypertension. Neither the current systolic nor the diastolic blood pressure differed between the two groups. Three of 10 hypertensive controls had an SCL volume ≥0.6% of brain tissue, indicating an overlap between the SVP patients and the controls. These results parallel the findings of Fazekas18 and Horikoshi et al19 who reported frequencies of 10 to 30% of partially or widely confluent lesions in asymptomatic elderly with vascular risk factors. Older persons without vascular risk factors may not serve as a control group, because of the probability of their having a lower SCL volume than our SVP patients who were not selected because of absence of vascular risk factors. PD patients are also not an optimal control group. They might have fewer vascular risk factors than most healthy individuals40,41; PD patients have a lower frequency of tobacco use,40,41 a known risk factor for arteriosclerotic vascular disease.42

In both SVP groups, SCLs were diffusely located, mainly in the watershed areas, in agreement with reports by others.9,10,30 Furthermore, all four SVPa patients had SCLs in the gray nuclei, also in agreement with other reports.7,8,36 In the four SVPa patients, subcortical gray nuclei lesions were located in the putamen or thalamus alone or in one of these two nuclei alone with the globus pallidus or caudate nucleus. There were no SCLs in the substantia nigra. The differentiation of vascular parkinsonism into two types on the basis of stage of onset and location of SCLs has not been examined previously. There probably are more types of vascular parkinsonism in which other locations are involved, such as types resembling progressive supranuclear palsy.43,44

In patients with dementia11,46,47 or in whom mental impairment was not excluded,48 the presence of gait impairment was associated with SCLs. We did not find a significant correlation between the severity of symptoms in the SVP patients and the volume or location of SCLs, probably because of the rather low SCL volume in our slightly affected SVP patients.

Thompson and Marsden9 and FitzGerald and Jankovic10 suggested that the parkinsonism in patients showing deep white matter lesions on MRI or CT might be due to subcortical ischemia.9,10 However, in a previous study48 with proton magnetic resonance spectroscopy in SVP patients, we could not detect metabolic signs of ischemia (increased lactate) in the deep white matter or in the striatum. Meguro et al49 reported impaired circulation in brains with severe SCLs, although oxygen metabolism was not measurably affected. Vascular parkinsonism is probably due to multiple acute ischemic microinfarcts resulting in neuronal cell loss, while, later on, lactate normalizes by diffusion and active transport and mechanisms appear that compensate for the decreased oxygen supply resulting from decreased circulation.49 The location of SCLs mainly in the watershed areas indicates their ischemic nature.

In conclusion, we showed that SVP patients had more SCLs than patients with PD and hypertension. This suggests a causal relationship between SCLs and parkinsonism in our patients with SVP. We observed two types of vascular parkinsonism: one had an insidious onset and vascular lesions that were diffusely located in the watershed areas; the other had an acute onset and lesions located in the subcortical gray nuclei (striatum, globus pallidus, thalamus). To prove the accuracy of clinical symptoms and SCLs in the diagnosis of vascular parkinsonism, postmortem examination studies of SVP patients are necessary.

References
17. Fazekas F. Magnetic resonance signal abnormalities in December 1995 NEUROLOGY 45 2187


